Clinical trial results:
A Phase II, global, randomized study to evaluate the efficacy and safety of Danirixin (GSK1325756) co-administered with a standard-of-care antiviral (oseltamivir), in the treatment of adults hospitalized with influenza

Summary

EudraCT number	2016-002512-40
Trial protocol	SE ES NL FR
Global end of trial date	24 May 2017

Results information

Result version number	v1
This version publication date	04 May 2018
First version publication date	04 May 2018

Trial information

Trial identification

Sponsor protocol code	201023

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, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	27 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 May 2017
Global end of trial reached?	Yes
Global end of trial date	24 May 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of treatment with IV DNX twice daily given with oral oseltamivir compared to oral oseltamivir twice daily on time to clinical response (TTCR)

Protection of trial subjects:

Not Applicable.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	10
EEA total number of subjects	2

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)	4
From 65 to 84 years	5
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This was a randomized study to evaluate the efficacy and safety of Danirixin (DNX) co-administered with a standard-of-care antiviral (oseltamivir [OSV]), in the treatment of adults hospitalized with influenza. The study enrolled participants in 7 centers across 3 countries (Romania,Sweden and United States) and was terminated due to poor enrollment

Pre-assignment

Screening details:

A total of 14 participants were screened for the study, of which 4 participants were screening failures. 10 participants received study treatment.

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 + OSV

Arm description:

Participants received matching placebo given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 milligram (mg) twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received matching placebo given as a 1-hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour.

Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

All participants received open-label oral Oseltamivir 75 mg twice daily given as standard of care.

Arm title	DNX 15 mg + OSV

Arm description:

Participants received DNX 15 mg given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 mg twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.

Arm type	Experimental

Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

All participants received open-label oral Oseltamivir 75 mg twice daily given as standard of care.

Investigational medicinal product name	Danirixin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received Danirixin 15 mg or 50 mg given as a 1-hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour.

Arm title	DNX 50 mg + OSV

Arm description:

Participants received DNX 50 mg given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 mg twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.

Arm type	Experimental
Investigational medicinal product name	Oseltamivir
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

All participants received open-label oral Oseltamivir 75 mg twice daily given as standard of care.

Investigational medicinal product name	Danirixin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Participants received Danirixin 15 mg or 50 mg given as a 1-hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour.

Number of subjects in period 1	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV
Started	2	4	4
Completed	2	4	3
Not completed	0	0	1
Consent withdrawn by subject	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo + OSV
Reporting group description:	
Participants received matching placebo given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 milligram (mg) twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.	
Reporting group title	DNX 15 mg + OSV
Reporting group description:	
Participants received DNX 15 mg given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 mg twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.	
Reporting group title	DNX 50 mg + OSV
Reporting group description:	
Participants received DNX 50 mg given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 mg twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.	

Reporting group values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV
Number of subjects	2	4	4
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	61.0	66.0	63.0
standard deviation	± 24.04	± 8.76	± 24.90
Gender categorical Units: Subjects			
Female	1	2	3
Male	1	2	1
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	1	0	1
Asian-Central/South Asian Heritage	0	0	1
White-White/Caucasian/European Heritage	1	4	2

Reporting group values	Total		
Number of subjects	10		
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean			

standard deviation	-		

Gender categorical Units: Subjects			
Female	6		
Male	4		
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	2		
Asian-Central/South Asian Heritage	1		
White-White/Caucasian/European Heritage	7		

End points

End points reporting groups

Reporting group title	Placebo + OSV

Reporting group description:

Participants received matching placebo given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 milligram (mg) twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.

Reporting group title	DNX 15 mg + OSV

Reporting group description:

Participants received DNX 15 mg given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 mg twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.

Reporting group title	DNX 50 mg + OSV

Reporting group description:

Participants received DNX 50 mg given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 mg twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.

Primary: Time to Clinical Response (TTCR)

End point title	Time to Clinical Response (TTCR)[1]

End point description:

The clinical response was defined as Hospital discharge due to clinical improvement OR normalization of temperature; and oxygen saturation; and respiratory status/heart rate/systolic blood pressure (normalization of 2 out of these 3 parameters). The clinical response based on vital signs/ventilation status required 24-hour confirmation. Considering 2-hour assessment window, the response confirmation period was 22 hours. Kaplan Meier estimates for the median of TTCR was provided. One participant had vital sign resolution at Baseline and was counted as having a clinical response but was not included in the Kaplan Meier Estimates. Influenza Positive Population (IPP) Population comprised of all participants in the Intent to Treat Exposed (ITT-E) Population with influenza infection (positive influenza Polymerase Chain Reaction [PCR] or culture at any time point) confirmed by central lab testing. Only those participants with data available at the indicated time point were analyzed.

End point type	Primary

End point timeframe:

Up to 45 Days

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

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[2]	3[3]	4[4]	
Units: Days				
median (inter-quartile range (Q1-Q3))				
Days	1.33 (0.71 to 1.95)	4.53 (2.95 to 5.71)	4.76 (3.66 to 5.08)	

Notes:

[2] - IPP Population

[3] - IPP Population

[4] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Respiratory Response (TTRR)

End point title	Time to Respiratory Response (TTRR)

End point description:

Time to Respiratory Response was defined as meeting at least one of the following criteria, and maintained for 24 hours: return to pre-morbid oxygen requirement (participants with chronic oxygen use or ventilator support), or return to no requirement of supplemental oxygen, or respiratory rate <=24 per minute (without supplemental oxygen). Kaplan Meier estimates for the median of TTRR for each treatment group was provided. 99999 indicates data is not available. Due to limited data, no TTRR estimate could be calculated for any of the treatment groups.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[5]	4[6]	4[7]	
Units: Days				
median (inter-quartile range (Q1-Q3))				
Days	99999 (1.95 to 99999)	99999 (1.07 to 99999)	99999 (3.04 to 99999)	

Notes:

[5] - IPP Population

[6] - IPP Population

[7] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to absence of fever

End point title	Time to absence of fever

End point description:

Time from first dose of treatment to time to afebrile status (<=36.6 degree celsius-axilla/temporal or <=37.2 degree celsius- oral, or <=37.7 degree celsius-rectal/core, tympanic) was to be evaluated. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[8]	0[9]	0[10]	
Units: Days				
median (full range (min-max))				
Days	(to)	(to)	(to)	

Notes:

[8] - IPP Population

[9] - IPP Population

[10] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to improved oxygen saturation

End point title	Time to improved oxygen saturation

End point description:

Time from first dose of treatment to time of improved oxygen saturation was to be calculated. A participant with a history of chronic hypoxia (without supplemental oxygen) satisfied normalization criteria for oxygen saturation if the value (without supplemental oxygen) is <=2 percent from participant's historical oxygen saturation Baseline as recorded within 12 months prior to enrollment as documented in the participant's medical records. This requirement was to be waived for participants with a history of chronic supplemental oxygen requirement who had a Baseline oxygen saturation <95 percent with supplemental oxygen, within 12 months prior to enrollment as documented in the participant's medical records. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[11]	0[12]	0[13]	
Units: Days				
median (full range (min-max))				
Days	(to)	(to)	(to)	

Notes:

[11] - IPP Population

[12] - IPP Population

[13] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to improved heart rate

End point title	Time to improved heart rate

End point description:

Time from first dose of treatment to time of heart rate <=100 beats per minute was to be evaluated. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[14]	0[15]	0[16]	
Units: Days				
median (full range (min-max))				
Days	(to)	(to)	(to)	

Notes:

[14] - IPP Population

[15] - IPP Population

[16] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to improved systolic blood pressure (SBP)

End point title	Time to improved systolic blood pressure (SBP)

End point description:

Time from first dose of treatment to time of SBP at >=90 millimeters of mercury (mmHg) was to be evaluated. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[17]	0[18]	0[19]	
Units: Days				
median (full range (min-max))				
Days	(to)	(to)	(to)	

Notes:

[17] - IPP Population

[18] - IPP Population

[19] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with clinical response over time

End point title	Percentage of participants with clinical response over time

End point description:

The clinical response was defined as Hospital discharge due to clinical improvement OR normalization of temperature; and oxygen saturation; and respiratory status/heart rate/systolic blood pressure (normalization of 2 out of these 3 parameters). The clinical response based on vital signs/ventilation status required 24-hour confirmation. Considering 2-hour assessment window, the response confirmation period was 22 hours. Percentage of participants with positive clinical response are presented.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[20]	4[21]	4[22]	
Units: Percentage of Participants				
Percentage of Participants	100	100	100	

Notes:

[20] - IPP Population

[21] - IPP Population

[22] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with improved respiratory status over time

End point title	Percentage of participants with improved respiratory status over time

End point description:

The Respiratory Response was defined as meeting at least one of the following criteria, and maintained for 24 hours: return to pre-morbid oxygen requirement (participants with chronic oxygen use or ventilator support), or return to no requirement of supplemental oxygen, or respiratory rate <=24 per minute (without supplemental oxygen). Percentage of participants with improved respiratory status has been presented.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[23]	4[24]	4[25]	
Units: Percentage of Participants				
Percentage of Participants	50	50	50	

Notes:

[23] - IPP Population

[24] - IPP Population

[25] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to improvement of ventilation status

End point title	Time to improvement of ventilation status

End point description:

Time to improvement of ventilation status was assessed by modality, frequencies and durations of invasive and non-invasive ventilator support, duration of oxygen supplementation. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[26]	0[27]	0[28]	
Units: Days				
median (full range (min-max))				
Days	(to)	(to)	(to)	

Notes:

[26] - IPP Population

[27] - IPP Population

[28] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days of stay in the intensive care unit (ICU)

End point title	Number of days of stay in the intensive care unit (ICU)

End point description:

Number of days of stay in the ICU over the treatment period and post treatment period was to be recorded. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[29]	0[30]	0[31]	
Units: Days				
median (full range (min-max))				
Days	(to)	(to)	(to)	

Notes:

[29] - IPP Population

[30] - IPP Population

[31] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants requiring ICU admission and readmission

End point title	Number of participants requiring ICU admission and readmission

End point description:

Number of participants requiring ICU admission during treatment period and after post treatment was to be recorded. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[32]	0[33]	0[34]	
Units: Participants				
Participants				

Notes:

[32] - IPP Population

[33] - IPP Population

[34] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of days of stay in the hospital

End point title	Number of days of stay in the hospital

End point description:

Number of days of stay in the hospital over treatment period and post treatment period was to be recorded. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[35]	0[36]	0[37]	
Units: Days				
median (full range (min-max))				
Days	(to)	(to)	(to)	

Notes:

[35] - IPP Population

[36] - IPP Population

[37] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with development of septic shock

End point title	Number of participants with development of septic shock

End point description:

Development of septic shock was to be assessed by occurrence of hypotension requiring vasopressive therapy and serum lactate level >2 millimeter (mm) after adequate fluid resuscitation. Number of participants with development of septic shock were planned to be presented. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[38]	0[39]	0[40]	
Units: Participants				
Participants				

Notes:

[38] - IPP Population

[39] - IPP Population

[40] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants used antibiotics for complications of influenza

End point title	Number of participants used antibiotics for complications of influenza

End point description:

Complications of influenza such as bacterial pneumonia, pneumothorax, pleural effusion, acute respiratory distress syndrome (ARDS), myositis, encephalitis, myocarditis, and associated antibiotic use was recorded. Number of participants who reqruied use of associated antibiotics for complications of influenza is presented.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[41]	4[42]	4[43]	
Units: Participants				
Participants	1	1	1	

Notes:

[41] - IPP Population

[42] - IPP Population

[43] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with improvement in ordinal scale of clinical efficacy over time

End point title	Number of participants with improvement in ordinal scale of clinical efficacy over time

End point description:

Number of participants with improvement in ordinal scale of clinical efficacy over time was to be assessed by: death, mechanical vent, in the ICU, non-ICU hospitalization, and hospital discharge. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[44]	0[45]	0[46]	
Units: Participants				
Participants				

Notes:

[44] - IPP Population

[45] - IPP Population

[46] - IPP Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with any non-serious adverse event (AE); any serious AE (SAE); any AEs of special interest (AESIs)

End point title	Number of participants with any non-serious adverse event (AE); any serious AE (SAE); any AEs of special interest (AESIs)

End point description:

An AE is any untoward medical occurrence in a participant or clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Any untoward event resulting in death, life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, congenital anomaly/birth defect, any other situation according to medical or scientific judgment 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 or event associated with liver injury and impaired liver function were categorized as SAE. Participants who received any of the study treatment and had any AE or SAE or AESI were considered for analysis. Safety Population comprised of all participants who received at least 1 dose of study treatment.

End point type	Secondary

End point timeframe:

Up to 45 Days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[47]	4	4	
Units: Participants				
Any non-SAE	0	4	4	
Any SAE	0	0	2	
Any AESI	0	1	1	

Notes:

[47] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in albumin and total protein

End point title	Change from Baseline in albumin and total protein

End point description:

Blood samples were collected to evaluate albumin and total protein at indicated time points. Values at Day 1 were considered as Baseline values. Change from Baseline at each visit was calculated by subtracting Baseline value from post-dose visit value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates data was not available.

End point type	Secondary

End point timeframe:

Baseline and up to 45 days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[48]	4[49]	4[50]	
Units: Gram per Liter (G/L)				
arithmetic mean (standard deviation)				
Albumin, Day 2, n=1,0,0	2.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Albumin, Day 2, sample 2, n=0,0,1	99999 (± 99999)	99999 (± 99999)	0.0 (± 99999)	
Albumin, Day 3, n=1,2,2	0.0 (± 99999)	-5.0 (± 1.41)	-2.0 (± 2.83)	
Albumin, Day 3, sample 2, n=0,1,2	99999 (± 99999)	-9.0 (± 99999)	-4.5 (± 4.95)	
Albumin, Day 4, n=0,1,2	99999 (± 99999)	-1.0 (± 99999)	-3.0 (± 4.24)	
Albumin, Day 4, sample 2, n=0,1,1	99999 (± 99999)	-8.0 (± 99999)	-5.0 (± 99999)	
Albumin, Day 5, n=1,1,3	0.0 (± 99999)	-5.0 (± 99999)	-3.7 (± 6.03)	
Albumin, Day 6, n=1,1,4	1.0 (± 99999)	-6.0 (± 99999)	-2.8 (± 4.99)	
Albumin, Day 7, n=1,1,1	-2.0 (± 99999)	-5.0 (± 99999)	-3.0 (± 99999)	
Albumin, Day 8, n=1,0,0	0.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Albumin, Discharge/Day 45, n=2,2,3	2.5 (± 2.12)	-0.5 (± 0.71)	5.7 (± 6.81)	
Albumin, Day 3 post last dose, n=1,3,3	0.0 (± 99999)	-1.3 (± 1.15)	-2.3 (± 1.15)	
Total Protein, Day 2, n=1,0,1	1.0 (± 99999)	99999 (± 99999)	-1.0 (± 99999)	
Total Protein, Day 3, n=1,2,2	1.0 (± 99999)	-5.5 (± 4.95)	-3.0 (± 4.24)	
Total Protein, Day 3, sample 2, n=0,1,2	99999 (± 99999)	-13.0 (± 99999)	-4.0 (± 4.24)	
Total Protein, Day 4, n=0,1,2	99999 (± 99999)	-1.0 (± 99999)	-4.0 (± 5.66)	
Total Protein, Day 4, sample 2, n=0,1,1	99999 (± 99999)	-10.0 (± 99999)	-7.0 (± 99999)	
Total Protein, Day 5, n=1,1,3	-1.0 (± 99999)	-7.0 (± 99999)	-5.7 (± 10.97)	
Total Protein, Day 6, n=1,1,4	0.0 (± 99999)	-7.0 (± 99999)	-4.0 (± 6.98)	
Total Protein, Day 7, n=1,1,1	-3.0 (± 99999)	-5.0 (± 99999)	-2.0 (± 99999)	
Total Protein, Day 8, n=1,0,0	0.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Total Protein, Discharge/Day 45, n=2,2,3	0.0 (± 2.83)	-1.5 (± 2.12)	6.7 (± 11.02)	
Total Protein, Day 3 post last dose, n=1,3,3	-0.3 (± 99999)	-3.0 (± 2.00)	-3.3 (± 3.51)	

Notes:

[48] - Safety Population

[49] - Safety Population

[50] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in white blood cell count (WBC) and absolute neutrophil count (ANC)

End point title	Change from Baseline in white blood cell count (WBC) and absolute neutrophil count (ANC)

End point description:

Blood samples were collected to evaluate WBC and ANC at indicated time points. Values at Day 1 were considered as Baseline values. Change from Baseline at each visit was calculated by subtracting Baseline value from post-dose visit value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates data was not available.

End point type	Secondary

End point timeframe:

Baseline and up to 45 days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[51]	4[52]	4[53]	
Units: Giga cells per Liter (GI/L)				
arithmetic mean (standard deviation)				
WBC, Day 2, n=1,0,0	-2.70 (± 99999)	99999 (± 99999)	99999 (± 99999)	
WBC, Day 3, n=1,1,0	-5.10 (± 99999)	-3.00 (± 99999)	99999 (± 99999)	
WBC, Day 4, n=0,2,1	99999 (± 99999)	1.15 (± 3.889)	-7.10 (± 99999)	
WBC, Day 5, n=1,1,1	-2.90 (± 99999)	-3.70 (± 99999)	-5.30 (± 99999)	
WBC, Day 6, n=1,0,0	-2.40 (± 99999)	99999 (± 99999)	99999 (± 99999)	
WBC, Day 7, n=1,0,0	-2.90 (± 99999)	99999 (± 99999)	99999 (± 99999)	
WBC, Day 8, n=1,0,0	-3.10 (± 99999)	99999 (± 99999)	99999 (± 99999)	
WBC, Discharge/Day 45, n=2,3,1	-3.55 (± 2.051)	3.97 (± 2.765)	-9.50 (± 99999)	
WBC, Day 3 post last dose, n=1,4,1	-4.60 (± 99999)	1.95 (± 2.594)	-8.00 (± 99999)	
ANC, Day 2, n=1,0,0	-3.880 (± 99999)	99999 (± 99999)	99999 (± 99999)	
ANC, Day 3, n=1,1,0	-5.640 (± 99999)	-4.070 (± 99999)	99999 (± 99999)	
ANC, Day 4, n=0,2,1	99999 (± 99999)	1.410 (± 3.2810)	-7.420 (± 99999)	
ANC, Day 5, n=1,1,1	-4.250 (± 99999)	-4.250 (± 99999)	-6.260 (± 99999)	
ANC, Day 6, n=1,0,0	-3.540 (± 99999)	99999 (± 99999)	99999 (± 99999)	
ANC, Day 7, n=1,0,0	-4.180 (± 99999)	99999 (± 99999)	99999 (± 99999)	
ANC, Day 8, n=1,0,0	-4.580 (± 99999)	99999 (± 99999)	99999 (± 99999)	
ANC, Discharge/Day 45, n=2,3,1	-4.650 (± 1.9092)	3.050 (± 2.9511)	-9.720 (± 99999)	

ANC, Day 3 post last dose, n=1,4,1	-5.680 (± 99999)	1.033 (± 2.9818)	-9.060 (± 99999)	

Notes:

[51] - Safety Population

[52] - Safety Population

[53] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Total Bilirubin (T. Bilirubin), creatinine and Direct Bilirubin (D. Bilirubin)

End point title	Change from Baseline in Total Bilirubin (T. Bilirubin), creatinine and Direct Bilirubin (D. Bilirubin)

End point description:

Blood samples were collected to evaluate T. Bilirubin, creatinine and D. Bilirubin at indicated time points. Values at Day 1 were considered as Baseline values. Change from Baseline at each visit was calculated by subtracting Baseline value from post-dose visit value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates data was not available.

End point type	Secondary

End point timeframe:

Baseline and up to 45 days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[54]	4[55]	4[56]	
Units: Micromole per Liter (µmol/L)				
arithmetic mean (standard deviation)				
D. Bilirubin, Day 2, n=1,0,0	-2.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
D. Bilirubin, Day 2, sample 2, n=0,0,1	99999 (± 99999)	99999 (± 99999)	0.0 (± 99999)	
D. Bilirubin, Day 3, n=1,2,2	-2.0 (± 99999)	-2.0 (± 0.00)	0.0 (± 2.83)	
D. Bilirubin, Day 3, sample 2, n=0,1,2	99999 (± 99999)	-2.0 (± 99999)	0.0 (± 2.83)	
D. Bilirubin, Day 4, n=0,1,2	99999 (± 99999)	0.0 (± 99999)	0.0 (± 0.00)	
D. Bilirubin, Day 4, sample 2, n=0,1,1	99999 (± 99999)	-2.0 (± 99999)	-2.0 (± 99999)	
D. Bilirubin, Day 5, n=1,1,3	0.0 (± 99999)	0.0 (± 99999)	0.0 (± 2.00)	
D. Bilirubin, Day 6, n=1,1,4	0.0 (± 99999)	0.0 (± 99999)	-0.5 (± 1.91)	
D. Bilirubin, Day 7, n=1,1,1	0.0 (± 99999)	0.0 (± 99999)	2.0 (± 99999)	
D. Bilirubin, Day 8, n=1,0,0	-2.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
D. Bilirubin, Discharge/Day 45, n=2,2,3	-3.0 (± 4.24)	-1.0 (± 1.41)	-0.7 (± 1.15)	
D. Bilirubin, Day 3 post last dose, n=1,3,3	0.0 (± 99999)	0.0 (± 0.00)	0.7 (± 2.31)	
T. Bilirubin, Day 2, n=1,0,0	0.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
T. Bilirubin, Day 2, sample 2, n=0,0,1	99999 (± 99999)	99999 (± 99999)	-4.00 (± 99999)	

T. Bilirubin, Day 3, n=1,2,2	-2.0 (± 99999)	-2.0 (± 2.828)	-1.00 (± 1.414)	
T. Bilirubin, Day 3, sample 2, n=0,1,2	99999 (± 99999)	-6.0 (± 99999)	-2.00 (± 0.000)	
T. Bilirubin, Day 4, n=0,1,2	99999 (± 99999)	0.0 (± 99999)	-2.00 (± 2.828)	
T. Bilirubin, Day 4, sample 2, n=0,1,1	99999 (± 99999)	-6.0 (± 99999)	0.00 (± 99999)	
T. Bilirubin, Day 5, n=1,1,3	0.0 (± 99999)	-2.0 (± 99999)	0.67 (± 1.155)	
T. Bilirubin, Day 6, n=1,1,4	-2.0 (± 99999)	2.0 (± 99999)	-0.50 (± 1.000)	
T. Bilirubin, Day 7, n=1,1,1	-6.0 (± 99999)	2.0 (± 99999)	0.00 (± 99999)	
T. Bilirubin, Day 8, n=1,0,0	-6.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
T. Bilirubin, Discharge/Day 45, n=2,2,3	-1.0 (± 1.414)	0.0 (± 2.828)	-0.67 (± 1.155)	
T. Bilirubin, Day 3 post last dose, n=1,3,3	-4.0 (± 99999)	0.0 (± 2.000)	-4.60 (± 4.503)	
Creatinine, Day 2, n=2,2,4	-7.95 (± 18.738)	-0.50 (± 5.657)	-3.35 (± 1.323)	
Creatinine, Day 2, sample 2, n=1,1,2	3.50 (± 99999)	7.90 (± 99999)	-8.40 (± 0.566)	
Creatinine, Day 3, n=1,2,3	-33.60 (± 99999)	-3.60 (± 1.273)	-4.77 (± 1.012)	
Creatinine, Day 3, sample 2, n=0,2,4	99999 (± 99999)	-9.30 (± 6.930)	1.32 (± 8.397)	
Creatinine, Day 4, n=1,3,4	-39.80 (± 99999)	-5.90 (± 6.222)	-4.20 (± 6.975)	
Creatinine, Day 4, sample 2, n=0,2,3	99999 (± 99999)	0.45 (± 15.627)	-2.40 (± 7.375)	
Creatinine, Day 5, n=1,2,3	-40.60 (± 99999)	-1.35 (± 9.405)	-2.67 (± 4.070)	
Creatinine, Day 5, sample 2, n=0,1,0	99999 (± 99999)	-15.90 (± 99999)	99999 (± 99999)	
Creatinine, Day 6, n=1,1,4	-44.20 (± 99999)	-10.60 (± 99999)	3.52 (± 4.396)	
Creatinine, Day 7, n=1,1,1	-38.00 (± 99999)	-10.60 (± 99999)	-1.80 (± 99999)	
Creatinine, Day 8, n=1,0,0	-26.50 (± 99999)	99999 (± 99999)	99999 (± 99999)	
Creatinine, Discharge/Day 45, n=2,2,3	-16.80 (± 22.486)	-3.55 (± 8.697)	6.50 (± 4.521)	
Creatinine, Day 3 post last dose, n=1,3,3	-23.00 (± 99999)	-4.47 (± 9.750)	2.93 (± 9.304)	

Notes:

[54] - Safety Population

[55] - Safety Population

[56] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST) and Alkaline Phosphatase (ALP)

End point title	Change from Baseline in Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST) and Alkaline Phosphatase (ALP)

End point description:

Blood samples were collected to evaluate ALT, AST and ALP at indicated time points. Values at Day 1

were considered as Baseline values. Change from Baseline at each visit was calculated by subtracting Baseline value from post-dose visit value. Only those participants with data available at the specified time points were analyzed (represented by n=X in the category titles). 99999 indicates data was not available.

End point type	Secondary

End point timeframe:

Baseline and up to 45 days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[57]	4[58]	4[59]	
Units: International unit per Liter (IU/L)				
arithmetic mean (standard deviation)				
ALT, Day 2, n=1,0,0	10.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
ALT, Day 2, sample 2, n=0,0,1	99999 (± 99999)	99999 (± 99999)	-1.0 (± 99999)	
ALT, Day 3, n=1,2,2	4.0 (± 99999)	3.0 (± 1.41)	2.0 (± 5.66)	
ALT, Day 3, sample 2, n=0,1,2	99999 (± 99999)	-1.0 (± 99999)	-1.0 (± 5.66)	
ALT, Day 4, n=0,1,2	99999 (± 99999)	-18.0 (± 99999)	-3.5 (± 2.12)	
ALT, Day 4, sample 2, n=0,1,1	99999 (± 99999)	1.0 (± 99999)	10.0 (± 99999)	
ALT, Day 5, n=1,1,3	0.0 (± 99999)	-2.0 (± 99999)	-0.3 (± 3.79)	
ALT, Day 6, n=1,1,4	-1.0 (± 99999)	-37.0 (± 99999)	-2.3 (± 3.86)	
ALT, Day 7, n=1,1,1	-2.0 (± 99999)	-42.0 (± 99999)	-6.0 (± 99999)	
ALT, Day 8, n=1,0,0	-1.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
ALT, Discharge/Day 45, n=2,2,3	-6.0 (± 4.24)	-30.0 (± 35.36)	0.7 (± 2.08)	
ALT, Day 3 post last dose, n=1,3,3	2.0 (± 99999)	-17.0 (± 19.08)	-4.0 (± 3.61)	
AST, Day 2, n=1,0,0	14.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
AST, Day 2, sample 2, n=0,0,1	99999 (± 99999)	99999 (± 99999)	-4.0 (± 99999)	
AST, Day 3, n=1,2,2	11.0 (± 99999)	6.0 (± 8.49)	-2.0 (± 2.83)	
AST, Day 3, sample 2, n=0,1,2	99999 (± 99999)	8.0 (± 99999)	-1.5 (± 4.95)	
AST, Day 4, n=0,1,2	99999 (± 99999)	-29.0 (± 99999)	-8.0 (± 2.83)	
AST, Day 4, sample 2, n=0,1,1	99999 (± 99999)	16.0 (± 99999)	0.0 (± 99999)	
AST, Day 5, n=1,1,3	-10.0 (± 99999)	-9.0 (± 99999)	-7.3 (± 2.08)	
AST, Day 6, n=1,1,4	-12.0 (± 99999)	-46.0 (± 99999)	-5.8 (± 7.32)	
AST, Day 7, n=1,1,1	-11.0 (± 99999)	-51.0 (± 99999)	-11.0 (± 99999)	
AST, Day 8, n=1,0,0	-12.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
AST, Discharge/Day 45, n=2,2,3	-12.0 (± 11.31)	-27.5 (± 30.41)	-3.0 (± 5.57)	

AST, Day 3 post last dose, n=1,3,3	-10.0 (± 99999)	-21.7 (± 23.76)	-10.7 (± 5.86)	
ALP, Day 2, n=1,0,0	8.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
ALP, Day 2,sample 2, n=0,0,1	99999 (± 99999)	99999 (± 99999)	-3.0 (± 99999)	
ALP, Day 3, n=1,2,2	2.0 (± 99999)	-6.0 (± 8.49)	-8.0 (± 2.83)	
ALP, Day 3, sample 2, n=0,1,2	99999 (± 99999)	-23.0 (± 99999)	-14.0 (± 7.07)	
ALP, Day 4, n=0,1,2	99999 (± 99999)	-25.0 (± 99999)	-5.5 (± 0.71)	
ALP, Day 4, sample 2, n=0,1,1	99999 (± 99999)	-22.0 (± 99999)	-4.0 (± 99999)	
ALP, Day 5, n=1,1,3	6.0 (± 99999)	-8.0 (± 99999)	-11.0 (± 7.81)	
ALP, Day 6, n=1,1,4	5.0 (± 99999)	-51.0 (± 99999)	-9.5 (± 8.19)	
ALP, Day 7, n=1,1,1	2.0 (± 99999)	-50.0 (± 99999)	17.0 (± 99999)	
ALP, Day 8, n=1,0,0	3.0 (± 99999)	99999 (± 99999)	99999 (± 99999)	
ALP, Discharge/Day 45, n=2,2,3	10.0 (± 0.00)	-25.5 (± 30.41)	2.0 (± 9.64)	
ALP, Day 3 post last dose, n=1,3,3	1.0 (± 99999)	-19.7 (± 22.03)	-9.3 (± 7.51)	

Notes:

[57] - Safety Population

[58] - Safety Population

[59] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinically significant abnormality in electrocardiogram (ECG)

End point title	Number of participants with clinically significant abnormality in electrocardiogram (ECG)

End point description:

Single 12-lead ECGs were obtained at Baseline and on the day of last dose during the study using an ECG machine that automatically calculates the heart rate (HR) and measures PR, QRS, QT, and QT duration corrected for heart rate (QTc). Number of participants with clinically significant abnormality in ECG are presented.

End point type	Secondary

End point timeframe:

Up to 6 days

End point values	Placebo + OSV	DNX 15 mg + OSV	DNX 50 mg + OSV	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2[60]	4[61]	4[62]	
Units: Participants				
Participants	0	0	1	

Notes:

[60] - Safety Population

[61] - Safety Population

[62] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed plasma concentration (Cmax) of intravenous (IV) DNX

End point title	Maximum observed plasma concentration (Cmax) of intravenous (IV) DNX[63]

End point description:

Cmax of IV DNX was to be derived from the Pharmacokinetics (PK) samples collected at Day 1 pre-dose, Day 3 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours post-dose and Day 5 pre-dose. PK Population comprised of all participants who underwent blood PK sampling during the study and from whom one or more blood concentration was determined. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed due to limited sample size.

End point type	Secondary

End point timeframe:

Day 1 pre-dose, Day 3 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours post-dose and Day 5 pre-dose

Notes:

[63] - 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	DNX 15 mg + OSV	DNX 50 mg + OSV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[64]	0[65]		
Units: Nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Nanogram per milliliter (ng/mL)	()	()		

Notes:

[64] - PK Population

[65] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUC [0-t]) of IV DNX

End point title	Area under the concentration-time curve from time zero to the time of the last quantifiable concentration (AUC [0-t]) of IV DNX[66]

End point description:

AUC (0-t) of IV DNX was to be derived from the PK samples collected at Day 1 pre-dose, Day 3 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours post-dose and Day 5 pre-dose. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed due to limited sample size.

End point type	Secondary

End point timeframe:

Day 1 pre-dose, Day 3 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours post-dose and Day 5 pre-dose

Notes:

[66] - 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	DNX 15 mg + OSV	DNX 50 mg + OSV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[67]	0[68]		
Units: Hour*nanogram per milliliter(hour*ng/mL)				
geometric mean (geometric coefficient of variation)				
Hour*nanogram per milliliter(hour*ng/mL)	()	()		

Notes:

[67] - PK Population

[68] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach Cmax (Tmax) of IV DNX

End point title	Time to reach Cmax (Tmax) of IV DNX[69]

End point description:

Tmax of IV DNX was to be derived from the PK samples collected at Day 1 pre-dose, Day 3 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours post-dose and Day 5 pre-dose. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed due to limited PK parameters available.

End point type	Secondary

End point timeframe:

Day 1 pre-dose, Day 3 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours post-dose and Day 5 pre-dose

Notes:

[69] - 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	DNX 15 mg + OSV	DNX 50 mg + OSV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[70]	0[71]		
Units: Hour				
median (full range (min-max))				
Hour	(to)	(to)		

Notes:

[70] - PK Population

[71] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Average concentration (Cavg) of IV DNX

End point title	Average concentration (Cavg) of IV DNX[72]

End point description:

Cavg of IV DNX was to be derived from the PK samples collected at Day 1 pre-dose, Day 3 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours post-dose and Day 5 pre-dose. As the study was terminated, only a selected set of originally planned analysis were performed and hence this endpoint was not analyzed due to limited sample size.

End point type	Secondary

End point timeframe:

Day 1 pre-dose, Day 3 at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 8 and 12 hours post-dose and Day 5 pre-dose

Notes:

[72] - 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: There are no statistical data to report.

End point values	DNX 15 mg + OSV	DNX 50 mg + OSV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[73]	0[74]		
Units: ng/mL				
arithmetic mean (standard deviation)				
ng/mL	()	()		

Notes:

[73] - PK Population

[74] - PK Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment SAEs and non-serious AEs were collected from the start of the study treatment up to Day 45.

Adverse event reporting additional description:

On treatment SAEs and non-serious AEs were reported for the Safety Population.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Placebo + OSV

Reporting group description:

Participants received matching placebo given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 mg twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.

Reporting group title	DNX 50 mg + OSV

Reporting group description:

Participants received DNX 50 mg given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 mg twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.

Reporting group title	DNX 15 mg + OSV

Reporting group description:

Participants received DNX 15 mg given as a 1 hour infusion twice daily for up to 5 days. Infusion was administered at a constant rate over approximately 1 hour +- 10 minutes and approximately 12 hours apart +- 1 hour. All participants also received open-label oral OSV 75 mg twice daily given as standard of care. The investigator could elect to continue treatment with OSV after 5 days of study treatment.

Serious adverse events	Placebo + OSV	DNX 50 mg + OSV	DNX 15 mg + OSV
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (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

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo + OSV	DNX 50 mg + OSV	DNX 15 mg + OSV
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Infusion site extravasation			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Monocytosis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2

Atelectasis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Cough			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Clostridium difficile infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Fungal infection			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pneumonia bacterial			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 2 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	0 / 2 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

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

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

Interpretation of data is limited by the few participants enrolled prior to termination of the study due to poor recruitment.

Notes: