Clonidine for Sedation of Paediatric Patients in the Intensive Care Unit

### Reporting

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<td><strong>CLOSED</strong></td>
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<tr>
<td>Grant agreement ID: 602453</td>
</tr>
<tr>
<td>Status</td>
</tr>
<tr>
<td>Closed project</td>
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<tr>
<td>Start date</td>
</tr>
<tr>
<td>1 December 2013</td>
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<tr>
<td>End date</td>
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<td>30 November 2018</td>
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**Funded under**
FP7-HEALTH

**Overall budget**
€ 7,386,671.74

**EU contribution**
€ 5,997,404.75

**Coordinated by**
UNIVERSITATSKLINIKUM ERLANGEN
Germany

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**Final Report Summary - CLOSED (Clonidine for Sedation of Paediatric Patients in the Intensive Care Unit)**

**Executive Summary:**
The majority of critically ill children admitted to the Paediatric Intensive Care Unit (PICU) require sedation and analgesia, which is commonly achieved with combination therapy, usually a benzodiazepine and an opioid. However, these agents have a significant side-effect profile, including tolerance, withdrawal and respiratory/circulatory depression. In addition, data suggest that these compounds cause negative long-term neurological effects because of neurodegeneration through neuroapoptosis or impaired synaptogenesis. [Smits A, 2011; Mellon RD, 2007; Olney JW, 2004; Young C, 2005; Traudt CW, 2012; Atici S, 2004]

Clonidine (N-(2,6-dichlorophenyl)-4,5-dihydro-1H-imidazol-2-amine hydrochloride) is an imidazole derivative which is authorised for use throughout the EU and the USA as a centrally acting hypotensive agent (adults only) and as treatment for migraines (adults and children over 12 years only), as well in the USA for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children aged 6 to 17 years.
In addition to its approved indications, clonidine is commonly used off-label in paediatric anaesthesia and intensive care medicine. Its effects on central sympathetic outflow and centrally based analgesia mechanisms reduce intraoperative anaesthetic requirements and metabolic responses to surgery. [Nishina K, 1998] In anaesthesia of the critically ill neonatal cardiac patients, this has long been shown to improve outcome in terms of survival. [Anand KJ, 1992] Clonidine is recommended to be used for sedation in critically ill children in PICUs by the UK and German consensus guidelines [Playfor SD, 2006; Martin J, 2010] and local hospital guidelines across Europe. However, despite this widespread use of clonidine, there are limited data on efficacy, dose requirement and safety when used for sedation on PICUs and clonidine was included in the EMA Revised Priority List for Studies into Off-Patent Paediatric Medicinal Products July 2012 (Doc ref EMA/98717/2012).

The CloSed project, implemented by an international Consortium (12 partners from 8 countries), aimed to develop an age-appropriate formulation of clonidine for sedation in PICU and to pave the way for a Paediatric Use Marketing Authorisation (PUMA) in accordance with Regulation EC No 1901/2006. In order to specifically meet this therapeutic need, a comprehensive development plan in the form of a Paediatric Investigation Plan (PIP) was submitted to the EMA Paediatric Committee (PDCO) in July 2012 and a positive opinion was received from PDCO on 8th February 2013 which was agreed and adopted by EMA on 26th March 2013. (EMEA-001316-PIP01-12). In the course of the project, the PIP was modified according to the Clinical Study Protocol and the updated version agreed with the EMA.

The drug development activities implemented in the framework of CloSed primarily regarded the following actions:

- development of a new age appropriate clonidine formulation with three different product strengths (5 mcg/ml, 10 mcg/ml and 50 mcg/ml) to enable delivery of the drug accurately based on administration dose/volume and weight of the patient,
- conduct of a prospective, phase III, double-blind, randomised-controlled, multicentre clinical trial (RCT) to assess the pharmacokinetics, efficacy and safety of IV clonidine for sedation in PICU patients to complete a robust clinical package.

The project’s primary activity therefore regarded the implementation of CloSed1, 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 (EudraCT number: 2014-003582-24).

Project Context and Objectives:
Project context and objectives

Clonidine is commonly used in a variety of indications. Following experience with clonidine in paediatric anaesthesia and its use in adults withdrawing symptoms from alcohol and opioids, it has become increasingly used for sedation and analgesia in the critically ill child in PICU and as a treatment for drug withdrawal in children after prolonged exposure to sedatives. [Jenkins IA, 2007; Ambrose C, 2000] However, despite its widespread use the effectiveness, optimal dose requirements and safety have not been fully studied in a standardised way and/or properly designed randomised controlled trials.

Furthermore, with respect to the pharmaceutical formulation, there is the need for an age-appropriate
Furthermore, with respect to the pharmaceutical formulation, there is the need for an age-appropriate clonidine parenteral formulation (adequate strengths and volume, acceptable excipients). For the use of clonidine in the intended indication, the dose needs to be adjusted based on the individual patient requirements. Thus, a flexible yet accurate dosing form is required. Although oral formulations are sometimes used for PICU sedation, the IV formulation is the most frequently used and appropriate for the PICU setting and therefore of greater therapeutic need than an oral formulation; thus, the IV delivery route was selected for development.

CloSed comprised four main objectives:

Objective 1
To develop an age appropriate, GMP manufactured IV clonidine formulation at 3 different product strengths to enable the accurate delivery of the drug, based on dose per volume and patient weight.

Objective 2
To conduct a randomized, phase III, double-blind, active-controlled, parallel-group clinical trial in children from birth to 18 years in order to
- investigate the sedative efficacy and safety of IV clonidine vs IV midazolam (the most commonly used and authorised sedative) in children and adolescents from birth to <18 years admitted to the PICU/NICU;
- determine dose-dependent effects on sedation as measured by COMFORT-B Score and to establish the PK-PD relationship of clonidine for sedation in PICU/NICU;
- establish the safety profile of clonidine with respect to withdrawal symptoms, cardiocirculatory and respiratory parameters and neurodevelopmental outcomes when compared with midazolam.

Objective 3
To make available the results and apply for a Paediatric Use Marketing Authorisation (PUMA).

Objective 4
To develop an European consensus guideline for sedation of critically ill newborns and children.

Project Results:

The overall project strategy aimed to provide the data package necessary to proceed successfully to a PUMA application for clonidine. To achieve this goal, activities were dedicated to the implementation of the developmental plan outlined in the PIP.

Pharmaceutical Development

There are no appropriate clonidine drug formulations available to allow weight-adapted dosing and administration as continuous infusion in children. The active compound concentration of the marketed products is too high and the ampoule volume too small (e.g. Catapres 150 micrograms per 1 millilitre ampoule). For the preparation of a continuous infusion (50 ml syringe for injection pump), up to 17 ampoules depending on the patient’s weight may be required, with an associated potentially high risk for dosing errors.

Therefore, an important objective of the CloSed project was to develop a new clonidine formulation.
Therefore, an important objective of the CloSed project was to develop a new clonidine formulation specifically for intravenous use (e.g. continuous infusion) in children which can directly be administered without further manipulations or frequent change of vials.

The most appropriate starting and maintenance dose in critically ill children admitted to PICU had to be determined first. This was done using PK-PD simulations. Other multiple possible scenarios, including ensuring that blinding will be maintained between the clonidine and midazolam arms in the trial, had to be considered.

For this purpose, a detailed literature review was undertaken to identify PK studies of clonidine and midazolam in children, and PK-PD studies relating to sedation for both drugs in adults or children. PD targets were identified as target circulating concentrations and exhaustive simulations were carried out to identify a dose for each drug to attain the target yet but to maintain double blinding with midazolam, which is 100-fold more concentrated than clonidine. Due to clonidine's long elimination half-life, a loading dose is necessary and a higher infusion rate over 15 minutes was opted for as opposed to a bolus loading dose (only a single syringe needs to be prepared).

The analysis revealed that a dose of 2 micrograms/kg of clonidine or 200 micrograms/kg of midazolam over 15 minutes, followed by a continuous infusion of 1 microgram/kg/h of clonidine or 100 micrograms/kg/h of midazolam would be most appropriate. A dose increase or decrease scheme was developed for the clinical trial protocol.

The Investigational Medicinal Products (IMPs) developed specifically for use in the clinical study CloSed1 regard clonidine hydrochloride 5 mcg/mL, 10 mcg/mL and 50 mcg/mL solution for intravenous (i.v.) infusion.

The IMP was produced according to GMP requirements and tested in line with the appropriate Ph. Eur. monographs, Committee for Proprietary Medicinal Products (CPMP) guidelines and notes for guidance. All specifications were within the given ranges.

Stability testing was done in accordance with CPMP/QWP/122/02, rev 1 corr. The stability testing of the first IMP batches was started in September 2015. The drug products clonidine hydrochloride 5 mcg/ml, 10 mcg/mL and 50 mcg/mL solution for i.v. infusion in 50 mL vials were stored over a period of 36 months at the following storage temperature and relative humidity (r.h.) conditions: 25 °C / 60 % r.h. The analysis of the stability batches were completed in November 2017. After 36 months, all results were within the given specification; therefore the IMPs could be labelled with a shelf life of 36 months.

The assay methodology is published, along with a communication on clonidine optimal dosing, and a justification of the study design (BMJ-Open paper).

Clinical Study

The project implemented CloSed1, 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 (EudraCT number: 2014-003582-24).
Investigational products:

Clonidine Hydrochloride
5 mcg/ml solution for intravenous infusion
10 mcg/ml solution for intravenous infusion
50 mcg/ml solution for intravenous infusion

Midazolam
0.5 mg/ml solution for intravenous infusion
1 mg/ml solution for intravenous infusion
5 mg/ml solution for intravenous infusion

This clinical trial involved 11 trial sites in 7 countries, i.e. Germany, The Netherlands, Sweden, Italy, the Czech Republic, Estonia and Spain.

The subjects concerned were underage patients (minors) in a paediatric/neonatal intensive care unit (PICU/NICU) with a study-independent indication for intubation and mechanical ventilation with a requirement for sedation. The clinical trial thus took into account a clinical condition from which the patients personally suffer. Both emergency patients and patients with an elective medical procedure with indication for mechanical ventilation were eligible for the study.

The primary objective of the trial regarded the assessment of 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). Logistic regression, with treatment group, baseline sedation assessment, centre and age group as covariates, will be used to compare the clonidine versus midazolam arms on sedation success proportion. Non-inferiority of clonidine will be shown if the lower bound of the one-sided 97.5% Wald confidence interval (CI) for the odds ratio of sedation success proportion is not less than 0.583.

Secondary objectives of the trial regarded:
- To evaluate the safety and tolerability (including withdrawal effects) of clonidine compared with midazolam in long-term ventilated children and adolescents admitted to PICU.
- To determine clonidine dose-dependent effects on sedation.
- To establish the pharmacokinetics - pharmacodynamics (PK-PD) 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 investigational medical product (IMP) administration.
- To determine if candidate genes predict adequate response to clonidine and midazolam in critically ill paediatric patients.
- To identify polymorphisms of clinical relevance to the sedative action of clonidine, midazolam and morphine.
- To correlate midazolam pharmacokinetics to polymorphisms of candidate genes.
- To correlate clonidine pharmacokinetics to polymorphisms of candidate genes.
- To correlate morphine pharmacokinetics to polymorphisms of candidate genes.
To correlate morphine pharmacokinetics to polymorphisms of candidate genes.

The trial set out to recruit 300 subjects. During its conduct a series of complex issues impacted on the possibility to achieve this goal. The high regulatory requirements, necessary for the data to be used for a marketing authorization, while extremely important, also impacted on the size of the eligible patient pool. Hundreds of patients were screened but only very few were eligible for the trial. Additionally, a high level of time-consuming bureaucracy caused by the still lacking harmony of regulatory frameworks in different European countries, as well as the need for import/export licenses had a massive impact on the project’s timelines and caused many delays during site setups. Midazolam is considered a controlled drug in all participating countries and therefore requires import and export licenses for shipment. The bureaucratic framework for such license applications was extremely time-consuming, in various cases it included the need for intermediary organisations and additional contracts or required processing times of up to 90 days.

Finally, the CloSed trial includes a highly sensible patient population (children and adolescents below 18 years of age treated in the Intensive Care Unit) for which treatment strategies are changing to constantly improve. The standard-of-care changed drastically since project application and during the lifetime of the project, resulting in less patients being in need for sedation for more than 24 hours. This further impacted on the number of possible eligible patients at the involved sites.

In order to widen the patient pool, 3 substantial Protocol amendments were elaborated and submitted to CA and ECs. While this action represents a mitigating measure, it also impacted on the recruiting site’s workload. Team members had to deviate attention from screening and recruitment to the submission of Protocol amendments and to the interaction with Ethics Committees/Competent Authorities. The Consortium further identified and set up additional trial sites. The initial 5 recruiting sites were brought to 11, integrating 6 hospitals in 4 countries.

7 patients were recruited into the CloSed trial by October 2017. Having overcome many of the setup hurdles and having included additional recruiting sites by that time, the total patient number steadily increased to 22 by April 2018. Recruitment turned out to be slower again with the start of the warmer season and confirmed an additional seasonal fluctuation in the patient pool with lower numbers in the spring/summer months, compared to the colder period from September to March with more respiratory support patients. From December 2017 to April 2018, 15 patients were recruited compared to 1 from May to August 2018. Recruitment did indeed pick up again in September 2018 (2 additional patients) and continued in October 2018 (3 additional patients). However, in October 2018, the clinical trial had to be terminated early, with a final number of 28 recruited patients.

Outlook

The final statistical and PK-PD analysis will be carried out after the end of the project, using alternative sources of financing. The clinical study report and a final PK-PD paper will be elaborated after the analyses are finalised.

The CloSed Consortium is further planning to develop additional publications as a result of its experiences and lessons learned from the project in order to share knowledge and information and to support future trials that may face similar challenges.
trials that may face similar challenges.

Potential Impact:

Even though the final number of recruited patients is unlikely to power the study’s primary endpoint, the endpoint of the PK/PD modelling, which regards the evolution of Comfort-B Scores in relation to the PK data in the different treatment arms, continues to represent an achievable objective and the available data have the potential to significantly contribute to the scientific research on Clonidine. The particular importance of these PK data is that they have been collected by investigators blinded to the allocated treatment and therefore with low risk of bias (rare in PK-PD studies). Analysed adequately, these data may play an important part towards a Paediatric Marketing Authorisation for clonidine in the paediatric intensive care setting in the future.

In order to obtain a PUMA, a new PIP would have to be agreed with the EMA which would define the further clinical efficacy/safety study that would be required. After analysis, the PK/PD data might be supportive in defining the dose to be used in such a study. Clonidine is also being considered for other indications and the PK data may be beneficial in supporting potential other treatments.

For the other indications, the route of delivery would need to be assessed and a suitable formulation of clonidine would need to be developed i.e. parenteral, oral, intranasal etc. Further research would be needed into the particular PK-PD relationship in the sub-population affected and it is considered likely that larger efficacy and safety trials will be needed to achieve a licensed product. The importance of contributing to the development of a licensed clonidine product remains unchanged.

Dissemination activities

During the lifetime of the project, the following peer-reviewed publications were released:


4. Veigure R1, Aro R1, Metsvaht T2, Standing JF3, Lutsar I4, Herodes K1, Kipper K5; CloSed Consortium. A highly sensitive method for the simultaneous UHPLC-MS/MS analysis of clonidine, morphine, midazolam and their metabolites in blood plasma using HFIP as the eluent additive. J


Additionally, the thesis "All quiet on the bedside front? : Pain and sedation management in the PICU" has been prepared and published (M. Baarslag, Dec-2018).

The following posters were prepared, showed and discussed in the framework of scientific events:


- UNIVERZITA KARLOVA - Pharmacogenetics and pharmacodynamics of withdrawal following analgosedation in PICU patients - 24-10-2016.

- UNIVERZITA KARLOVA - Neurodevelopment at two years of age in newborns undergoing hypothermia and protocolized analgosedation for hypoxic-ischaemic encephalopathy - 29-09-2018.

Wider project dissemination activities were performed in the context of Work Package (WP8) and aimed at raising awareness on the project among interested stakeholders, including regulatory agencies, clinical centres, patient/parent associations, scientific and professional communities, interested public, institutions and governments.

During the project’s implementation, regular communication activities were implemented through diverse channels, communication tools were developed and informative material made available on the project website. In particular, news on the project activities and outcomes were regularly published on the project website and its social media channels, and seven newsletters were produced and distributed in order to raise awareness about the project, to keep audiences informed, to promote project outcomes, events and initiatives and to continue stimulating interest.
Two leaflets were developed for the general presentation of the project, one for the scientific audience, and one layman version. The leaflets are available on the project website in the section "Communication Tools".

All project partners have supported dissemination and networking activities publishing information on CloSed activities and outcomes on their websites, releasing press releases. Consortium members also presented the project and implemented networking actions in the framework of scientific and wider public initiatives, as for example:

- Lygature Stakeholder meeting – 01/11/2018
- COSYN Multistakeholder meeting – 17/10/2018
- C4C Kick off meeting – 18/09/2018
- European Association of Centres of Medical Ethics - Annual Conference – 07/09/2018
- PedCRIN annual meeting – 02/04/2018
- APS meeting – 20-03-2018
- Goed Gebruik Geneesmiddelen; kennis van nu=inspiratie voor morgen - 06/04/2017
- PedCRIN kick-off meeting – 09/01/2017
- VII Foresight Training Course, Castellaneta Marina (Ta), Italy – 03-10-2014.

Planned near-future publications include amongst others:
• the final PKPD analysis;
• experiences and lessons learned from the CloSed trial.

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Last update: 11 April 2019
Record number: 267962