Clinical trial results:
A Prospective, Open-Label, Single-Arm, Multi-Center Study to Assess The Pharmacokinetics/Pharmacodynamics (PK/PD) AND Safety Of Different Cangrelor Doses In Neonatal Subjects At Risk Of Thrombosis.

Summary

EudraCT number	2016-000134-22
Trial protocol	Outside EU/EEA
Global end of trial date	30 August 2019

Results information

Result version number	v1 (current)
This version publication date	10 June 2021
First version publication date	10 June 2021

Trial information

Trial identification

Sponsor protocol code	MDCO-CAN-15-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02765633
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Chiesi Farmaceutici S.p.A
Sponsor organisation address	Via Palermo 26/A, Parma, Italy,
Public contact	Clinical Trial Trasparency, Chiesi Farmaceutici S.p.A., clinicaltrials_info@chiesi.com
Scientific contact	Clinical Trial Trasparency, Chiesi Farmaceutici S.p.A., clinicaltrials_info@chiesi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 April 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To assess the safety and PK / PD profile in this dose finding study of cangrelor in this neonatal population.
- To determine the plasma concentrations of cangrelor and its primary metabolite, AR-C69712, during administration and after cessation of the infusion in neonates.
- To determine the PD of cangrelor at various doses in neonates as assessed by light transmittance aggregometry (LTA) (primary)and microfluidic flow chamber (exploratory).
- To assess recovery of platelet function in neonates by LTA after cessation of the infusion.
- To determine the appropriate dose(s) to evaluate in future safety and efficacy trials in neonates.
- To evaluate the safety of cangrelor in neonatal subjects by evaluating adverse events (AEs), serious adverse events (SAEs) and Adverse Events of special interest (AESIs).

Protection of trial subjects:

An independent Data Monitoring Committee (DMC) was convened for this study for the purpose of reviewing safety data following completion of each initial cohort. A recommendation was to be provided by the DMC to the Sponsor to either continue the study without modification, to modify the study, or to discontinue the study following review of safety data from each cohort. The DMC was not charged with review of data from the Cohort 1 or Cohort 2 expansions.
This study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 Good Clinical Practices (GCP) guidelines, the Declaration of Helsinki, and other local regulations as applicable.
Written informed consent was obtained from all subjects' parents, guardians, or legally authorized representatives as per IRB guidelines before any study-related procedures (including any protocol-specified pre-treatment procedures) were performed. However, standard-of-care laboratory tests obtained prior to informed consent could have been utilized for screening to assess subject eligibility for the study if obtained within 72 hours prior to signing the informed consent.

Background therapy:

Cangrelor is an antiplatelet agent which is a non-thienopyridine adenosine triphosphate analogue. Cangrelor is an antagonist of the P2Y12 receptor that is given intravenously (IV) and is characterized by rapid, direct, potent, predictable, and reversible platelet inhibition with rapid offset of effect. Adenosine diphosphate (ADP) secreted from platelet-dense granules provides important autocrine and paracrine stimulation of platelet aggregation. Cangrelor effectively blocks ADP-induced platelet activation and aggregation as demonstrated in preclinical studies and clinical studies in the adult population.

Evidence for comparator:

No comparator expected.

Actual start date of recruitment	03 January 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 20

Worldwide total number of subjects	20
EEA total number of subjects	0

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	20
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 22 subjects were enrolled consisting of 20 eligible subjects who were assigned to cohorts and 2 subjects that failed screening. The first cohort (1-1E) includes 13 subjects (only 8 subjects have received cangrelor 0.5 µg/kg/min); the second cohort (2-2E) includes 7 subjects and all of them receive cangrelor 0.25 µg/kg/min.

Pre-assignment

Screening details:

During screening (Day -7 to Day -2), eligibility (inclusion/exclusion criteria) was assessed, medical history and concomitant medications were recorded, and the following assessments were performed: physical examination, clinical laboratory tests (complete blood count [CBC],chemistry panel), and an ultrasound examination of the head.

Pre-assignment period milestones

Number of subjects started	22[1]
Number of subjects completed	15

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Physician decision: 1
Reason: Number of subjects	Protocol deviation: 2
Reason: Number of subjects	Consent withdrawn by subject: 2
Reason: Number of subjects	no central venous access post-surgery: 1
Reason: Number of subjects	subdural hemorrhage - hematoma: 1

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: According to the protocol, 22 subjects were screened for the study, but only 20 subjects were enrolled and 15 were treated as follow:
COHORT 1-1E: 13 subjects enrolled and cohort-assigned, but only 8 subjects have received the treatment.
COHORT 2-2E: 7 subjects enrolled and cohort-assigned, and all the 7 subjects have received the treatment.

Period 1

Period 1 title	1_Treatment and FU (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment - Cohort 1-1E

Arm description:

Active treatment with cangrelor 0.5 µg/kg/min was administered as a single-dose continuous IV infusion for approximately 1 hour via a peripheral IV or central venous line.

Arm type	Experimental
Investigational medicinal product name	Cangrelor
Investigational medicinal product code	
Other name	Kengreal®
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Cangrelor is a sterile lyophilized powder for reconstitution and dilution for administration.
Diluted cangrelor was administered intravenously (IV) at 0.5 µg/kg/min, as a single-dose continuous infusion for approximately 1 hour via a peripheral IV or central venous line.

Arm title	Treatment - Cohort 2-2E

Arm description:

Active treatment with cangrelor 0.25 µg/kg/min was administered as a single-dose continuous IV infusion for approximately 1 hour via a peripheral IV or central venous line.

Arm type	Experimental
Investigational medicinal product name	Cangrelor
Investigational medicinal product code	
Other name	Kengreal®
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Cangrelor is a sterile lyophilized powder for reconstitution and dilution for administration.
Diluted cangrelor was administered intravenously (IV) at 0.25 µg/kg/min, as a single-dose continuous infusion for approximately 1 hour via a peripheral IV or central venous line.

Number of subjects in period 1[2]	Treatment - Cohort 1-1E	Treatment - Cohort 2-2E
Started	8	7
Completed	8	7

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: According to the protocol, 22 subjects were screened for the study, but only 20 subjects were enrolled and 15 were treated as follow:
COHORT 1-1E: 13 subjects enrolled and cohort-assigned, but only 8 subjects have received the treatment.
COHORT 2-2E: 7 subjects enrolled and cohort-assigned, and all the 7 subjects have received the treatment.

Baseline characteristics

Reporting groups

Reporting group title	Treatment - Cohort 1-1E

Reporting group description:

Active treatment with cangrelor 0.5 µg/kg/min was administered as a single-dose continuous IV infusion for approximately 1 hour via a peripheral IV or central venous line.

Reporting group title	Treatment - Cohort 2-2E

Reporting group description:

Active treatment with cangrelor 0.25 µg/kg/min was administered as a single-dose continuous IV infusion for approximately 1 hour via a peripheral IV or central venous line.

Reporting group values	Treatment - Cohort 1-1E	Treatment - Cohort 2-2E	Total
Number of subjects	8	7	15
Age categorical Units: Subjects			
Newborns (0-28 days)	8	7	15
Age continuous Units: days			
arithmetic mean	3.8	4.7	
standard deviation	± 2.87	± 3.15	-
Gender categorical Units: Subjects			
Female	4	5	9
Male	4	2	6
Race characteristic Units: Subjects			
white	6	6	12
black/african american	2	1	3
Baseline weight Units: Subjects			
Baseline weight 2.60-3.00 Kg	3	6	9
Baseline weight 3.01-3.31 Kg	4	1	5
Baseline weight not recorded	1	0	1

Subject analysis sets

Subject analysis set title	Treatment Cohort 1-1E - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all subjects who received any infusion length of study drug. Treatment classification was based on the actual cangrelor dosage received. This was the primary population for the safety analyses.

Subject analysis set title	Treatment Cohort 2-2E - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all subjects who received any infusion length of study drug. Treatment classification was based on the actual cangrelor dosage received. This was the primary population for the safety analyses.

Subject analysis set title	Treatment Cohort 1-1E - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Sub-group analysis is referred to the PK population, that includes all subjects who had any valid samples measured for study drug concentrations. Treatment classification was based on the actual treatment received.

Subject analysis set title	Treatment Cohort 2-2E - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Sub-group analysis is referred to the PK population,that includes all subjects who had any valid samples measured for study drug concentrations. Treatment classification was based on the actual treatment received.

Reporting group values	Treatment Cohort 1-1E - Safety	Treatment Cohort 2-2E - Safety	Treatment Cohort 1-1E - PK
Number of subjects	8	7	8
Age categorical Units: Subjects			
Newborns (0-28 days)	8	7	8
Age continuous Units: days			
arithmetic mean	3.8	4.7	3.8
standard deviation	± 2.87	± 3.15	± 2.87
Gender categorical Units: Subjects			
Female	4	5	4
Male	4	2	4
Race characteristic Units: Subjects			
white	6	6	6
black/african american	2	1	2
Baseline weight Units: Subjects			
Baseline weight 2.60-3.00 Kg	3	6	3
Baseline weight 3.01-3.31 Kg	4	1	4
Baseline weight not recorded	1	0	1

Reporting group values	Treatment Cohort 2-2E - PK		
Number of subjects	7		
Age categorical Units: Subjects			
Newborns (0-28 days)	7		
Age continuous Units: days			
arithmetic mean	4.7		
standard deviation	± 3.15		
Gender categorical Units: Subjects			
Female	5		
Male	2		
Race characteristic Units: Subjects			
white	6		
black/african american	1		

Baseline weight Units: Subjects			
Baseline weight 2.60-3.00 Kg	6		
Baseline weight 3.01-3.31 Kg	1		
Baseline weight not recorded	0		

End points

End points reporting groups

Reporting group title	Treatment - Cohort 1-1E

Reporting group description:

Active treatment with cangrelor 0.5 µg/kg/min was administered as a single-dose continuous IV infusion for approximately 1 hour via a peripheral IV or central venous line.

Reporting group title	Treatment - Cohort 2-2E

Reporting group description:

Active treatment with cangrelor 0.25 µg/kg/min was administered as a single-dose continuous IV infusion for approximately 1 hour via a peripheral IV or central venous line.

Subject analysis set title	Treatment Cohort 1-1E - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all subjects who received any infusion length of study drug. Treatment classification was based on the actual cangrelor dosage received. This was the primary population for the safety analyses.

Subject analysis set title	Treatment Cohort 2-2E - Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Included all subjects who received any infusion length of study drug. Treatment classification was based on the actual cangrelor dosage received. This was the primary population for the safety analyses.

Subject analysis set title	Treatment Cohort 1-1E - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Sub-group analysis is referred to the PK population, that includes all subjects who had any valid samples measured for study drug concentrations. Treatment classification was based on the actual treatment received.

Subject analysis set title	Treatment Cohort 2-2E - PK
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Sub-group analysis is referred to the PK population,that includes all subjects who had any valid samples measured for study drug concentrations. Treatment classification was based on the actual treatment received.

Primary: 1_Proportion of subjects who achieved ≥90% inhibition of maximal and final platelet aggregation

End point title	1_Proportion of subjects who achieved ≥90% inhibition of maximal and final platelet aggregation[1]

End point description:

Proportion of subjects in each cohort who achieved ≥90% inhibition of maximal and final platelet aggregation as measured by LTA using 5 µM and 20 µM ADP in platelet rich plasma. % Inhibition is defined, only for timepoints during and after infusion, as (the pre-infusion value - the value during or after infusion)/the pre-infusion value) * 100. Data are presented as % of subjects who achieved ≥90% inhibition of maximal and final platelet aggregation, with their 95% confidence intervals (CIs).

End point type	Primary

End point timeframe:

Inhibition of aggregation was measured by LTA at baseline, at 15 min before completing the cangrelor infusion, and at 60 min after completing the cangrelor infusion.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is planned for this end point.

End point values	Treatment Cohort 1-1E - Safety	Treatment Cohort 2-2E - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[2]	7[3]		
Units: percentage of subjects				
number (confidence interval 95%)				
A≥90% inhibition of final aggregation using 5µM	100 (29.2 to 100)	100 (29.2 to 100)		
B≥90% inhibition of maximal aggregation using 5µM	80 (28.4 to 99.5)	60 (14.7 to 94.7)		
C≥90% inhibition of maximal aggregation using 20µM	50 (11.8 to 88.2)	28.6 (3.7 to 71.0)		
D≥90% inhibition of final aggregation using 20µM	50 (11.8 to 88.2)	80 (28.4 to 99.5)		

Notes:

[2] - Patients reached target/patients evaluable:
A:3/3(100%)
B:4/5(80%)
C:3/6(50%)
D:3/6(50%)

[3] - Patients reached target/patients evaluable:
A:3/3(100%)
B:3/5(60%)
C:2/7(28.6%)
D:4/5(80%)

Statistical analyses

No statistical analyses for this end point

Primary: 1_Percent inhibition of platelet aggregation by LTA during the infusion-mean values

End point title	1_Percent inhibition of platelet aggregation by LTA during the infusion-mean values[4]

End point description:

Inhibition of platelet aggregation was measured by LTA at baseline (15 to 60 minutes before the start of the cangrelor infusion), at 15 minutes before completing the cangrelor infusion, and at 60 minutes after completing the cangrelor infusion. The percent inhibition of platelet aggregation 45 minutes into the cangrelor infusion was measured by LTA using 5 µM and 20 µM ADP in platelet-rich plasma. Data are presented as % inhibition of maximal and final platelet aggregation reporting mean and relevant standard deviation.

End point type	Primary

End point timeframe:

Inhibition of aggregation was measured by LTA at baseline, at 15 min before completing the cangrelor infusion, and at 60 min after completing the cangrelor infusion.

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is planned for this end point.

End point values	Treatment Cohort 1-1E - Safety	Treatment Cohort 2-2E - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[5]	7[6]		
Units: percentage				
arithmetic mean (standard deviation)				
A inhibition of final aggregation using 5 µM	99 (± 1.75)	100 (± 0)		

B inhibition of maximal aggregation using 5 µM	93.7 (± 6.45)	88.2 (± 13.49)		
C inhibition of final aggregation using 20 µM	89 (± 12.5)	94.1 (± 8.68)		
D inhibition of maximal aggregation using 20 µM	89 (± 11.42)	76.3 (± 16.89)		

Notes:

[5] - number of patients evaluated:
A:3
B:5
C:6
D:6

[6] - number of patients evaluated:
A:3
B:5
C:5
D:7

Statistical analyses

No statistical analyses for this end point

Primary: 1_Percent inhibition of platelet aggregation by LTA during the infusion-median values

End point title	1_Percent inhibition of platelet aggregation by LTA during the infusion-median values[7]

End point description:

Inhibition of platelet aggregation was measured by LTA at baseline (15 to 60 minutes before the start of the cangrelor infusion), at 15 minutes before completing the cangrelor infusion, and at 60 minutes after completing the cangrelor infusion. The percent inhibition of platelet aggregation 45 minutes into the cangrelor infusion was measured by LTA using 5 µM and 20 µM ADP in platelet-rich plasma. Data are presented as inhibition of maximal and final platelet aggregation reporting median (min and max).

End point type	Primary

End point timeframe:

Inhibition of aggregation was measured by LTA at baseline, at 15 min before completing the cangrelor infusion, and at 60 min after completing the cangrelor infusion.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is planned for this end point.

End point values	Treatment Cohort 1-1E - Safety	Treatment Cohort 2-2E - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[8]	7[9]		
Units: percentage				
median (full range (min-max))				
A inhibition of final aggregation using 5 µM	100 (97 to 100)	100 (100 to 100)		
B inhibition of maximal aggregation using 5 µM	92.9 (84.8 to 100)	96 (68.1 to 100)		
C inhibition of final aggregation using 20 µM	91.7 (73.1 to 100)	97.3 (79.2 to 100)		
Dinhibition of maximal aggregation using 20 µM	91.2 (69 to 100)	69.6 (53.2 to 98.3)		

Notes:

[8] - number of patients evaluated:
A:3
B:5
C:6

D:6

[9] - number of patients evaluated:
A:3
B:5
C:5
D:7

Statistical analyses

No statistical analyses for this end point

Primary: 2_Percent recovery of platelet function by LTA assay after the infusion

End point title	2_Percent recovery of platelet function by LTA assay after the infusion[10]

End point description:

Recovery of platelet function in neonates was defined, only for timepoints after infusion, as 100 - percent inhibition. The recovery of platelet was measured by LTA using 5 µM and 20 µM ADP in platelet-rich plasma. Data are presented as % of subjects who achieved ≥ 90% recovery of maximal and final platelet aggregation.

End point type	Primary

End point timeframe:

Percent recovery of platelet function was measured by LTA assay 1 hour after completion of the cangrelor infusion.

Notes:

[10] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point.

End point values	Treatment Cohort 1-1E - Safety	Treatment Cohort 2-2E - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[11]	7[12]		
Units: percentage of subjects				
number (not applicable)				
A≥90% recovery of final aggregation using 5µM	33.3	66.7		
B≥90% recovery of maximal aggregation using 5µM	40.0	60		
C≥90% recovery of final aggregation using 20 µM	66.7	60		
D ≥90% recovery of maximal aggregation using 20µM	66.7	71.4		

Notes:

[11] - Patients reached target/patients evaluable:
A:1/3(33.3%)
B:2/5(40%)
C:4/6(66.7%)
D:4/6(66.7%)
[12] - Patients reached target/patients evaluable:
A:2/3(66.7%)
B:3/5(60%)
C:3/5(60%)
D:5/7(71.4%)

Statistical analyses

No statistical analyses for this end point

Primary: 2_Percent recovery of platelet function by LTA assay after the infusion-mean values

End point title	2_Percent recovery of platelet function by LTA assay after the infusion-mean values[13]

End point description:

Recovery of platelet was measured by LTA (1 hour after completion of the cangrelor infusion).
The percent inhibition of platelet aggregation 1 hour after cangrelor infusion was measured by LTA using 5 µM and 20 µM ADP in platelet-rich plasma. Data are presented as ≥ 90% inhibition of maximal and final platelet aggregation (mean and relevant standard deviation).

End point type	Primary

End point timeframe:

Percent recovery of platelet function was measured by LTA assay 1 hour after completion of the cangrelor infusion.

Notes:

[13] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is planned for this end point.

End point values	Treatment Cohort 1-1E - Safety	Treatment Cohort 2-2E - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[14]	7[15]		
Units: percentage				
arithmetic mean (standard deviation)				
A≥90% recovery of final aggregation using 5 µM	77 (± 11.51)	66.2 (± 57.31)		
B≥90% recovery of maximal aggregation using 5 µM	86.9 (± 12.42)	68.5 (± 44.28)		
C ≥90% recovery of final aggregation using 20 µM	82.6 (± 32.62)	64.6 (± 48.69)		
D≥90% recovery of maximal aggregation using 20µM	84.5 (± 30.02)	82.5 (± 32.07)		

Notes:

[14] - number of patients evaluated:
A:3
B:5
C:6
D:6
[15] - number of patients evaluated:
A:3
B:5
C:5
D:7

Statistical analyses

No statistical analyses for this end point

Primary: 3_Summary of PK parameters by dose (Cmax)

End point title	3_Summary of PK parameters by dose (Cmax)[16]

End point description:

PK parameter was measured by Cmax (ng/mL) after 60-minute IV infusion with a cangrelor dose of 0.50 µg/kg/min and 0.25 µg/kg/min.
Cmax was mesaured for cangrelor and AR-C69712XX (Cangrelor metabolite). The maximum measured cangrelor plasma concentrations were observed at the first sampling time point at 45 minutes post-start of infusion. Data was expressed with mean and standard deviation.

End point type	Primary

End point timeframe:

Following the 60-minute IV infusion with a cangrelor dose of 0.50 µg/kg/min and 0.25 µg/kg/min, the maximum measured cangrelor plasma concentrations were observed at the first sampling time point at 45 minutes post-start of infusion.

Notes:

[16] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is planned for this end point.

End point values	Treatment Cohort 1-1E - PK	Treatment Cohort 2-2E - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[17]	7[18]		
Units: ng/mL				
arithmetic mean (standard deviation)				
Cangrelor	59.5 (± 15.1)	18.9 (± 7.43)		
AR-C69712XX	18.6 (± 5.29)	9.6 (± 3.44)		

Notes:

[17] - PK population

[18] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: 3_Summary of PK parameters by dose (Tmax)

End point title	3_Summary of PK parameters by dose (Tmax)[19]

End point description:

PK parameter was measured by Tmax (min) for cangrelor and AR-C69712XX (Cangrelor metabolite). Cangrelor was administrated at the following dose: 0.50 µg/kg/min and 0.25 µg/kg/min. Tmax for cangrelor was occurred at the first sampling time near to the end of infusion. Tmax for AR-C69712XX occurred at the end of IV infusion duration of 1 hour or at the first sampling time post end of infusion. Data was expressed with median (minimum-maximum).

End point type	Primary

End point timeframe:

Tmax for cangrelor was occurred at the first sampling time near to the end of infusion.
Tmax for AR-C69712XX occurred at the end of IV infusion duration of 1 hour or at the first sampling time post end of infusion.

Notes:

[19] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is planned for this end point.

End point values	Treatment Cohort 1-1E - PK	Treatment Cohort 2-2E - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[20]	7[21]		
Units: minutes				
median (full range (min-max))				
Cangrelor	45 (30 to 55)	45 (30 to 55)		
AR-C69712XX	70 (45 to 90)	65 (55 to 70)		

Notes:

[20] - PK population

[21] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: 3_Summary of PK parameters by dose (AUC 0-t)

End point title	3_Summary of PK parameters by dose (AUC 0-t)[22]

End point description:

PK parameter was measured by AUC 0-t from the start of dosing (zero) until the time of the last measurable concentration (AUC0-t) values. AUC 0-t was mesaured for cangrelor and AR-C69712XX (Cangrelor metabolite). The subjects received the following dose of cangrelor: 0.50 µg/kg/min and 0.25 µg/kg/min. Data was expressed with mean and standard deviation.

End point type	Primary

End point timeframe:

Area under the plasma concentration time curve was mesaured from the start of dosing (zero) until the time of the last measurable concentration (AUC0-t) values.

Notes:

[22] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is planned for this end point.

End point values	Treatment Cohort 1-1E - PK	Treatment Cohort 2-2E - PK		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[23]	7[24]		
Units: min*ng/mL				
arithmetic mean (standard deviation)				
Cangrelor	1985 (± 643)	519 (± 161)		
AR-C69712XX	3400 (± 2110)	1540 (± 650)		

Notes:

[23] - PK population

[24] - PK population

Statistical analyses

No statistical analyses for this end point

Primary: 4_Summary of TEAEs (number of subject %)

End point title	4_Summary of TEAEs (number of subject %)[25]

End point description:

TEAEs were recorded from the time of the start of the cangrelor infusion until 48 ±6 hours post-treatment. TEAE includes any TEAE, Treatment emergent AESI and Treatment emergent SAE. Data were expressed with percent of number of subjects.

End point type	Primary

End point timeframe:

TEAEs were recorded from the time of the start of the cangrelor infusion until 48 ±6 hours post-treatment.

Notes:

[25] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is planned for this end point.

End point values	Treatment Cohort 1-1E - Safety	Treatment Cohort 2-2E - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[26]	7[27]		
Units: percentage of subjects				
number (not applicable)				
Any TEAE	100	85.7		
Treatment-Emergent AESI	12.5	14.3		
Treatment-Emergent SAE	12.5	14.3		

Notes:

[26] - safety population

[27] - safety population

Statistical analyses

No statistical analyses for this end point

Primary: 4_Summary of TEAEs (event)

End point title	4_Summary of TEAEs (event)[28]

End point description:

TEAEs were recorded from the time of the start of the cangrelor infusion until 48 ±6 hours post-treatment. TEAE includes any TEAE, Treatment emergent AESI and Treatment emergent SAE. Data were expressed as number of events.

End point type	Primary

End point timeframe:

TEAEs were recorded from the time of the start of the cangrelor infusion until 48 ±6 hours post-treatment.

Notes:

[28] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is planned for this end point.

End point values	Treatment Cohort 1-1E - Safety	Treatment Cohort 2-2E - Safety		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8[29]	7[30]		
Units: event				
Any TEAE	24	27		
Treatment-Emergent AESI	2	1		
Treatment-Emergent SAE	2	1		

Notes:

[29] - safety population

[30] - safety population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: AEs recorded from the time of the start of cangrelor infusion until 48 ±6 hours post-treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Treatment- Cohort 1-1E
Reporting group description: 8 subjects treated with 0.5 µg/kg/min of cangrelor.	
Reporting group title	Treatment- Cohort 2-2E
Reporting group description: 7 subjects treated with 0.25 µg/kg/min of cangrelor.	

Serious adverse events	Treatment- Cohort 1-1E	Treatment- Cohort 2-2E	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Supraventricular tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment- Cohort 1-1E	Treatment- Cohort 2-2E	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	6 / 7 (85.71%)	
Investigations			
Blood magnesium			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
C-reactive protein increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Calcium ionised decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Haematocrit decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Oxygen saturation decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Prothrombin time prolonged			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Urine output decreased			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 8 (50.00%)	0 / 7 (0.00%)	
occurrences (all)	4	0	
Haemoglobin			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Vascular disorders			
Capillary leak syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Deep vein thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hypotension			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	2 / 7 (28.57%)	
occurrences (all)	1	2	
Peripheral artery thrombosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Thrombosis			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Low cardiac output syndrome			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 8 (25.00%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Oedema			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Renal and urinary disorders			

Hydronephrosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Fluid overload			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hyperglycaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	3 / 7 (42.86%)	
occurrences (all)	0	3	
Hyperkalaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hypervolaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hypocalcaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 8 (37.50%)	3 / 7 (42.86%)	
occurrences (all)	3	3	
Hypokalaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	2 / 7 (28.57%)	
occurrences (all)	1	2	
Hypomagnesaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Hyponatraemia			
alternative assessment type: Non-systematic			

subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hypovolaemia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Metabolic acidosis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 April 2016	Amendment #1 - The main changes from original version to Version 1 are: - Made the microfluidic flow chamber measurements an exploratory endpoint; - Inclusion criterion #2 modified to more specifically identify populations at high risk of a thrombotic event; - Exclusion criterion #5 changed to exclude subjects with weight 2.5 kg.
27 May 2016	Amendment #2 - The main changes from Version 1 to Version 2 are: - LTA to be performed using 5 µM and 20 µM ADP in platelet rich plasma to provide as complete information as possible on the PD profile of cangrelor in this population; - AEs and bleeding events to be graded using the 5-point scale recommended by the CTCAE (changed from grading AEs and bleeding events as mild, moderate, or severe for more accurate grading of the severity of AEs.
05 May 2017	Amendment # 3 - The main changes from Version 2 to Version 3 are: - The study was to include a minimum of 20 neonatal subjects; - The references to the volume of blood to be collected for PK and PD assessments was removed, and maximum mL/kg specified. The volumes of blood collected would be based on weight. - Added that any abnormal clinical laboratory test result obtained after treatment with cangrelor and/or during the follow up period which met the definition of AE or SAE. To provide guidelines to assist with determination of laboratory abnormalities as AEs and SAEs and to ensure they were properly recorded and repored. - Medication errors associated with AEs or SAEs to be reported as protocol deviations.
20 June 2017	Amendment #4 - The main changes from Version 3 to Version 4 are: - Added that the baseline ultrasound of the head could be performed up until 2 hours prior to surgery.To define the initial head ultrasound as baseline ultrasound and clarify the time frame in which the baseline ultrasound was performed.
22 January 2018	Amendment #5 - The main changes from Version 4 to Version 5 are: - Exclusion criterion #8 modified to “chest and/or mediastinal tube total fluid volume output of >3 mL/kg/hr at the time cangrelor is to be administered”. To clarify that the exclusionary volume of 3mL/kg/hr applied to the total output from both chest and mediastinal tubes, inclusive of all types of fluid output (e.g., clear, serosanguinous fluid,grossly bloody); - Exclusion criterion #9 modified to “subjects with evidence of sever hepatic or renal impairmen". To clarify that subjects with hepatic and renal impairment rather than failure were excluded per protocol criteria; - Safety endpoint(s) were revised to specify “clinically relevant” bleeding and to include bleeding in the urinary tract. To provide clarification regarding bleeding asAESI; add reference to urinary tract as bleeding is also assessed via urinalysis post-infusion.

25 September 2018	Amendment #6 - The main changes from Version 5 to Version 6 are: - Added expansion Cohort 1 and Cohort 2 To specify the expansion of the number of subjects in Cohort 1 and Cohort 2 and to obtain complete data from at least 5 subjects in each cohort; - Changed the PK and PD sample collection schedule for the expansion Cohorts 1 and 2 compared with the original PK and PD time points used for the first 5 subjects in Cohorts 1 and 2; - Addition of "diagnosed intravascular thrombosis" and "a confirmed decrease in either hemoglobin or hematocrit of >20% from the most proximate value measured at a protocol-required time point" to the list of AESIs to comply with the request of the DMC to include intravascular thrombosis as an AESI.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33078501