Clinical trial results:
A Phase 2, Multicenter, Randomised, Double-Blind, Placebo-Controlled Study to Assess the Hemodynamic Effects, Safety, Tolerability, and Pharmacokinetics of APD418 in Subjects with Heart Failure with Reduced Ejection Fraction

Summary

EudraCT number	2020-006131-10
Trial protocol	PL
Global end of trial date	19 September 2022

Results information

Result version number	v1 (current)
This version publication date	30 September 2023
First version publication date	30 September 2023

Trial information

Trial identification

Sponsor protocol code	C5061001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05139615
WHO universal trial number (UTN)	-
Other trial identifiers	APD418-201: Other study ID

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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	01 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 September 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of intravenous (IV) infusion of APD418 on hemodynamic status based on cardiac index (CI) in subjects with heart failure with reduced ejection fraction (HFrEF).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trials subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 December 2021
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	Germany: 1
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Serbia: 13
Worldwide total number of subjects	22
EEA total number of subjects	7

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)	13

From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study was planned to be conducted in two parts (Part A and B); however, study was terminated during Part A due to a business decision by Sponsor and Part B was not initiated and no subjects were enrolled in Part B.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1- 0.17 mg/kg/hr APD418

Arm description:

Subjects were administered a single dose of 0.17 milligrams per kilogram per hour (mg/kg/hr) (total dose of 1 mg/kg) APD418 as an intravenous (IV) infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.

Arm type	Experimental
Investigational medicinal product name	APD418
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.17 mg/kg/h (1 mg/kg) single 6-hour IV infusion

Arm title	Cohort 1- Placebo

Arm description:

Subjects were administered a single dose of matching placebo as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.

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

Dosage and administration details:

Single dose

Arm title	Cohort 2- 0.5 mg/kg/hr APD418

Arm description:

Subjects were administered a single dose of 0.5 mg/kg/hr (total dose of 3 mg/kg) APD418 as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.

Arm type	Experimental

Investigational medicinal product name	APD418
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.50 mg/kg/h (3 mg/kg) single 6-hour IV infusion

Arm title	Cohort 2- Placebo

Arm description:

Subjects were administered a single dose of matching placebo as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.

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

Dosage and administration details:

Single use

Number of subjects in period 1	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418
Started	4	3	11
Completed	4	3	11

Number of subjects in period 1	Cohort 2- Placebo
Started	4
Completed	4

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1- 0.17 mg/kg/hr APD418
Reporting group description:	
Subjects were administered a single dose of 0.17 milligrams per kilogram per hour (mg/kg/hr) (total dose of 1 mg/kg) APD418 as an intravenous (IV) infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	
Reporting group title	Cohort 1- Placebo
Reporting group description:	
Subjects were administered a single dose of matching placebo as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	
Reporting group title	Cohort 2- 0.5 mg/kg/hr APD418
Reporting group description:	
Subjects were administered a single dose of 0.5 mg/kg/hr (total dose of 3 mg/kg) APD418 as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	
Reporting group title	Cohort 2- Placebo
Reporting group description:	
Subjects were administered a single dose of matching placebo as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	

Reporting group values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418
Number of subjects	4	3	11
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)	2	2	8
From 65-84 years	2	1	3
85 years and over	0	0	0
Age Continuous			
Units: Years			
arithmetic mean	62.0	62.0	57.0
standard deviation	± 9.56	± 3.61	± 10.82
Sex: Female, Male			
Units: Subjects			
Female	1	0	4
Male	3	3	7
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	0	0	0
White	4	3	11
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	4	3	11
Unknown or Not Reported	0	0	0

Reporting group values	Cohort 2- Placebo	Total	
Number of subjects	4	22	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1	13	
From 65-84 years	3	9	
85 years and over	0	0	
Age Continuous Units: Years			
arithmetic mean	68.0		
standard deviation	± 6.88	-	
Sex: Female, Male Units: Subjects			
Female	0	5	
Male	4	17	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	4	22	
More than one race	0	0	
Unknown or Not Reported	0	0	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Not Hispanic or Latino	4	22	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Cohort 1- 0.17 mg/kg/hr APD418
Reporting group description:	
Subjects were administered a single dose of 0.17 milligrams per kilogram per hour (mg/kg/hr) (total dose of 1 mg/kg) APD418 as an intravenous (IV) infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	
Reporting group title	Cohort 1- Placebo
Reporting group description:	
Subjects were administered a single dose of matching placebo as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	
Reporting group title	Cohort 2- 0.5 mg/kg/hr APD418
Reporting group description:	
Subjects were administered a single dose of 0.5 mg/kg/hr (total dose of 3 mg/kg) APD418 as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	
Reporting group title	Cohort 2- Placebo
Reporting group description:	
Subjects were administered a single dose of matching placebo as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	

Primary: Part A: Change in Cardiac Index (CI) Measured by Right Heart Catheterisation (RHC) From Baseline to end of Intravenous (IV) Infusion at 6 Hours

End point title	Part A: Change in Cardiac Index (CI) Measured by Right Heart Catheterisation (RHC) From Baseline to end of Intravenous (IV) Infusion at 6 Hours[1]
End point description:	
Cardiac index (CI) is a hemodynamic parameter that relates the cardiac output (CO) from left ventricle in one minute to body surface area (BSA), thus relating heart performance to the body size of the subject. It was measured by RHC. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment.	
End point type	Primary
End point timeframe:	
Baseline (within 2 hours prior to start of study treatment administration) up to 6 Hours (end of IV infusion)	

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: No statistical analyses were planned for this primary end point.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Liter per minute per meter square				
arithmetic mean (standard deviation)	0.33 (± 0.660)	0.10 (± 0.100)	0.25 (± 0.372)	0.10 (± 0.245)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Stroke Volume (SV), Left Ventricular end-Systolic Volume (LVESV) and Left Ventricular end-Diastolic Volume (LVEDV) Measured by Echocardiogram (ECHO) From Baseline to end of IV Infusion at 6 Hours

End point title	Part A: Change in Stroke Volume (SV), Left Ventricular end-Systolic Volume (LVESV) and Left Ventricular end-Diastolic Volume (LVEDV) Measured by Echocardiogram (ECHO) From Baseline to end of IV Infusion at 6 Hours

End point description:

SV is the volume of blood pumped from the left ventricle per beat. LVESV is the volume of blood in the left ventricle at the end of contraction and at diastole. LVEDV is the amount of blood in the heart's left ventricle just before the heart contracts. All these parameters were measured by ECHO. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration) up to 6 Hours (end of IV infusion)

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	1	9	4
Units: Milliliter				
arithmetic mean (standard deviation)				
Stroke Volume	3.13 (± 10.623)	-0.80 (± 99999)	5.94 (± 10.183)	-3.15 (± 7.152)
LVESV	-11.05 (± 22.837)	4.10 (± 99999)	8.28 (± 25.689)	8.92 (± 29.804)
LVEDV	-7.92 (± 15.531)	3.30 (± 99999)	14.20 (± 31.021)	7.30 (± 38.006)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Stroke Volume Index (SVI) Measured by ECHO From Baseline to end of IV Infusion at 6 Hours

End point title	Part A: Change in Stroke Volume Index (SVI) Measured by ECHO From Baseline to end of IV Infusion at 6 Hours

End point description:

SVI was calculated as stroke volume divided by BSA. This was measured by ECHO. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration) up to 6 Hours (end of IV infusion)

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	1	9	4
Units: Milliliter per meter square				
arithmetic mean (standard deviation)	1.50 (± 5.518)	-0.30 (± 99999)	2.62 (± 4.615)	-2.00 (± 4.492)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Fractional Shortening (FS) Measured by ECHO From Baseline to end of IV Infusion at 6 Hours

End point title	Part A: Change in Fractional Shortening (FS) Measured by ECHO From Baseline to end of IV Infusion at 6 Hours

End point description:

FS was calculated by measuring the percentage reduction in left ventricular diameter during systole. This was measured by ECHO. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration) up to 6 Hours (end of IV infusion)

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Percentage reduction				
arithmetic mean (standard deviation)	-2.60 (± 7.791)	0.47 (± 5.710)	-1.55 (± 1.924)	-4.50 (± 7.444)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Left Ventricular Ejection Fraction (LVEF) Measured by ECHO From Baseline to end of IV Infusion at 6 Hours

End point title	Part A: Change in Left Ventricular Ejection Fraction (LVEF) Measured by ECHO From Baseline to end of IV Infusion at 6 Hours

End point description:

LVEF is the central measure of left ventricular systolic function. LVEF is the fraction of chamber volume ejected in systole (stroke volume) in relation to the volume of the blood in the ventricle at the end of diastole (end-diastolic volume). This was measured by ECHO. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration) up to 6 Hours (end of IV infusion)

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Percentage of end diastolic volume				
arithmetic mean (standard deviation)	1.90 (± 6.009)	0.47 (± 1.457)	1.14 (± 3.204)	-1.68 (± 0.900)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Left Ventricular end-Systolic and Left Ventricular end-Diastolic Diameter Measured by ECHO From Baseline to end of IV Infusion at 6 Hours

End point title	Part A: Change in Left Ventricular end-Systolic and Left Ventricular end-Diastolic Diameter Measured by ECHO From Baseline to end of IV Infusion at 6 Hours

End point description:

Left ventricular end-systolic diameter and left ventricular end-diastolic diameter were measured using ECHO. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration) up to 6 Hours (end of IV infusion)

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Centimeter (cm)				
arithmetic mean (standard deviation)				
Left ventricular end-systolic diameter	0.10 (± 0.361)	-0.04 (± 0.384)	0.22 (± 0.321)	0.35 (± 0.544)

Left ventricular end-diastolic diameter	-0.04 (± 0.087)	-0.02 (± 0.098)	0.15 (± 0.363)	0.16 (± 0.243)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Left Ventricular Global Longitudinal Strain (LVGLS) and Left Ventricular Global Circumferential Strain (LVGCS) Measured by ECHO From Baseline to end of IV Infusion at 6 Hours

End point title	Part A: Change in Left Ventricular Global Longitudinal Strain (LVGLS) and Left Ventricular Global Circumferential Strain (LVGCS) Measured by ECHO From Baseline to end of IV Infusion at 6 Hours

End point description:

LVGLS is the average strain of the cardiac chamber wall. LVGCS measured the chamber deformation along the circumference of the cardiac wall in a tangential xy-direction. Both the parameters were measured by ECHO. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint and 'n' signifies subjects evaluable for the specified rows.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration) up to 6 Hours (end of IV infusion)

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	5	4
Units: Percentage systolic deformation				
arithmetic mean (standard deviation)				
LVGLS (n= 1, 1, 4, 4)	0.30 (± 99999)	-1.10 (± 99999)	1.10 (± 1.337)	-1.29 (± 0.987)
LVGCS (n= 1, 0, 5, 2)	-6.70 (± 99999)	99999 (± 99999)	0.05 (± 2.105)	0.00 (± 3.111)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in CI Measured by RHC at 0.5, 1, 2, 3, 4 and 5 Hours During 6 Hour IV Infusion

End point title	Part A: Change in CI Measured by RHC at 0.5, 1, 2, 3, 4 and 5 Hours During 6 Hour IV Infusion

End point description:

CI is a hemodynamic parameter that relates the CO from left ventricle in one minute to BSA, thus

relating heart performance to the body size of the subject. It was measured by RHC. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration), 0.5, 1, 2, 3, 4 and 5 hours of IV infusion

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Liter per minute per meter square				
arithmetic mean (standard deviation)				
0.5 hours	-0.05 (± 0.252)	0.27 (± 0.379)	0.10 (± 0.167)	-0.10 (± 0.183)
1 hour	0.35 (± 0.252)	0.27 (± 0.379)	0.06 (± 0.112)	0.05 (± 0.208)
2 hours	0.45 (± 0.370)	0.13 (± 0.058)	0.11 (± 0.104)	-0.08 (± 0.126)
3 hours	0.68 (± 0.427)	0.20 (± 0.265)	0.20 (± 0.279)	0.15 (± 0.129)
4 hours	0.25 (± 0.100)	0.10 (± 0.100)	0.09 (± 0.221)	0.10 (± 0.346)
5 hours	0.23 (± 0.457)	0.17 (± 0.153)	0.11 (± 0.274)	0.08 (± 0.096)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Cardiac Output (CO) Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point title	Part A: Change in Cardiac Output (CO) Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point description:

Change in CO measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 hours during the 6-hour IV infusion was reported in this outcome measure. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration), 0.5, 1, 2, 3, 4, 5 and 6 hours of IV infusion

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Liter per minute				
arithmetic mean (standard deviation)				

0.5 hours	-0.15 (± 0.420)	0.63 (± 0.777)	0.20 (± 0.329)	-0.15 (± 0.300)
1 hour	0.68 (± 0.457)	0.67 (± 0.907)	0.15 (± 0.230)	0.13 (± 0.340)
2 hours	0.90 (± 0.876)	0.43 (± 0.231)	0.21 (± 0.212)	-0.08 (± 0.189)
3 hours	1.28 (± 0.877)	0.47 (± 0.643)	0.41 (± 0.568)	0.33 (± 0.299)
4 hours	0.43 (± 0.222)	0.27 (± 0.231)	0.18 (± 0.467)	0.20 (± 0.560)
5 hours	0.43 (± 0.911)	0.43 (± 0.379)	0.25 (± 0.559)	0.15 (± 0.191)
6 hours	0.75 (± 1.420)	0.30 (± 0.346)	0.53 (± 0.742)	0.23 (± 0.499)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Pulmonary Capillary Wedge Pressure (PCWP), Right Atrial Pressure (RAP), Systolic Pulmonary Arterial Pressure/Diastolic Pulmonary Arterial Pressure (PAS/PAD) Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point title	Part A: Change in Pulmonary Capillary Wedge Pressure (PCWP), Right Atrial Pressure (RAP), Systolic Pulmonary Arterial Pressure/Diastolic Pulmonary Arterial Pressure (PAS/PAD) Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point description:

PCWP estimated the left atrial pressure and was the pressure measured by wedging a pulmonary artery catheter with an inflated balloon into a small pulmonary arterial branch. PCWP was assessed by 2 successive measurements at least 10 minutes apart. RAP is the blood pressure in the right atrium of the heart. Change in PCWP, RAP, PAS/PAD at 0.5, 1, 2, 3, 4, 5 and 6 hours during the 6-hour IV infusion was reported in this endpoint. All the parameters were measured by RHC. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration), 0.5, 1, 2, 3, 4, 5 and 6 hours of IV infusion

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Millimeters of mercury				
arithmetic mean (standard deviation)				
PCWP: 0.5 hours (n= 4, 3, 9, 3)	1.50 (± 2.887)	0.67 (± 3.055)	-0.78 (± 3.456)	-2.67 (± 4.726)
PCWP: 1 hour (n= 4, 3, 9, 3)	-0.25 (± 8.808)	-2.33 (± 4.041)	-2.00 (± 2.828)	-2.67 (± 8.145)
PCWP: 2 hours (n= 4, 3, 9, 3)	-1.50 (± 5.000)	-3.33 (± 1.528)	1.56 (± 3.609)	-0.67 (± 7.506)
PCWP: 3 hours (n= 4, 3, 9, 3)	-3.75 (± 3.594)	-0.33 (± 4.509)	-3.67 (± 3.464)	-3.67 (± 7.506)
PCWP: 4 hours (4, 3, 10, 3)	-2.75 (± 3.948)	-0.67 (± 5.033)	-2.90 (± 5.384)	-5.00 (± 9.165)

PCWP: 5 hours (n= 4, 3, 9, 3)	-0.50 (± 6.137)	-1.33 (± 6.110)	-1.56 (± 2.698)	-3.33 (± 9.018)
PCWP: 6 hours (n= 4, 3, 8, 3)	-0.75 (± 7.411)	-1.67 (± 5.686)	-1.25 (± 2.315)	-1.67 (± 9.504)
RAP: 0.5 hours (n= 4, 3, 10, 3)	0.50 (± 1.291)	0.00 (± 1.732)	1.40 (± 3.836)	-1.33 (± 2.517)
RAP: 1 hour (n= 4, 3, 10, 3)	2.50 (± 3.317)	0.33 (± 2.309)	0.00 (± 2.867)	3.33 (± 6.658)
RAP: 2 hours (n= 4, 3, 10, 3)	1.00 (± 0.816)	-1.00 (± 1.000)	1.00 (± 4.397)	2.67 (± 7.234)
RAP: 3 hours (n= 4, 3, 10, 3)	-0.25 (± 1.258)	0.33 (± 2.517)	0.40 (± 2.366)	3.33 (± 8.505)
RAP: 4 hours (n= 4, 3, 10, 3)	-0.75 (± 4.500)	-0.67 (± 1.155)	-0.20 (± 4.315)	4.00 (± 6.083)
RAP: 5 hours (n= 4, 3, 10, 3)	-1.50 (± 3.416)	-2.67 (± 1.155)	0.50 (± 4.301)	1.67 (± 8.327)
RAP: 6 hours (n= 3, 3, 10, 3)	-0.67 (± 4.041)	-1.67 (± 1.528)	-0.50 (± 5.233)	4.00 (± 8.660)
PAS: 0.5 hours (n= 4, 3, 10, 3)	1.50 (± 5.196)	-1.00 (± 2.646)	0.20 (± 6.033)	-0.67 (± 6.110)
PAS: 1 hour (n= 4, 3, 10, 3)	4.50 (± 9.147)	-0.67 (± 4.041)	-1.50 (± 4.859)	-0.67 (± 6.028)
PAS: 2 hours (n= 4, 3, 10, 3)	6.25 (± 4.717)	0.67 (± 0.577)	0.90 (± 6.740)	0.33 (± 4.933)
PAS: 3 hours (n= 4, 3, 10, 3)	7.25 (± 6.185)	1.67 (± 5.033)	-1.40 (± 9.383)	-3.33 (± 9.292)
PAS: 4 hours (n= 4, 3, 10, 3)	5.75 (± 13.525)	2.00 (± 4.359)	-1.70 (± 6.201)	-8.33 (± 15.631)
PAS: 5 hours (n= 4, 3, 10, 3)	6.00 (± 11.195)	5.00 (± 1.000)	-1.30 (± 6.945)	-1.33 (± 6.658)
PAS: 6 hours (n= 4, 3, 10, 3)	4.25 (± 9.179)	2.67 (± 2.309)	-0.90 (± 8.569)	-4.33 (± 9.609)
PAD: 0.5 hours (n= 4, 3, 10, 3)	-1.25 (± 3.500)	0.00 (± 0.000)	-1.00 (± 2.789)	0.33 (± 4.509)
PAD: 1 hour (n= 4, 3, 10, 3)	0.50 (± 2.646)	-1.33 (± 0.577)	-0.90 (± 3.872)	-1.67 (± 4.041)
PAD: 2 hours (n= 4, 3, 10, 3)	-0.25 (± 2.217)	-0.67 (± 2.517)	-0.70 (± 3.860)	-1.00 (± 3.000)
PAD: 3 hours (n= 4, 3, 10, 3)	-1.25 (± 4.193)	1.00 (± 2.646)	-3.60 (± 5.168)	0.00 (± 6.245)
PAD: 4 hours (n= 4, 3, 10, 3)	-3.50 (± 8.888)	1.33 (± 1.155)	-2.40 (± 4.061)	-3.00 (± 7.937)
PAD: 5 hours (n= 4, 3, 10, 3)	-2.50 (± 4.041)	1.00 (± 2.646)	-2.40 (± 3.688)	1.33 (± 5.033)
PAD: 6 hours (n= 4, 3, 10, 3)	-4.00 (± 5.831)	1.33 (± 3.215)	-1.80 (± 4.984)	0.67 (± 5.686)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Pulmonary Artery Pulsatility Index (PAPi) Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point title	Part A: Change in Pulmonary Artery Pulsatility Index (PAPi) Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point description:

PAPi is a hemodynamic parameter that is derived from right atrial and pulmonary artery pulse pressures. PAPi = (PAS − PAD)/right atrial pressure. Change in PAPi measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 hours during the 6-hour IV infusion was reported in this endpoint. Full analysis set included all

randomised subjects, irrespective of whether they received any study treatment. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration), 0.5, 1, 2, 3, 4, 5 and 6 hours of IV infusion

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Ratio				
arithmetic mean (standard deviation)				
PAPi: 0.5 hours (n= 4, 3, 10, 3)	0.28 (± 0.411)	-0.17 (± 0.833)	-0.11 (± 0.713)	0.37 (± 1.343)
PAPi: 1 hour (n= 4, 3, 10, 3)	-0.08 (± 0.562)	0.17 (± 0.306)	-0.21 (± 0.835)	-0.17 (± 0.603)
PAPi: 2 hours (n= 4, 3, 10, 3)	0.38 (± 0.435)	0.33 (± 0.058)	-0.14 (± 1.011)	0.20 (± 0.900)
PAPi: 3 hours (n= 4, 3, 10, 3)	0.65 (± 0.624)	0.43 (± 0.777)	0.03 (± 0.897)	-0.33 (± 0.611)
PAPi: 4 hours (n= 4, 3, 10, 3)	1.35 (± 1.838)	0.83 (± 1.834)	0.27 (± 1.203)	-1.03 (± 0.907)
PAPi: 5 hours (n= 4, 3, 10, 3)	0.95 (± 0.597)	2.33 (± 1.818)	-0.01 (± 0.872)	0.87 (± 2.639)
PAPi: 6 hour (n= 3, 3, 10, 3)	0.93 (± 0.929)	1.27 (± 0.929)	0.77 (± 2.470)	-0.90 (± 0.173)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Systemic Vascular Resistance Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point title	Part A: Change in Systemic Vascular Resistance Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point description:

Systemic vascular resistance is the amount of force exerted on circulating blood by the vasculature of the body. SVR was calculated as 80*(mean arterial pressure - mean venous pressure) divided by cardiac output. Change in SVR measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 hours during the 6-hour IV infusion was reported in this endpoint. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration), 0.5, 1, 2, 3, 4, 5 and 6 hours of IV infusion

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Millimeter of mercury*minute/milliliter				
arithmetic mean (standard deviation)				
SVR: 0.5 hours (n= 4, 3, 10, 3)	10.30 (± 74.776)	-71.27 (± 55.492)	-47.30 (± 139.874)	74.13 (± 198.427)
SVR: 1 hour (n= 4, 3, 10, 3)	-80.50 (± 57.295)	-86.30 (± 80.694)	16.71 (± 231.657)	-131.93 (± 91.886)
SVR: 2 hours (n= 4, 3, 10, 3)	-48.83 (± 71.811)	-46.23 (± 28.762)	-42.16 (± 205.772)	-49.40 (± 136.124)
SVR: 3 hours (n= 4, 3, 10, 3)	-67.63 (± 56.169)	-8.10 (± 102.327)	-101.20 (± 188.863)	-195.77 (± 101.041)
SVR: 4 hours (n= 4, 3, 10, 3)	-27.20 (± 104.351)	73.90 (± 136.245)	-33.91 (± 241.040)	-311.03 (± 145.094)
SVR: 5 hours (n= 4, 3, 10, 3)	21.10 (± 112.824)	132.63 (± 171.630)	-92.29 (± 94.834)	-110.57 (± 222.498)
SVR: 6 hours (n= 3, 3, 10, 3)	33.10 (± 106.652)	90.37 (± 137.576)	-70.00 (± 116.681)	-104.23 (± 90.537)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Systemic Vascular Resistance Index (SVRI) Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point title	Part A: Change in Systemic Vascular Resistance Index (SVRI) Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point description:

SVRI was calculated by dividing the difference between mean arterial pressure and central venous pressure by cardiac index and multiplying by 80. Change in SVRI measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 hours during the 6 hour IV infusion was reported in this endpoint. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration), 0.5, 1, 2, 3, 4, 5 and 6 hours of IV infusion

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Dynes*second*meter^2 per centimeter^5				
arithmetic mean (standard deviation)				
SVRI: 0.5 hours (n= 4, 3, 10, 3)	5.00 (± 157.514)	-171.20 (± 154.962)	-98.41 (± 270.327)	107.83 (± 428.022)
SVRI: 1 hour (n= 4, 3, 10, 3)	-156.58 (± 105.011)	-202.73 (± 185.527)	16.20 (± 404.144)	-289.57 (± 102.838)
SVRI: 2 hours (n= 4, 3, 10, 3)	-115.13 (± 165.795)	-85.30 (± 63.286)	-94.82 (± 407.893)	-64.77 (± 281.682)
SVRI: 3 hours (n= 4, 3, 10, 3)	-152.98 (± 108.934)	-42.57 (± 192.932)	-190.53 (± 315.500)	-403.47 (± 271.919)
SVRI: 4 hours (n= 4, 3, 10, 3)	-85.05 (± 224.198)	201.20 (± 357.587)	-31.66 (± 414.786)	-649.80 (± 360.988)
SVRI: 5 hours (n= 4, 3, 10, 3)	12.80 (± 208.554)	350.47 (± 458.646)	-172.77 (± 186.678)	-260.83 (± 484.601)
SVRI: 6 hours (n= 3, 3, 10, 3)	61.47 (± 205.227)	152.63 (± 171.695)	-94.08 (± 306.599)	-227.17 (± 126.337)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Pulmonary Vascular Resistance (PVR) Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point title	Part A: Change in Pulmonary Vascular Resistance (PVR) Measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point description:

PVR is the resistance against blood flow from the pulmonary artery to the left atrium. Change in PVR measured by RHC at 0.5, 1, 2, 3, 4, 5 and 6 hours during the 6 hour IV infusion was reported in this endpoint. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment. All subjects reported under 'Number of Subjects Analysed' contributed data to the table but may not have evaluable data for every row. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration), 0.5, 1, 2, 3, 4, 5 and 6 hours of IV infusion

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: dynes*second per centimeter^5				
arithmetic mean (standard deviation)				
PVR: 0.5 hours (n= 4, 3, 9, 3)	-28.98 (± 21.955)	-97.13 (± 134.474)	14.83 (± 115.974)	83.40 (± 80.442)

PVR: 1 hour (n= 4, 3, 9, 3)	5.80 (± 108.571)	-37.57 (± 102.284)	78.37 (± 235.884)	6.40 (± 115.783)
PVR: 2 hours (n= 4, 3, 9, 3)	37.68 (± 106.364)	46.43 (± 27.918)	-1.64 (± 290.121)	-0.10 (± 136.989)
PVR: 3 hours (n= 4, 3, 9, 3)	29.70 (± 99.607)	-11.60 (± 69.295)	36.04 (± 171.091)	18.13 (± 107.316)
PVR: 4 hours (n= 4, 3, 9, 3)	32.28 (± 190.279)	10.03 (± 72.673)	32.44 (± 191.341)	-44.03 (± 121.310)
PVR: 5 hours (n= 4, 3, 9, 3)	29.08 (± 163.825)	44.57 (± 38.099)	22.61 (± 195.626)	53.70 (± 211.590)
PVR: 6 hours (n= 4, 3, 8, 3)	2.70 (± 150.529)	54.57 (± 15.245)	38.10 (± 291.188)	19.53 (± 86.649)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point title	Part A: Change in Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP) and Mean Arterial Pressure (MAP) at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point description:

SBP, DBP and MAP were measured in a supine or seated position after subject had at least 5 minutes of rest. MAP is the average pressure of the blood circulating through a subject's arteries during the cardiac cycle. MAP was derived by using the following formula: DBP + 1/3(SBP-DBP). Full analysis set included all randomised subjects, irrespective of whether they received any study treatment.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration), 0.5, 1, 2, 3, 4, 5 and 6 hours of IV infusion

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Millimeters of mercury				
arithmetic mean (standard deviation)				
SBP: 0.5 hours	7.3 (± 10.21)	-11.0 (± 10.15)	-2.2 (± 11.47)	-0.5 (± 6.35)
SBP: 1 hour	6.8 (± 10.56)	-7.3 (± 1.53)	-3.8 (± 9.44)	-0.8 (± 6.18)
SBP: 2 hours	8.0 (± 14.54)	-6.3 (± 9.81)	-2.6 (± 11.21)	0.5 (± 6.14)
SBP: 3 hours	-1.0 (± 14.07)	-4.7 (± 7.77)	-3.9 (± 10.35)	-1.0 (± 10.30)
SBP: 4 hours	2.5 (± 15.11)	-2.7 (± 8.33)	-3.9 (± 9.66)	0.5 (± 14.93)
SBP: 5 hours	5.5 (± 14.82)	1.0 (± 12.12)	-8.3 (± 11.86)	1.5 (± 13.03)
SBP: 6 hours	9.8 (± 12.45)	-5.0 (± 6.00)	-1.4 (± 8.90)	-1.0 (± 12.57)
DBP: 0.5 hours	3.0 (± 16.06)	-6.7 (± 7.02)	-0.2 (± 4.92)	0.0 (± 4.24)
DBP: 1 hour	3.0 (± 14.85)	-4.0 (± 5.29)	-2.2 (± 5.74)	7.0 (± 18.20)
DBP: 2 hours	10.0 (± 16.12)	-7.0 (± 2.65)	0.0 (± 7.92)	-1.5 (± 5.92)
DBP: 3 hours	-4.0 (± 12.46)	-3.3 (± 5.13)	-4.8 (± 9.26)	-1.0 (± 7.79)

DBP: 4 hours	-2.8 (± 13.10)	0.3 (± 7.77)	-6.3 (± 5.76)	-1.0 (± 5.72)
DBP: 5 hours	-0.8 (± 13.67)	-2.0 (± 1.73)	-6.8 (± 6.52)	-1.0 (± 6.98)
DBP: 6 hours	1.3 (± 13.57)	1.3 (± 2.08)	-0.3 (± 6.87)	3.8 (± 7.93)
MAP: 0.5 hours	4.42 (± 13.723)	-8.11 (± 8.002)	-0.85 (± 4.994)	-0.17 (± 4.041)
MAP: 1 hour	4.25 (± 12.971)	-5.11 (± 3.097)	-2.73 (± 4.718)	4.42 (± 10.651)
MAP: 2 hours	9.33 (± 13.891)	-6.78 (± 4.623)	-0.88 (± 6.634)	-0.83 (± 5.828)
MAP: 3 hours	-3.00 (± 12.640)	-3.78 (± 5.274)	-4.52 (± 7.752)	-1.00 (± 8.551)
MAP: 4 hours	-1.00 (± 13.101)	-0.67 (± 6.960)	-5.48 (± 5.768)	-0.50 (± 8.131)
MAP: 5 hours	1.33 (± 13.570)	-1.00 (± 5.196)	-7.30 (± 5.742)	-0.17 (± 7.466)
MAP: 6 hours	4.08 (± 12.900)	-0.78 (± 1.388)	-0.64 (± 5.934)	2.17 (± 9.406)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Change in Heart Rate at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point title	Part A: Change in Heart Rate at 0.5, 1, 2, 3, 4, 5 and 6 Hours

End point description:

Heart rate was measured in a supine or seated position after subject had at least 5 minutes of rest. Full analysis set included all randomised subjects, irrespective of whether they received any study treatment.

End point type	Secondary

End point timeframe:

Baseline (within 2 hours prior to start of study treatment administration), 0.5, 1, 2, 3, 4, 5 and 6 hours of IV infusion

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Beats per minute				
arithmetic mean (standard deviation)				
0.5 hours	-8.8 (± 9.00)	-7.3 (± 12.66)	0.0 (± 5.93)	3.5 (± 9.11)
1 hour	-2.5 (± 2.65)	-3.3 (± 14.19)	-1.6 (± 4.86)	-9.0 (± 13.29)
2 hours	-2.3 (± 5.32)	-0.7 (± 9.07)	-1.5 (± 6.62)	-7.0 (± 13.49)
3 hours	2.0 (± 8.87)	0.0 (± 9.17)	-0.6 (± 8.31)	-5.3 (± 11.18)
4 hours	-0.5 (± 6.24)	0.3 (± 14.22)	-1.1 (± 5.80)	1.0 (± 20.02)
5 hours	-6.3 (± 6.08)	-1.7 (± 5.86)	-1.5 (± 5.77)	-5.0 (± 13.49)
6 hours	4.5 (± 9.00)	1.0 (± 5.57)	4.2 (± 9.22)	-1.5 (± 17.82)

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point title	Part A: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs)

End point description:

An AE was any untoward medical occurrence that did not necessarily have a causal relationship with study treatment. TEAEs were defined as those AEs with onset after start date/timepoint of study drug administration. Safety set included all randomised subjects who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

From start of study treatment on Day 1 up to Day 9

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 1- Placebo	Cohort 2- 0.5 mg/kg/hr APD418	Cohort 2- Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	3	11	4
Units: Subjects	1	1	3	1

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Area Under the Plasma Concentration Time Curve From Time Zero to Last Quantifiable Plasma Concentration (AUCLast) of APD418

End point title	Part A: Area Under the Plasma Concentration Time Curve From Time Zero to Last Quantifiable Plasma Concentration (AUCLast) of APD418[2]

End point description:

AUClast was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18 and 24 hours post infusion start

Notes:

[2] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Hours*nanogram per milliliter				
geometric mean (geometric coefficient of variation)	9410 (± 84.3)	9230 (± 164)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Area Under the Plasma Concentration Time Curve From Time Zero to 6 Hours (AUC[0-6]) of APD418

End point title	Part A: Area Under the Plasma Concentration Time Curve From Time Zero to 6 Hours (AUC[0-6]) of APD418[3]

End point description:

AUC [0-6] was reported in this endpoint. Pharmacokinetic (PK) set included all subjects in the safety set with at least 1 post-dose PK measurement.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6 hours post infusion start

Notes:

[3] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Hours*nanogram per milliliter				
geometric mean (geometric coefficient of variation)	6620 (± 68.7)	5970 (± 268)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Maximum Observed Plasma Concentration (Cmax) of APD418

End point title	Part A: Maximum Observed Plasma Concentration (Cmax) of APD418[4]

End point description:

Cmax of APD418 was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18 and 24 hours post infusion start

Notes:

[4] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)	1540 (± 88.8)	1480 (± 277)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Area Under the Plasma Concentration Time Curve From Time Zero up to Infinity (AUC[0-Infinity]) of APD418

End point title	Part A: Area Under the Plasma Concentration Time Curve From Time Zero up to Infinity (AUC[0-Infinity]) of APD418[5]

End point description:

AUC [0-infinity] was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18 and 24 hours post infusion start

Notes:

[5] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	9		
Units: Hours*nanogram per milliliter				
geometric mean (geometric coefficient of variation)	9660 (± 87.0)	13400 (± 34.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Time to Maximum Observed Plasma Concentration (Tmax) for APD418

End point title	Part A: Time to Maximum Observed Plasma Concentration (Tmax) for APD418[6]

End point description:

Tmax of APD418 was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18 and 24 hours post infusion start

Notes:

[6] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Hours				
median (full range (min-max))	5.42 (4.00 to 6.08)	5.00 (0.500 to 6.18)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Distributional Half-Life (t1/2a) for APD418

End point title	Part A: Distributional Half-Life (t1/2a) for APD418[7]

End point description:

Distributional t1/2 of APD418 was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18 and 24 hours post infusion start

Notes:

[7] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	9		
Units: Hours				
arithmetic mean (standard deviation)	0.579 (± 0.381)	0.381 (± 0.119)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Terminal Elimination Half-Life (t1/2) for APD418

End point title	Part A: Terminal Elimination Half-Life (t1/2) for APD418[8]

End point description:

Terminal t1/2 of APD418 was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18 and 24 hours post infusion start

Notes:

[8] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	9		
Units: Hours				
arithmetic mean (standard deviation)	5.26 (± 0.960)	5.26 (± 0.998)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Mean Residence Time From Time Zero to Time of Last Quantifiable Plasma Concentration (MRTlast) for APD418

End point title	Part A: Mean Residence Time From Time Zero to Time of Last Quantifiable Plasma Concentration (MRTlast) for APD418[9]

End point description:

MRTlast of APD418 was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18 and 24 hours post infusion start

Notes:

[9] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Hours				
geometric mean (geometric coefficient of variation)	2.44 (± 33.6)	2.54 (± 74.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Volume of Distribution at Steady State (Vdss) for APD418

End point title	Part A: Volume of Distribution at Steady State (Vdss) for APD418[10]

End point description:

Vdss of APD418 was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18 and 24 hours post infusion start

Notes:

[10] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	9		
Units: Liter				
geometric mean (geometric coefficient of variation)	27.7 (± 42.2)	46.0 (± 34.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Total Volume of Distribution Based on the Terminal Phase (Vdz) for APD418

End point title	Part A: Total Volume of Distribution Based on the Terminal Phase (Vdz) for APD418[11]

End point description:

Vdz of APD418 was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18 and 24 hours post infusion start

Notes:

[11] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	9		
Units: Liter				
geometric mean (geometric coefficient of variation)	68.6 (± 74.5)	133 (± 28.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Average Plasma Concentration During Dosing Interval (Cave) for ADP418

End point title	Part A: Average Plasma Concentration During Dosing Interval (Cave) for ADP418[12]

End point description:

Average plasma concentration calculated over the 6-hour infusion time was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6 hours post infusion start

Notes:

[12] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Nanogram per milliliter				
geometric mean (geometric coefficient of variation)	1100 (± 68.7)	996 (± 268)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Total Clearance (CL) for APD418

End point title	Part A: Total Clearance (CL) for APD418[13]

End point description:

IV CL of APD418 was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement. Here, 'Number of Subjects Analysed' signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 1, 2, 3, 4, 5, 6, 6.083, 6.167, 6.25, 6.5, 7, 8, 10, 18 and 24 hours post infusion start

Notes:

[13] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	9		
Units: Liter per hour				
geometric mean (geometric coefficient of variation)	9.16 (± 92.7)	17.8 (± 23.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part A: Renal Clearance (CLr) for ADP418

End point title	Part A: Renal Clearance (CLr) for ADP418[14]

End point description:

CLr for APD418 was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement.

End point type	Secondary

End point timeframe:

Pre-dose (0) to 24 hours post infusion start, collected over 0 to 6 hour, 6 to 10 hour and 10 to 24-hour intervals

Notes:

[14] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Liter per hour				
geometric mean (geometric coefficient of variation)	2.14 (± 55.3)	3.78 (± 54.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part A: Total Amount of Unchanged Drug Excreted in Urine Over the Collection Period (Amount Excreted [Ae])

End point title	Part A: Total Amount of Unchanged Drug Excreted in Urine Over the Collection Period (Amount Excreted [Ae])[15]

End point description:

Total amount of unchanged drug excreted in urine over the collection period was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement.

End point type	Other pre-specified

End point timeframe:

Pre-dose (0) to 24 hours post infusion start, collected over 0 to 6 hour, 6 to 10 hour and 10 to 24-hour intervals

Notes:

[15] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Milligrams				
geometric mean (geometric coefficient of variation)	20.1 (± 28.8)	48.5 (± 38.0)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part A: Amount of Unchanged Drug Excreted in Urine During Each Collection Interval From t1 to t2 (Aet1-t2)

End point title	Part A: Amount of Unchanged Drug Excreted in Urine During Each Collection Interval From t1 to t2 (Aet1-t2)[16]

End point description:

Amount of unchanged drug excreted in urine during each collection interval from t1 to t2 was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement.

End point type	Other pre-specified

End point timeframe:

Anytime between 0 to 6 hours, 6 to 10 hours and 10 to 24 hours post infusion start

Notes:

[16] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Milligrams				
geometric mean (geometric coefficient of variation)				
Ae 0-6	11.8 (± 26.7)	25.6 (± 56.9)		
Ae 6-10	4.47 (± 27.3)	7.68 (± 68.4)		
Ae 10-24	2.83 (± 136)	7.93 (± 172)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Part A: Fraction of Drug Excreted Unchanged (Fe) in Urine

End point title	Part A: Fraction of Drug Excreted Unchanged (Fe) in Urine[17]

End point description:

Fraction of drug excreted in urine was reported in this endpoint. PK set included all subjects in the safety set with at least 1 post-dose PK measurement.

End point type	Other pre-specified

End point timeframe:

Pre-dose (0) to 24 hours post infusion start, collected over 0 to 6 hour, 6 to 10 hour and 10 to 24-hour intervals

Notes:

[17] - 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 reporting statistics for the arms specified.

End point values	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- 0.5 mg/kg/hr APD418		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	11		
Units: Percentage of unchanged drug				
geometric mean (geometric coefficient of variation)	22.7 (± 31.2)	19.7 (± 39.8)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study treatment on Day 1 up to Day 9	
Adverse event reporting additional description:	
Safety set included all randomised subjects who received at least one dose of study treatment.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Cohort 1- 0.17 mg/kg/hr APD418
Reporting group description:	
Subjects were administered a single dose of 0.17 milligrams per kilogram per hour (mg/kg/hr) (total dose of 1 mg/kg) APD418 as an intravenous (IV) infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	
Reporting group title	Cohort 2- Placebo
Reporting group description:	
Subjects were administered a single dose of matching placebo as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	
Reporting group title	Cohort 2- 0.5 mg/kg/hr APD418
Reporting group description:	
Subjects were administered a single dose of 0.5 mg/kg/hr (total dose of 3mg/kg) APD418 as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	
Reporting group title	Cohort 1- Placebo
Reporting group description:	
Subjects were administered a single dose of matching placebo as an IV infusion over a duration of 6 hours on Day 1 (Dosing Period) followed by an 18 to 24-hour in-clinic observation period.	

Serious adverse events	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- Placebo	Cohort 2- 0.5 mg/kg/hr APD418
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 11 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 1- Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Cohort 1- 0.17 mg/kg/hr APD418	Cohort 2- Placebo	Cohort 2- 0.5 mg/kg/hr APD418
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	1 / 4 (25.00%)	3 / 11 (27.27%)
Investigations			
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Vascular disorders			
Vein rupture			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 11 (9.09%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 1- Placebo		
Total subjects affected by non-serious adverse events			

subjects affected / exposed	1 / 3 (33.33%)		
Investigations			
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Vein rupture			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Ventricular extrasystoles			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 3 (33.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2021	Updates to the exclusion criteria. Prolonged the screening period for Part A to 21 days prior to and including Day 1 (Days - 21 to 1).
19 October 2021	Updates to provide additional guidance for IV administration and interruption procedures, and selection and monitoring of the infusion site. For exclusion criteria, new criterion was added for conditions that in the opinion of the Investigator may have increased the risk of infusion site reactions (ISRs) and/or compromised subject assessment of the ISRs. Revised reasons in which the study must have been terminated and those that may have terminated the study for clarity. Added safety related criteria for stopping study treatment. Provided further clarification for dose escalation stopping criteria.
26 April 2022	Modified eligibility criteria that were not safety related. Added organic-anion-transporting polypeptide (OATP) genotype assessment to the exploratory objectives.

Notes:

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.

This study was terminated early due to a business decision that was not due to any safety concerns. The number of subjects was smaller than originally planned and only summary statistics were therefore generated for primary and secondary endpoints.

Notes: