Clinical trial results:
Randomized double blind (sponsor unblind) study evaluating the effect of 14 days of treatment with danirixin (GSK1325756) on neutrophil extracellular traps (NETs) formation in participants with stable chronic obstructive pulmonary disease (COPD)

Summary

EudraCT number	2017-001069-25
Trial protocol	GB
Global end of trial date	08 October 2018

Results information

Result version number	v1
This version publication date	21 September 2019
First version publication date	21 September 2019

Trial information

Trial identification

Sponsor protocol code	207551

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	03 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 October 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the change from baseline in NETs formation in participants with COPD following 14 days treatment with danirixin hydrobromide (HBr) 35 milligram (mg) twice daily

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 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	United Kingdom: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	8
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at single center in United Kingdom. This study was terminated early due to a change in the benefit risk profile of danirixin observed in another study NCT03034967, leading to cessation of the overall danirixin development program.

Pre-assignment

Screening details:

A total of 43 participants were screened, of which 23 were screen failures (23 participants did not meet inclusion/exclusion criteria). From the 20 participants who passed screening, 1 was not randomized due to study being terminated early. Hence, 19 participants were enrolled and received treatment in this study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Participants received one tablet of matching placebo twice daily orally with food for 14 days.

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 one tablet of matching placebo twice daily orally with food for 14 days.

Arm title	Danirixin hydrobromide 35 mg

Arm description:

Participants received one tablet of danirixin hydrobromide 35 milligram (mg) twice daily orally with food for 14 days.

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

Dosage and administration details:

Participants received one tablet of danirixin hydrobromide 35 mg twice daily orally with food for 14 days.

Number of subjects in period 1	Placebo	Danirixin hydrobromide 35 mg
Started	5	14
Completed	5	14

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received one tablet of matching placebo twice daily orally with food for 14 days.	
Reporting group title	Danirixin hydrobromide 35 mg
Reporting group description:	
Participants received one tablet of danirixin hydrobromide 35 milligram (mg) twice daily orally with food for 14 days.	

Reporting group values	Placebo	Danirixin hydrobromide 35 mg	Total
Number of subjects	5	14	19
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)	4	4	8
From 65-84 years	1	10	11
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	61.6	65.3	
standard deviation	± 6.02	± 7.03	-
Sex: Female, Male Units: Subjects			
Female	2	6	8
Male	3	8	11
Race/Ethnicity, Customized Units: Subjects			
White: White/Caucasian/European Heritage	5	14	19

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received one tablet of matching placebo twice daily orally with food for 14 days.	
Reporting group title	Danirixin hydrobromide 35 mg
Reporting group description:	
Participants received one tablet of danirixin hydrobromide 35 milligram (mg) twice daily orally with food for 14 days.	

Primary: Percentage change from Baseline in sputum neutrophil extracellular traps (NETs) quantified by Histone-Elastase Complexes

End point title	Percentage change from Baseline in sputum neutrophil extracellular traps (NETs) quantified by Histone-Elastase Complexes[1]

End point description:

Sputum samples were collected at indicated time points to assess NET formation via histone elastase complexes. Baseline was considered as Day 1. If Day 1 values were missing, screening value was imputed for Baseline. Change from Baseline was calculated as post-Baseline value minus Baseline value. Percentage change from Baseline was calculated by dividing change from Baseline value by Baseline value and multiplied by 100. Analysis was performed using a mixed effect repeated measures model with covariates of treatment group, log(Baseline NETs) and treatment group by day interaction. The response variable was the log of the ratio of post-Baseline NETs to Baseline NETs. Primary completer population consisted of all participants in the Modified Intent-To-Treat population who had completed the assessments supporting the primary endpoint (sputum NETs). Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Primary

End point timeframe:

Baseline (Day 1), Day 7 and Day 14

Notes:

[1] - 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 hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[2]	8[3]		
Units: Percent change				
arithmetic mean (confidence interval 95%)				
Day 7, n=3,6	-3.2 (-77.0 to 306.6)	-9.4 (-64.4 to 130.6)		
Day 14, n=3,8	-30.5 (-71.7 to 70.7)	-13.6 (-49.1 to 46.5)		

Notes:

[2] - Primary Completer Population.

[3] - Primary Completer Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in sputum NETs quantified by deoxyribonucleic acid (DNA)-elastase complexes

End point title	Change from Baseline in sputum NETs quantified by deoxyribonucleic acid (DNA)-elastase complexes

End point description:

Sputum samples were collected at indicated time points to assess NET formation via DNA elastase complexes. Baseline was considered as Day 1. If Day 1 values were missing, screening value was imputed for Baseline. Change from Baseline was calculated as post-Baseline value minus Baseline value. 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:

Baseline (Day 1), Day 7 and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[4]	8[5]		
Units: Units per milliliter				
arithmetic mean (standard error)				
Day 7, n=3,6	1.83 (± 4.610)	0.63 (± 1.859)		
Day 14, n=3,8	-4.53 (± 2.696)	2.08 (± 4.072)		

Notes:

[4] - Primary Completer Population.

[5] - Primary Completer Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in sputum NETs area quantified by microscopy

End point title	Change from Baseline in sputum NETs area quantified by microscopy

End point description:

Sputum samples were collected at indicated time points and NETs area was quantified by microscopy. Baseline was considered as Day 1. If Day 1 values were missing, screening value was imputed for Baseline. Change from Baseline was calculated as post-Baseline value minus Baseline value. Only those participants with data available at the specified data points were analyzed. 99999 indicates data was not collected because 7 days treatment was insufficient to observe the changes in the sputum NETs via microscopy.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 7 and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[6]	7[7]		
Units: Percentage of NETs per field				
arithmetic mean (standard error)				
Day 7	99999 (± 99999)	99999 (± 99999)		
Day 14	0.900 (± 0.9200)	-0.259 (± 0.5183)		

Notes:

[6] - Primary Completer Population.

[7] - Primary Completer Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of participants with adverse events (AEs) and serious adverse events (SAEs)

End point description:

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. A SAE is defined as any untoward medical occurrence that, at any dose results in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, congenital anomaly/birth defect or any other situation according to medical or scientific judgment such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes, Modified Intent-to-Treat Population consisted of all randomized participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to Day 21

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[8]	14[9]		
Units: Participants				
AEs	3	6		
SAEs	0	0		

Notes:

[8] - Modified Intent-to-Treat Population.

[9] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in systolic blood pressure (SBP) and diastolic

blood pressure (DBP)	
End point title	Change from Baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP)

End point description:

SBP and DBP were measured in seated position after 5 minutes rest for the participants at indicated time points. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 7 and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[10]	14[11]		
Units: Millimeters of mercury				
arithmetic mean (standard deviation)				
SBP, Day 7	-11.2 (± 17.01)	-4.1 (± 17.70)		
SBP, Day 14	-1.4 (± 16.10)	-5.3 (± 15.77)		
DBP, Day 7	-2.2 (± 9.91)	-2.1 (± 10.34)		
DBP, Day 14	2.6 (± 11.01)	-5.3 (± 7.98)		

Notes:

[10] - Modified Intent-to-Treat Population.

[11] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in heart rate	
End point title	Change from Baseline in heart rate

End point description:

Heart rate was measured in seated position after 5 minutes rest for the participants at indicated time points. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 7 and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[12]	14[13]		
Units: Beats per minute				
arithmetic mean (standard deviation)				
Day 7	6.8 (± 6.02)	1.6 (± 11.28)		

Day 14	4.0 (± 6.89)	0.1 (± 6.86)		

Notes:

[12] - Modified Intent-to-Treat Population.

[13] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in respiration rate

End point title	Change from Baseline in respiration rate

End point description:

Respiration rate was measured in seated position after 5 minutes rest for the participants at indicated time points. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1), Day 7 and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[14]	14[15]		
Units: Breaths per minute				
arithmetic mean (standard deviation)				
Day 7	-0.6 (± 1.95)	1.8 (± 2.67)		
Day 14	0.2 (± 0.84)	2.1 (± 3.43)		

Notes:

[14] - Modified Intent-to-Treat Population.

[15] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in PR Interval, QRS Duration, QT Interval and QT Interval Corrected for Heart Rate According to Fridericia's Formula (QTcF)

End point title	Change from Baseline in PR Interval, QRS Duration, QT Interval and QT Interval Corrected for Heart Rate According to Fridericia's Formula (QTcF)

End point description:

Triplicate 12-lead electrocardiograms (ECG) were obtained to measure PR Interval, QRS Duration, QT Interval and QTcF Interval. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[16]	14[17]		
Units: Milliseconds				
arithmetic mean (standard deviation)				
PR Interval	7.6 (± 20.44)	-4.8 (± 15.69)		
QRS Duration	-0.3 (± 1.12)	0.5 (± 5.55)		
QT Interval	-4.8 (± 10.05)	3.7 (± 15.67)		
QTcF Interval	-4.6 (± 0.38)	-1.6 (± 5.96)		

Notes:

[16] - Modified Intent-to-Treat Population.

[17] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Spirometry: Forced expiratory volume in one second (FEV1) at indicated time points

End point title	Spirometry: Forced expiratory volume in one second (FEV1) at indicated time points

End point description:

FEV1 is the amount of air that can be forcefully exhaled from the lungs in the first second of a forced exhalation. It was measured by spirometry test. Mean and standard deviation data of FEV1 measured at Day 1 and Day 14 have been presented.

End point type	Secondary

End point timeframe:

Day 1 and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[18]	14[19]		
Units: Liter				
arithmetic mean (standard deviation)				
Day 1	2.458 (± 0.6331)	1.914 (± 0.7267)		
Day 14	2.344 (± 0.7174)	1.910 (± 0.7428)		

Notes:

[18] - Modified Intent-to-Treat Population.

[19] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Spirometry: Forced vital capacity (FVC) at indicated time points

End point title	Spirometry: Forced vital capacity (FVC) at indicated time points

End point description:

FVC is defined as the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. It was measured by spirometry test. Mean and standard deviation data of FVC measured at Day 1 and Day 14 have been presented.

End point type	Secondary

End point timeframe:

Day 1 and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[20]	14[21]		
Units: Liter				
arithmetic mean (standard deviation)				
Day 1	4.026 (± 1.2021)	3.416 (± 1.1304)		
Day 14	4.036 (± 1.3992)	3.369 (± 1.1456)		

Notes:

[20] - Modified Intent-to-Treat Population.

[21] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameters: Basophils, Eosinophils, Lymphocytes, Monocytes, Platelets counts, Total neutrophils, White Blood Cell (WBC) count

End point title	Change from Baseline in hematology parameters: Basophils, Eosinophils, Lymphocytes, Monocytes, Platelets counts, Total neutrophils, White Blood Cell (WBC) count

End point description:

Blood samples were collected to analyze the hematology parameters: Basophils, Eosinophils, Lymphocytes, Monocytes, Platelets counts, Total neutrophils and WBC count. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[22]	14[23]		
Units: Giga cells per liter				
arithmetic mean (standard deviation)				
Basophils	0.00 (± 0.000)	-0.02 (± 0.058)		
Eosinophils	0.040 (± 0.0686)	-0.020 (± 0.0609)		
Lymphocytes	-0.20 (± 0.316)	-0.08 (± 0.269)		
Monocytes	-0.04 (± 0.114)	0.02 (± 0.080)		
Platelets counts	8.2 (± 18.94)	-7.9 (± 41.66)		
Total neutrophils	-0.38 (± 0.965)	0.29 (± 0.943)		
WBC count	-0.56 (± 0.948)	0.16 (± 1.075)		

Notes:

[22] - Modified Intent-to-Treat Population.

[23] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter: Hematocrit

End point title	Change from Baseline in hematology parameter: Hematocrit

End point description:

Blood samples were collected to analyze the hematology parameter: Hematocrit. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[24]	14[25]		
Units: Percentage of red blood cells in blood				
arithmetic mean (standard deviation)	-0.0058 (± 0.02279)	-0.0115 (± 0.02085)		

Notes:

[24] - Modified Intent-to-Treat Population.

[25] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter: Hemoglobin

End point title	Change from Baseline in hematology parameter: Hemoglobin

End point description:

Blood samples were collected to analyze the hematology parameter: Hemoglobin. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[26]	14[27]		
Units: Grams per liter				
arithmetic mean (standard deviation)	-2.2 (± 6.72)	-5.4 (± 7.99)		

Notes:

[26] - Modified Intent-to-Treat Population.

[27] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter: Mean Corpuscular Volume

End point title	Change from Baseline in hematology parameter: Mean Corpuscular Volume

End point description:

Blood samples were collected to analyze the hematology parameter: Mean Corpuscular Volume. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[28]	14[29]		
Units: Femtoliter				
arithmetic mean (standard deviation)	0.06 (± 1.339)	0.31 (± 1.263)		

Notes:

[28] - Modified Intent-to-Treat Population.

[29] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter: Mean Corpuscular Hemoglobin

End point title	Change from Baseline in hematology parameter: Mean Corpuscular Hemoglobin

End point description:

Blood samples were collected to analyze the hematology parameter: Mean Corpuscular Hemoglobin. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[30]	14[31]		
Units: Picograms				
arithmetic mean (standard deviation)	-0.08 (± 0.920)	-0.22 (± 0.749)		

Notes:

[30] - Modified Intent-to-Treat Population.

[31] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematology parameter: Red Blood Cell count

End point title	Change from Baseline in hematology parameter: Red Blood Cell count

End point description:

Blood samples were collected to analyze the hematology parameter: Red Blood Cell count. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[32]	14[33]		
Units: Trillion cells per liter				
arithmetic mean (standard deviation)	-0.070 (± 0.2081)	-0.154 (± 0.2171)		

Notes:

[32] - Modified Intent-to-Treat Population.

[33] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in chemistry parameters: Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST)

End point title	Change from Baseline in chemistry parameters: Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST)

End point description:

Blood samples were collected to analyze the chemistry parameters: ALT, ALP and AST. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[34]	14[35]		
Units: International units per liter				
arithmetic mean (standard deviation)				
ALT	-1.6 (± 4.39)	-1.9 (± 8.24)		
ALP	2.8 (± 6.26)	1.3 (± 13.89)		
AST	-0.6 (± 2.61)	-3.1 (± 2.11)		

Notes:

[34] - Modified Intent-to-Treat Population.

[35] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in chemistry parameters: Calcium, Glucose, Potassium, Sodium, Urea

End point title	Change from Baseline in chemistry parameters: Calcium, Glucose, Potassium, Sodium, Urea

End point description:

Blood samples were collected to analyze the chemistry parameters: Calcium, Glucose, Potassium, Sodium and Urea. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[36]	14[37]		
Units: Millimoles per liter				
arithmetic mean (standard deviation)				
Calcium	-0.032 (± 0.0782)	-0.034 (± 0.0947)		
Glucose	0.36 (± 0.635)	0.12 (± 0.398)		
Potassium	-0.12 (± 0.148)	0.06 (± 0.287)		
Sodium	0.0 (± 1.58)	0.2 (± 2.04)		
Urea	-0.42 (± 0.867)	0.26 (± 0.777)		

Notes:

[36] - Modified Intent-to-Treat Population.

[37] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in chemistry parameters: Creatinine, Direct Bilirubin, Total Bilirubin

End point title	Change from Baseline in chemistry parameters: Creatinine, Direct Bilirubin, Total Bilirubin

End point description:

Blood samples were collected to analyze the chemistry parameters: Creatinine, Direct Bilirubin and Total Bilirubin. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[38]	14[39]		
Units: Micromoles per liter				
arithmetic mean (standard deviation)				
Creatinine	2.6 (± 5.86)	1.2 (± 6.99)		
Direct Bilirubin	-0.4 (± 0.55)	0.7 (± 1.65)		
Total Bilirubin	0.8 (± 0.84)	-1.2 (± 3.26)		

Notes:

[38] - Modified Intent-to-Treat Population.

[39] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in urinalysis parameter: Specific Gravity

End point title	Change from Baseline in urinalysis parameter: Specific Gravity

End point description:

Urinary specific gravity measurement is a part of routine urinalysis. Urine specific gravity is a measure of the concentration of solutes in the urine. It measures the ratio of urine density compared with water density and provides information on the kidney’s ability to concentrate urine. The concentration of the excreted molecules determines the urine's specific gravity. Urine samples were collected from participants at indicated time points for analysis of specific gravity. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[40]	14[41]		
Units: Grams per milliliter				
arithmetic mean (standard deviation)	0.0030 (± 0.00908)	0.0046 (± 0.00887)		

Notes:

[40] - Modified Intent-to-Treat Population.

[41] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in urinalysis parameter: Potential of hydrogen (pH)

End point title	Change from Baseline in urinalysis parameter: Potential of hydrogen (pH)

End point description:

Urine samples were collected from participants at indicated time points for analysis of pH. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[42]	14[43]		
Units: pH				
arithmetic mean (standard deviation)	1.00 (± 1.225)	-0.25 (± 0.672)		

Notes:

[42] - Modified Intent-to-Treat Population.

[43] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in sputum resistin levels

End point title	Change from Baseline in sputum resistin levels

End point description:

Sputum samples were collected at indicated time points to analyze resistin levels. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value. 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:

Baseline (Day 1), Day 7 and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[44]	8[45]		
Units: Nanograms per milliliter				
arithmetic mean (standard error)				
Day 7, n=3,6	8.93 (± 15.513)	-2.01 (± 4.629)		
Day 14, n=3,8	15.28 (± 27.619)	2.61 (± 2.711)		

Notes:

[44] - Primary Completer Population.

[45] - Primary Completer Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the ratio of sputum NETs to sputum neutrophils

End point title	Change from Baseline in the ratio of sputum NETs to sputum neutrophils

End point description:

Sputum samples were collected to calculate ratio of sputum NETs to sputum neutrophils. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value. The ratio is calculated as the sputum NETs divided by the number of sputum neutrophils. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2[46]	7[47]		
Units: Ratio				
arithmetic mean (standard error)	0.5200 (± 0.41000)	0.4557 (± 0.53149)		

Notes:

[46] - Primary Completer Population.

[47] - Primary Completer Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in sputum elastase activity

End point title	Change from Baseline in sputum elastase activity

End point description:

Sputum samples were collected at indicated time points to analyze sputum elastase activity. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value. 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:

Baseline (Day 1), Day 7 and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[48]	8[49]		
Units: Nanograms per milliliter				
arithmetic mean (standard error)				
Day 7, n=3,6	638.0 (± 381.36)	238.0 (± 224.50)		
Day 14, n=3,8	411.3 (± 439.20)	66.1 (± 45.64)		

Notes:

[48] - Primary Completer Population.

[49] - Primary Completer Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in peripheral blood neutrophil NETs formation quantified by DNA release

End point title	Change from Baseline in peripheral blood neutrophil NETs formation quantified by DNA release

End point description:

Blood samples were collected at indicated time points to analyze peripheral blood neutrophil NETs formation by DNA release. Stimulation of phorbol 12-myristate 13-acetate (PMA) induces inflammation and was intended to induce NETs formation. If PMA was not stimulated to induce inflammation that resulted in increased NET formation. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus Baseline value. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[50]	12[51]		
Units: Relative fluorescence units				
arithmetic mean (standard error)				
Not PMA stimulated	3044.8 (± 4251.78)	-721.1 (± 731.82)		
PMA stimulated	-96.8 (± 9418.43)	-1211.0 (± 5102.21)		

Notes:

[50] - Modified Intent-to-Treat Population.

[51] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage change from Baseline in peripheral blood neutrophil NETs formation quantified by microscopy

End point title	Percentage change from Baseline in peripheral blood neutrophil NETs formation quantified by microscopy

End point description:

Blood samples were collected at indicated time points to analyze peripheral blood neutrophil NETs formation by microscopy. Stimulation of PMA induces inflammation and was intended to induce NETs formation. If PMA was not stimulated to induce inflammation that resulted in increased NET formation. Baseline was considered as Day 1. Change from Baseline was calculated as post-Baseline value minus

Baseline value. Percentage change from Baseline was calculated by dividing change from Baseline value by Baseline value and multiplied by 100. Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and Day 14

End point values	Placebo	Danirixin hydrobromide 35 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4[52]	11[53]		
Units: Percent change				
arithmetic mean (standard error)				
Not PMA stimulated	927.5 (± 585.03)	560.5 (± 395.72)		
PMA stimulated	44.7 (± 41.79)	90.6 (± 60.33)		

Notes:

[52] - Modified Intent-to-Treat Population.

[53] - Modified Intent-to-Treat Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed concentration (Cmax) of danirixin

End point title	Maximum observed concentration (Cmax) of danirixin[54]

End point description:

Blood samples were collected to evaluate the pharmacokinetic (PK) of danirixin at the indicated time points for the analysis of Cmax. PK population consisted of all participants in the Modified Intent-To-Treat population who had at least 1 non-missing PK assessment (non-quantifiable values were considered as non-missing values). 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 14: Pre-dose and 0.5, 1, 2 and 4 hours post-dose

Notes:

[54] - 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 hydrobromide 35 mg			
Subject group type	Reporting group			
Number of subjects analysed	14[55]			
Units: Nanograms per milliliter				
geometric mean (geometric coefficient of variation)				
Day 1, n=14	855.2 (± 52.29)			

Day 14, n=13	1135.2 (± 65.73)			

Notes:

[55] - PK Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Cmax (Tmax) of danirixin

End point title	Time to Cmax (Tmax) of danirixin[56]

End point description:

Blood samples were collected to evaluate the PK of danirixin at the indicated time points for the analysis of Tmax. 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 14: Pre-dose and 0.5, 1, 2 and 4 hours post-dose

Notes:

[56] - 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 hydrobromide 35 mg			
Subject group type	Reporting group			
Number of subjects analysed	14[57]			
Units: Hours				
median (full range (min-max))				
Day 1, n=14	1.000 (0.50 to 4.00)			
Day 14, n=13	1.000 (0.50 to 4.00)			

Notes:

[57] - PK Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the blood concentration-time curve [AUC(0-t)] of danirixin

End point title	Area under the blood concentration-time curve [AUC(0-t)] of danirixin[58]

End point description:

Blood samples were collected to evaluate the PK of danirixin at the indicated time points for the analysis of AUC(0-t). Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Days 1 and 14: Pre-dose and 0.5, 1, 2 and 4 hours post-dose

Notes:

[58] - 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 hydrobromide 35 mg			
Subject group type	Reporting group			
Number of subjects analysed	13[59]			
Units: Hours * nanograms per milliliter				
geometric mean (geometric coefficient of variation)				
Day 1	2173.4 (± 39.57)			
Day 14	2751.1 (± 51.24)			

Notes:

[59] - PK Population.

Statistical analyses

No statistical analyses for this end point

Secondary: Time of last observed concentration (Tlast) of danirixin

End point title	Time of last observed concentration (Tlast) of danirixin[60]

End point description:

Blood samples were collected to evaluate the PK of danirixin at the indicated time points for the analysis of Tlast. 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 14: Pre-dose and 0.5, 1, 2 and 4 hours post-dose

Notes:

[60] - 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 hydrobromide 35 mg			
Subject group type	Reporting group			
Number of subjects analysed	14[61]			
Units: Hours				
median (full range (min-max))				
Day 1, n=14	4.000 (4.00 to 4.05)			
Day 14, n=13	4.000 (4.00 to 4.00)			

Notes:

[61] - PK Population.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs were collected from start of the treatment up to Day 21

Adverse event reporting additional description:

AEs and SAEs were collected for modified Intent-to-Treat Population which consisted of all randomized participants who received at least one dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Danirixin hydrobromide 35 mg

Reporting group description:

Participants received one tablet of danirixin hydrobromide 35 milligram (mg) twice daily orally with food for 14 days.

Reporting group title	Placebo

Reporting group description:

Participants received one tablet of matching placebo twice daily orally with food for 14 days.

Serious adverse events	Danirixin hydrobromide 35 mg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 14 (0.00%)	0 / 5 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			

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

Non-serious adverse events	Danirixin hydrobromide 35 mg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 14 (42.86%)	3 / 5 (60.00%)	
Injury, poisoning and procedural complications			
Procedural complication			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Dysgeusia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Catheter site haematoma			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Peripheral swelling			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 14 (7.14%)	1 / 5 (20.00%)	
occurrences (all)	1	1	
Dyspnoea			
subjects affected / exposed	1 / 14 (7.14%)	1 / 5 (20.00%)	
occurrences (all)	1	1	

Sputum increased			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Night sweats			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 14 (7.14%)	0 / 5 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 14 (0.00%)	1 / 5 (20.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported