



Clinical trial results:

Phase IIa study to evaluate the safety, pharmacokinetics, and pharmacodynamics of repeated administrations over 4 weeks of the hepcidin antagonist PRS-080#022-DP in anemic chronic kidney disease patients undergoing hemodialysis

Summary

EudraCT number	2016-004472-21
Trial protocol	DE CZ
Global end of trial date	20 March 2019

Results information

Result version number	v1 (current)
This version publication date	06 March 2020
First version publication date	06 March 2020

Trial information

Trial identification

Sponsor protocol code	PCS_03_16
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03325621
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pieris Pharmaceuticals GmbH
Sponsor organisation address	Lise-Meitner-Straße 30, Freising-Weihenstephan, Germany, 85354
Public contact	Project leader, Pieris Pharmaceuticals GmbH, +1 3479520110, bruns@pieris.com
Scientific contact	Project leader, Pieris Pharmaceuticals GmbH, +1 3479520110, bruns@pieris.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	20 March 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 March 2019
Global end of trial reached?	Yes
Global end of trial date	20 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine the safety and tolerability of five repeated intravenous administrations of PRS-080#022-DP at 4 and 8 mg/kg body weight (BW) in anemic stage 5 CKD patients requiring hemodialysis.

Protection of trial subjects:

Safety data were weekly reviewed by a drug safety monitoring board (DSMB) during the study. During the study, three DSMB meetings were performed to review safety, pharmacokinetic (PK) and pharmacodynamic (PD) data to recommend:

I) a continuation of patient enrollment in the 4 mg/kg BW cohort after the treatment of sentinel patients;

II) a dose escalation to 8 mg/kg BW after all patients in the 4 mg/kg BW cohort completed Day 18;

III) a continuation of patient enrollment in the 8 mg/kg BW cohort after the treatment of sentinel patients.

At the end of the study, a final evaluation of all safety, PD and PK data was performed by the DSMB.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 October 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	Czech Republic: 8
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	7
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male and post-menopausal female patients with an age of ≥ 18 years were recruited in two centers in Germany and three centers in the Czech Republic. The first patient signed the informed consent form on 17-Oct-2017 and the last patient on 05-Nov-2018.

Pre-assignment

Screening details:

24 patients were screened. 12 eligible patients were included in two cohorts of six patients. In each cohort, the first two patients were randomized in a 1:1 ratio and the remaining patients in a 3:1 ratio to active (4 mg/kg PRS-080#022-DP in cohort 1 and 8 mg/kg PRS-080#022-DP in cohort 2) or placebo treatment.

Period 1

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

Blinding implementation details:

Double-blinding in the study was ensured by identical infusion bags, labeling, and appearance of PRS-080#022-DP and placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

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:

Patients received five doses of placebo once a week over five weeks by slow intravenous infusion over 60 minutes using an infusion pump.

Arm title	4 mg/kg BW PRS-080#022-DP
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Arm description: -

Arm type	Experimental
Investigational medicinal product name	PRS-080#022-DP
Investigational medicinal product code	
Other name	Anticalin® protein targeting hepcidin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received five doses of 4 mg/kg BW PRS-080#022-DP once a week over five weeks by slow intravenous infusion over 60 minutes using an infusion pump.

Arm title	8 mg/kg BW PRS-080#022-DP
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Arm description: -

Arm type	Experimental
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Investigational medicinal product name	PRS-080#022-DP
Investigational medicinal product code	
Other name	Anticalin® protein targeting hepcidin
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received five doses of 8 mg/kg BW PRS-080#022-DP once a week over five weeks by slow intravenous infusion over 60 minutes using an infusion pump.

Number of subjects in period 1	Placebo	4 mg/kg BW PRS-080#022-DP	8 mg/kg BW PRS-080#022-DP
Started	4	4	4
Completed	4	4	3
Not completed	0	0	1
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	4 mg/kg BW PRS-080#022-DP
Reporting group description: -	
Reporting group title	8 mg/kg BW PRS-080#022-DP
Reporting group description: -	

Reporting group values	Placebo	4 mg/kg BW PRS-080#022-DP	8 mg/kg BW PRS-080#022-DP
Number of subjects	4	4	4
Age categorical Units: Subjects			
Adults (≥18 years)	4	4	4
Age continuous Units: years			
median	67.0	60.5	51.5
full range (min-max)	30 to 79	30 to 71	39 to 70
Gender categorical Units: Subjects			
Female	1	0	2
Male	3	4	2
Body weight Units: kilogram(s)			
median	76.3	72.5	71.0
full range (min-max)	68.7 to 76.5	57.2 to 81.5	55.0 to 87.1
Body mass index Units: kilogram(s)/square meter			
median	24.5	22.4	25.7
full range (min-max)	22.4 to 25.2	18.7 to 27.8	19.0 to 29.4

Reporting group values	Total		
Number of subjects	12		
Age categorical Units: Subjects			
Adults (≥18 years)	12		
Age continuous Units: years			
median	-		
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	3		
Male	9		
Body weight Units: kilogram(s)			
median			

full range (min-max)	-		
Body mass index			
Units: kilogram(s)/square meter			
median			
full range (min-max)	-		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	4 mg/kg BW PRS-080#022-DP
Reporting group description: -	
Reporting group title	8 mg/kg BW PRS-080#022-DP
Reporting group description: -	

Primary: Safety and tolerability

End point title	Safety and tolerability ^[1]
End point description: The safety and tolerability of repeated constant dose administrations of PRS-080#022-DP were evaluated by the assessment of adverse events (AEs), laboratory parameters (hematology, biochemistry, coagulation), vital signs, physical examination, and electrocardiogram (ECG) during the treatment period and follow-up.	
End point type	Primary
End point timeframe: From first study treatment (Day 0) until the end of the follow-up period (Day 112).	

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 analysis for this endpoint was done.

End point values	Placebo	4 mg/kg BW PRS-080#022- DP	8 mg/kg BW PRS-080#022- DP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	4	
Units: Subject(s)				
All treatment-emergent AEs (TEAEs)	4	4	4	
Study drug-related TEAEs	0	1	0	
Clinical laboratory abnormalities reported as TEAE	1	1	2	
Clinically significant (CS) changes in vital signs	0	0	0	
CS changes in ECG values	0	0	0	
CS changes in physical examination results	0	1	2	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic end point Cmax

End point title	Pharmacokinetic end point Cmax ^[2]
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End point description:

The maximum plasma concentration (Cmax) of total and free PRS-080#022-DP were directly obtained from the measured concentrations.

End point type	Secondary
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End point timeframe:

Blood samples were collected after dialysis immediately before study drug infusion and immediately after infusion end on Days 0, 7, 14, 21 and 28. Additional blood samples were taken before dialysis on Days 2, 9, 16, 18, 23, 30, 35, 42, 49, 56, 84 and 112

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: No pharmacokinetics of PRS-080#022-DP was done for placebo treated patients.

End point values	4 mg/kg BW PRS-080#022-DP	8 mg/kg BW PRS-080#022-DP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: microgram(s)/millilitre				
geometric mean (geometric coefficient of variation)				
total PRS-080#022-DP	119 (± 24.5)	317 (± 43.6)		
free PRS-080#022-DP	67.4 (± 51.6)	170 (± 57.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic end point Ctrough

End point title	Pharmacokinetic end point Ctrough ^[3]
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End point description:

The plasma concentration immediately before the drug infusion (Ctrough) was directly obtained from the measured concentrations.

End point type	Secondary
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End point timeframe:

Blood samples for Ctrough assessment were collected after dialysis immediately before study drug infusion on Days 7, 14, 21 and 28.

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: No pharmacokinetics of PRS-080#022-DP was done for placebo treated patients.

End point values	4 mg/kg BW PRS-080#022-DP	8 mg/kg BW PRS-080#022-DP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: microgram(s)/millilitre				
geometric mean (geometric coefficient of variation)				
Day 7 for total PRS-080#022-DP	18.9 (± 17.3)	45.1 (± 28.2)		
Day 7 for free PRS-080#022-DP	0.815 (± 24.5)	2.85 (± 22.1)		
Day 14 for total PRS-080#022-DP	30.7 (± 20.5)	64.7 (± 30.8)		

Day 14 for free PRS-080#022-DP	1.17 (\pm 32.6)	3.97 (\pm 22.9)		
Day 21 for total PRS-080#022-DP	37.3 (\pm 5.5)	93.2 (\pm 24.1)		
Day 21 for free PRS-080#022-DP	2.05 (\pm 23.3)	7.37 (\pm 83.8)		
Day 28 for total PRS-080#022-DP	44.5 (\pm 9.0)	114 (\pm 8.0)		
Day 28 for free PRS-080#022-DP	2.43 (\pm 7.3)	5.66 (\pm 30.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic end point tmax

End point title	Pharmacokinetic end point tmax ^[4]
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End point description:

The time of observed maximum concentration (tmax) for total and free PRS-080#022-DP were directly obtained from the measured plasma concentrations.

End point type	Secondary
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End point timeframe:

Blood samples were collected after dialysis immediately before study drug infusion and immediately after infusion end on Days 0, 7, 14, 21 and 28. Additional blood samples were taken before dialysis on Days 2, 9, 16, 18, 23, 30, 35, 42, 49, 56, 84 and 112

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: No pharmacokinetics of PRS-080#022-DP was done for placebo treated patients.

End point values	4 mg/kg BW PRS-080#022-DP	8 mg/kg BW PRS-080#022-DP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: hour				
median (full range (min-max))				
total PRS-080#022-DP	504.9 (1.0 to 672.9)	528.7 (337.8 to 672.7)		
free PRS-080#022-DP	504.4 (1.0 to 672.9)	528.9 (505.3 to 672.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic end point changes in plasma hepcidin levels from baseline

End point title	Pharmacodynamic end point changes in plasma hepcidin levels from baseline
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End point description:

End point type	Secondary
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End point timeframe:

Blood samples were collected before dialysis as well as immediately and two hours after infusion end on

Days 0, 7, 14, 21 and 28. Additional blood samples were taken before dialysis on Days 2, 4, 9, 11, 16, 18, 23, 30, 32, 35, 42, 49 and 56.

End point values	Placebo	4 mg/kg BW PRS-080#022- DP	8 mg/kg BW PRS-080#022- DP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4 ^[5]	4	3	
Units: nanomole(s)				
arithmetic mean (full range (min-max))				
Day 0 (infusion end)	-10.7 (-20.4 to -0.9)	-13.9 (-25.4 to -8.2)	-11.0 (-13.2 to -7.5)	
Day 0 (2 h after infusion end)	-2.8 (-15.6 to 20.2)	-13.7 (-25.4 to -8.2)	-10.6 (-12.5 to -7.1)	
Day 2 (before dialysis)	7.6 (-10.1 to 15.3)	59.7 (20.0 to 88.8)	27.9 (-2.0 to 76.0)	
Day 7 (before dialysis)	6.6 (-11.8 to 34.0)	30.1 (14.2 to 47.9)	83.4 (57.6 to 103.7)	
Day 7 (infusion end)	-6.3 (-21.5 to 14.5)	-11.2 (-23.5 to -6.9)	-5.0 (-9.1 to -2.9)	
Day 7 (2 h after infusion end)	-4.0 (-24.7 to 23.1)	-11.9 (-23.3 to -6.5)	-3.1 (-6.7 to -1.1)	
Day 9 (before dialysis)	0.1 (-8.4 to 9.0)	64.8 (12.4 to 130.6)	69.4 (11.3 to 165.8)	
Day 14 (before dialysis)	-4.8 (-26.1 to 9.3)	38.5 (22.6 to 50.5)	163.3 (135.5 to 201.7)	
Day 14 (infusion end)	-5.4 (-19.0 to 6.4)	-11.1 (-23.4 to -6.6)	-4.7 (-8.4 to 0.3)	
Day 14 (2 h after infusion end)	0.6 (-12.3 to 15.3)	-11.7 (-23.2 to -6.3)	-0.9 (-3.0 to 1.5)	
Day 16 (before dialysis)	-3.5 (-30.5 to 12.6)	71.6 (31.8 to 110.6)	121.2 (33.2 to 183.8)	
Day 21 (before dialysis)	-4.3 (-18.9 to 10.3)	51.4 (30.8 to 77.3)	162.0 (119.5 to 219.7)	
Day 21 (infusion end)	-9.6 (-25.6 to 3.6)	-10.6 (-23.5 to -3.31)	-3.6 (-9.2 to 2.8)	
Day 21 (2 h after infusion end)	-5.6 (-21.4 to 12.6)	-9.7 (-24.0 to -1.2)	9.3 (-8.1 to 26.5)	
Day 23 (before dialysis)	0.5 (-27.4 to 16.7)	122.9 (94.8 to 142.2)	79.4 (34.3 to 149.8)	
Day 28 (before dialysis)	-7.0 (-28.1 to 2.0)	47.5 (42.5 to 54.0)	193.3 (115.5 to 315.7)	
Day 28 (infusion end)	-14.6 (-30.2 to -2.8)	-10.6 (-23.2 to -5.4)	5.4 (-7.4 to 22.2)	
Day 28 (2 h after infusion end)	-8.8 (-28.0 to 9.8)	-11.1 (-21.6 to -6.9)	0.4 (-6.5 to 14.0)	
Day 30 (before dialysis)	-4.2 (-20.7 to 8.4)	83.0 (43.5 to 103.8)	40.6 (16.3 to 62.0)	
Day 35 (before dialysis)	-5.8 (-27.3 to 8.6)	55.0 (36.0 to 100.8)	160.7 (148.8 to 180.7)	
Day 42 (before dialysis)	-6.1 (-26.1 to 11.2)	27.2 (19.9 to 40.9)	97.7 (92.7 to 104.8)	
Day 49 (before dialysis)	-4.8 (-27.6 to 10.3)	19.0 (3.1 to 48.1)	73.9 (40.5 to 111.8)	
Day 56 (before dialysis)	-1.9 (-17.3 to 6.9)	8.1 (-1.6 to 13.2)	31.4 (22.4 to 41.7)	

Notes:

[5] - N=3 on Day 14 (infusion end and 2 h after infusion end) and Day 42

Attachments (see zip file)	Hepcidin plasma levels – Mean change from baseline/Figure
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Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic end point AUC of serum iron

End point title	Pharmacodynamic end point AUC of serum iron
End point description: The area under the curve (AUC) _{0-t} (t = Days 7, 28, and 35) was calculated relative to the baseline value using the linear trapezoidal rule.	
End point type	Secondary
End point timeframe: Blood samples were collected before dialysis and two hours after infusion end on Days 0, 7, 14, 21 and 28. Additional blood samples were taken before dialysis on Days 2, 4, 9, 11, 16, 18, 23, 30, 32, 35, 42, 49 and 56.	

End point values	Placebo	4 mg/kg BW PRS-080#022- DP	8 mg/kg BW PRS-080#022- DP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	3	
Units: h*µmol/L				
arithmetic mean (full range (min-max))				
AUC ₀ -Day 7	1302 (1152 to 1422)	3677 (2147 to 4703)	4219 (3571 to 5413)	
AUC ₀ -Day 28	6866 (6205 to 8537)	14625 (10443 to 17595)	16360 (12328 to 21331)	
AUC ₀ -Day 35	8514 (7407 to 10844)	18247 (12342 to 22379)	20519 (16050 to 26446)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic end point AUC of transferrin saturation in serum

End point title	Pharmacodynamic end point AUC of transferrin saturation in serum
End point description: The area under the curve (AUC) _{0-t} (t = Days 7, 28, and 35) was calculated relative to the baseline value using the linear trapezoidal rule.	
End point type	Secondary

End point timeframe:

Blood samples were collected before dialysis and two hours after infusion end on Days 0, 7, 14, 21 and 28. Additional blood samples were taken before dialysis on Days 2, 4, 9, 11, 16, 18, 23, 30, 32, 35, 42, 49 and 56.

End point values	Placebo	4 mg/kg BW PRS-080#022- DP	8 mg/kg BW PRS-080#022- DP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4	4	3	
Units: h*% arithmetic mean (full range (min-max))				
AUC0-Day 7	3242 (2280 to 3695)	6956 (3936 to 8832)	8130 (7461 to 9355)	
AUC0-Day 28	16952 (12588 to 23004)	28833 (20412 to 36254)	32495 (27879 to 35865)	
AUC0-Day 35	20974 (15842 to 29303)	36189 (24767 to 46152)	41252 (37492 to 44555)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From before dialysis at day of first study treatment (Day 0) to the end of the follow-up period (Day 112)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo once weekly intravenous over 5 weeks

Reporting group title	4 mg/kg BW PRS-080#022-DP
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Reporting group description:

4 mg/kg BW PRS-080#022-DP once weekly intravenous over 5 weeks

Reporting group title	8 mg/kg BW PRS-080#022-DP
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Reporting group description:

8 mg/kg BW PRS-080#022-DP once weekly intravenous over 5 weeks

Serious adverse events	Placebo	4 mg/kg BW PRS-080#022-DP	8 mg/kg BW PRS-080#022-DP
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma	Additional description: Event was considered not related to study medication.		
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension	Additional description: Event was considered not related to study medication.		
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Migraine	Additional description: Event was considered not related to study medication.		

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Inguinal hernia	Additional description: Event was considered not related to study medication.		
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Malnutrition	Additional description: Event was considered not related to study medication.		
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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	4 mg/kg BW PRS-080#022-DP	8 mg/kg BW PRS-080#022-DP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 4 (100.00%)	4 / 4 (100.00%)	4 / 4 (100.00%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 4 (25.00%)	2 / 4 (50.00%)	0 / 4 (0.00%)
occurrences (all)	6	2	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Oedema peripheral			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	4	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Dyspnoea			

subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 3	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Nasal congestion subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Investigations Body temperature increased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 3	0 / 4 (0.00%) 0
Haemoglobin decreased subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Injury, poisoning and procedural complications Laceration subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Post procedural haemorrhage subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Procedural hypotension subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 6	2 / 4 (50.00%) 5	0 / 4 (0.00%) 0
Procedural pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Cardiac disorders Pericardial effusion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Sinus tachycardia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1

Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Phantom pain			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Restless legs syndrome			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 4 (0.00%)	1 / 4 (25.00%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Colitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Diarrhoea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Nausea			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Vomiting subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	2 / 4 (50.00%) 4
Skin and subcutaneous tissue disorders			
Decubitus ulcer subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Pruritus generalised subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Renal and urinary disorders			
Bladder hypertrophy subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1
Renal pain subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Musculoskeletal and connective tissue disorders			
Muscle spasms subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	3 / 4 (75.00%) 16	2 / 4 (50.00%) 4
Pain in extremity subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Infections and infestations			
Conjunctivitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0
Localised infection subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 4 (0.00%) 0	0 / 4 (0.00%) 0
Nasopharyngitis			

subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pharyngitis			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Pneumonia			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Respiratory tract infection			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 4 (0.00%)	0 / 4 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Fluid overload			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hyperkalaemia			
subjects affected / exposed	1 / 4 (25.00%)	0 / 4 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hyperphosphataemia			
subjects affected / exposed	0 / 4 (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? Yes

Date	Amendment
06 December 2017	Changes to v1.1: I) Time window to be on stable erythropoiesis-stimulating agent (ESA) dose before Screening was changed to 'at the beginning of Screening' (Inclusion Criterion 3); II) Time window to be on stable oral or intravenous iron doses before Screening was changed to 'at the beginning of Screening' (Inclusion Criterion 4). Additionally, it was specified, that iron was to be kept stable for a minimum of two weeks during the screening period before it was discontinued one week before the first treatment until Day 56 (one month follow-up); III) Inclusion Criterion serum ferritin concentration was changed to ≥ 200 ng/mL; IV) Screening serum folate and vitamin B12 below the lower limit of normal were allowed if the abnormal values were judged to be not clinically significant by the investigator; V) It was specified that glucose was no longer assessed as biochemistry parameter; VI) Body weight (BW) was to be assessed after dialysis at the day of the third hemoglobin (Hb) sample taken.
29 March 2018	Changes to v2.0: I) It was specified that slow pharmacodynamic (PD) parameters (Hb, reticulocyte count, reticulocyte hemoglobin) will be additionally assessed at Visits 3, 5, 8 and 10 (Days 7, 14, 21 and 28) before dialysis to ensure a better comparability to the pre-treatment samples which were taken before dialysis and to exclude a dialysis effect.
20 September 2018	Changes to v2.0 and Amendment No.1: I) Additional visits (i.e. at Days 4, 11, 25, and 32) and additional blood collections (i.e. at visit Day 18) to assess slow and fast PD and hepcidin were added; II) Additional blood collections to assess slow PD parameters at visits Day 2, 9, 16, and 23 added; III) History of malignancy was added as an exclusion criterion, recommended by the DSMB; IV) Sample size was increased to 13 patients. However, the planned unblinded assignment (placebo or study drug) of a 13th patient to cohort 2 (8 mg/kg BW) by the sponsor was not performed due to insufficient amount of the PRS-080#02-DP. Therefore, the study was terminated after 12 patients had completed the study.

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.

Two patients were treated with a one week delay due to investigation and resolution of particles detected while preparing infusion bags.

Notes: