STATISTICAL ANALYSIS PLAN

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Protocol Number: MDCO-CLV-12-01

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

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Statistical Analysis Plan Approval

PROTOCOL TITLE:
Open label study to assess the efficacy, safety and dosing of clevidipine in pediatric patients undergoing surgery

PROTOCOL NUMBER: MDCO-CLV-12-01

STUDY DRUG: Clevidipine

DATE: May 20, 2014

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ABBREVIATIONS

AE	adverse event
ALT/SGPT	alanine transaminase/serum glutamic-pyruvic transaminase
AST/SGOT	aspartate transaminase/ serum glutamic oxaloacetic transaminase
AUC	area under the curve
AUC_{inf}	area under the curve of the blood concentration to infinity
AUC_{last}	area under the curve of the blood concentration to the last measurable concentration
BP	blood pressure
BUN	blood urea nitrogen
CI	confidence interval
CL	total clearance
CSR	clinical study report
C_{max}	maximum peak plasma concentration
DBP	dystolic blood pressure
dL	deciliter
DSMB	Data Safety Monitoring Board
eCRF	electronic case report form
GPV	Global Pharmacovigilence
h	hour
HDL	high density lipoprotein
HR	heart rate
ITT	intent-to-treat
IV	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
kg	kilogram
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LLN	lower limit of the standard reference (normal) range
MAP	mean arterial pressure
max	maximum

MDCO	The Medicines Company
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minimum
min	minute
mmHg	millimeter(s) of mercury
MRT	mean residence time
M1	carboxylic acid metabolite
NONMEM	Nonlinear Mixed-Effect Modeling
PCS	potentially clinically significant
PD	pharmacodynamics
PK	pharmacokinetics
Q	quartile
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SBP	systolic blood pressure
SD	standard deviation
sec	seconds
SEM	standard error of mean
$t_{1/2}$	half-life
TBPR	target blood pressure rate
TEAE	treatment emergent adverse event
t_{max}	time to reach maximum peak plasma concentration
ULN	upper limit of the standard reference (normal) range
U/L	units per liter
VLDL	very low density lipoprotein
Vss	volume of distribution at a steady state
Vz	volume of distribution based in the terminal phase
WHO	World Health Organization
µg	microgram
λ_z	terminal rate constant

1. INTRODUCTION

1.1. TRIAL INTRODUCTION

This is a Phase IV open-label study in pediatric patients undergoing elective surgery requiring anesthesia ≥ 1 hour and for whom parenteral intravenous (IV) antihypertensive therapy for blood pressure (BP) management is expected for at least 30 minutes.

Approximately 80-100 patients are to be enrolled in a stepwise approach to ensure 80 patients can be evaluated for efficacy. Patients will be enrolled in a stepwise approach, starting with the adolescent cohort. An interim analysis of safety and dosing of the adolescent cohort will be performed before the initiation of the next cohort.

- Cohort 1: 20 adolescent patients (12 years to less than 18 years old)
- 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)

A Data Safety Monitoring Board (DSMB) will be set up to monitor the safety and dosing on an ongoing basis for all cohorts. Following the completion of each cohort starting with Cohort 1, the DSMB will review the safety and dosing data and make any safety recommendations to the Sponsor prior to enrolling the next cohort. The DSMB will determine if it is appropriate to proceed with enrollment of the next cohort, and whether adjustments in dosing scheme are required.

The investigator will pre-specify a target range for the desired reduction in systolic blood pressure (SBP) for each patient prior to drug exposure. This patient-specific target SBP range will be recorded via the interactive voice/web response system (IVRS/IWRS) and cannot be changed for the first 30-minute treatment period. The difference between the upper and lower limits of the specified target SBP range should be not less than 20 mmHg and not more than 40 mmHg.

Cohort 1 (ages 12 to less than 18 years) will receive an initial weight based dose of CCI [redacted]; this rate will be maintained for the first 1.5 minutes. If the target SBP range is not achieved within 1.5 minutes, the clevidipine infusion rate may be up-titrated incrementally per the protocol dosing, progressing to CCI [redacted], CCI [redacted], CCI [redacted] up to the maximum dose of CCI [redacted] every 1.5 minutes until a SBP within the pre-specified target range is reached. The initial dose and the subsequent up-titration doses for Cohorts 2, 3 and 4 will be determined after an interim analysis of data from the preceding cohort. As the blood pressure approaches the desired range, dosing may be increased by less than doubling, and the time between dose adjustments may be

lengthened to greater than 1.5 minutes. If the target SBP range is achieved at any of the titration doses, that rate may be maintained for up to 96 hours to maintain the BP, or titrated up or down as necessary to maintain SBP within the target range. Clevidipine infusion may be terminated at any time for safety reasons.

During the initial 30 minutes of the treatment period, clevidipine should be administered continuously as monotherapy. The use of an alternative IV antihypertensive agent is discouraged and should be limited to situations where it is medically necessary to maintain patient safety. If the desired BP control effect is not attained using the maximum dose of clevidipine, rescue therapy with the use of an alternative IV antihypertensive agent should be implemented.

After the first 30-minute treatment period, it may be necessary to alter the desired SBP target range over the course of the remaining treatment period. Any changes in the target range will be captured in the electronic case report form (eCRF).

Patients who receive alternative intravenous rescue therapy in addition to clevidipine may continue in the study. If transition from clevidipine to an oral antihypertensive agent is required, the clevidipine infusion may be down-titrated or terminated as appropriate to maintain the desired blood pressure. If the BP rises to an undesirable level upon cessation of clevidipine infusion, additional therapy may be administered or clevidipine infusion may be restarted (and continue until successful transition to an oral therapy has been achieved). Patients who receive prolonged clevidipine infusions and are not transitioned to other antihypertensive therapies should be monitored for the possibility of rebound hypertension for at least 8 hours after the infusion is stopped [Cleviprex Prescribing Information, 2011].

If treatment with an IV anti-hypertensive agent is still required after 96 hours of clevidipine therapy, the patient will be transitioned to an alternative IV antihypertensive agent according to the institutional standard of care.

The schedule of events/assessments is shown in Table 1 and the pharmacokinetic (PK) sampling time is shown in Table 2.

Table 1: Schedule of Events/Assessments

Study assessment	Screening Period 0 to -7 Days (prior to study drug initiation)	Treatment Period			Follow-up Period Post Study Drug Termination (up to 7 days after final dose)			
		Treatment Phase 1 ***Initial Dosing*** 0 -1.5 minutes	Treatment Phase 2 ***Titration & Maintenance Phase*** >1.5 to 30 minutes & >30 minutes up to 96 hours	Treatment Phase 3 ***Transition & Termination Phase***	Follow-up 1 Hour (+ 30 minutes	Follow-up 12 Hour (+ 30 minutes)	Follow-up 24 Hour (+ 30 minutes)	Follow-up 7- Day[10] (+ 1 day)
Informed consent	X[1]							
Medical history & Physical exam	X[2]							
Height & Weight	X[2]							
Prior Medications	X[2]							
BP (SBP, DBP) /HR	X[2,3]	X[3]	X[4,5]	X[4,5]	X[6]	X[6]		
Pregnancy test	X[2]							
Hematology (Protocol Section 6.3)	X[2]							
Serum chemistry every 24 hours (Protocol Section 6.3)	X[2]		X		X[11]			
SBP Target Range	X[2]		X[9]					
Enrollment via IVRS/IWRS	X[2]							
Study drug administration		X[7]	X[7]	X[7]				
PK sampling	X[3,8]	X[3,8]	X[8]	X[8]	X[8]			
Concomitant Medications		X	X	X	X	X	X	
Oral Antihypertensive Administration				X				
AE and SAE reporting	←			X[12]				→

[1] Written informed consent from parent or legal guardian and verbal assent (as per institutional policy) before initiation of any study-related procedures.

[2] Assessment(s) must be performed prior to treatment to determine eligibility for enrollment into the study.

[3] BP (SBP, DBP) and hear rate (HR) are measured using an intra-arterial catheter with electronic transducer. PK Sample1 is to be taken up to 30 minutes prior to start of clevidipine infusion with BP and HR measured, immediately followed by PK Sample 1 collection. Baseline BP and HR are recorded at 60 sec, 45 sec, 30 sec, and 0 sec prior to initiation of clevidipine. PK Sample 2 is taken at 1.5 minutes after the start of clevidipine infusion (before first dose titration) with BP and HR measured, immediately followed by PK Sample 2 collection. The actual time of BP, HR and PK sample must be recorded using devices that are time synchronized.

[4] BP and HR will be recorded every 1.5 minutes (+ 30 second window where a PK sample is required) for a period of at least 30 minutes, every 10 minutes for the next hour, every 30 minutes for the next 2 hours and every 1 hour until study drug is terminated (up to 96 hours). BP and HR will also be recorded immediately before each PK blood draw (Table 2) is obtained.

[5] If a dose adjustment is indicated, BP and HR should be recorded just prior to each study drug dose change as well as every 1.5 minutes for 15 minutes after the dose adjustment, then return to the BP assessment schedule just prior to the dose adjustment.

[6] BP and HR will be recorded every 1 hour until study drug has been stopped for 12 hours post-study drug termination.

[7] Clevidipine administered as a continuous IV infusion.

[8] Blood samples for PK analysis will be obtained from an arterial line per the time intervals included in Table 2 below (1 before clevidipine infusion; 4-5 during clevidipine infusion; 4 post clevidipine infusion). NOTE: BP and HR will be recorded immediately before each PK blood draw. The actual time of BP, HR and PK sample must be recorded using devices that are time synchronized.

[9] Beyond the first 30-minute treatment period, it may be necessary to alter the desired SBP target range over the course of the remaining treatment period. Any changes in the target range will be captured in the case report form (eCRF).

[10] The 7 day (+1 day) follow-up can occur by phone, if applicable.

[11]. Serum chemistry within 1 (+30 minutes) hour after study drug termination

[12]. AE and SAE reporting will be from time of consent through 7 days day) following termination of study drug infusion.

Table 2: PK Sampling Times

Sample	Time point
1	Up to 30 minutes prior to start of clevidipine infusion
2	1.5 minutes post initiation of clevidipine infusion (before first dose titration)
3	1.5 minutes after first dose titration (must be performed before proceeding to second dose titration)
4	Once target SBP range is reached or 30 minutes after the initiation of clevidipine infusion, whichever comes first
5 (if applicable)	If transition to an additional antihypertensive is desired and concurrent administration is needed, a sample should be taken right before beginning administration of the additional antihypertensive agent
6	Right before the termination of the clevidipine infusion
7	0.5 minutes post termination of the clevidipine infusion
8	3 minutes post termination of the clevidipine infusion
9	15 minutes post termination of clevidipine infusion
10	1hour (+30 minutes) post final termination of the clevidipine infusion

2. OBJECTIVES

2.1. PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the dosing, efficacy and safety of an intravenous (IV) infusion of clevidipine for blood pressure (BP) management in pediatric patients in the perioperative setting.

2.2. SECONDARY OBJECTIVES

The secondary objectives of the study are to evaluate additional efficacy, safety and dosing parameters associated with IV infusion of clevidipine for BP management in pediatric patients in the perioperative setting.

2.3. EXPLORATORY OBJECTIVES

Efficacy will be evaluated in the subgroups of patients with and without pre-existing hypertension. Additional analyses may be performed for efficacy and/or safety when applicable.

3. STUDY POPULATIONS

Three patient populations will be considered in the statistical analyses of this study.

3.1. SAFETY POPULATION

The safety population consists of all patients who are dosed with any study drug. This will be the primary population used for the safety analyses.

3.2. INTENT-TO-TREAT (ITT) POPULATION

The ITT population consists of all patients who are dosed with any study drug and have baseline and at least one post-baseline SBP measurement. This will be the primary population used for the efficacy analyses.

3.3. PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) POPULATION

The PK/PD population consists of all patients who are dosed with any study drug, have at least one documented and evaluable blood concentration and/or SBP observation and documented dose records. This will be the primary population for PK/PD analyses.

4. GENERAL STATISTICAL METHODOLOGY

All statistical analyses and summary information will be generated according to this statistical analysis plan (SAP). Any deviations from this SAP will be documented in the clinical study report (CSR).

Patient disposition, demographic and background characteristics will be presented for the safety, ITT and PK/PD populations. Unless otherwise specified, all efficacy analyses will be performed using the ITT population, all safety analyses will be performed using the safety population and all PK/PD analyses will be performed using the PK/PD population.

Continuous variables will be summarized using descriptive statistics including the number of patients reflected in the calculation (n), mean, standard deviation (SD), median, interquartile range (Q1 and Q3), minimum (min), and maximum (max). Frequencies and percentages will be displayed for categorical variables.

Because of the descriptive nature of this study, no formal statistical hypothesis testing will be performed. However, p-values and/or two-tailed 95% confidence intervals may be generated to demonstrate the strength of the findings whenever appropriate.

All data will be summarized for overall and by age cohort. Data listings will be provided for all data collected in the eCRF.

Unless otherwise specified for repeat pre-baseline assessments, the results from the final assessment made before or at the start of study medication will be used as baseline. If post-baseline assessments are repeated or unscheduled, the non-missing values from the first assessment will be used for generating summary statistics.

Unless otherwise specified (eg, in Section 8), missing data will not be imputed and will be excluded from the associated analysis.

5. PATIENT DISPOSITION AND STUDY COMPLETION

The number of patients included in each study population (i.e., safety, ITT and PK/PD) will be presented. The number and percentage of patients who completed and discontinued from the study, as recorded on the patient "End of Study" page of the eCRF, will be displayed for the three study populations. Reasons for discontinuation will be summarized descriptively.

The number of patients included in each of three study populations for each study center will be tabulated.

Listings of populations, discontinuation from the study along with the reason, will be provided by age cohort.

6. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Demographics including sex, age, ethnicity, height, weight, and BMI, baseline characteristics including blood pressure and heart rate, relevant medical history, as well as relevant past surgical/interventional procedure will be summarized with descriptive statistics for all populations (safety, ITT and PK/PD).

Listings of demographics, baseline characteristics, medical history and surgical/interventional procedures will be presented for each patient, including those who are enrolled but not treated with the study medication.

7. PROTOCOL DEVIATION

Any protocol deviations that occur during the study will be recorded in the eCRF. The number and percentage of patients who had at least one protocol deviation will be summarized by violation type.

8. EXTENT OF STUDY DRUG EXPOSURE

Study drug exposure will be summarized using the safety population by the following timeframes.

1. From initiation to the end of the first 30-minute treatment period, representing the protocol-specified initial and titration phases
2. From the end of the first 30-minute treatment period to the end of treatment, representing the protocol-specified maintenance phase
3. From initiation to the end of treatment, representing the overall treatment period

Exposure will be quantified and descriptively summarized using the following variables.

For timeframes 1 only:

- Receive at least 30 minutes of continuous clevidipine monotherapy (yes/no)
- Reason if did not receive at least 30 minutes of clevidipine monotherapy (SBP Target Range not reached, Adverse Event/Serious Adverse Event, Other)
- Attempted maximum allowed dose CCI within 30 minutes of clevidipine infusion if did not receive at least 30 minutes clevidipine monotherapy (yes/no)

For timeframes 1 and 3 only:

- Number of patients who initiated the study drug infusion before surgery (yes/no)
- Primary reason for initiating study drug (Treatment for pre-existing hypertension, Controlled hypotension during surgery, Treatment for intra-operative hypertension, Control post-surgical hypertension)
- Initial infusion rate (µg/kg/min)

For timeframe 3 only

- Reason for termination of IV clevidipine infusion
- IV clevidipine infusion successfully terminated at the first attempt (i.e., was not restarted) (yes/no)
- Overall infusion duration (h)

For timeframes 1, 2 and 3

- Maximum infusion rate (µg/kg/min)
- Median infusion rate (µg/kg/min)

- On-drug infusion duration (h) (the summation of the durations of all the time segments when clevidipine was administered with an infusion rate of > 0 µg/kg/min)
- Total dose infused (mg)
- Average infusion rate (µg/kg/min) (equals the total dose infused divided by on-drug infusion duration in minutes and baseline weight in kg)

Missing infusion rates will be imputed by linear interpolation between two observed infusion rates when the associated infusion start and stop times are observed. No missing rates will be imputed by extrapolation.

9. PRIOR AND CONCOMITANT MEDICATION

Prior and concomitant medications in addition to the study drug will be summarized descriptively using the safety and the ITT populations. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary.

10. EFFICACY ANALYSES

Unless otherwise specified, all efficacy analyses will be using the defined ITT population.

10.1. PRIMARY EFFICACY ANALYSIS

- **The time to and percent of patients who attain the initial pre-specified SBP target range within the first 30 minutes of study drug initiation.**

The time to attain the initial pre-specified SBP target range is in minutes and is the duration between the initiation of study medication and the time a patient first achieves the initial pre-specified target SBP range (TBPR) during the first 30 minutes of clevidipine infusion. The time will be summarized using descriptive statistics and the Kaplan-Meier curve. The estimated median time with its two-tailed 95% confidence interval (CI) [Simon and Lee, 1982] will be presented. If a patient does not reach TBPR within 30 minutes from the initial treatment with study medication, or another antihypertensive agent is administered, the patient will be considered censored at 30 minutes or the time when another antihypertensive agent is given, whichever comes first.

The percentage of patients achieving the TBPR will be calculated using the number of ITT patients achieving TBPR divided by the number of ITT patients, and multiplied by 100. Two-tailed 95% CIs will be computed for these percentages.

- **The 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.**

The dose to attain the initial pre-specified target SBP consists of the infusion rate (μg/kg/min), total dose (mg) infused, and number of titrations made when TBPR is reached.

The summary statistics on infusion rate, total dose infused, and number of titrations made when TBPR is reached will be presented.

All the aforementioned analyses will be performed using the ITT population and also for data exploration using the safety population.

10.2. SECONDARY EFFICACY ANALYSIS

The secondary efficacy analysis will be performed on the following measures.

All the secondary efficacy analyses will be performed using the ITT population and also for data exploration using the safety population.

10.2.1. 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 reaching this endpoint will be calculated using the number of patients reaching the endpoint divided by total number of patients in the analysis population, and multiplied by 100. Two-tailed 95% CIs will be computed for these percentages.

Number and percent of patients achieving the endpoint during first 30 minutes of clevidipine infusion along with the calculated 95% CI will be presented.

10.2.2. 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 of treatment and at any time during the entire study drug treatment period

Two analyses will be presented: 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 of treatment period and below the lower limit of the target range at any time during the entire study drug treatment period. Both endpoints will be calculated using the number of patients achieving the endpoint divided by total number of patients in the analysis population, and multiplied by 100. Two-tailed 95% CIs will be computed for these percentages.

Number and percent of patients achieving the endpoints along with the calculated 95% CI will be presented.

10.2.3. The percentage of patients in whom the SBP is within target range at each hour after the first 30 minutes of clevidipine infusion

The percentage of patients who stayed within target range at each hour after first 30 minutes of clevidipine infusion will be calculated using the number of patients who reached the endpoint divided by total number of patients in the analysis population, and multiplied by 100. Two-tailed 95% CIs will be computed for these percentages.

Time windows specified in Section 20.1.1 will be applied if the hemodynamic assessment is missing at a specific timepoint.

Number and percent of patients achieving the endpoint at each hour after first 30 minutes of clevidipine infusion along with the calculated 95% CI will be presented.

10.2.4. 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 adverse events

The percentage of patients achieving this endpoint will be calculated using the number of patients achieving the endpoint divided by total number of patients, and multiplied by 100. Two-tailed 95% CIs will be computed for these percentages.

Number and percent of patients achieving the endpoints along with the calculated 95% CI will be presented.

10.2.5. Percent change in SBP from baseline at each time point during the 30 minutes of clevidipine infusion, at each hour after the first 30 minutes of clevidipine infusion up to the cessation of infusion, and over the first 12 hours post study drug termination

Blood pressure will be measured every 1.5 minutes for the first 30 minutes of infusion, every 10 minutes in the next hour, every 30 minutes for the next 2 hours then every hour until the study drug is terminated or maximum 96 hours from initiation of study drug is reached, whichever is earlier. Blood pressure will also be measured just prior to each PK blood draw and each dose adjustment, as well as every 1.5 minutes for 15 minutes after the dose adjustment. After termination of the clevidipine infusion, blood pressure will be taken every 15 minutes for the first hour, then every hour for a maximum of 12 hours.

Descriptive statistics on changes and percent changes from baseline in SBP will be summarized at each specified timepoint. A graph will be presented on percent change in SBP during the first 30 minutes after initiation of study medication by age cohort.

Individual patient graphs will present SBP across all timepoints along with the study drug dose levels in mg/h.

10.2.6. Percent change from baseline in heart rate during the first 30 minutes of clevidipine infusion and the rest of the treatment period

Heart rate (HR) will be measured every 1.5 minutes for the first 30 minutes of study drug infusion, every 10 minutes in the next hour, every 30 minutes for the next 2 hours then every hour until the study drug is terminated or maximum 96 hours from initiation of study drug is reached whichever is earlier.

Descriptive statistics on changes and percent changes from baseline in HR will be summarized at each specified timepoint within 30 minutes of clevidipine infusion. A graph will be made of percent change in HR during the first 30 minutes after initiation of study medication by age cohort.

10.3. OTHER EFFICACY ANALYSIS

The following endpoint will be summarized and presented:

- **Percent change from baseline in diastolic blood pressure (DBP) over time**
- **Percent change from baseline in mean arterial pressure (MAP) over time**

11. SAFETY ANALYSES

Safety of a prolonged infusion of clevidipine up to 96 hours will be assessed according to adverse events (AE)/serious adverse events (SAE) up to 7 (+ 1) days following study treatment termination, and clinical laboratory parameters.

Unless otherwise specified, all safety analyses will use the defined safety population.

11.1. ADVERSE EVENTS

The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding AEs. An AE (classified as preferred term) occurring after initiation of study drug will be counted as a treatment emergent AE (TEAE) either if it is not present at baseline or if it is present at baseline but increased in severity after initiation of study drug. If more than one AE with the same preferred term was reported pre-baseline, then the report with the greatest intensity is used as the benchmark for comparison to post-baseline reports of events with that preferred term.

The number (percentage) of patients reporting TEAEs for each preferred term will be tabulated by system-organ class, by system-organ class and severity, and by system-organ class and relationship to study drug. If more than one event occurred with the same preferred term for the same patient, the patient will be counted only once for that preferred term using the most severe or related occurrence for the summary by severity, or relationship to study drug, respectively. An individual patient will be counted only once for any specific preferred term regardless of the number of times that preferred term occurred for that patient.

The incidence of SAEs and AEs leading to discontinuation of study drug will be summarized separately by system-organ class, preferred term for the safety population.

Listings will be presented for patients with SAEs/AEs leading to a discontinuation or death.

11.2. LABORATORY PARAMETERS

Serum chemistry including serum creatinine, triglycerides, lipase, total cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), alanine transaminase/serum glutamic-pyruvic transaminase (ALT/SGPT), aspartate transaminase/ serum glutamic oxaloacetic transaminase (AST/SGOT), total bilirubin, lactate dehydrogenase, blood urea nitrogen, sodium, potassium, calcium, and magnesium will be assessed at screening and then every 24 hours (+/- 1 hour) during study drug administration up to 96 hours (or at the termination of study drug infusion if less than the 24 hour timepoint). A blood sample will also be drawn 4 hours (+/- 30 minutes) after termination of study drug infusion.

Hematology including red blood cells, hemoglobin, hematocrit, white blood cells, and platelets will be collected only at screening.

11.2.1. Laboratory normalization

Because values of laboratory parameters in this study are provided from different local laboratories with different units and normal ranges, all numerical laboratory values will be converted to the conventional units and normalized to a standard set of reference/normal ranges [Chuang-Stein, 1992 and 2001]. The normalization process will be performed for each of the laboratory parameters. The method was adapted by a scale model described in Karvanen [2003] for values outside the normal local range and in the case of only one-sided defined standardized normal ranges. Details of the standardization process are described in the Appendix (Section 20.2). Normalized laboratory values will be used for the analyses of summary statistics, including relative and percent changes from baseline, described in Section 11.2.2.

11.2.2. Laboratory analysis

Descriptive statistics for the values of serum chemistry as well as relative and percent changes from baseline will be summarized by time point: baseline (screening), every 24 hours during study drug administration (or at the termination of study drug infusion if less than the 24 hours timepoint), and at 4 hours after termination of study drug infusion. Values for each hematology parameter will be presented only at screening.

Values of laboratory tests are considered potentially clinically significant (PCS) if they meet the PCS criteria listed in Table 3. The number (percentage) of patients with post-baseline PCS values who do not have PCS values at baseline will be analyzed for the safety population. For calculation of the percentages, the denominator is based on the number of patients with non-PCS baseline values and at least one post-baseline assessment for the laboratory parameter being analyzed. The numerator is based on patients from the denominator who had at least one post-baseline PCS value for the laboratory parameter being analyzed. A supportive listing of patients with all PCS values will be provided including the patient number, age, gender, treatment time. Both raw and standardized pre-baseline, baseline, and post-baseline values and normal ranges will be in the listing, along with the standardized abnormality flag.

Table 3: Criteria for Potentially Clinically Significant Abnormal Laboratory Tests

Parameter	Low Limit	High Limit
Serum Chemistry		
Serum Creatinine, mg/dL	_	≥2 mg/dL
Triglycerides, mg/dL	_	≥300 mg/dL
Lipase, U/L	_	≥3 × ULN
Total Cholesterol, mg/dL	_	≥300 mg/dL
HDL, mg/dL	_	≤20 mg/dL
LDL, mg/dL	_	≥200 mg/dL
VLDL, mg/dL	_	≥100 mg/dL
Alanine Transaminase (ALT/SGPT), U/L	_	≥3 × ULN
Aspartate Transaminase (AST/SGOT), U/L	_	≥3 × ULN
Total Bilirubin, mg/dL	_	≥1.5 × ULN
Lactate Dehydrogenase (LDH)	_	≥3 × ULN
Blood Urea Nitrogen (BUN), mg/dL	_	≥1.5 × ULN
Electrolytes		
Sodium, mg/L	≤0.9 × LLN	≥1.1 × ULN
Potassium, mg/L	≤0.9 × LLN	≥1.1 × ULN
Calcium, mg/dL	≤0.9 × LLN	≥1.1 × ULN
Magnesium	≤0.9 × LLN	≥1.1 × ULN

LLN: Lower limit of the standard reference (normal) range.

ULN: Upper limit of the standard reference (normal) range.

12. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

12.1. PRIMARY PK ANALYSIS

Blood concentration versus time data will be analyzed using non-compartmental analysis and/or Nonlinear Mixed-Effect Modeling (NONMEM). The following pharmacokinetic parameters will be estimated:

- Maximum observed blood concentration (C_{max})
- Time to reach C_{max} (t_{max})
- Area under the curve of the blood concentration to the last measurable concentration (AUC_{last})
- Area under the curve of the blood concentration to infinity (AUC_{inf})
- Terminal rate constant (λ_z) and its associated half-life ($t_{1/2}$)
- Mean residence time (MRT)
- Total clearance (CL).
- Volume of distribution at steady state (V_{ss})
- Volume of distribution based in the terminal phase (V_z)

All concentration data will be presented descriptively at each time point. Descriptive statistics comprising N, mean, geometric mean, SD, standard error of mean (SEM), median, %CV, minimum and maximum will be presented for the pharmacokinetic variables (half-life, area under curve [AUC], volume of distribution, clearance, etc.) established by sparse population methodology.

All PK and PD analyses will be using the defined PK/PD population.

12.2. ADDITIONAL PK ANALYSIS

The following additional PK analysis will be performed:

- Blood concentration of clevidipine and its carboxylic acid metabolite (M1) over time

Blood concentration of clevidipine and M1 will be plotted over time by cohort. PK modeling of blood concentration of clevidipine versus any or all of weight, height, body surface area, age, sex or ethnicity may be explored when appropriate.

- Relationship between dose and blood concentration of clevidipine for overall and by cohort

Blood concentration will be plotted over dose for overall and by cohort. Dose proportionality will be explored. PK modeling of blood concentration of clevidipine versus dose plus any or all of weight, height, body surface area, age, sex or ethnicity may

be performed to explore the potential effect of covariance on the dose-concentration relationship.

- Relationship between first on-study blood concentration of clevidipine and body weight

First on-study blood concentration of clevidipine will be plotted over body weight. This might be done by age, sex or ethnicity.

We may also perform analysis to explore the following:

- Potential effect of body weight, height, body surface area, age, sex, ethnicity or dose on total clearance (CL)
- Potential effect of body weight, body surface area, age, sex ethnicity or dose on volume of distribution (Vss)

12.3. PK/PD RELATIONSHIP

The following analyses will be performed for PK/PD relationship:

- Relationship between change and/or percent change from baseline in SBP and first on-study blood concentration of clevidipine for overall and by cohort

Change and/or percent change from baseline in SBP will be plotted over first on-study blood concentration for overall and by cohort. Appropriate PK/PD modeling may be explored whenever necessary.

- Relationship between dose and change or percent change from baseline in SBP for overall and by cohort

Change and/or percent change from baseline in SBP will be plotted over dose for overall and by cohort. Appropriate PK/PD modeling may be explored whenever necessary.

- Relationship between blood concentration of clevidipine and change or percent change from baseline in SBP will be explored for overall and by cohort

Change and/or percent change from baseline in SBP will be plotted over blood concentration for overall and by cohort. Appropriate PK/PD modeling may be explored whenever necessary.

13. SUBGROUP ANALYSES

Subgroup analysis in patients with and without pre-existing hypertension will be performed for efficacy and safety endpoints for the cohorts with reasonable number of patients in each subgroup to warrant feasible analysis.

Pre-existing hypertension for children of 1 to 17 years old will be defined as the average of SBP or DBP that is $\geq 95^{th}$ percentile for gender, age and height on at least 3 separate occasions on or before baseline according to the definition specified in ”The Fourth Report on the Treatment of High Blood Pressure in Children and Adolescents” [NIH Publication, 2005]. The pre-existing hypertension for neonates will be defined according to the definition specified in “Neonatal hypertension: diagnosis and management” [Flynn, 2000].

14. OTHER/EXPLORATORY ANALYSIS

14.1. SURGICAL PROCEDURE

Surgery related parameters will be analyzed in this study including:

- Type of surgery
- Pump used for cardiac surgery (yes or no)
- Duration of surgery (initial incision to last suture placed)
- Duration of time on pump for cardiac surgery

Descriptive statistics for each of the above endpoints will be provided by treatment group whenever appropriate. Patient data listings will also be provided.

14.2. TARGET SBP RANGE

Prior to enrollment, the investigator predetermines a patient-specific SBP target range for the desired BP reduction. The pre-specified SBP target range cannot be changed for the first 30 minutes of treatment and the difference between upper and lower limits of the specified target SBP range should be no less than 20 mmHg and no more than 40 mmHg. After completing the initial 30 minutes of treatment the SBP target range can be changed as needed.

Initial target SBP range, new target SBP range along with the SBP, HR values at the time the range change was initiated will be summarized for overall and by age cohort.

15. INTERIM ANALYSIS

Following completion of each cohort, the DSMB will review both safety and dosing data provided by the Sponsor and make safety and dosing recommendations to the Sponsor according to the DSMB charter prior to enrolling the next cohort. DSMB review of each completed cohort will be required before proceeding to the next cohort to determine if it is appropriate to proceed with enrollment of subsequent cohorts and whether an adjustment in dosing scheme is required.

In addition, the Sponsor will perform an analysis based on the number of patients reaching TBPR within first 30 minutes of study drug infusion to assess the precision of the efficacy findings at the end of each cohort to ensure that sample size for the following cohort is sufficient based on clinical judgement.

16. SAMPLE SIZE CONSIDERATIONS

The total sample size of 80 evaluable patients is primarily based on clinical judgment to provide adequate precision of the findings for this non-comparative study. For example, assuming that 90% of patients will achieve the initial target SBP range within the first 30 minutes of infusion, a sample size of 80 patients can provide a 95% confidence interval with a precision of ±6.6%. This precision will become ±7.8% if 85% of patients are assumed to achieve the initial target SBP range. The precision will be assessed at the end of each cohort and sample size for the next cohort may be adjusted.

Approximately 10-20 patients per pediatric age group are considered adequate to assess the PK/PD model, based on prior clinical experience in adults.

17. COMPUTER METHODS

Statistical analyses will be performed using Statistical Analysis System (SAS) (version 9.0 or later version).

18. CHANGES TO ANALYSES SPECIFIED IN THE PROTOCOL

In Protocol Section 10.3.3.3, it was stated to analyze vital signs at each collection time point. In this study, the only vital signs that are collected are SBP, DBP and HR which are already analyzed as individual efficacy endpoint hence there is no additional analysis on vital signs performed.

19. REFERENCES

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20. APPENDIX

20.1. TIME WINDOWS

20.1.1. Visit windows for hemodynamic data (SBP, DBP and HR)

Hemodynamic data (SBP, DBP and HR) will be presented at every 1.5 minutes within 30 minutes of study drug infusion, at every 30 minutes for the next 3 hours, at every hour thereafter till the cessation of infusion and over 12 hours post study treatment. The time window is 30 seconds for 1.5 minutes presentation, 10 minutes for every 30 minutes presentation and 30 minutes for hourly presentation.

20.1.2. Visit windows for laboratory parameters

The following are the time windows (in hours) used for the summary tables of laboratory parameters during the study drug infusion.

>0 to <36 for 24

≥36 to <60 for 48

≥60 to <84 for 72

≥84 to <106 for 96

The following are the windows used for the data measured post the cessation of study drug infusion.

≥1 h post-infusion to ≤5 h post-infusion for 4 hours post-infusion

For example, if there is no 48-h measurement, the data measured in the time window between 36 h and 60 h will be considered. The values measured closest to 48 h in the window will be considered as the 48-hrs. value. If two values are both equally close to 48 h in the window, the one measured in the earlier time will be used for the analysis. The assessment at 48-h will be considered missing if there are no assessments in the time window from 36 h to 60 h.

20.2. LABORATORY NORMALIZATION

Because values of laboratory parameters are provided from different study centers with different local laboratories, and with inconsistent units and normal ranges, all numerical laboratory values will be converted to conventional units and normalized to a standard set of reference/normal ranges by a location-scale model as described by Chuang-Stein (1992 and 2001). The method was adapted by a scale model described in Karvanen [2003] for values outside normal local range and in the case of only one-sided defined standardized normal ranges.

The normalization process will be performed for each laboratory parameter.

For numerical laboratory values, the normalized values will be proportional to the ratio of the widths of reference ranges and aligned with the corresponding lower limits. For example, let (L_S, U_S) denote the standard reference range. Let φ denote the laboratory value provided from Laboratory A, which is to be normalized. The normalized value, φ_S, can be derived from the formula,

$$\varphi_S = L_S + \beta \times (\varphi - L_A),$$

where (LA, UA) represents the reference range from Laboratory A and β denotes the ratio of the width from standard reference range over the width from Laboratory A (ie, β = (US – LS) / (UA - LA)).

If one, say the lower, of the limits of a reference range is missing then the missing limit will be imputed according to the ratio of the limits from one of the closest reference ranges provided in this study. For example, let LM denote the missing lower limits from Laboratory M. Its corresponding higher limit, UM, is found to be closest to the upper limit, UC from Laboratory C among all the reference upper limits in the study. Then, LM will be imputed by the formula,

$$L_M = L_C \times (U_M / U_C),$$

where LC denotes the lower limit from Laboratory C. For cases where only the upper local limits are missing (i.e., the lower ones are not missing), the same imputation process will be performed. For cases where both limits of a local reference range are missing, the missing upper and lower limits will be imputed by the largest upper and lowest lower limit among all the observed local reference ranges, respectively.

For laboratory parameters with one-sided standard reference ranges the scale normalization formula (see formula 21 in Karvanen, 2003) will be applied as follows:

Let L_S and U_S denote either side of the standard reference range.

Let w, L_w and U_w denote the value and either side of the local reference range.

If only L_S is available the normalized value will equal w * L_S / L_w.

If only U_S is available the normalized value will equal w * U_S / U_w.

For values outside the local reference ranges, the same formula will be applied to avoid complications by negative normalized values using the notation above:

If w is below L_w, then the normalized value will equal w * L_S / L_w.

If w is above U_w, then the normalized value will equal w * U_S / U_w.