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	v1
This version publication date	13 October 2019
First version publication date	13 October 2019

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Arm title	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.

Number of subjects in period 1	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

Number of subjects in period 1	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:	
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.	

Reporting group values	Placebo	Danirixin 5 mg	Danirixin 10 mg
Number of subjects	102	102	103
Age categorical 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)	43	38	45
From 65-84 years	59	64	58
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	66.2	66.3	65.7
standard deviation	± 7.31	± 6.79	± 7.48
Sex: Female, Male Units: Subjects			
Female	29	36	32
Male	73	66	71

Race/Ethnicity, Customized 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 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 Units: Years			
arithmetic mean	66.3	65.1	65.7
standard deviation	± 7.28	± 7.58	± 6.98
Sex: Female, Male Units: Subjects			
Female	38	35	32
Male	65	67	70
Race/Ethnicity, Customized 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 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:	
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.	

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:	
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:	
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[1]	95[2]	87[3]	91[4]
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[5]	86[6]		
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:	
4-parameter Emax model selected.	
Comparison groups	Danirixin 5 mg v Placebo
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other[7]
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:	
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[8]
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.

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 25 mg

Statistical analysis description:

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[9]
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.

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 35 mg

Statistical analysis description:

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[10]
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.

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 50 mg

Statistical analysis description:

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[11]
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

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[12]	95[13]	87[14]	91[15]
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.

End point values	Danirixin 35 mg	Danirixin 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	85[16]	86[17]		
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

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[18]
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.

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 10 mg
Statistical analysis description:	
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[19]
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.

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 25 mg
Statistical analysis description:	
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[20]
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.

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 35 mg

Statistical analysis description:

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[21]
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.

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 50 mg

Statistical analysis description:

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[22]
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-

	RS in COPD (E-RS: COPD Cough and Sputum 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[23]	95[24]	87[25]	91[26]
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[27]	86[28]		
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[29]
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.

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 10 mg
Statistical analysis description:	
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[30]
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.

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 25 mg
Statistical analysis description:	
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

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 35 mg
Statistical analysis description:	
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[31]
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.

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 50 mg

Statistical analysis description:

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[32]
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 (± 0.148)	-0.35 (± 0.061)	-0.34 (± 0.062)	-0.34 (± 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 (± 0.073)	-0.34 (± 0.078)		

Statistical analyses

Statistical analysis title	Statistical Analysis of Placebo Vs Danirixin 5 mg
Statistical analysis description:	
Log-linear model.	
Comparison groups	Placebo v Danirixin 5 mg
Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	other[33]
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:	
Log-linear model	
Comparison groups	Placebo v Danirixin 10 mg
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	other[34]
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.

Statistical analysis title	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[35]
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.

Statistical analysis title	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[36]
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.

Statistical analysis title	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[37]
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)[38]

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. mIIT 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: There are no statistical analysis to report.

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[39]	102[40]	103[41]	103[42]
Units: Participants				
Any AE	63	63	69	68
Any SAE	8	7	13	10

Notes:

[39] - mIIT population.

[40] - mIIT population.

[41] - mIIT population.

[42] - mIIT population.

End point values	Danirixin 35 mg	Danirixin 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[43]	102[44]		
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)[45]

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.)(10^12cells/L)(Low0.93x,high1.07x),Hematocrit(Ratio of1)(Low0.50x,high0.50x),Hemoglobin g/liter (L)(Low0.85x,high1.20x),Leukocytes(x10^9/L)(Low0.70x,high1.60x),Lymphocytes%(Low0.80x,high1.20x),Monocytes%(Low0.80x,high1.60x),Neutrophils%(Low0.65x,high1.50x),Platelets(x10^9cells/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: There are no statistical analysis to report.

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[46]	102[47]	103[48]	103[49]
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[50]	102[51]		
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[52]

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: There are no statistical analysis to report.

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[53]	102[54]	103[55]	103[56]
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=99,102,102,102,1	98	102	102	102
Direct bilirubin,High,n=99,102,102,102,101,10	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, 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 mg	Danirixin 50 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102[57]	102[58]		
Units: Participants				
ALT, No change,n=99,102,102,102,101,100	101	100		
ALT, High, n=99,102,102,102,101,100	0	0		
ALP, No change,n=99,102,102,102,101,100	101	100		
ALP, High, n=99,102,102,102,101,100	0	0		
AST, No change,n=99,102,102,102,101,100	101	100		
AST, High, n=99,102,102,102,101,100	0	0		
Bilirubin, No change, n=99,102,102,102,101,100	101	100		
Bilirubin, High, n=99, 102,102,102,101,100	0	0		
Calcium, Low, n=96,102,101,101,101,99	0	0		
Calcium, No change, n=96,102,101,101,101,99	101	99		
Calcium, High, n=96,102,101,101,101,99	0	0		
CO2, Low, n=96,102,101,101,101,99	0	1		
CO2, No change, n=96,102,101,101,101,99	101	98		
CO2, High, n=96,102,101,101,101,99	0	0		
Chloride, Low, n=96,102,101,101,101,99	0	0		
Chloride, No change, n=96,102,101,101,101,99	101	99		
Chloride, High, n=96,102,101,101,101,99	0	0		
Creatinine, No change, n=96,102,101,101,101,99	99	99		
Creatinine, High, n=96, 102, 101, 101, 101, 99	2	0		
Direct bilirubin,NoChange,n=99,102,102,102,1	101	100		
Direct bilirubin,High,n=99,102,102,102,101,10	0	0		
Glucose, Low, n=96, 102, 101, 101, 101, 99	0	0		
Glucose, No change, n=96, 102, 101, 101, 101, 99	101	99		
Glucose, High, n=96, 102, 101, 101, 101, 99	0	0		
Potassium, Low, n=96, 102, 101, 101, 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[59]

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: There are no statistical analysis to report.

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[60]	102[61]	101[62]	101[63]
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[64]	99[65]		
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[66]

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: There are no statistical analysis to report.

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[67]	102[68]	101[69]	101[70]
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[71]	99[72]		
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[73]	102[74]	100[75]	103[76]
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[77]	99[78]		
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[79]	95[80]	87[81]	91[82]
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[83]	86[84]		
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 [85]
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 [86]
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.

Statistical analysis title	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 [87]
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.

Statistical analysis title	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 [88]
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.

Statistical analysis title	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 [89]
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[90]	102[91]	100[92]	103[93]
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[94]	99[95]		

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[96]	102[97]	100[98]	103[99]
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[100]	99[101]		
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

Statistical analysis title	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[102]
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 (<=1/>=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:

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[103]
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 (<=1/>=2 moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

Statistical analysis title	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[104]
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 (<=1/>=2 moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

Statistical analysis title	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[105]
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 (<=1/>=2 moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

Statistical analysis title	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[106]
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 (<=1/>=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[107]	15[108]	9[109]	13[110]
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[111]	16[112]		
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[113]	15[114]	9[115]	13[116]
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[117]	16[118]		
Units: Days				
arithmetic mean (standard deviation)	17.6 (± 16.28)	18.7 (± 37.75)		

Notes:

[117] - Per Protocol Population.

[118] - Per Protocol Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to first HCRU-defined COPD exacerbation

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[119]	102[120]	100[121]	103[122]
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	Danirixin 50		

	mg	mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100[123]	99[124]		
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[125]
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 (<=1/>=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[126]
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 (<=1/>=2 moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

Statistical analysis title	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[127]
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 (<=1/>=2 moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

Statistical analysis title	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[128]
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 (<=1/>=2 moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

Statistical analysis title	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[129]
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 (<=1/>=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:

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:

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[130]	102[131]	100[132]	103[133]
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[134]	99[135]		
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

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[136]
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 (<=1/>=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[137]
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 (<=1/>=2 moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

Statistical analysis title	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[138]
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 (<=1/>=2 moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

Statistical analysis title	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[139]
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 (<=1/>=2 moderate/severe), smoking status at Screening, country and post-bronchodilator %predicted FEV1 at Screening.

Statistical analysis title	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[140]
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 (<=1/>=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[141]	75[142]	58[143]	56[144]
Units: Days				
arithmetic mean (standard deviation)	10.3 (± 7.37)	12.3 (± 8.95)	12.9 (± 9.58)	14.0 (± 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[145]	65[146]		
Units: Days				
arithmetic mean (standard deviation)	10.7 (± 7.21)	14.2 (± 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[147]	102[148]	100[149]	103[150]
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[151]	99[152]		
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[153]	102[154]	100[155]	103[156]
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[157]	99[158]		
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 [159]
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 [160]
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.

Statistical analysis title	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 [161]
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.

Statistical analysis title	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 [162]
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.

Statistical analysis title	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 [163]
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[164]	102[165]	100[166]	103[167]
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[168]	99[169]		
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[170]	102[171]	100[172]	103[173]
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[174]	99[175]		
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:	
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 [176]
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:	
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 [177]
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.

Statistical analysis title	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 [178]
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.

Statistical analysis title	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 [179]
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.

Statistical analysis title	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 [180]
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[181]	102[182]	103[183]	103[184]
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[185]	102[186]		
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 FEVI 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[187]	102[188]	100[189]	103[190]
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[191]	99[192]		
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

No statistical analyses for this end point

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[193]	102[194]	103[195]	103[196]
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[197]	102[198]		
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[199]	102[200]	103[201]	103[202]
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[203]	102[204]		
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[205]	102[206]	100[207]	103[208]
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[209]	99[210]		
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[211]	102[212]	100[213]	103[214]
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[215]	99[216]		
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 (± 11.708)	-4.14 (± 12.522)		
Difficult score, Day 84, n=29, 22, 18, 19, 24, 14	2.79 (± 9.278)	4.50 (± 9.598)		

Difficult score, Day 168, n=29, 20, 18, 19, 25, 15	1.52 (± 9.687)	4.87 (± 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[217]

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[218]	103[219]	102[220]	102[221]
Units: Nanogram per milliliter				
arithmetic mean (standard deviation)				
Day 1, Pre-dose, n=97, 99, 102, 102, 100	2.1 (± 19.41)	0.4 (± 3.92)	0.3 (± 3.06)	17.2 (± 169.33)
Day 1, 0.5 hour, n=16, 19, 24, 26, 19	86.7 (± 85.73)	210.4 (± 207.54)	730.5 (± 1046.42)	976.1 (± 839.37)
Day 1, 1 hour, n=16, 18, 24, 26, 19	148.3 (± 104.75)	343.3 (± 228.66)	822.0 (± 527.47)	1183.5 (± 760.02)
Day 1, 2 hours, n=16, 19, 24, 26, 19	115.3 (± 46.00)	277.7 (± 245.32)	707.7 (± 256.63)	1011.2 (± 398.82)
Day 1, 4 hours, n=16, 19, 24, 26, 19	59.2 (± 17.79)	165.3 (± 136.50)	401.5 (± 188.75)	591.5 (± 302.96)
Day 1, 6 hours, n=16, 19, 24, 26, 19	34.4 (± 12.32)	100.6 (± 84.26)	270.0 (± 169.37)	371.5 (± 335.23)
Day 1, 8 hours, n=15, 19, 24, 26, 19	26.1 (± 13.54)	67.8 (± 61.02)	213.8 (± 162.24)	325.8 (± 359.79)
Day 1, 10 hours, n=16, 18, 22, 26, 19	42.5 (± 67.85)	61.5 (± 56.67)	265.0 (± 396.25)	274.5 (± 328.04)
Day 1, 12 hours, n=16, 16, 21, 26, 18	87.2 (± 174.14)	74.7 (± 82.51)	188.2 (± 188.27)	232.8 (± 316.67)
Day 56, Pre-dose, n=94, 91, 94, 95, 92	53.2 (± 73.19)	91.8 (± 102.43)	252.3 (± 295.15)	372.1 (± 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[222]			
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[223]

End point description:

Blood samples were collected at indicated timepoints for the analysis of phamacokinetic 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[224]	103[225]	102[226]	102[227]
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[228]			
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[229]

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[230]	103[231]	102[232]	102[233]
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[234]			
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[235]

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[236]	103[237]	102[238]	102[239]
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.

End point values	Danirixin 50 mg			
Subject group type	Reporting group			
Number of subjects analysed	101[240]			

Units: Hours				
median (full range (min-max))				
Day 1, n=17, 19, 24, 26, 19 Day 168, n=14, 13, 17, 18, 16	1.000 (0.50 to 12.00) 1.000 (0.50 to 11.77)			

Notes:

[240] - Pharmacokinetic Population.

Statistical analyses

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
Blood and lymphatic system disorders			
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
Ear and labyrinth disorders			
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
Gastrointestinal disorders			
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

Gastrooesophageal 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

Serious adverse events	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			
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
Vascular disorders			
Deep vein thrombosis			
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
General disorders and administration site conditions			
Death			
subjects affected / exposed	2 / 103 (1.94%)	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 / 2	0 / 0	0 / 0
Sudden death			
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 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
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
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 103 (1.94%)	2 / 102 (1.96%)	0 / 102 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
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
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 %

Non-serious adverse events	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

Non-serious adverse events	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:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported