SYNOPSIS

Title of Study:	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
Study Numbers:	Sponsor Study No.: CLON01
EudraCT Number:	2014-003582-24
Investigational Medicinal Products (IMPs):	Clonidine Hydrochloride solution for intravenous infusion 5 mcg/ml, 10 mcg/ml and 50 mcg/ml Midazolam solution for intravenous infusion 0.5 mg/ml, 1 mg/ml and 5 mg/ml
Development Phase:	III (Three)
Sponsor:	Universitätsklinikum Erlangen represented by the Dean (Medizinische Fakultät) Friedrich-Alexander-Universität Erlangen-Nürnberg Maximiliansplatz 2, 91054 Erlangen Sponsor's designee: Prof. Dr, rer. nat. Antje Neubert
Coordinating Investigator:	Prof. Dr. Dick Tibboel, Sophia Children's Hospital, Erasmus Universitair Medisch Centrum, Rotterdam
Study Centres:	10 Study centres across 7 countries The Netherlands (Erasmus Universitair Medisch Centrum/Rotterdam) Sweden (Karolinska Institutet/Stockholm) Germany (Universitätsklinikum Erlangen, Cnopf'sche Kinderklinik/Nürnberg) Czech Republic (Univerzita Karlova V Praze in Prague) Italy (Ospedale Pediatrico Bambino Gesu/Rome, Policlinico Bari, ARNAS Civico/Palermo) Estonia (Tallinn Children's Hospital/Tallinn) Spain (Hospital 12 de Octubre/ Madrid)
Studied Period:	**First subject first visit:** 23 Nov 2016 *(first signing of Informed Consent)* **Last subject last visit:** 06/11/2018 *(last subject last visit [Visit 6])* Subjects were screened at 9 sites when the study was early terminated (End of Trial DE, SE, EE: 12.11.2018, ES, IT, CZ: 22.10.2018, NL: 26.06.2018).

Study Objectives:

Primary Objective:

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).

Secondary Objectives:

- To evaluate the safety and tolerability (including withdrawal effects) of clonidine compared with midazolam in ventilated children and adolescents admitted to PICU.
- To determine clonidine dose-dependent effects on sedation.
- To establish the pharmacokinetic-pharmacodynamic relationship of clonidine for sedation in PICU.
- To compare the cumulative total morphine consumption/kg between the two arms in the first 48 hours of IMP administration.

Study Design and Methodology:

This was a double blind, randomised, active-controlled, parallel group, multicentre, phase III study in children from birth to less than 18 years of age. There was a 5-day screening period followed by randomisation to a treatment period of a maximum of 7 days (168 hours) and a post-dose monitoring period of up to 5 days. Follow-up visits occurred 14 days following completion of the treatment period, and after one year (for the neonate age group only).

Subjects were randomly assigned to receive clonidine or midazolam by i.v. infusion. The formulation strength and infusion rate were selected on the basis of the subject's weight. The study population was divided as equally as possible between the two arms, and was stratified into the following three age group subsets:

- Age group 1: From birth to 27 days of age (with at least 10% of these being preterm neonates born ≥34 weeks of gestational age [GA])
- Age group 2: From 28 days to < 2 years of age
- Age group 3: From 2 years to < 18 years

Number of subjects (planned and analysed):

300 subjects were planned to be enrolled.

28 subjects were randomised and enrolled (25 subjects completed as per protocol, 28 subjects analysed)

Inclusion Criteria:

- Male or Female.
- Aged from birth (≥34 weeks GA) to <17 years, 11 months, 1 week old.
- Admitted or expected to be admitted (post-operatively) to PICU.
- Existing or expected indication for invasive or non-invasive ventilation (except CPAP).
- Anticipated need for continuous sedation for at least 24 hours.
- Informed consent (or deferred consent) obtained from the subject's parent(s) or legal guardian(s).

Exclusion Criteria*:

- Body weight less than 1200 g. Gestational age of <34 weeks.
- Body weight: 3 kg or less AND 28 days or older; less than 10 kg AND 2 years old or older; greater than 85 kg.
- Known hypersensitivity to the IMP test (clonidine) or comparator (midazolam), or non-investigational medical product (morphine, propofol) or any of their formulation ingredients and their rescue medication.
- Subjects being treated with forbidden concomitant medications (e.g. continuous infusion of muscle relaxants).
- Subjects less than 24 hours post-resuscitation.
- Subjects who had been under sedation for more than 72 hours immediately prior to assessment.
- Subjects currently being treated with Extra Corporeal Membrane Oxygenation (ECMO).
- Subjects with treatment-induced whole body hypothermia.
- Subjects with severe organ insufficiencies e.g.
  - Renal insufficiency grade 3, 4 or 5
  - Cardiovascular insufficiency
  - Systemic arterial hypotension in subjects ≤ 3 days old (identified using postnatal age and GA)
  - Circulatory failure
  - Liver dysfunction
- Subjects with traumatic brain injury all grades, intracranial pathology (tumour, haemorrhage, infections) with an effect on level of consciousness, severe mental retardation with or without a well-defined syndrome
- Subjects with Myasthenia gravis, Spinal muscular atrophy, or other rare neurologic diseases and conditions which preclude performance of a COMFORT-B Score, major congenital anomalies of the central nervous system, phaeochromocytoma.
- Subjects with severe bradyarrhythmia resulting from either sick-sinus syndrome or AV block of 2nd or 3rd degree.
- Subjects with current status epilepticus or active fitting (2 or more seizures regularly on a daily basis) at admission.
- Known arterial hypertension requiring chronic treatment in medical history.
- Females who are pregnant, lactating or planning to become pregnant.

*Main exclusion criteria, for details please see the CSP V4.1)

Reference Product, Dose and Mode of Administration, Batch Number:

Generic name:	Midazolam Solution for i.v. Infusion
Dosage form:	Solution for i.v. infusion
Dose:	Formulation 1: 0.5 mg/ml Formulation 2: 1 mg/ml Formulation 3: 5 mg/ml
Manufacturer:	Universitätsklinikum Erlangen (UKER), Germany
Batch numbers:	Formulation 1: H066.15, H042.18 Formulation 2: H067.15, H043.18 Formulation 3: H065.15, H028.18

Test Product, Dose and Mode of Administration, Batch Number:	
Generic name:	Clonidine Solution for i.v. Infusion
Dosage form:	Solution for intravenous infusion
Dose:	Formulation 1: 5 mcg/ml Formulation 2: 10 mcg/ml Formulation 3: 50 mcg/ml
Manufacturer:	Universitätsklinikum Erlangen (UKER), Germany
Batch numbers:	Formulation 1: H062.15, H046.18 Formulation 2: H063.15, H047.18 Formulation 3: H064.15, H026.18

Duration of Treatment:

Subjects received treatment with IMP for a maximum of 7 days (168 hours).

Treatment Compliance:

The IMP infusions were administered at the study site (PICU) under supervision of the investigator or suitably qualified and delegated member of the study team (such as a PICU study nurse).

Criteria for Evaluation:

Efficacy Parameters:

COMFORT behaviour (COMFORT B) score, Numerical Rating Scale pain (NRS) score, Nurse Interpretation of Sedation (NISS) score

Sedation failure was defined as: NRS score <4 and COMFORT-B score >22 OR
NRS score <4 and COMFORT-B score ≤22-≥11 AND (NISS) score 1 at a point during the study where no further increase in IMP dose was permitted.

Pharmacokinetic Parameters:

Drug concentrations were used to derive estimates of PK model parameters including clearances and volume of distributions, observed maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC), terminal half-life ($t_{1/2}$), $C_{steady\ state}$ (observed plasma concentration at steady state), C_{trough} (observed plasma concentration at lowest level) for clonidine, midazolam, morphine and major metabolites.

Pharmacodynamic Parameter:

COMFORT-B score was used to estimate PK/PD parameters including EC50 (half maximal effective concentration) for clonidine and midazolam.

Pharmacogenomics Parameter: 20 polymorphisms of candidate genes coding for metabolism enzymes or receptors

Safety Variables:

Frequency, nature and severity of any adverse events (AEs) occurring during the study; Laboratory assessments; Vital signs; Physical examination; Mechanical ventilation assessment; Sophia Observation withdrawal Symptoms-Paediatric Delirium (SOS-PD) scale; Neurodevelopment assessment (birth – 27 days age group only).

Other variables:

Subject demographic data, baseline characteristics, concomitant medication, drug accountability, adverse events and procedures.

Statistical Methods:

Descriptive statistics included n (number of observations), nmiss (missing number), mean, standard deviation, coefficient of variation, median (first and third quartile, as needed), minimum and maximum for continuous variables, and frequencies and percentages for categorical variables, and were provided by treatment group unless otherwise specified.

Efficacy Analysis:

Due to the low number of subjects, the statistical analysis could not be performed as planned. Only descriptive analysis was used to compare the clonidine and midazolam arms, stratified by age and treatment group.

Pharmacokinetic Analysis:

PK models for this study evaluate the pattern and extent of covariates affecting the PK profiles. Population PK models were developed for clonidine, midazolam and morphine. Concentrations of the main metabolites of midazolam (1-hydroxymidazolam) and morphine (M3G and M6G) were included in the models. Population pharmacokinetic modelling was undertaken with NONMEM 7.4. using non linear mixed effect.

The covariates tested were: weight, age, creatinine concentration and liver function. Body weight and age were included in the three PK models using an allometric weight scaling and a maturation function, respectively.

Once the PK models were built, the influence of genetic variants was tested on the individual clearances using linear regression with the software PLINK 1.9.

The final PK models were evaluated using visual predictive check (VPC).

Pharmacokinetic/pharmacodynamic analysis:

Population pharmacokinetic/pharmacodynamic models were developed for clonidine and midazolam. These PK/PD models establish a relationship between concentration and COMFORT-B score in order to provide information about the drug efficacy and the optimal dose in this population for future clinical practice. Population PK/PD modelling was undertaken with NONMEM 7.4. using non linear mixed effect.

COMFORT-B score was treated as a continuous variable. A postanesthesia effect was included in the models for the patients who underwent surgery before receiving clonidine or midazolam. The influence of co-medications (propofol, morphine and ketamine) was tested and included in the models if it improved the fit.

Safety Analysis:

Listings of AEs/SAEs were provided. Laboratory evaluations (including clinical chemistry, haematology, coagulation and urinalysis variables), vital signs (values and changes from baseline) were analysed descriptively and screened for individual notable values and/or changes.

Results

Study population

A total of 28 subjects were enrolled and randomised in the study. Unblinding revealed that 15 subjects received clonidine and 13 subjects received midazolam (clonidine: age group 1 n=6, age group 2 n=6, age group 3: n=3; midazolam: age group 1 n=8, age group 2 n=3, age group 3 n=2).

All 28 patients were analysed (ITT). In 3 patients the primary endpoint was not assessable as decided by the BDRM due to major protocol deviations and thus 25 patients were included to the FAS/PPS.

The overall gender distribution of the subjects was equal (14 male, 14 female). Within the midazolam-group were 8 female subjects (age-group 1: n=6, age group 3=2) and 5 male subjects (age group1: n=2, age group 2: n=3). Within the clonidine group were 6 female subjects (age group 1: n=2, age group 2: n=2, age group 3: n=2) and 9 male subjects (age group 1: n=4, age group 2: n=4, age group 3 n=1).

The age distribution showed that in the midazolam group more subjects belonged to age group 1 (n=14) than age group 2 (n=9) and age group 3 (n=5). In the clonidine group, subjects belonged more often to age group 1 and 2 (n=6 each) than age group 3 (n=3). Please see Table 1.

Table 1: Demographic data

				Midazolam		total	Clonidine		total
age range	male	female	total	male	female		male	female	
0-27 days	6	8	14	2	6	8	4	2	6
28 days - <2 years	7	2	9	3	0	3	4	2	6
2 years - < 18 years	1	4	5	0	2	2	1	2	3

Efficacy Results

The descriptive analysis of the primary endpoint revealed that in the clonidine group (n=12) sedation failure was observed in 4 patients and in the midazolam group (n=13) in 2 patients. Please see Table 2.

Table 2: Descriptive results of the primary endpoint

	Clonidine Hydrochloride	Midazolam
No. of subjects analysed	12 *	13
Sedation Failure	4	2
Sedation Success	8	11

*In 3 of 15 subjects receiving clonidine the primary endpoint was not assessable

Pharmacokinetic Results:

The median dose administered to the patients In the clonidine-group was 7.7 mcg/kg if the duration of IMP-treatment was <1d; it was 50.1 mcg/kg if the IMP-treatment was ≥1 and <2d and 44.6 mcg/kg if the IMP-treatment was ≥ 2d. In the midazolam-group, the median dose administered to the patients was 1.4 mcg/kg if the duration of IMP-treatment was <1d, was 2 mcg/kg if the IMP-treatment was ≥1 and <2d and 10 mcg/kg if the IMP-treatment was ≥ 2d. Please see Table 3 and Table 4.

Table 3: Clonidine: Duration of IMP-treatment and median dose

Duration (days)	N (total)	Median dose (mcg/kg)	Age range	N (by age range)	Sex	N (by sex)
< 1	5	7.7	0-27 days	1	M	1
			28 days - <2 years	1	F	4
			2 years - < 18 years	3		
>=1 and <2	7	50.1	0-27 days	3	M	5
			28 days - <2 years	4	F	2
			2 years - < 18 years	0		
>= 2	3	44.6	0-27 days	2	M	3
			28 days - <2 years	1	F	0
			2 years - < 18 years	0		

Table 4: Midazolam: Duration of IMP-treatment and median dose

Duration (days)	N (total)	Median dose (mcg/kg)	Age range	N (by age range)	Sex	N (by sex)
< 1	4	1.4	0-27 days	2	M	2
			28 days - <2 years	1	F	2
			2 years - < 18 years	1		
>=1 and <2	8	2	0-27 days	6	M	2
			28 days - <2 years	1	F	6
			2 years - < 18 years	1		
>= 2	1	10	0-27 days	0	M	1
			28 days - <2 years	1	F	0
			2 years - < 18 years	0		

CLONIDINE:
The model which best described the clonidine concentrations was a one-compartment model. Age was included on the clonidine clearance using a sigmoidal maturation function.

MIDAZOLAM:
A one-compartment model for the parent and the metabolite 1-hydroxymidazolam (1-OH-M) provided the best fit for midazolam concentrations. Clearances were best described using a sigmoidal maturation function.

MORPHINE:
The model which best described the morphine data was a one-compartment model for morphine and both metabolites (M3G and M6G). Age was included on the metabolite formation clearances using a sigmoidal maturation function. Different maturation functions were included in the model to describe the elimination clearances of both metabolites and the central volume of distribution.

The PK parameters of the three drugs were best scaled by fixing the allometric exponent to 0.75 for clearances and 1 for volumes of distribution.
No significant influence of other covariates was found on clonidine and midazolam PK parameters. However, a significant influence of creatinine concentration was found on two of the morphine clearances.
For the 3 drugs, no relationship was found between individual clearances and genetic variants.

Safety Results:

28 Patients have been exposed to the IMP (clonidine or midazolam). All patients have been included in the safety analysis. AEs were grouped by body system (MedDRA-code) and were divided into severity groups.

The overall adverse event experience is that few adverse events occurred.

Only 7 AEs were classified to be possibly related to the IMP and 54 unlikely to be related to the IMP. In the clonidine group, 3 AEs classified as mild were related to the IMP: hypotension (n=2), bradycardia (n=1). In the midazolam group, 3 AEs classified as mild were related to the IMP: hypotension (n=1), constipation (n=1) and thrombopenia (n=1). 1 AE was classified as moderate (hypotension, n=1) in the midazolam group.

None of the severe AEs were related to the IMP. Please see Table 5.

Table 5: Total Number of AEs/ARs

	Clonidine group	Midazolam group	Total
All AR (related)	3	4	7
All AEs (not related)	51	9	60
Total	54	13	

Throughout the study, only 1 serious adverse event (SAE) has been reported. It was a diaphragmic hernia (SOC: Gastrointestinal disorders) and was not related to the administered IMP clonidine.

No deaths or AEs leading to discontinuation were reported in the study. No clinical laboratory changes that could signify a safety concern were observed in the study. Overall, no new safety issues were identified in the clinical laboratory values.

In summary, there were no new or unexpected safety findings identified in this study. The safety findings from this study are consistent with the previously reported safety profile for clonidine.

PK-PD Results:

For the PK/PD analysis, all patients who received the IMP were included (15 for clonidine and 13 for midazolam).

For the patients who didn't undergo surgery before starting the treatment (n=2 for midazolam / n=7 for clonidine), the relationship between drug concentration and COMFORT-B score was best described by a simple Emax model. The base (score before drug administration) was estimated for clonidine. In the midazolam group, the individual bases were included in the model.

For the patients who underwent surgery before starting the treatment (n=11 for midazolam / n=8 for clonidine), the change of COMFORT-B score was characterized with a post-anesthesia effect and a drug effect. The base corresponding to the score at the end of surgery (BASE) was fixed to the minimum COMFORT-B score.

Post-anesthesia effect was assumed to wash out in time postoperatively by an Emax model until reaching the minimum sedation due to anesthesia (PAEMAX). PAEMAX was estimated by the model for midazolam and fixed for clonidine. The drug effect was related to the PK with a simple Emax model.

A significant effect of propofol on COMFORT-B score was found for midazolam, therefore it was included in the model using a K-PD approach for which propofol parameters were estimated.

To improve the fit of clonidine model, a join model combining midazolam and clonidine data was used.

Discussion and Conclusion:

This 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.

- Enrollment in this study was too limited to determine the comparable efficacy and safety of clonidine compared to midazolam in this study.
- Clonidine administered in the reported dosages were generally safe and well tolerated in this study in all age groups. There were no new safety findings identified in subjects treated with clonidine in this study.

Population PK models for clonidine, midazolam and morphine have been developed successfully despite the limited number of patients.

- Age and weight have been found to be significant covariates for the clearance of both drugs. These results confirm that the clearance is reduced in younger children.
- No influence of genetic variants was found on the clearances for the three drugs. These results were expected due to the limited number of patients.

Population PK/PD models have been developed successfully for midazolam and clonidine.

- The models show that the maximal comfort score decrease is modest. This result suggests that in order to reach a higher sedation effect, both drugs may need to be given in combination with other sedatives.
- Both models estimated a very large interindividual variability on the EC50, therefore a larger number of patients would be necessary to reduce this variability and improve the models.

Date of Report: 06/07/2020

This study was conducted in compliance with International Conference for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, Good Clinical Practice guidelines and the Declaration of Helsinki.

Appendix

Appendix Table 1: Adverse events Clonidine-Group: Number observed and Rate (%)

Treatment Group Clonidine (n=15)	Mild		Moderate		Severe		Total	
	Related	NR	Related	NR	Related	NR	Related	NR
Hypotension	2 (13%)	2 (13%)					2 (13%)	2 (13%)
Withdrawal				2 (13%)				2 (13%)
Pruritus		1 (7%)						1 (7%)
Respiratory disorder		4 (26%)		1 (7%)		3 (20%)		8 (53%)
Renal insufficiency		1 (7%)						1 (7%)
Oliguria				1 (7%)				1 (7%)
Psychosis				1 (7%)				1 (7%)
Hypokalaemia		2 (13%)		1 (7%)				3 (20%)
Hypocalcaemia				1 (7%)				1 (7%)
Feeding problem		1 (7%)		1 (7%)				2 (13%)
Endotracheal extubation		1 (7%)						1 (7%)
Infection		2 (13%)		2 (13%)				4 (26%)
Oedema		5 (33 %)						5 (33 %)
Fever				1 (7%)				1 (7%)
Gastrointestinal symptoms		1 (7%)		1 (7%)				2 (13%)
Diaphragmatic hernia						1 (7%)		1 (7%)
Ductus arteriosus patent		1 (7%)						1 (7%)
Undescended testicle		1 (7%)						1 (7%)
Bradycardia	1 (7%)						1 (7%)	
Leukocytosis		1 (7%)		1 (7%)				2 (13%)
INR increased		1 (7%)						1 (7%)
Elevated liver enzymes		1 (7%)						1 (7%)
Arterial oxygen saturation decreased				1 (7%)				1 (7%)
CRP increased				1 (7%)				1 (7%)
Haemoglobin low				1 (7%)				1 (7%)

Appendix Table 2: Adverse events Midazolam-Group: Number observed and Rate (%)

Treatment Group Midazolam (n=13)	Mild		Moderate		Severe		Total	
	Related	NR	Related	NR	Related	NR	Related	NR
Hypotension	1 (7%)		1 (7%)				2 (15%)	
Febrile seizure		1 (7%)						1 (7%)
Hyponatraemia Hypokalaemia Hypochloraemia		1 (7%)						1 (7%)
Fluid retention		1 (7%)						1 (7%)
Infection		1 (7%)		1 (7%)				2 (15%)
Oedema		3 (23%)						3 (23%)
Constipation	1 (7%)						1 (7%)	
Nausea		1 (7%)						1 (7%)
Thrombopenia	1 (7%)						1 (7%)	
INR increased				1 (7%)				1 (7%)
Albumine		1 (7%)						1 (7%)