CLINICAL STUDY REPORT

STUDY CODE No.: MDCO-CLV-12-01

EudraCT/IND number: 2013-001268-44/65114

OPEN LABEL STUDY TO ASSESS THE EFFICACY, SAFETY AND DOSING OF CLEVIDIPINE IN PEDIATRIC PATIENTS UNDERGOING SURGERY (PIONEER STUDY)

Version No.: Final 1.0
Version Date: 26 June 2024

Chiesi Farmaceutici S.p.A.
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1. TITLE PAGE

Study Title:	Open label study to assess the efficacy, safety and dosing of clevidipine in pediatric patients undergoing surgery (PIONEER study)
Test drug/investigational product:	Cleviprex® (clevidipine) injectable emulsion
Pharmaceutical Form:	Injectable emulsion
Study design:	Open-label study of clevidipine (initial weight-based dose of CCI, increasing up to CCI as needed to achieve systolic blood pressure within the pre-specified target range) administered for a minimum of 30 minutes up to 96 hours, with an up to 7-day follow-up, in paediatric patients undergoing surgery.
Indication studied:	Blood pressure management in paediatric patients undergoing a surgical procedure.
Sponsor:	Chiesi Farmaceutici S.p.A.
Protocol identification:	MDCO-CLV-12-01
Development phase of study:	Phase 4
Study initiation date (First Patient First Visit [FPFV]):	17 March 2014
Study completion date (Last Patient Last Visit [LPLV]):	30 September 2014
Principal Investigator	Joseph D. Tobias, MD
Name of Company/Sponsor signatory	PPD MD, Clinical Research Physician PPD Chiesi Biostatistician

"This study was conducted in compliance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Research Practices (ICH E6), including the archiving of essential documents".

VERSION HISTORY

Version	Date	Change History
1.0	26 June 2024	First version

2. SYNOPSIS

Name of Company: Chiesi Farmaceutici S.p.A.	**Individual Study Table Referring to Part of the Dossier**	*(for National Authority Use only)*
Name of Finished Product: Cleviprex® (clevidipine) injectable emulsion	**Volume:**	
Name of Active Ingredient: Clevidipine	**Page:**	

Title of Study: Open label study to assess the efficacy, safety and dosing of clevidipine in pediatric patients undergoing surgery (PIONEER study)

Investigators: Two Investigators in the United States (US)

Study Centre(s): Two centres in the US

Publication (reference): None

Studied Period:	**Phase of Development:**
FPFV: 17 MAR 2014 LPLV: 30 SEP 2014	Phase 4

Objectives:

Primary Objective:

To evaluate the dosing, efficacy and safety of an intravenous (IV) infusion of clevidipine for blood pressure (BP) management in paediatric patients in the perioperative setting.

Secondary Objectives:

To evaluate additional efficacy, safety and dosing parameters associated with IV infusion of clevidipine for BP management in paediatric patients in the perioperative setting.

Methodology *(Study Design):*

This was an open-label, multicentre, phase 4 study conducted in the US. The study was conducted in paediatric patients undergoing elective surgery requiring anaesthesia ≥1 hour and for whom parenteral IV antihypertensive therapy for BP management was expected for at least 30 minutes. Approximately 80 to 100 patients were planned to be enrolled at 2 centres within 24 months of study initiation using a stepwise approach, starting with the adolescent cohort, as follows:

- **Cohort 1:** 20 adolescent patients (12 to less than 18 years);
- **Cohort 2:** 20 children (2 to less than 12 years, including 10 patients in each age group 6 to less than 12 years and 2 to less than 6 years);
- **Cohort 3:** 20 infants and toddlers (28 days to less than 24 months);
- **Cohort 4:** 20 preterm and newborn infants (0 to less than 28 days).

An interim analysis of safety and dosing of the adolescent cohort was performed by a Data Safety Monitoring Board (DSMB) before the initiation of the remaining cohorts.

All patients were to receive IV clevidipine. A target systolic blood pressure (SBP) range was specified for

each patient prior to study drug initiation by the Investigator and could not be changed for the first 30 minutes of the treatment period. Adolescent patients received an initial weight-based dose of CCI, to be maintained for the first 1.5 minutes. If the pre-specified target SBP range for that individual patient was not achieved, the infusion rate could be up-titrated incrementally every 1.5 minutes to CCI, up to a maximum dose of CCI until an SBP within the pre-specified target range was reached. The initial dose for the children, infant and toddler cohorts and the subsequent up-titration doses were to be determined after an interim analysis of data from the preceding cohorts.

Once initiated, clevidipine infusion could be administered continuously for a maximum duration of 96 hours. During the first 30 minutes of treatment, clevidipine was preferably administered continuously as a monotherapy. However, if the desired BP control effect was not attained at the maximum dose, rescue therapy with an alternative IV antihypertensive agent could be implemented. Patients who received alternative IV rescue therapy along with clevidipine were allowed to continue in the study. After the first 30 minutes of treatment, it may have been necessary to alter the target SBP range over the course of the remaining treatment period.

The study included the following periods:

- Screening period: between 0 and 7 days prior to their scheduled surgical procedure and study drug initiation;
- Treatment period: from study drug initiation to termination of infusion (up to 96 hours):
  - Phase 1: initial dosing (0 to 1.5 minutes);
  - Phase 2: titration (>1.5 to 30 minutes) and maintenance phase (>30 minutes up to 96 hours);
  - Phase 3: transition and termination phase where the study drug is ceased, and the patient is transitioned to an alternative IV or oral antihypertensive if required.
- Follow-up period: follow-up visits at 1, 12 and 24 hours and 7 days after study drug termination. The 7-day follow-up could be conducted by phone.

At the end of the treatment period (Phase 3), patients could be transitioned from clevidipine to an oral antihypertensive agent, if required, prior to ceasing the study drug. Or if treatment with an IV antihypertensive agent was still required after 96 hours of clevidipine treatment, the patient was transitioned to an alternative IV antihypertensive agent in accordance with the institution's standard of care.

A DSMB was set up to monitor the safety and dosing on an ongoing basis for all cohorts. The DSMB was to review the safety and dosing data from each cohort and make recommendations to the Sponsor according to the DSMB charter prior to enrolling the remaining cohorts in sequential order. In addition, an analysis of efficacy data was to be performed at the end of each cohort to ensure that sample size for the subsequent cohort was sufficient.

The study end was considered as the last 7-day follow-up visit of the last patient.

CCI

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Number of Patients *(planned and analysed)*:

A total of 80 to 100 patients were planned to be enrolled, with 80 evaluable for efficacy (20 patients per cohort). This number of patients was not finally achieved owing to the study not enrolling further cohorts after completion of Cohort 1 (see note in section above).

A total of 22 patients were enrolled, of whom 21 were included in the efficacy, safety and pharmacokinetic (PK)/pharmacodynamic (PD) analyses.

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

Patients had to meet all the following inclusion criteria to be eligible for enrolment into the study:

1. Patient had to be less than 18 years old;
2. Written informed consent obtained before initiation of any study-related procedures;
3. The enrolling physician determined that the patient will likely require a 15% reduction in BP during the perioperative course;
4. Intra-arterial line was available for BP monitoring;
5. Surgical procedure required at minimum 1 hour of anaesthesia, in which IV antihypertensive therapy to control BP for at least 30 minutes was anticipated.

Exclusion Criteria:

The presence of any of the following excluded a patient from study enrolment:

1. Administration of an IV or oral antihypertensive agent within 2 hours prior to the study drug administration;
2. Congenital heart disease described as single ventricle;
3. Evidence of liver failure, severe liver disease, pulmonary disease (e.g., uncontrolled asthma), hyperlipidaemia, lipoid nephrosis, lipid dysfunction or acute pancreatitis;
4. Allergy to soya bean oil or egg lecithin;
5. Known to be intolerant to calcium channel blockers;
6. Haemophilia or blood coagulation disorders;
7. Any serious medical condition which, in the opinion of the Investigator, was likely to interfere with study procedures;
8. Clinically significant abnormal physical findings at the screening evaluation;
9. Any serious surgical or medical condition which, in the opinion of the Investigator, was likely to interfere with study procedures or with the PK or PD of the study drug;
10. Patient was terminally ill (death likely to occur within 48 hours);
11. Use of methylphenidate, calcium channel blockers, aripiprazole and other atypical anti-psychotics and antihypertensive used for BP control within 2 hours prior to the study drug initiation;
12. Positive serum or urine pregnancy test for any female of childbearing potential;

13. Participation in other clinical research studies which involved the evaluation of other investigational drugs or devices within 30 days of enrolment;
14. Patients who, for any reason, were deemed by the Investigator to be inappropriate for this study;
15. Patient was a relative of the Investigator or his/her deputy, research assistant, pharmacist, study coordinator, other staff directly involved in the conduct of the study.

Patients excluded for any of the above reasons could be re-screened for participation at any time if the exclusion characteristic had changed.

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

Clevidipine (Cleviprex®) injectable phospholipid emulsion (0.5 mg/mL) in ready-to-use, sterile, single use glass vials. Clevidipine is intended for IV administration by infusion via a single dedicated peripheral or central venous line.

Due to the rapidity with which clevidipine reduces BP, the dosage and rate of infusion was titrated until the desired clinical effect was achieved. The first cohort (adolescent patients) received an initial weight-based dose of CCI to be maintained for the first 1.5 minutes. If the pre-specified target SBP range for that individual patient was not achieved, the infusion rate could be up-titrated incrementally every 1.5 minutes to CCI, up to a maximum dose of CCI until an SBP within the pre-specified target range was reached. As BP approached the desired target range, dosing could be up titrated by less than doubling, and the time between up-titrations could be lengthened to greater than 1.5 minutes. If the pre-specified target SBP range was achieved at any of the titration doses, that rate could be maintained for up to 96 hours to maintain BP or titrated up or down as necessary to maintain SBP within the specified target range.

If rescue therapy during the treatment period, or transition to another antihypertensive at the end of the treatment period was required, clevidipine infusion could be down-titrated or terminated, or restarted thereafter, as appropriate to maintain the desired BP.

The initial dose for the children, infant and toddler cohorts and the subsequent up-titration doses were to be determined after an interim analysis of data from the preceding cohorts.

Batch numbers for the study drug are provided below.

	Batch/Lot number	Expiry date
Clevidipine 50 mL (25 mg/50 mL)	N108223-001L001/16FL0272	31 May 2014
	N108223-0002L001/16GI0025	31 March 2015

Duration of Treatment:

Eligible patients were expected to require BP management for at least 30 minutes. Once initiated, clevidipine infusion could be administered continuously for a maximum duration of 96 hours.

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

None.

Criteria for Evaluation:

Primary endpoints:

Efficacy:

- Median time and dose to attain the initial pre-specified target SBP range (minimum of 20 mmHg and a maximum of 40 mmHg apart) during the first 30 minutes of clevidipine infusion;
- Percentage of patients achieving the initial pre-specified target SBP range during the first 30 minutes of clevidipine infusion.

PK/PD:

- PK variables (half-life [$t_{1/2}$], AUC, volume of distribution, clearance) established by non-compartmental analysis and non-linear mixed effects modelling (NONMEM);

- PD variables (relationship between change from baseline in SBP versus blood concentration and infusion rate).

Safety:

- Safety of a prolonged infusion of clevidipine (up to 96 hours) assessed according to adverse events (AEs), serious adverse events (SAEs) and clinical laboratory parameters. Adverse events were assessed from time of consent through 7 days following termination of study drug infusion.

Secondary efficacy endpoints:

- Percent change from baseline in SBP at each time point during the 30 minutes of clevidipine infusion;
- Percent change from baseline in SBP at each hour after the first 30 minutes of clevidipine infusion up to the cessation of infusion;
- Percent change from baseline in SBP over the first 12 hours post-study drug termination;
- The percentage of patients who reach the initial pre-specified target SBP range without falling below the lower limit of the pre-specified target range during the first 30 minutes of clevidipine infusion;
- The percentage of patients in whom the SBP falls below the lower limit of the pre-specified target range at any time during the first 30 minutes and at any time during the entire study drug treatment period;
- The percentage of patients in whom the SBP is within target range at each hour after the first 30 minutes of clevidipine infusion;
- Percent change from baseline in heart rate (HR) during the first 30 minutes of clevidipine infusion and the rest of the treatment period;
- The percentage of patients who require rescue therapy (i.e., receive any alternative IV antihypertensive drug) at any time during study drug treatment period, or discontinuation due to AEs.

Statistical Methods:

The following populations were used for analysis:

- **Safety population:** all patients who were dosed with any study drug. This was the primary population used for the safety analyses.
- **Intent-to-treat (ITT) population:** all patients who were dosed with any study drug and had baseline and at least one post-baseline SBP measurement. This was the primary population used for the efficacy analyses.
- **PK/PD population:** all patients who were dosed with any study drug, had at least one documented and evaluable blood concentration and/or SBP observation and documented dose records. This was the primary population for PK/PD analyses.

Due to the descriptive nature of this study, no formal statistical hypothesis testing was performed. However, p-values and/or two-tailed 95% confidence intervals (CIs) were generated to demonstrate the strength of the findings whenever appropriate.

Primary Efficacy Analysis:

The duration in minutes between the initiation of the study drug infusion and the time a patient first achieved the initial pre-specified target SBP range during the first 30 minutes of clevidipine infusion time was summarised using descriptive statistics. The estimated median time with its two-tailed 95% CI was presented. If a patient did not reach the initial pre-specified target SBP range within 30 minutes from study drug initiation, or another antihypertensive agent was administered, the patient was considered censored at 30 minutes or the time when another antihypertensive agent was given, whichever came first.

The percentage of patients achieving the initial pre-specified target SBP range was calculated using the number of ITT patients achieving the target divided by the number of ITT patients and multiplied by 100. Two-tailed 95% CIs were computed for these percentages.

Summary statistics were presented for the dose to attain the initial pre-specified target SBP, which consisted of the infusion rate (µg/kg/minute), total dose (mg) infused, and the number of titrations made to attain the target.

Secondary Efficacy Analyses:

The number and percentage of patients reaching each endpoint (percentage calculated using the number of patients reaching the endpoint divided by the total number of patients in the analysis population, multiplied by 100), along with the two tailed 95% CIs, were calculated.

Descriptive statistics for the changes and percent change from baseline in SBP and HR were summarised at each specified time point. A graph by age cohort of percent change in SBP and HR during the first 30 minutes after study drug initiation was to be presented. Individual patient graphs for SBP across all time points along with the study drug dose in mg/hour were presented.

Other Efficacy Analysis:

The percent change from baseline in diastolic blood pressure (DBP) and mean arterial pressure over time was summarised.

PK/PD Analysis:

Blood concentration versus time data was analysed using non-compartmental analysis and NONMEM. The following PK parameters were estimated: total clearance, volume of distribution at steady state (V_{ss}) and based in the terminal phase (V_z), maximum observed blood concentration (C_{max}), time to reach C_{max} (t_{max}), AUC of the blood concentration to the last measurable concentration (AUC_{last}), AUC of the blood concentration to infinity (AUC_{inf}), terminal rate constant (λ_z) and its associated $t_{1/2}$ and mean residence time. All concentration data were presented descriptively at each time point. PK variables were established by (non)compartmental modelling approach.

The blood concentration of clevidipine and its carboxylic acid metabolite (M1) over time was also presented. As was the relationship between dose and blood concentration; first on-study blood concentration and body weight; change and/or percent change from baseline in SBP and first on-study blood concentration; dose and change or percent change from baseline in SBP; and blood concentration of clevidipine and change or percent change from baseline in SBP.

Safety Analysis:

The number and percentage of patients experiencing treatment-emergent adverse events (TEAEs) for each preferred term (PT) was tabulated by system organ class (SOC), by SOC and severity, and by SOC and relationship to the study drug. The incidence of SAEs and AEs leading to study drug discontinuation was summarised separately by SOC and PT. Listings were presented for patients with SAEs/AEs leading to discontinuation or death.

Summary statistics were presented for normalised laboratory values. The number and percentage of patients with post-baseline potentially clinically significant (PCS) values who did not have PCS values at baseline was tabulated.

Summary – Conclusions:

A total of 22 adolescent patients (mean [standard deviation, SD] age of 15.0 [1.56] years) were enrolled in Cohort 1, of whom 21 were treated with clevidipine and included in the safety and ITT population.

All 21 patients completed the study. All patients required a clinically indicated BP reduction for the purpose of controlled hypotension during surgery.

Efficacy Results:

Primary efficacy endpoints

All 21 patients in Cohort 1 achieved the initial, pre-specified target SBP range within the first 30 minutes of clevidipine infusion. The median time and infusion rate to first attain an SBP value within the initial pre-specified target SBP range was 7.9 minutes (95% CI: 7.2; 10.5) and CCI [redacted], respectively. However, as per protocol, patients in this study also received general anaesthetics and/or narcotic analgesics as concomitant medications, which may have influenced BP.

Clevidipine had a mean (SD) high clearance (113 [54] mL/minutes/kg), small volume of distribution (789 [1165] mL/kg) and an ultrashort $t_{1/2}$ (λ1: 4.3 [3.6] minutes). The PK parameters were proportional to dose across the dose and concentration range tested.

Secondary efficacy endpoints

Systolic Blood Pressure:

All patients had an initial reduction in SBP by 7.5 minutes and achieved at least 15% SBP reduction within 30 minutes. A mean (SD) decrease in SBP of 18.2% (8.09%) was demonstrated in patients at 15 minutes and 20.8% (7.62%) at 30 minutes.

Of the 21 patients reaching the initial pre-specified target SBP range within the first 30 minutes of clevidipine infusion, only 1 (4.8%) patient fell below the lower limit of the target SBP range within the first 30 minutes. In total, 5 (23.8%) patients (95% CI: 5.6; 42.0) fell below the lower limit 'at any time' during study drug administration.

A total of 8/21 (38.1%) patients (95% CI: 17.3; 58.9) and 5/12 (41.7%) patients (95% CI: 13.8; 69.6) were within the target SBP range at 1 and 2 hours, respectively, after the first 30 minutes of clevidipine infusion. Thereafter, there were only a few patients with SBP readings each hour (≤6 patients), up to 6 hours.

Heart Rate:

Mean (SD) HR at baseline was 79.1 (13.33) beats per minute (bpm). During study drug infusion, there was a mean (SD) HR increase of 12.2% (17.97%) to 88.6 (18.26) bpm at 9 minutes after initiation of study drug infusion. Thereafter, HR remained stable during the remainder of the infusion and up to 12 hours post-study drug termination. The maximum mean (SD) percent increase from baseline during the infusion was +15.2% (16.26%), observed at 25.5 minutes after initiation of study drug infusion.

Rescue Medication and Discontinuations Due to AEs:

No patient required rescue, bailout or transition therapy at any time during clevidipine administration and no patients discontinued the study drug due to an AE.

Other efficacy analyses

Mean (SD) DBP at baseline was 63.4 (5.84) mmHg. Values remained similar or below the baseline value during study drug infusion and up to 12 hours post-study drug termination. The largest mean (SD) percentage reduction from baseline was a decrease of 25.08% (5.67%), observed at 5 hours after initiation of study drug infusion.

Safety Results:

A total of 21 patients were treated with clevidipine in Cohort 1. The mean (SD) duration of study drug exposure was 2.3 (1.5) hours (range: 0.8 to 5.9 hours). All patients received at least 30 minutes of clevidipine monotherapy.

All 21 patients in Cohort 1 experienced at least one TEAE, all of which were mild or moderate in severity. Tachycardia was reported in 1 patient; however, this was considered not to be related to the study drug. No TEAEs of hypotension were reported. No TEAEs were considered related to the study drug. One patient experienced a serious TEAE (PT: respiratory depression), which was considered to be related to

intraoperative opioids; it was moderate in severity, not related to the study drug and resolved. No TEAEs led to study drug discontinuation. No deaths occurred in this study.

In terms of vital signs, mean (SD) SBP returned to the approximate baseline value after 5 hours (107.8 [14.22] mmHg) and remained at or below the baseline value up until 12 hours post-study drug termination. Seven patients had increases in SBP of ≥20 mmHg compared to baseline values after termination of the study drug, of whom three received pressor medication prior to the increase in SBP. Mean DBP values remained similar to or below the baseline value from termination of the study drug to 12 hours post-study drug termination. There was a mean (SD) HR increase of 12.2% (17.97%) to 88.6 (18.26) bpm at 9 minutes after initiation of study drug infusion. Thereafter, HR remained stable during the remainder of the infusion and up to 12 hours post-study drug termination.

Changes were noted for some serum chemistry parameters; however, they were not considered to be clinically relevant.

Conclusion:

Results from the adolescent cohort showed that clevidipine effectively lowered BP within the patient-specific pre-specified target SBP range during surgery, however, the effect of maintaining hypotension may have been confounded by concomitant administration of general anaesthetics and narcotic analgesics. As it is not possible to completely separate the effect of the concomitant medications from the effect of clevidipine, a general conclusion on the efficacy of clevidipine in lowering blood pressure in adolescent patients cannot be drawn based on this study. The safety profile of clevidipine was acceptable in adolescent patients.

Date of Report: 26 June 2024