Clinical trial results:
Neuroprotection with Dexmedetomidine in patients undergoing elective cardiac or abdominal surgery

Summary

EudraCT number	2013-000823-15
Trial protocol	DE
Global end of trial date	30 July 2018

Results information

Result version number	v1 (current)
This version publication date	29 October 2020
First version publication date	29 October 2020

Trial information

Trial identification

Sponsor protocol code	NEUPRODEX

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02096068
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Charité - Universitätsmedizin Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Univ.-Prof. Dr. C. Spies, Department of Anesthesiology and Operative Intensive Care Medicine (CCM/CVK), +49 30450 551001 , claudia.spies@charite.de
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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	16 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Incidence of postoperative delirium measured with the Confusion Assessment Method for the ICU (CAM-ICU)"or the „Confusion Assessment Method (CAM) and/or Chart Review and/or DSM V/ICD-10 "

Protection of trial subjects:

During anesthesia changes of hemodynamic parameters in the intraoperative transoseophageal echocardiography and in the processive electroencephalography and eletromyography were measured. Incidence of adverse events which start after the application of the study drug were evaluated for five postoperative days.

Background therapy:

Surgical patients received standard of care in the university hospital.

Evidence for comparator:

not applicable, Placebo use

Actual start date of recruitment	13 July 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	3 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 75
Worldwide total number of subjects	75
EEA total number of subjects	75

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)	17
From 65 to 84 years	57
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Study group: 13.07.2014 - 08.03.2016 (Last study patient in)
POCD control group: 17.10.2015 - 20.04.2018 (Last control subject in)

Pre-assignment

Screening details:

n= 484 patients were screened, n= 421 screening failure (1. n= 49 refused participation; n= 119 did not meet inclusion criteria; 3. other)
n= 63 were included. n=3 patients drop-out criteria occurred after inclusion, reasons: 1. one patient refused study participation; 2. received no heart lung machine surgery, 3. emergency operation

Period 1

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

Blinding implementation details:

All role members were unblinded after database closure on May 15, 2019.

Arms

Are arms mutually exclusive?	Yes
Arm title	Verum

Arm description:

Experimental: Study group
Application of Dexmedetomidine (Dexdor®) perioperatively for a maximum of 48 hours

Dosing Scheme:
during operation and mechanical ventilation: 0,7µg/kgABW/h; recovery time until extubation: 0,4µg/kgABW/h; after extubation: 0,2-1,4µg/kgABW/h
Dexmedetomidine was supplied in a 2 ml ampoule containing 200 µg (100 µg/ml) dexmedetomidine (as a base) for dilution with 48 ml 0.9% sodium chloride injection (giving a solution containing 4 µg/ml) in 50 ml syringe.

Arm type	Experimental
Investigational medicinal product name	Dexdor 100 Mikrogramm/ml
Investigational medicinal product code	ATC code N05CM18
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravascular use

Dosage and administration details:

Dexmedetomidine was supplied in a 2 ml ampoule containing 200 µg (100 µg/ml) dexmedetomidine (as a base) for dilution with 48 ml 0.9% sodium chloride injection (giving a solution containing 4 µg/ml) in 50 ml syringe.
During operation and mechnical ventilation: 0,7µg/kgABW/h
recovery time until extubation: 0,4µg/kgABW/h
after extubation: 0,2-1,4µg/kgABW/h

Arm title	Placebo

Arm description:

Placebo Comparator: Control group
Application of placebo for a maximum of 48 hours
Placebo for dexmedetomidine was a 50 ml syringe containing 0.9% sodium chloride isotonic infusion solution/0.9 % sodium chloride injection solution

Arm type	Placebo
Investigational medicinal product name	0.9% sodium chloride isotonic physiological solution
Investigational medicinal product code	ATC code: B05BB01
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo for dexmedetomidine was a 50 ml syringe containing 0.9% sodium chloride isotonic infusion solution/0.9 % sodium chloride injection solution

During operation and mechnical ventilation: 0,7µg/kgABW/h
recovery time until extubation: 0,4µg/kgABW/h
after extubation: 0,2-1,4µg/kgABW/h

Arm title	Control POCD

Arm description:

No Intervention: POCD (postoperative cognitive deficit) control group
A non-surgical control group of 15 ASA II/III- patients is collected for measuring the learning experience during the cognitive testings. The participants are matched on age, education, and gender to the study patients.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Verum	Placebo	Control POCD
Started	28	32	15
Completed	28	32	15

Baseline characteristics

Reporting groups	
Reporting group title	overall trial
Reporting group description:	
The intention-to-treat population includes 28 patients in the dexmedetomidine group and 32 patients in the placebo group. A non-surgical control group of 15 ASA II/III- patients is collected for measuring the learning experience during the cognitive testings.	

Reporting group values	overall trial	Total	
Number of subjects	75	75	
Age categorical Units: Subjects			
60-64 years	17	17	
65-84 years	57	57	
85 years and over	1	1	
not recorded	0	0	
Gender categorical Units: Subjects			
Female	28	28	
Male	47	47	
ASA-Status			
The ASA physical status classification system is a system for assessing the fitness of patients before surgery. In 1963 the American Society of Anesthesiologists (ASA) adopted the five-category physical status classification system; a sixth category was later added. These are: Healthy person. Mild systemic disease. Severe systemic disease. Severe systemic disease that is a constant threat to life. A moribund person who is not expected to survive without the operation. A declared brain-dead person whose organs are being removed for donor purposes.			
Units: Subjects			
ASA 1	1	1	
ASA 2	38	38	
ASA 3	36	36	
not recorded	0	0	

End points

End points reporting groups

Reporting group title	Verum

Reporting group description:

Experimental: Study group
Application of Dexmedetomidine (Dexdor®) perioperatively for a maximum of 48 hours

Dosing Scheme:
during operation and mechanical ventilation: 0,7µg/kgABW/h; recovery time until extubation: 0,4µg/kgABW/h; after extubation: 0,2-1,4µg/kgABW/h
Dexmedetomidine was supplied in a 2 ml ampoule containing 200 µg (100 µg/ml) dexmedetomidine (as a base) for dilution with 48 ml 0.9% sodium chloride injection (giving a solution containing 4 µg/ml) in 50 ml syringe.

Reporting group title	Placebo

Reporting group description:

Placebo Comparator: Control group
Application of placebo for a maximum of 48 hours
Placebo for dexmedetomidine was a 50 ml syringe containing 0.9% sodium chloride isotonic infusion solution/0.9 % sodium chloride injection solution

Reporting group title	Control POCD

Reporting group description:

No Intervention: POCD (postoperative cognitive deficit) control group
A non-surgical control group of 15 ASA II/III- patients is collected for measuring the learning experience during the cognitive testings. The participants are matched on age, education, and gender to the study patients.

Primary: Delirium

End point title	Delirium[1]

End point description:

Incidence of postoperative delirium measured with the Confusion Assessment Method for the ICU (CAM-ICU) or the Confusion Assessment Method (CAM)

End point type	Primary

End point timeframe:

Unitil the fifth postoperative day

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 primary end point is reporting statistics for all the study arms e.g. verum arm and placebo arm in the baseline period. In the POCD control group no delirium (primary endpoint) was measured.

End point values	Verum	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	32		
Units: yes/no				
yes	5	14		
no	23	18		

Statistical analyses

Statistical analysis title	Primary endpoint
Statistical analysis description: Fisher-Boschloo-Test	
Comparison groups	Verum v Placebo
Number of subjects included in analysis	60
Analysis specification	Post-hoc
Analysis type	equivalence[2]
P-value	< 0.05
Method	Fisher-Boschloo-Test

Notes:

[2] - For the primary endpoint we found a reduction of delirium incidence measured by CAM-ICU / CAM within the first five postoperative days from 43.8% (n=14) in the placebo group to 17.9% (n=5) in the verum group. According to the Fisher-Boschloo-Test this difference is significant with p=0.038. The Fisher-Boschloo test was used because it constitutes an alternative to the Fisher's Exact Test with larger statistical power, while ensuring the same level of type-I-error.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Incidence of adverse events which start after the application of the study medication within 5 postoperative days.

Adverse event reporting additional description:

Every adverse event that started within 5 postoperative days has to be followed up until decrease of the symptoms or stabilisation.
Patients were evaluated regarding their safety profil during ech study visit twice per day.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Verum

Reporting group description:

This group received study medication Dexdor.

Reporting group title	Placebo

Reporting group description:

This group received 0.9% NaCl

Serious adverse events	Verum	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 28 (25.00%)	9 / 32 (28.13%)	
number of deaths (all causes)	0	5	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Oversedation	Additional description: In this study one serious adverse drug reaction was reported.		
subjects affected / exposed	1 / 28 (3.57%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Expired study medication			
subjects affected / exposed	1 / 28 (3.57%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anesthesia overhang			
subjects affected / exposed	2 / 28 (7.14%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Delayed awakening			
subjects affected / exposed	0 / 28 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hematoma			
subjects affected / exposed	0 / 28 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotonia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative bleeding			
subjects affected / exposed	1 / 28 (3.57%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enhanced secretion production			
subjects affected / exposed	0 / 28 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 28 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asystolia			
subjects affected / exposed	0 / 28 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation with tachyarrhythmia absoluta			
subjects affected / exposed	0 / 28 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Myocardial ischemia			
subjects affected / exposed	1 / 28 (3.57%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhtyhmia absoluta			
subjects affected / exposed	0 / 28 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Necrotic pancreatitis			
subjects affected / exposed	1 / 28 (3.57%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophageal occlusion			
subjects affected / exposed	0 / 28 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Increased liver values			
subjects affected / exposed	1 / 28 (3.57%)	0 / 32 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	0 / 28 (0.00%)	1 / 32 (3.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Verum	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 28 (100.00%)	32 / 32 (100.00%)	
Investigations			

Hyperglycemia			
subjects affected / exposed	1 / 28 (3.57%)	4 / 32 (12.50%)	
occurrences (all)	1	4	
Pateint state index decreased			
subjects affected / exposed	8 / 28 (28.57%)	8 / 32 (25.00%)	
occurrences (all)	8	8	
Injury, poisoning and procedural complications			
Hypothermia			
subjects affected / exposed	4 / 28 (14.29%)	2 / 32 (6.25%)	
occurrences (all)	4	2	
Delayed awakening			
subjects affected / exposed	2 / 28 (7.14%)	5 / 32 (15.63%)	
occurrences (all)	2	5	
Inadequate awakening			
subjects affected / exposed	1 / 28 (3.57%)	4 / 32 (12.50%)	
occurrences (all)	1	4	
Vascular disorders			
Hypertonia			
subjects affected / exposed	3 / 28 (10.71%)	10 / 32 (31.25%)	
occurrences (all)	3	10	
Hypotension			
subjects affected / exposed	3 / 28 (10.71%)	4 / 32 (12.50%)	
occurrences (all)	3	4	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	20 / 28 (71.43%)	21 / 32 (65.63%)	
occurrences (all)	20	21	
Tachyarrhythmia absoluta			
subjects affected / exposed	2 / 28 (7.14%)	3 / 32 (9.38%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	3 / 28 (10.71%)	1 / 32 (3.13%)	
occurrences (all)	3	1	
Hypovolaemia			

subjects affected / exposed	2 / 28 (7.14%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Oedema			
subjects affected / exposed	3 / 28 (10.71%)	2 / 32 (6.25%)	
occurrences (all)	3	2	
Pain			
subjects affected / exposed	2 / 28 (7.14%)	6 / 32 (18.75%)	
occurrences (all)	2	6	
Gastrointestinal disorders			
PONV			
subjects affected / exposed	5 / 28 (17.86%)	7 / 32 (21.88%)	
occurrences (all)	5	7	
Obstipation			
subjects affected / exposed	2 / 28 (7.14%)	1 / 32 (3.13%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	1 / 28 (3.57%)	3 / 32 (9.38%)	
occurrences (all)	1	3	
Diarrhoea			
subjects affected / exposed	3 / 28 (10.71%)	4 / 32 (12.50%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Dystelectasis			
subjects affected / exposed	1 / 28 (3.57%)	4 / 32 (12.50%)	
occurrences (all)	1	4	
Pleural effusion			
subjects affected / exposed	9 / 28 (32.14%)	10 / 32 (31.25%)	
occurrences (all)	9	10	
Psychiatric disorders			
Subsyndromal delirium			
subjects affected / exposed	20 / 28 (71.43%)	21 / 32 (65.63%)	
occurrences (all)	20	21	
Infections and infestations			
SIRS			
subjects affected / exposed	10 / 28 (35.71%)	5 / 32 (15.63%)	
occurrences (all)	10	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2014	Amendment 01: changes of the protocol 1.0 to 1.1 within the ethical applications, submitted to BfArM again as substantial Amendment 01.
14 August 2015	Amendment 02: Substantial Amendment changes of the protocol 1.1 to 1.2: Primary reason for amendment were changes in study design: a POCD-control group of 15 patients was requested and three inclusion and exclusion criteria were specified. Three secondary endpoints were added. The time schedule of the study was adapted.and changes of the summary of product characteristics Dexdor 11/2014, sodium chloride Fresenius (07/2013), sodiume chloride BBraun (06/2014) were included in the new protocol version and patient information sheets. Safety documentation was set for 5 postoperative days. Fulfilling conditions of the ethical committee: Changes of the protocol 1.2 to 1.4: Including to the safety documentation that every adverse event that started within 5 postoperative days has to be followed up until decrease of the symptoms or stabilisation.
02 March 2016	Amendment 03 changes of the protocol 1.4 to 1.5 Primary reason for amendment were changes in study design: the study title was changed. The inclusion criterion was expanded to abdominal surgery. Specific protocol exceptions to expected SAE Reporting were added. Measurement of Cortisol is collected from blood samples and salivary juice.
27 May 2016	Amendment 04 changes of the protocol 1.5 to 1.6 to fulfill the conditions of the BfArM: The benefit risk evaluation regarding the inclusion of study patients undergoing hepatic, gastric and intestinal surgery was added. The safety documentation and annual reporting was specified in the study protocol according to ICH Topic E2F and the importance of the reporting of SUSARS after unblinding of adverse events which fulfil the criteria causal relationship and unexspectedness was emphasized.
29 December 2016	Amendment 05 changes of the protocol 1.6 to 1.7 Primary endpoint time measurement is reduced from 7 to 5 postoperative days. POCD measurements are specified to baseline, 5 (+/-2) postoperative days and between 90 postoperative days. Changes of the summary of product characteristics Dexdor 05/2016 were updated. The study drug could patient develops delirium within 2 hours of pausing be restarted up to 48 hours postoperatively if the patient develops delirium within 2 hours of pausing.

05 January 2018	Amendment 06 changes of the protocol 1.7 to 1.8 Following Changes in study design: Primary and secondary endpoints Delirium measurement are expanded by validated Delirium scores. The enrollment rates are adapted by a current lower Drop-Out rate. The SUMMARY OF PRODUCT CHARACTERISTICS of NaCl (Placebo) is updated. The biometric institute, that has to perform the statistical analysis, was changed
15 May 2018	Amendment 07 to fulfill the conditions of the ethical committee: changes of the protocol 1.8 to 1.9 Primary and secondary endpoints Delirium measurement are reduced to validated Delirium scores according to protocol V1.7.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

not applicable

Notes: