Clinical trial results:
A randomised, controlled, open-label study to confirm the efficacy and safety of sedation with isoflurane in invasively ventilated ICU patients using the AnaConDa administration system

Summary

EudraCT number	2016-004551-67
Trial protocol	DE SI
Global end of trial date	11 February 2020

Results information

Result version number	v1 (current)
This version publication date	27 February 2021
First version publication date	27 February 2021

Trial information

Trial identification

Sponsor protocol code	SED001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Sedana Medical AB
Sponsor organisation address	Vendevägen 89, Danderyd, Sweden, 18232
Public contact	Peter Sackey, MD, PhD, Chief Medical Officer, Sedana Medical AB, peter.sackey@sedanamedical.com
Scientific contact	Peter Sackey, MD, PhD, Chief Medical Officer, Sedana Medical AB, peter.sackey@sedanamedical.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	29 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 February 2020
Global end of trial reached?	Yes
Global end of trial date	11 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that sedation with isoflurane is non-inferior to propofol in terms of maintaining adequate sedation without rescue sedation.

Protection of trial subjects:

Serious adverse event collection started at signing of the informed consent, adverse event collection started from first administration of IP and continued until the follow-up assessments.
Additional safety assessements were safety laboratory, ECG, physical examination, vital signs, ventilator parameters, CAM-ICU, SOFA, SAPS II, SBT, ICU length of stay, ICU-free days, ventilator time, ventilator free days.
In case of inadequate sedation or acute agitation which was not controlled by administration of maximum allowed study sedation level, study sedation bolus doses and co-treatment with analgesic agent was allowed.
Patient had the right to withdraw consent to participation at any time and without providing reasons.
The study was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference of Harmonization (ICH)/Good Clinical Practice (GCP) E6 (R1), European Union (EU) Clinical Trials Directive, and applicable local regulatory requirements. In accordance with the EU Data Protection Directive (95/46/EC), the data will not identify any persons taking part in the study.

Background therapy:

Apart from study treatments, all subjects in the study was given standard of care treatment in ICU.

Evidence for comparator: -

Actual start date of recruitment	05 June 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	Slovenia: 15
Country: Number of subjects enrolled	Germany: 286
Worldwide total number of subjects	301
EEA total number of subjects	301

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	138
From 65 to 84 years	152
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

In total 26 sites in Germany and three sites in Slovenia were approved for the study; 21 of the German sites and three of the Slovenian sites enrolled patients into the study. First patient in: 2 July 2017. Last patient completed: 11 February 2020.

Pre-assignment

Screening details:

A pre-screening was done on all mechanically ventilated patients who entered the ICU. The most common main reason for exclusion for participation was "Not clinically likely to need invasive ventilation and sedation ≥24 hours at randomisation". Patients that passed the pre-screening were then formally screened.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This study was open-label thus no treatment kit blinding was applied for subjects and/or site personnel. Cumulative data, used for example for sample size re-estimation (SSRE) and data safety review, was blinded. Also data analyst and sponsor was blinded to treatment allocation during the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Isoflurane

Arm description:

Isoflurane administered by inhalation via AnaConDa

Arm type	Experimental
Investigational medicinal product name	Isoflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, liquid
Routes of administration	Inhalation use

Dosage and administration details:

Isoflurane was given continuously during the treatment period via the AnaConDa device.
Dosage was titrated stepwise by increasing/decreasing the infusion rate by 0.5 to 1.0 mL/h as needed up to maximum 1.5 volume % (Vol%) to achieve the prescribed target sedation depth i.e. within RASS -1 to -4.

Arm title	Propofol

Arm description:

Propofol infusion

Arm type	Active comparator
Investigational medicinal product name	Propofol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection/infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Propofol was given IV continuously during the treatment period.
Dosage was titrated stepwise by increasing/decreasing approximately 0.5-0.8 mg/kg/h each time as needed between 0.3 and 4.0 mg/kg/h to achieve the target sedation depth i.e. within RASS -1 to -4.

Number of subjects in period 1	Isoflurane	Propofol
Started	150	151
Completed	150	151

Period 2	
Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Isoflurane

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Isoflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, liquid
Routes of administration	Inhalation use

Dosage and administration details:

Isoflurane was given continuously during the treatment period via the AnaConDa device.
Dosage was titrated stepwise by increasing/decreasing the infusion rate by 0.5 to 1.0 mL/h as needed up to maximum 1.5 volume % (Vol%) to achieve the prescribed target sedation depth i.e. within RASS -1 to -4.

Arm title	Propofol

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Propofol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Emulsion for injection/infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Propofol was given IV continuously during the treatment period.
Dosage was titrated stepwise by increasing/decreasing approximately 0.5-0.8 mg/kg/h each time as needed between 0.3 and 4.0 mg/kg/h to achieve the target sedation depth i.e. within RASS -1 to -4.

Number of subjects in period 2	Isoflurane	Propofol
Started	150	151
Completed	146	146
Not completed	4	5
Adverse event, serious fatal	2	2
Physician decision	-	1
Adverse event, non-fatal	1	-
NOT APPLICABLE	1	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Isoflurane
Reporting group description:	
Isoflurane administered by inhalation via AnaConDa	
Reporting group title	Propofol
Reporting group description:	
Propofol infusion	

Reporting group values	Isoflurane	Propofol	Total
Number of subjects	150	151	301
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)	68	70	138
From 65-84 years	78	74	152
85 years and over	4	7	11
Age continuous Units: years			
arithmetic mean	65.8	64.3	
standard deviation	± 11.82	± 12.92	-
Gender categorical Units: Subjects			
Female	46	53	99
Male	104	98	202

End points

End points reporting groups

Reporting group title	Isoflurane
Reporting group description: Isoflurane administered by inhalation via AnaConDa	
Reporting group title	Propofol
Reporting group description: Propofol infusion	
Reporting group title	Isoflurane
Reporting group description: -	
Reporting group title	Propofol
Reporting group description: -	
Subject analysis set title	Isoflurane Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

Patients in the PP analysis was a subset of the FAS population fulfilling the following criteria;
- Meeting all inclusion criteria and none of the exclusion criteria
- Receiving study treatments for more than 12 hours
- At least 5 scheduled RASS assessments performed during the study treatment for patients sedated more than 14 hours. For patients sedated for less than 14 hours 4 scheduled RASS assessments will be required for PP analysis set inclusion.
- No major protocol violations that would impact non-inferiority analysis or ef-ficacy analysis.

Subject analysis set title	Propofol Per Protocol Population
Subject analysis set type	Per protocol

Subject analysis set description:

Patients in the PP analysis was a subset of the FAS population fulfilling the following criteria;
- Meeting all inclusion criteria and none of the exclusion criteria
- Receiving study treatments for more than 12 hours
- At least 5 scheduled RASS assessments performed during the study treatment for patients sedated more than 14 hours. For patients sedated for less than 14 hours 4 scheduled RASS assessments will be required for PP analysis set inclusion.
- No major protocol violations that would impact non-inferiority analysis or ef-ficacy analysis.

Primary: Percentage of time on adequate sedation depth

End point title	Percentage of time on adequate sedation depth

End point description:

Endpoint measures percentage of time with adequate sedation depth without any rescue medication. Adequate sedation depth is defined as having a Richmond agitation sedation scale (RASS-value) between (-1 to -4).
The percentage of time on adequate sedation depth was derived as the total amount of time that the patient remained within the prescribed target RASS range (-1 to -4) without rescue medication divided by the amount of time the patient is receiving the study treatment, multiplied by 100%.

End point type	Primary

End point timeframe:

Minimum sedation time 12 hours maximum sedation time 48 + 6 hours.

End point values	Isoflurane Per Protocol Population	Propofol Per Protocol Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	146	148		
Units: percent				
least squares mean (confidence interval 95%)	90.691 (86.770 to 94.612)	91.143 (87.232 to 95.054)		

Statistical analyses

Statistical analysis title	Non-inferiority analysis

Statistical analysis description:

Non-inferiority comparison of isoflurane compared to propofol. Least square means and model-based estimate of the difference between the treatment groups, including a 2-sided 95% confidence interval was reported in the statistical analysis.

Comparison groups	Isoflurane Per Protocol Population v Propofol Per Protocol Population
Number of subjects included in analysis	294
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	-0.452
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.996
upper limit	2.093

Notes:

[1] - The non-inferiority criterion was treatment relative difference of less than 15%.

Secondary: Wake-up test 24H

End point title	Wake-up test 24H

End point description:

Time (in minutes) from start of wake-up test until reaching RASS ≥0

End point type	Secondary

End point timeframe:

Wake-up test performed at 24 hours after start of study sedation

End point values	Isoflurane	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	122	121		
Units: Minutes				
median (confidence interval 95%)	15.0 (11.0 to 29.0)	19.0 (15.0 to 30.0)		

Statistical analyses

Statistical analysis title	Time to wake-up, Wake-up test 24H

Statistical analysis description:

The statistical analysis of time to wake-up in the Wake-up test at 24h was conducted using a Cox regression-model.

Comparison groups	Isoflurane v Propofol
Number of subjects included in analysis	243
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.099
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.955
upper limit	1.717

Notes:

[2] - Treatment groups were compared using a hazard ratio with corresponding 95 % confidence interval. A hazard ratio above 1 means shorter time to event (in average) in the Isoflurane group.

Secondary: Wake-up test 48H

End point title	Wake-up test 48H

End point description:

Time (in minutes) from start of wake-up test until reaching RASS ≥0

End point type	Secondary

End point timeframe:

Wake-up test performed at 48 hours after start of study sedation

End point values	Isoflurane	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	65		
Units: Minutes				
median (confidence interval 95%)	20 (15 to 30)	30 (15 to 45)		

Statistical analyses

Statistical analysis title	Time to wake-up, Wake-up test 48H

Statistical analysis description:

The statistical analysis of time to wake-up in the Wake-up test at 48h was conducted using a Cox regression-model.

Comparison groups	Isoflurane v Propofol
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	2.081
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.339
upper limit	3.233

Notes:

[3] - Treatment groups were compared using a hazard ratio with corresponding 95 % confidence interval. A hazard ratio above 1 means shorter time to event (in average) in the Isoflurane group.

Secondary: Opiate analgesic dose intensity

End point title	Opiate analgesic dose intensity

End point description:

For each patient, opiate analgesic dose intensity was derived.

End point type	Secondary

End point timeframe:

Total sedation period up to 48±6 hours treatment.

End point values	Isoflurane	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	146	145		
Units: dose intensity				
least squares mean (confidence interval 95%)	0.228 (0.125 to 0.331)	0.321 (0.218 to 0.424)		

Statistical analyses

Statistical analysis title	Opiate dose intensity

Statistical analysis description:

Opiate analgesic dose intensity adjusted for Behavioral Pain Scale (BPS) was compared between Isoflurane and Propofol.

Comparison groups	Isoflurane v Propofol

Number of subjects included in analysis	291
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.003
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.093
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.154
upper limit	-0.032

Notes:

[4] - A negative value on point estimate indicate lower average opiate analgesic dose intensities for patients on Isoflurane adjusted for BPS.

Secondary: Time to extubation

End point title	Time to extubation

End point description:

Only patients extubated (end of sedation before successful extubation) within 54h(48+6h) from study sedation start are included

End point type	Secondary

End point timeframe:

Time to extubation is the time between final sedation stop prior to a successful extubation

End point values	Isoflurane	Propofol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	67		
Units: Hours				
median (inter-quartile range (Q1-Q3))	0.5 (0.2 to 2.3)	0.7 (0.3 to 2.1)		

Statistical analyses

Statistical analysis title	Time to extubation

Statistical analysis description:

Time to extubation was analysed using a Cox regression model.

Comparison groups	Isoflurane v Propofol
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.212
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.29

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.864
upper limit	1.926

Notes:

[5] - Treatment groups were compared using a hazard ratio with corresponding 95 % confidence interval. A hazard ratio above 1 means shorter time to event (in average) in the Isoflurane group.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE collection started at signing of the informed consent; adverse event collection started from first administration of IP.
Collection of (new) SAEs and AEs ended at the 24h follow-up visit.

Adverse event reporting additional description:

AEs or SAEs starting after the 24h follow-up was not recorded in the study database.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Isoflurane

Reporting group description:

In the Isoflurane group there were 10 SAEs among 9 patients. None of the SAEs were judged as causally related.

Reporting group title	Propofol

Reporting group description:

In the Propofol group there were 7 SAEs among 6 patients. None of the SAEs were judged as causally related.

Serious adverse events	Isoflurane	Propofol	
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 150 (6.00%)	6 / 151 (3.97%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events	3	3	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 150 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low cardiac output syndrome			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Ventricular fibrillation			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 150 (0.67%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Laryngeal oedema			

subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Metabolic acidosis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

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

Non-serious adverse events	Isoflurane	Propofol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	63 / 150 (42.00%)	50 / 151 (33.11%)	
Vascular disorders			
Hypertension			

subjects affected / exposed	10 / 150 (6.67%)	2 / 151 (1.32%)	
occurrences (all)	15	2	
Hypotension			
subjects affected / exposed	3 / 150 (2.00%)	3 / 151 (1.99%)	
occurrences (all)	3	3	
Hypertensive crisis			
subjects affected / exposed	1 / 150 (0.67%)	3 / 151 (1.99%)	
occurrences (all)	1	3	
Haemodynamic instability			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Peripheral venous disease			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Thrombosis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Orchidopexy			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Debridement			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Withdrawal syndrome			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Hyperthermia malignant			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			

Hypoxia			
subjects affected / exposed	0 / 150 (0.00%)	2 / 151 (1.32%)	
occurrences (all)	0	2	
Bronchospasm			
subjects affected / exposed	0 / 150 (0.00%)	2 / 151 (1.32%)	
occurrences (all)	0	2	
Haemoptysis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Pulmonary congestion			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Pleural disorder			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Mediastinal haemorrhage			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Respiratory failure			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Hypercapnia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Respiration Abnormal			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	8 / 150 (5.33%)	7 / 151 (4.64%)	
occurrences (all)	8	7	
Agitation			
subjects affected / exposed	3 / 150 (2.00%)	6 / 151 (3.97%)	
occurrences (all)	3	6	
Anxiety			

subjects affected / exposed	2 / 150 (1.33%)	0 / 151 (0.00%)	
occurrences (all)	2	0	
Insomnia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Restlessness			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Investigations			
Red blood cell count decreased			
subjects affected / exposed	1 / 150 (0.67%)	4 / 151 (2.65%)	
occurrences (all)	1	4	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 150 (1.33%)	2 / 151 (1.32%)	
occurrences (all)	2	2	
Blood pressure increased			
subjects affected / exposed	2 / 150 (1.33%)	1 / 151 (0.66%)	
occurrences (all)	2	1	
Blood glucose increased			
subjects affected / exposed	1 / 150 (0.67%)	1 / 151 (0.66%)	
occurrences (all)	1	1	
Body temperature increased			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Blood potassium increased			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Platelet count decreased			

subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Blood calcium decreased			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Blood bilirubin increased			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Blood albumin decreased			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Postoperative delirium			
subjects affected / exposed	2 / 150 (1.33%)	1 / 151 (0.66%)	
occurrences (all)	2	1	
Endotracheal Intubation Complication			
subjects affected / exposed	0 / 150 (0.00%)	2 / 151 (1.32%)	
occurrences (all)	0	2	
Procedural pneumothorax			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Post procedural complication			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	5 / 150 (3.33%)	4 / 151 (2.65%)	
occurrences (all)	5	5	
Tachycardia			
subjects affected / exposed	4 / 150 (2.67%)	3 / 151 (1.99%)	
occurrences (all)	4	3	
Sinus tachycardia			

subjects affected / exposed	3 / 150 (2.00%)	0 / 151 (0.00%)	
occurrences (all)	3	0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 150 (0.67%)	1 / 151 (0.66%)	
occurrences (all)	1	1	
Tachyarrhythmia			
subjects affected / exposed	0 / 150 (0.00%)	2 / 151 (1.32%)	
occurrences (all)	0	2	
Bradycardia			
subjects affected / exposed	1 / 150 (0.67%)	1 / 151 (0.66%)	
occurrences (all)	1	1	
Ventricular tachycardia			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Left ventricular failure			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Bundle branch block right			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Cardiovascular disorder			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Nervous system disorders			
Myoclonus			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Seizure			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 150 (2.00%)	1 / 151 (0.66%)	
occurrences (all)	3	1	
Leukocytosis			

subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Anaemia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 150 (2.67%)	2 / 151 (1.32%)	
occurrences (all)	4	2	
Vomiting			
subjects affected / exposed	3 / 150 (2.00%)	1 / 151 (0.66%)	
occurrences (all)	3	1	
Tongue haematoma			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Tooth disorder			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Small intestinal perforation			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Swelling face			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Renal and urinary disorders			

Oliguria			
subjects affected / exposed	7 / 150 (4.67%)	6 / 151 (3.97%)	
occurrences (all)	7	6	
Renal failure			
subjects affected / exposed	4 / 150 (2.67%)	0 / 151 (0.00%)	
occurrences (all)	4	0	
Renal impairment			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Anuria			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Chronic kidney disease			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Acute kidney injury			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 150 (0.00%)	3 / 151 (1.99%)	
occurrences (all)	0	3	
Pneumonia			
subjects affected / exposed	0 / 150 (0.00%)	2 / 151 (1.32%)	
occurrences (all)	0	2	
Peritonitis			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Intervertebral discitis			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Septic encephalopathy			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Diverticulitis			

subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	
Abdominal infection			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 150 (0.00%)	1 / 151 (0.66%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	1 / 150 (0.67%)	0 / 151 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2017	BfArM and EC requested the following clarifications were made : • Use of gas monitor and elimination system with AnaConDa • That warnings, contraindications and interactions in SmPC for applicable investigational product must be followed • ICF procedure • Randomisation stratified by site • Adding creatine kinase lab test • Adding an independent data safety monitoring board
19 May 2017	The following changes were made due to clarifications, change of details and removal of inconsistencies: • Adding methodology section in synopsis • Change of biostatistician • Clarification of wordings of objectives and endpoints • Administrative changes to clarify inconsistencies and order of study procedures • Clarification of wordings of incl/excl criteria • Clarification on replacement for withdrawn subjects • Clarification on blinding procedures • Clarification of rescue sedation and sedation failure • Modification of procedure after surgery or anaestesia • Corrections/clarifications on vital signs, ventilator parameters and concomitant meds to be collected • Modification of SBT procedure • Adding collection of data for extubation • Change of follow-up adverse event and concomitant medication data collection • Clarifications in statistical methods
24 June 2018	The following changes were made: • Extending safety follow-up to include seven days of organ systems function and 30 days mortality and health economy in terms of days in ICU and days with invasive ventilation. • Adding secondary objectives and endpoints related to the extended follow-up of organ function, mortality and health economy • Clarifying informed consent procedure and the emergency situation • Adding the AnaConDa-S device to be used for isoflurane administration • Changing sponsor representative • Correcting errors and clarifying inconsistencies
27 March 2019	To reduce number of secondary objectives and endpoints and for clarifications and removal of inconsistencies the following changes were made: • Re-structuring of objectives and endpoints • Clarifications in Table 1, Study plan • Clarification of exclusion criteria 5, 6 and 13 • Clarification of concomitant medication/prohibited medication section. • Clarification of AE collection timeframes • Adding written consent or putative consent for collection of 30 day f/u data for subjects included before amendment 3 • Changing Last Subject completed to Q1 2020

09 December 2019	For clarification the following updates were made: • Restructuring of objectives • Ordering of secondary safety endpoints • Repositioning of endpoints

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported