Clinical trial results:
A Randomized Open Label, Parallel Group Study to Evaluate the Hemodynamic Effects of Cafedrine/Theodrenaline vs Norepinephrine in the Treatment of Intraoperative Arterial Hypotension in Adults after Induction of General Anesthesia

Summary

EudraCT number	2021-001954-76
Trial protocol	DE
Global end of trial date	29 December 2023

Results information

Result version number	v1 (current)
This version publication date	28 December 2024
First version publication date	28 December 2024

Trial information

Trial identification

Sponsor protocol code	TV48531-CV-40190

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Ratiopharm GmbH Teva EU Medical Affairs
Sponsor organisation address	Graf-Arco-Str. 3, Ulm, Germany, 89079
Public contact	Medical Affairs Germany, ratiopharm GmbH, medical.affairs@teva.de
Scientific contact	Medical Affairs Germany, ratiopharm GmbH, medical.affairs@teva.de

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 October 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 December 2023
Global end of trial reached?	Yes
Global end of trial date	29 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the hemodynamic effects of the test (Cafedrine/Theodrenaline) and reference (Noradrenaline) IMPs administered as bolus injection and subsequently as continuous infusion in a surgical cohort of at-risk adult patients who develop intraoperative hypotension

Protection of trial subjects:

This study was conducted in full accordance with the ICH Harmonised Tripartite Guideline, Guideline for Good Clinical Practice. The leading ethic committee of the Medical Faculty of the Philipps-University Marburg approved this trial on 23rd February 2022 (Az.202/21 A-ff). All participating hospitals obtained approval by their responsible ethics committees. Written informed consent was obtained from each patient before any study specific procedures or assessments were done.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 May 2022
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 212
Worldwide total number of subjects	212
EEA total number of subjects	212

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)	49
From 65 to 84 years	149

85 years and over	14

Subject disposition

Recruitment

Recruitment details:

Study duration: one and a half years

Pre-assignment

Screening details:

221 participants with planned elective vascular surgery and 212 participants were randomly assigned; 192 of the randomized participants received treatment and were evaluable for safety and efficacy-analysis; 190 participants completed the trial.

Period 1

Period 1 title	Overall Study Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cafedrine/Theodrenaline

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Akrinor®, Cafedrine/Theodrenaline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Study Phase 1: Bolus injection at MAP <70 mmHg: 1.0 mg Cafedrine/kg body weight (idealized).
Additional bolus at MAP <70 mmHg: 1.0 mg Cafedrine/kg body weight (idealized).

Study Phase 2: Continuous Infusion: Initial Infusion Rate:
MAP <70 mmHg: 160 mg Cafedrine/h PLUS Rescue Bolus (0.5 mg Cafedrine/kg IBW);
MAP: 70-90 mmHg: 80 mg Cafedrine/h;
MAP >90 mmHg: 40 mg Cafedrine/h.

Arm title	Noradrenaline

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Sinora 1 mg/ml concentrate for solution for infusion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Study Phase 1: Bolus injection at MAP <70 mmHg: 0.1 mcg Noradrenaline/kg body weight (idealized).
Additional bolus at MAP <70 mmHg: 0.1 mcg Noradrenaline/kg body weight (idealized).

Study Phase 2: Continuous Infusion:
Initial Infusion Rate:
MAP <70 mmHg: 180 mcg Noradrenaline/h PLUS Rescue Bolus (0.05 mcg Noradrenaline/kg IBW); MAP = 70-90 mmHg: 60 mcg Noradrenaline/h
MAP >90 mmHg: 30 mcg Noradrenaline/h

Number of subjects in period 1	Cafedrine/Theodrenaline	Noradrenaline
Started	108	104
Treated	99	93
Modified Intent-to-treat	98	92
Completed	98	92
Not completed	10	12
Adverse event, serious fatal	1	-
Consent withdrawn by subject	3	2
Did not develop IOH	2	1
Physician decision	2	2
Surgery postponed/canceled or nobody available	2	5
Not specified	-	1
Surgery (cut) started prior or during study	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Cafedrine/Theodrenaline
Reporting group description: -	
Reporting group title	Noradrenaline
Reporting group description: -	

Reporting group values	Cafedrine/Theodrenaline	Noradrenaline	Total
Number of subjects	108	104	212
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	32	17	49
From 65-84 years	67	82	149
85 years and over	9	5	14
Age Continuous Units: years			
arithmetic mean	70	71	
standard deviation	± 9	± 8	-
Gender Categorical Units: Subjects			
Female	36	34	70
Male	72	70	142

End points

End points reporting groups

Reporting group title	Cafedrine/Theodrenaline
Reporting group description: -	
Reporting group title	Noradrenaline
Reporting group description: -	

Primary: The treatment related difference in average CI [DaCI] during study phase 1

End point title	The treatment related difference in average CI [DaCI] during study phase 1
End point description:	
The treatment related difference is calculated as the difference in means of individual area above the CI ref* (CI ref is individually defined as the CI-measurement at the start of the treatment)	
End point type	Primary
End point timeframe:	
0-20 minutes after initial treatment	

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: units				
arithmetic mean (confidence interval 95%)	0.189 (0.123 to 0.254)	0.075 (0.035 to 0.116)		

Statistical analyses

Statistical analysis title	Difference in average CI during study phase 1
Comparison groups	Cafedrine/Theodrenaline v Noradrenaline
Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	ANOVA
Parameter estimate	Difference in average CI above reference
Point estimate	0.113
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	0.036

Primary: Treatment-related difference in average MAP [DaMAP] during study phase 2

End point title	Treatment-related difference in average MAP [DaMAP] during study phase 2

End point description:

Difference calculated as the mean difference between areas below the target MAP value (90 mmHg). Non-inferiority is concluded, if DaMAP can be shown to be lower than the non-inferiority margin (5 mmHg) at one-sided alpha-level 0.025

End point type	Primary

End point timeframe:

>20-40 minutes after initial treatment with IMP-bolus injection

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	92		
Units: mmHg				
arithmetic mean (confidence interval 95%)	3.16 (2.27 to 4.05)	5.35 (4.41 to 6.29)		

Statistical analyses

Statistical analysis title	Difference in average MAP in study phase 2

Statistical analysis description:

Non-inferiority

Comparison groups	Cafedrine/Theodrenaline v Noradrenaline
Number of subjects included in analysis	190
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Difference in average MAP below 90 mmHg
Point estimate	-2.19
Confidence interval	
level	Other: 97.5 %
sides	1-sided
upper limit	-0.91

Notes:

[1] - CT arm - NR arm

Secondary: Treatment related difference in average MAP [DaMAP] below the target MAP value (90 mmHg) during study phase 1

End point title	Treatment related difference in average MAP [DaMAP] below the target MAP value (90 mmHg) during study phase 1

End point description:

End point type	Secondary

End point timeframe:

0-20 minutes after initial treatment with IMP-bolus injection

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: mmHg				
arithmetic mean (confidence interval 95%)	8.80 (7.62 to 9.97)	13.64 (12.65 to 14.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment related differences in change in SVRI (systemic vascular resistance index) (study phase 1)

End point title	Treatment related differences in change in SVRI (systemic vascular resistance index) (study phase 1)

End point description:

End point type	Secondary

End point timeframe:

0-20 minutes after initial treatment with IMP-bolus injection

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: dyne-s/cm5/m2				
arithmetic mean (confidence interval 95%)	2666.75 (2646.21 to 2687.29)	2614.60 (2593.04 to 2636.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment related differences in change in SVI (Stroke volume index) (study phase 1)

End point title	Treatment related differences in change in SVI (Stroke volume index) (study phase 1)

End point description:

End point type	Secondary

End point timeframe:

0-20 minutes after initial treatment with IMP-bolus injection

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: ml/beat/m2				
arithmetic mean (confidence interval 95%)	38.22 (38.01 to 38.42)	38.47 (38.26 to 38.68)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment related differences in heart rate (study phase 1)

End point title	Treatment related differences in heart rate (study phase 1)

End point description:

End point type	Secondary

End point timeframe:

0-20 minutes after initial treatment with IMP-bolus injection

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: bpm				
arithmetic mean (confidence interval 95%)	70.69 (70.43 to 70.95)	62.72 (62.45 to 62.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment related differences in change of dP/dtmax (study phase 1)

End point title	Treatment related differences in change of dP/dtmax (study phase 1)

End point description:

End point type	Secondary

End point timeframe:

0-20 minutes after initial treatment with IMP-bolus injection

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: mmHg/sec				
arithmetic mean (confidence interval 95%)	975.24 (968.23 to 982.25)	765.40 (758.16 to 772.63)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment related differences in change of CI (Cardiac Index) (study phase 1)

End point title	Treatment related differences in change of CI (Cardiac Index) (study phase 1)

End point description:

End point type	Secondary

End point timeframe:

0-20 minutes after initial treatment with IMP-bolus injection

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: L/min/m2				
arithmetic mean (confidence interval 95%)	2.63 (2.62 to 2.64)	2.36 (2.35 to 2.38)		

Statistical analyses

No statistical analyses for this end point

Secondary: Difference in change of MAP (mean arterial blood pressure) (study phase 1)

End point title	Difference in change of MAP (mean arterial blood pressure) (study phase 1)

End point description:

End point type	Secondary

End point timeframe:

0-20 minutes after initial treatment with IMP-bolus injection

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: mmHg				
arithmetic mean (confidence interval 95%)	86.62 (86.24 to 87.01)	78.47 (78.08 to 78.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of treatment specific incidence rates of overshooting blood pressure (MAP 110 mmHg) events during study phase 1

End point title	Ratio of treatment specific incidence rates of overshooting blood pressure (MAP 110 mmHg) events during study phase 1

End point description:

End point type	Secondary

End point timeframe:

0-20 minutes after initial treatment with IMP-bolus injection

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: Overshooting events/100 measurements				
arithmetic mean (confidence interval 95%)	9.33 (8.57 to 10.14)	3.45 (2.98 to 3.97)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio of treatment specific incidence rates of low blood pressure (MAP <80 mmHg) events during study phase 1

End point title	Ratio of treatment specific incidence rates of low blood pressure (MAP <80 mmHg) events during study phase 1

End point description:

blood pressure (bp)

End point type	Secondary

End point timeframe:

0-20 minutes after initial treatment with IMP-bolus injection

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: low bp events/100 measurements				
arithmetic mean (confidence interval 95%)	41.0 (39.4 to 42.7)	62.6 (60.5 to 64.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment related differences in number of additional bolus-injections during study phase 1

End point title	Treatment related differences in number of additional bolus-injections during study phase 1

End point description:

End point type	Secondary

End point timeframe:

First IMP-application until start of infusion

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: bolus injections per 100 minutes				
arithmetic mean (confidence interval 95%)	9.9 (8.585 to 11.392)	39.9 (37.060 to 42.837)		

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment related differences in extra measures to stabilize blood pressure during study phase 1

End point title	Treatment related differences in extra measures to stabilize blood pressure during study phase 1

End point description:

Measures include: `Volume/Fluid´, `Medication´, `Position´, `Anesthesia depth´ and `Other´

End point type	Secondary

End point timeframe:

First IMP-application until start of infusion

End point values	Cafedrine/Theodrenaline	Noradrenaline		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	93		
Units: measures per 100 minutes				
arithmetic mean (confidence interval 95%)	0.448 (0.205 to 0.851)	0.481 (0.220 to 0.913)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The study period was defined for each patient as the time period from the first administration of the IMP to the end of study for the patient.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.1

Reporting groups

Reporting group title	Cafedrine/Theodrenaline
Reporting group description: -	
Reporting group title	Noradrenaline

Reporting group description: -

Serious adverse events	Cafedrine/Theodrenaline	Noradrenaline	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 99 (2.02%)	3 / 93 (3.23%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Vascular disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 99 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 99 (1.01%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 99 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	0 / 99 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
septic shock			
subjects affected / exposed	1 / 99 (1.01%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Cafedrine/Theodrenaline	Noradrenaline	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 99 (6.06%)	9 / 93 (9.68%)	
Investigations			
Troponin T increased			
subjects affected / exposed	2 / 99 (2.02%)	1 / 93 (1.08%)	
occurrences (all)	2	1	
Troponin I increased			
subjects affected / exposed	0 / 99 (0.00%)	2 / 93 (2.15%)	
occurrences (all)	0	2	
Vascular disorders			
Procedural hypertension			
subjects affected / exposed	1 / 99 (1.01%)	3 / 93 (3.23%)	
occurrences (all)	1	3	
Arterial hemorrhage			
subjects affected / exposed	1 / 99 (1.01%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Compartment syndrome			
subjects affected / exposed	1 / 99 (1.01%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 99 (1.01%)	0 / 93 (0.00%)	
occurrences (all)	1	0	
Sinus node dysfunction			

subjects affected / exposed occurrences (all)	0 / 99 (0.00%) 0	1 / 93 (1.08%) 1	
Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all)	 0 / 99 (0.00%) 0	 1 / 93 (1.08%) 1	
Metabolism and nutrition disorders Acidosis subjects affected / exposed occurrences (all)	 0 / 99 (0.00%) 0	 1 / 93 (1.08%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2023	The following major procedural changes (not all-inclusive) were made to the protocol: 1) Definition of Reference Cardiac Index (CIref) was changed (Primary Endpoint 1): Old: CImin is individually defined as the mean of three measurements obtained directly prior to induction of anesthesia. New: CI ref is individually defined as the CI-measurement obtained at the start of the treatment
25 September 2023	1) Time specification (Study Phase 2): old: 21-40 min. new: 20-40 min. 2) Secondary endpoint 2e and 2f was added 3) Exploratory endpoint 1f and 1g was added 4) Collection of basal parameters (prior anesthesia induction): HR was added 5) Clinical laboratory test, parameter evaluated: Troponin T was added 6) Recording and Reporting of Adverse Events: time period for recording of (serious) adverse event was changed: old: from signature of informed consent to the end of the study; new: from first administration of IMP to the end of the study for the patient. All events occurring between signing the informed consent form to the first administration of the IMP will be recorded in CRF as Medical events and are not considered as adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported