Clinical trial results:
Open-Label, Multicentre, Multiple Dose Study to Evaluate Pharmacokinetics, Safety and Tolerability of Cariprazine in Adolescent Subjects with Schizophrenia, Schizoaffective- and Schizophreniform Disorders Compared to Adults

Summary

EudraCT number	2016-002327-29
Trial protocol	BG
Global end of trial date	19 June 2018

Results information

Result version number	v1 (current)
This version publication date	15 August 2019
First version publication date	15 August 2019

Trial information

Trial identification

Sponsor protocol code	RGH-188-201

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Gedeon Richter Plc
Sponsor organisation address	Gyömrői út 19-21, Budapest, Hungary, 1103
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001652-PIP01-14
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	08 August 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2018
Global end of trial reached?	Yes
Global end of trial date	19 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

•Assess PK, safety and tolerability of up to 3 doses of once daily cariprazine capsules
•Investigate dosing requirements of cariprazine in adolescents
•Determination of the PK parameters of cariprazine (CAR) and its two metabolites, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR) in adolescents at steady state, compared to adults
•Estimation of the inter-individual variability of the PK parameters in the adolescent population
•Evaluation of the relationship between different covariates (age, body weight) and the PK parameters
•Examination of the dose linearity of exposure in adolescents

Protection of trial subjects:

Measures to reduce pain during blood draws may be applied if needed (lidocaine/prilocaine cream, etc).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 March 2017
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	Russian Federation: 28
Country: Number of subjects enrolled	Bulgaria: 35
Worldwide total number of subjects	63
EEA total number of subjects	35

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)	43
Adults (18-64 years)	20

From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adolescent (13 to < 15 or 15 to < 18 years old) and adult (18 to 40 years old) patients with schizophrenia, schizoaffective, or schizophreniform disorder (per DSM-5).

Pre-assignment

Screening details:

During the screening phase of up to 14 days the patients were evaluated for inclusion and exclusion criteria, followed by 28 days of treatment and 14 days of follow-up phase.

Period 1

Period 1 title	Treatment phase
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1, Age group A

Arm description:

Cariprazine 1.5 mg, age 13 to < 15 years

Arm type	Experimental
Investigational medicinal product name	Cariprazine 1.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1.5 mg Cariprazine capsule, once daily

Arm title	Cohort 1, Age group B

Arm description:

Cariprazine 1.5 mg, age 15 to < 18 years

Arm type	Experimental
Investigational medicinal product name	Cariprazine 1.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

1.5 mg Cariprazine capsule, once daily

Arm title	Cohort 1, Age group C

Arm description:

Cariprazine 1.5 mg, age 18 to < 40 years

Arm type	Experimental

Investigational medicinal product name	Cariprazine 1.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:
1.5 mg Cariprazine capsule, once daily

Arm title	Cohort 2, Age group A

Arm description:
Cariprazine 3.0 mg, age 13 to < 15 years

Arm type	Experimental
Investigational medicinal product name	Cariprazine 3.0 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:
3.0 mg cariprazine capsule, hard, once daily

Arm title	Cohort 2, Age group B

Arm description:
Cariprazine 3.0 mg, age 15 to < 18 years

Arm type	Experimental
Investigational medicinal product name	Cariprazine 3.0 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:
3.0 mg cariprazine capsule, hard, once daily

Arm title	Cohort 2, Age group C

Arm description:
Cariprazine 3.0 mg, age 18 to < 40 years

Arm type	Experimental
Investigational medicinal product name	Cariprazine 3.0 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:
3.0 mg cariprazine capsule, hard, once daily

Arm title	Cohort 3, Age group A

Arm description:
Cariprazine 6.0 mg, age 13 to < 15 years

Arm type	Experimental
Investigational medicinal product name	Cariprazine 6.0 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:
6.0 mg Cariprazine capsule, once daily

Arm title	Cohort 3, Age group B
Arm description: Cariprazine 6.0 mg, age 15 to < 18 years	
Arm type	Experimental
Investigational medicinal product name	Cariprazine 6.0 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 6.0 mg Cariprazine capsule, once daily	
Arm title	Cohort 3, Age group C
Arm description: Cariprazine 6.0 mg, age 18 to < 40 years	
Arm type	Experimental
Investigational medicinal product name	Cariprazine 6.0 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details: 6.0 mg Cariprazine capsule, once daily	

Number of subjects in period 1	Cohort 1, Age group A	Cohort 1, Age group B	Cohort 1, Age group C
Started	6	6	6
Completed	6	6	6
Not completed	0	0	0
early discontinuation	-	-	-

Number of subjects in period 1	Cohort 2, Age group A	Cohort 2, Age group B	Cohort 2, Age group C
Started	10	9	8
Completed	9	8	8
Not completed	1	1	0
early discontinuation	1	1	-

Number of subjects in period 1	Cohort 3, Age group A	Cohort 3, Age group B	Cohort 3, Age group C
Started	6	6	6
Completed	6	6	6
Not completed	0	0	0
early discontinuation	-	-	-

Period 2	
Period 2 title	Follow-up phase
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded
Blinding implementation details: Not blinded	

Arms	
Arm title	Follow-up arm
Arm description: IMP was discontinued without down-titration. Safety and PK follow-up performed.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 2	Follow-up arm
Started	61
Completed	61

Baseline characteristics

Reporting groups	
Reporting group title	Treatment phase

Reporting group description: -

Reporting group values	Treatment phase	Total	
Number of subjects	63	63	
Age categorical Units: Subjects			
13 to <15 years	22	22	
15 to <18 years	21	21	
18 to <40 years	20	20	
Gender categorical Units: Subjects			
Female	19	19	
Male	44	44	

End points

End points reporting groups

Reporting group title	Cohort 1, Age group A
Reporting group description: Cariprazine 1.5 mg, age 13 to < 15 years	
Reporting group title	Cohort 1, Age group B
Reporting group description: Cariprazine 1.5 mg, age 15 to < 18 years	
Reporting group title	Cohort 1, Age group C
Reporting group description: Cariprazine 1.5 mg, age 18 to < 40 years	
Reporting group title	Cohort 2, Age group A
Reporting group description: Cariprazine 3.0 mg, age 13 to < 15 years	
Reporting group title	Cohort 2, Age group B
Reporting group description: Cariprazine 3.0 mg, age 15 to < 18 years	
Reporting group title	Cohort 2, Age group C
Reporting group description: Cariprazine 3.0 mg, age 18 to < 40 years	
Reporting group title	Cohort 3, Age group A
Reporting group description: Cariprazine 6.0 mg, age 13 to < 15 years	
Reporting group title	Cohort 3, Age group B
Reporting group description: Cariprazine 6.0 mg, age 15 to < 18 years	
Reporting group title	Cohort 3, Age group C
Reporting group description: Cariprazine 6.0 mg, age 18 to < 40 years	
Reporting group title	Follow-up arm
Reporting group description: IMP was discontinued without down-titration. Safety and PK follow-up performed.	

Primary: Determination of the Cmax

End point title	Determination of the Cmax[1]
End point description:	

End point type	Primary
End point timeframe: at steady state on Day 28	

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: Descriptive statistics was provided for plasma concentrations and PK parameters.

End point values	Cohort 1, Age group A	Cohort 1, Age group B	Cohort 1, Age group C	Cohort 2, Age group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	6
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cariprazine	4.39 (± 48.2)	4.33 (± 26.9)	3.91 (± 30)	8.43 (± 28.7)
Desmethyl-Cariprazine	0.91 (± 47.6)	1.09 (± 59.2)	1.01 (± 43.3)	2.62 (± 75)
Didesmethyl-Cariprazine	6.15 (± 54.9)	7.03 (± 57.8)	6.66 (± 40.4)	17.12 (± 61.9)

End point values	Cohort 2, Age group B	Cohort 2, Age group C	Cohort 3, Age group A	Cohort 3, Age group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cariprazine	9.12 (± 20.8)	7.65 (± 29.6)	16.02 (± 40.1)	18.67 (± 18.5)
Desmethyl-Cariprazine	2.33 (± 57.5)	2.01 (± 5.6)	5.11 (± 39.8)	3.85 (± 30)
Didesmethyl-Cariprazine	15 (± 30.8)	15.18 (± 29.9)	33.49 (± 51.1)	23.78 (± 81.9)

End point values	Cohort 3, Age group C			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cariprazine	16.6 (± 17.8)			
Desmethyl-Cariprazine	4.67 (± 34.7)			
Didesmethyl-Cariprazine	24.02 (± 50)			

Statistical analyses

No statistical analyses for this end point

Primary: Determination of AUC

End point title	Determination of AUC[2]

End point description:

End point type	Primary

End point timeframe:

at steady state on Day 28

Notes:

[2] - 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: Descriptive statistics was provided for plasma concentrations and PK parameters.

End point values	Cohort 1, Age group A	Cohort 1, Age group B	Cohort 1, Age group C	Cohort 2, Age group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	6
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
Cariprazine	70.4 (± 41.9)	67.7 (± 34.1)	68.2 (± 33.1)	123.1 (± 37.1)
Desmethyl-Cariprazine	18.06 (± 45.3)	20.28 (± 55.5)	19.58 (± 34.4)	46.47 (± 75.9)
Didesmethyl-Cariprazine	140.2 (± 51.8)	157.4 (± 59.5)	153.6 (± 39.3)	381.3 (± 64)

End point values	Cohort 2, Age group B	Cohort 2, Age group C	Cohort 3, Age group A	Cohort 3, Age group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
Cariprazine	143 (± 27.4)	124.6 (± 36.6)	242.3 (± 31.9)	318.1 (± 28.9)
Desmethyl-Cariprazine	46.07 (± 54.1)	39.7 (± 4.7)	94.12 (± 31.4)	77.2 (± 27.1)
Didesmethyl-Cariprazine	338.2 (± 33.2)	333.3 (± 30.3)	726.7 (± 52)	502.8 (± 85.2)

End point values	Cohort 3, Age group C			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng*h/mL				
geometric mean (geometric coefficient of variation)				
Cariprazine	262.7 (± 19.3)			
Desmethyl-Cariprazine	90.67 (± 40.2)			
Didesmethyl-Cariprazine	529.4 (± 50)			

Statistical analyses

No statistical analyses for this end point

Primary: Determination of CLss/F

End point title	Determination of CLss/F[3]

End point description:

apparent oral plasma clearence at steady state

End point type	Primary

End point timeframe:

at steady state on Day 28

Notes:

[3] - 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: Descriptive statistics was provided for plasma concentrations and PK parameters.

End point values	Cohort 1, Age group A	Cohort 1, Age group B	Cohort 1, Age group C	Cohort 2, Age group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	6
Units: L/h				
geometric mean (geometric coefficient of variation)				
Cariprazine	21.3 (± 41.9)	22.2 (± 34.1)	22 (± 33.1)	24.4 (± 37.1)
Desmethyl-Cariprazine	83.1 (± 45.3)	74 (± 55.5)	76.6 (± 34.4)	64.6 (± 75.9)
Didesmethyl-Cariprazine	10.7 (± 51.8)	9.53 (± 59.5)	9.77 (± 39.3)	7.87 (± 64)

End point values	Cohort 2, Age group B	Cohort 2, Age group C	Cohort 3, Age group A	Cohort 3, Age group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: L/h				
geometric mean (geometric coefficient of variation)				
Cariprazine	21 (± 27.4)	24.1 (± 36.6)	24.8 (± 31.9)	18.9 (± 28.9)
Desmethyl-Cariprazine	65.1 (± 54.1)	75.6 (± 4.7)	63.7 (± 31.4)	77.7 (± 27.1)
Didesmethyl-Cariprazine	8.87 (± 33.2)	9 (± 30.3)	8.26 (± 52)	11.93 (± 85.2)

End point values	Cohort 3, Age group C			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: L/h				
geometric mean (geometric coefficient of variation)				
Cariprazine	22.8 (± 19.3)			
Desmethyl-Cariprazine	66.2 (± 40.2)			
Didesmethyl-Cariprazine	11.33 (± 50)			

Statistical analyses

No statistical analyses for this end point

Primary: Determination of T1/2

End point title	Determination of T1/2[4]
End point description: apparent terminal half-life	
End point type	Primary
End point timeframe: at steady state on Day 28	

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: Descriptive statistics was provided for plasma concentrations and PK parameters.

End point values	Cohort 1, Age group A	Cohort 1, Age group B	Cohort 1, Age group C	Cohort 2, Age group A
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	5	6
Units: hour				
geometric mean (geometric coefficient of variation)				
Cariprazine	41.3 (± 25.6)	38.8 (± 6.5)	50.8 (± 33.7)	40 (± 32)
Desmethyl-Cariprazine	50.9 (± 32.5)	42.1 (± 35)	44.1 (± 50.9)	32.4 (± 0)
Didesmethyl-Cariprazine	165 (± 24.3)	176 (± 23.6)	229 (± 35.1)	137 (± 23.1)

End point values	Cohort 2, Age group B	Cohort 2, Age group C	Cohort 3, Age group A	Cohort 3, Age group B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6	6	6	6
Units: hour				
geometric mean (geometric coefficient of variation)				
Cariprazine	37.4 (± 25.6)	32.2 (± 8.8)	31.9 (± 24.8)	32.8 (± 32.5)
Desmethyl-Cariprazine	25 (± 43.8)	38.2 (± 55.9)	24.9 (± 0)	0 (± 0)
Didesmethyl-Cariprazine	154 (± 25.6)	171 (± 21.6)	137 (± 32.3)	143 (± 14.6)

End point values	Cohort 3, Age group C			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: hour				
geometric mean (geometric coefficient of variation)				
Cariprazine	27 (± 9.2)			
Desmethyl-Cariprazine	22.8 (± 46)			
Didesmethyl-Cariprazine	157 (± 22.2)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time points for adverse event assessment: -14 day, baseline, days 2, 3, 4, 5, 14, 21, 28, 29 (end of study), follow up visits on days 31, 35, 42.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Age group 13-<15 years, Cariprazine 1.5 mg - 6 mg
Reporting group description: -	
Reporting group title	Age group 15-<18 years, Cariprazine 1.5 mg - 6 mg
Reporting group description: -	
Reporting group title	Age group 18-40 years, Cariprazine 1.5 mg - 6 mg

Reporting group description: -

Serious adverse events	Age group 13-<15 years, Cariprazine 1.5 mg - 6 mg	Age group 15-<18 years, Cariprazine 1.5 mg - 6 mg	Age group 18-40 years, Cariprazine 1.5 mg - 6 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	0 / 20 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Age group 13-<15 years, Cariprazine 1.5 mg - 6 mg	Age group 15-<18 years, Cariprazine 1.5 mg - 6 mg	Age group 18-40 years, Cariprazine 1.5 mg - 6 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 22 (50.00%)	11 / 21 (52.38%)	9 / 20 (45.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 22 (0.00%)	2 / 21 (9.52%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Cardiac disorders			
Sinus arrhythmia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Tachycardia			

subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Nervous system disorders			
Sedation			
subjects affected / exposed	3 / 22 (13.64%)	2 / 21 (9.52%)	0 / 20 (0.00%)
occurrences (all)	3	4	0
Akathisia			
subjects affected / exposed	0 / 22 (0.00%)	5 / 21 (23.81%)	0 / 20 (0.00%)
occurrences (all)	0	7	0
Dizziness postural			
subjects affected / exposed	0 / 22 (0.00%)	2 / 21 (9.52%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Somnolence			
subjects affected / exposed	0 / 22 (0.00%)	5 / 21 (23.81%)	2 / 20 (10.00%)
occurrences (all)	0	12	3
Tension headache			
subjects affected / exposed	0 / 22 (0.00%)	4 / 21 (19.05%)	0 / 20 (0.00%)
occurrences (all)	0	10	0
Disturbance in attention			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Tremor			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 22 (0.00%)	2 / 21 (9.52%)	0 / 20 (0.00%)
occurrences (all)	0	2	0
Asthenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	2 / 20 (10.00%)
occurrences (all)	0	0	2
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 22 (0.00%)	3 / 21 (14.29%)	1 / 20 (5.00%)
occurrences (all)	0	11	1
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Dry mouth			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Hyperhidrosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Abnormal dreams			
subjects affected / exposed	0 / 22 (0.00%)	2 / 21 (9.52%)	0 / 20 (0.00%)
occurrences (all)	0	3	0
Sleep disorder			
subjects affected / exposed	0 / 22 (0.00%)	2 / 21 (9.52%)	1 / 20 (5.00%)
occurrences (all)	0	2	1
Tension			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 21 (0.00%)	1 / 20 (5.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2017	Modification of the following items was implemented during the global amandement of the final protocol: • ECG related exclusion criterion has been revised to implement age-specific and gender-specific values for bradycardia and tachycardia diagnosis • use of certain EPS medications has been allowed • involvement of at least one investigator into the interim data review meeting after completion of subgroup 2B and 2A • replacement procedures • list of Adverse Event of Special Interest has been modified • change in the definition of PK Analysis Population • protocol deviations and violations • Administrative changes, clarifications (central ECG lab procedures, use of catheter, nominal sampling time point with allowed time deviation for Day 31, Day 35 and Day 42 PK samples), correction of in-text discrepancies and spelling errors

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported