Clinical trial results:
A double blind, randomised, multicentre, active controlled, parallel-group, phase III trial to evaluate the efficacy, safety and pharmacokinetics of intravenous clonidine (hydrochloride) compared to midazolam for sedation in children from birth to less than 18 years of age.

Summary

EudraCT number	2014-003582-24
Trial protocol	NL DE SE IT CZ EE ES
Global end of trial date	06 November 2018

Results information

Result version number	v1 (current)
This version publication date	27 July 2020
First version publication date	27 July 2020
Summary attachment (see zip file)	CloSed CSR-Synopsis V1.0 06.07.2020 (CloSed_CSR_Synopsis_v1.0_200706.pdf)

Trial information

Trial identification

Sponsor protocol code	CLON01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02509273
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Universitätsklinikum Erlangen
Sponsor organisation address	Maximiliansplatz 2, Erlangen, Germany, 91054
Public contact	Department of Paediatric and Adolescents Medicine, Universitätsklinikum Erlangen, +49 91318533118, paed-studienzentrale@uk-erlangen.de
Scientific contact	Department of Paediatric and Adolescents Medicine, Universitätsklinikum Erlangen, +49 91318533118, paed-studienzentrale@uk-erlangen.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001316-PIP01-12
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	06 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 November 2018
Global end of trial reached?	Yes
Global end of trial date	06 November 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the non-inferiority of the sedative properties of continuous intravenous (i.v.) clonidine compared to continuous i.v. midazolam in mechanically ventilated children and adolescents (0 - <18 years) admitted to a paediatric intensive care unit (PICU).

Protection of trial subjects:

Full comprehensive information (on the research's goals, potential and direct benefits, the nature, extent and duration of the procedures, details of the additional burden caused by the research project, the alternative treatment possibilities, possible adverse events, and the protective measures to address the potential problems) were given to all families participating in the CloSed study. An Independent Data Safety Monitoring Board has been included within this trial to ensure the protection of the subjects. Subjects were closely followed using standard PICU monitoring of vital functions (continuous assessment of heart rate and peripheral arterial oxygen saturation, intermittent assessment of systolic and diastolic blood pressure), intermittent assessment of pain and depth of sedation, documentation of mechanical ventilation parameters, intermittent arterial blood gas analysis and calculation of fluid balance (only in subjects already catheterised under standard care). In addition, qualified PICU staff was close to subjects around the clock, minimizing reaction time in case of alarms or deterioration of clinical parameters.

Background therapy:

Propofol was given to subjects who required pre-sedation and was stopped within the first half an hour of IMP administration. It could also be given during procedures if required. All subjects received morphine as a background infusion continously. Morphine and propofol were NIMPs in this study.

Evidence for comparator:

Every patient enrolled in the study was in need of sedation, thus a placebo could not be considered as a control and an active comparator was needed. Intravenous midazolam is the standard treatment for longer-term sedation in children. It is licensed in this population, regarded as standard of care, and recommended by treatment guidelines.

Actual start date of recruitment	21 March 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 2
Country: Number of subjects enrolled	Sweden: 4

Country: Number of subjects enrolled	Estonia: 13
Country: Number of subjects enrolled	Germany: 9
Worldwide total number of subjects	28
EEA total number of subjects	28

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	2
Newborns (0-27 days)	12
Infants and toddlers (28 days-23 months)	9
Children (2-11 years)	5
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment started on 23/11/2016 (first informed consent signed, FSFV) and finished on 06/11/2018, LPLV (visit 6).
In 7 EU Countries, 10 centers were open for recruitment: Netherlands (1), Sweden (1), Germany (2), Estonia (1), Czech Republic (1), Italy (3) and Spain (1).

Pre-assignment

Screening details:

There was a 5 day screening period for eligibility of the subjects according to the inclusion-/exclusion-criteria. The main screening criteria was the anticipated need of 24hs of sedation.

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:

Reference product (midazolam) vials had the same appearance as the test product (clonidine) vials. A simple three colour scheme was used for the different product strengths of both clonidine and midazolam (blue: low strength, black: medium strength and orange: high strength). To maintain the blinding during infusion, the midazolam concentration was 100-fold higher than clonidine (i.e. 1 mcg/kg/h clonidine HCl equates to 100 mcg/kg/h of midazolam) so that the infusion rates were identical.

Arms

Are arms mutually exclusive?	Yes
Arm title	Clonidine Hydrochloride

Arm description:

5 mcg/ml, 10 mcg/ml or 50 mcg/ml solution for intravenous infusion.

Arm type	Experimental
Investigational medicinal product name	Clonidine Hydrochloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects were stratified by age, but only the subject's weight was used to determine the formulation strength. Hence subjects within an age category may be administered different formulation strengths: Formulation 1: 5 mcg/ml (250 mcg/50 ml) for ≥ 1.5 kg ≤ 3 kg; Formulation 2: 10 mcg/ml (500 mcg/50 ml) for > 3 kg < 10 kg; Formulation 3: 50 mcg/ml (2500 mcg/50 ml) for ≥ 10 kg ≤ 85 kg.
Dosing of the blinded IMP was based on units [unit/kg/h]: 1 Unit = 1.0 mcg (max. 100 mcg/h) Clonidine HCl. Dosing units of the IMP were converted to infusion rates according to specific schemes.
The IMP was administered according to a dosing algorithm in which adjustment of the IMP was based on the results of the sedation assessment using COMFORT-B Score and NISS.

Arm title	Midazolam

Arm description:

0.5 mg/ml, 1 mg/ml or 5 mg/ml solution for intravenous infusion.

Arm type	Active comparator

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

Dosage and administration details:

Subjects were stratified by age, but only the subject's weight was used to determine the formulation strength. Hence subjects within an age category may be administered different formulation strengths: Formulation 1: 0.5mcg/ml (25mg/50 ml) for ≥ 1.5 kg ≤ 3 kg; Formulation 2: 1mcg/ml (50mg/50 ml) for > 3 kg < 10 kg; Formulation 3: 5mcg/ml (250mcg/50 ml) for ≥ 10 kg ≤ 85 kg.
Dosing of the blinded IMP was based on units [unit/kg/h]: 1 Unit = 0.1mg (max. 10mg/h) Midazolam. Dosing units of the IMP were converted to infusion rates according to specific schemes.
The IMP was administered according to a dosing algorithm in which adjustment of the IMP was based on the results of the sedation assessment using COMFORT-B Score and NISS.

Number of subjects in period 1	Clonidine Hydrochloride	Midazolam
Started	15	13
Completed	15	13

Baseline characteristics

Reporting groups	
Reporting group title	Clonidine Hydrochloride
Reporting group description: 5 mcg/ml, 10 mcg/ml or 50 mcg/ml solution for intravenous infusion.	
Reporting group title	Midazolam
Reporting group description: 0.5 mg/ml, 1 mg/ml or 5 mg/ml solution for intravenous infusion.	

Reporting group values	Clonidine Hydrochloride	Midazolam	Total
Number of subjects	15	13	28
Age categorical			
The study population was stratified into the following three age group subsets			
Units: Subjects			
age group 1 (GA ≥34w to 27d)	6	8	14
age group 2 (28d to < 2 yrs)	6	3	9
age group 3 (2yrs to <18 yrs)	3	2	5
Gender categorical Units: Subjects			
Female	6	8	14
Male	9	5	14

End points

End points reporting groups

Reporting group title	Clonidine Hydrochloride
Reporting group description:	
5 mcg/ml, 10 mcg/ml or 50 mcg/ml solution for intravenous infusion.	
Reporting group title	Midazolam
Reporting group description:	
0.5 mg/ml, 1 mg/ml or 5 mg/ml solution for intravenous infusion.	

Primary: Sedation Failure

End point title	Sedation Failure[1]

End point description:

Sedation failure is defined as: When a subject's assessment results are:
Numerical Rating Scale (NRS) score <4 and COMFORT-B score >22
OR
Numerical Rating Scale (NRS) score <4 and COMFORT-B score ≤22-≥11 AND Nurse's Interpretation of Sedation (NISS) score 1

at a point during the study where no further increase in IMP dose is permitted as described in the dose escalation scheme.

End point type	Primary

End point timeframe:

Within the study treatment period (a maximum of seven days).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Due to the limited number of enrolled patients (28) only descriptive analysis have been performed.

End point values	Clonidine Hydrochloride	Midazolam		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12[2]	13		
Units: Number of subjects				
Sedation Failure	4	2		
Sedation Success	8	11		

Notes:

[2] - in 3 subjects the primary endpoint was not assessable

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation for an AE included the time of first administration of an IMP until the subject´s last study visit.

Adverse event reporting additional description:

Pre-existing conditions that did not worsen during the course of the study were not reportable as AEs. To determine whether a condition had worsened, it was compared to the condition of the subject at baseline assessment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Clonidine Group

Reporting group description:

The Safety Analysis Set (SES) is the subset of all subjects who were randomised into the trial and exposed to study medication = Intention To Treat (ITT) Population.

Reporting group title	Midazolam Group

Reporting group description:

The Safety Analysis Set (SES) is the subset of all subjects who were randomised into the trial and exposed to study medication = Intention To Treat (ITT) Population.

Serious adverse events	Clonidine Group	Midazolam Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Diaphragmatic hernia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (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	Clonidine Group	Midazolam Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 15 (93.33%)	10 / 13 (76.92%)	
Vascular disorders			

Arterial hypotension			
subjects affected / exposed	2 / 15 (13.33%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Hypotension			
subjects affected / exposed	2 / 15 (13.33%)	1 / 13 (7.69%)	
occurrences (all)	2	1	
Surgical and medical procedures			
Treatment withdrawal			
subjects affected / exposed	2 / 15 (13.33%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Oedema			
subjects affected / exposed	6 / 15 (40.00%)	3 / 13 (23.08%)	
occurrences (all)	7	3	
Fever			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	2 / 15 (13.33%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Bronchospasm			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Chylothorax			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Difficulty breathing			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Pulmonary hypertension			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Respiratory distress			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Respiratory insufficiency			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Stridor			
subjects affected / exposed	2 / 15 (13.33%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Stridor inspiratory			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Reactive psychosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Investigations			
Arterial oxygen saturation decreased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
CRP increased			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Elevated liver enzymes			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Haemoglobin low			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
INR increased			
subjects affected / exposed	1 / 15 (6.67%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Albumin			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Unintened endotracheal extubation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

Congenital, familial and genetic disorders			
Ductus arteriosus patent			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Undescended testicle			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Febrile seizure			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Thrombopenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Leukocytosis			
subjects affected / exposed	2 / 15 (13.33%)	0 / 13 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Infantile colic			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Diaphragmic hernia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Nausea			

subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Itching			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Renal insufficiency			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Oliguria			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Superinfection bacterial			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Neonatal infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Nosocomial infection			
subjects affected / exposed	1 / 15 (6.67%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
Croup			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Breast feeding problem (infant)			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Fluid retention			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hypocalcaemia			

subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
Hypochloraemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	3 / 15 (20.00%)	1 / 13 (7.69%)	
occurrences (all)	4	1	
Hyponatraemia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Poor feeding neonatal			
subjects affected / exposed	1 / 15 (6.67%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 February 2016	Amendment 01 (Protocol version 2.0) -Previous text instructed a sedation re-assessment after 30 min for both dose increases and dose reductions. However, according to clinical experience and PK properties of the sedative drugs (IMP) a longer observation period after dose decrease was considered to be more appropriate to evaluate the desired effects. For the sedation assessment, different intervals of re assessment after increase (30 min) compared to decrease (3 hours) of the IMP dose were introduced. The change in protocol allowed sufficient time (a 6 hour observation period) after a dose decrease of IMP for it to take effect prior to re-assessing level of pain and sedation. Some flexibility was included to allow investigators to judge, in certain cases, that a further dose decrease was required and could be given without deviating from the dose adjustment regimen of the protocol. - Patients within the hospital of the study site, (e.g. patients who come to the PICU department from another ward), and who would already have been intubated and initially treated with sedative/analgesic therapy, were considered eligible for inclusion in the study. - The use of propofol as a short term bridging therapy for any relevant patient was allowed and not restricted to only subjects acutely admitted to PICU. - An instruction was introduced to more precisely define how and at what point investigators should return subjects to the dose escalation regimen after a dose decrease. - Clarification that urine samples for PK analysis purposes were optional was added.
21 October 2016	Amendment 02 (Protocol version 3.0) - In order to enhance recruitment, the exclusion criterion excluding patients who had received clonidine in the 7 days prior to admission to PICU was removed and a PK sample immediately prior to IMP administration was made mandatory in all patients that had received either clonidine or midazolam at least once within 5 days prior to IMP administration. -The exclusion criterion regarding patients on CPAP was removed as it was considered that there was no medical reason for this requirement because from the experience of the investigators, patients could be on CPAP at screening and undergo surgery later followed by >24h mechanical ventilation and sedation. - The definition of circulatory failure, was redefined using criteria adapted from Goldstein et al 2005. - From the experience of the investigators, there was no medical reason why subjects with acute asthma and paralytic ileus should have been excluded from the study and therefore the relevant exclusion criteria were removed. Please note that following review of the amendment by the Czech CA (SUKL), this specific amendment point did not apply in that territory. -A new section regarding interaction and incompatibilities with concomitant drugs was added at the request of the Swedish Competent Authority (MPA). -The text regarding emergency unblinding was revised to achieve conformity with ICH-GCP in accordance with the requirements of the MPA. -Text regarding the definition, recording and reporting of suspected unexpected serious adverse reactions (SUSARs) was added in response to a comment from the MPA.
19 January 2018	Amendment 03 (Protocol Version 3.1) This amendment provided only clarifications and corrections to the protocol and was submitted to the Competent Authorities and ECs only and approved in Germany only. No site received this protocol amendment.

03 May 2018	Amendment 04 (Protocol version 4.0) - A section was added to take into account local standard practice for tapering patients off sedatives to clarify how the IMP may have been stopped by dose tapering. - The renal insufficiency exclusion criterion was removed and others were simplified to be more inclusive of the PICU-patient population and enlarge the eligible study population, without compromising subject safety. It was left to the investigators' discretion if the condition would impact the sedation evaluations. - As the infusion pumps were mostly only accurate to 1 decimal place, information regarding infusion rates to be used in the study was amended to allow for dose changes as required in the protocol. Additionally, sites were no longer permitted to calculate the dose by hand but to use the study-specific tables provided. - The reduction of the morphine background infusion doses was amended to be at the discretion of the investigator and not mandated. - The use of propofol was amended to be more in alignment with standard of care. - As additional sedatives and analgesia during a procedure could have increased the subject's level of sedation temporarily, advice regarding over sedation was added into the section on dose adjustment of IMP and morphine according to level of sedation and pain. - To simplify the dosing regimen, the additional pain and sedation score required 2 hours after the 2nd or 3rd loading dose and at the end of the lock-out period was removed. - It was sufficient to collect only the medication and dosing information for 1 week prior to Visit 1 instead of 3 weeks. -Time windows were added for vital signs and a paragraph regarding the recording of vital signs in patients without arterial lines was introduced in order to reduce inappropriate stress on the subjects. - The exact periodicity of PK sample shipments was removed based on the availability of new sample stability data.
20 July 2018	Amendment 5 (Protocol version 4.1) This amendment was an amendment to protocol version 3.1. It included all changes detailed in amendment 4 and information regarding the risk-benefit of changes made in amendment 4 were added as requested by the German CA (BfArM). No subjects were recruited under this amendment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 October 2018	A recruitment stop was decided in all countries due to the slow recruitment and not on any safety concerns.	-

Notes:

Limitations and caveats

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

The study was terminated early not related to safety concerns or issues. As such, the limited enrollment precludes a meaningful conclusion about the efficacy and safety of clonidine compared with midazolam.

Notes: