



## Clinical trial results:

### Randomised, Double-Blind (Sponsor Open), Placebo-Controlled, Multicentre, Dose Ranging Study to Evaluate the Efficacy and Safety of Danirixin Tablets Administered Twice Daily Compared With Placebo for 24 Weeks in Adult Participants With Chronic Obstructive Pulmonary Disease (COPD)

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2016-003675-21  |
| Trial protocol           | ES DE NL PL RO  |
| Global end of trial date | 05 October 2018 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 27 November 2019 |
| First version publication date | 13 October 2019  |
| Version creation reason        |                  |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | 205724 |
|-----------------------|--------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | GlaxoSmithKline  |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom,                       |
| Public contact               | GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com |
| Scientific contact           | GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                 |
|--|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 21 March 2019   |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 05 October 2018 |
| Was the trial ended prematurely?                     | No              |

Notes:

## General information about the trial

Main objective of the trial:

To characterize the dose response of danirixin compared with placebo, on the incidence and severity of respiratory symptoms in participant with COPD and the annual rate of moderate/severe COPD exacerbations in participants with COPD.

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 25 April 2017 |
| 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 | Australia: 37          |
| Country: Number of subjects enrolled | Canada: 48             |
| Country: Number of subjects enrolled | Germany: 103           |
| Country: Number of subjects enrolled | Korea, Republic of: 79 |
| Country: Number of subjects enrolled | Netherlands: 38        |
| Country: Number of subjects enrolled | Poland: 82             |
| Country: Number of subjects enrolled | Romania: 106           |
| Country: Number of subjects enrolled | Spain: 62              |
| Country: Number of subjects enrolled | United States: 59      |
| Worldwide total number of subjects   | 614                    |
| EEA total number of subjects         | 391                    |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23          | 0 |

|                           |     |
|---------------------------|-----|
| months)                   |     |
| Children (2-11 years)     | 0   |
| Adolescents (12-17 years) | 0   |
| Adults (18-64 years)      | 259 |
| From 65 to 84 years       | 355 |
| 85 years and over         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This study investigated the dose response and safety of danirixin compared with placebo in COPD participants with respiratory symptoms including cough, increased sputum production and dyspnoea.

### Pre-assignment

Screening details:

A total of 614 participants were randomized in this study across 9 countries.

### Period 1

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

### Arms

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

Arm description:

Participants received placebo film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|  |                    |
|--|--------------------|
| Arm type                               | Placebo            |
| Investigational medicinal product name | Placebo            |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants received placebo white film coated tablets either round or oval in shape, orally twice daily with food and standard care of treatment for 24 weeks.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Danirixin 5 mg |
|------------------|----------------|

Arm description:

Participants received danirixin 5 milligram (mg) film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Danirixin          |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants received danirixin 5 mg white film coated tablets either round or oval in shape, orally twice daily with food and standard care of treatment for 24 weeks.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Danirixin 10 mg |
|------------------|-----------------|

Arm description:

Participants received danirixin 10 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Danirixin          |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants received danirixin 10 mg white film coated tablets either round or oval in shape, orally twice daily with food and standard care of treatment for 24 weeks.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Danirixin 25 mg |
|------------------|-----------------|

Arm description:

Participants received danirixin 25 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Danirixin          |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants received danirixin 25 mg white film coated tablets either round or oval in shape, orally twice daily with food and standard care of treatment for 24 weeks.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Danirixin 35 mg |
|------------------|-----------------|

Arm description:

Participants received danirixin 35 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Danirixin          |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants received danirixin 35 mg white film coated tablets either round or oval in shape, orally twice daily with food and standard care of treatment for 24 weeks.

|                  |                 |
|------------------|-----------------|
| <b>Arm title</b> | Danirixin 50 mg |
|------------------|-----------------|

Arm description:

Participants received danirixin 50 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Danirixin          |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants received danirixin 50 mg white film coated tablets either round or oval in shape, orally twice daily with food and standard care of treatment for 24 weeks.

| <b>Number of subjects in period 1</b> | Placebo | Danirixin 5 mg | Danirixin 10 mg |
|---------------------------------------|---------|----------------|-----------------|
| Started                               | 102     | 102            | 103             |
| Completed                             | 88      | 97             | 90              |
| Not completed                         | 14      | 5              | 13              |
| Consent withdrawn by subject          | 9       | 2              | 6               |
| Physician decision                    | 1       | -              | 1               |
| Adverse Event, Serious Fatal          | -       | 1              | 1               |
| Adverse Event, non-fatal              | 3       | 1              | 2               |
| Liver function test abnormality       | -       | -              | 1               |
| Lost to follow-up                     | -       | -              | -               |
| Protocol deviation                    | 1       | -              | -               |
| Lack of efficacy                      | -       | 1              | 2               |

| <b>Number of subjects in period 1</b> | Danirixin 25 mg | Danirixin 35 mg | Danirixin 50 mg |
|---------------------------------------|-----------------|-----------------|-----------------|
| Started                               | 103             | 102             | 102             |
| Completed                             | 92              | 88              | 87              |
| Not completed                         | 11              | 14              | 15              |
| Consent withdrawn by subject          | 6               | 9               | 2               |
| Physician decision                    | 1               | 1               | -               |
| Adverse Event, Serious Fatal          | 2               | 1               | 1               |
| Adverse Event, non-fatal              | -               | 2               | 8               |
| Liver function test abnormality       | -               | -               | -               |
| Lost to follow-up                     | 1               | -               | 2               |
| Protocol deviation                    | -               | -               | 2               |
| Lack of efficacy                      | 1               | 1               | -               |

## Baseline characteristics

### Reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | Placebo         |
| Reporting group description:<br>Participants received placebo film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.                    |                 |
| Reporting group title  | Danirixin 5 mg  |
| Reporting group description:<br>Participants received danirixin 5 milligram (mg) film coated tablets orally twice daily with food and standard care of treatment for 24 weeks. |                 |
| Reporting group title  | Danirixin 10 mg |
| Reporting group description:<br>Participants received danirixin 10 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.            |                 |
| Reporting group title  | Danirixin 25 mg |
| Reporting group description:<br>Participants received danirixin 25 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.            |                 |
| Reporting group title  | Danirixin 35 mg |
| Reporting group description:<br>Participants received danirixin 35 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.            |                 |
| Reporting group title  | Danirixin 50 mg |
| Reporting group description:<br>Participants received danirixin 50 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.            |                 |

| Reporting group values                                | Placebo | Danirixin 5 mg | Danirixin 10 mg |
|---|---------|----------------|-----------------|
| Number of subjects                                    | 102     | 102            | 103             |
| Age categorical<br>Units: Subjects                    |         |                |                 |
| In utero  | 0       | 0              | 0               |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0       | 0              | 0               |
| Newborns (0-27 days)                                  | 0       | 0              | 0               |
| Infants and toddlers (28 days-23 months)              | 0       | 0              | 0               |
| Children (2-11 years)                                 | 0       | 0              | 0               |
| Adolescents (12-17 years)                             | 0       | 0              | 0               |
| Adults (18-64 years)                                  | 43      | 38             | 45              |
| From 65-84 years                                      | 59      | 64             | 58              |
| 85 years and over                                     | 0       | 0              | 0               |
| Age Continuous<br>Units: Years                        |         |                |                 |
| arithmetic mean                                       | 66.2    | 66.3           | 65.7            |
| standard deviation                                    | ± 7.31  | ± 6.79         | ± 7.48          |
| Sex: Female, Male<br>Units: Subjects                  |         |                |                 |
| Female  | 29      | 36             | 32              |
| Male  | 73      | 66             | 71              |

|   |    |    |    |
|---|----|----|----|
| Race/Ethnicity, Customized<br>Units: Subjects |    |    |    |
| Asian - East Asian Heritage                   | 10 | 6  | 18 |
| Asian - South East Asian Heritage             | 1  | 0  | 0  |
| Black or African American                     | 2  | 2  | 1  |
| Native Hawaiian or other Pacific Islander     | 1  | 0  | 0  |
| White - Arabic/North African Heritage         | 1  | 1  | 0  |
| White - White/Caucasian/European Heritage     | 87 | 93 | 84 |

| Reporting group values                             | Danirixin 25 mg | Danirixin 35 mg | Danirixin 50 mg |
|--|-----------------|-----------------|-----------------|
| Number of subjects                                 | 103             | 102             | 102             |
| Age categorical<br>Units: Subjects                 |                 |                 |                 |
| In utero   | 0               | 0               | 0               |
| Preterm newborn infants (gestational age < 37 wks) | 0               | 0               | 0               |
| Newborns (0-27 days)                               | 0               | 0               | 0               |
| Infants and toddlers (28 days-23 months)           | 0               | 0               | 0               |
| Children (2-11 years)                              | 0               | 0               | 0               |
| Adolescents (12-17 years)                          | 0               | 0               | 0               |
| Adults (18-64 years)                               | 40              | 46              | 47              |
| From 65-84 years                                   | 63              | 56              | 55              |
| 85 years and over                                  | 0               | 0               | 0               |
| Age Continuous<br>Units: Years                     |                 |                 |                 |
| arithmetic mean                                    | 66.3            | 65.1            | 65.7            |
| standard deviation                                 | ± 7.28          | ± 7.58          | ± 6.98          |
| Sex: Female, Male<br>Units: Subjects               |                 |                 |                 |
| Female   | 38              | 35              | 32              |
| Male   | 65              | 67              | 70              |
| Race/Ethnicity, Customized<br>Units: Subjects      |                 |                 |                 |
| Asian - East Asian Heritage                        | 17              | 10              | 17              |
| Asian - South East Asian Heritage                  | 0               | 0               | 0               |
| Black or African American                          | 0               | 0               | 1               |
| Native Hawaiian or other Pacific Islander          | 0               | 0               | 0               |
| White - Arabic/North African Heritage              | 0               | 0               | 0               |
| White - White/Caucasian/European Heritage          | 86              | 92              | 84              |

| Reporting group values                             | Total |  |  |
|--|-------|--|--|
| Number of subjects                                 | 614   |  |  |
| Age categorical<br>Units: Subjects                 |       |  |  |
| In utero   | 0     |  |  |
| Preterm newborn infants (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)                      | 259 |  |  |
| From 65-84 years                          | 355 |  |  |
| 85 years and over                         | 0   |  |  |
| Age Continuous                            |     |  |  |
| Units: Years                              |     |  |  |
| arithmetic mean                           |     |  |  |
| standard deviation                        | -   |  |  |
| Sex: Female, Male                         |     |  |  |
| Units: Subjects                           |     |  |  |
| Female                                    | 202 |  |  |
| Male                                      | 412 |  |  |
| Race/Ethnicity, Customized                |     |  |  |
| Units: Subjects                           |     |  |  |
| Asian - East Asian Heritage               | 78  |  |  |
| Asian - South East Asian Heritage         | 1   |  |  |
| Black or African American                 | 6   |  |  |
| Native Hawaiian or other Pacific Islander | 1   |  |  |
| White - Arabic/North African Heritage     | 2   |  |  |
| White - White/Caucasian/European Heritage | 526 |  |  |

## End points

### End points reporting groups

|  |                 |
|--|-----------------|
| Reporting group title  | Placebo         |
| Reporting group description:<br>Participants received placebo film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.                    |                 |
| Reporting group title  | Danirixin 5 mg  |
| Reporting group description:<br>Participants received danirixin 5 milligram (mg) film coated tablets orally twice daily with food and standard care of treatment for 24 weeks. |                 |
| Reporting group title  | Danirixin 10 mg |
| Reporting group description:<br>Participants received danirixin 10 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.            |                 |
| Reporting group title  | Danirixin 25 mg |
| Reporting group description:<br>Participants received danirixin 25 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.            |                 |
| Reporting group title  | Danirixin 35 mg |
| Reporting group description:<br>Participants received danirixin 35 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.            |                 |
| Reporting group title  | Danirixin 50 mg |
| Reporting group description:<br>Participants received danirixin 50 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.            |                 |

### Primary: Change from Baseline in respiratory symptoms measured by evaluating respiratory symptoms (E-RS) in COPD. E-RS: COPD Total Score

|   |   |
|---|---|
| End point title   | Change from Baseline in respiratory symptoms measured by evaluating respiratory symptoms (E-RS) in COPD. E-RS: COPD Total Score |
| End point description:<br>E-RS: COPD is a subset of Exacerbations of Chronic pulmonary Disease Tool (EXACT). E-RS is a tool that consists of 11 items from the 14 item EXACT instrument. The domains include: respiratory symptoms (RS)-breathlessness (RS-BRL comprised of 5 items, score range [0-17]), RS-cough and sputum (RS-CSP comprised of 3 items, score range [0-11]), and RS-chest symptoms (RS-CSY comprised of 3 items, score range [0-12]). The total score ranged between 0-40 and higher values indicates severe respiratory symptoms. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Per protocol population included all participants from the mITT population who did not have a protocol deviation considered to impact efficacy. Posterior mean change and standard deviation has been presented. Only those participants with data available at the specified data points was analyzed. |   |
| End point type  | Primary   |
| End point timeframe:<br>Baseline and Month 6  |   |

| End point values                     | Placebo           | Danirixin 5 mg    | Danirixin 10 mg   | Danirixin 25 mg   |
|--------------------------------------|-------------------|-------------------|-------------------|-------------------|
| Subject group type                   | Reporting group   | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed          | 86 <sup>[1]</sup> | 95 <sup>[2]</sup> | 87 <sup>[3]</sup> | 91 <sup>[4]</sup> |
| Units: Scores on a scale             |                   |                   |                   |                   |
| arithmetic mean (standard deviation) | -2.11 (± 0.345)   | -1.93 (± 0.289)   | -1.47 (± 0.349)   | -0.87 (± 0.286)   |

Notes:

[1] - Per Protocol Population.

[2] - Per Protocol Population.

[3] - Per Protocol Population.

[4] - Per Protocol Population.

| End point values                     | Danirixin 35 mg   | Danirixin 50 mg   |  |  |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type                   | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed          | 85 <sup>[5]</sup> | 86 <sup>[6]</sup> |  |  |
| Units: Scores on a scale             |                   |                   |  |  |
| arithmetic mean (standard deviation) | -0.76 (± 0.259)   | -0.71 (± 0.281)   |  |  |

Notes:

[5] - Per Protocol Population.

[6] - Per Protocol Population.

## Statistical analyses

| Statistical analysis title  | Statistical Analysis of Placebo Vs Danirixin 5mg |
|---|--|
| Statistical analysis description:<br>4-parameter Emax model selected. |  |
| Comparison groups   | Placebo v Danirixin 5 mg                         |
| Number of subjects included in analysis                               | 181  |
| Analysis specification  | Pre-specified                                    |
| Analysis type   | other <sup>[7]</sup>                             |
| Parameter estimate  | Median Posterior Difference                      |
| Point estimate  | 0.08   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0  |
| upper limit   | 0.66   |

Notes:

[7] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 5 mg has been presented.

| Statistical analysis title                                  | Statistical Analysis of Placebo Vs Danirixin 10 mg |
|---|--|
| Statistical analysis description:<br>4-parameter Emax model |  |
| Comparison groups   | Placebo v Danirixin 10 mg                          |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 173                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other <sup>[8]</sup>        |
| Parameter estimate                      | Median Posterior Difference |
| Point estimate                          | 0.61                        |
| Confidence interval                     |                             |
| level                                   | 90 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0                           |
| upper limit                             | 1.52                        |

Notes:

[8] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 10 mg has been presented.

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Statistical Analysis of Placebo Vs Danirixin 25 mg |
| Statistical analysis description:<br>4-parameter Emax model selected. |  |
| Comparison groups   | Placebo v Danirixin 25 mg                          |
| Number of subjects included in analysis                               | 177  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other <sup>[9]</sup>                               |
| Parameter estimate  | Median Posterior Difference                        |
| Point estimate  | 1.25   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.43   |
| upper limit   | 1.97   |

Notes:

[9] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 25 mg has been presented.

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Statistical Analysis of Placebo Vs Danirixin 35 mg |
| Statistical analysis description:<br>4-parameter Emax model selected. |  |
| Comparison groups   | Placebo v Danirixin 35 mg                          |
| Number of subjects included in analysis                               | 171  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other <sup>[10]</sup>                              |
| Parameter estimate  | Median Posterior Difference                        |
| Point estimate  | 1.34   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.72   |
| upper limit   | 2.03   |

Notes:

[10] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 35 mg has been presented.

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Statistical Analysis of Placebo Vs Danirixin 50 mg |
| Statistical analysis description:<br>4-parameter Emax model selected. |  |

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Placebo v Danirixin 50 mg   |
| Number of subjects included in analysis | 172                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other <sup>[11]</sup>       |
| Parameter estimate                      | Median Posterior Difference |
| Point estimate                          | 1.38                        |
| Confidence interval                     |                             |
| level                                   | 90 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.79                        |
| upper limit                             | 2.07                        |

Notes:

[11] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 50 mg has been presented.

### **Primary: Change from Baseline in respiratory symptoms measured by E-RS in COPD (E-RS: COPD Breathlessness Score)**

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in respiratory symptoms measured by E-RS in COPD (E-RS: COPD Breathlessness Score) |
|-----------------|---|

End point description:

E-RS: COPD is a subset of EXACT. E-RS is a tool that consists of 11 items from the 14 item EXACT instrument. The domains include: RS-BRL comprised of 5 items, score range (0-17), RS-CSP comprised of 3 items, score range (0-11), and RS-CSY comprised of 3 items, score range (0-12). The total score ranged between 0-40 and higher values indicates severe respiratory symptoms. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Posterior mean change and standard deviation has been presented. Only those participants with available data at the specified time points were analyzed.

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

End point timeframe:

Baseline and Month 6

| <b>End point values</b>              | Placebo            | Danirixin 5 mg     | Danirixin 10 mg    | Danirixin 25 mg    |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type                   | Reporting group    | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed          | 86 <sup>[12]</sup> | 95 <sup>[13]</sup> | 87 <sup>[14]</sup> | 91 <sup>[15]</sup> |
| Units: Scores on a scale             |                    |                    |                    |                    |
| arithmetic mean (standard deviation) | -0.82 (± 0.202)    | -0.69 (± 0.162)    | -0.41 (± 0.183)    | -0.15 (± 0.148)    |

Notes:

[12] - Per protocol population.

[13] - Per protocol population.

[14] - Per protocol population.

[15] - Per protocol population.

| <b>End point values</b>              | Danirixin 35 mg    | Danirixin 50 mg    |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 85 <sup>[16]</sup> | 86 <sup>[17]</sup> |  |  |
| Units: Scores on a scale             |                    |                    |  |  |
| arithmetic mean (standard deviation) | -0.10 (± 0.141)    | -0.09 (± 0.158)    |  |  |

Notes:

[16] - Per protocol population.

[17] - Per protocol population.

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>                                     | Statistical Analysis of Placebo Vs Danirixin 5 mg |
| Statistical analysis description:<br>4-parameter Emax model selected. |   |
| Comparison groups   | Placebo v Danirixin 5 mg                          |
| Number of subjects included in analysis                               | 181   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | other <sup>[18]</sup>                             |
| Parameter estimate  | Median Posterior Difference                       |
| Point estimate  | 0.09  |
| Confidence interval   |   |
| level   | 90 %  |
| sides   | 2-sided   |
| lower limit   | 0   |
| upper limit   | 0.42  |

Notes:

[18] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 5 mg has been presented.

|   |  |
|---|--|
| <b>Statistical analysis title</b>                           | Statistical Analysis of Placebo Vs Danirixin 10 mg |
| Statistical analysis description:<br>4-parameter Emax model |  |
| Comparison groups   | Placebo v Danirixin 10 mg                          |
| Number of subjects included in analysis                     | 173  |
| Analysis specification                                      | Pre-specified                                      |
| Analysis type   | other <sup>[19]</sup>                              |
| Parameter estimate  | Median Posterior Difference                        |
| Point estimate  | 0.43   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0  |
| upper limit   | 0.87   |

Notes:

[19] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 10 mg has been presented.

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Statistical Analysis of Placebo Vs Danirixin 25 mg |
| Statistical analysis description:<br>4-parameter Emax model selected. |  |
| Comparison groups   | Placebo v Danirixin 25 mg                          |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 177                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other <sup>[20]</sup>       |
| Parameter estimate                      | Median Posterior Difference |
| Point estimate                          | 0.68                        |
| Confidence interval                     |                             |
| level                                   | 90 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.23                        |
| upper limit                             | 1.08                        |

Notes:

[20] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 25 mg has been presented.

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Statistical Analysis of Placebo Vs Danirixin 35 mg |
| Statistical analysis description:<br>4-parameter Emax model selected. |  |
| Comparison groups   | Placebo v Danirixin 35 mg                          |
| Number of subjects included in analysis                               | 171  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other <sup>[21]</sup>                              |
| Parameter estimate  | Median Posterior Difference                        |
| Point estimate  | 0.72   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.37   |
| upper limit   | 1.1  |

Notes:

[21] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 35 mg has been presented.

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Statistical Analysis of Placebo Vs Danirixin 50 mg |
| Statistical analysis description:<br>4-parameter Emax model selected. |  |
| Comparison groups   | Placebo v Danirixin 50 mg                          |
| Number of subjects included in analysis                               | 172  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other <sup>[22]</sup>                              |
| Parameter estimate  | Median Posterior Difference                        |
| Point estimate  | 0.73   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.4  |
| upper limit   | 1.12   |

Notes:

[22] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 50 mg has been presented.

### **Primary: Change from Baseline in respiratory symptoms measured by E-RS in COPD (E-RS: COPD Cough and Sputum Score)**

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in respiratory symptoms measured by E- |
|-----------------|---|

## End point description:

E-RS: COPD is a subset of EXACT. E-RS is a tool that consists of 11 items from the 14 item EXACT instrument. The domains include: RS-BRL comprised of 5 items, score range (0-17), RS-CSP comprised of 3 items, score range (0-11), and RS-CSY comprised of 3 items, score range (0-12). The total score ranged between 0-40 and higher values indicates severe respiratory symptoms. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Posterior mean change and standard deviation has been presented. Only those participants with available data at the specified time points were analyzed.

|                      |         |
|----------------------|---------|
| End point type       | Primary |
| End point timeframe: |         |
| Baseline and Month 6 |         |

| End point values                     | Placebo            | Danirixin 5 mg     | Danirixin 10 mg    | Danirixin 25 mg    |
|--------------------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type                   | Reporting group    | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed          | 86 <sup>[23]</sup> | 95 <sup>[24]</sup> | 87 <sup>[25]</sup> | 91 <sup>[26]</sup> |
| Units: Scores on a scale             |                    |                    |                    |                    |
| arithmetic mean (standard deviation) | -0.83 (± 0.107)    | -0.79 (± 0.090)    | -0.67 (± 0.109)    | -0.46 (± 0.104)    |

## Notes:

[23] - Per protocol population.

[24] - Per protocol population.

[25] - Per protocol population.

[26] - Per protocol population.

| End point values                     | Danirixin 35 mg    | Danirixin 50 mg    |  |  |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type                   | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed          | 85 <sup>[27]</sup> | 86 <sup>[28]</sup> |  |  |
| Units: Scores on a scale             |                    |                    |  |  |
| arithmetic mean (standard deviation) | -0.40 (± 0.088)    | -0.37 (± 0.098)    |  |  |

## Notes:

[27] - Per protocol population.

[28] - Per protocol population.

## Statistical analyses

| Statistical analysis title              | Statistical Analysis of Placebo Vs Danirixin 5 mg |
|---|---|
| Statistical analysis description:       |   |
| 4-parameter Emax model selected.        |   |
| Comparison groups                       | Placebo v Danirixin 5 mg                          |
| Number of subjects included in analysis | 181   |
| Analysis specification                  | Pre-specified                                     |
| Analysis type                           | other <sup>[29]</sup>                             |
| Parameter estimate                      | Median Posterior Difference                       |
| Point estimate                          | 0.01  |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0       |
| upper limit         | 0.16    |

Notes:

[29] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 5 mg has been presented.

|   |  |
|---|--|
| <b>Statistical analysis title</b>                           | Statistical Analysis of Placebo Vs Danirixin 10 mg |
| Statistical analysis description:<br>4-parameter Emax model |  |
| Comparison groups   | Placebo v Danirixin 10 mg                          |
| Number of subjects included in analysis                     | 173  |
| Analysis specification                                      | Pre-specified                                      |
| Analysis type   | other <sup>[30]</sup>                              |
| Parameter estimate  | Median Posterior Difference                        |
| Point estimate  | 0.12   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0  |
| upper limit   | 0.43   |

Notes:

[30] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 10 mg has been presented.

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Statistical Analysis of Placebo Vs Danirixin 25 mg |
| Statistical analysis description:<br>4-parameter Emax model selected. |  |
| Comparison groups   | Placebo v Danirixin 25 mg                          |
| Number of subjects included in analysis                               | 177  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   |  |
| Parameter estimate  | Median Posterior Difference                        |
| Point estimate  | 0.38   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.04   |
| upper limit   | 0.61   |

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Statistical Analysis of Placebo Vs Danirixin 35 mg |
| Statistical analysis description:<br>4-parameter Emax model selected. |  |
| Comparison groups   | Placebo v Danirixin 35 mg                          |

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 171                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other <sup>[31]</sup>       |
| Parameter estimate                      | Median Posterior Difference |
| Point estimate                          | 0.42                        |
| Confidence interval                     |                             |
| level                                   | 90 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 0.21                        |
| upper limit                             | 0.64                        |

Notes:

[31] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 35 mg has been presented.

|   |  |
|---|--|
| <b>Statistical analysis title</b>                                     | Statistical Analysis of Placebo Vs Danirixin 50 mg |
| Statistical analysis description:<br>4-parameter Emax model selected. |  |
| Comparison groups   | Placebo v Danirixin 50 mg                          |
| Number of subjects included in analysis                               | 172  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other <sup>[32]</sup>                              |
| Parameter estimate  | Median Posterior Difference                        |
| Point estimate  | 0.45   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.26   |
| upper limit   | 0.66   |

Notes:

[32] - Emax. Median posterior difference, 90% credible interval for Placebo and Danirixin 50 mg has been presented.

### **Primary: Change from Baseline in respiratory symptoms measured by E-RS in COPD (E-RS: COPD Chest Symptoms Score)**

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in respiratory symptoms measured by E-RS in COPD (E-RS: COPD Chest Symptoms Score) |
|-----------------|---|

End point description:

E-RS: COPD is a subset of EXACT. E-RS is a tool that consists of 11 items from the 14 item EXACT instrument. The domains include: RS-BRL comprised of 5 items, score range (0-17), RS-CSP comprised of 3 items, score range (0-11), and RS-CSY comprised of 3 items, score range (0-12). The total score ranged between 0-40 and higher values indicates severe respiratory symptoms. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Posterior mean change and standard deviation has been presented. Only those participants with available data at the specified time points were analyzed.

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

End point timeframe:

Baseline and Month 6

| End point values                     | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed          | 86                   | 95                   | 87                   | 91                   |
| Units: Scores on a scale             |                      |                      |                      |                      |
| arithmetic mean (standard deviation) | -0.36 ( $\pm$ 0.148) | -0.35 ( $\pm$ 0.061) | -0.34 ( $\pm$ 0.062) | -0.34 ( $\pm$ 0.069) |

| End point values                     | Danirixin 35 mg      | Danirixin 50 mg      |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 85                   | 86                   |  |  |
| Units: Scores on a scale             |                      |                      |  |  |
| arithmetic mean (standard deviation) | -0.34 ( $\pm$ 0.073) | -0.34 ( $\pm$ 0.078) |  |  |

## Statistical analyses

| Statistical analysis title                             | Statistical Analysis of Placebo Vs Danirixin 5 mg |
|--|---|
| Statistical analysis description:<br>Log-linear model. |   |
| Comparison groups                                      | Placebo v Danirixin 5 mg                          |
| Number of subjects included in analysis                | 181   |
| Analysis specification                                 | Pre-specified                                     |
| Analysis type  | other <sup>[33]</sup>                             |
| Parameter estimate                                     | Median Posterior Difference                       |
| Point estimate   | 0.01  |
| Confidence interval                                    |   |
| level  | 90 %  |
| sides  | 2-sided   |
| lower limit  | -0.21   |
| upper limit  | 0.23  |

Notes:

[33] - Log-linear. Median posterior difference, 90% credible interval for Placebo and Danirixin 5 mg has been presented.

| Statistical analysis title                            | Statistical Analysis of Placebo Vs Danirixin 10 mg |
|---|--|
| Statistical analysis description:<br>Log-linear model |  |
| Comparison groups                                     | Placebo v Danirixin 10 mg                          |
| Number of subjects included in analysis               | 173  |
| Analysis specification                                | Pre-specified                                      |
| Analysis type   | other <sup>[34]</sup>                              |
| Parameter estimate                                    | Median Posterior Difference                        |
| Point estimate  | 0.01   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | -0.23   |
| upper limit         | 0.25    |

Notes:

[34] - Log-linear. Median posterior difference, 90% credible interval for Placebo and Danirixin 10 mg has been presented.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 25 mg |
|-----------------------------------|--|

Statistical analysis description:

Log-linear model

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Placebo v Danirixin 25 mg   |
| Number of subjects included in analysis | 177                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other <sup>[35]</sup>       |
| Parameter estimate                      | Median Posterior Difference |
| Point estimate                          | 0.01                        |
| Confidence interval                     |                             |
| level                                   | 90 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -0.27                       |
| upper limit                             | 0.29                        |

Notes:

[35] - Log-linear. Median posterior difference, 90% credible interval for Placebo and Danirixin 25 mg has been presented.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 35 mg |
|-----------------------------------|--|

Statistical analysis description:

Log-linear model

|   |                             |
|---|-----------------------------|
| Comparison groups                       | Placebo v Danirixin 35 mg   |
| Number of subjects included in analysis | 171                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other <sup>[36]</sup>       |
| Parameter estimate                      | Median Posterior Difference |
| Point estimate                          | 0.01                        |
| Confidence interval                     |                             |
| level                                   | 90 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -0.28                       |
| upper limit                             | 0.3                         |

Notes:

[36] - Log-linear. Median posterior difference, 90% credible interval for Placebo and Danirixin 35 mg has been presented.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 50 mg |
|-----------------------------------|--|

Statistical analysis description:

Log-linear model

|                   |                           |
|-------------------|---------------------------|
| Comparison groups | Placebo v Danirixin 50 mg |
|-------------------|---------------------------|

|   |                             |
|---|-----------------------------|
| Number of subjects included in analysis | 172                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | other <sup>[37]</sup>       |
| Parameter estimate                      | Median Posterior Difference |
| Point estimate                          | 0.01                        |
| Confidence interval                     |                             |
| level                                   | 90 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | -0.29                       |
| upper limit                             | 0.31                        |

Notes:

[37] - Log-linear. Median posterior difference, 90% credible interval for Placebo and Danirixin 50 mg has been presented.

### Primary: Number of participants with adverse events (AE) and serious adverse events (SAE)

|                 |  |
|-----------------|--|
| End point title | Number of participants with adverse events (AE) and serious adverse events (SAE) <sup>[38]</sup> |
|-----------------|--|

End point description:

AE is any untoward medical occurrence in a participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. SAE is any untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, congenital anomaly/birth defect or any other situation according to medical or scientific judgment is categorized as SAE. Modified Intent-to-Treat (mITT) population. mITT population comprised of all randomized participants who were randomized apart from those randomized in error, received a treatment randomization number, modified and data for this population were based on actual treatment received.

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

End point timeframe:

Up to Day 196

Notes:

[38] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

| End point values            | Placebo             | Danirixin 5 mg      | Danirixin 10 mg     | Danirixin 25 mg     |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type          | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed | 102 <sup>[39]</sup> | 102 <sup>[40]</sup> | 103 <sup>[41]</sup> | 103 <sup>[42]</sup> |
| Units: Participants         |                     |                     |                     |                     |
| Any AE                      | 63                  | 63                  | 69                  | 68                  |
| Any SAE                     | 8                   | 7                   | 13                  | 10                  |

Notes:

[39] - mITT population.

[40] - mITT population.

[41] - mITT population.

[42] - mITT population.

| End point values            | Danirixin 35 mg     | Danirixin 50 mg     |  |  |
|-----------------------------|---------------------|---------------------|--|--|
| Subject group type          | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed | 102 <sup>[43]</sup> | 102 <sup>[44]</sup> |  |  |
| Units: Participants         |                     |                     |  |  |
| Any AE                      | 63                  | 71                  |  |  |
| Any SAE                     | 7                   | 11                  |  |  |

Notes:

[43] - mIIT population.

[44] - mIIT population.

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with worst case hematology parameter results by potential clinical importance (PCI)

|                 |  |
|-----------------|--|
| End point title | Number of participants with worst case hematology parameter results by potential clinical importance (PCI) <sup>[45]</sup> |
|-----------------|--|

End point description:

Blood samples were collected from participants for analysis of following hematology parameters with PCI low and high values: Basophils %(High5.00x),Eosinophils %(High 2.00x),Mean corpuscular hemoglobin concentration(MCHC)gram per deciliter(g/dL)(Low0.85x,high1.10x),Mean corpuscular hemoglobin(MCH)picograms(pg)(Low0.85x,high1.20x),Mean corpuscular volume(MCV)femtoliter(fL)(low0.25x,high2.00x),Erythrocytes(Ery.)(10<sup>12</sup>cells/L)(Low0.93x,high1.07x),Hematocrit(Ratio of1)(Low0.50x,high0.50x),Hemoglobin g/liter (L)(Low0.85x,high1.20x),Leukocytes(x10<sup>9</sup>/L)(Low0.70x,high1.60x),Lymphocytes%(Low0.80x,high1.20x),Monocytes%(Low0.80x,high1.60x),Neutrophils%(Low0.65x,high1.50x),Platelets(x10<sup>9</sup>cells/L)(Low0.90x,high 1.10x).Multipliers are identified by"x",otherwise actual comparison values are provided with units.Values above and below this range were considered of PCI.Only those participants with available data at the specified time points were analyzed(represented by n=X in the category titles).

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

End point timeframe:

Up to Day 196

Notes:

[45] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

| End point values                                     | Placebo             | Danirixin 5 mg      | Danirixin 10 mg     | Danirixin 25 mg     |
|--|---------------------|---------------------|---------------------|---------------------|
| Subject group type                                   | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed                          | 102 <sup>[46]</sup> | 102 <sup>[47]</sup> | 103 <sup>[48]</sup> | 103 <sup>[49]</sup> |
| Units: Participants                                  |                     |                     |                     |                     |
| Basophils, No change, n=97, 102, 101, 101, 101, 99   | 97                  | 102                 | 101                 | 101                 |
| Basophils, High, n=97, 102, 101, 101, 101, 99        | 0                   | 0                   | 0                   | 0                   |
| Eosinophils, No change, n=97, 102, 101, 101, 101, 99 | 97                  | 101                 | 101                 | 98                  |
| Eosinophils, High, n=97, 102, 101, 101, 101, 99      | 0                   | 1                   | 0                   | 3                   |
| Ery. MCHC, Low, n=97, 102, 101, 101, 102, 99         | 0                   | 0                   | 0                   | 0                   |
| Ery. MCHC, No change, n=97, 102, 101, 101, 102, 99   | 97                  | 102                 | 101                 | 101                 |
| Ery. MCHC, High, n=97, 102, 101, 101, 102, 99        | 0                   | 0                   | 0                   | 0                   |
| Ery. MCH, Low, n=97, 102, 101, 101, 102, 99          | 0                   | 0                   | 0                   | 0                   |
| Ery. MCH, No Change, n=97, 102, 101, 101, 102, 99    | 97                  | 102                 | 101                 | 101                 |

|   |    |     |     |     |
|---|----|-----|-----|-----|
| Ery. MCH, High, n=97, 102, 101, 101, 102, 99          | 0  | 0   | 0   | 0   |
| Ery. MCV, Low, n=97, 102, 101, 101, 102, 99           | 0  | 0   | 0   | 0   |
| Ery. MCV, No Change, n=97, 102, 101, 101, 102, 99     | 97 | 102 | 101 | 101 |
| Ery. MCV, High, n=97, 102, 101, 101, 102, 99          | 0  | 0   | 0   | 0   |
| Erythrocytes, Low, n=97, 102, 101, 101, 102, 99       | 2  | 1   | 3   | 3   |
| Erythrocytes, No change, n=97, 102, 101, 101, 102, 99 | 93 | 99  | 97  | 97  |
| Erythrocytes, High, n=97, 102, 101, 101, 102, 99      | 2  | 2   | 1   | 1   |
| Hematocrit, Low, n=97, 102, 101, 101, 102, 99         | 0  | 0   | 0   | 0   |
| Hematocrit, No Change, n=97, 102, 101, 101, 102, 99   | 97 | 102 | 101 | 101 |
| Hematocrit, High, n=97, 102, 101, 101, 102, 99        | 0  | 0   | 0   | 0   |
| Hemoglobin, Low, n=97, 102, 101, 101, 102, 99         | 1  | 1   | 2   | 0   |
| Hemoglobin, No change, n=97, 102, 101, 101, 102, 99   | 96 | 101 | 99  | 101 |
| Hemoglobin, High, n=97, 102, 101, 101, 102, 99        | 0  | 0   | 0   | 0   |
| Leukocytes, Low, n=97, 102, 101, 101, 102, 99         | 0  | 0   | 0   | 0   |
| Leukocytes, No change, n=97, 102, 101, 101, 102, 99   | 97 | 102 | 101 | 101 |
| Leukocytes, High, n=97, 102, 101, 101, 102, 99        | 0  | 0   | 0   | 0   |
| Lymphocytes, Low, n=97, 102, 101, 101, 101, 99        | 3  | 7   | 5   | 8   |
| Lymphocytes, No change, n=97, 102, 101, 101, 101, 99  | 94 | 95  | 96  | 92  |
| Lymphocytes, High, n=97, 102, 101, 101, 101, 99       | 0  | 0   | 0   | 1   |
| Monocytes, No change, n=97, 102, 101, 101, 101, 99    | 97 | 101 | 99  | 101 |
| Monocytes, High, n=97, 102, 101, 101, 101, 99         | 0  | 1   | 2   | 0   |
| Neutrophils, Low, n=97, 102, 101, 101, 101, 99        | 0  | 0   | 0   | 1   |
| Neutrophils, No change, n=97, 102, 101, 101, 101, 99  | 97 | 102 | 101 | 100 |
| Neutrophils, High, n=97, 102, 101, 101, 101, 99       | 0  | 0   | 0   | 0   |
| Platelets, Low, n=97, 102, 101, 101, 101, 99          | 0  | 1   | 0   | 0   |
| Platelets, No change, n=97, 102, 101, 101, 101, 99    | 97 | 99  | 100 | 101 |
| Platelets, High, n=97, 102, 101, 101, 101, 99         | 0  | 2   | 1   | 0   |

Notes:

[46] - mITT population.

[47] - mITT population.

[48] - mITT population.

[49] - mITT population.

| End point values                                      | Danirixin 35 mg     | Danirixin 50 mg     |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                                    | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                           | 102 <sup>[50]</sup> | 102 <sup>[51]</sup> |  |  |
| Units: Participants                                   |                     |                     |  |  |
| Basophils, No change, n=97, 102, 101, 101, 101, 99    | 101                 | 99                  |  |  |
| Basophils, High, n=97, 102, 101, 101, 101, 99         | 0                   | 0                   |  |  |
| Eosinophils, No change, n=97, 102, 101, 101, 101, 99  | 100                 | 98                  |  |  |
| Eosinophils, High, n=97, 102, 101, 101, 101, 99       | 1                   | 1                   |  |  |
| Ery. MCHC, Low, n=97, 102, 101, 101, 102, 99          | 0                   | 0                   |  |  |
| Ery. MCHC, No change, n=97, 102, 101, 101, 102, 99    | 102                 | 99                  |  |  |
| Ery. MCHC, High, n=97, 102, 101, 101, 102, 99         | 0                   | 0                   |  |  |
| Ery. MCH, Low, n=97, 102, 101, 101, 102, 99           | 0                   | 1                   |  |  |
| Ery. MCH, No Change, n=97, 102, 101, 101, 102, 99     | 102                 | 98                  |  |  |
| Ery. MCH, High, n=97, 102, 101, 101, 102, 99          | 0                   | 0                   |  |  |
| Ery. MCV, Low, n=97, 102, 101, 101, 102, 99           | 0                   | 0                   |  |  |
| Ery. MCV, No Change, n=97, 102, 101, 101, 102, 99     | 102                 | 99                  |  |  |
| Ery. MCV, High, n=97, 102, 101, 101, 102, 99          | 0                   | 0                   |  |  |
| Erythrocytes, Low, n=97, 102, 101, 101, 102, 99       | 2                   | 2                   |  |  |
| Erythrocytes, No change, n=97, 102, 101, 101, 102, 99 | 99                  | 97                  |  |  |
| Erythrocytes, High, n=97, 102, 101, 101, 102, 99      | 1                   | 0                   |  |  |
| Hematocrit, Low, n=97, 102, 101, 101, 102, 99         | 0                   | 0                   |  |  |
| Hematocrit, No Change, n=97, 102, 101, 101, 102, 99   | 102                 | 99                  |  |  |
| Hematocrit, High, n=97, 102, 101, 101, 102, 99        | 0                   | 0                   |  |  |
| Hemoglobin, Low, n=97, 102, 101, 101, 102, 99         | 2                   | 0                   |  |  |
| Hemoglobin, No change, n=97, 102, 101, 101, 102, 99   | 100                 | 99                  |  |  |
| Hemoglobin, High, n=97, 102, 101, 101, 102, 99        | 0                   | 0                   |  |  |
| Leukocytes, Low, n=97, 102, 101, 101, 102, 99         | 0                   | 1                   |  |  |
| Leukocytes, No change, n=97, 102, 101, 101, 102, 99   | 102                 | 98                  |  |  |
| Leukocytes, High, n=97, 102, 101, 101, 102, 99        | 0                   | 0                   |  |  |
| Lymphocytes, Low, n=97, 102, 101, 101, 101, 99        | 7                   | 4                   |  |  |
| Lymphocytes, No change, n=97, 102, 101, 101, 101, 99  | 93                  | 94                  |  |  |
| Lymphocytes, High, n=97, 102, 101, 101, 101, 99       | 1                   | 1                   |  |  |



|  |     |    |  |  |
|--|-----|----|--|--|
| Monocytes, No change, n=97, 102, 101, 101, 101, 99 | 100 | 98 |  |  |
| Monocytes, High, n=97, 102, 101, 101, 101, 99      | 1   | 1  |  |  |
| Neutrophils, Low, n=97, 102, 101, 101, 101, 99     | 3   | 1  |  |  |
| Neutrophils, No change, n=97,102,101,101,101,99    | 98  | 98 |  |  |
| Neutrophils, High, n=97, 102, 101, 101, 101, 99    | 0   | 0  |  |  |
| Platelets, Low, n=97, 102, 101, 101, 101, 99       | 0   | 0  |  |  |
| Platelets, No change, n=97, 102, 101, 101, 101, 99 | 99  | 99 |  |  |
| Platelets, High, n=97, 102, 101, 101, 101, 99      | 2   | 0  |  |  |

Notes:

[50] - mITT population.

[51] - mITT population.

## Statistical analyses

No statistical analyses for this end point

### Primary: Number of participants with worst case clinical chemistry parameter results by PCI

|                 |  |
|-----------------|--|
| End point title | Number of participants with worst case clinical chemistry parameter results by PCI <sup>[52]</sup> |
|-----------------|--|

End point description:

Blood samples were collected from participants for analysis of following chemistry parameters with PCI low and high values: Alanine aminotransferase (ALT) International units per liter (IU/L) (High => 3x ULN), Alkaline phosphatase (ALP) (IU/L) (High ≥ 2x ULN); Aspartate aminotransferase (AST) (IU/L) (High=> 3x ULN); Bilirubin micromole per liter (umol/L) (High ≥ 2x ULN); Calcium millimole per liter (mmol/L) (Low 0.85x, high 1.08x), Chloride (mmol/L) (Low 0.90x, high 1.10x), Creatinine (umol/L) (High 1.30x), Direct bilirubin (umol/L) (High ≥ 2x ULN), Glucose (mmol/L) (Low <0.6x, high >4x), Potassium (mmol/L) (Low 0.75x, high 1.30x); Protein (g/L) (High 1.25x), Sodium (mmol/L) (Low 0.80x, high 1.15x), Multipliers are identified by "x", otherwise actual comparison values are provided with units. Values above and below this range were considered of PCI. Only those participants with available data at the specified time points were analyzed (represented by n= X in the category titles).

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

End point timeframe:

Up to Day 196

Notes:

[52] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

| End point values                         | Placebo             | Danirixin 5 mg      | Danirixin 10 mg     | Danirixin 25 mg     |
|--|---------------------|---------------------|---------------------|---------------------|
| Subject group type                       | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed              | 102 <sup>[53]</sup> | 102 <sup>[54]</sup> | 103 <sup>[55]</sup> | 103 <sup>[56]</sup> |
| Units: Participants                      |                     |                     |                     |                     |
| ALT, No change, n=99,102,102,102,101,100 | 99                  | 102                 | 101                 | 102                 |
| ALT, High, n=99,102,102,102,101,100      | 0                   | 0                   | 1                   | 0                   |
| ALP, No change, n=99,102,102,102,101,100 | 99                  | 102                 | 102                 | 102                 |
| ALP, High, n=99,102,102,102,101,100      | 0                   | 0                   | 0                   | 0                   |

|  |    |     |     |     |
|--|----|-----|-----|-----|
| AST, No change,n=99,102,102,102,101,100            | 99 | 102 | 101 | 102 |
| AST, High, n=99,102,102,102,101,100                | 0  | 0   | 1   | 0   |
| Bilirubin, No change, n=99,102,102,102,101,100     | 99 | 101 | 102 | 102 |
| Bilirubin, High, n=99, 102,102,102,101,100         | 0  | 1   | 0   | 0   |
| Calcium, Low, n=96,102,101,101,101,99              | 0  | 0   | 0   | 0   |
| Calcium, No change, n=96,102,101,101,101,99        | 96 | 102 | 101 | 101 |
| Calcium, High, n=96,102,101,101,101,99             | 0  | 0   | 0   | 0   |
| CO2, Low, n=96,102,101,101,101,99                  | 1  | 0   | 2   | 1   |
| CO2, No change, n=96,102,101,101,101,99            | 94 | 102 | 99  | 99  |
| CO2, High, n=96,102,101,101,101,99                 | 1  | 0   | 0   | 1   |
| Chloride, Low, n=96,102,101,101,101,99             | 0  | 0   | 0   | 0   |
| Chloride, No change, n=96,102,101,101,101,99       | 96 | 102 | 101 | 101 |
| Chloride, High, n=96,102,101,101,101,99            | 0  | 0   | 0   | 0   |
| Creatinine, No change, n=96,102,101,101,101,99     | 94 | 100 | 99  | 99  |
| Creatinine, High, n=96, 102, 101, 101, 101, 99     | 2  | 2   | 2   | 2   |
| Direct bilirubin,NoChange,n=99,102,102,102,101,100 | 98 | 102 | 102 | 102 |
| Direct bilirubin,High,n=99,102,102,102,101,100     | 1  | 0   | 0   | 0   |
| Glucose, Low, n=96, 102, 101, 101, 101, 99         | 0  | 0   | 0   | 0   |
| Glucose, No change, n=96, 102, 101, 101, 101, 99   | 96 | 102 | 101 | 101 |
| Glucose, High, n=96, 102, 101, 101, 101, 99        | 0  | 0   | 0   | 0   |
| Potassium, Low, n=96, 102, 101, 101, 101, 99       | 0  | 0   | 0   | 0   |
| Potassium, No change, n=96, 102, 101, 101, 101, 99 | 96 | 102 | 101 | 101 |
| Potassium, High, n=96, 102, 101, 101, 101, 99      | 0  | 0   | 0   | 0   |
| Protein, No change, n=99, 102, 102, 102, 101, 100  | 99 | 102 | 102 | 102 |
| Protein, High, n=99, 102, 102, 102, 101, 100       | 0  | 0   | 0   | 0   |
| Sodium, Low, n=96, 102, 101, 101, 101, 99          | 0  | 0   | 0   | 0   |
| Sodium, No change, n=96, 102, 101, 101, 101, 99    | 96 | 102 | 101 | 101 |
| Sodium, High, n=96, 102, 101, 101, 101, 99         | 0  | 0   | 0   | 0   |
| Urea, Low, n=96, 102, 101, 101, 101, 99            | 0  | 0   | 0   | 0   |
| Urea, No change, n=96, 102, 101, 101, 101, 99      | 96 | 101 | 101 | 100 |
| Urea, High, n=96, 102, 101, 101, 101, 99           | 0  | 1   | 0   | 1   |
| Bilirubin/ALT,No change,n=99,102,102,102,101,100   | 99 | 102 | 102 | 102 |

|   |   |   |   |   |
|---|---|---|---|---|
| Bilirubin/ALT,<br>High,n=99,102,102,102,101,100 | 0 | 0 | 0 | 0 |
|---|---|---|---|---|

Notes:

[53] - mITT population.

[54] - mITT population.

[55] - mITT population.

[56] - mITT population.

| End point values                                    | Danirixin 35<br>mg  | Danirixin 50<br>mg  |  |  |
|---|---------------------|---------------------|--|--|
| Subject group type                                  | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed                         | 102 <sup>[57]</sup> | 102 <sup>[58]</sup> |  |  |
| Units: Participants                                 |                     |                     |  |  |
| ALT, No<br>change,n=99,102,102,102,101,100          | 101                 | 100                 |  |  |
| ALT, High, n=99,102,102,102,101,100                 | 0                   | 0                   |  |  |
| ALP, No<br>change,n=99,102,102,102,101,100          | 101                 | 100                 |  |  |
| ALP, High, n=99,102,102,102,101,100                 | 0                   | 0                   |  |  |
| AST, No<br>change,n=99,102,102,102,101,100          | 101                 | 100                 |  |  |
| AST, High, n=99,102,102,102,101,100                 | 0                   | 0                   |  |  |
| Bilirubin, No change,<br>n=99,102,102,102,101,100   | 101                 | 100                 |  |  |
| Bilirubin, High, n=99,<br>102,102,102,101,100       | 0                   | 0                   |  |  |
| Calcium, Low,<br>n=96,102,101,101,101,99            | 0                   | 0                   |  |  |
| Calcium, No change,<br>n=96,102,101,101,101,99      | 101                 | 99                  |  |  |
| Calcium, High,<br>n=96,102,101,101,101,99           | 0                   | 0                   |  |  |
| CO2, Low, n=96,102,101,101,101,99                   | 0                   | 1                   |  |  |
| CO2, No change,<br>n=96,102,101,101,101,99          | 101                 | 98                  |  |  |
| CO2, High, n=96,102,101,101,101,99                  | 0                   | 0                   |  |  |
| Chloride, Low,<br>n=96,102,101,101,101,99           | 0                   | 0                   |  |  |
| Chloride, No change,<br>n=96,102,101,101,101,99     | 101                 | 99                  |  |  |
| Chloride, High,<br>n=96,102,101,101,101,99          | 0                   | 0                   |  |  |
| Creatinine, No change,<br>n=96,102,101,101,101,99   | 99                  | 99                  |  |  |
| Creatinine, High, n=96, 102, 101, 101,<br>101, 99   | 2                   | 0                   |  |  |
| Direct<br>bilirubin,NoChange,n=99,102,102,102,1     | 101                 | 100                 |  |  |
| Direct<br>bilirubin,High,n=99,102,102,102,101,10    | 0                   | 0                   |  |  |
| Glucose, Low, n=96, 102, 101, 101,<br>101, 99       | 0                   | 0                   |  |  |
| Glucose, No change, n=96, 102, 101,<br>101, 101, 99 | 101                 | 99                  |  |  |
| Glucose, High, n=96, 102, 101, 101,<br>101, 99      | 0                   | 0                   |  |  |
| Potassium, Low, n=96, 102, 101, 101,<br>101, 99     | 0                   | 0                   |  |  |

|   |     |     |  |  |
|---|-----|-----|--|--|
| Potassium, No change, n=96, 102, 101, 101, 101, 99      | 101 | 99  |  |  |
| Potassium, High, n=96, 102, 101, 101, 101, 99           | 0   | 0   |  |  |
| Protein, No change, n=99, 102, 102, 102, 101, 100       | 101 | 100 |  |  |
| Protein, High, n=99, 102, 102, 102, 101, 100            | 0   | 0   |  |  |
| Sodium, Low, n=96, 102, 101, 101, 101, 99               | 0   | 0   |  |  |
| Sodium, No change, n=96, 102, 101, 101, 101, 99         | 101 | 99  |  |  |
| Sodium, High, n=96, 102, 101, 101, 101, 99              | 0   | 0   |  |  |
| Urea, Low, n=96, 102, 101, 101, 101, 99                 | 0   | 0   |  |  |
| Urea, No change, n=96, 102, 101, 101, 101, 99           | 101 | 98  |  |  |
| Urea, High, n=96, 102, 101, 101, 101, 99                | 0   | 1   |  |  |
| Bilirubin/ALT, No change, n=99, 102, 102, 102, 101, 100 | 101 | 100 |  |  |
| Bilirubin/ALT, High, n=99, 102, 102, 102, 101, 100      | 0   | 0   |  |  |

Notes:

[57] - mITT population.

[58] - mITT population.

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants with worst case vital signs parameter results by PCI

|                 |   |
|-----------------|---|
| End point title | Number of participants with worst case vital signs parameter results by PCI <sup>[59]</sup> |
|-----------------|---|

End point description:

Vital signs parameters includes systolic blood pressure (SBP) and diastolic blood pressure (DBP), pulse rate and respiration rate were measured in a semi-supine position after 5 minutes rest for the participants at indicated time points. PCI ranges for vital signs parameters were as follows: <90 to >160 millimeters of mercury (mmHg) for SBP and <40 to >110 mmHg for DBP, <35 or >120 beats per minute for heart rate and <8 or >30 breaths per minute for respiration rate. Values above and below this range were considered of PCI. Only those participants with available data at the specified time points were analyzed.

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

End point timeframe:

Up to Day 168

Notes:

[59] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

| End point values            | Placebo            | Danirixin 5 mg      | Danirixin 10 mg     | Danirixin 25 mg     |
|-----------------------------|--------------------|---------------------|---------------------|---------------------|
| Subject group type          | Reporting group    | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed | 96 <sup>[60]</sup> | 102 <sup>[61]</sup> | 101 <sup>[62]</sup> | 101 <sup>[63]</sup> |
| Units: Participants         |                    |                     |                     |                     |
| SBP, Low                    | 0                  | 0                   | 0                   | 0                   |
| SBP, No change              | 93                 | 92                  | 95                  | 98                  |
| SBP, High                   | 3                  | 10                  | 6                   | 3                   |
| DBP, Low                    | 0                  | 0                   | 0                   | 0                   |
| DBP, No change              | 96                 | 102                 | 101                 | 101                 |
| DBP, High                   | 0                  | 0                   | 0                   | 0                   |
| Pulse rate                  | 0                  | 0                   | 0                   | 0                   |
| Pulse rate, No change       | 96                 | 102                 | 99                  | 100                 |
| Pulse rate, High            | 0                  | 0                   | 2                   | 1                   |
| Respiratory rate, Low       | 0                  | 0                   | 0                   | 0                   |
| Respiratory rate, No change | 96                 | 102                 | 101                 | 101                 |
| Respiratory rate, High      | 0                  | 0                   | 0                   | 0                   |

Notes:

[60] - mITT population.

[61] - mITT population.

[62] - mITT population.

[63] - mITT population.

| End point values            | Danirixin 35 mg     | Danirixin 50 mg    |  |  |
|-----------------------------|---------------------|--------------------|--|--|
| Subject group type          | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed | 102 <sup>[64]</sup> | 99 <sup>[65]</sup> |  |  |
| Units: Participants         |                     |                    |  |  |
| SBP, Low                    | 0                   | 1                  |  |  |
| SBP, No change              | 98                  | 94                 |  |  |
| SBP, High                   | 4                   | 4                  |  |  |
| DBP, Low                    | 0                   | 0                  |  |  |
| DBP, No change              | 102                 | 99                 |  |  |
| DBP, High                   | 0                   | 0                  |  |  |
| Pulse rate                  | 0                   | 0                  |  |  |
| Pulse rate, No change       | 102                 | 98                 |  |  |
| Pulse rate, High            | 0                   | 1                  |  |  |
| Respiratory rate, Low       | 0                   | 0                  |  |  |
| Respiratory rate, No change | 102                 | 98                 |  |  |
| Respiratory rate, High      | 0                   | 1                  |  |  |

Notes:

[64] - mITT population.

[65] - mITT population.

## Statistical analyses

No statistical analyses for this end point

## Primary: Number of participants with worst case post-Baseline abnormal 12-lead electrocardiogram (ECG) findings

|                 |  |
|-----------------|--|
| End point title | Number of participants with worst case post-Baseline abnormal 12-lead electrocardiogram (ECG) findings <sup>[66]</sup> |
|-----------------|--|

End point description:

Triplicate 12-lead ECG obtained to measure PR, QRS, QT, and Corrected QT intervals. Only those participants with worst case post-Baseline data have been represented for abnormal - not clinical significant and abnormal - clinical significant. Day 1 was considered as Baseline. Only those participants with available data at the specified time points were analyzed.

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

End point timeframe:

Baseline and Day 168

Notes:

[66] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

| End point values            | Placebo            | Danirixin 5 mg      | Danirixin 10 mg     | Danirixin 25 mg     |
|-----------------------------|--------------------|---------------------|---------------------|---------------------|
| Subject group type          | Reporting group    | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed | 96 <sup>[67]</sup> | 102 <sup>[68]</sup> | 101 <sup>[69]</sup> | 101 <sup>[70]</sup> |
| Units: Participants         |                    |                     |                     |                     |
| Not Clinical significant    | 52                 | 65                  | 68                  | 67                  |
| Clinical significant        | 2                  | 1                   | 1                   | 0                   |

Notes:

[67] - mITT population.

[68] - mITT population.

[69] - mITT population.

[70] - mITT population.

| End point values            | Danirixin 35 mg     | Danirixin 50 mg    |  |  |
|-----------------------------|---------------------|--------------------|--|--|
| Subject group type          | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed | 102 <sup>[71]</sup> | 99 <sup>[72]</sup> |  |  |
| Units: Participants         |                     |                    |  |  |
| Not Clinical significant    | 62                  | 53                 |  |  |
| Clinical significant        | 3                   | 1                  |  |  |

Notes:

[71] - mITT population.

[72] - mITT population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of moderate or severe Healthcare Resource Utilization (HCRU) exacerbations per participant

|                 |   |
|-----------------|---|
| End point title | Number of moderate or severe Healthcare Resource Utilization (HCRU) exacerbations per participant |
|-----------------|---|

End point description:

Participants with moderate or severe COPD exacerbations, i.e. breathlessness, cough, sputum production, chest congestion and chest tightness analyzed. Mild exacerbations are defined as exacerbations that did not require treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization, Emergency Room [ER] visit or resulting in death). Moderate exacerbations are defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization, ER visit or resulting in death). Severe exacerbations are defined as exacerbations that required hospitalization, ER visit or resulted in death. Number of moderate or severe HCRU exacerbations per participant has been presented, where 0= participants in each treatment group who did not experience an event; 1= participants in each treatment group who experienced 1 event and >=2= participants in each treatment group who experienced 2 or more events.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Up to Day 196        |           |

| End point values                     | Placebo             | Danirixin 5 mg      | Danirixin 10 mg     | Danirixin 25 mg     |
|--------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed          | 101 <sup>[73]</sup> | 102 <sup>[74]</sup> | 100 <sup>[75]</sup> | 103 <sup>[76]</sup> |
| Units: Exacerbations per participant |                     |                     |                     |                     |
| Zero (0)                             | 66                  | 51                  | 61                  | 63                  |
| One (1)                              | 28                  | 34                  | 23                  | 28                  |
| >=2                                  | 7                   | 17                  | 16                  | 12                  |

Notes:

[73] - Per Protocol Population.

[74] - Per Protocol Population.

[75] - Per Protocol Population.

[76] - Per Protocol Population.

| End point values                     | Danirixin 35 mg     | Danirixin 50 mg    |  |  |
|--------------------------------------|---------------------|--------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed          | 100 <sup>[77]</sup> | 99 <sup>[78]</sup> |  |  |
| Units: Exacerbations per participant |                     |                    |  |  |
| Zero (0)                             | 55                  | 50                 |  |  |
| One (1)                              | 30                  | 36                 |  |  |
| >=2                                  | 15                  | 13                 |  |  |

Notes:

[77] - Per Protocol Population.

[78] - Per Protocol Population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of responders E-RS in COPD (E-RS): COPD Total Score

|  |  |
|--|--|
| End point title  | Number of responders E-RS in COPD (E-RS): COPD Total Score |
| End point description:   |  |
| E-RS: COPD is a subset of EXACT. E-RS is a tool that consists of 11 items from the 14 item EXACT instrument. E-RS is intended to capture information related to the respiratory symptoms of COPD, i.e. breathlessness, cough, sputum production, chest congestion and chest tightness. The E-RS has a scoring range of 0-40; higher scores indicate more severe symptoms. Response is defined as an E-RS: COPD total score of 2 units below baseline or lower. Non-response is defined as an E-RS: COPD total score higher than 2 units below Baseline. Number of participants presented represent those with data available at the time point being presented; however, all participants in the per protocol population without missing covariate information and with at least one post baseline measurement are included in the analysis. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Month 6  |  |

| End point values            | Placebo            | Danirixin 5 mg     | Danirixin 10 mg    | Danirixin 25 mg    |
|-----------------------------|--------------------|--------------------|--------------------|--------------------|
| Subject group type          | Reporting group    | Reporting group    | Reporting group    | Reporting group    |
| Number of subjects analysed | 86 <sup>[79]</sup> | 95 <sup>[80]</sup> | 87 <sup>[81]</sup> | 91 <sup>[82]</sup> |
| Units: Participants         | 33                 | 48                 | 33                 | 30                 |

Notes:

[79] - Per Protocol Population.

[80] - Per Protocol Population.

[81] - Per Protocol Population.

[82] - Per Protocol Population.

| End point values            | Danirixin 35 mg    | Danirixin 50 mg    |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 85 <sup>[83]</sup> | 86 <sup>[84]</sup> |  |  |
| Units: Participants         | 29                 | 32                 |  |  |

Notes:

[83] - Per Protocol Population.

[84] - Per Protocol Population.

## Statistical analyses

| Statistical analysis title | Statistical Analysis of Placebo Vs Danirixin 5 mg |
|----------------------------|---|
|----------------------------|---|

Statistical analysis description:

Odds Ratio, 90% credible interval for Placebo and Danirixin 5 mg has been presented.

|   |                          |
|---|--------------------------|
| Comparison groups                       | Placebo v Danirixin 5 mg |
| Number of subjects included in analysis | 181                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | other                    |
| P-value                                 | = 0.089 <sup>[85]</sup>  |
| Method                                  | linear mixed model       |
| Parameter estimate                      | Odds ratio (OR)          |
| Point estimate                          | 1.71                     |
| Confidence interval                     |                          |
| level                                   | 90 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 1.02                     |
| upper limit                             | 2.86                     |

Notes:

[85] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, relevant baseline E-RS: COPD score, smoking status at Screening, country, month, baseline by month and treatment by month interactions.

| Statistical analysis title  | Statistical Analysis of Placebo Vs Danirixin 10 mg |
|---|--|
| Statistical analysis description:   |  |
| Odds Ratio, 90% credible interval for Placebo and Danirixin 10 mg has been presented. |  |
| Comparison groups   | Placebo v Danirixin 10 mg                          |



|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 173                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | other                   |
| P-value                                 | = 0.881 <sup>[86]</sup> |
| Method                                  | linear mixed model      |
| Parameter estimate                      | Odds ratio (OR)         |
| Point estimate                          | 1.05                    |
| Confidence interval                     |                         |
| level                                   | 90 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.62                    |
| upper limit                             | 1.79                    |

Notes:

[86] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, relevant baseline E-RS: COPD score, smoking status at Screening, country, month, baseline by month and treatment by month interactions.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Statistical Analysis of Placebo Vs Danirixin 25 mg |
| Statistical analysis description:   |  |
| Odds Ratio, 90% credible interval for Placebo and Danirixin 25 mg has been presented. |  |
| Comparison groups   | Placebo v Danirixin 25 mg                          |
| Number of subjects included in analysis   | 177  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other  |
| P-value   | = 0.674 <sup>[87]</sup>                            |
| Method  | linear mixed model                                 |
| Parameter estimate  | Odds ratio (OR)                                    |
| Point estimate  | 0.87   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.51   |
| upper limit   | 1.48   |

Notes:

[87] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, relevant baseline E-RS: COPD score, smoking status at Screening, country, month, baseline by month and treatment by month interactions.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Statistical Analysis of Placebo Vs Danirixin 35 mg |
| Statistical analysis description:   |  |
| Odds Ratio, 90% credible interval for Placebo and Danirixin 35 mg has been presented. |  |
| Comparison groups   | Placebo v Danirixin 35 mg                          |
| Number of subjects included in analysis   | 171  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other  |
| P-value   | = 0.804 <sup>[88]</sup>                            |
| Method  | linear mixed model                                 |
| Parameter estimate  | Odds ratio (OR)                                    |
| Point estimate  | 0.92   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.54    |
| upper limit         | 1.58    |

Notes:

[88] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, relevant baseline E-RS: COPD score, smoking status at Screening, country, month, baseline by month and treatment by month interactions.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 50 mg |
|-----------------------------------|--|

Statistical analysis description:

Odds Ratio, 90% credible interval for Placebo and Danirixin 50 mg has been presented.

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v Danirixin 50 mg |
| Number of subjects included in analysis | 172                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other                     |
| P-value                                 | = 0.987 <sup>[89]</sup>   |
| Method                                  | linear mixed model        |
| Parameter estimate                      | Odds ratio (OR)           |
| Point estimate                          | 1.01                      |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.59    |
| upper limit         | 1.71    |

Notes:

[89] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, relevant baseline E-RS: COPD score, smoking status at Screening, country, month, baseline by month and treatment by month interactions.

## Secondary: Number of EXACT events per participant

|                 |  |
|-----------------|--|
| End point title | Number of EXACT events per participant |
|-----------------|--|

End point description:

EXACT is a 14 item patient reported outcome (PRO) instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in participants with COPD. The total score for EXACT-PRO ranges from 0-100, higher scores indicate more severe symptoms. Events were categorized as recovered, censored, or persistent worsening. Number of EXACT events per participant has been presented, where 0= participants in each treatment group who did not experience an event; 1= participants in each treatment group who experienced 1 event and >=2= participants in each treatment group who experienced 2 or more events.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Day 196

| End point values            | Placebo             | Danirixin 5 mg      | Danirixin 10 mg     | Danirixin 25 mg     |
|-----------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type          | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed | 101 <sup>[90]</sup> | 102 <sup>[91]</sup> | 100 <sup>[92]</sup> | 103 <sup>[93]</sup> |
| Units: Events               |                     |                     |                     |                     |
| Zero (0)                    | 92                  | 92                  | 92                  | 92                  |
| One (1)                     | 9                   | 6                   | 7                   | 9                   |

|     |   |   |   |   |
|-----|---|---|---|---|
| >=2 | 0 | 4 | 1 | 2 |
|-----|---|---|---|---|

Notes:

[90] - Per protocol Population

[91] - Per protocol Population

[92] - Per protocol Population

[93] - Per protocol Population

| End point values            | Danirixin 35 mg     | Danirixin 50 mg    |  |  |
|-----------------------------|---------------------|--------------------|--|--|
| Subject group type          | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed | 100 <sup>[94]</sup> | 99 <sup>[95]</sup> |  |  |
| Units: Events               |                     |                    |  |  |
| Zero (0)                    | 86                  | 86                 |  |  |
| One (1)                     | 10                  | 10                 |  |  |
| >=2                         | 4                   | 3                  |  |  |

Notes:

[94] - Per protocol Population

[95] - Per protocol Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to first EXACT event

|  |                           |
|--|---------------------------|
| End point title  | Time to first EXACT event |
| End point description:   |                           |
| The time to first on-treatment EXACT event was calculated as the onset date of the first on-treatment EXACT event minus date of start of treatment plus 1. 99999 indicates, if <25% of participants experienced the event within a treatment then Q1 time to event are displayed as NA (not applicable) for that treatment. 88888 indicates, if <50% of participants experienced the event within a treatment then median time to event are displayed as NA (not applicable) for that treatment. |                           |
| End point type   | Secondary                 |
| End point timeframe:   |                           |
| Up to Day 168  |                           |

| End point values                  | Placebo             | Danirixin 5 mg      | Danirixin 10 mg     | Danirixin 25 mg     |
|-----------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type                | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed       | 101 <sup>[96]</sup> | 102 <sup>[97]</sup> | 100 <sup>[98]</sup> | 103 <sup>[99]</sup> |
| Units: Days                       |                     |                     |                     |                     |
| First quartile (Q1) time to event | 99999               | 99999               | 99999               | 99999               |
| Median time to event              | 88888               | 88888               | 88888               | 88888               |

Notes:

[96] - Per protocol population

[97] - Per protocol population

[98] - Per protocol population

[99] - Per protocol population

| End point values | Danirixin 35 mg | Danirixin 50 mg |  |  |
|------------------|-----------------|-----------------|--|--|
|------------------|-----------------|-----------------|--|--|

|                                   |                      |                     |  |  |
|-----------------------------------|----------------------|---------------------|--|--|
| Subject group type                | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed       | 100 <sup>[100]</sup> | 99 <sup>[101]</sup> |  |  |
| Units: Days                       |                      |                     |  |  |
| First quartile (Q1) time to event | 99999                | 99999               |  |  |
| Median time to event              | 88888                | 88888               |  |  |

Notes:

[100] - Per protocol population

[101] - Per protocol population

## Statistical analyses

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 5 mg |
|-----------------------------------|---|

Statistical analysis description:

Median Posterior Hazard Ratio, 90% credible interval for Placebo and Danirixin 5 mg has been presented.

|   |                               |
|---|-------------------------------|
| Comparison groups                       | Placebo v Danirixin 5 mg      |
| Number of subjects included in analysis | 203                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | other <sup>[102]</sup>        |
| Parameter estimate                      | Median Posterior Hazard Ratio |
| Point estimate                          | 1.2                           |
| Confidence interval                     |                               |
| level                                   | 90 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.5                           |
| upper limit                             | 2.6                           |

Notes:

[102] - DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator % predicted FEV1 at Screening.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 10 mg |
|-----------------------------------|--|

Statistical analysis description:

Median Posterior Hazard Ratio, 90% credible interval for Placebo and Danirixin 10 mg has been presented.

|   |                               |
|---|-------------------------------|
| Comparison groups                       | Placebo v Danirixin 10 mg     |
| Number of subjects included in analysis | 201                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | other <sup>[103]</sup>        |
| Parameter estimate                      | Median Posterior Hazard Ratio |
| Point estimate                          | 1                             |
| Confidence interval                     |                               |
| level                                   | 90 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.4                           |
| upper limit                             | 2.4                           |

Notes:

[103] - DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 25 mg |
|-----------------------------------|--|

---

**Statistical analysis description:**

Median Posterior Hazard Ratio, 90% credible interval for Placebo and Danirixin 25 mg has been presented.

|   |                               |
|---|-------------------------------|
| Comparison groups                       | Placebo v Danirixin 25 mg     |
| Number of subjects included in analysis | 204                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | other <sup>[104]</sup>        |
| Parameter estimate                      | Median Posterior Hazard Ratio |
| Point estimate                          | 1.4                           |
| Confidence interval                     |                               |
| level                                   | 90 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.6                           |
| upper limit                             | 3.2                           |

**Notes:**

[104] - DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 35 mg |
|-----------------------------------|--|

**Statistical analysis description:**

Median Posterior Hazard Ratio, 90% credible interval for Placebo and Danirixin 35 mg has been presented.

|   |                               |
|---|-------------------------------|
| Comparison groups                       | Placebo v Danirixin 35 mg     |
| Number of subjects included in analysis | 201                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | other <sup>[105]</sup>        |
| Parameter estimate                      | Median Posterior Hazard Ratio |
| Point estimate                          | 2                             |
| Confidence interval                     |                               |
| level                                   | 90 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 1                             |
| upper limit                             | 4.3                           |

**Notes:**

[105] - DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 50 mg |
|-----------------------------------|--|

**Statistical analysis description:**

Median Posterior Hazard Ratio, 90% credible interval for Placebo and Danirixin 50 mg has been presented.

|   |                               |
|---|-------------------------------|
| Comparison groups                       | Placebo v Danirixin 50 mg     |
| Number of subjects included in analysis | 200                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | other <sup>[106]</sup>        |
| Parameter estimate                      | Median Posterior Hazard Ratio |
| Point estimate                          | 2                             |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.9     |
| upper limit         | 4.5     |

Notes:

[106] - DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

## Secondary: Severity of EXACT event

|                 |                         |
|-----------------|-------------------------|
| End point title | Severity of EXACT event |
|-----------------|-------------------------|

End point description:

EXACT is a 14 item PRO instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in participants with COPD. The total score for EXACT-PRO ranges from 0-100, higher scores indicate more severe symptoms. Severity is the highest EXACT total score during the period from onset to recovery. Only those participants with data available at the specified data points were analyzed

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Day 168

| End point values                     | Placebo            | Danirixin 5 mg      | Danirixin 10 mg    | Danirixin 25 mg     |
|--------------------------------------|--------------------|---------------------|--------------------|---------------------|
| Subject group type                   | Reporting group    | Reporting group     | Reporting group    | Reporting group     |
| Number of subjects analysed          | 9 <sup>[107]</sup> | 15 <sup>[108]</sup> | 9 <sup>[109]</sup> | 13 <sup>[110]</sup> |
| Units: Scores on a scale             |                    |                     |                    |                     |
| arithmetic mean (standard deviation) | 22.1 (± 6.60)      | 26.7 (± 3.71)       | 22.9 (± 5.28)      | 28.6 (± 5.68)       |

Notes:

[107] - Per Protocol Population.

[108] - Per Protocol Population.

[109] - Per Protocol Population.

[110] - Per Protocol Population.

| End point values                     | Danirixin 35 mg     | Danirixin 50 mg     |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 19 <sup>[111]</sup> | 16 <sup>[112]</sup> |  |  |
| Units: Scores on a scale             |                     |                     |  |  |
| arithmetic mean (standard deviation) | 25.0 (± 5.54)       | 26.4 (± 6.36)       |  |  |

Notes:

[111] - Per Protocol Population.

[112] - Per Protocol Population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: EXACT event duration for all events

|                 |                                     |
|-----------------|-------------------------------------|
| End point title | EXACT event duration for all events |
|-----------------|-------------------------------------|

---

**End point description:**

EXACT is a 14 item PRO instrument designed to capture information on the occurrence, frequency, severity, and duration of exacerbations of disease in participants with COPD. The total score for EXACT-PRO ranges from 0-100, higher scores indicate more severe symptoms. Severity is the highest EXACT total score during the period from onset to recovery. Duration of EXACT events has been reported. Only those participants with data available at the specified data points were analyzed.

---

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

---

**End point timeframe:**

Up to Day 168

---

| End point values                     | Placebo            | Danirixin 5 mg      | Danirixin 10 mg    | Danirixin 25 mg     |
|--------------------------------------|--------------------|---------------------|--------------------|---------------------|
| Subject group type                   | Reporting group    | Reporting group     | Reporting group    | Reporting group     |
| Number of subjects analysed          | 9 <sup>[113]</sup> | 15 <sup>[114]</sup> | 9 <sup>[115]</sup> | 13 <sup>[116]</sup> |
| Units: Days                          |                    |                     |                    |                     |
| arithmetic mean (standard deviation) | 45.3 (± 50.37)     | 11.6 (± 10.15)      | 45.8 (± 51.97)     | 25.5 (± 42.11)      |

**Notes:**

[113] - Per Protocol Population.

[114] - Per Protocol Population.

[115] - Per Protocol Population.

[116] - Per Protocol Population.

| End point values                     | Danirixin 35 mg     | Danirixin 50 mg     |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 19 <sup>[117]</sup> | 16 <sup>[118]</sup> |  |  |
| Units: Days                          |                     |                     |  |  |
| arithmetic mean (standard deviation) | 17.6 (± 16.28)      | 18.7 (± 37.75)      |  |  |

**Notes:**

[117] - Per Protocol Population.

[118] - Per Protocol Population.

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Time to first HCRU-defined COPD exacerbation**

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|                 |  |
|-----------------|--|
| End point title | Time to first HCRU-defined COPD exacerbation |
|-----------------|--|

---

**End point description:**

The time to first on-treatment Moderate/Severe HCRU exacerbation was calculated as exacerbation onset date of first on-treatment moderate or severe on-treatment exacerbation – date of start of treatment +1. 99999 indicates, if <50% of participants experienced the event within a treatment then median time to event are displayed as NA (not applicable) for that treatment.

---

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

---

**End point timeframe:**

Up to Day 196

---

| End point values            | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed | 101 <sup>[119]</sup> | 102 <sup>[120]</sup> | 100 <sup>[121]</sup> | 103 <sup>[122]</sup> |
| Units: Days                 |                      |                      |                      |                      |
| Q1 time to event            | 110                  | 47                   | 63                   | 79                   |
| Median time to event        | 99999                | 99999                | 99999                | 99999                |

Notes:

[119] - Per Protocol Population

[120] - Per Protocol Population

[121] - Per Protocol Population

[122] - Per Protocol Population

| End point values            | Danirixin 35 mg      | Danirixin 50 mg     |  |  |
|-----------------------------|----------------------|---------------------|--|--|
| Subject group type          | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed | 100 <sup>[123]</sup> | 99 <sup>[124]</sup> |  |  |
| Units: Days                 |                      |                     |  |  |
| Q1 time to event            | 70                   | 57                  |  |  |
| Median time to event        | 99999                | 99999               |  |  |

Notes:

[123] - Per Protocol Population

[124] - Per Protocol Population

## Statistical analyses

| Statistical analysis title   | Statistical Analysis of Placebo Vs Danirixin 5 mg |
|--|---|
| Statistical analysis description:  |   |
| Hazard Ratio, 90% credible interval for Placebo and Danirixin 5 mg has been presented. |   |
| Comparison groups  | Placebo v Danirixin 5 mg                          |
| Number of subjects included in analysis  | 203   |
| Analysis specification   | Pre-specified                                     |
| Analysis type  | other <sup>[125]</sup>                            |
| Parameter estimate   | Hazard ratio (HR)                                 |
| Point estimate   | 1.5   |
| Confidence interval  |   |
| level  | 90 %  |
| sides  | 2-sided   |
| lower limit  | 1   |
| upper limit  | 2.2   |

Notes:

[125] - Bayesian proportional hazards model. DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

| Statistical analysis title  | Statistical Analysis of Placebo Vs Danirixin 10 mg |
|---|--|
| Statistical analysis description:   |  |
| Hazard Ratio, 90% credible interval for Placebo and Danirixin 10 mg has been presented. |  |
| Comparison groups   | Placebo v Danirixin 10 mg                          |



|   |                        |
|---|------------------------|
| Number of subjects included in analysis | 201                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | other <sup>[126]</sup> |
| Parameter estimate                      | Hazard ratio (HR)      |
| Point estimate                          | 1.1                    |
| Confidence interval                     |                        |
| level                                   | 90 %                   |
| sides                                   | 2-sided                |
| lower limit                             | 0.8                    |
| upper limit                             | 1.7                    |

Notes:

[126] - Bayesian proportional hazards model. DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 25 mg |
|-----------------------------------|--|

Statistical analysis description:

Hazard Ratio, 90% credible interval for Placebo and Danirixin 25 mg has been presented.

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v Danirixin 25 mg |
| Number of subjects included in analysis | 204                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other <sup>[127]</sup>    |
| Parameter estimate                      | Hazard ratio (HR)         |
| Point estimate                          | 1.1                       |
| Confidence interval                     |                           |
| level                                   | 90 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.7                       |
| upper limit                             | 1.6                       |

Notes:

[127] - Bayesian proportional hazards model. DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 35 mg |
|-----------------------------------|--|

Statistical analysis description:

Hazard Ratio, 90% credible interval for Placebo and Danirixin 35 mg has been presented.

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v Danirixin 35 mg |
| Number of subjects included in analysis | 201                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other <sup>[128]</sup>    |
| Parameter estimate                      | Hazard ratio (HR)         |
| Point estimate                          | 1.4                       |
| Confidence interval                     |                           |
| level                                   | 90 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 1                         |
| upper limit                             | 2.1                       |

Notes:

[128] - Bayesian proportional hazards model. DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Statistical Analysis of Placebo Vs Danirixin 50 mg |
| Statistical analysis description:<br>Hazard Ratio, 90% credible interval for Placebo and Danirixin 50 mg has been presented. |  |
| Comparison groups  | Placebo v Danirixin 50 mg                          |
| Number of subjects included in analysis  | 200  |
| Analysis specification   | Pre-specified                                      |
| Analysis type  | other <sup>[129]</sup>                             |
| Parameter estimate   | Hazard ratio (HR)                                  |
| Point estimate   | 1.6  |
| Confidence interval  |  |
| level  | 90 %   |
| sides  | 2-sided  |
| lower limit  | 1.1  |
| upper limit  | 2.3  |

Notes:

[129] - Bayesian proportional hazards model. DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

## Secondary: Time to first severe HCRU-defined COPD exacerbation

|   |   |
|---|---|
| End point title   | Time to first severe HCRU-defined COPD exacerbation |
| End point description:<br>A COPD exacerbation defined as a severe exacerbation if it requires hospitalization or emergency room visit or extended observation. The time to first on-treatment Moderate/Severe HCRU exacerbation was calculated as exacerbation onset date of first on-treatment moderate or severe on-treatment exacerbation – date of start of treatment +1. 99999 indicates, if <25% of participants experienced the event within a treatment then Q1 time to event are displayed as NA (not applicable) for that treatment. 88888 indicates, if <50% of participants experienced the event within a treatment then median time to event are displayed as NA (not applicable) for that treatment. |   |
| End point type  | Secondary   |
| End point timeframe:<br>Up to Day 196   |   |

| End point values            | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed | 101 <sup>[130]</sup> | 102 <sup>[131]</sup> | 100 <sup>[132]</sup> | 103 <sup>[133]</sup> |
| Units: Days                 |                      |                      |                      |                      |
| Q1 time to event            | 99999                | 99999                | 99999                | 99999                |
| Median time to event        | 88888                | 88888                | 88888                | 88888                |

Notes:

[130] - Per Protocol Population

[131] - Per Protocol Population

[132] - Per Protocol Population

[133] - Per Protocol Population

| End point values | Danirixin 35 mg | Danirixin 50 mg |  |  |
|------------------|-----------------|-----------------|--|--|
|------------------|-----------------|-----------------|--|--|

|                             |                      |                     |  |  |
|-----------------------------|----------------------|---------------------|--|--|
| Subject group type          | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed | 100 <sup>[134]</sup> | 99 <sup>[135]</sup> |  |  |
| Units: Days                 |                      |                     |  |  |
| Q1 time to event            | 99999                | 99999               |  |  |
| Median time to event        | 88888                | 88888               |  |  |

Notes:

[134] - Per Protocol Population

[135] - Per Protocol Population

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Statistical Analysis of Placebo Vs Danirixin 5 mg |
| Statistical analysis description:  |   |
| Hazard Ratio, 90% credible interval for Placebo and Danirixin 5 mg has been presented. |   |
| Comparison groups  | Placebo v Danirixin 5 mg                          |
| Number of subjects included in analysis  | 203   |
| Analysis specification   | Pre-specified                                     |
| Analysis type  | other <sup>[136]</sup>                            |
| Parameter estimate   | Hazard ratio (HR)                                 |
| Point estimate   | 1.8   |
| Confidence interval  |   |
| level  | 90 %  |
| sides  | 2-sided   |
| lower limit  | 0.7   |
| upper limit  | 5.5   |

Notes:

[136] - Bayesian proportional hazards model. DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Statistical Analysis of Placebo Vs Danirixin 10 mg |
| Statistical analysis description:   |  |
| Hazard Ratio, 90% credible interval for Placebo and Danirixin 10 mg has been presented. |  |
| Comparison groups   | Placebo v Danirixin 10 mg                          |
| Number of subjects included in analysis   | 201  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other <sup>[137]</sup>                             |
| Parameter estimate  | Hazard ratio (HR)                                  |
| Point estimate  | 1.9  |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.7  |
| upper limit   | 5.8  |

Notes:

[137] - Bayesian proportional hazards model. DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Statistical Analysis of Placebo Vs Danirixin 25 mg |
| Statistical analysis description:   |  |
| Hazard Ratio, 90% credible interval for Placebo and Danirixin 25 mg has been presented. |  |

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v Danirixin 25 mg |
| Number of subjects included in analysis | 204                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other <sup>[138]</sup>    |
| Parameter estimate                      | Hazard ratio (HR)         |
| Point estimate                          | 1.8                       |
| Confidence interval                     |                           |
| level                                   | 90 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.7                       |
| upper limit                             | 5.6                       |

Notes:

[138] - Bayesian proportional hazards model. DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Statistical Analysis of Placebo Vs Danirixin 35 mg |
| Statistical analysis description:   |  |
| Hazard Ratio, 90% credible interval for Placebo and Danirixin 35 mg has been presented. |  |
| Comparison groups   | Placebo v Danirixin 35 mg                          |
| Number of subjects included in analysis   | 201  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other <sup>[139]</sup>                             |
| Parameter estimate  | Hazard ratio (HR)                                  |
| Point estimate  | 2.3  |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.9  |
| upper limit   | 6.9  |

Notes:

[139] - Bayesian proportional hazards model. DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Statistical Analysis of Placebo Vs Danirixin 50 mg |
| Statistical analysis description:   |  |
| Hazard Ratio, 90% credible interval for Placebo and Danirixin 50 mg has been presented. |  |
| Comparison groups   | Placebo v Danirixin 50 mg                          |
| Number of subjects included in analysis   | 200  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other <sup>[140]</sup>                             |
| Parameter estimate  | Hazard ratio (HR)                                  |
| Point estimate  | 0.8  |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.2  |
| upper limit   | 2.7  |

Notes:

[140] - Bayesian proportional hazards model. DNX vs. Placebo statistics calculated using a Bayesian proportional hazards model including treatment, gender, exacerbation history ( $\leq 1/\geq 2$  moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

### Secondary: HCRU-defined exacerbation duration

|                 |                                    |
|-----------------|------------------------------------|
| End point title | HCRU-defined exacerbation duration |
|-----------------|------------------------------------|

End point description:

The duration of HCRU exacerbation were determined. The duration of the exacerbation was calculated as (exacerbation resolution date or date of death - exacerbation onset date + 1). For exacerbations which were not resolved but where the participant later died from other causes, the duration was calculated using date of death as the end date of the event. Only those participants with data available at the specified data points were analyzed.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to Day 196

| End point values                     | Placebo             | Danirixin 5 mg      | Danirixin 10 mg     | Danirixin 25 mg     |
|--------------------------------------|---------------------|---------------------|---------------------|---------------------|
| Subject group type                   | Reporting group     | Reporting group     | Reporting group     | Reporting group     |
| Number of subjects analysed          | 44 <sup>[141]</sup> | 75 <sup>[142]</sup> | 58 <sup>[143]</sup> | 56 <sup>[144]</sup> |
| Units: Days                          |                     |                     |                     |                     |
| arithmetic mean (standard deviation) | 10.3 ( $\pm$ 7.37)  | 12.3 ( $\pm$ 8.95)  | 12.9 ( $\pm$ 9.58)  | 14.0 ( $\pm$ 8.71)  |

Notes:

[141] - Per Protocol Population.

[142] - Per Protocol Population.

[143] - Per Protocol Population.

[144] - Per Protocol Population.

| End point values                     | Danirixin 35 mg     | Danirixin 50 mg     |  |  |
|--------------------------------------|---------------------|---------------------|--|--|
| Subject group type                   | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed          | 66 <sup>[145]</sup> | 65 <sup>[146]</sup> |  |  |
| Units: Days                          |                     |                     |  |  |
| arithmetic mean (standard deviation) | 10.7 ( $\pm$ 7.21)  | 14.2 ( $\pm$ 9.29)  |  |  |

Notes:

[145] - Per Protocol Population.

[146] - Per Protocol Population.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) Total Score

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) Total Score |
|-----------------|---|

End point description:

The SGRQ-C consists of 40 items aggregated into 3 component scores: Symptoms, Activity, Impacts, and a Total score. Each response to a question is assigned a weight. Component scores are calculated by summing the weights from all positive items in that component, dividing by the sum of weights for all items in that component, and multiplying this number by 100. Component scores could range from 0-100, with a higher component score indicating greater disease burden. Day 1 was considered as

Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Posterior mean change and standard deviation is presented. Number of participants presented represent those with data available at the time point being presented; however, all participants in the per protocol population without missing covariate information and with at least one post baseline measurement are included in the analysis.

|                           |           |
|---------------------------|-----------|
| End point type            | Secondary |
| End point timeframe:      |           |
| Baseline, Days 84 and 168 |           |

| End point values                     | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed          | 101 <sup>[147]</sup> | 102 <sup>[148]</sup> | 100 <sup>[149]</sup> | 103 <sup>[150]</sup> |
| Units: Scores on a scale             |                      |                      |                      |                      |
| arithmetic mean (standard deviation) |                      |                      |                      |                      |
| Day 84, n=93, 97, 94, 96, 91, 90     | -3.79 (± 1.172)      | -3.63 (± 1.150)      | -1.31 (± 1.146)      | -3.19 (± 1.148)      |
| Day 168, n=85, 96, 86, 90, 86, 85    | -4.11 (± 1.292)      | -3.44 (± 1.246)      | -4.19 (± 1.292)      | -4.94 (± 1.251)      |

Notes:

[147] - Per Protocol Population.

[148] - Per Protocol Population.

[149] - Per Protocol Population.

[150] - Per Protocol Population.

| End point values                     | Danirixin 35 mg      | Danirixin 50 mg     |  |  |
|--------------------------------------|----------------------|---------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed          | 100 <sup>[151]</sup> | 99 <sup>[152]</sup> |  |  |
| Units: Scores on a scale             |                      |                     |  |  |
| arithmetic mean (standard deviation) |                      |                     |  |  |
| Day 84, n=93, 97, 94, 96, 91, 90     | -2.83 (± 1.189)      | -2.48 (± 1.175)     |  |  |
| Day 168, n=85, 96, 86, 90, 86, 85    | -4.12 (± 1.287)      | -3.41 (± 1.302)     |  |  |

Notes:

[151] - Per Protocol Population.

[152] - Per Protocol Population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of SGRQ responder

|  |                          |
|--|--------------------------|
| End point title  | Number of SGRQ responder |
| End point description:   |                          |
| A participant was consider Responder according to SGRQ total score if their change from Baseline SGRQ total score of 4 units below Baseline or lower. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles). |                          |
| End point type   | Secondary                |
| End point timeframe:   |                          |
| Day 84 and Day 168   |                          |

| End point values                  | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed       | 101 <sup>[153]</sup> | 102 <sup>[154]</sup> | 100 <sup>[155]</sup> | 103 <sup>[156]</sup> |
| Units: Participants               |                      |                      |                      |                      |
| Day 84, n=93, 97, 94, 96, 91, 90  | 39                   | 40                   | 35                   | 49                   |
| Day 168, n=85, 96, 86, 90, 86, 85 | 35                   | 47                   | 40                   | 47                   |

Notes:

[153] - Per Protocol Population.

[154] - Per Protocol Population.

[155] - Per Protocol Population.

[156] - Per Protocol Population.

| End point values                  | Danirixin 35 mg      | Danirixin 50 mg     |  |  |
|-----------------------------------|----------------------|---------------------|--|--|
| Subject group type                | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed       | 100 <sup>[157]</sup> | 99 <sup>[158]</sup> |  |  |
| Units: Participants               |                      |                     |  |  |
| Day 84, n=93, 97, 94, 96, 91, 90  | 35                   | 38                  |  |  |
| Day 168, n=85, 96, 86, 90, 86, 85 | 41                   | 34                  |  |  |

Notes:

[157] - Per Protocol Population.

[158] - Per Protocol Population.

## Statistical analyses

| Statistical analysis title   | Statistical Analysis of Placebo Vs Danirixin 5 mg |
|--|---|
| Statistical analysis description:  |   |
| Odds Ratio, 90% credible interval for Placebo and Danirixin 5 mg has been presented. |   |
| Comparison groups  | Placebo v Danirixin 5 mg                          |
| Number of subjects included in analysis  | 203   |
| Analysis specification   | Pre-specified                                     |
| Analysis type  | other   |
| P-value  | = 0.208 <sup>[159]</sup>                          |
| Method   | Linear mixed model                                |
| Parameter estimate   | Odds ratio (OR)                                   |
| Point estimate   | 1.51  |
| Confidence interval  |   |
| level  | 90 %  |
| sides  | 2-sided   |
| lower limit  | 0.88  |
| upper limit  | 2.59  |

Notes:

[159] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, baseline SGRQ total score, smoking status at Screening, country, visit, baseline by visit and treatment by visit interactions.

| Statistical analysis title | Statistical Analysis of Placebo Vs Danirixin 10 mg |
|----------------------------|--|
|----------------------------|--|

Statistical analysis description:

Odds Ratio, 90% credible interval for Placebo and Danirixin 10 mg has been presented.

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v Danirixin 10 mg |
| Number of subjects included in analysis | 201                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other                     |
| P-value                                 | = 0.482 <sup>[160]</sup>  |
| Method                                  | Linear mixed model        |
| Parameter estimate                      | Odds ratio (OR)           |
| Point estimate                          | 1.27                      |
| Confidence interval                     |                           |
| level                                   | 90 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.73                      |
| upper limit                             | 2.2                       |

Notes:

[160] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, baseline SGRQ total score, smoking status at Screening, country, visit, baseline by visit and treatment by visit interactions.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Statistical Analysis of Placebo Vs Danirixin 25 mg |
| Statistical analysis description:   |  |
| Odds Ratio, 90% credible interval for Placebo and Danirixin 25 mg has been presented. |  |
| Comparison groups   | Placebo v Danirixin 25 mg                          |
| Number of subjects included in analysis   | 204  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other  |
| P-value   | = 0.239 <sup>[161]</sup>                           |
| Method  | Linear mixed model                                 |
| Parameter estimate  | Odds ratio (OR)                                    |
| Point estimate  | 1.47   |
| Confidence interval   |  |
| level   | 90 %   |
| sides   | 2-sided  |
| lower limit   | 0.86   |
| upper limit   | 2.53   |

Notes:

[161] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, baseline SGRQ total score, smoking status at Screening, country, visit, baseline by visit and treatment by visit interactions.

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Statistical Analysis of Placebo Vs Danirixin 35 mg |
| Statistical analysis description:   |  |
| Odds Ratio, 90% credible interval for Placebo and Danirixin 35 mg has been presented. |  |
| Comparison groups   | Placebo v Danirixin 35 mg                          |
| Number of subjects included in analysis   | 201  |
| Analysis specification  | Pre-specified                                      |
| Analysis type   | other  |
| P-value   | = 0.426 <sup>[162]</sup>                           |
| Method  | Linear mixed model                                 |
| Parameter estimate  | Odds ratio (OR)                                    |
| Point estimate  | 1.31   |



|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.75    |
| upper limit         | 2.26    |

Notes:

[162] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, baseline SGRQ total score, smoking status at Screening, country, visit, baseline by visit and treatment by visit interactions.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 50 mg |
|-----------------------------------|--|

Statistical analysis description:

Odds Ratio, 90% credible interval for Placebo and Danirixin 50 mg has been presented.

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v Danirixin 50 mg |
| Number of subjects included in analysis | 200                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other                     |
| P-value                                 | = 0.763 <sup>[163]</sup>  |
| Method                                  | Linear mixed model        |
| Parameter estimate                      | Odds ratio (OR)           |
| Point estimate                          | 0.9                       |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.52    |
| upper limit         | 1.58    |

Notes:

[163] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, baseline SGRQ total score, smoking status at Screening, country, visit, baseline by visit and treatment by visit interactions.

## Secondary: Change from Baseline COPD Assessment Test (CAT) total score

|                 |   |
|-----------------|---|
| End point title | Change from Baseline COPD Assessment Test (CAT) total score |
|-----------------|---|

End point description:

CAT is 8 item questionnaire(cough,sputum,chest tightness,breathlessness,going up hills/stairs, activity limitation at home,confidence leaving home/sleep and energy)that measures health status of participants with COPD.Participants were completed each question by rating their experience on 6point scale ranging from 0(maximum impairment)to 5(no impairment) with total scoring range of 0-40;higher scores indicate worse health status.CAT score was calculated by summing non-missing scores on 8items.Individual items are scored from 0 to 5 with total score range from 0-40, higher scores indicate greater disease impact.Day1 was Baseline.Change from Baseline was calculated by subtracting Baseline value from specified time point value.Number of participants presented represent those with data available at time point being presented;however,all participants in per protocol population without missing covariate information and with at least 1 post Baseline measurement are included in analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Days 84 and 168

| End point values                     | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed          | 101 <sup>[164]</sup> | 102 <sup>[165]</sup> | 100 <sup>[166]</sup> | 103 <sup>[167]</sup> |
| Units: Scores on a scale             |                      |                      |                      |                      |
| arithmetic mean (standard deviation) |                      |                      |                      |                      |
| Day 84, n=89, 97, 92, 89, 88, 85     | -2.02 (± 0.536)      | -0.86 (± 0.525)      | -0.63 (± 0.524)      | -0.55 (± 0.542)      |
| Day 168, n=84, 94, 86, 87, 85, 83    | -1.39 (± 0.557)      | -1.39 (± 0.537)      | -1.23 (± 0.548)      | -0.97 (± 0.560)      |

Notes:

[164] - Per Protocol Population.

[165] - Per Protocol Population.

[166] - Per Protocol Population.

[167] - Per Protocol Population.

| End point values                     | Danirixin 35 mg      | Danirixin 50 mg     |  |  |
|--------------------------------------|----------------------|---------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed          | 100 <sup>[168]</sup> | 99 <sup>[169]</sup> |  |  |
| Units: Scores on a scale             |                      |                     |  |  |
| arithmetic mean (standard deviation) |                      |                     |  |  |
| Day 84, n=89, 97, 92, 89, 88, 85     | -1.51 (± 0.543)      | -0.36 (± 0.549)     |  |  |
| Day 168, n=84, 94, 86, 87, 85, 83    | -1.56 (± 0.560)      | -1.32 (± 0.565)     |  |  |

Notes:

[168] - Per Protocol Population.

[169] - Per Protocol Population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of CAT responder

|  |                         |
|--|-------------------------|
| End point title  | Number of CAT responder |
| End point description:   |                         |
| A participant was considered as a responder according to CAT score if their change from Baseline CAT score 2.0 units below Baseline or lower. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles). |                         |
| End point type   | Secondary               |
| End point timeframe:   |                         |
| Day 84 and Day 168   |                         |

| End point values                  | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|-----------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed       | 101 <sup>[170]</sup> | 102 <sup>[171]</sup> | 100 <sup>[172]</sup> | 103 <sup>[173]</sup> |
| Units: Participants               |                      |                      |                      |                      |
| Day 84, n=89, 97, 92, 89, 88, 85  | 46                   | 44                   | 38                   | 37                   |
| Day 168, n=84, 94, 86, 87, 85, 83 | 41                   | 44                   | 39                   | 42                   |

Notes:

[170] - Per Protocol Population.

[171] - Per Protocol Population.

[172] - Per Protocol Population.

[173] - Per Protocol Population.

| End point values                  | Danirixin 35 mg      | Danirixin 50 mg     |  |  |
|-----------------------------------|----------------------|---------------------|--|--|
| Subject group type                | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed       | 100 <sup>[174]</sup> | 99 <sup>[175]</sup> |  |  |
| Units: Participants               |                      |                     |  |  |
| Day 84, n=89, 97, 92, 89, 88, 85  | 43                   | 36                  |  |  |
| Day 168, n=84, 94, 86, 87, 85, 83 | 46                   | 44                  |  |  |

Notes:

[174] - Per Protocol Population.

[175] - Per Protocol Population.

## Statistical analyses

| Statistical analysis title  | Statistical Analysis of Placebo Vs Danirixin 5 mg |
|---|---|
| Statistical analysis description:<br>Odds Ratio, 90% credible interval for Placebo and Danirixin 5 mg has been presented. |   |
| Comparison groups   | Placebo v Danirixin 5 mg                          |
| Number of subjects included in analysis   | 203   |
| Analysis specification  | Pre-specified                                     |
| Analysis type   | other   |
| P-value   | = 0.973 <sup>[176]</sup>                          |
| Method  | Linear mixed model                                |
| Parameter estimate  | Odds ratio (OR)                                   |
| Point estimate  | 1.01  |
| Confidence interval   |   |
| level   | 90 %  |
| sides   | 2-sided   |
| lower limit   | 0.58  |
| upper limit   | 1.76  |

Notes:

[176] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, baseline CAT score, smoking status at Screening, country, visit, baseline by visit and treatment by visit interactions.

| Statistical analysis title   | Statistical Analysis of Placebo Vs Danirixin 10 mg |
|--|--|
| Statistical analysis description:<br>Odds Ratio, 90% credible interval for Placebo and Danirixin 10 mg has been presented. |  |
| Comparison groups  | Placebo v Danirixin 10 mg                          |
| Number of subjects included in analysis  | 201  |
| Analysis specification   | Pre-specified                                      |
| Analysis type  | other  |
| P-value  | = 0.825 <sup>[177]</sup>                           |
| Method   | Linear mixed model                                 |
| Parameter estimate   | Odds ratio (OR)                                    |
| Point estimate   | 0.93   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.53    |
| upper limit         | 1.63    |

Notes:

[177] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, baseline CAT score, smoking status at Screening, country, visit, baseline by visit and treatment by visit interactions.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 25 mg |
|-----------------------------------|--|

Statistical analysis description:

Odds Ratio, 90% credible interval for Placebo and Danirixin 25 mg has been presented.

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v Danirixin 25 mg |
| Number of subjects included in analysis | 204                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other                     |
| P-value                                 | = 0.887 <sup>[178]</sup>  |
| Method                                  | Linear mixed model        |
| Parameter estimate                      | Odds ratio (OR)           |
| Point estimate                          | 0.95                      |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.55    |
| upper limit         | 1.66    |

Notes:

[178] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, baseline CAT score, smoking status at Screening, country, visit, baseline by visit and treatment by visit interactions.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 35 mg |
|-----------------------------------|--|

Statistical analysis description:

Odds Ratio, 90% credible interval for Placebo and Danirixin 35 mg has been presented.

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v Danirixin 35 mg |
| Number of subjects included in analysis | 201                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other                     |
| P-value                                 | = 0.567 <sup>[179]</sup>  |
| Method                                  | Linear mixed model        |
| Parameter estimate                      | Odds ratio (OR)           |
| Point estimate                          | 1.21                      |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 90 %    |
| sides               | 2-sided |
| lower limit         | 0.69    |
| upper limit         | 2.13    |

Notes:

[179] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, baseline CAT score, smoking status at Screening, country, visit, baseline by visit and treatment by visit interactions.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Statistical Analysis of Placebo Vs Danirixin 50 mg |
|-----------------------------------|--|

Statistical analysis description:

Odds Ratio, 90% credible interval for Placebo and Danirixin 50 mg has been presented.

|   |                           |
|---|---------------------------|
| Comparison groups                       | Placebo v Danirixin 50 mg |
| Number of subjects included in analysis | 200                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | other                     |
| P-value                                 | = 0.501 <sup>[180]</sup>  |
| Method                                  | Linear mixed model        |
| Parameter estimate                      | Odds ratio (OR)           |
| Point estimate                          | 1.26                      |
| Confidence interval                     |                           |
| level                                   | 90 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.72                      |
| upper limit                             | 2.2                       |

Notes:

[180] - Analysis performed using a generalised linear mixed model with a logit link function including treatment, baseline CAT score, smoking status at Screening, country, visit, baseline by visit and treatment by visit interactions.

### Secondary: Change from Baseline in post-bronchodilator FEV1 as a lung function assessment

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in post-bronchodilator FEV1 as a lung function assessment |
|-----------------|--|

End point description:

Spirometric analysis was done to determine FEV1. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Least square mean change from Baseline and standard error has been presented. Number of participants presented represent those with data available at the time point being presented; however, all participants in the mITT population without missing covariate information and with at least one post baseline measurement are included in the analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Days 84 and 168

| End point values                    | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed         | 102 <sup>[181]</sup> | 102 <sup>[182]</sup> | 103 <sup>[183]</sup> | 103 <sup>[184]</sup> |
| Units: Liters                       |                      |                      |                      |                      |
| least squares mean (standard error) |                      |                      |                      |                      |
| Day 84, n=94, 99, 98, 97, 92, 93    | 0.016 (± 0.0208)     | -0.031 (± 0.0203)    | -0.029 (± 0.0204)    | -0.018 (± 0.0206)    |
| Day 168, n=88, 97, 90, 90, 88, 86   | -0.016 (± 0.0199)    | -0.043 (± 0.0191)    | -0.033 (± 0.0197)    | -0.058 (± 0.0198)    |

Notes:

[181] - mITT Population.

[182] - mITT Population.

[183] - mITT Population.

[184] - mITT Population.

| End point values | Danirixin 35 mg | Danirixin 50 mg |  |  |
|------------------|-----------------|-----------------|--|--|
|------------------|-----------------|-----------------|--|--|

|                                     |                      |                      |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed         | 102 <sup>[185]</sup> | 102 <sup>[186]</sup> |  |  |
| Units: Liters                       |                      |                      |  |  |
| least squares mean (standard error) |                      |                      |  |  |
| Day 84, n=94, 99, 98, 97, 92, 93    | -0.027 (± 0.0211)    | 0.027 (± 0.0210)     |  |  |
| Day 168, n=88, 97, 90, 90, 88, 86   | -0.012 (± 0.0201)    | -0.011 (± 0.0202)    |  |  |

Notes:

[185] - mITT Population.

[186] - mITT Population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percent predicted normal FEV1

|  |                               |
|--|-------------------------------|
| End point title  | Percent predicted normal FEV1 |
| End point description:   |                               |
| Spirometric analysis was done to determine percent predicted FEV1 at screening. FEV1 is forced expiratory volume in one second. Percent predicted FEV1 is defined as the percent FEV1 of the participant is divided by average FEV1 percent in the population of any person similar age, sex and body composition. Only those participants with available data at the specified time points were analyzed. |                               |
| End point type   | Secondary                     |
| End point timeframe:   |                               |
| At Screening   |                               |

| End point values                     | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed          | 100 <sup>[187]</sup> | 102 <sup>[188]</sup> | 100 <sup>[189]</sup> | 103 <sup>[190]</sup> |
| Units: Percent predicted FEV1        |                      |                      |                      |                      |
| arithmetic mean (standard deviation) | 58.98 (± 12.838)     | 56.75 (± 12.038)     | 56.62 (± 11.848)     | 56.84 (± 12.813)     |

Notes:

[187] - Per Protocol Population.

[188] - Per Protocol Population.

[189] - Per Protocol Population.

[190] - Per Protocol Population.

| End point values                     | Danirixin 35 mg      | Danirixin 50 mg     |  |  |
|--------------------------------------|----------------------|---------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed          | 100 <sup>[191]</sup> | 99 <sup>[192]</sup> |  |  |
| Units: Percent predicted FEV1        |                      |                     |  |  |
| arithmetic mean (standard deviation) | 57.51 (± 14.076)     | 57.84 (± 12.794)    |  |  |

Notes:

[191] - Per Protocol Population.

[192] - Per Protocol Population.

## Statistical analyses

**Secondary: Change from Baseline in post-bronchodilator Forced Vital Capacity (FVC) as a lung function assessment**

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in post-bronchodilator Forced Vital Capacity (FVC) as a lung function assessment |
|-----------------|---|

## End point description:

Spirometric analysis was done to determine FVC. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Least square mean change from Baseline and standard error has been presented. Number of participants presented represent those with data available at the time point being presented; however, all participants in the mITT population without missing covariate information and with at least one post baseline measurement are included in the analysis.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Baseline, Days 84 and 168

| End point values                    | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|-------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                  | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed         | 102 <sup>[193]</sup> | 102 <sup>[194]</sup> | 103 <sup>[195]</sup> | 103 <sup>[196]</sup> |
| Units: Liters                       |                      |                      |                      |                      |
| least squares mean (standard error) |                      |                      |                      |                      |
| Day 84, n=94, 99, 98, 97, 92, 93    | 0.024 (± 0.0321)     | -0.054 (± 0.0313)    | -0.043 (± 0.0315)    | 0.027 (± 0.0317)     |
| Day 168, n=88, 97, 90, 90, 88, 86   | -0.011 (± 0.0348)    | -0.079 (± 0.0335)    | -0.043 (± 0.0344)    | -0.024 (± 0.0345)    |

## Notes:

[193] - mITT Population.

[194] - mITT Population.

[195] - mITT Population.

[196] - mITT Population.

| End point values                    | Danirixin 35 mg      | Danirixin 50 mg      |  |  |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type                  | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed         | 102 <sup>[197]</sup> | 102 <sup>[198]</sup> |  |  |
| Units: Liters                       |                      |                      |  |  |
| least squares mean (standard error) |                      |                      |  |  |
| Day 84, n=94, 99, 98, 97, 92, 93    | -0.049 (± 0.0326)    | 0.014 (± 0.0323)     |  |  |
| Day 168, n=88, 97, 90, 90, 88, 86   | -0.036 (± 0.0351)    | -0.016 (± 0.0353)    |  |  |

## Notes:

[197] - mITT Population.

[198] - mITT Population.

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from Baseline in post-bronchodilator FEV1/FVC ratio as a lung function assessment**

|  |  |
|--|--|
| End point title  | Change from Baseline in post-bronchodilator FEV1/FVC ratio as a lung function assessment |
| End point description:   |  |
| Spirometric analysis was done to determine FEV1 and FVC. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Number of participants presented represent those with data available at the time point being presented; however, all participants in the mITT population without missing covariate information and with at least one post baseline measurement are included in the analysis. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| Baseline, Days 84 and 168  |  |

| End point values                     | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|--------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                   | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed          | 102 <sup>[199]</sup> | 102 <sup>[200]</sup> | 103 <sup>[201]</sup> | 103 <sup>[202]</sup> |
| Units: Ratio of FEV1/FVC             |                      |                      |                      |                      |
| arithmetic mean (standard deviation) |                      |                      |                      |                      |
| Day 84, n=94, 99, 98, 97, 92, 93     | -0.003 (± 0.0543)    | -0.001 (± 0.0554)    | -0.000 (± 0.0453)    | -0.013 (± 0.0630)    |
| Day 168, n=88, 97, 90, 90, 88, 86    | -0.007 (± 0.0622)    | -0.003 (± 0.0555)    | 0.003 (± 0.0420)     | -0.015 (± 0.0610)    |

Notes:

[199] - mITT Population.

[200] - mITT Population.

[201] - mITT Population.

[202] - mITT Population.

| End point values                     | Danirixin 35 mg      | Danirixin 50 mg      |  |  |
|--------------------------------------|----------------------|----------------------|--|--|
| Subject group type                   | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed          | 102 <sup>[203]</sup> | 102 <sup>[204]</sup> |  |  |
| Units: Ratio of FEV1/FVC             |                      |                      |  |  |
| arithmetic mean (standard deviation) |                      |                      |  |  |
| Day 84, n=94, 99, 98, 97, 92, 93     | -0.000 (± 0.0402)    | 0.014 (± 0.1636)     |  |  |
| Day 168, n=88, 97, 90, 90, 88, 86    | 0.002 (± 0.0495)     | -0.002 (± 0.0385)    |  |  |

Notes:

[203] - mITT Population.

[204] - mITT Population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline number of puffs of rescue medication per day

|                 |   |
|-----------------|---|
| End point title | Change from Baseline number of puffs of rescue medication per day |
|-----------------|---|

End point description:

The mean number of puffs of rescue per day was calculated over the same time periods and using the same assumptions as rescue use via diary. Day 1 was considered as Baseline. Change from Baseline was calculated by subtracting Baseline value from the specified time point value. Least square mean change from Baseline and standard error has been presented. Number of participants presented



represent those with data available at the time point being presented; however, all participants in the per protocol population without missing covariate information and with at least one post baseline measurement are included in the analysis.

|                                      |           |
|--------------------------------------|-----------|
| End point type                       | Secondary |
| End point timeframe:                 |           |
| Baseline, Months 1, 2, 3, 4, 5 and 6 |           |

| End point values                      | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|---------------------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type                    | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed           | 101 <sup>[205]</sup> | 102 <sup>[206]</sup> | 100 <sup>[207]</sup> | 103 <sup>[208]</sup> |
| Units: Puffs per day                  |                      |                      |                      |                      |
| arithmetic mean (standard error)      |                      |                      |                      |                      |
| Month 1, n=100, 102, 100, 102, 98, 99 | 0.00 (± 0.132)       | 0.36 (± 0.130)       | 0.28 (± 0.132)       | 0.15 (± 0.130)       |
| Month 2, n=96, 100, 98, 97, 98, 96    | -0.22 (± 0.187)      | 0.42 (± 0.184)       | 0.18 (± 0.186)       | 0.35 (± 0.185)       |
| Month 3, n=95, 100, 95, 97, 94, 92    | -0.18 (± 0.184)      | 0.29 (± 0.181)       | 0.21 (± 0.184)       | 0.25 (± 0.182)       |
| Month 4, n=92, 98, 92, 97, 90, 90     | -0.18 (± 0.193)      | 0.27 (± 0.189)       | 0.27 (± 0.192)       | 0.21 (± 0.190)       |
| Month 5, n=88, 97, 88, 94, 87, 87     | -0.16 (± 0.190)      | 0.17 (± 0.186)       | 0.19 (± 0.190)       | 0.25 (± 0.187)       |
| Month 6, n=86, 95, 88, 91, 85, 86     | -0.17 (± 0.196)      | 0.21 (± 0.191)       | 0.10 (± 0.195)       | 0.15 (± 0.193)       |

Notes:

[205] - Per Protocol Population.

[206] - Per Protocol Population.

[207] - Per Protocol Population.

[208] - Per Protocol Population.

| End point values                      | Danirixin 35 mg      | Danirixin 50 mg     |  |  |
|---------------------------------------|----------------------|---------------------|--|--|
| Subject group type                    | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed           | 100 <sup>[209]</sup> | 99 <sup>[210]</sup> |  |  |
| Units: Puffs per day                  |                      |                     |  |  |
| arithmetic mean (standard error)      |                      |                     |  |  |
| Month 1, n=100, 102, 100, 102, 98, 99 | -0.03 (± 0.133)      | 0.28 (± 0.133)      |  |  |
| Month 2, n=96, 100, 98, 97, 98, 96    | 0.07 (± 0.187)       | 0.33 (± 0.188)      |  |  |
| Month 3, n=95, 100, 95, 97, 94, 92    | 0.07 (± 0.185)       | 0.27 (± 0.186)      |  |  |
| Month 4, n=92, 98, 92, 97, 90, 90     | -0.04 (± 0.194)      | 0.44 (± 0.195)      |  |  |
| Month 5, n=88, 97, 88, 94, 87, 87     | -0.06 (± 0.191)      | 0.29 (± 0.192)      |  |  |
| Month 6, n=86, 95, 88, 91, 85, 86     | 0.04 (± 0.197)       | 0.28 (± 0.198)      |  |  |

Notes:

[209] - Per Protocol Population.

[210] - Per Protocol Population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Participant experience of physical activity measured using PROactive physical activity in COPD (C-PPAC) questionnaire

|   |   |
|---|---|
| End point title   | Participant experience of physical activity measured using PROactive physical activity in COPD (C-PPAC) questionnaire |
| End point description:  |   |
| Clinical Visit PROactive Physical Activity in COPD(C-PPAC) tool is a designed for intermittent use within a clinical study.PROactive Total Score and 2domain scores(amount/difficulty) are derived using data from C-PPAC questionnaire and physical activity monitor worn for 7days prior to questionnaire.C-PPAC is 12 item questionnaire.PROactive tools are scored from0 to 100 with higher scores indicating greater disease impact.It was implemented in subset of approximately 50% of participants.Amount domain is calculated using 2items from C-PPAC questionnaire(amount of walking outside/chores outside) and 2activity monitor outputs(vector magnitude units per minute (VMU/min) and steps/day). Each domain score is based on the addition of items(0-15 for amount and 0-40 for difficulty) and then scaled from 0-100. Total score is calculated as (amount+difficulty)/2. Only those participants with data available at specified data points were analyzed(represented by n=X in the category titles). |   |
| End point type  | Secondary   |
| End point timeframe:  |   |
| Days 84 and 168   |   |

| End point values                                   | Placebo              | Danirixin 5 mg       | Danirixin 10 mg      | Danirixin 25 mg      |
|--|----------------------|----------------------|----------------------|----------------------|
| Subject group type                                 | Reporting group      | Reporting group      | Reporting group      | Reporting group      |
| Number of subjects analysed                        | 101 <sup>[211]</sup> | 102 <sup>[212]</sup> | 100 <sup>[213]</sup> | 103 <sup>[214]</sup> |
| Units: Scores on a scale                           |                      |                      |                      |                      |
| arithmetic mean (standard deviation)               |                      |                      |                      |                      |
| Total score, Day 84, n=8, 4, 6, 6, 10, 6           | 3.00 (± 5.964)       | -5.75 (± 6.035)      | -3.83 (± 12.754)     | 0.42 (± 2.635)       |
| Total score, Day 168, n=13, 7, 9, 8, 6, 7          | -0.96 (± 13.266)     | 1.86 (± 9.344)       | 2.11 (± 5.878)       | 1.25 (± 3.423)       |
| Amount score, Day 84, n=8, 4, 6, 6, 10, 6          | 2.25 (± 5.825)       | -8.50 (± 7.937)      | -4.00 (± 19.204)     | 0.00 (± 6.957)       |
| Amount score, Day 168, n=13, 7, 9, 8, 6, 7         | -3.69 (± 14.733)     | -0.43 (± 8.810)      | 2.11 (± 9.558)       | 1.25 (± 9.161)       |
| Difficult score, Day 84, n=29, 22, 18, 19, 24, 14  | 6.38 (± 9.511)       | 1.64 (± 8.301)       | -0.17 (± 7.679)      | 1.89 (± 11.704)      |
| Difficult score, Day 168, n=29, 20, 18, 19, 25, 15 | 3.03 (± 14.409)      | 2.20 (± 11.039)      | 2.11 (± 7.553)       | 0.63 (± 11.413)      |

Notes:

[211] - Per Protocol Population.

[212] - Per Protocol Population.

[213] - Per Protocol Population.

[214] - Per Protocol Population.

| End point values                          | Danirixin 35 mg      | Danirixin 50 mg     |  |  |
|---|----------------------|---------------------|--|--|
| Subject group type                        | Reporting group      | Reporting group     |  |  |
| Number of subjects analysed               | 100 <sup>[215]</sup> | 99 <sup>[216]</sup> |  |  |
| Units: Scores on a scale                  |                      |                     |  |  |
| arithmetic mean (standard deviation)      |                      |                     |  |  |
| Total score, Day 84, n=8, 4, 6, 6, 10, 6  | -1.20 (± 8.453)      | 2.33 (± 2.677)      |  |  |
| Total score, Day 168, n=13, 7, 9, 8, 6, 7 | 4.08 (± 6.492)       | 0.43 (± 7.607)      |  |  |
| Amount score, Day 84, n=8, 4, 6, 6, 10, 6 | -4.20 (± 10.706)     | -0.83 (± 5.345)     |  |  |

|  |                      |                       |  |  |
|--|----------------------|-----------------------|--|--|
| Amount score, Day 168, n=13, 7, 9, 8, 6, 7         | 3.67 ( $\pm$ 11.708) | -4.14 ( $\pm$ 12.522) |  |  |
| Difficult score, Day 84, n=29, 22, 18, 19, 24, 14  | 2.79 ( $\pm$ 9.278)  | 4.50 ( $\pm$ 9.598)   |  |  |
| Difficult score, Day 168, n=29, 20, 18, 19, 25, 15 | 1.52 ( $\pm$ 9.687)  | 4.87 ( $\pm$ 8.887)   |  |  |

Notes:

[215] - Per Protocol Population.

[216] - Per Protocol Population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Danirixin Whole Blood Pharmacokinetic Concentration-Time Data

|                 |  |
|-----------------|--|
| End point title | Danirixin Whole Blood Pharmacokinetic Concentration-Time Data <sup>[217]</sup> |
|-----------------|--|

End point description:

Blood samples were collected from the participants for the analysis of blood pharmacokinetic concentration-time data. All participants in the mITT population who had at least 1 non-missing Pharmacokinetic assessment obtained and analyzed whilst on treatment with danirixin were included Pharmacokinetic population. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Pre-dose on Days 1, 56, 84 and 168; 0.5, 1, 2, 4, 6, 8, 10, 12 hours post-dose on Days 1 and 168

Notes:

[217] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

| End point values                         | Danirixin 5 mg        | Danirixin 10 mg       | Danirixin 25 mg        | Danirixin 35 mg        |
|--|-----------------------|-----------------------|------------------------|------------------------|
| Subject group type                       | Reporting group       | Reporting group       | Reporting group        | Reporting group        |
| Number of subjects analysed              | 102 <sup>[218]</sup>  | 103 <sup>[219]</sup>  | 102 <sup>[220]</sup>   | 102 <sup>[221]</sup>   |
| Units: Nanogram per milliliter           |                       |                       |                        |                        |
| arithmetic mean (standard deviation)     |                       |                       |                        |                        |
| Day 1, Pre-dose, n=97, 99, 102, 102, 100 | 2.1 ( $\pm$ 19.41)    | 0.4 ( $\pm$ 3.92)     | 0.3 ( $\pm$ 3.06)      | 17.2 ( $\pm$ 169.33)   |
| Day 1, 0.5 hour, n=16, 19, 24, 26, 19    | 86.7 ( $\pm$ 85.73)   | 210.4 ( $\pm$ 207.54) | 730.5 ( $\pm$ 1046.42) | 976.1 ( $\pm$ 839.37)  |
| Day 1, 1 hour, n=16, 18, 24, 26, 19      | 148.3 ( $\pm$ 104.75) | 343.3 ( $\pm$ 228.66) | 822.0 ( $\pm$ 527.47)  | 1183.5 ( $\pm$ 760.02) |
| Day 1, 2 hours, n=16, 19, 24, 26, 19     | 115.3 ( $\pm$ 46.00)  | 277.7 ( $\pm$ 245.32) | 707.7 ( $\pm$ 256.63)  | 1011.2 ( $\pm$ 398.82) |
| Day 1, 4 hours, n=16, 19, 24, 26, 19     | 59.2 ( $\pm$ 17.79)   | 165.3 ( $\pm$ 136.50) | 401.5 ( $\pm$ 188.75)  | 591.5 ( $\pm$ 302.96)  |
| Day 1, 6 hours, n=16, 19, 24, 26, 19     | 34.4 ( $\pm$ 12.32)   | 100.6 ( $\pm$ 84.26)  | 270.0 ( $\pm$ 169.37)  | 371.5 ( $\pm$ 335.23)  |
| Day 1, 8 hours, n=15, 19, 24, 26, 19     | 26.1 ( $\pm$ 13.54)   | 67.8 ( $\pm$ 61.02)   | 213.8 ( $\pm$ 162.24)  | 325.8 ( $\pm$ 359.79)  |
| Day 1, 10 hours, n=16, 18, 22, 26, 19    | 42.5 ( $\pm$ 67.85)   | 61.5 ( $\pm$ 56.67)   | 265.0 ( $\pm$ 396.25)  | 274.5 ( $\pm$ 328.04)  |
| Day 1, 12 hours, n=16, 16, 21, 26, 18    | 87.2 ( $\pm$ 174.14)  | 74.7 ( $\pm$ 82.51)   | 188.2 ( $\pm$ 188.27)  | 232.8 ( $\pm$ 316.67)  |
| Day 56, Pre-dose, n=94, 91, 94, 95, 92   | 53.2 ( $\pm$ 73.19)   | 91.8 ( $\pm$ 102.43)  | 252.3 ( $\pm$ 295.15)  | 372.1 ( $\pm$ 427.41)  |

|  |                  |                  |                  |                    |
|--|------------------|------------------|------------------|--------------------|
| Day 84, Pre-dose, n=97, 94, 96, 91, 90   | 50.2 (± 77.78)   | 76.2 (± 106.86)  | 212.3 (± 211.35) | 342.8 (± 411.28)   |
| Day 168, Pre-dose, n=92, 85, 89, 85, 84  | 41.2 (± 38.02)   | 99.5 (± 138.00)  | 217.9 (± 221.92) | 350.7 (± 336.07)   |
| Day 168, 0.5 hours, n=14, 12, 17, 18, 16 | 147.7 (± 91.51)  | 248.3 (± 189.30) | 530.5 (± 536.75) | 1449.5 (± 949.00)  |
| Day 168, 1 hours, n=14, 13, 17, 18, 16   | 162.1 (± 108.88) | 314.0 (± 157.04) | 681.2 (± 630.86) | 1590.3 (± 1019.32) |
| Day 168, 2 hours, n=14, 13, 17, 18, 16   | 127.4 (± 88.80)  | 331.9 (± 164.10) | 574.7 (± 445.85) | 1045.2 (± 414.21)  |
| Day 168, 4 hours, n=13, 11, 16, 18, 16   | 90.5 (± 53.67)   | 190.9 (± 103.35) | 452.8 (± 289.44) | 805.0 (± 346.87)   |
| Day 168, 6 hours, n=13, 13, 16, 18, 15   | 55.6 (± 26.36)   | 135.5 (± 87.39)  | 289.6 (± 188.04) | 554.8 (± 313.52)   |
| Day 168, 8 hours, n=13, 13, 17, 18, 15   | 41.5 (± 19.75)   | 102.6 (± 60.14)  | 245.1 (± 165.40) | 444.9 (± 298.69)   |
| Day 168, 10 hours, n=13, 12, 17, 18, 15  | 42.4 (± 35.98)   | 76.6 (± 56.95)   | 193.9 (± 128.42) | 380.2 (± 285.81)   |
| Day 168, 12 hours, n=13, 12, 17, 18, 15  | 42.2 (± 41.29)   | 73.1 (± 41.21)   | 169.7 (± 114.20) | 481.2 (± 640.17)   |

Notes:

[218] - Pharmacokinetic Population.

[219] - Pharmacokinetic Population.

[220] - Pharmacokinetic Population.

[221] - Pharmacokinetic Population.

| End point values                         | Danirixin 50 mg      |  |  |  |
|--|----------------------|--|--|--|
| Subject group type                       | Reporting group      |  |  |  |
| Number of subjects analysed              | 101 <sup>[222]</sup> |  |  |  |
| Units: Nanogram per milliliter           |                      |  |  |  |
| arithmetic mean (standard deviation)     |                      |  |  |  |
| Day 1, Pre-dose, n=97, 99, 102, 102, 100 | 3.9 (± 39.10)        |  |  |  |
| Day 1, 0.5 hour, n=16, 19, 24, 26, 19    | 1331.0 (± 1220.06)   |  |  |  |
| Day 1, 1 hour, n=16, 18, 24, 26, 19      | 1846.2 (± 979.95)    |  |  |  |
| Day 1, 2 hours, n=16, 19, 24, 26, 19     | 1472.8 (± 858.49)    |  |  |  |
| Day 1, 4 hours, n=16, 19, 24, 26, 19     | 904.6 (± 599.85)     |  |  |  |
| Day 1, 6 hours, n=16, 19, 24, 26, 19     | 594.9 (± 525.00)     |  |  |  |
| Day 1, 8 hours, n=15, 19, 24, 26, 19     | 428.2 (± 398.16)     |  |  |  |
| Day 1, 10 hours, n=16, 18, 22, 26, 19    | 302.3 (± 255.81)     |  |  |  |
| Day 1, 12 hours, n=16, 16, 21, 26, 18    | 459.3 (± 561.53)     |  |  |  |
| Day 56, Pre-dose, n=94, 91, 94, 95, 92   | 572.0 (± 738.28)     |  |  |  |
| Day 84, Pre-dose, n=97, 94, 96, 91, 90   | 484.3 (± 527.47)     |  |  |  |
| Day 168, Pre-dose, n=92, 85, 89, 85, 84  | 459.5 (± 421.30)     |  |  |  |
| Day 168, 0.5 hours, n=14, 12, 17, 18, 16 | 1635.6 (± 1077.48)   |  |  |  |
| Day 168, 1 hours, n=14, 13, 17, 18, 16   | 1725.4 (± 870.79)    |  |  |  |

|   |                   |  |  |  |
|---|-------------------|--|--|--|
| Day 168, 2 hours, n=14, 13, 17, 18, 16  | 1736.6 (± 592.51) |  |  |  |
| Day 168, 4 hours, n=13, 11, 16, 18, 16  | 1459.9 (± 909.32) |  |  |  |
| Day 168, 6 hours, n=13, 13, 16, 18, 15  | 960.4 (± 633.37)  |  |  |  |
| Day 168, 8 hours, n=13, 13, 17, 18, 15  | 760.8 (± 679.30)  |  |  |  |
| Day 168, 10 hours, n=13, 12, 17, 18, 15 | 715.0 (± 840.54)  |  |  |  |
| Day 168, 12 hours, n=13, 12, 17, 18, 15 | 662.4 (± 877.91)  |  |  |  |

Notes:

[222] - Pharmacokinetic Population.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to Last Time of Quantifiable Concentration [AUC(0-t)] of Danirixin in whole blood using dried blood spot

|                 |   |
|-----------------|---|
| End point title | Area Under the Plasma Concentration-time Curve From Time Zero to Last Time of Quantifiable Concentration [AUC(0-t)] of Danirixin in whole blood using dried blood spot <sup>[223]</sup> |
|-----------------|---|

End point description:

Blood samples were collected at indicated timepoints for the analysis of pharmacokinetic parameter. All participants in the PK population who had at least 1 non-missing PK assessment obtained and analyzed whilst on treatment with danirixin from a dry blood spot sample and corresponding wet whole blood sample were included in Pharmacokinetic population. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 1 and 168

Notes:

[223] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

| End point values                         | Danirixin 5 mg          | Danirixin 10 mg           | Danirixin 25 mg           | Danirixin 35 mg           |
|--|-------------------------|---------------------------|---------------------------|---------------------------|
| Subject group type                       | Reporting group         | Reporting group           | Reporting group           | Reporting group           |
| Number of subjects analysed              | 102 <sup>[224]</sup>    | 103 <sup>[225]</sup>      | 102 <sup>[226]</sup>      | 102 <sup>[227]</sup>      |
| Units: Hour*nanogram per milliliter      |                         |                           |                           |                           |
| geometric mean (confidence interval 95%) |                         |                           |                           |                           |
| Day 1, n=17, 19, 24, 26, 19              | 543.0 (354.9 to 830.8)  | 1373.1 (1081.7 to 1743.0) | 3851.5 (3136.7 to 4729.2) | 5485.1 (4604.8 to 6533.8) |
| Day 168, n=14, 13, 17, 18, 16            | 752.1 (546.8 to 1034.4) | 1701.8 (1257.2 to 2303.7) | 4170.1 (3198.1 to 5437.6) | 7682.6 (6384.8 to 9244.0) |

Notes:

[224] - Pharmacokinetic Population.

[225] - Pharmacokinetic Population.

[226] - Pharmacokinetic Population.

[227] - Pharmacokinetic Population.

| End point values                         | Danirixin 50 mg             |  |  |  |
|--|-----------------------------|--|--|--|
| Subject group type                       | Reporting group             |  |  |  |
| Number of subjects analysed              | 101 <sup>[228]</sup>        |  |  |  |
| Units: Hour*nanogram per milliliter      |                             |  |  |  |
| geometric mean (confidence interval 95%) |                             |  |  |  |
| Day 1, n=17, 19, 24, 26, 19              | 8073.4 (6591.3 to 9888.7)   |  |  |  |
| Day 168, n=14, 13, 17, 18, 16            | 11538.0 (9313.4 to 14294.0) |  |  |  |

Notes:

[228] - Pharmacokinetic Population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Concentration maximum (Cmax) of Danirixin in whole blood using dried blood spots

|                 |   |
|-----------------|---|
| End point title | Concentration maximum (Cmax) of Danirixin in whole blood using dried blood spots <sup>[229]</sup> |
|-----------------|---|

End point description:

Blood samples were collected from the participants for the analysis of pharmacokinetic parameter. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 1 and 168

Notes:

[229] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

| End point values                         | Danirixin 5 mg         | Danirixin 10 mg        | Danirixin 25 mg          | Danirixin 35 mg           |
|--|------------------------|------------------------|--------------------------|---------------------------|
| Subject group type                       | Reporting group        | Reporting group        | Reporting group          | Reporting group           |
| Number of subjects analysed              | 102 <sup>[230]</sup>   | 103 <sup>[231]</sup>   | 102 <sup>[232]</sup>     | 102 <sup>[233]</sup>      |
| Units: Nanogram per milliliter           |                        |                        |                          |                           |
| geometric mean (confidence interval 95%) |                        |                        |                          |                           |
| Day 1, n=17, 19, 24, 26, 19              | 164.9 (119.5 to 227.5) | 343.1 (264.1 to 445.6) | 1028.8 (818.2 to 1293.7) | 1386.2 (1172.1 to 1639.3) |
| Day 168, n=14, 13, 17, 18, 16            | 171.9 (123.5 to 239.4) | 357.3 (274.4 to 465.4) | 821.2 (570.9 to 1181.2)  | 1695.0 (1285.8 to 2234.5) |

Notes:

[230] - Pharmacokinetic Population.

[231] - Pharmacokinetic Population.

[232] - Pharmacokinetic Population.

[233] - Pharmacokinetic Population.

| End point values                         | Danirixin 50 mg           |  |  |  |
|--|---------------------------|--|--|--|
| Subject group type                       | Reporting group           |  |  |  |
| Number of subjects analysed              | 101 <sup>[234]</sup>      |  |  |  |
| Units: Nanogram per milliliter           |                           |  |  |  |
| geometric mean (confidence interval 95%) |                           |  |  |  |
| Day 1, n=17, 19, 24, 26, 19              | 2119.1 (1728.9 to 2597.4) |  |  |  |
| Day 168, n=14, 13, 17, 18, 16            | 2390.5 (2014.6 to 2836.5) |  |  |  |

Notes:

[234] - Pharmacokinetic Population.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to reach maximum plasma concentration (tmax) of Danirixin in whole blood using dried blood spots

|                 |  |
|-----------------|--|
| End point title | Time to reach maximum plasma concentration (tmax) of Danirixin in whole blood using dried blood spots <sup>[235]</sup> |
|-----------------|--|

End point description:

Blood samples were collected from the participants for the analysis of pharmacokinetic parameter.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 1 and 168

Notes:

[235] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is only reporting on a subset of the arms that are contained in the Baseline period.

| End point values              | Danirixin 5 mg        | Danirixin 10 mg       | Danirixin 25 mg       | Danirixin 35 mg       |
|-------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Subject group type            | Reporting group       | Reporting group       | Reporting group       | Reporting group       |
| Number of subjects analysed   | 102 <sup>[236]</sup>  | 103 <sup>[237]</sup>  | 102 <sup>[238]</sup>  | 102 <sup>[239]</sup>  |
| Units: Hours                  |                       |                       |                       |                       |
| median (full range (min-max)) |                       |                       |                       |                       |
| Day 1, n=17, 19, 24, 26, 19   | 1.000 (0.58 to 11.80) | 1.000 (0.50 to 12.00) | 1.000 (0.50 to 10.08) | 1.000 (0.48 to 5.85)  |
| Day 168, n=14, 13, 17, 18, 16 | 1.000 (0.50 to 11.78) | 1.000 (0.50 to 2.00)  | 1.000 (0.33 to 10.00) | 1.000 (0.48 to 11.87) |

Notes:

[236] - Pharmacokinetic Population.

[237] - Pharmacokinetic Population.

[238] - Pharmacokinetic Population.

[239] - Pharmacokinetic Population.

|                               |                       |  |  |  |
|-------------------------------|-----------------------|--|--|--|
| <b>End point values</b>       | Danirixin 50 mg       |  |  |  |
| Subject group type            | Reporting group       |  |  |  |
| Number of subjects analysed   | 101 <sup>[240]</sup>  |  |  |  |
| Units: Hours                  |                       |  |  |  |
| median (full range (min-max)) |                       |  |  |  |
| Day 1, n=17, 19, 24, 26, 19   | 1.000 (0.50 to 12.00) |  |  |  |
| Day 168, n=14, 13, 17, 18, 16 | 1.000 (0.50 to 11.77) |  |  |  |

Notes:

[240] - Pharmacokinetic Population.

### Statistical analyses

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No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

On-treatment serious adverse events (SAEs) and non serious AEs were collected from the start of study treatment up to 196 days

Adverse event reporting additional description:

mITT population comprised of all randomized participants who were randomized apart from those randomized in error, received a treatment randomization number, modified and data for this population were based on actual treatment received. SAEs and AEs were reported for mITT Population.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 21.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Participants received placebo film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Danirixin 5 mg |
|-----------------------|----------------|

Reporting group description:

Participants received danirixin 5 milligram (mg) film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Danirixin 10 mg |
|-----------------------|-----------------|

Reporting group description:

Participants received danirixin 10 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Danirixin 25 mg |
|-----------------------|-----------------|

Reporting group description:

Participants received danirixin 25 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Danirixin 35 mg |
|-----------------------|-----------------|

Reporting group description:

Participants received danirixin 35 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

|                       |                 |
|-----------------------|-----------------|
| Reporting group title | Danirixin 50 mg |
|-----------------------|-----------------|

Reporting group description:

Participants received danirixin 50 mg film coated tablets orally twice daily with food and standard care of treatment for 24 weeks.

| Serious adverse events  | Placebo         | Danirixin 5 mg  | Danirixin 10 mg   |
|---|-----------------|-----------------|-------------------|
| Total subjects affected by serious adverse events                   |                 |                 |                   |
| subjects affected / exposed   | 8 / 102 (7.84%) | 7 / 102 (6.86%) | 13 / 103 (12.62%) |
| number of deaths (all causes)                                       | 0               | 0               | 1                 |
| number of deaths resulting from adverse events                      |                 |                 |                   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                 |                 |                   |
| Bladder cancer  |                 |                 |                   |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 102 (0.00%) | 1 / 102 (0.98%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Lung neoplasm malignant                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Bladder papilloma                                    |                 |                 |                 |
| subjects affected / exposed                          | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac neoplasm unspecified                         |                 |                 |                 |
| subjects affected / exposed                          | 1 / 102 (0.98%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Oesophageal adenocarcinoma                           |                 |                 |                 |
| subjects affected / exposed                          | 1 / 102 (0.98%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Prostate cancer                                      |                 |                 |                 |
| subjects affected / exposed                          | 1 / 102 (0.98%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Squamous cell carcinoma                              |                 |                 |                 |
| subjects affected / exposed                          | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                                   |                 |                 |                 |
| Deep vein thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Death   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sudden death                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                 |                 |
| Epistaxis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary disease           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 102 (0.98%) | 1 / 102 (0.98%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemoptysis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Facial bones fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Atrial fibrillation                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 102 (0.00%) | 1 / 102 (0.98%) | 2 / 103 (1.94%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 102 (0.98%) | 1 / 102 (0.98%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic cardiomyopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mitral valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 1 / 102 (0.98%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 1 / 102 (0.98%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders                        |                 |                 |                 |
| Diabetic neuropathy                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hemiparesis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sciatica  |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |                 |
| Anaemia   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lymphadenopathy                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Ear and labyrinth disorders</b>              |                 |                 |                 |
| Vertigo   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Gastrointestinal disorders</b>               |                 |                 |                 |
| Anal prolapse                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic gastritis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 102 (0.98%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Faecaloma                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal perforation                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 1 / 102 (0.98%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Gastroesophageal reflux disease                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhoids                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine perforation                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 102 (0.98%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis chronic                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Hepatic cyst                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic steatosis                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 102 (0.98%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ankylosing spondylitis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal chest pain                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 2 / 103 (1.94%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthritis bacterial                             |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metapneumovirus infection                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 1 / 102 (0.98%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Perichondritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pilonidal cyst                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 1 / 103 (0.97%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psoas abscess                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 1 / 102 (0.98%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis acute                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Decreased appetite                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 102 (0.98%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetes mellitus                               |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 102 (0.00%) | 0 / 102 (0.00%) | 0 / 103 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

| <b>Serious adverse events</b>                                       | Danirixin 25 mg  | Danirixin 35 mg | Danirixin 50 mg   |
|---|------------------|-----------------|-------------------|
| Total subjects affected by serious adverse events                   |                  |                 |                   |
| subjects affected / exposed   | 10 / 103 (9.71%) | 7 / 102 (6.86%) | 11 / 102 (10.78%) |
| number of deaths (all causes)                                       | 2                | 1               | 1                 |
| number of deaths resulting from adverse events                      |                  |                 |                   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                 |                   |
| Bladder cancer  |                  |                 |                   |
| subjects affected / exposed   | 0 / 103 (0.00%)  | 0 / 102 (0.00%) | 0 / 102 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0           | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0           | 0 / 0             |
| Lung neoplasm malignant   |                  |                 |                   |
| subjects affected / exposed   | 1 / 103 (0.97%)  | 0 / 102 (0.00%) | 0 / 102 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 2            | 0 / 0           | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0           | 0 / 0             |
| Bladder papilloma   |                  |                 |                   |
| subjects affected / exposed   | 0 / 103 (0.00%)  | 0 / 102 (0.00%) | 1 / 102 (0.98%)   |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0           | 0 / 1             |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0           | 0 / 0             |
| Cardiac neoplasm unspecified  |                  |                 |                   |
| subjects affected / exposed   | 0 / 103 (0.00%)  | 0 / 102 (0.00%) | 0 / 102 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0           | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0           | 0 / 0             |
| Oesophageal adenocarcinoma  |                  |                 |                   |
| subjects affected / exposed   | 0 / 103 (0.00%)  | 0 / 102 (0.00%) | 0 / 102 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0           | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0           | 0 / 0             |
| Prostate cancer   |                  |                 |                   |
| subjects affected / exposed   | 0 / 103 (0.00%)  | 0 / 102 (0.00%) | 0 / 102 (0.00%)   |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 0           | 0 / 0             |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0           | 0 / 0             |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Squamous cell carcinoma<br>subjects affected / exposed  | 0 / 103 (0.00%) | 1 / 102 (0.98%) | 0 / 102 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                                      |                 |                 |                 |
| Deep vein thrombosis<br>subjects affected / exposed     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration<br>site conditions |                 |                 |                 |
| Death<br>subjects affected / exposed                    | 2 / 103 (1.94%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all           | 0 / 2           | 0 / 0           | 0 / 0           |
| Sudden death<br>subjects affected / exposed             | 0 / 103 (0.00%) | 1 / 102 (0.98%) | 0 / 102 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 1           | 0 / 0           |
| Respiratory, thoracic and mediastinal<br>disorders      |                 |                 |                 |
| Epistaxis<br>subjects affected / exposed                | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic obstructive pulmonary<br>disease                |                 |                 |                 |
| subjects affected / exposed                             | 2 / 103 (1.94%) | 2 / 102 (1.96%) | 0 / 102 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemoptysis<br>subjects affected / exposed              | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to<br>treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| Pulmonary embolism                                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Facial bones fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders                               |                 |                 |                 |
| Atrial fibrillation                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Coronary artery disease                         |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ischaemic cardiomyopathy                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 1 / 102 (0.98%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mitral valve incompetence                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Myocardial infarction                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Nervous system disorders                        |                 |                 |                 |
| Diabetic neuropathy                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hemiparesis                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Sciatica  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                 |                 |
| Anaemia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lymphadenopathy                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ear and labyrinth disorders                     |                 |                 |                 |
| Vertigo   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Anal prolapse                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Chronic gastritis                               |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Faecaloma                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal perforation                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrooesophageal reflux disease                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhoids                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine perforation                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Large intestine polyp                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 103 (0.00%) | 1 / 102 (0.98%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pancreatitis chronic                            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Hepatic cyst                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatic steatosis                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ankylosing spondylitis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Musculoskeletal chest pain                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 1 / 102 (0.98%) | 4 / 102 (3.92%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 1 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arthritis bacterial                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Metapneumovirus infection                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Perichondritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pilonidal cyst                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Psoas abscess                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pyelonephritis acute                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 1 / 102 (0.98%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 1           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Decreased appetite                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 103 (0.00%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Diabetes mellitus                               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 103 (0.97%) | 0 / 102 (0.00%) | 0 / 102 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

| <b>Non-serious adverse events</b>                     | Placebo           | Danirixin 5 mg    | Danirixin 10 mg   |
|---|-------------------|-------------------|-------------------|
| Total subjects affected by non-serious adverse events |                   |                   |                   |
| subjects affected / exposed                           | 20 / 102 (19.61%) | 24 / 102 (23.53%) | 22 / 103 (21.36%) |
| Nervous system disorders                              |                   |                   |                   |
| Headache  |                   |                   |                   |
| subjects affected / exposed                           | 2 / 102 (1.96%)   | 4 / 102 (3.92%)   | 6 / 103 (5.83%)   |
| occurrences (all)                                     | 2                 | 4                 | 6                 |
| Musculoskeletal and connective tissue disorders       |                   |                   |                   |
| Back pain   |                   |                   |                   |
| subjects affected / exposed                           | 4 / 102 (3.92%)   | 7 / 102 (6.86%)   | 4 / 103 (3.88%)   |
| occurrences (all)                                     | 4                 | 7                 | 4                 |
| Infections and infestations                           |                   |                   |                   |
| Nasopharyngitis                                       |                   |                   |                   |
| subjects affected / exposed                           | 12 / 102 (11.76%) | 8 / 102 (7.84%)   | 9 / 103 (8.74%)   |
| occurrences (all)                                     | 13                | 8                 | 11                |
| Upper respiratory tract infection                     |                   |                   |                   |
| subjects affected / exposed                           | 5 / 102 (4.90%)   | 7 / 102 (6.86%)   | 7 / 103 (6.80%)   |
| occurrences (all)                                     | 6                 | 7                 | 8                 |

| <b>Non-serious adverse events</b>                     | Danirixin 25 mg | Danirixin 35 mg | Danirixin 50 mg |
|---|-----------------|-----------------|-----------------|
| Total subjects affected by non-serious adverse events |                 |                 |                 |



| subjects affected / exposed                     | 31 / 103 (30.10%) | 27 / 102 (26.47%) | 27 / 102 (26.47%) |
|---|-------------------|-------------------|-------------------|
| Nervous system disorders                        |                   |                   |                   |
| Headache  |                   |                   |                   |
| subjects affected / exposed                     | 5 / 103 (4.85%)   | 8 / 102 (7.84%)   | 8 / 102 (7.84%)   |
| occurrences (all)                               | 8                 | 9                 | 8                 |
| Musculoskeletal and connective tissue disorders |                   |                   |                   |
| Back pain                                       |                   |                   |                   |
| subjects affected / exposed                     | 6 / 103 (5.83%)   | 5 / 102 (4.90%)   | 5 / 102 (4.90%)   |
| occurrences (all)                               | 7                 | 6                 | 5                 |
| Infections and infestations                     |                   |                   |                   |
| Nasopharyngitis                                 |                   |                   |                   |
| subjects affected / exposed                     | 12 / 103 (11.65%) | 14 / 102 (13.73%) | 10 / 102 (9.80%)  |
| occurrences (all)                               | 14                | 16                | 14                |
| Upper respiratory tract infection               |                   |                   |                   |
| subjects affected / exposed                     | 9 / 103 (8.74%)   | 5 / 102 (4.90%)   | 6 / 102 (5.88%)   |
| occurrences (all)                               | 12                | 8                 | 8                 |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 31 October 2017 | This amendment adds a second, optional, detailed pharmacokinetic profiling at Visit 10 in a subset of participants to allow for a better understanding of danirixin pharmacokinetics. This amendment also removes the Participant Exit Interview from the exploratory endpoints. Additionally, this amendment provides additional information and clarification for the following: spirometry assessments, exclusion for cancers other than lung cancer, permitted use of supplemental oxygen, permitted uses of chronic steroids, participant numbering requirement for re-screening, additional text to explain the timing of the planned interim analysis and updates to the analysis populations. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported