Clinical trial results:
A Randomised Active-controlled Study to Compare Efficacy and Safety of Inhaled Isoflurane Delivered by the AnaConDa-S (Anaesthetic Conserving Device) to Intravenous Midazolam for Sedation in Mechanically Ventilated Paediatric Patients 3 to 17 (Less than 18) Years Old

Summary

EudraCT number	2020-000578-31
Trial protocol	DE SE FR
Global end of trial date	19 January 2023

Results information

Result version number	v1 (current)
This version publication date	11 November 2023
First version publication date	11 November 2023

Trial information

Trial identification

Sponsor protocol code	SED002

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,
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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)	Yes
EMA paediatric investigation plan number(s)	EMEA-002320-PIP01-17
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	27 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 January 2023
Global end of trial reached?	Yes
Global end of trial date	19 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the percentage of time adequate sedation depth is maintained within the individually prescribed target range in absence of rescue sedation as assessed according to the COMFORT Behavior (COMFORT-B) scale, in isoflurane vs midazolam treated paediatric patients for an expected minimum of 12 hours.

(The COMFORT-B scale is a valid and reliable scale measuring distress/sedation of intubated paediatric patients)

Protection of trial subjects:

Informed consent was obtained from the legal guardian(s) of patients prior to initiation of the study. If appropriate and possible (if the patient was not sedated at the time of recruitment) the patient was approached to provide assent for participation in the study. For patients sedated at the time of recruitment the assent process was completed as appropriate after the patient awakened. If the child was able to understand the information given about the study and after consideration declined participation, this was respected and the child did not enter the study, even if his/her legal guardian(s) had provided informed consent.

Rescue sedation (defined as sedative agents other than the investigational medicinal product [IMP]) was allowed in case of inadequate sedation due to e.g. observed acute agitation or immediate risk of extubation which was not controlled
by administration of study treatment maintenance dose, bolus doses of study treatment and co-treatment with analgesic agent.

Patients (or their legal guardian[s]) had the right to withdraw consent to participation at any time and without providing reasons. The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki (2013) that are consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator:

Current methods of sedation in mechanically ventilated paediatric patients often involve co-administration of intravenous (IV) midazolam and opioids, and sometimes ketamine and α2-adrenergic agonists. However, midazolam, is associated with relatively long wake up times after discontinuation and, in general, cause severe withdrawal and delirium symptoms after prolonged use.

Actual start date of recruitment	14 January 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Spain: 44

Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 19
Worldwide total number of subjects	96
EEA total number of subjects	92

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)	77
Adolescents (12-17 years)	19
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were children aged 3-17 years who required planned or unplanned mechanical ventilation in the intensive care unit (ICU). Recruitment was monitored to ensure adherence to the target number of patients per age group (3-7, 8-11, 12-17 years).

Pre-assignment

Screening details:

Pre-screening was done by sites based on available clinical or chart information to identify potential study patients among patients admitted to the study site. Potential candidates/their legal guardian(s) were invited to formal screening. In total, 111 patients were screened, 96 were randomised (i.e., 15 screen failures), 2 were not treated.

Period 1

Period 1 title	Randomisation
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:

Isoflurane administered by inhalation via Sedaconda ACD-S (old name: AnaConDa-S)

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 Sedaconda ACD-S device. The device was either placed at standard placement or on the inspiratory limb. The Sedaconda ACD-S was primed with 1.2 mL isoflurane and the syringe pump was started at an initial dose-rate of isoflurane (2.0 mL/hour). In case of ongoing sedative treatment, all other sedatives were simultaneously turned off. During initiation and until the prescribed sedation target depth was achieved and considered stable, sedation depth was assessed regularly, and isoflurane dosage was titrated stepwise by increasing/decreasing the infusion rate by 0.5 - 1.0 mL/hour (bolus 0.2 - 0.3 mL). The dose-titration was expected to be completed within 2 hours of initiating study treatment. After the initial dose titration was completed, further titration and bolus doses were allowed to maintain the prescribed sedation target depth. The maintenance dose should not result in exceeding 1.0% end-tidal isoflurane.

Arm title	Midazolam

Arm description:

Intravenously (IV) administered Midazolam

Arm type	Active comparator
Investigational medicinal product name	Midazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Study treatment started by initiating an IV infusion of midazolam at a start infusion dose rate of 50-100 µg/kg/hour. Other sedatives were simultaneously turned off. The dose was titrated stepwise based on achievement of sedation target depth, by decreasing/increasing 20-50 µg/kg/hour IV (bolus: 50-100

µg/kg). After the initial dose titration was completed (within 2 hours after start of study treatment), further titration and bolus doses were allowed to maintain the prescribed sedation target depth. The maintenance dose should not exceed 300 µg/kg/hour (0.3 mg/kg/hour) midazolam.

Number of subjects in period 1	Isoflurane	Midazolam
Started	63	33
Completed	61	33
Not completed	2	0
Protocol deviation	2	-

Period 2

Period 2 title	Baseline (BL)
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Isoflurane

Arm description:

Isoflurane administered by inhalation via Sedaconda ACD-S (old name: AnaConDa-S)

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 Sedaconda ACD-S device. The device was either placed at standard placement or on the inspiratory limb. The Sedaconda ACD-S was primed with 1.2 mL isoflurane and the syringe pump was started at an initial dose-rate of isoflurane (2.0 mL/hour). In case of ongoing sedative treatment, all other sedatives were simultaneously turned off. During initiation and until the prescribed sedation target depth was achieved and considered stable, sedation depth was assessed regularly, and isoflurane dosage was titrated stepwise by increasing/decreasing the infusion rate by 0.5 - 1.0 mL/hour (bolus 0.2 - 0.3 mL). The dose-titration was expected to be completed within 2 hours of initiating study treatment. After the initial dose titration was completed, further titration and bolus doses were allowed to maintain the prescribed sedation target depth. The maintenance dose should not result in exceeding 1.0% end-tidal isoflurane.

Arm title	Midazolam

Arm description:

Intravenously (IV) administered Midazolam

Arm type	Active comparator

Investigational medicinal product name	Midazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Study treatment started by initiating an IV infusion of midazolam at a start infusion dose rate of 50-100 µg/kg/hour. Other sedatives were simultaneously turned off. The dose was titrated stepwise based on achievement of sedation target depth, by decreasing/increasing 20-50 µg/kg/hour IV (bolus: 50-100 µg/kg). After the initial dose titration was completed (within 2 hours after start of study treatment), further titration and bolus doses were allowed to maintain the prescribed sedation target depth. The maintenance dose should not exceed 300 µg/kg/hour (0.3 mg/kg/hour) midazolam.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: "Randomisation" has been defined as period 1 due to the discrepancy of the number of randomised patients (N=96) and the number of patients with baseline data (N=94). Therefore, the "Baseline" period has been defined as period 2.

Number of subjects in period 2[2]	Isoflurane	Midazolam
Started	61	33
Completed	61	33

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 96 patients were enrolled/randomised but data was only collected for 94 patients (included in the safety analysis set) as 2 patients did not start treatment.

Period 3

Period 3 title	Study treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study was an open-label study with an assessor-blinded design. At each site, a group assessors were blinded for treatment allocation and prescribed sedation target. The assessors performed the COMFORT-B assessments every 2 h during the study treatment period. Specific measures were taken to ensure treatment allocation was unknown to the blinded assessor upon entry to the room where the patient was being treated, including visually obscuring the Sedaconda ACD-S.

Arms

Are arms mutually exclusive?	Yes
Arm title	Isoflurane

Arm description:

Isoflurane administered by inhalation via Sedaconda ACD-S (old name: AnaConDa-S)

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 Sedaconda ACD-S device. The device was either placed at standard placement or on the inspiratory limb. The Sedaconda ACD-S was

primed with 1.2 mL isoflurane and the syringe pump was started at an initial dose-rate of isoflurane (2.0 mL/hour). In case of ongoing sedative treatment, all other sedatives were simultaneously turned off. During initiation and until the prescribed sedation target depth was achieved and considered stable, sedation depth was assessed regularly, and isoflurane dosage was titrated stepwise by increasing/decreasing the infusion rate by 0.5 - 1.0 mL/hour (bolus 0.2 - 0.3 mL). The dose-titration was expected to be completed within 2 hours of initiating study treatment. After the initial dose titration was completed, further titration and bolus doses were allowed to maintain the prescribed sedation target depth. The maintenance dose should not result in exceeding 1.0% end-tidal isoflurane.

Arm title	Midazolam

Arm description:

Intravenously (IV) administered Midazolam

Arm type	Active comparator
Investigational medicinal product name	Midazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Study treatment started by initiating an IV infusion of midazolam at a start infusion dose rate of 50-100 µg/kg/hour. Other sedatives were simultaneously turned off. The dose was titrated stepwise based on achievement of sedation target depth, by decreasing/increasing 20-50 µg/kg/hour IV (bolus: 50-100 µg/kg). After the initial dose titration was completed (within 2 hours after start of study treatment), further titration and bolus doses were allowed to maintain the prescribed sedation target depth. The maintenance dose should not exceed 300 µg/kg/hour (0.3 mg/kg/hour) midazolam.

Number of subjects in period 3	Isoflurane	Midazolam
Started	61	33
Completed	52	27
Not completed	9	6
Lack of efficacy/treatment failure	1	3
Patient required continuous neuromuscular blockade	2	1
Consent withdrawn by subject	1	-
Medical emergency	1	-
Worsening bronchospasm	1	-
Sudden wake-up	1	-
Accidental extubation	1	-
Midazolam bottle was empty and not renewed	-	1
Accidently received non-study drug midazolam	-	1
New risk to the patient	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Isoflurane
Reporting group description:	
Isoflurane administered by inhalation via Sedaconda ACD-S (old name: AnaConDa-S)	
Reporting group title	Midazolam
Reporting group description:	
Intravenously (IV) administered Midazolam	

Reporting group values	Isoflurane	Midazolam	Total
Number of subjects	61	33	94
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)	47	28	75
Adolescents (12-17 years)	14	5	19
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	8.0	7.0	
standard deviation	± 4.2	± 3.9	-
Gender categorical Units: Subjects			
Female	23	13	36
Male	38	20	58

Subject analysis sets	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety analysis set was defined as all patients who received any dose of the IMP.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS included all randomised patients who received IMP and had at least a 6-hour sedation period and at least 3 blinded COMFORT-B-assessments. The FAS followed the intention-to-treat (ITT) principle, i.e., patients were analysed according to the treatment group they were assigned to at randomisation. The main statistical analysis was performed on this population.	
Subject analysis set title	Per protocol (PP) analysis set
Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set included all patients in the FAS without any major protocol deviation affecting the primary analysis. To be included in the PP analysis set patients had to have been sedated for at least 12 h (which was interpreted as 12 h of study sedative treatment from start of IMP), with at least 50% of the planned COMFORT-B assessments performed. Furthermore, if two or more changes in prescribed target sedation depth occurred (one change was allowed), the patient was excluded from the PP analysis set.

Reporting group values	Safety analysis set	Full analysis set (FAS)	Per protocol (PP) analysis set
Number of subjects	94	92	85
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)	75	73	68
Adolescents (12-17 years)	19	19	17
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	7.6	7.7	7.8
standard deviation	± 4.1	± 4.1	± 4.1
Gender categorical Units: Subjects			
Female	36	35	30
Male	58	57	55

End points

End points reporting groups

Reporting group title	Isoflurane
Reporting group description: Isoflurane administered by inhalation via Sedaconda ACD-S (old name: AnaConDa-S)	
Reporting group title	Midazolam
Reporting group description: Intravenously (IV) administered Midazolam	
Reporting group title	Isoflurane
Reporting group description: Isoflurane administered by inhalation via Sedaconda ACD-S (old name: AnaConDa-S)	
Reporting group title	Midazolam
Reporting group description: Intravenously (IV) administered Midazolam	
Reporting group title	Isoflurane
Reporting group description: Isoflurane administered by inhalation via Sedaconda ACD-S (old name: AnaConDa-S)	
Reporting group title	Midazolam
Reporting group description: Intravenously (IV) administered Midazolam	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description: The Safety analysis set was defined as all patients who received any dose of the IMP.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The FAS included all randomised patients who received IMP and had at least a 6-hour sedation period and at least 3 blinded COMFORT-B-assessments. The FAS followed the intention-to-treat (ITT) principle, i.e., patients were analysed according to the treatment group they were assigned to at randomisation. The main statistical analysis was performed on this population.	
Subject analysis set title	Per protocol (PP) analysis set
Subject analysis set type	Per protocol
Subject analysis set description: The PP analysis set included all patients in the FAS without any major protocol deviation affecting the primary analysis. To be included in the PP analysis set patients had to have been sedated for at least 12 h (which was interpreted as 12 h of study sedative treatment from start of IMP), with at least 50% of the planned COMFORT-B assessments performed. Furthermore, if two or more changes in prescribed target sedation depth occurred (one change was allowed), the patient was excluded from the PP analysis set.	

Primary: Percentage of time of adequately maintained sedation within the COMFORT-B interval (light, moderate or deep sedation) prescribed at randomisation, monitored every 2 h for a minimum of 12 h (up to 48 h ± 6 h) - FAS

End point title	Percentage of time of adequately maintained sedation within the COMFORT-B interval (light, moderate or deep sedation) prescribed at randomisation, monitored every 2 h for a minimum of 12 h (up to 48 h ± 6 h) - FAS
End point description:	
End point type	Primary
End point timeframe: From start of study treatment until end of study treatment	

End point values	Isoflurane	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[1]	33[2]		
Units: percent				
least squares mean (confidence interval 95%)	68.94 (52.83 to 85.05)	62.37 (44.70 to 80.04)		

Notes:

[1] - FAS

[2] - FAS

Statistical analyses

Statistical analysis title	Percent time of adequately maintained sedation

Statistical analysis description:

Least square means of the difference between the treatment groups, including a 2-sided 95% confidence interval was reported in the statistical analysis. The noninferiority criterion was a relative difference of less than 15% between treatment groups.

Comparison groups	Isoflurane v Midazolam
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.403 [4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	6.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.99
upper limit	22.13

Notes:

[3] - Superiority was not met, as the entire 95% CI was not above 0. Noninferiority was met as the entire 95% CI for the difference was above the noninferiority margin for the relative difference of -15% (corresponding to a margin of -9.36% units).

[4] - Testing the hypothesis of no difference between isoflurane and midazolam.

Primary: Percentage of time of adequately maintained sedation within the COMFORT-B interval (light, moderate or deep sedation) prescribed at randomisation, monitored every 2 h for a minimum of 12 h (up to 48 h ± 6 h) - PP analysis set

End point title	Percentage of time of adequately maintained sedation within the COMFORT-B interval (light, moderate or deep sedation) prescribed at randomisation, monitored every 2 h for a minimum of 12 h (up to 48 h ± 6 h) - PP analysis set

End point description:

End point type	Primary

End point timeframe:

From start of study treatment until end of study treatment

End point values	Isoflurane	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	56[5]	29[6]		
Units: percent				
least squares mean (confidence interval 95%)	70.91 (50.75 to 91.07)	65.57 (44.03 to 87.11)		

Notes:

[5] - PP analysis set

[6] - PP analysis set

Statistical analyses

Statistical analysis title	Supplementary analysis 1
Comparison groups	Midazolam v Isoflurane
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.504 [8]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	5.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.48
upper limit	21.17

Notes:

[7] - Superiority was not met, as the entire 95% CI was not above 0. Noninferiority was not met, as the entire 95% CI for the difference was not above the noninferiority margin for the relative difference of -15%.

[8] - Testing the hypothesis of no difference between isoflurane and midazolam

Secondary: Dose of opioids from first blinded COMFORT-B assessment (at +2 h) to end of study treatment period

End point title	Dose of opioids from first blinded COMFORT-B assessment (at +2 h) to end of study treatment period

End point description:

This was a key secondary efficacy endpoint. Dose of opioids was expressed as fentanyl IV equivalents.

End point type	Secondary

End point timeframe:

From first blinded COMFORT-B assessment to end of the study treatment period

End point values	Isoflurane	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[9]	33[10]		
Units: µg/kg/h				
least squares mean (confidence interval 95%)	2.1 (1.3 to 2.9)	4.6 (3.5 to 5.6)		

Notes:

[9] - FAS

[10] - FAS

Statistical analyses

Statistical analysis title	Dose of opioids (total study treatment period)
Comparison groups	Isoflurane v Midazolam
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	-1.1

Secondary: Dose of opioids during the last 4 h of study treatment, as compared to the first 4 h of study treatment after first blinded COMFORT-B assessment

End point title	Dose of opioids during the last 4 h of study treatment, as compared to the first 4 h of study treatment after first blinded COMFORT-B assessment

End point description:

This was a key secondary efficacy endpoint. Dose of opioids is expressed as fentanyl IV equivalents.

End point type	Secondary

End point timeframe:

Last 4 hours of study treatment compared to first 4 hours of study treatment after first blinded COMFORT-B assessment.

End point values	Isoflurane	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57[11]	31[12]		
Units: µg/kg/h				
least squares mean (confidence interval 95%)	-0.19 (-0.74 to 0.35)	0.58 (-0.16 to 1.32)		

Notes:

[11] - FAS; 2 patients with <8 hours on study treatment from first blinded COMFORT-B assessment excluded
[12] - FAS; 2 patients with <8 hours on study treatment from first blinded COMFORT-B assessment excluded

Statistical analyses

Statistical analysis title	Change in dose of opioids

Statistical analysis description:

Results display comparison between isoflurane and midazolam and are based on an analysis of variance model with treatment group as fixed effect and baseline opioid dose as covariate.

Comparison groups	Isoflurane v Midazolam
Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.096
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.69
upper limit	0.14

Secondary: Time from end of study drug administration to extubation if study drug was terminated for extubation

End point title	Time from end of study drug administration to extubation if study drug was terminated for extubation

End point description:

This was a key secondary safety endpoint.

End point type	Secondary

End point timeframe:

From end of study drug administration to extubation

End point values	Isoflurane	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	35[13]	20[14]		
Units: hour				
median (inter-quartile range (Q1-Q3))	0.75 (0.25 to 1.5)	1.09 (0.49 to 5.50)		

Notes:

[13] - Subgroup of patients with endotracheal tube where wake-up was initiated at end of study treatment
[14] - Subgroup of patients with endotracheal tube where wake-up was initiated at end of study

treatment

Statistical analyses

Statistical analysis title	Time to extubation
Statistical analysis description:	
This analysis evaluated a treatment difference between isoflurane and midazolam.	
Comparison groups	Isoflurane v Midazolam
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0021
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	3.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.54
upper limit	7.07

Secondary: Proportion of observations with spontaneous breathing efforts during study treatment

End point title	Proportion of observations with spontaneous breathing efforts during study treatment
End point description:	
This was a key secondary safety endpoint.	
End point type	Secondary
End point timeframe:	
From the first blinded COMFORT-B assessment to end of study treatment period	

End point values	Isoflurane	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[15]	33[16]		
Units: percent				
least squares mean (confidence interval 95%)	0.48 (0.36 to 0.60)	0.44 (0.28 to 0.59)		

Notes:

[15] - FAS

[16] - FAS

Statistical analyses

Statistical analysis title	Spontaneous breathing efforts

Statistical analysis description:

Results display a comparison between isoflurane and midazolam and are based on a mixed effects analysis of variance model with treatment group as fixed effect.

Comparison groups	Isoflurane v Midazolam
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.636
Method	ANOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.15
upper limit	0.25

Secondary: Need for additional inotropic/vasopressor agent defined by change in vasoactive-inotropic score (VIS) during study treatment period compared to baseline

End point title	Need for additional inotropic/vasopressor agent defined by change in vasoactive-inotropic score (VIS) during study treatment period compared to baseline

End point description:

Change from baseline in VIS was assessed a ≤24 hours and >24 hours.

End point type	Secondary

End point timeframe:

From start of study treatment to end of study treatment

End point values	Isoflurane	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	61[17]	33[18]		
Units: change from baseline in VIS				
arithmetic mean (standard deviation)				
≤24 hours	3.4 (± 19.9)	5.4 (± 19.3)		
>24 hours	8.8 (± 44.4)	1.9 (± 9.7)		

Notes:

[17] - Safety analysis set; data available for 26 patients at >24 hours

[18] - Safety analysis set; data available for 32 patients at ≤24 hours and 10 patients at >24 hours

Statistical analyses

Statistical analysis title	Need for inotropic/vasopressor agent at ≤24 hours

Statistical analysis description:

At ≤24 hours, data was only available for 32 patients in the Midazolam group.

Comparison groups	Isoflurane v Midazolam

Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.55
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - Results display comparison between isoflurane and midazolam and are based on a Wilcoxon rank-sum test.

Statistical analysis title	Need for inotropic/vasopressor agent at >24 hours

Statistical analysis description:

At >24 hours, data was only available for 26 patients in the Isoflurane group and 10 patients in the Midazolam group.

Comparison groups	Isoflurane v Midazolam
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.637
Method	Wilcoxon (Mann-Whitney)

Secondary: Ventilator-free days at 30 days from start of study treatment period

End point title	Ventilator-free days at 30 days from start of study treatment period

End point description:

This was a secondary safety endpoint. Patients that were withdrawn prior to day 30 were excluded from the analysis. Patients who died before day 30 were not considered withdrawals. For these patients, the days up to day 30 were considered ventilator days.

End point type	Secondary

End point timeframe:

From start of study treatment until day 30.

End point values	Isoflurane	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[20]	33[21]		
Units: Number of ventilator-free days				
arithmetic mean (standard deviation)	25.00 (± 6.74)	22.55 (± 10.62)		

Notes:

[20] - Safety analysis set (only patients not withdrawn prior to day 30)

[21] - Safety analysis set (only patients not withdrawn prior to day 30)

Statistical analyses

No statistical analyses for this end point

Secondary: Time in ICU at 30 days from start of study treatment period

End point title	Time in ICU at 30 days from start of study treatment period

End point description:

This was a secondary safety endpoint. Patients that were withdrawn prior to day 30 were excluded from the analysis. Patients who died before day 30 were not considered withdrawals. For these patients, the days in ICU until day of death were considered ICU days.

End point type	Secondary

End point timeframe:

From start of study treatment until day 30.

End point values	Isoflurane	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[22]	33[23]		
Units: Number of ICU days				
arithmetic mean (standard deviation)	9.65 (± 7.87)	10.21 (± 9.13)		

Notes:

[22] - Safety analysis set (only patients not withdrawn prior to day 30)

[23] - Safety analysis set (only patients not withdrawn prior to day 30)

Statistical analyses

No statistical analyses for this end point

Secondary: Days alive and not in the ICU at day 30 from start of study treatment period

End point title	Days alive and not in the ICU at day 30 from start of study treatment period

End point description:

This was a secondary safety endpoint. Patients that were withdrawn prior to day 30 were excluded from the analysis. Patients who died before day 30 were not considered withdrawals. For these patients, the days in ICU until day of death were considered ICU days.

End point type	Secondary

End point timeframe:

From start of study treatment until day 30.

End point values	Isoflurane	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60[24]	33[25]		
Units: Number of days alive and not in the ICU				
arithmetic mean (standard deviation)	20.35 (± 7.87)	18.58 (± 10.26)		

Notes:

[24] - Safety analysis set (only patients not withdrawn prior to day 30)

[25] - Safety analysis set (only patients not withdrawn prior to day 30)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from start of IMP until the end of the 48-hour post-study treatment monitoring.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Isoflurane
Reporting group description: -	
Reporting group title	Midazolam

Reporting group description: -

Serious adverse events	Isoflurane	Midazolam	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 61 (31.15%)	8 / 33 (24.24%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	2	
Investigations			
Magnetic resonance imaging head abnormal	Additional description: Preferred term: Magnetic resonance imaging brain abnormal		
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaesthetic complication neurological			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complications of transplanted liver			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrostomy tube site complication			

subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative thoracic procedure complication			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postpericardiotomy syndrome			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (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			
Cerebrovascular accident			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hemiparesis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxic-ischaemic encephalopathy	Additional description: The patient who had this serious adverse event (SAE) also had two additional SAEs (Preferred terms "Acute kidney injury" and "Acute respiratory distress syndrome") which were considered to have led to death of the patient.		
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (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			
Complication associated with device			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 61 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Urinary tract infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric ulcer haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute respiratory distress syndrome	Additional description: The patient who had this serious adverse event (SAE) also had two additional SAEs (Preferred terms "Acute kidney injury" and "Hypoxic-ischaemic encephalopathy") which were considered to have led to death of the patient.		
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chylothorax			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillar haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (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	Additional description: One of the patients who had this serious adverse event (SAE) also had two additional SAEs (Preferred terms "Hypoxic-ischaemic encephalopathy" and "Acute respiratory distress syndrome") which were considered to have led to death of the patient.		

subjects affected / exposed	3 / 61 (4.92%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Isoflurane	Midazolam	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 61 (83.61%)	21 / 33 (63.64%)	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	9 / 61 (14.75%)	1 / 33 (3.03%)	
occurrences (all)	20	1	
Hypotension			
subjects affected / exposed	15 / 61 (24.59%)	5 / 33 (15.15%)	
occurrences (all)	33	11	
Superior vena cava stenosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	

Surgical and medical procedures			
Endotracheal intubation			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hyperthermia			
subjects affected / exposed	1 / 61 (1.64%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Hypothermia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Mucosal inflammation			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Oedema			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	1 / 61 (1.64%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Pyrexia			
subjects affected / exposed	8 / 61 (13.11%)	2 / 33 (6.06%)	
occurrences (all)	13	2	
Withdrawal syndrome			
subjects affected / exposed	1 / 61 (1.64%)	1 / 33 (3.03%)	
occurrences (all)	1	1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Graft versus host disease			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	

Transplant rejection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Aphonia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Atelectasis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Bradypnoea			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Bronchospasm			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Chylothorax			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Haemoptysis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Hypoxia			
subjects affected / exposed	4 / 61 (6.56%)	1 / 33 (3.03%)	
occurrences (all)	12	3	
Pleural effusion			
subjects affected / exposed	5 / 61 (8.20%)	1 / 33 (3.03%)	
occurrences (all)	6	2	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Anger			

subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Anxiety			
subjects affected / exposed	2 / 61 (3.28%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Delirium			
subjects affected / exposed	5 / 61 (8.20%)	1 / 33 (3.03%)	
occurrences (all)	5	1	
Hallucination			
subjects affected / exposed	2 / 61 (3.28%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Hallucination, visual			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	2 / 61 (3.28%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Mood swings			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Sleep disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 61 (4.92%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Blood lactic acid increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Blood pressure decreased			

subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Blood prolactin increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Blood uric acid increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Electrocardiogram repolarisation abnormality			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Inflammatory marker increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Liver function test abnormal			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Neutrophil count decreased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	1 / 61 (1.64%)	1 / 33 (3.03%)	
occurrences (all)	3	2	
Urine output decreased			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Endotracheal intubation complication			
subjects affected / exposed	2 / 61 (3.28%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Fall			

subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Vasoplegia syndrome			
subjects affected / exposed	2 / 61 (3.28%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Atrial flutter			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Atrioventricular block			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Bradycardia			
subjects affected / exposed	3 / 61 (4.92%)	3 / 33 (9.09%)	
occurrences (all)	12	10	
Cardiac arrest			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Nodal rhythm			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	4 / 61 (6.56%)	0 / 33 (0.00%)	
occurrences (all)	8	0	
Nervous system disorders			
Extrapyramidal disorder			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Poor quality sleep			

subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Seizure			
subjects affected / exposed	2 / 61 (3.28%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Tremor			
subjects affected / exposed	2 / 61 (3.28%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Thrombocytopenia			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	12 / 61 (19.67%)	4 / 33 (12.12%)	
occurrences (all)	12	4	
Ileus paralytic			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Hepatobiliary disorders			
Hepatic artery stenosis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Hepatic function abnormal			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 61 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	2 / 61 (3.28%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Oliguria			
subjects affected / exposed	2 / 61 (3.28%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Renal failure			
subjects affected / exposed	2 / 61 (3.28%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Epstein-Barr virus infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Viral myositis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Septic shock			
subjects affected / exposed	1 / 61 (1.64%)	0 / 33 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Food intolerance			
subjects affected / exposed	0 / 61 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	1 / 61 (1.64%)	1 / 33 (3.03%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 October 2020	Clinical study protocol (CSP) amendment 1: Updates included addition of an exclusion criterion, clarification of the pregnancy test procedure and addition of a section on study stopping criteria. Also, the future use of biological samples and reporting procedures for serious events were clarified as well as an addition of an adverse event of special interest (AESI). In addition, a few of the defined study assessments were re-evaluated which triggered minor updates in their definition to provide further clarification or minor adjustments in the data collection. One planned supplementary analysis was re-defined to be considered an additional analysis, to support a future filing in the US. This was a global amendment submitted to the Competent Authorities (CAs) and Ethics Committees (EC) in all involved countries except for the German EC. A local amendment (CSP Version 2.1 [DEU] dated 15-Dec-2020) was submitted to the German EC and CA where the use of highly effective contraception methods was added as inclusion criteria in Section 9.3.1 as requested by the leading EC in Germany.
04 October 2022	CSP amendment 2 (non-substantial): The main changes included revision of inconsistencies regarding how the structured recruitment was specified in the previous version of the CSP, to clarify rules for when to stop randomisation per age group. To ensure enough patients across all age groups for the safety evaluation, the structured recruitment was adjusted to include more adolescent patients '12 to less than 18 years of age'. Furthermore, country specific updates in Germany (CSP Version 2.1 [DEU], 15-Dec-2020, and the United Kingdom (CSP Version 2.2 [UK], 13-Jan-2022), were included in this version to have one global CSP version. In addition, some administrative changes were made and the planned "last patient completed date" was updated in line with the increase of the study duration. This amendment was not submitted in Sweden as the EC confirmed that they did not want to receive non-substantial updates.
30 December 2022	CSP amendment 3: The Sponsor's rationale and justification for the amendment was: Alignment with a modified Paediatric Investigation Plan supported by the Paediatric Committee (PDCO) on 16-Dec-2022 (EMA/PDCO/773923/2022). Given a low recruitment rate despite efforts to stimulate recruitment, and the view of the PDCO to not extend the study further, it was agreed to a switch of the statistical approach, i.e., a change from superiority ambition to non-inferiority ambition. The protocol already had a pre-defined non-inferiority margin. A switch of the statistical approach would solve the recruitment problems identified to finalise the study. An adequate number of patients, i.e., a minimum of 90 evaluable patients, would be available for a non-inferior efficacy evaluation as well as safety evaluations by strata, and thus the study could be finalised and still provide data for the safe and efficacious use in the paediatric population. This was a global amendment submitted to the CAs and ECs in all involved countries.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported