Clinical trial results:
A 29-day, randomized, double-blinded, placebo-controlled, parallel-group, multi-center study to evaluate the efficacy, safety and pharmacokinetics of three-times weekly dosing of GSK1278863 in hemodialysis-dependent subjects with anemia associated with chronic kidney disease who are switched from a stable dose of an erythropoiesis-stimulating agent.

Summary

EudraCT number	2015-004790-32
Trial protocol	ES DE
Global end of trial date	25 January 2017

Results information

Result version number	v1
This version publication date	27 January 2018
First version publication date	27 January 2018

Trial information

Trial identification

Sponsor protocol code	204836

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Characterize the dose-response relationship between GSK1278863 administered three-times weekly and hemoglobin (Hgb) at Day 29.

Protection of trial subjects:

The protocol included stopping criteria for hemoglobin (including limits for both increases and decreases) for the participants' safety

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 February 2016
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	Spain: 28
Country: Number of subjects enrolled	United States: 47
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Germany: 4
Worldwide total number of subjects	103
EEA total number of subjects	32

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)	53
From 65 to 84 years	45

85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Participants on Hemodialysis (HD) with anemia associated with chronic kidney disease (CKD) switching from Erythropoiesis-Stimulating Agent (ESA) treatment were recruited in this randomized, dose-ranging study. Participants with hemoglobin (Hgb) values between 9.0- 11.5 grams per deciliter (g/dL) were considered as eligible for recruitment.

Pre-assignment

Screening details:

A total of 211 participants were screened; of which 108 were screen failures and 103 were randomized to receive at least one dose of either placebo or 10, 15, 25 or 30 milligrams (mg) of daprodustat (dapro). One participant, who was randomized to the placebo group, erroneously received 25 mg dapro treatment throughout the 29-day treatment period.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Randomized participants received placebo tablet via oral route three times weekly for 29 days.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets will be available as round, biconvex, white film coated tablets. Placebo tablets were administered three times weekly for 29 days via oral route.

Arm title	Dapro 10 mg

Arm description:

Randomized participants received dapro 10 mg tablet via oral route three times weekly for 29 days.

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

Dosage and administration details:

Daprodustat tablets will be available as round, biconvex, white film coated tablets. Daprodustat tablets were administered three times weekly for 29 days via oral route.

Arm title	Dapro 15 mg

Arm description:

Randomized participants received dapro 15 mg tablet via oral route three times weekly for 29 days.

Arm type	Experimental

Investigational medicinal product name	Daprodustat
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Daprodustat tablets will be available as round, biconvex, white film coated tablets. Daprodustat tablets were administered three times weekly for 29 days via oral route.

Arm title	Dapro 25 mg

Arm description:

Randomized participants received dapro 25 mg tablet via oral route three times weekly for 29 days.

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

Dosage and administration details:

Daprodustat tablets will be available as round, biconvex, white film coated tablets. Daprodustat tablets were administered three times weekly for 29 days via oral route.

Arm title	Dapro 30 mg

Arm description:

Randomized participants received dapro 30 mg tablet via oral route three times weekly for 29 days

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

Dosage and administration details:

Daprodustat tablets will be available as round, biconvex, white film coated tablets. Daprodustat tablets were administered three times weekly for 29 days via oral route.

Number of subjects in period 1	Placebo	Dapro 10 mg	Dapro 15 mg
Started	20	20	20
Completed	17	19	16
Not completed	3	1	4
Physician decision	1	-	-
Consent withdrawn by subject	1	-	1
Other: Reached stopping criteria	-	1	2
Adverse event, non-fatal	-	-	1
Protocol deviation	1	-	-

Number of subjects in period 1	Dapro 25 mg	Dapro 30 mg
Started	21	22

Completed	17	14
Not completed	4	8
Physician decision	-	-
Consent withdrawn by subject	-	-
Other: Reached stopping criteria	3	4
Adverse event, non-fatal	-	2
Protocol deviation	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Randomized participants received placebo tablet via oral route three times weekly for 29 days.	
Reporting group title	Dapro 10 mg
Reporting group description:	
Randomized participants received dapro 10 mg tablet via oral route three times weekly for 29 days.	
Reporting group title	Dapro 15 mg
Reporting group description:	
Randomized participants received dapro 15 mg tablet via oral route three times weekly for 29 days.	
Reporting group title	Dapro 25 mg
Reporting group description:	
Randomized participants received dapro 25 mg tablet via oral route three times weekly for 29 days.	
Reporting group title	Dapro 30 mg
Reporting group description:	
Randomized participants received dapro 30 mg tablet via oral route three times weekly for 29 days	

Reporting group values	Placebo	Dapro 10 mg	Dapro 15 mg
Number of subjects	20	20	20
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	61.0	63.6	59.5
standard deviation	± 13.06	± 16.98	± 12.26
Gender categorical Units: Subjects			
Female	11	8	6
Male	9	12	14
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	6	6	7
American Indian Or Alaskan Native	0	1	0
Asian - Central/South Asian Heritage	0	1	1
Native Hawaiian Or Other Pacific Islander	0	0	0
White- Arabic/North African Heritage	0	0	0
White-White/Caucasian/European Heritage	14	12	12

Reporting group values	Dapro 25 mg	Dapro 30 mg	Total
Number of subjects	21	22	103

Age categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	67.2	65.4	
standard deviation	± 15.22	± 13.97	-
Gender categorical Units: Subjects			
Female	9	8	42
Male	12	14	61
Race/Ethnicity, Customized Units: Subjects			
African American/African Heritage	5	6	30
American Indian Or Alaskan Native	0	1	2
Asian - Central/South Asian Heritage	0	0	2
Native Hawaiian Or Other Pacific Islander	1	0	1
White- Arabic/North African Heritage	1	0	1
White-White/Caucasian/European Heritage	14	15	67

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Randomized participants received placebo tablet via oral route three times weekly for 29 days.	
Reporting group title	Dapro 10 mg
Reporting group description:	
Randomized participants received dapro 10 mg tablet via oral route three times weekly for 29 days.	
Reporting group title	Dapro 15 mg
Reporting group description:	
Randomized participants received dapro 15 mg tablet via oral route three times weekly for 29 days.	
Reporting group title	Dapro 25 mg
Reporting group description:	
Randomized participants received dapro 25 mg tablet via oral route three times weekly for 29 days.	
Reporting group title	Dapro 30 mg
Reporting group description:	
Randomized participants received dapro 30 mg tablet via oral route three times weekly for 29 days	
Subject analysis set title	Dapro 25 mg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Randomized participants received dapro 25 mg tablet via oral route three times weekly for 29 days.	

Primary: Change from Baseline in Hgb levels at Day 29

End point title	Change from Baseline in Hgb levels at Day 29
End point description:	
Blood samples were collected from participants for measurement of Hgb values. Baseline is the average of Hgb measured at Week -2 and Day 1 visits. Change from Baseline at Day 29 was defined as post dose value at Day 29 minus Baseline value. The analysis was performed on intent-to-treat (ITT) Population which comprised of all randomized participants who received at least one dose of study treatment, had a Baseline and at least one corresponding on treatment assessment, including Hgb.	
End point type	Primary
End point timeframe:	
Baseline and Day 29	

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17[1]	19[2]	16[3]	17[4]
Units: g/dL				
arithmetic mean (standard deviation)				
Category title 1	-0.61 (± 0.646)	-0.19 (± 1.750)	-0.13 (± 1.088)	0.64 (± 1.453)

Notes:

[1] - ITT Population

[2] - ITT Population

[3] - ITT Population

[4] - ITT Population

End point values	Dapro 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	15[5]			
Units: g/dL				
arithmetic mean (standard deviation)				
Category title 1	0.55 (± 1.167)			

Notes:

[5] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Analysis using a Repeated Measures Model with terms included for baseline, treatment, time and treatment*time. Model-adjusted treatment difference of dapro 10 mg arm from Placebo along with 95 percent CI are presented.

Comparison groups	Dapro 10 mg v Placebo
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.31
upper limit	1.45

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Analysis using a Repeated Measures Model with terms included for baseline, treatment, time and treatment*time. Model-adjusted treatment difference of dapro 15 mg arm from Placebo along with 95 percent CI are presented.

Comparison groups	Dapro 15 mg v Placebo
Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	1.42

Statistical analysis title	Statistical analysis 3

Statistical analysis description:

Analysis using a Repeated Measures Model with terms included for baseline, treatment, time and treatment*time. Model-adjusted treatment difference of dapro 25 mg arm from Placebo along with 95 percent CI are presented.

Comparison groups	Placebo v Dapro 25 mg
Number of subjects included in analysis	34
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.35

Statistical analysis title	Statistical analysis 4

Statistical analysis description:

Analysis using a Repeated Measures Model with terms included for baseline, treatment, time and treatment*time. Model-adjusted treatment difference of dapro 30 mg arm from Placebo along with 95 percent CI are presented.

Comparison groups	Placebo v Dapro 30 mg
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	2.57

Secondary: Maximum observed change from Baseline in plasma erythropoietin (EPO)

End point title	Maximum observed change from Baseline in plasma erythropoietin (EPO)

End point description:

Blood samples were collected at Day 1, Day 15 and Day 29 for pharmacodynamic analysis of effect of dapro three times weekly dose regimens on EPO. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. The change from Baseline at each given post-Baseline time point was calculated and the maximum change from Baseline was determined.

End point type	Secondary

End point timeframe:

Baseline and up to Day 29

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[6]	20[7]	18[8]	21[9]
Units: International unit per liter (IU/L)				
arithmetic mean (standard deviation)				
Category title 1	53.761 (± 132.6875)	2.255 (± 84.8921)	73.369 (± 95.9772)	302.529 (± 469.8312)

Notes:

[6] - ITT Population

[7] - ITT Population

[8] - ITT Population

[9] - ITT Population

End point values	Dapro 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	20[10]			
Units: International unit per liter (IU/L)				
arithmetic mean (standard deviation)				
Category title 1	477.644 (± 388.9757)			

Notes:

[10] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed percent change from Baseline in Vascular Endothelial Growth Factor (VEGF)

End point title	Maximum observed percent change from Baseline in Vascular Endothelial Growth Factor (VEGF)

End point description:

Blood samples were collected at Day 1, Day 15 and Day 29 for pharmacodynamic analysis of effect of dapro three times weekly dose regimens on VEGF. Day 1 values were considered as Baseline values. The percent change from Baseline at each given post-Baseline time point was calculated (expressed as geometric mean) and the maximum percent change from Baseline was determined.

End point type	Secondary

End point timeframe:

Baseline and up to Day 29

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[11]	20[12]	18[13]	21[14]
Units: Nanograms per liter (ng/L)				
geometric mean (confidence interval 95%)				
Category title 1	20.35 (-0.48 to 45.55)	43.75 (16.44 to 77.45)	32.16 (-4.77 to 83.41)	53.34 (17.17 to 100.68)

Notes:

[11] - ITT Population

[12] - ITT Population

[13] - ITT Population

[14] - ITT Population

End point values	Dapro 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	20[15]			
Units: Nanograms per liter (ng/L)				
geometric mean (confidence interval 95%)				
Category title 1	76.09 (34.89 to 129.88)			

Notes:

[15] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from Baseline in hepcidin at Day 29

End point title	Percent change from Baseline in hepcidin at Day 29

End point description:

Blood samples were collected at Day 1, Day 15 and Day 29 for pharmacodynamic analysis of effect of dapro three times weekly dose regimens on hepcidin. Day 1 values were considered as Baseline values. The Percent change from Baseline at Day 29 post-Baseline time point was calculated and expressed as geometric mean and the maximum change from Baseline was determined.

End point type	Secondary

End point timeframe:

Baseline and Day 29

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17[16]	19[17]	15[18]	17[19]
Units: Micrograms per liter (µg/L)				
geometric mean (confidence interval 95%)				
Category title 1	27.81 (-12.68 to 87.08)	35.37 (-1.13 to 85.34)	3.83 (-17.85 to 31.24)	-36.74 (-49.91 to -20.12)

Notes:

[16] - ITT Population

[17] - ITT Population

[18] - ITT Population

[19] - ITT Population

End point values	Dapro 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	15[20]			
Units: Micrograms per liter (µg/L)				
geometric mean (confidence interval 95%)				
Category title 1	-36.09 (-57.24 to -4.48)			

Notes:

[20] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in hematocrit levels

End point title	Change from Baseline in hematocrit levels

End point description:

Blood samples were collected at Day 1, Day 15 and Day 29 for pharmacodynamic analysis of effect Dapro three times weekly dose regimens on hematocrit. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-dose visit values minus Baseline value. The change from Baseline at Day 29 post-Baseline time point was calculated.

End point type	Secondary

End point timeframe:

Baseline and Day 29

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[21]	19[22]	14[23]	16[24]
Units: Proportion of red blood cells in blood				
arithmetic mean (standard deviation)				
Category title 1	-0.0218 (± 0.02469)	-0.0127 (± 0.05396)	-0.0149 (± 0.05379)	0.0150 (± 0.04511)

Notes:

[21] - ITT Population

[22] - ITT Population

[23] - ITT Population

[24] - ITT Population

End point values	Dapro 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	15[25]			
Units: Proportion of red blood cells in				

blood				
arithmetic mean (standard deviation)				
Category title 1	0.0215 (± 0.03852)			

Notes:

[25] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in red blood cell (RBC) count

End point title	Change from Baseline in red blood cell (RBC) count

End point description:

Blood samples were collected at Day 1, Day 15 and Day 29 for pharmacodynamic analysis of effect Dapro three times weekly dose regimens on RBC count. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-dose visit values minus Baseline value. The change from Baseline at Day 29 post-Baseline time point was calculated.

End point type	Secondary

End point timeframe:

Baseline and Day 29

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[26]	19[27]	14[28]	16[29]
Units: 10^12/L				
arithmetic mean (standard deviation)				
Category title 1	-0.19 (± 0.263)	-0.12 (± 0.494)	-0.13 (± 0.500)	0.12 (± 0.420)

Notes:

[26] - ITT Population

[27] - ITT Population

[28] - ITT Population

[29] - ITT Population

End point values	Dapro 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	15[30]			
Units: 10^12/L				
arithmetic mean (standard deviation)				
Category title 1	0.15 (± 0.342)			

Notes:

[30] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in reticulocyte count

End point title	Change from Baseline in reticulocyte count

End point description:

Blood samples were collected at Day 1, Day 15 and Day 29 for pharmacodynamic analysis of effect Dapro three times weekly dose regimens on reticulocyte count. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. The change from Baseline at Day 29 post-Baseline time point was calculated.

End point type	Secondary

End point timeframe:

Baseline and Day 29

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[31]	18[32]	14[33]	16[34]
Units: Percentage of reticulocyte				
arithmetic mean (standard deviation)				
Category title 1	-0.08 (± 0.848)	-0.11 (± 0.803)	-0.04 (± 0.581)	0.43 (± 0.547)

Notes:

[31] - ITT Population

[32] - ITT Population

[33] - ITT Population

[34] - ITT Population

End point values	Dapro 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	15[35]			
Units: Percentage of reticulocyte				
arithmetic mean (standard deviation)				
Category title 1	0.09 (± 0.695)			

Notes:

[35] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in reticulocyte hemoglobin (CHr)

End point title	Change from Baseline in reticulocyte hemoglobin (CHr)

End point description:

Blood samples were collected at Day 1, Day 15 and Day 29 for pharmacodynamic analysis of effect Dapro three times weekly dose regimens on CHr. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. The change from Baseline at Day 29 post-Baseline time point was calculated.

End point type	Secondary

End point timeframe:

Baseline and Day 29

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[36]	19[37]	14[38]	16[39]
Units: Picograms (pg)				
arithmetic mean (standard deviation)				
Category title 1	-0.15 (± 1.375)	0.23 (± 1.335)	0.26 (± 1.103)	0.23 (± 1.040)

Notes:

[36] - ITT Population

[37] - ITT Population

[38] - ITT Population

[39] - ITT Population

End point values	Dapro 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	15[40]			
Units: Picograms (pg)				
arithmetic mean (standard deviation)				
Category title 1	0.59 (± 1.436)			

Notes:

[40] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the curve (AUC) from time zero to the time of the last quantifiable concentration (AUC[0-t]) and AUC from time zero to infinity (AUC[0-inf]) of Dapro

End point title	Area under the curve (AUC) from time zero to the time of the last quantifiable concentration (AUC[0-t]) and AUC from time zero to infinity (AUC[0-inf]) of Dapro[41]

End point description:

Blood samples were collected at indicated time points for pharmacokinetic (PK) analysis of dapro. The data from each PK sampling day was combined to generate a single profile, and normalized to a 24-hour period to create a "Day 1" profile for non-compartmental analysis (NCA). Metabolite plasma concentrations were analyzed but PK parameters could not be calculated as the metabolites were partially eliminated through dialysis and the dialysis start and end times were not consistent on both PK days. Therefore, a representative metabolite PK profile could not be generated. The analysis was performed on PK Population, which comprised of all participants from whom a PK sample has been obtained and analyzed. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Pre-dose on Day 1; 6-10 hours, 7-11 hours, 8-12 hours, 9-13 hours post dose on Day 15; pre-dose and 1, 2, 3 hours post-dose on Day 29

Notes:

[41] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	20[42]	20[43]	22[44]	22[45]
Units: hour into nanograms/milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)				
AUC (0-t); n= 19, 15, 14,16	311.7 (± 91.4)	416.7 (± 168.6)	1010 (± 92.3)	513.9 (± 396.1)
AUC (0-inf); n= 12, 9, 11, 8	348.2 (± 78.2)	383.5 (± 142.7)	1369 (± 59.3)	1214 (± 41.6)

Notes:

[42] - PK Population

[43] - PK Population

[44] - PK Population

[45] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed concentration of dapro in plasma (Cmax)

End point title	Maximum observed concentration of dapro in plasma

End point description:

Blood samples were collected at indicated time points for PK analysis of dapro. The data from each PK sampling day was combined to generate a single profile, and normalized to a 24-hour period to create a "Day 1" profile for NCA. Metabolite plasma concentrations were analyzed but PK parameters could not be calculated as the metabolites were partially eliminated through dialysis and the dialysis start and end times were not consistent on both PK days. Therefore, a representative metabolite PK profile could not be generated.

End point type	Secondary

End point timeframe:

Pre-dose on Day 1; 6-10 hours, 7-11 hours, 8-12 hours, 9-13 hours post dose on Day 15; pre-dose and 1, 2, 3 hours post-dose on Day 29

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Dapro 10 mg	Dapro 15 mg	Dapro 25 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[47]	15[48]	16[49]	14[50]
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Category title 1	140.0 (± 104.0)	141.4 (± 248.8)	246.9 (± 311.5)	387.3 (± 99.4)

Notes:

[47] - PK Population

[48] - PK Population

[49] - PK Population

[50] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach Cmax (Tmax) and Apparent terminal half-life (t1/2) of dapro

End point title	Time to reach Cmax (Tmax) and Apparent terminal half-life (t1/2) of dapro[51]

End point description:

Blood samples were collected at indicated time points for PK analysis of dapro. The data from each PK sampling day was combined to generate a single profile, and normalized to a 24-hour period to create a "Day 1" profile for NCA. Metabolite plasma concentrations were analyzed but PK parameters could not be calculated as the metabolites were partially eliminated through dialysis and the dialysis start and end times were not consistent on both PK days. Therefore, a representative metabolite PK profile could not be generated. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Pre-dose on Day 1; 6-10 hours, 7-11 hours, 8-12 hours, 9-13 hours post dose on Day 15; pre-dose and 1, 2, 3 hours post-dose on Day 29

Notes:

[51] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	20[52]	20[53]	22[54]	22[55]
Units: Hour				
geometric mean (geometric coefficient of variation)				
Tmax; n= 19, 15, 14, 16	2.456 (± 78.9)	2.106 (± 82.1)	1.718 (± 58.0)	2.297 (± 96.5)
T1/2; n= 12, 9, 11, 8	2.086 (± 50.0)	1.886 (± 62.3)	2.897 (± 38.7)	1.418 (± 58.4)

Notes:

[52] - PK Population

[53] - PK Population

[54] - PK Population

[55] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants who discontinued study treatment

End point title	Number of participants who discontinued study treatment[56]

End point description:

Reasons of study treatment discontinuation included adverse events (AEs), protocol deviation, participants reached protocol defined stopping criteria, physician decision and withdrawal by participants. Number of participants who discontinued study treatment are presented. Analysis was performed on Safety Population which comprised of all participants who received at least one dose of study treatment.

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[56] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[57]	20[58]	20[59]	22[60]
Units: Participants				
AEs	0	0	1	1
Protocol deviation	1	0	0	2
Participant reached stopping criteria	0	1	2	4
Physician decision	1	0	0	0
Withdrawal by subject	1	0	1	0

Notes:

[57] - Safety Population

[58] - Safety Population

[59] - Safety Population

[60] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[61]			
Units: Participants				
AEs	0			
Protocol deviation	1			
Participant reached stopping criteria	3			
Physician decision	0			
Withdrawal by subject	0			

Notes:

[61] - Safety Population

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of participants with AEs and serious adverse events (SAEs)[62]

End point description:

An AE is any untoward medical occurrence in a clinical investigation participant, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. SAE is defined as any untoward medical occurrence that, at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability, is a congenital anomaly/ birth effect, other situations and is associated with liver injury or impaired liver function.

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[62] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[63]	20[64]	20[65]	22[66]
Units: Participants				
Any AE	10	10	6	7
Any SAE	4	3	2	3

Notes:

[63] - Safety Population

[64] - Safety Population

[65] - Safety Population

[66] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[67]			
Units: Participants				
Any AE	7			
Any SAE	1			

Notes:

[67] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Sodium, potassium, glucose, calcium, phosphate levels in blood at indicated time points

End point title	Sodium, potassium, glucose, calcium, phosphate levels in blood at indicated time points[68]

End point description:

Serum sodium, potassium, glucose, corrected calcium and phosphate levels were assessed as a clinical chemistry laboratory parameter from Baseline up to follow up visit at Day 43. Day 1 values were considered as Baseline values. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[68] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[69]	20[70]	20[71]	22[72]
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Sodium; Day 1; n= 18, 20, 20, 22, 22	138.8 (± 2.85)	138.1 (± 2.31)	138.7 (± 2.83)	138.4 (± 1.76)
Sodium; Day 15; n= 17, 20, 18, 20, 22	137.7 (± 3.16)	137.5 (± 2.72)	138.1 (± 1.60)	137.2 (± 1.74)
Sodium; Day 29; n= 17, 19, 18, 17, 19	137.8 (± 3.96)	136.8 (± 2.70)	137.9 (± 2.85)	137.1 (± 2.46)
Sodium; Day 43; n= 15, 20, 18, 21, 21	139.2 (± 2.88)	138.1 (± 1.77)	137.9 (± 2.37)	137.6 (± 1.88)
Potassium; Day 1; n= 18, 20, 20, 22, 22	4.68 (± 0.840)	4.73 (± 0.768)	4.64 (± 0.826)	4.83 (± 0.685)
Potassium; Day 15; n= 17, 20, 18, 20, 22	4.72 (± 0.763)	4.77 (± 0.542)	4.57 (± 0.635)	4.80 (± 0.791)
Potassium; Day 29; n= 17, 19, 18, 17, 19	4.78 (± 0.919)	4.87 (± 0.751)	4.57 (± 0.472)	4.96 (± 0.941)
Potassium; Day 43; n= 15, 20, 18, 21, 21	4.69 (± 0.951)	4.68 (± 0.562)	4.59 (± 0.657)	4.80 (± 0.946)
Glucose; Day 1; n= 18, 20, 20, 22, 22	6.66 (± 3.088)	6.66 (± 2.716)	6.41 (± 3.507)	8.95 (± 5.012)
Glucose; Day 15; n= 17, 20, 18, 20, 22	7.89 (± 3.425)	7.16 (± 2.844)	7.03 (± 3.236)	8.67 (± 4.198)
Glucose; Day 29; n= 17, 19, 18, 17, 19	8.21 (± 4.951)	7.49 (± 3.949)	7.21 (± 3.953)	8.75 (± 5.708)
Glucose; Day 43; n= 15, 20, 18, 21, 21	6.93 (± 3.126)	6.72 (± 2.965)	7.09 (± 3.533)	8.93 (± 4.280)
Calcium corrected; Day 1; n= 18, 20, 20, 22, 22	2.286 (± 0.2116)	2.270 (± 0.1244)	2.241 (± 0.1675)	2.215 (± 0.1163)
Calcium corrected; Day 15; n= 17, 20, 18, 20, 22	2.261 (± 0.1698)	2.219 (± 0.1252)	2.213 (± 0.1723)	2.203 (± 0.1111)
Calcium corrected; Day 29; n= 17, 19, 18, 17, 19	2.205 (± 0.1431)	2.248 (± 0.1352)	2.244 (± 0.1577)	2.225 (± 0.1810)
Calcium corrected; Day 43; n= 15, 20, 18, 21, 21	2.251 (± 0.1582)	2.235 (± 0.1593)	2.271 (± 0.1823)	2.256 (± 0.1473)
Phosphate; Day 1; n= 18, 20, 20, 22, 22	1.608 (± 0.5143)	1.528 (± 0.5557)	1.498 (± 0.5265)	1.566 (± 0.4269)
Phosphate; Day 15; n= 17, 20, 18, 20. 22	1.621 (± 0.4221)	1.710 (± 0.3912)	1.642 (± 0.5021)	1.645 (± 0.4785)
Phosphate; Day 29; n= 17, 19, 18, 17, 19	1.709 (± 0.5872)	1.592 (± 0.4121)	1.644 (± 0.5322)	1.550 (± 0.3575)
Phosphate; Day 43; n= 15, 20, 18, 21, 21	1.550 (± 0.5828)	1.460 (± 0.4550)	1.472 (± 0.4240)	1.398 (± 0.4718)

Notes:

[69] - Safety Population

[70] - Safety Population

[71] - Safety Population

[72] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[73]			
Units: Millimoles per liter (mmol/L)				
arithmetic mean (standard deviation)				
Sodium; Day 1; n= 18, 20, 20, 22, 22	139.4 (± 2.38)			
Sodium; Day 15; n= 17, 20, 18, 20, 22	138.0 (± 2.36)			
Sodium; Day 29; n= 17, 19, 18, 17, 19	138.8 (± 2.74)			
Sodium; Day 43; n= 15, 20, 18, 21, 21	138.8 (± 2.02)			
Potassium; Day 1; n= 18, 20, 20, 22, 22	4.79 (± 0.514)			
Potassium; Day 15; n= 17, 20, 18, 20, 22	4.82 (± 0.765)			

Potassium; Day 29; n= 17, 19, 18, 17, 19	4.86 (± 0.619)			
Potassium; Day 43; n= 15, 20, 18, 21, 21	4.76 (± 0.752)			
Glucose; Day 1; n= 18, 20, 20, 22, 22	7.05 (± 2.491)			
Glucose; Day 15; n= 17, 20, 18, 20, 22	7.26 (± 2.852)			
Glucose; Day 29; n= 17, 19, 18, 17, 19	7.77 (± 4.621)			
Glucose; Day 43; n= 15, 20, 18, 21, 21	6.27 (± 1.958)			
Calcium corrected; Day 1; n= 18, 20, 20, 22, 22	2.219 (± 0.1589)			
Calcium corrected; Day 15; n= 17, 20, 18, 20, 22	2.188 (± 0.1360)			
Calcium corrected; Day 29; n= 17, 19, 18, 17, 19	2.198 (± 0.1343)			
Calcium corrected; Day 43; n= 15, 20, 18, 21, 21	2.201 (± 0.1206)			
Phosphate; Day 1; n= 18, 20, 20, 22, 22	1.318 (± 0.3647)			
Phosphate; Day 15; n= 17, 20, 18, 20. 22	1.348 (± 0.3138)			
Phosphate; Day 29; n= 17, 19, 18, 17, 19	1.453 (± 0.4489)			
Phosphate; Day 43; n= 15, 20, 18, 21, 21	1.412 (± 0.4441)			

Notes:

[73] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Albumin and protein levels in blood at indicated tme points

End point title	Albumin and protein levels in blood at indicated tme points[74]

End point description:

Serum albumin and protein levels were assessed as a clinical chemistry laboratory parameter from Baseline up to follow up visit at Day 43. Day 1 values were considered as Baseline values. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[74] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[75]	20[76]	20[77]	22[78]
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)				
Albumin; Day 1; n= 18, 20, 20, 22, 22	37.6 (± 2.89)	38.6 (± 2.46)	38.7 (± 3.84)	38.1 (± 3.52)
Albumin; Day 15; n= 17, 20, 18, 20, 22	38.1 (± 2.68)	38.1 (± 2.65)	38.4 (± 3.42)	37.2 (± 3.01)
Albumin; Day 29; n= 17, 19, 18, 17, 19	36.5 (± 3.22)	37.2 (± 3.26)	37.6 (± 3.62)	36.9 (± 4.15)

Albumin; Day 43; n= 15, 20, 18, 21, 21	37.1 (± 2.85)	38.1 (± 3.02)	37.9 (± 3.95)	37.5 (± 2.86)
Protein; Day 1; n= 18, 20 ,20, 22, 22	67.3 (± 4.90)	66.9 (± 5.42)	67.4 (± 4.89)	65.7 (± 4.65)
Protein; Day 15; n= 17, 20, 18, 20, 22	68.1 (± 4.87)	66.5 (± 4.88)	67.3 (± 4.28)	64.3 (± 4.70)
Protein; Day 29; n= 17, 19, 18, 17, 19	66.1 (± 4.52)	65.7 (± 4.75)	66.0 (± 4.51)	65.3 (± 5.30)
Protein; Day 43; n= 15, 20, 18, 21, 21	67.2 (± 4.25)	67.4 (± 5.14)	66.8 (± 4.02)	66.6 (± 6.34)

Notes:

[75] - Safety Population

[76] - Safety Population

[77] - Safety Population

[78] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[79]			
Units: grams per liter (g/L)				
arithmetic mean (standard deviation)				
Albumin; Day 1; n= 18, 20, 20, 22, 22	38.8 (± 2.22)			
Albumin; Day 15; n= 17, 20, 18, 20, 22	38.4 (± 2.52)			
Albumin; Day 29; n= 17, 19, 18, 17, 19	37.4 (± 2.17)			
Albumin; Day 43; n= 15, 20, 18, 21, 21	39.0 (± 3.11)			
Protein; Day 1; n= 18, 20 ,20, 22, 22	66.4 (± 5.16)			
Protein; Day 15; n= 17, 20, 18, 20, 22	65.6 (± 5.13)			
Protein; Day 29; n= 17, 19, 18, 17, 19	65.5 (± 6.50)			
Protein; Day 43; n= 15, 20, 18, 21, 21	66.7 (± 7.70)			

Notes:

[79] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (alk. phosph) levels in blood at indicated time points

End point title	Alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (alk. phosph) levels in blood at indicated time points[80]

End point description:

Serum ALT, AST and alk. phosph. levels were assessed as a clinical chemistry laboratory parameter from Baseline up to follow up visit at Day 43. Day 1 values were considered as Baseline values. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[80] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[81]	20[82]	20[83]	22[84]
Units: IU/L				
arithmetic mean (standard deviation)				
ALT; Day 1; n= 18, 20, 20, 22, 22	12.6 (± 9.36)	13.4 (± 7.51)	14.6 (± 11.39)	11.5 (± 5.94)
ALT; Day 15; n= 17, 20, 18, 20, 22	16.5 (± 13.80)	13.9 (± 10.58)	12.4 (± 7.87)	8.4 (± 2.11)
ALT; Day 29; n= 17, 19, 18, 17, 19	24.4 (± 32.34)	12.8 (± 6.43)	12.2 (± 6.40)	8.6 (± 3.12)
ALT; Day 43; n= 15, 20, 18, 21, 21	14.3 (± 8.55)	13.8 (± 8.03)	12.8 (± 6.89)	11.2 (± 5.57)
AST; Day 1; n= 18, 20, 20, 22, 22	14.9 (± 5.58)	14.2 (± 5.19)	17.2 (± 12.31)	13.6 (± 3.63)
AST; Day 15; n= 17, 20, 18, 20, 22	17.1 (± 7.30)	14.3 (± 5.67)	15.0 (± 7.72)	12.4 (± 2.89)
AST; Day 29; n= 17, 19, 18, 17, 19	26.8 (± 30.04)	13.8 (± 5.01)	16.0 (± 8.44)	13.5 (± 3.12)
AST; Day 43; n= 15, 20, 18, 21, 21	15.9 (± 6.65)	14.9 (± 6.07)	17.2 (± 11.40)	14.3 (± 4.76)
Alk. phosph; Day 1; n= 18, 20, 20, 22, 22	97.0 (± 33.07)	112.3 (± 74.61)	106.8 (± 84.85)	115.4 (± 72.35)
Alk. phosph; Day 15; n= 17, 20, 18, 20, 22	102.4 (± 34.70)	115.4 (± 73.37)	114.5 (± 82.29)	110.0 (± 62.65)
Alk. phosph.; Day 29; n= 17, 19, 18, 17, 19	94.1 (± 35.07)	120.2 (± 81.15)	109.2 (± 83.14)	120.4 (± 67.51)
Alk. phosph.; Day 43; n= 15, 20, 18, 21,21	96.5 (± 34.12)	117.6 (± 76.61)	113.8 (± 78.69)	108.6 (± 50.49)

Notes:

[81] - Safety Population

[82] - Safety Population

[83] - Safety Population

[84] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[85]			
Units: IU/L				
arithmetic mean (standard deviation)				
ALT; Day 1; n= 18, 20, 20, 22, 22	10.7 (± 5.75)			
ALT; Day 15; n= 17, 20, 18, 20, 22	11.9 (± 6.58)			
ALT; Day 29; n= 17, 19, 18, 17, 19	10.9 (± 5.67)			
ALT; Day 43; n= 15, 20, 18, 21, 21	13.1 (± 5.19)			
AST; Day 1; n= 18, 20, 20, 22, 22	14.4 (± 5.85)			
AST; Day 15; n= 17, 20, 18, 20, 22	15.4 (± 6.33)			
AST; Day 29; n= 17, 19, 18, 17, 19	15.0 (± 6.35)			
AST; Day 43; n= 15, 20, 18, 21, 21	15.7 (± 6.31)			
Alk. phosph; Day 1; n= 18, 20, 20, 22, 22	99.4 (± 47.26)			
Alk. phosph; Day 15; n= 17, 20, 18, 20, 22	101.5 (± 56.44)			
Alk. phosph.; Day 29; n= 17, 19, 18, 17, 19	93.5 (± 42.92)			
Alk. phosph.; Day 43; n= 15, 20, 18, 21,21	116.2 (± 96.02)			

Notes:

[85] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Bilirubin, direct bilirubin and indirect bilirubin levels in blood at indicated time points

End point title	Bilirubin, direct bilirubin and indirect bilirubin levels in blood at indicated time points[86]

End point description:

Serum bilirubin, direct bilirubin and indirect bilirubin levels were assessed as a clinical chemistry laboratory parameter from Baseline up to follow up visit at Day 43. Day 1 values were considered as Baseline values. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[86] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[87]	20[88]	20[89]	22[90]
Units: Micromoles per liter (µmol/L)				
arithmetic mean (standard deviation)				
Bilirubin; Day 1; n= 18, 20, 20, 22, 22	6.6 (± 1.65)	7.8 (± 3.11)	6.6 (± 1.31)	7.2 (± 2.44)
Bilirubin; Day 15; n= 17, 20, 18, 20, 22	6.7 (± 3.08)	7.1 (± 2.29)	7.2 (± 2.67)	7.8 (± 2.24)
Bilirubin; Day 29; n= 17, 19, 18, 17, 19	6.8 (± 2.24)	6.9 (± 1.93)	7.6 (± 2.12)	7.8 (± 2.44)
Bilirubin; Day 43; n= 15, 20 ,18, 21, 21	6.0 (± 1.07)	7.0 (± 2.38)	7.2 (± 2.07)	7.5 (± 2.44)
Direct bilirubin; Day 1; n= 18, 20, 20, 22, 22	1.8 (± 1.17)	1.9 (± 0.79)	2.0 (± 1.12)	2.4 (± 1.33)
Direct bilirubin; Day 15; n= 17, 20, 18, 20, 22	1.5 (± 1.66)	2.2 (± 0.62)	2.4 (± 1.29)	2.6 (± 1.14)
Direct bilirubin; Day 29; n= 17, 19, 18, 17, 19	2.5 (± 2.29)	1.6 (± 1.07)	2.7 (± 0.97)	2.4 (± 1.46)
Direct bilirubin; Day 43; n= 15, 20, 18, 21,21	1.3 (± 1.23)	1.9 (± 0.45)	2.3 (± 0.77)	2.3 (± 1.31)
Indirect bilirubin; Day 1; n= 18, 20, 20, 22, 22	4.8 (± 1.22)	5.9 (± 2.94)	4.6 (± 0.94)	4.8 (± 1.92)
Indirect bilirubin; Day 15; n= 17, 20, 18, 20, 22	5.2 (± 2.01)	4.9 (± 2.10)	4.8 (± 1.83)	5.2 (± 1.77)
Indirect bilirubin; Day 29; n= 17, 19, 18, 17, 19	4.4 (± 2.03)	5.4 (± 1.64)	4.9 (± 1.57)	5.4 (± 1.70)
Indirect bilirubin; Day 43; n= 15, 20, 18, 21, 21	4.7 (± 0.98)	5.1 (± 2.38)	4.9 (± 1.41)	5.2 (± 1.73)

Notes:

[87] - Safety Population

[88] - Safety Population

[89] - Safety Population

[90] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[91]			
Units: Micromoles per liter (µmol/L)				

arithmetic mean (standard deviation)				
Bilirubin; Day 1; n= 18, 20, 20, 22, 22	6.5 (± 1.10)			
Bilirubin; Day 15; n= 17, 20, 18, 20, 22	6.5 (± 1.10)			
Bilirubin; Day 29; n= 17, 19, 18, 17, 19	6.5 (± 1.47)			
Bilirubin; Day 43; n= 15, 20 ,18, 21, 21	6.5 (± 1.25)			
Direct bilirubin; Day 1; n= 18, 20, 20, 22, 22	1.9 (± 0.75)			
Direct bilirubin; Day 15; n= 17, 20, 18, 20, 22	1.8 (± 0.85)			
Direct bilirubin; Day 29; n= 17, 19, 18, 17, 19	1.8 (± 0.63)			
Direct bilirubin; Day 43; n= 15, 20, 18, 21,21	1.7 (± 0.72)			
Indirect bilirubin; Day 1; n= 18, 20, 20, 22, 22	4.6 (± 1.14)			
Indirect bilirubin; Day 15; n= 17, 20, 18, 20, 22	4.7 (± 0.98)			
Indirect bilirubin; Day 29; n= 17, 19, 18, 17, 19	4.7 (± 1.52)			
Indirect bilirubin; Day 43; n= 15, 20, 18, 21, 21	4.8 (± 1.48)			

Notes:

[91] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in sodium, potassium, glucose, calcium and phosphate levels

End point title	Change from Baseline in sodium, potassium, glucose, calcium and phosphate levels[92]

End point description:

Blood samples were collected from participants to evaluate clinical chemistry parameters including sodium, potassium, glucose, calcium and phosphate. Change from Baseline in clinical chemistry parameters at Day 15, Day 29 and Day 43 are presented. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Day 43

Notes:

[92] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[93]	20[94]	20[95]	22[96]
Units: Mmol/L				
arithmetic mean (standard deviation)				
Sodium; Day 15; n= 17, 20, 18, 20, 22	-0.9 (± 2.73)	-0.6 (± 2.62)	-0.5 (± 2.64)	-1.0 (± 2.13)
Sodium; Day 29; n= 17, 19, 18, 17, 19	-1.1 (± 2.26)	-1.2 (± 3.08)	-0.9 (± 2.26)	-1.2 (± 2.70)

Sodium; Day 43; n= 15, 20, 18, 21, 21	0.7 (± 2.06)	0.1 (± 2.35)	-0.6 (± 2.28)	-0.6 (± 2.23)
Potassium; Day 15; n= 17, 20, 18, 20, 22	0.04 (± 0.462)	0.05 (± 0.526)	-0.09 (± 1.099)	-0.08 (± 0.635)
Potassium; Day 29; n= 17, 19, 18, 17, 19	0.20 (± 0.744)	0.05 (± 0.660)	-0.14 (± 0.651)	0.11 (± 0.673)
Potassium; Day 43; n= 15, 20, 18, 21, 21	0.04 (± 0.565)	-0.05 (± 0.674)	-0.06 (± 1.004)	-0.02 (± 0.932)
Glucose; Day 15; n= 17, 20, 18, 20, 22	1.14 (± 3.339)	0.51 (± 2.959)	0.45 (± 1.740)	-0.03 (± 2.364)
Glucose; Day 29; n= 17, 19, 18, 17, 19	1.48 (± 3.771)	0.70 (± 3.756)	0.73 (± 1.135)	-0.36 (± 3.786)
Glucose; Day 43; n= 15, 20, 18, 21, 21	0.23 (± 1.335)	0.06 (± 3.072)	0.52 (± 1.383)	-0.12 (± 3.619)
Calcium; Day 15; n= 17, 20, 18, 20, 22	-0.011 (± 0.1227)	-0.051 (± 0.1354)	-0.026 (± 0.1439)	-0.010 (± 0.0912)
Calcium; Day 29; n= 17, 19, 18, 17, 19	-0.054 (± 0.1486)	-0.025 (± 0.1129)	-0.009 (± 0.1556)	0.001 (± 0.1019)
Calcium; Day 43; n= 15, 20, 18, 21, 21	-0.015 (± 0.1576)	-0.035 (± 0.1261)	0.018 (± 0.1852)	0.033 (± 0.1489)
Phosphate; Day 15; n= 17, 20, 18, 20, 22	-0.091 (± 0.4051)	0.183 (± 0.5184)	0.111 (± 0.5715)	0.095 (± 0.3367)
Phosphate; Day 29; n= 17, 19, 18, 17, 19	0.091 (± 0.3882)	0.011 (± 0.4932)	0.069 (± 0.4950)	-0.026 (± 0.3653)
Phosphate; Day 43; n= 15, 20, 18, 21, 21	-0.067 (± 0.4337)	-0.068 (± 0.5324)	-0.053 (± 0.5400)	-0.117 (± 0.5117)

Notes:

[93] - Safety Population

[94] - Safety Population

[95] - Safety Population

[96] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[97]			
Units: Mmol/L				
arithmetic mean (standard deviation)				
Sodium; Day 15; n= 17, 20, 18, 20, 22	-1.4 (± 2.06)			
Sodium; Day 29; n= 17, 19, 18, 17, 19	-0.5 (± 2.82)			
Sodium; Day 43; n= 15, 20, 18, 21, 21	-0.5 (± 2.60)			
Potassium; Day 15; n= 17, 20, 18, 20, 22	0.03 (± 0.944)			
Potassium; Day 29; n= 17, 19, 18, 17, 19	0.02 (± 0.640)			
Potassium; Day 43; n= 15, 20, 18, 21, 21	-0.06 (± 0.579)			
Glucose; Day 15; n= 17, 20, 18, 20, 22	0.21 (± 1.620)			
Glucose; Day 29; n= 17, 19, 18, 17, 19	0.61 (± 4.188)			
Glucose; Day 43; n= 15, 20, 18, 21, 21	-0.81 (± 2.516)			
Calcium; Day 15; n= 17, 20, 18, 20, 22	-0.031 (± 0.0956)			
Calcium; Day 29; n= 17, 19, 18, 17, 19	-0.012 (± 0.0939)			
Calcium; Day 43; n= 15, 20, 18, 21, 21	0.001 (± 0.0742)			
Phosphate; Day 15; n= 17, 20, 18, 20, 22	0.030 (± 0.3268)			

Phosphate; Day 29; n= 17, 19, 18, 17, 19	0.129 (± 0.2740)			
Phosphate; Day 43; n= 15, 20, 18, 21, 21	0.102 (± 0.3433)			

Notes:

[97] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in albumin and protein levels

End point title	Change from Baseline in albumin and protein levels[98]

End point description:

Blood samples were collected from participants to evaluate clinical chemistry parameters including albumin and protein. Change from Baseline in clinical chemistry parameters at Day 15, Day 29 and Day 43 are presented. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Day 43

Notes:

[98] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[99]	20[100]	20[101]	22[102]
Units: g/L				
arithmetic mean (standard deviation)				
Albumin; Day 15; n= 17, 20, 18, 20, 22	0.8 (± 1.60)	-0.5 (± 1.64)	0.2 (± 2.24)	-1.0 (± 2.34)
Albumin; Day 29; n= 17, 19, 18, 17, 19	-0.5 (± 2.24)	-1.3 (± 2.03)	-0.7 (± 2.00)	-0.9 (± 1.76)
Albumin; Day 43; n= 15, 20, 18, 21, 21	0.1 (± 2.00)	-0.6 (± 2.14)	-0.7 (± 2.22)	-0.3 (± 1.74)
Protein; Day 15; n= 17, 20, 18, 20, 22	0.8 (± 2.97)	-0.4 (± 3.25)	0.3 (± 3.65)	-1.5 (± 3.03)
Protein; Day 29; n= 17, 19, 18, 17, 19	-1.1 (± 4.26)	-0.8 (± 3.82)	-1.2 (± 2.90)	0.1 (± 2.56)
Protein; Day 43; n= 15, 20, 18, 21, 21	-0.1 (± 4.19)	0.6 (± 4.38)	-0.9 (± 3.17)	1.2 (± 3.95)

Notes:

[99] - Safety Population

[100] - Safety Population

[101] - Safety Population

[102] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[103]			
Units: g/L				
arithmetic mean (standard deviation)				
Albumin; Day 15; n= 17, 20, 18, 20, 22	-0.5 (± 1.44)			
Albumin; Day 29; n= 17, 19, 18, 17, 19	-1.3 (± 1.85)			

Albumin; Day 43; n= 15, 20, 18, 21, 21	0.1 (± 3.85)			
Protein; Day 15; n= 17, 20, 18, 20, 22	-0.7 (± 2.35)			
Protein; Day 29; n= 17, 19, 18, 17, 19	-1.0 (± 3.28)			
Protein; Day 43; n= 15, 20, 18, 21, 21	0.3 (± 4.84)			

Notes:

[103] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ALT, AST, Alk. phosph. levels

End point title	Change from Baseline in ALT, AST, Alk. phosph. levels[104]

End point description:

Blood samples were collected from participants to evaluate clinical chemistry parameters including ALT, AST, Alk. phosph. Change from Baseline in clinical chemistry parameters at Day 15, Day 29 and Day 43 are presented. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Day 43

Notes:

[104] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[105]	20[106]	20[107]	22[108]
Units: IU/L				
arithmetic mean (standard deviation)				
ALT; Day 15; n= 17, 20, 18, 20, 22	3.6 (± 9.59)	0.5 (± 5.65)	-3.1 (± 5.53)	-3.4 (± 5.52)
ALT; Day 29; n= 17, 19, 18, 17, 19	11.8 (± 32.39)	-0.9 (± 4.65)	-3.4 (± 9.83)	-3.6 (± 4.72)
ALT; Day 43; n= 15, 20, 18, 21, 21	0.9 (± 4.32)	0.4 (± 5.29)	-2.5 (± 8.97)	-0.4 (± 3.69)
AST; Day 15; n= 17, 20, 18, 20, 22	2.3 (± 5.70)	0.1 (± 2.45)	-2.7 (± 6.29)	-1.6 (± 3.32)
AST; Day 29; n= 17, 19, 18, 17, 19	11.5 (± 30.64)	-0.3 (± 3.30)	-1.8 (± 5.60)	-0.3 (± 3.67)
AST; Day 43; n= 15, 20, 18, 21, 21	0.6 (± 3.94)	0.7 (± 2.49)	-0.6 (± 7.99)	0.7 (± 3.41)
Alk.phosph.; Day 15; n= 17, 20, 18, 20, 22	3.2 (± 10.28)	3.2 (± 16.13)	2.7 (± 29.73)	-4.7 (± 18.90)
Alk.phosph.; Day 29; n= 17, 19, 18, 17, 19	-0.4 (± 19.31)	5.1 (± 19.09)	-0.9 (± 30.13)	-1.2 (± 28.60)
Alk.phosph.; Day 43; n= 15, 20, 18, 21, 21	-1.5 (± 17.01)	5.4 (± 21.34)	2.7 (± 31.96)	-8.4 (± 56.06)

Notes:

[105] - Safety Population

[106] - Safety Population

[107] - Safety Population

[108] - Safety Population

End point values	Dapro 25 mg			

Subject group type	Subject analysis set			
Number of subjects analysed	22[109]			
Units: IU/L				
arithmetic mean (standard deviation)				
ALT; Day 15; n= 17, 20, 18, 20, 22	1.1 (± 4.79)			
ALT; Day 29; n= 17, 19, 18, 17, 19	-0.2 (± 3.87)			
ALT; Day 43; n= 15, 20, 18, 21, 21	2.2 (± 4.08)			
AST; Day 15; n= 17, 20, 18, 20, 22	1.0 (± 5.26)			
AST; Day 29; n= 17, 19, 18, 17, 19	0.9 (± 3.60)			
AST; Day 43; n= 15, 20, 18, 21, 21	1.5 (± 3.71)			
Alk.phosph.; Day 15; n= 17, 20, 18, 20, 22	2.1 (± 17.23)			
Alk.phosph.; Day 29; n= 17, 19, 18, 17, 19	0.9 (± 13.47)			
Alk.phosph.; Day 43; n= 15, 20, 18, 21, 21	18.0 (± 66.44)			

Notes:

[109] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in bilirubin, direct bilirubin, indirect bilirubin levels

End point title	Change from Baseline in bilirubin, direct bilirubin, indirect bilirubin levels[110]

End point description:

Blood samples were collected from participants to evaluate clinical chemistry parameters including bilirubin, direct bilirubin and indirect bilirubin. Change from Baseline in clinical chemistry parameters at Day 15, Day 29 and Day 43 are presented. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Day 43

Notes:

[110] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[111]	20[112]	20[113]	22[114]
Units: µmol/L				
arithmetic mean (standard deviation)				
Bilirubin; Day 15; n= 17, 20, 18, 20, 22	0.2 (± 1.56)	-0.7 (± 1.49)	0.8 (± 2.07)	0.5 (± 1.93)
Bilirubin; Day 29; n= 17, 19, 18, 17, 19	0.2 (± 0.97)	-0.3 (± 1.20)	1.0 (± 1.41)	0.2 (± 0.97)
Bilirubin; Day 43; n= 15, 20, 18, 21, 21	-0.1 (± 0.52)	-0.8 (± 1.51)	0.6 (± 2.04)	0.4 (± 1.36)
Direct bilirubin; Day 15; n= 17, 20, 18, 20, 22	-0.1 (± 1.11)	0.3 (± 0.73)	0.6 (± 0.92)	0.2 (± 1.11)

Direct bilirubin; Day 29; n= 17, 19, 18, 17, 19	0.7 (± 1.86)	-0.3 (± 1.00)	0.7 (± 0.97)	-0.1 (± 1.50)
Direct bilirubin; Day 43; n= 15, 20, 18, 21, 21	-0.1 (± 1.19)	0.0 (± 0.92)	0.3 (± 1.03)	-0.1 (± 1.34)
Indirect bilirubin; Day 15; n= 17, 20, 18, 20, 22	0.4 (± 1.46)	-1.0 (± 1.38)	0.2 (± 1.80)	0.3 (± 1.75)
Indirect bilirubin; Day 29; n= 17, 19, 18, 17, 19	-0.5 (± 1.66)	0.0 (± 1.15)	0.3 (± 1.71)	0.4 (± 1.46)
Indirect bilirubin; Day 43; n= 15, 20, 18, 21, 21	0.0 (± 1.07)	-0.8 (± 1.64)	0.2 (± 1.66)	0.5 (± 1.40)

Notes:

[111] - Safety Population

[112] - Safety Population

[113] - Safety Population

[114] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[115]			
Units: µmol/L				
arithmetic mean (standard deviation)				
Bilirubin; Day 15; n= 17, 20, 18, 20, 22	0.0 (± 1.38)			
Bilirubin; Day 29; n= 17, 19, 18, 17, 19	0.1 (± 1.56)			
Bilirubin; Day 43; n= 15, 20, 18, 21, 21	0.1 (± 1.34)			
Direct bilirubin; Day 15; n= 17, 20, 18, 20, 22	-0.1 (± 0.97)			
Direct bilirubin; Day 29; n= 17, 19, 18, 17, 19	-0.1 (± 1.05)			
Direct bilirubin; Day 43; n= 15, 20, 18, 21, 21	-0.2 (± 1.08)			
Indirect bilirubin; Day 15; n= 17, 20, 18, 20, 22	0.1 (± 1.44)			
Indirect bilirubin; Day 29; n= 17, 19, 18, 17, 19	0.2 (± 1.62)			
Indirect bilirubin; Day 43; n= 15, 20, 18, 21, 21	0.3 (± 1.82)			

Notes:

[115] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Leukocytes, neutrophils, basophils, eosinophils,lymphocytes, monocytes, platelet levels in blood at indicated time points

End point title	Leukocytes, neutrophils, basophils, eosinophils,lymphocytes, monocytes, platelet levels in blood at indicated time points[116]

End point description:

Serum leukocytes, neutrophils, basophils, eosinophils, lymphocytes, monocytes and platelet levels were assessed as a clinical hematology laboratory parameter from Baseline up to follow up visit at Day 43. Day 1 values were considered as Baseline values. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[116] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

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

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[117]	20[118]	20[119]	22[120]
Units: 10^9/ L				
arithmetic mean (standard deviation)				
Leukocytes; Day 1; n= 18, 19, 19, 21, 20	6.28 (± 1.750)	6.07 (± 1.601)	5.88 (± 1.510)	5.90 (± 1.825)
Leukocytes; Day 15; n= 17, 19, 17, 21, 21	7.01 (± 2.140)	5.85 (± 1.720)	6.21 (± 1.918)	5.87 (± 1.961)
Leukocytes; Day 29; n= 16, 19, 17, 17, 18	6.66 (± 1.707)	6.59 (± 1.890)	5.88 (± 1.685)	6.11 (± 2.574)
Leukocytes; Day 43; n= 16, 20, 19, 19, 20	7.05 (± 2.006)	7.25 (± 2.520)	6.00 (± 1.694)	6.42 (± 2.010)
Neutrophils; Day 1; n= 18, 19, 19, 21, 20	4.030 (± 1.6128)	4.097 (± 1.5763)	3.522 (± 1.3492)	3.785 (± 1.5024)
Neutrophils; Day 15; n= 17, 19, 17, 21, 21	4.666 (± 1.8113)	3.887 (± 1.5659)	3.707 (± 1.6592)	4.129 (± 1.6604)
Neutrophils; Day 29; n= 16, 18, 17, 15, 17	4.123 (± 1.2229)	4.591 (± 1.9586)	3.522 (± 1.4546)	4.224 (± 2.2017)
Neutrophils; Day 43; n= 16, 20, 19, 19, 19	4.687 (± 1.8919)	5.049 (± 2.3848)	3.545 (± 1.4027)	4.343 (± 1.6235)
Basophils; Day 1; n= 18, 19, 19, 21, 20	0.018 (± 0.0131)	0.016 (± 0.0134)	0.025 (± 0.0174)	0.017 (± 0.0142)
Basophils; Day 15; n= 17, 19, 17, 21, 21	0.027 (± 0.0214)	0.026 (± 0.0161)	0.022 (± 0.0139)	0.024 (± 0.0140)
Basophils; Day 29; n= 16, 18, 17, 15, 17	0.035 (± 0.0462)	0.021 (± 0.0128)	0.021 (± 0.0150)	0.027 (± 0.0315)
Basophils; Day 43; n= 16, 20, 19, 19, 19	0.028 (± 0.0217)	0.018 (± 0.0136)	0.020 (± 0.0183)	0.024 (± 0.0130)
Eosinophils; Day 1; n= 18, 19, 19, 21, 20	0.189 (± 0.1946)	0.174 (± 0.1593)	0.184 (± 0.1696)	0.240 (± 0.2115)
Eosinophils; Day 15; n= 17, 19, 17, 21, 21	0.161 (± 0.1245)	0.166 (± 0.1804)	0.192 (± 0.2355)	0.186 (± 0.1914)
Eosinophils; Day 29; n= 16, 18, 17, 15, 17	0.176 (± 0.1917)	0.149 (± 0.0950)	0.145 (± 0.1136)	0.185 (± 0.0798)
Eosinophils; Day 43; n= 16, 20, 19, 19, 19	0.216 (± 0.2458)	0.210 (± 0.1969)	0.232 (± 0.2727)	0.217 (± 0.1899)
Lymphocytes; Day 1; n= 18, 19, 19, 21, 20	1.631 (± 0.4264)	1.393 (± 0.4587)	1.739 (± 0.6964)	1.442 (± 0.4998)
Lymphocytes; Day 15; n= 17, 19, 17, 21, 21	1.735 (± 0.6699)	1.416 (± 0.5670)	1.842 (± 0.7381)	1.206 (± 0.4609)
Lymphocytes; Day 29; n= 16, 18, 17, 15, 17	1.870 (± 0.7427)	1.427 (± 0.4187)	1.775 (± 0.6767)	1.181 (± 0.3418)
Lymphocytes; Day 43; n= 16, 20, 19, 19, 19	1.648 (± 0.5294)	1.509 (± 0.4386)	1.736 (± 0.3916)	1.399 (± 0.5562)
Monocytes; Day 1; n= 18, 19, 20, 21, 20	0.401 (± 0.1511)	0.396 (± 0.1591)	0.435 (± 0.2703)	0.421 (± 0.1722)
Monocytes; Day 15; n= 17, 19, 17, 21, 21	0.420 (± 0.2243)	0.352 (± 0.1457)	0.436 (± 0.2402)	0.384 (± 0.2160)
Monocytes; Day 29; n= 16, 18, 17, 15, 17	0.444 (± 0.2076)	0.457 (± 0.1503)	0.403 (± 0.1385)	0.426 (± 0.2628)
Monocytes; Day 43; n= 16, 20, 19, 19, 19	0.461 (± 0.1878)	0.459 (± 0.1916)	0.461 (± 0.2614)	0.429 (± 0.2047)

Platelet; Day 1; n= 16, 19, 20, 21, 19	219.0 (± 65.04)	189.9 (± 36.70)	198.0 (± 71.03)	192.3 (± 70.85)
Platelet; Day 15; n= 17, 18, 17, 21, 20	205.4 (± 63.00)	175.4 (± 44.08)	198.5 (± 73.65)	181.5 (± 66.59)
Platelet; Day 29; n= 16, 19, 17, 17, 17	198.1 (± 76.39)	174.7 (± 52.50)	187.5 (± 62.66)	194.8 (± 81.57)
Platelet; Day 43; n= 15, 20, 19, 20, 21	220.8 (± 61.57)	195.8 (± 68.33)	188.6 (± 69.28)	170.0 (± 44.61)

Notes:

[117] - Safety Population

[118] - Safety Population

[119] - Safety Population

[120] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[121]			
Units: 10^9/ L				
arithmetic mean (standard deviation)				
Leukocytes; Day 1; n= 18, 19, 19, 21, 20	6.44 (± 1.595)			
Leukocytes; Day 15; n= 17, 19, 17, 21, 21	6.52 (± 1.427)			
Leukocytes; Day 29; n= 16, 19, 17, 17, 18	6.33 (± 1.820)			
Leukocytes; Day 43; n= 16, 20, 19, 19, 20	6.77 (± 2.547)			
Neutrophils; Day 1; n= 18, 19, 19, 21, 20	3.954 (± 1.4097)			
Neutrophils; Day 15; n= 17, 19, 17, 21, 21	4.346 (± 1.2240)			
Neutrophils; Day 29; n= 16, 18, 17, 15, 17	3.978 (± 1.7026)			
Neutrophils; Day 43; n= 16, 20, 19, 19, 19	4.477 (± 2.2480)			
Basophils; Day 1; n= 18, 19, 19, 21, 20	0.028 (± 0.0204)			
Basophils; Day 15; n= 17, 19, 17, 21, 21	0.025 (± 0.0325)			
Basophils; Day 29; n= 16, 18, 17, 15, 17	0.024 (± 0.0111)			
Basophils; Day 43; n= 16, 20, 19, 19, 19	0.025 (± 0.0204)			
Eosinophils; Day 1; n= 18, 19, 19, 21, 20	0.196 (± 0.2310)			
Eosinophils; Day 15; n= 17, 19, 17, 21, 21	0.187 (± 0.2186)			
Eosinophils; Day 29; n= 16, 18, 17, 15, 17	0.237 (± 0.2785)			
Eosinophils; Day 43; n= 16, 20, 19, 19, 19	0.243 (± 0.2670)			
Lymphocytes; Day 1; n= 18, 19, 19, 21, 20	1.747 (± 0.7325)			
Lymphocytes; Day 15; n= 17, 19, 17, 21, 21	1.526 (± 0.6697)			
Lymphocytes; Day 29; n= 16, 18, 17, 15, 17	1.612 (± 0.5775)			
Lymphocytes; Day 43; n= 16, 20, 19, 19, 19	1.721 (± 0.6644)			

Monocytes; Day 1; n= 18, 19, 20, 21, 20	0.518 (± 0.2077)			
Monocytes; Day 15; n= 17, 19, 17, 21, 21	0.446 (± 0.2085)			
Monocytes; Day 29; n= 16, 18, 17, 15, 17	0.600 (± 0.3465)			
Monocytes; Day 43; n= 16, 20, 19, 19, 19	0.513 (± 0.2739)			
Platelet; Day 1; n= 16, 19, 20, 21, 19	196.0 (± 61.12)			
Platelet; Day 15; n= 17, 18, 17, 21, 20	194.8 (± 49.08)			
Platelet; Day 29; n= 16, 19, 17, 17, 17	198.9 (± 55.07)			
Platelet; Day 43; n= 15, 20, 19, 20, 21	194.1 (± 50.35)			

Notes:

[121] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean corpuscular hemoglobin (MCH) levels in blood at indicated time points

End point title	Mean corpuscular hemoglobin (MCH) levels in blood at indicated time points[122]

End point description:

Serum MCH levels were assessed as a clinical hematology laboratory parameter from Baseline up to follow up visit at Day 43. Day 1 values were considered as Baseline values. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[122] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[123]	20[124]	20[125]	22[126]
Units: Pg				
arithmetic mean (standard deviation)				
Day 1; n= 18, 19, 20, 21, 20	31.19 (± 2.538)	30.95 (± 1.889)	30.19 (± 2.145)	31.46 (± 1.942)
Day 15; n= 17, 19, 17, 21, 21	30.83 (± 2.100)	2.100 (± 1.866)	30.74 (± 1.476)	31.70 (± 2.315)
Day 29; n= 16, 19, 17, 17, 18	30.97 (± 2.290)	31.60 (± 2.194)	30.56 (± 2.236)	31.68 (± 2.224)
Day 43; n= 16, 20, 19, 20, 21	30.86 (± 1.992)	31.04 (± 1.870)	30.49 (± 2.155)	31.84 (± 2.143)

Notes:

[123] - Safety Population

[124] - Safety Population

[125] - Safety Population

[126] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[127]			
Units: Pg				
arithmetic mean (standard deviation)				
Day 1; n= 18, 19, 20, 21, 20	30.70 (± 1.781)			
Day 15; n= 17, 19, 17, 21, 21	30.85 (± 1.619)			
Day 29; n= 16, 19, 17, 17, 18	31.16 (± 1.729)			
Day 43; n= 16, 20, 19, 20, 21	30.67 (± 1.846)			

Notes:

[127] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean corpuscular hemoglobin concentration (MCHC) levels in blood at indicated time points

End point title	Mean corpuscular hemoglobin concentration (MCHC) levels in blood at indicated time points[128]

End point description:

Serum MCHC levels were assessed as a clinical hematology laboratory parameter from Baseline up to follow up visit at Day 43. Day 1 values were considered as Baseline values. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[128] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[129]	20[130]	20[131]	22[132]
Units: g/L				
arithmetic mean (standard deviation)				
Day 1; n= 18, 19, 20, 21, 20	322.9 (± 13.39)	321.7 (± 12.61)	319.5 (± 15.36)	327.6 (± 12.65)
Day 15; n= 17, 19, 17, 21, 21	321.5 (± 11.22)	324.0 (± 7.79)	324.8 (± 8.35)	322.7 (± 14.75)
Day 29; n= 16, 19, 17, 17, 18	323.3 (± 14.90)	329.6 (± 12.61)	325.4 (± 10.25)	323.9 (± 11.73)

Day 43; n= 16, 20, 19, 20, 21	321.9 (± 13.22)	325.2 (± 11.98)	325.5 (± 11.23)	327.0 (± 10.66)

Notes:

[129] - Safety Population

[130] - Safety Population

[131] - Safety Population

[132] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[133]			
Units: g/L				
arithmetic mean (standard deviation)				
Day 1; n= 18, 19, 20, 21, 20	321.5 (± 12.91)			
Day 15; n= 17, 19, 17, 21, 21	318.3 (± 12.06)			
Day 29; n= 16, 19, 17, 17, 18	323.6 (± 8.61)			
Day 43; n= 16, 20, 19, 20, 21	321.0 (± 11.00)			

Notes:

[133] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Corpuscular volume (MCV) levels in blood at indicated time points

End point title	Mean Corpuscular volume (MCV) levels in blood at indicated time points[134]

End point description:

Serum MCV levels were assessed as a clinical hematology laboratory parameter from Baseline up to follow up visit at Day 43. Day 1 values were considered as Baseline values. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[134] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[135]	20[136]	20[137]	22[138]
Units: Femtoliter (fL)				
arithmetic mean (standard deviation)				
Day 1; n= 18, 19, 20, 21, 20	96.7 (± 5.94)	96.4 (± 5.68)	94.7 (± 5.28)	96.1 (± 5.61)
Day 15; n= 17, 19, 17, 21, 21	95.9 (± 6.02)	95.8 (± 6.27)	94.8 (± 4.53)	98.3 (± 5.57)
Day 29; n= 16, 19, 17, 17, 18	95.8 (± 5.83)	95.9 (± 6.05)	94.1 (± 5.94)	97.8 (± 4.96)
Day 43; n= 16, 20, 19, 20, 21	96.1 (± 5.91)	95.4 (± 5.08)	93.7 (± 6.09)	97.5 (± 5.98)

Notes:

[135] - Safety Population

[136] - Safety Population

[137] - Safety Population

[138] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[139]			
Units: Femtoliter (fL)				
arithmetic mean (standard deviation)				
Day 1; n= 18, 19, 20, 21, 20	95.7 (± 4.91)			
Day 15; n= 17, 19, 17, 21, 21	97.0 (± 6.41)			
Day 29; n= 16, 19, 17, 17, 18	96.3 (± 4.76)			
Day 43; n= 16, 20, 19, 20, 21	95.6 (± 5.27)			

Notes:

[139] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Erythrocyte distribution width levels in blood at indicated time points

End point title	Erythrocyte distribution width levels in blood at indicated time points[140]

End point description:

Erythrocyte distribution width levels were assessed as a clinical hematology laboratory parameter from Baseline up to follow up visit at Day 43. Day 1 values were considered as Baseline values. Only those participants available at the specified time points were analyzed (represented by n=X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[140] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[141]	20[142]	20[143]	22[144]
Units: Percentage of width				
arithmetic mean (standard deviation)				
Day 1; n= 18, 19, 20, 21, 20	15.13 (± 2.607)	16.40 (± 2.082)	15.41 (± 1.627)	15.68 (± 1.725)
Day 15; n= 17, 19, 17, 21, 21	15.05 (± 2.088)	15.77 (± 1.569)	15.26 (± 1.197)	16.74 (± 1.912)
Day 29; n= 16, 19, 17, 17, 18	15.15 (± 2.530)	15.69 (± 1.750)	15.36 (± 1.287)	16.23 (± 1.668)
Day 43; n= 16, 20, 19, 20, 21	15.53 (± 2.866)	15.53 (± 2.018)	14.95 (± 1.269)	15.48 (± 1.389)

Notes:
[141] - Safety Population
[142] - Safety Population
[143] - Safety Population
[144] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[145]			
Units: Percentage of width				
arithmetic mean (standard deviation)				
Day 1; n= 18, 19, 20, 21, 20	15.81 (± 2.504)			
Day 15; n= 17, 19, 17, 21, 21	16.30 (± 2.331)			
Day 29; n= 16, 19, 17, 17, 18	15.76 (± 1.253)			
Day 43; n= 16, 20, 19, 20, 21	15.61 (± 1.297)			

Notes:
[145] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MCH levels

End point title	Change from Baseline in MCH levels[146]

End point description:

Blood samples were collected from participants to evaluate clinical hematology parameters including MCH. Change from Baseline in clinical hematology parameters at Day 15, Day 29, Day 43 are presented. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Day 43

Notes:

[146] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[147]	20[148]	20[149]	22[150]
Units: Pg				
arithmetic mean (standard deviation)				
Day 15; n= 17, 19, 17, 21, 21	0.16 (± 0.602)	0.19 (± 0.817)	0.27 (± 0.685)	0.25 (± 0.870)
Day 29; n= 16, 19, 17, 17, 18	0.16 (± 0.982)	0.58 (± 1.185)	0.42 (± 0.824)	0.15 (± 0.987)
Day 43; n= 16, 20, 19, 20, 21	0.11 (± 0.981)	0.13 (± 0.948)	0.34 (± 0.993)	0.29 (± 0.809)

Notes:

[147] - Safety Population

[148] - Safety Population

[149] - Safety Population

[150] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[151]			
Units: Pg				
arithmetic mean (standard deviation)				
Day 15; n= 17, 19, 17, 21, 21	0.16 (± 0.520)			
Day 29; n= 16, 19, 17, 17, 18	0.41 (± 0.744)			
Day 43; n= 16, 20, 19, 20, 21	0.11 (± 0.842)			

Notes:

[151] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MCHC levels

End point title	Change from Baseline in MCHC levels[152]

End point description:

Blood samples were collected from participants to evaluate clinical hematology parameters including MCHC. Change from Baseline in clinical hematology parameters at Day 15, Day 29, Day 43 are presented. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Day 43

Notes:

[152] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[153]	20[154]	20[155]	22[156]
Units: g/L				
arithmetic mean (standard deviation)				
Day 15; n= 17, 19, 17, 21, 21	2.6 (± 11.09)	3.0 (± 14.21)	3.5 (± 10.87)	-5.0 (± 12.92)
Day 29; n= 16, 19, 17, 17, 18	5.6 (± 12.81)	7.3 (± 16.92)	7.6 (± 8.27)	-4.4 (± 12.30)
Day 43; n= 16, 20, 19, 20, 21	3.9 (± 15.92)	3.0 (± 16.53)	6.0 (± 11.44)	-0.3 (± 9.14)

Notes:

[153] - Safety Population

[154] - Safety Population

[155] - Safety Population

[156] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[157]			
Units: g/L				
arithmetic mean (standard deviation)				
Day 15; n= 17, 19, 17, 21, 21	-3.2 (± 11.48)			
Day 29; n= 16, 19, 17, 17, 18	0.8 (± 10.04)			
Day 43; n= 16, 20, 19, 20, 21	-1.0 (± 12.12)			

Notes:

[157] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in MCV levels

End point title	Change from Baseline in MCV levels[158]

End point description:

Blood samples were collected from participants to evaluate clinical hematology parameters including MCV. Change from Baseline in clinical hematology parameters at Day 15, Day 29, Day 43 are presented. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Day 43

Notes:

[158] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[159]	20[160]	20[161]	22[162]
Units: fL				
arithmetic mean (standard deviation)				
Day 15; n= 17, 19, 17, 21, 21	-0.4 (± 2.98)	-0.2 (± 3.39)	-0.3 (± 2.57)	2.2 (± 3.21)
Day 29; n= 16, 19, 17, 17, 18	-1.4 (± 3.24)	-0.5 (± 2.86)	-0.9 (± 2.36)	1.6 (± 2.40)
Day 43; n= 16, 20, 19, 20, 21	-0.8 (± 3.15)	-0.7 (± 3.37)	-0.8 (± 3.28)	0.9 (± 2.10)

Notes:

[159] - Safety Population

[160] - Safety Population

[161] - Safety Population

[162] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[163]			
Units: fL				
arithmetic mean (standard deviation)				

Day 15; n= 17, 19, 17, 21, 21	1.3 (± 3.15)			
Day 29; n= 16, 19, 17, 17, 18	0.9 (± 2.54)			
Day 43; n= 16, 20, 19, 20, 21	0.6 (± 3.06)			

Notes:

[163] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in erythrocyte distribution width levels

End point title	Change from Baseline in erythrocyte distribution width

End point description:

Blood samples were collected from participants to evaluate clinical hematology parameters including erythrocyte distribution width. Change from Baseline in clinical hematology parameters at Day 15, Day 29, Day 43 are presented. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Day 43

Notes:

[164] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[165]	20[166]	20[167]	22[168]
Units: Percentage of width				
arithmetic mean (standard deviation)				
Day 15; n= 17, 19, 17, 21, 21	-0.18 (± 1.025)	-0.48 (± 1.276)	-0.09 (± 1.047)	1.06 (± 1.337)
Day 29; n= 16, 19, 17, 17, 18	-0.31 (± 1.019)	-0.64 (± 1.332)	-0.23 (± 1.021)	0.40 (± 1.342)
Day 43; n= 16, 20, 19, 20, 21	0.18 (± 1.329)	-0.74 (± 1.728)	-0.50 (± 1.094)	-0.22 (± 1.165)

Notes:

[165] - Safety Population

[166] - Safety Population

[167] - Safety Population

[168] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[169]			
Units: Percentage of width				
arithmetic mean (standard deviation)				
Day 15; n= 17, 19, 17, 21, 21	0.54 (± 1.162)			
Day 29; n= 16, 19, 17, 17, 18	0.58 (± 1.202)			
Day 43; n= 16, 20, 19, 20, 21	0.23 (± 1.410)			

Notes:
[169] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in leukocytes, neutrophils, basophils, eosinophils, lymphocytes, monocytes, platelets levels

End point title	Change from Baseline in leukocytes, neutrophils, basophils, eosinophils, lymphocytes, monocytes, platelets levels[170]

End point description:

Blood samples were collected from participants to evaluate clinical hematology parameters including leukocytes, neutrophils, basophils, eosinophils, lymphocytes, monocytes, platelets. Change from Baseline in clinical hematology parameters at Day 15, Day 29, Day 43 are presented. Day 1 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and up to Day 43

Notes:

[170] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[171]	20[172]	20[173]	22[174]
Units: 10^9/L				
arithmetic mean (standard deviation)				
Leukocytes; Day 15; n= 17, 19, 17, 21, 21	0.47 (± 1.271)	-0.21 (± 1.051)	0.40 (± 1.116)	-0.03 (± 1.463)
Leukocytes; Day 29; n= 16, 19, 17, 17, 18	0.49 (± 1.849)	0.40 (± 1.784)	0.00 (± 1.084)	0.20 (± 1.526)
Leukocytes; Day 43; n= 16, 20, 19, 19, 20	0.54 (± 1.041)	1.08 (± 1.662)	0.23 (± 1.101)	0.67 (± 1.580)
Neutrophils; Day 15; n= 17, 19, 17, 21, 21	0.391 (± 1.2323)	-0.146 (± 0.9163)	0.280 (± 1.0681)	0.344 (± 1.2469)
Neutrophils; Day 29; n= 16, 18, 17, 15, 17	0.237 (± 1.6283)	0.469 (± 1.5717)	-0.021 (± 1.0157)	0.273 (± 1.5729)
Neutrophils; Day 43; n= 16, 20, 19, 19, 19	0.423 (± 1.0535)	0.904 (± 1.3737)	0.112 (± 1.0449)	0.691 (± 1.5221)
Basophils; Day 15; n= 17, 19, 17, 21, 21	0.005 (± 0.0302)	0.009 (± 0.0200)	-0.002 (± 0.0210)	0.007 (± 0.0102)
Basophils; Day 29; n= 16, 18, 17, 15, 17	0.013 (± 0.0510)	0.006 (± 0.0195)	-0.004 (± 0.0187)	0.012 (± 0.0328)
Basophils; Day 43; n= 16, 20, 19, 19, 19	0.006 (± 0.0268)	0.001 (± 0.0148)	-0.004 (± 0.0203)	0.007 (± 0.0192)
Eosinophils; Day 15; n= 17, 19, 17, 21, 21	0.009 (± 0.0698)	-0.017 (± 0.1313)	-0.006 (± 0.1345)	-0.053 (± 0.1478)

Eosinophils; Day 29; n= 16, 18, 17, 15, 17	0.020 (± 0.0859)	-0.002 (± 0.1226)	-0.006 (± 0.1129)	0.007 (± 0.0880)
Eosinophils; Day 43; n= 16, 20, 19, 19, 19	0.061 (± 0.1193)	0.030 (± 0.1439)	0.051 (± 0.1647)	-0.024 (± 0.1876)
Lymphocytes; Day 15; n= 17, 19, 17, 21, 21	0.082 (± 0.4256)	-0.019 (± 0.3163)	0.106 (± 0.4617)	-0.236 (± 0.4298)
Lymphocytes; Day 29; n= 16, 18, 17, 15, 17	0.194 (± 0.6605)	0.026 (± 0.4130)	0.019 (± 0.4421)	-0.154 (± 0.3058)
Lymphocytes; Day 43; n= 16, 20, 19, 19, 19	0.018 (± 0.3427)	0.061 (± 0.3332)	0.007 (± 0.4824)	-0.041 (± 0.2801)
Monocytes; Day 15; n= 17, 19, 17, 21, 21	-0.005 (± 0.1518)	-0.042 (± 0.1504)	-0.016 (± 0.2285)	-0.037 (± 0.1460)
Monocytes; Day 29; n= 16, 18, 17, 15, 17	0.027 (± 0.1553)	0.053 (± 0.1483)	-0.031 (± 0.2194)	0.015 (± 0.1878)
Monocytes; Day 43; n= 16, 20, 19, 19, 19	0.033 (± 0.1631)	0.065 (± 0.1629)	0.026 (± 0.2652)	0.023 (± 0.1249)
Platelet; Day 15; n= 17, 18, 17, 21, 20	-14.2 (± 26.24)	-16.2 (± 27.46)	-3.2 (± 38.13)	-10.8 (± 31.95)
Platelet; Day 29; n= 16, 18, 17, 17, 17	-17.1 (± 40.58)	-12.8 (± 36.55)	-18.1 (± 29.63)	-2.4 (± 33.65)
Platelet; Day 43; n= 15, 19, 19, 20, 21	-4.9 (± 37.30)	4.4 (± 50.34)	-10.4 (± 35.12)	-7.1 (± 31.95)

Notes:

[171] - Safety Population

[172] - Safety Population

[173] - Safety Population

[174] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[175]			
Units: 10^9/L				
arithmetic mean (standard deviation)				
Leukocytes; Day 15; n= 17, 19, 17, 21, 21	-0.03 (± 1.476)			
Leukocytes; Day 29; n= 16, 19, 17, 17, 18	-0.14 (± 1.701)			
Leukocytes; Day 43; n= 16, 20, 19, 19, 20	0.21 (± 2.615)			
Neutrophils; Day 15; n= 17, 19, 17, 21, 21	0.259 (± 1.3874)			
Neutrophils; Day 29; n= 16, 18, 17, 15, 17	-0.009 (± 1.8718)			
Neutrophils; Day 43; n= 16, 20, 19, 19, 19	0.504 (± 2.3110)			
Basophils; Day 15; n= 17, 19, 17, 21, 21	-0.002 (± 0.0383)			
Basophils; Day 29; n= 16, 18, 17, 15, 17	0.000 (± 0.0242)			
Basophils; Day 43; n= 16, 20, 19, 19, 19	-0.001 (± 0.0228)			
Eosinophils; Day 15; n= 17, 19, 17, 21, 21	-0.006 (± 0.1183)			
Eosinophils; Day 29; n= 16, 18, 17, 15, 17	0.025 (± 0.0990)			
Eosinophils; Day 43; n= 16, 20, 19, 19, 19	0.021 (± 0.0984)			
Lymphocytes; Day 15; n= 17, 19, 17, 21, 21	-0.208 (± 0.5095)			

Lymphocytes; Day 29; n= 16, 18, 17, 15, 17	-0.074 (± 0.7018)			
Lymphocytes; Day 43; n= 16, 20, 19, 19, 19	-0.064 (± 0.4759)			
Monocytes; Day 15; n= 17, 19, 17, 21, 21	-0.068 (± 0.1895)			
Monocytes; Day 29; n= 16, 18, 17, 15, 17	0.077 (± 0.2532)			
Monocytes; Day 43; n= 16, 20, 19, 19, 19	-0.021 (± 0.1855)			
Platelet; Day 15; n= 17, 18, 17, 21, 20	-3.3 (± 27.78)			
Platelet; Day 29; n= 16, 18, 17, 17, 17	1.3 (± 35.58)			
Platelet; Day 43; n= 15, 19, 19, 20, 21	-1.6 (± 30.95)			

Notes:

[175] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with abnormal Electrocardiogram (ECG) findings at indicated time points

End point title	Number of participants with abnormal Electrocardiogram (ECG) findings at indicated time points[176]

End point description:

Single measurements of 12-lead ECG were obtained in supine position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT interval. Number of participants who had abnormal non clinically significant (NCS) and abnormal clinically significant (CS) ECG findings at Baseline (Week -4) and Day 29 are presented.

End point type	Secondary

End point timeframe:

Up to Day 29

Notes:

[176] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[177]	20[178]	20[179]	22[180]
Units: Participants				
Baseline(Week -4);Abnormal; NCS;n=19,20,20,22,22	10	15	18	16
Baseline(Week-4);Abnormal;CS;n=19,20,20,22,22	0	0	0	0
Day 29; Abnormal; NCS; n=17,19,18,17, 19	12	14	16	12
Day 29; Abnormal; CS; n=17,19,18,17, 19	0	0	0	0

Notes:

[177] - Safety Population

[178] - Safety Population

[179] - Safety Population

[180] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[181]			
Units: Participants				
Baseline(Week -4);Abnormal; NCS;n=19,20,20,22,22	12			
Baseline(Week-4);Abnormal;CS;n=19,20,20,22,22	1			
Day 29; Abnormal; NCS; n=17,19,18,17, 19	8			
Day 29; Abnormal; CS; n=17,19,18,17, 19	1			

Notes:

[181] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ECG mean heart rate

End point title	Change from Baseline in ECG mean heart rate

End point description:

Single measurements of 12-lead ECG were obtained in supine position using an ECG machine to measure HR. Week -4 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values at Day 29 minus Baseline value.

End point type	Secondary

End point timeframe:

Baseline and Day 29

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 25 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	17[182]	19[183]	18[184]	19[185]
Units: Beats per minute				
arithmetic mean (standard deviation)				
Beats per minute	-2.0 (± 8.66)	0.5 (± 10.53)	1.1 (± 7.40)	2.2 (± 7.51)

Notes:

[182] - Safety Population

[183] - Safety Population

[184] - Safety Population

[185] - Safety Population

End point values	Dapro 30 mg			
Subject group type	Reporting group			
Number of subjects analysed	17[186]			
Units: Beats per minute				
arithmetic mean (standard deviation)				

Beats per minute	0.9 (± 7.09)			

Notes:

[186] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ECG parameters including PR interval, QRS duration, QT interval and QTcB

End point title	Change from Baseline in ECG parameters including PR interval, QRS duration, QT interval and QTcB[187]

End point description:

Single measurements of 12-lead ECG were obtained in supine position using an ECG machine to measure PR interval, QRS duration, QT interval and QTcB. Week -4 values were considered as Baseline values. Change from Baseline was calculated by subtracting post-Baseline visit values at Day 29 minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Baseline and Day 29

Notes:

[187] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[188]	20[189]	20[190]	22[191]
Units: Milliseconds (msec)				
arithmetic mean (standard deviation)				
PR interval; n= 17, 18, 18, 16, 17	7.8 (± 16.86)	7.3 (± 12.37)	-3.3 (± 23.04)	-11.5 (± 24.77)
QRS duration; n= 17, 19, 18, 17, 19	-1.4 (± 14.05)	-5.7 (± 13.36)	-4.7 (± 47.01)	2.5 (± 8.97)
QT interval; n= 17, 19, 18, 17, 19	10.5 (± 27.16)	0.7 (± 31.11)	-19.2 (± 62.37)	-8.2 (± 33.24)
QTcB; n= 17, 19, 18, 17, 19	0.0 (± 30.84)	5.6 (± 17.40)	-3.7 (± 44.86)	-5.7 (± 31.65)

Notes:

[188] - Safety Population

[189] - Safety Population

[190] - Safety Population

[191] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[192]			
Units: Milliseconds (msec)				
arithmetic mean (standard deviation)				
PR interval; n= 17, 18, 18, 16, 17	2.1 (± 27.13)			
QRS duration; n= 17, 19, 18, 17, 19	1.7 (± 14.33)			

QT interval; n= 17, 19, 18, 17, 19	-1.4 (± 17.72)			
QTcB; n= 17, 19, 18, 17, 19	1.1 (± 20.84)			

Notes:

[192] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values at pre-dialysis and post-dialysis

End point title	Systolic blood pressure (SBP) and diastolic blood pressure (DBP) values at pre-dialysis and post-dialysis[193]

End point description:

Vital sign measurements including SBP and DBP were taken in a seated or semi-supine position in the dialysis chair at specific time points. SBP and DBP were measured pre-dialysis and post-dialysis. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[193] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[194]	20[195]	20[196]	22[197]
Units: Millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP; pre-dialysis; Day 1; n= 19, 20, 20, 22, 22	142.5 (± 22.15)	136.6 (± 15.39)	149.2 (± 26.36)	144.1 (± 17.01)
SBP; pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	138.8 (± 24.12)	138.3 (± 16.14)	139.0 (± 22.77)	142.3 (± 14.90)
SBP; pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	143.0 (± 22.08)	133.1 (± 18.65)	143.1 (± 23.21)	148.7 (± 19.17)
SBP; pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	140.0 (± 22.01)	137.9 (± 13.21)	142.0 (± 24.23)	147.1 (± 19.18)
DBP; pre-dialysis; Day 1; n= 19, 20, 20, 22, 22	71.9 (± 14.84)	68.8 (± 11.02)	73.3 (± 12.96)	72.2 (± 13.64)
DBP; pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	72.5 (± 17.76)	70.0 (± 11.92)	70.1 (± 10.50)	69.7 (± 12.43)
DBP; pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	70.4 (± 15.43)	63.5 (± 13.55)	70.9 (± 12.86)	72.7 (± 9.96)
DBP; pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	72.5 (± 14.73)	66.8 (± 11.94)	69.9 (± 13.54)	72.8 (± 10.52)
SBP; post-dialysis; Day 1; n= 19, 20, 20, 22, 22	138.6 (± 18.57)	137.0 (± 22.10)	139.9 (± 22.24)	140.1 (± 20.10)
SBP; post-dialysis; Day 15; n= 17, 20, 18, 21, 22	138.6 (± 21.83)	135.5 (± 21.63)	137.7 (± 23.02)	140.9 (± 15.34)
SBP; post-dialysis; Day 29; n= 17, 19, 18, 17, 19	135.7 (± 26.04)	130.1 (± 18.50)	133.7 (± 23.88)	147.8 (± 19.09)

SBP; post-dialysis; Day 43; n= 16, 20, 19, 21, 21	137.5 (± 22.74)	135.8 (± 21.05)	130.4 (± 15.47)	137.5 (± 22.74)
DBP; post-dialysis; Day 1; n= 19, 20, 20, 22, 22	72.1 (± 15.11)	67.9 (± 11.49)	68.7 (± 11.64)	71.5 (± 11.17)
DBP; post-dialysis; Day 15; n= 17, 20, 18, 21, 22	72.4 (± 16.41)	70.1 (± 12.84)	67.8 (± 11.10)	71.1 (± 9.51)
DBP; post-dialysis; Day 29; n= 17, 19, 18, 17, 19	73.9 (± 15.11)	64.4 (± 9.83)	67.9 (± 12.00)	72.9 (± 11.18)
DBP; post-dialysis; Day 43; n= 16, 20, 19, 21, 21	69.5 (± 15.24)	67.4 (± 10.90)	67.4 (± 11.24)	75.3 (± 7.89)

Notes:

[194] - Safety Population

[195] - Safety Population

[196] - Safety Population

[197] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[198]			
Units: Millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
SBP; pre-dialysis; Day 1; n= 19, 20, 20, 22, 22	144.1 (± 24.27)			
SBP; pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	146.6 (± 20.75)			
SBP; pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	144.2 (± 23.27)			
SBP; pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	149.0 (± 23.32)			
DBP; pre-dialysis; Day 1; n= 19, 20, 20, 22, 22	71.8 (± 14.38)			
DBP; pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	73.5 (± 13.69)			
DBP; pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	73.3 (± 13.17)			
DBP; pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	77.9 (± 16.03)			
SBP; post-dialysis; Day 1; n= 19, 20, 20, 22, 22	136.7 (± 21.15)			
SBP; post-dialysis; Day 15; n= 17, 20, 18, 21, 22	137.4 (± 17.58)			
SBP; post-dialysis; Day 29; n= 17, 19, 18, 17, 19	142.8 (± 23.96)			
SBP; post-dialysis; Day 43; n= 16, 20, 19, 21, 21	145.2 (± 20.66)			
DBP; post-dialysis; Day 1; n= 19, 20, 20, 22, 22	71.1 (± 12.92)			
DBP; post-dialysis; Day 15; n= 17, 20, 18, 21, 22	71.3 (± 11.07)			
DBP; post-dialysis; Day 29; n= 17, 19, 18, 17, 19	72.4 (± 12.43)			
DBP; post-dialysis; Day 43; n= 16, 20, 19, 21, 21	72.9 (± 12.60)			

Notes:

[198] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Pulse rate values at pre-dialysis and post-dialysis

End point title	Pulse rate values at pre-dialysis and post-dialysis[199]

End point description:

Vital sign measurements including pulse rate values were taken in a seated or semi-supine position in the dialysis chair. Pulse rate was measured pre-dialysis and post-dialysis. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[199] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[200]	20[201]	20[202]	22[203]
Units: Beats per minute				
arithmetic mean (standard deviation)				
Pre-dialysis; Day 1; n= 19, 20, 20, 22, 22	68.5 (± 7.95)	69.9 (± 9.18)	66.7 (± 7.01)	76.5 (± 9.35)
Pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	76.1 (± 10.31)	67.3 (± 9.20)	68.3 (± 7.51)	75.1 (± 12.68)
Pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	70.4 (± 8.31)	70.3 (± 11.54)	69.6 (± 9.53)	73.4 (± 11.45)
Pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	71.5 (± 9.17)	69.9 (± 9.34)	66.9 (± 6.74)	75.8 (± 8.29)
Post-dialysis; Day 1; n= 19, 20, 20, 22, 22	71.0 (± 11.54)	68.7 (± 11.19)	66.3 (± 8.37)	78.8 (± 11.61)
Post-dialysis; Day 15; n= 17, 20, 18, 21, 22	72.5 (± 12.69)	67.7 (± 12.24)	70.1 (± 12.49)	78.1 (± 15.72)
Post-dialysis; Day 29; n= 17, 19, 18, 17, 19	73.6 (± 7.10)	69.9 (± 9.60)	68.8 (± 11.29)	77.4 (± 10.04)
Post-dialysis; Day 43; n= 16, 20, 19, 21, 21	72.0 (± 12.04)	69.1 (± 10.21)	68.0 (± 10.28)	77.3 (± 10.26)

Notes:

[200] - Safety Population

[201] - Safety Population

[202] - Safety Population

[203] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[204]			
Units: Beats per minute				
arithmetic mean (standard deviation)				
Pre-dialysis; Day 1; n= 19, 20, 20, 22, 22	71.4 (± 11.25)			
Pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	72.1 (± 11.89)			
Pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	70.8 (± 9.91)			

Pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	71.3 (± 10.08)			
Post-dialysis; Day 1; n= 19, 20, 20, 22, 22	73.2 (± 12.77)			
Post-dialysis; Day 15; n= 17, 20, 18, 21, 22	73.0 (± 12.07)			
Post-dialysis; Day 29; n= 17, 19, 18, 17, 19	72.2 (± 9.52)			
Post-dialysis; Day 43; n= 16, 20, 19, 21, 21	71.9 (± 11.02)			

Notes:

[204] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Weight values at post-dialysis

End point title	Weight values at post-dialysis[205]

End point description:

Vital sign measurements including weight values were taken in a seated or semi-supine position in the dialysis chair. Weight was measured post-dialysis. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[205] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[206]	20[207]	20[208]	22[209]
Units: Kilograms (kg)				
arithmetic mean (standard deviation)				
Day 1; n= 19, 20, 20, 22, 22	82.38 (± 25.941)	80.04 (± 25.996)	78.83 (± 21.331)	76.03 (± 16.877)
Day 15; n= 17, 20, 18, 21, 22	84.24 (± 26.652)	80.00 (± 25.887)	79.82 (± 22.200)	75.55 (± 17.595)
Day 29; n= 17, 19, 18, 17, 19	83.22 (± 27.198)	81.04 (± 25.925)	80.02 (± 22.286)	76.07 (± 18.135)
Day 43; n= 16, 20, 19, 21, 21	83.93 (± 27.589)	80.21 (± 26.683)	79.25 (± 21.757)	73.66 (± 11.614)

Notes:

[206] - Safety Population

[207] - Safety Population

[208] - Safety Population

[209] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[210]			

Units: Kilograms (kg)				
arithmetic mean (standard deviation)				
Day 1; n= 19, 20, 20, 22, 22	79.38 (± 23.345)			
Day 15; n= 17, 20, 18, 21, 22	79.44 (± 23.500)			
Day 29; n= 17, 19, 18, 17, 19	82.66 (± 23.036)			
Day 43; n= 16, 20, 19, 21, 21	80.64 (± 23.347)			

Notes:

[210] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in SBP and DBP values at pre-dialysis and post-dialysis

End point title	Change from Baseline in SBP and DBP values at pre-dialysis and post-dialysis[211]

End point description:

Vital sign measurements including SBP and DBP were taken in a seated or semi-supine position in the dialysis chair. SBP and DBP were measured pre-dialysis and post-dialysis. Pre-dialysis Baseline value was defined as SBP and DBP value obtained pre-dialysis on Day 1. Post-dialysis Baseline value was defined as SBP and DBP value obtained post-dialysis at Week -2. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[211] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[212]	20[213]	20[214]	22[215]
Units: mmHg				
arithmetic mean (standard deviation)				
SBP; pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	-2.9 (± 22.03)	1.7 (± 14.14)	-5.6 (± 14.77)	-1.4 (± 16.35)
SBP; pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	-0.6 (± 20.32)	-3.9 (± 19.72)	-4.7 (± 18.17)	4.5 (± 20.03)
SBP; pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	-2.1 (± 21.34)	1.2 (± 17.14)	-6.2 (± 13.83)	4.3 (± 10.03)
SBP; post-dialysis; Day 15; n= 17, 20, 18, 21, 22	5.4 (± 21.39)	-3.6 (± 20.13)	6.1 (± 20.81)	-0.7 (± 22.33)
SBP; post-dialysis; Day 29; n= 17, 19, 18, 17, 19	2.3 (± 19.72)	-9.4 (± 18.50)	0.8 (± 24.79)	4.0 (± 19.76)
SBP; post-dialysis; Day 43; n= 16, 20, 19, 21, 21	3.1 (± 22.22)	-3.2 (± 21.71)	-3.6 (± 17.88)	4.7 (± 20.11)
DBP; pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	1.1 (± 10.57)	1.2 (± 8.85)	-1.7 (± 9.78)	-2.1 (± 11.04)

DBP; pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	-0.3 (± 11.09)	-4.7 (± 10.04)	-3.0 (± 8.99)	-0.1 (± 13.80)
DBP; pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	2.2 (± 8.80)	-2.0 (± 9.47)	-3.1 (± 11.06)	2.1 (± 11.00)
DBP; post-dialysis; Day 15; n= 17, 20, 18, 21, 22	2.4 (± 11.41)	2.4 (± 7.71)	-2.9 (± 11.11)	-0.8 (± 14.13)
DBP; post-dialysis; Day 29; n= 17, 19, 18, 17, 19	3.7 (± 12.93)	-2.5 (± 8.52)	-3.2 (± 11.61)	0.2 (± 10.59)
DBP; post-dialysis; Day 43; n= 16, 20, 19, 21, 21	-0.6 (± 10.07)	-0.3 (± 9.53)	-3.8 (± 12.13)	4.8 (± 10.28)

Notes:

[212] - Safety Population

[213] - Safety Population

[214] - Safety Population

[215] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[216]			
Units: mmHg				
arithmetic mean (standard deviation)				
SBP; pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	2.5 (± 20.68)			
SBP; pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	1.3 (± 17.51)			
SBP; pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	3.3 (± 19.47)			
SBP; post-dialysis; Day 15; n= 17, 20, 18, 21, 22	5.7 (± 21.07)			
SBP; post-dialysis; Day 29; n= 17, 19, 18, 17, 19	9.3 (± 19.03)			
SBP; post-dialysis; Day 43; n= 16, 20, 19, 21, 21	12.0 (± 20.19)			
DBP; pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	1.8 (± 12.68)			
DBP; pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	1.4 (± 10.50)			
DBP; pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	5.2 (± 15.08)			
DBP; post-dialysis; Day 15; n= 17, 20, 18, 21, 22	3.6 (± 9.84)			
DBP; post-dialysis; Day 29; n= 17, 19, 18, 17, 19	4.1 (± 9.33)			
DBP; post-dialysis; Day 43; n= 16, 20, 19, 21, 21	4.5 (± 9.99)			

Notes:

[216] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in pulse rate value at pre-dialysis and post-dialysis

End point title	Change from Baseline in pulse rate value at pre-dialysis and post-dialysis[217]

End point description:

Vital sign measurements including pulse rate were taken in a seated or semi-supine position in the dialysis chair. Pulse rate was measured pre-dialysis and post-dialysis. Pre-dialysis Baseline value was defined as pulse rate value obtained pre-dialysis on Day 1. Post-dialysis Baseline value was defined as pulse rate value obtained post-dialysis at Week -2. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[217] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[218]	20[219]	20[220]	22[221]
Units: Beats per minute				
arithmetic mean (standard deviation)				
Pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	7.0 (± 9.50)	-2.6 (± 8.46)	2.3 (± 5.76)	-1.4 (± 11.15)
Pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	2.4 (± 6.92)	0.9 (± 12.86)	3.4 (± 7.58)	-3.0 (± 9.14)
Pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	3.1 (± 9.59)	0.1 (± 6.57)	0.8 (± 6.11)	0.2 (± 6.79)
Post-dialysis; Day 15; n= 17, 20, 18, 21, 22	2.2 (± 11.61)	-1.2 (± 12.86)	1.1 (± 10.15)	4.4 (± 13.28)
Post-dialysis; Day 29; n= 17, 19, 18, 17, 19	4.2 (± 9.13)	1.5 (± 13.13)	-0.8 (± 9.79)	6.0 (± 7.50)
Post-dialysis; Day 43; n= 16, 20, 19, 21, 21	2.3 (± 8.67)	0.3 (± 12.96)	-0.8 (± 9.32)	3.9 (± 9.32)

Notes:

[218] - Safety Population

[219] - Safety Population

[220] - Safety Population

[221] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[222]			
Units: Beats per minute				
arithmetic mean (standard deviation)				
Pre-dialysis; Day 15; n= 17, 20, 18, 21, 22	0.7 (± 11.46)			
Pre-dialysis; Day 29; n= 17, 19, 18, 17, 19	0.5 (± 10.01)			
Pre-dialysis; Day 43; n= 16, 20, 19, 21, 21	-0.6 (± 10.03)			
Post-dialysis; Day 15; n= 17, 20, 18, 21, 22	0.5 (± 8.00)			
Post-dialysis; Day 29; n= 17, 19, 18, 17, 19	2.6 (± 9.04)			
Post-dialysis; Day 43; n= 16, 20, 19, 21, 21	-0.1 (± 9.08)			

Notes:

[222] - Safety Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in weight at post-dialysis

End point title	Change from Baseline in weight at post-dialysis[223]

End point description:

Vital sign measurements including weight were taken in a seated or semi-supine position in the dialysis chair. Weight was measured post-dialysis. Post-dialysis Baseline value was defined as SBP and DBP value obtained post-dialysis at Week -2. Change from Baseline was calculated by subtracting post-Baseline visit values minus Baseline value. Only those participants with data available at the specified data points were analyzed (represented by n= X in the category titles).

End point type	Secondary

End point timeframe:

Up to Day 43

Notes:

[223] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	Placebo	Dapro 10 mg	Dapro 15 mg	Dapro 30 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19[224]	20[225]	20[226]	22[227]
Units: kg				
arithmetic mean (standard deviation)				
Day 15; n= 17, 20, 18, 21, 22	-0.16 (± 0.634)	0.16 (± 0.971)	-0.01 (± 0.617)	-0.31 (± 1.215)
Day 29; n= 17, 19, 18, 17, 19	-0.11 (± 1.053)	-0.05 (± 1.583)	-1.23 (± 5.913)	-0.19 (± 1.244)
Day 43; n= 16, 20, 19, 21, 21	-0.21 (± 0.665)	0.37 (± 2.760)	-1.39 (± 5.759)	0.33 (± 2.169)

Notes:

[224] - Safety Population

[225] - Safety Population

[226] - Safety Population

[227] - Safety Population

End point values	Dapro 25 mg			
Subject group type	Subject analysis set			
Number of subjects analysed	22[228]			
Units: kg				
arithmetic mean (standard deviation)				
Day 15; n= 17, 20, 18, 21, 22	0.06 (± 0.799)			
Day 29; n= 17, 19, 18, 17, 19	-0.16 (± 1.046)			
Day 43; n= 16, 20, 19, 21, 21	0.15 (± 1.472)			

Notes:
[228] - Safety Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-therapy serious adverse events (SAEs) and non-serious adverse events (AEs) are presented from the start of study treatment up to follow up visit at Day 43.

Adverse event reporting additional description:

On-therapy SAEs and non-serious AEs are reported for members of the safety Population, comprised of all participants who received at least one dose of investigational drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Dapro 10 mg

Reporting group description:

Randomized participants received dapro 10 mg tablet via oral route three times weekly for 29 days.

Reporting group title	Placebo

Reporting group description:

Randomized participants received placebo tablet via oral route three times weekly for 29 days.

Reporting group title	Dapro 25 mg

Reporting group description:

Randomized participants received dapro 25 mg tablet via oral route three times weekly for 29 days.

Reporting group title	Dapro 15 mg

Reporting group description:

Randomized participants received dapro 15 mg tablet via oral route three times weekly for 29 days.

Reporting group title	Dapro 30 mg

Reporting group description:

Randomized participants received dapro 30 mg tablet via oral route three times weekly for 29 days

Serious adverse events	Dapro 10 mg	Placebo	Dapro 25 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 20 (15.00%)	2 / 19 (10.53%)	1 / 22 (4.55%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural myocardial infarction			

subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina unstable			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (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
Cardiac failure congestive			
subjects affected / exposed	2 / 20 (10.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Mesenteric artery stenosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	1 / 22 (4.55%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Dapro 15 mg	Dapro 30 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	2 / 22 (9.09%)	

number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural myocardial infarction			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina unstable			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Mesenteric artery stenosis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			

Fluid overload			
subjects affected / exposed	0 / 20 (0.00%)	1 / 22 (4.55%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Dapro 10 mg	Placebo	Dapro 25 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 20 (40.00%)	5 / 19 (26.32%)	2 / 22 (9.09%)
Injury, poisoning and procedural complications			
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Procedural hypotension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	1 / 22 (4.55%)
occurrences (all)	1	0	1
Cardiac disorders			
Bundle branch block left			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 20 (5.00%)	1 / 19 (5.26%)	0 / 22 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 22 (0.00%)
occurrences (all)	0	1	0

Pyrexia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 20 (10.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Vomiting			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 20 (0.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Helicobacter gastritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 19 (5.26%)	0 / 22 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 19 (0.00%)	0 / 22 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Dapro 15 mg	Dapro 30 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 20 (20.00%)	0 / 22 (0.00%)	
Injury, poisoning and procedural complications			
Arteriovenous fistula site haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Procedural hypotension			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			

Bundle branch block left			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Headache			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Dyspepsia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			

Depression			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	1 / 20 (5.00%)	0 / 22 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Helicobacter gastritis			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Viral infection			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	
Hypoglycaemia			
subjects affected / exposed	0 / 20 (0.00%)	0 / 22 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 May 2016	1. Inclusion criterion number 5 was modified to include the complete timeframe in which this criterion is applicable. 2. Other eligibility criteria have been clarified or updated for consistency with project level requirements. 3. Minor clarifications were made throughout the protocol, including clarifications related to hemoglobin stopping criteria, wording of the adverse events of special interest (AESIs), visit windows and the Time and Events Table. 4. References to investigational brochure (IB) Supplements 1 and 2 were added, and corresponding updates to the Risk Assessment Table were made. 5. Flexible language was added to allow for subjects to be dosed outside of the study clinic in exceptional circumstances. 6. The definition of the pharmacokinetic (PK) analysis population was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported