



## Clinical trial results:

**A prospective, randomized, double blinded, crossover, two-treatment, two-sequence, short term pharmacokinetic, pharmacodynamic and tolerability, single centre study to compare AOP200704 vs. Esmolol in healthy subjects.**

### Summary

EudraCT number	2010-023311-34
Trial protocol	CZ
Global end of trial date	05 December 2011

### Results information

Result version number	v1 (current)
This version publication date	01 February 2017
First version publication date	01 February 2017

### Trial information

#### Trial identification

Sponsor protocol code	CPA 368-10
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#### Additional study identifiers

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

Notes:

### Sponsors

Sponsor organisation name	AOP Orphan Pharmaceuticals AG
Sponsor organisation address	Wilhelminenstrasse 91/II f, Vienna, Austria, 1160
Public contact	Dr. Michael Zörer, AOP Orphan Pharmaceuticals AG, 0043 1503724446, michael.zorer@aoporphan.com
Scientific contact	Univ.-Doz. Dr. Günther Krumpl, MRN Medical Research Network GmbH, 0043 6765667804, g.krumpl@medresnet.com

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 January 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2011
Global end of trial reached?	Yes
Global end of trial date	05 December 2011
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the short-term pharmacokinetics, pharmacodynamics and tolerability of Landiolol compared with Esmolol in Caucasians

Protection of trial subjects:

Subject's cardiovascular status was assessed at screening, including 2D echo. Study subjects' confinement period lasted from at least 11 hours before until at least 8 hours after study drug administration. The volunteers staid lying in bed from the start of dobutamine infusion until 2 hours after the end of landiolol or esmolol infusion. Continuous ECG monitoring, regular assessments of vital signs and local tolerability were performed. The group of 16 subjects was divided into subgroups. Max. 3 subjects in each subgroup were administered the study drug sequentially during one day.

Administration of dobutamine in each of the following subjects started not earlier than after 30 minutes of study medication infusion of the previous subject, i.e. at time when the hemodynamic response of the previous subject to administered medication was known.

A wash-out period of at least 2 days between doses in study cross-over periods was adhered to. Each subject completed an End-of-study examination within 72 hours after completion of Period 2.

Background therapy:

Dobutamin ADMEDA 250 (Dobutamine hydrochloride 280 mg (corresponding to dobutamine 250 mg)) was administered intravenously. A dose of 10 µg/kg/min was administered for ten minutes, incrementing by 5 µg/kg/min for ten minutes until the requested heart rate increase by 30 bpm above baseline value or a maximum dose of 30 µg/kg/min was reached. The infusion at the target rate was maintained for another 20 minutes, then during and after the Test or Reference (T/R) infusion until the heart rate returned to value before T/R infusion or for 60 minutes after the end of T/R infusion at maximum.

Evidence for comparator:

Esmolol, another short acting intravenous beta blocker registered since 2006 with a well known efficacy and safety profile was chosen as a comparator. Since the steady state effective doses of landiolol (10-40 µg/kg/min), and Esmolol (50-200 µg/kg/min) share a relation of 1:5 a dose of about 10 and 50 µg/kg/min was chosen for landiolol and esmolol.

Actual start date of recruitment	08 March 2011
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	Czech Republic: 16
Worldwide total number of subjects	16
EEA total number of subjects	16

Notes:

<b>Subjects enrolled per age group</b>	
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)	16
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All 16 subjects met the inclusion criteria and were randomized.

### Period 1

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

Blinding implementation details:

The study was conducted as a double-blinded study. Pharmacist and the pump operator were the unblinded parties. These two, however, had no influence either on data collection or data capturing, reporting or evaluation.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Treatment sequence A

Arm description:

Administration of AOP200704 in Period 1 (TEST treatment), administration of Esmolol in Period 2 (REFERENCE treatment).

Arm type	Experimental
Investigational medicinal product name	AOP200704
Investigational medicinal product code	CPA 368-10/T
Other name	Onoact® 50
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Test treatment - active ingredients: Landiolol hydrochloride. Dose: 10 µg/kg/min for 60 minutes. Infusion started 20 minutes after the effective dobutamine infusion rate had been started and was maintained for 60 minutes at the basic infusion rate if the basic infusion rate was effective. In case the heart rate was not reduced by 20 bpm or less within 40 minutes of the start of AOP200704 infusion at the basic rate, the rate of the infusion was planned to be doubled for the next 60 minutes.

Investigational medicinal product name	Esmolol
Investigational medicinal product code	CPA 368-10/R
Other name	Brevibloc
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Reference treatment. Dose: 50 µg/kg/min for 60 minutes.

Infusion started 20 minutes after the effective dobutamine infusion rate had been started and was maintained for 60 minutes at the basic infusion rate if the basic infusion rate was effective. In case the heart rate was not reduced by 20 bpm or less within 40 minutes of the start of Esmolol infusion at the basic rate, the rate of the infusion was planned to be doubled for the next 60 minutes.

<b>Arm title</b>	Treatment sequence B
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Arm description:

Administration of Esmolol in Period 1 (REFERENCE treatment), administration of AOP200704 in Period 2 (TEST treatment).

Arm type	Experimental
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Investigational medicinal product name	AOP200704
Investigational medicinal product code	CPA 368-10/T
Other name	Onoact® 50
Pharmaceutical forms	Powder for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Test treatment - active ingredients: Landiolol hydrochloride. Dose: 10 µg/kg/min for 60 minutes. Infusion started 20 minutes after the effective dobutamine infusion rate had been started and was maintained for 60 minutes at the basic infusion rate if the basic infusion rate was effective. In case the heart rate was not reduced by 20 bpm or less within 40 minutes of the start of AOP200704 infusion at the basic rate, the rate of the infusion was planned to be doubled for the next 60 minutes.

Investigational medicinal product name	Esmolol
Investigational medicinal product code	CPA 368-10/R
Other name	Brevibloc
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Reference treatment. Dose: 50 µg/kg/min for 60 minutes. Infusion started 20 minutes after the effective dobutamine infusion rate had been started and was maintained for 60 minutes at the basic infusion rate if the basic infusion rate was effective. In case the heart rate was not reduced by 20 bpm or less within 40 minutes of the start of Esmolol infusion at the basic rate, the rate of the infusion was planned to be doubled for the next 60 minutes.

<b>Number of subjects in period 1</b>	Treatment sequence A	Treatment sequence B
Started	8	8
Completed Period 1	8	8
Started Period 2	8	8
Completed	8	8

## Baseline characteristics

### Reporting groups

Reporting group title	Overall trial
Reporting group description: -	

Reporting group values	Overall trial	Total	
Number of subjects	16	16	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	16	16	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	33.1		
standard deviation	± 8.21	-	
Gender categorical			
Units: Subjects			
Female	8	8	
Male	8	8	
Race			
Units: Subjects			
Caucasian	16	16	
Smoking Habits			
Units: Subjects			
Non-smoker	12	12	
Smoker	4	4	
Weight			
Units: kilogram(s)			
arithmetic mean	75.9		
standard deviation	± 8.27	-	
Height			
Units: centimetre(s)			
arithmetic mean	176.9		
standard deviation	± 6.96	-	
BMI			
Units: kilogram(s)/square meter			
arithmetic mean	24.16		
standard deviation	± 1.715	-	

**Subject analysis sets**

Subject analysis set title	Landiolol
Subject analysis set type	Per protocol
Subject analysis set description: Group intended for analysis of PK parameters of landiolol.	
Subject analysis set title	Esmolol
Subject analysis set type	Per protocol
Subject analysis set description: Group intended for analysis of PK parameters of Esmolol.	
Subject analysis set title	Pharmacodynamic (PD) Set
Subject analysis set type	Per protocol
Subject analysis set description: The Pharmacodynamic set consists of all subjects who completed the trial without violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the pharmacodynamic analysis. Subject with protocol deviation that could affect pharmacodynamic analysis was excluded from the Pharmacodynamic Set. The Pharmacodynamic Set was used for Pharmacodynamic analysis.	
Subject analysis set title	AOP200704 (PD set)
Subject analysis set type	Per protocol
Subject analysis set description: Group intended for PD analysis of AOP200704.	
Subject analysis set title	Esmolol (PD set)
Subject analysis set type	Per protocol
Subject analysis set description: Group intended for PD analysis of Esmolol.	

<b>Reporting group values</b>	Landiolol	Esmolol	Pharmacodynamic (PD) Set
Number of subjects	16	16	15
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			15
Age continuous Units: years arithmetic mean standard deviation			33.7 ± 8.2
Gender categorical Units: Subjects			
Female			8
Male			7
Race Units: Subjects			
Caucasian			15

Smoking Habits			
Units: Subjects			
Non-smoker			11
Smoker			4
Weight			
Units: kilogram(s)			
arithmetic mean			75.2
standard deviation	±	±	± 8.04
Height			
Units: centimetre(s)			
arithmetic mean			176.3
standard deviation	±	±	± 6.65
BMI			
Units: kilogram(s)/square meter			
arithmetic mean			24.12
standard deviation	±	±	± 1.769

<b>Reporting group values</b>	AOP200704 (PD set)	Esmolol (PD set)	
Number of subjects	15	15	
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±	±	
Gender categorical			
Units: Subjects			
Female			
Male			
Race			
Units: Subjects			
Caucasian			
Smoking Habits			
Units: Subjects			
Non-smoker			
Smoker			
Weight			
Units: kilogram(s)			
arithmetic mean			
standard deviation	±	±	
Height			



Units: centimetre(s)			
arithmetic mean			
standard deviation	±	±	
BMI			
Units: kilogram(s)/square meter			
arithmetic mean			
standard deviation	±	±	

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## End points

### End points reporting groups

Reporting group title	Treatment sequence A
Reporting group description: Administration of AOP200704 in Period 1 (TEST treatment), administration of Esmolol in Period 2 (REFERENCE treatment).	
Reporting group title	Treatment sequence B
Reporting group description: Administration of Esmolol in Period 1 (REFERENCE treatment), administration of AOP200704 in Period 2 (TEST treatment).	
Subject analysis set title	Landiolol
Subject analysis set type	Per protocol
Subject analysis set description: Group intended for analysis of PK parameters of landiolol.	
Subject analysis set title	Esmolol
Subject analysis set type	Per protocol
Subject analysis set description: Group intended for analysis of PK parameters of Esmolol.	
Subject analysis set title	Pharmacodynamic (PD) Set
Subject analysis set type	Per protocol
Subject analysis set description: The Pharmacodynamic set consists of all subjects who completed the trial without violating the inclusion/exclusion criteria or other aspects of the protocol considered to potentially affect the pharmacodynamic analysis. Subject with protocol deviation that could affect pharmacodynamic analysis was excluded from the Pharmacodynamic Set. The Pharmacodynamic Set was used for Pharmacodynamic analysis.	
Subject analysis set title	AOP200704 (PD set)
Subject analysis set type	Per protocol
Subject analysis set description: Group intended for PD analysis of AOP200704.	
Subject analysis set title	Esmolol (PD set)
Subject analysis set type	Per protocol
Subject analysis set description: Group intended for PD analysis of Esmolol.	

### Primary: Maximum plasma concentration - Cmax

End point title	Maximum plasma concentration - Cmax
End point description: Maximum plasma concentration determined directly from the plasma concentration-time curve. (non-compartmental method)	
End point type	Primary
End point timeframe: Plasma concentration measured during infusion up to 60 min and after end of infusion up to 480 min.	

End point values	Landiolol	Esmolol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: microgram(s)/millilitre				
geometric mean (standard deviation)	0.188 (± 1.2028)	0.151 (± 1.486)		

## Statistical analyses

Statistical analysis title	Ratio of geometric means
Statistical analysis description:	
Actual number of subjects due to crossover design: 16	
Comparison groups	Landiolol v Esmolol
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Ratio of geometric means
Point estimate	1.2472
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.067
upper limit	1.4579

## Primary: Time point of maximum plasma concentration - tmax

End point title	Time point of maximum plasma concentration - tmax
End point description:	
Time point of maximum plasma concentration - tmax, determined directly from the plasma concentration-time curve. (non-compartmental method)	
End point type	Primary
End point timeframe:	
Plasma concentration measured during infusion up to 60 min and after end of infusion up to 480 min.	

End point values	Landiolol	Esmolol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: minute				
median (full range (min-max))	36 (12 to 60)	19.8 (6 to 43.8)		

## Statistical analyses

<b>Statistical analysis title</b>	Median difference
Comparison groups	Landiolol v Esmolol
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[1]</sup>
Parameter estimate	Median difference (final values)
Point estimate	12
Confidence interval	
level	90 %
sides	2-sided
lower limit	4.2
upper limit	21.9

Notes:

[1] - Actual number of subjects due to crossover design: 16

### Primary: Terminal half-life - t<sub>1/2</sub>

End point title	Terminal half-life - t <sub>1/2</sub>
End point description:	
Half-life of drug elimination during the terminal phase, estimated from the slope of linear regression of the semi-logarithmic plot of the terminal phase of the plasma concentration curve. (non-compartmental method)	
End point type	Primary
End point timeframe:	
Plasma concentration measured during infusion up to 60 min and after end of infusion up to 480 min.	

End point values	Landiolol	Esmolol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: minute				
geometric mean (standard deviation)	3.458 (± 1.1529)	2.846 (± 1.9225)		

### Statistical analyses

<b>Statistical analysis title</b>	Ratio of geometric means
Comparison groups	Landiolol v Esmolol
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[2]</sup>
Parameter estimate	Ratio of geometric means
Point estimate	1.2085
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.877
upper limit	1.6651

Notes:

[2] - Actual number of subjects due to crossover design: 16

### Primary: Area under the plasma concentration-time curve - AUC(0-t)

End point title	Area under the plasma concentration-time curve - AUC(0-t)
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End point description:

The area under the plasma concentration-time curve - AUC(0-t) was calculated by the linear trapezoidal rule from measured data points from time of administration until the time of last quantified concentration. (non-compartmental method)

End point type	Primary
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End point timeframe:

Plasma concentration measured during infusion up to 60 min and after end of infusion up to 480 min.

End point values	Landiolol	Esmolol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: µg.h/mL				
geometric mean (standard deviation)	0.16 (± 1.1752)	0.109 (± 1.4274)		

### Statistical analyses

Statistical analysis title	Ratio of geometric means
Comparison groups	Esmolol v Landiolol
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[3]</sup>
Parameter estimate	Ratio of geometric means
Point estimate	1.4709
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.2912
upper limit	1.6756

Notes:

[3] - Actual number of subjects due to crossover design: 16

### Primary: Area under the plasma concentration-time curve - AUC(0-∞)

End point title	Area under the plasma concentration-time curve - AUC(0-∞)
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End point description:

The area under the plasma concentration-time curve - AUC(0-∞) was be estimated by trapezoidal rule (AUC(0-t)) and extrapolation to infinity (AUC(t-∞)). (non-compartmental method)

End point type	Primary
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End point timeframe:

Plasma concentration measured during infusion up to 60 min and after end of infusion up to 480 min.

End point values	Landiolol	Esmolol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: µg.h/mL				
geometric mean (standard deviation)	0.162 (± 1.1734)	0.111 (± 1.4439)		

### Statistical analyses

Statistical analysis title	Ratio of geometric means
Comparison groups	Landiolol v Esmolol
Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[4]</sup>
Parameter estimate	Ratio of geometric means
Point estimate	1.4651
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.2758
upper limit	1.6826

Notes:

[4] - Actual number of subjects due to crossover design: 16

### Primary: Dose Necessary to Suppress the Dobutamine induced HR increase

End point title	Dose Necessary to Suppress the Dobutamine induced HR increase
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End point description:

Dose [µg/kg] was calculated as 10 [µg/kg/min] x t [min] (for AOP200704) and 50 [µg/kg] x t [min] (for Esmolol), where t [min] is time needed to suppress HR by 20 bpm after dobutamine induced HR increasing .

End point type	Primary
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End point timeframe:

From start of infusion to timepoint of suppressing HR by 20 bpm.

End point values	AOP200704 (PD set)	Esmolol (PD set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: microgram(s)/kilogram				
least squares mean (confidence interval 95%)	66.34 (14.5 to 118.2)	147.73 (94.6 to 200.9)		

## Statistical analyses

<b>Statistical analysis title</b>	Difference AOP - Esmolol
Comparison groups	AOP200704 (PD set) v Esmolol (PD set)
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other <sup>[5]</sup>
Parameter estimate	Mean difference (final values)
Point estimate	-81.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	-154.6
upper limit	-8.2

Notes:

[5] - Actual number of subjects due to crossover design: 15

## Primary: Dose/Efficacy Relation for the steady state condition

End point title	Dose/Efficacy Relation for the steady state condition
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End point description:

Time to steady state was 60 min for all subjects. The following parameter was evaluated: Ratio [ $\mu\text{g/kg/bpm}$ ] of dose [ $\mu\text{g/kg}$ ] (administered during 60 min of IP infusion) and reduction of HR from baseline [ $\text{bpm}$ ] at time of steady state conditions. This ratio presents the dose that is needed to be administered for the reduction of HR by 1 bpm (in steady state conditions).

End point type	Primary
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End point timeframe:

From start of infusion to time to steady state (4x half life) or 60 min.

<b>End point values</b>	AOP200704 (PD set)	Esmolol (PD set)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	15		
Units: microgram(s)/kilogram/bpm				
least squares mean (confidence interval 95%)	16.57 (5.24 to 27.91)	95.55 (83.95 to 107.15)		

## Statistical analyses

<b>Statistical analysis title</b>	Difference AOP-Esmolol
Comparison groups	AOP200704 (PD set) v Esmolol (PD set)

Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	other <sup>[6]</sup>
Parameter estimate	Mean difference (final values)
Point estimate	-78.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	-95.51
upper limit	-62.44

Notes:

[6] - Actual number of subjects due to crossover design: 15



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

In each study period subjects were queried on adverse events at the admission to the clinical unit and at scheduled intervals till 8 hours after end of test or reference drug administration.

Adverse event reporting additional description:

Moreover, the subjects were obliged to report immediately to the Investigator any adverse event, any other health related event that occurred between signing the informed consent and the end-of-study examination.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	14
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### Reporting groups

Reporting group title	AOP200704
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Reporting group description:

Adverse events that occurred during AOP200704 treatment period.

Reporting group title	Esmolol
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Reporting group description:

Adverse events that occurred during Esmolol treatment period.

Serious adverse events	AOP200704	Esmolol	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 16 (0.00%)	0 / 16 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0.1 %

Non-serious adverse events	AOP200704	Esmolol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 16 (43.75%)	5 / 16 (31.25%)	
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 16 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Ventricular extrasystoles			
subjects affected / exposed	3 / 16 (18.75%)	2 / 16 (12.50%)	
occurrences (all)	4	2	

Ventricular tachycardia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 16 (0.00%) 0	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	2 / 16 (12.50%) 2	1 / 16 (6.25%) 1	
Paraesthesia subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 16 (0.00%) 0	
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	0 / 16 (0.00%) 0	1 / 16 (6.25%) 1	
Feeling hot subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 16 (0.00%) 0	
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 16 (0.00%) 0	
Vomiting subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	0 / 16 (0.00%) 0	
Skin and subcutaneous tissue disorders Piloerection subjects affected / exposed occurrences (all)	1 / 16 (6.25%) 1	1 / 16 (6.25%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2011	PHAMOS Central & Eastern Europe s.r.o. was appointed as an organization in charge of study monitoring and ADDS s.r.o. as an organization responsible for data management and statistical evaluation. Corresponding sections of study protocol were modified as result of this Amendment 01.
24 October 2011	The results of the study showed unexpectedly short elimination of the reference drug esmolol both in pharmacokinetic and pharmacodynamic aspects. Amendment 02 to Study Protocol implements a simple pharmacokinetic branch studying esmolol pharmacokinetics under basal conditions (without dobutamine challenge) in three selected subjects of previous study group in order to obtain additional information for correct interpretation of the study results.

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported