Clinical trial results:
Comparative evaluation of the effects of dexmedetomidine and propofol on patient/ventilator interaction in difficult-to-wean mechanically ventilated patients; a prospective, open, randomised, multicentre study.

Summary

EudraCT number	2011-001490-40
Trial protocol	IT
Global end of trial date	31 October 2013

Results information

Result version number	v1 (current)
This version publication date	06 July 2016
First version publication date	23 July 2015

Trial information

Trial identification

Sponsor protocol code	3005019

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Orion Corporation Orion Pharma
Sponsor organisation address	Orionintie 1, Espoo, Finland, 02200
Public contact	Clinical Trials Information Desk, Orion Corporation, +358 10 4261, clinicaltrials@orionpharma.com
Scientific contact	Clinical Trials Information Desk, Orion Corporation, +358 10 4261, clinicaltrials@orionpharma.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	31 October 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2013
Global end of trial reached?	Yes
Global end of trial date	31 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to investigate effects of dexmedetomidine on diaphragmatic neural activity (EAdi) over 24 hours after starting study treatment in difficult to wean mechanically ventilated patients.

Protection of trial subjects:

Patient's sedative needs were met exclusively with the study treatments as far as possible. In the event that urgent additional sedation was required a small bolus of midazolam (not >5 mg) was administered. For patients' analgesia needs, paracetamol and then codeine were used as first-line analgesic agents. In the event that further analgesia was required, intermittent intravenous fentanyl could be administered as clinically required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 June 2012
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	Italy: 26
Worldwide total number of subjects	26
EEA total number of subjects	26

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	20
From 65 to 84 years	4
85 years and over	2

Subject disposition

Recruitment	
Recruitment details: -	
Pre-assignment	
Screening details: -	
Pre-assignment period milestones	
Number of subjects started	26
Number of subjects completed	26

Period 1	
Period 1 title	Treatment (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor
Blinding implementation details: 6 run-in subjects were not blinded (dexmedetomidine treated)	
Arms	
Are arms mutually exclusive?	Yes
Arm title	Open-label dexmedetomidine
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Dexmedetomidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details: 0.2-1.4 microg/kg/h	
Arm title	Dexmedetomidine randomised
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Dexmedetomidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details: 0.2-1.4 microg/kg/h	
Arm title	Propofol, randomised
Arm description: -	
Arm type	Active comparator

Investigational medicinal product name	Propofol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

0.3-4 mg/kg/h i.v.

Number of subjects in period 1	Open-label dexmedetomidine	Dexmedetomidine randomised	Propofol, randomised
Started	6	10	10
Completed	5	9	9
Not completed	1	1	1
Adverse event, serious fatal	-	-	1
Coma, RASS-value out of range	-	1	-
Unknown	1	-	-

Baseline characteristics

Reporting groups

Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	26	26	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
arithmetic mean	66.1		
standard deviation	± 17.6	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	16	16	

Subject analysis sets

Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised subjects who receive any study treatment will be included in the FAS.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All study subjects (including non-randomised run-in patients) who received any study treatment will be included in the evaluation of safety.

Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All randomised study subject who have received at least 24-hour study treatment, who have completed 24-hour neural assessments and who have had no major protocol deviations during the first 24-hour after starting treatment will be included in the per-protocol (PP) dataset.

Reporting group values	Full analysis set	Safety set	Per protocol
Number of subjects	20	26	20
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	68.8	66.1	68.8
standard deviation	± 15.7	± 17.6	± 15.7
Gender categorical Units: Subjects			
Female	9	10	9
Male	11	16	11

End points

End points reporting groups

Reporting group title	Open-label dexmedetomidine
Reporting group description: -	
Reporting group title	Dexmedetomidine randomised
Reporting group description: -	
Reporting group title	Propofol, randomised
Reporting group description: -	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

All randomised subjects who receive any study treatment will be included in the FAS.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All study subjects (including non-randomised run-in patients) who received any study treatment will be included in the evaluation of safety.

Subject analysis set title	Per protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All randomised study subject who have received at least 24-hour study treatment, who have completed 24-hour neural assessments and who have had no major protocol deviations during the first 24-hour after starting treatment will be included in the per-protocol (PP) dataset.

Primary: Asynchrony index (AI)

End point title	Asynchrony index (AI)[1]

End point description:

End point type	Primary

End point timeframe:

during 24 hours

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The open arm was included during the baseline period to allow ICU staff to get used to handling patients on dexmedetomidine. It is not a comparative arm in the study.

End point values	Dexmedetomidine randomised	Propofol, randomised		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: proportion				
arithmetic mean (full range (min-max))	3.89 (0 to 29.7)	5.81 (0 to 16)		

Statistical analyses

Statistical analysis title	Analysis of covariance
Comparison groups	Dexmedetomidine randomised v Propofol, randomised
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9193 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-15.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-313
upper limit	282.8
Variability estimate	Standard error of the mean
Dispersion value	149.63

Notes:

[2] - observed p-value

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From the start of study treatment to 30 days after it.	
Adverse event reporting additional description: description1	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups	
Reporting group title	Dexmedetomidine
Reporting group description: -	
Reporting group title	Propofol
Reporting group description: -	

Serious adverse events	Dexmedetomidine	Propofol	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 16 (37.50%)	3 / 10 (30.00%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events			
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 16 (25.00%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 4	0 / 1	
Haemodynamic instability			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Embolism arterial			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Agonal rhythm			

subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac arrest			
subjects affected / exposed	5 / 16 (31.25%)	3 / 10 (30.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 5	0 / 3	
Bradycardia			
subjects affected / exposed	1 / 16 (6.25%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			
Coma			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 16 (0.00%)	1 / 10 (10.00%)	
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 distress			
subjects affected / exposed	1 / 16 (6.25%)	1 / 10 (10.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pulmonary oedema			

subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (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			
Sepsis			
subjects affected / exposed	2 / 16 (12.50%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Lung infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	1 / 16 (6.25%)	2 / 10 (20.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	

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

Non-serious adverse events	Dexmedetomidine	Propofol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 16 (68.75%)	7 / 10 (70.00%)	
Injury, poisoning and procedural complications			
Gastrointestinal anastomotic leak			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

Surgical and medical procedures Tracheostomy subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1	 0 / 10 (0.00%) 0	
General disorders and administration site conditions Pain subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1	 0 / 10 (0.00%) 0	
Gastrointestinal disorders Duodenal ulcer subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1	 0 / 10 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders Cough decreased subjects affected / exposed occurrences (all) Increased bronchial secretion subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0 0 / 16 (0.00%) 0	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1	
Hepatobiliary disorders Hyperbilirubinaemia subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1	 0 / 10 (0.00%) 0	
Psychiatric disorders Delirium subjects affected / exposed occurrences (all)	 1 / 16 (6.25%) 1	 0 / 10 (0.00%) 0	
Infections and infestations Endocarditis bacterial subjects affected / exposed occurrences (all) Device related sepsis subjects affected / exposed occurrences (all)	 0 / 16 (0.00%) 0 1 / 16 (6.25%) 1	 1 / 10 (10.00%) 1 1 / 10 (10.00%) 1	

Pneumonia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperammonaemia			
subjects affected / exposed	1 / 16 (6.25%)	0 / 10 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 January 2011	Sample size adjusted according to additional clinical in-put on reasonable expected treatment differences.
14 February 2013	Standard of care safety blood tests acceptable at baseline if taken on same day as start of study treatment to reduce patient burden. If SOC safety blood tests not available, study specific tests to be taken within 2 hrs of starting treatment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported