THE MEDICINES COMPANY®

Clevidipine Pediatric Investigational Plan

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

Protocol No.: MDCO-CLV-12-01

U.S. IND No.: 65,114

EudraCT No.: 2013-001268-44

PROTOCOL VERSION: Version 3

Drug Development Phase:	IV
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Issue Date:	Date: 11 December 2013

This study will be conducted in compliance with Good Clinical Practice (GCP) and protection of the subject as required by the regulations and directives in operation at this time.

NCT01938547

Emergency Contact Information

Role in Study	Name	Telephone Number
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PROTOCOL SYNOPSIS

Name of Sponsor/Company:	The Medicines Company
Name of Finished Product:	Cleviprex® (clevidipine) Injectable Emulsion
Name of Active Ingredient:	clevidipine
Title of Study:	Open label study to assess the efficacy, safety and dosing of clevidipine in pediatric patients undergoing surgery
Phase of Development:	IV
Study Centers:	2 centers
Principal Investigator:	Joseph D. Tobias, MD
Study Period: Estimated date first subject enrolled: February 2014 Estimated date last subject completed: February 2016	
Objectives: To evaluate the efficacy, safety and dosing of an intravenous (IV) infusion of clevidipine for blood pressure (BP) management in pediatric patients in the perioperative setting.	
Methodology: Open label study to assess, in a stepwise approach from oldest to youngest, the efficacy and safety of clevidipine exposure for a minimum of 30 minutes and up to a maximum of 96 hours in pediatric patients undergoing a surgical procedure requiring anesthesia ≥1 hour, and for whom parenteral IV antihypertensive therapy for BP management is expected.	
Number of Patients: 80-100 planned; 80 evaluable for efficacy This study will evaluate the efficacy and safety of clevidipine in 80 pediatric patients presenting for surgery and anticipated to require BP management during the surgical procedure with parenteral IV antihypertensive therapy. Patients will be enrolled in a stepwise approach, starting with the adolescent cohort. An interim analysis of safety and dosing will be performed by the Data Safety Monitoring Board (DSMB) before initiation of each of the remaining cohorts. • 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).	

A DSMB will be set up to monitor the safety and dosing data on an ongoing basis for all cohorts. Following completion of the adolescent cohort, the DSMB will review the safety data and make safety recommendations to the Sponsor according to the DSMB Charter. The DSMB review of each completed cohort will be required before proceeding to the subsequent cohort to determine if it is appropriate to proceed with enrollment of subsequent cohorts and whether an adjustment in dosing scheme is required.

An analysis to confirm appropriate sample size for desired precision will be conducted by the Sponsor following complete enrollment of each cohort.

Diagnosis and Main Criteria for Selection:

Patients will be eligible for inclusion if they satisfy the following criteria:

- Less than 18 years of age
- Written informed consent obtained before initiation of any study-related procedures
- The enrolling physician determines that the patient will likely require a 15% reduction in BP during the perioperative course
- Intra-arterial line is available for blood pressure monitoring
- Surgical procedure requiring at minimum of 1 hour of anesthesia, in which IV antihypertensive therapy to control BP for at least 30 minutes is anticipated

Patients will be excluded if they present with any of the following exclusion criteria:

- Administration of an IV or oral antihypertensive agent within 2 hours prior to study drug administration
- Congenital heart disease described as single ventricle
- Evidence of liver failure, severe liver disease, pulmonary disease (e.g., uncontrolled asthma), hyperlipidemia, lipoid nephrosis, lipid dysfunction or acute pancreatitis
- Allergy to soya bean oil or egg lecithin
- Known to be intolerant to calcium channel blockers
- Hemophilia or blood coagulation disorders
- Any serious medical condition which, in the opinion of the investigator, is likely to interfere with study procedures
- Clinically significant abnormal physical findings at the screening evaluation
- Any serious surgical or medical condition which, in the opinion of the investigator, is likely to interfere with study procedures or with the pharmacokinetics or pharmacodynamics of the study drug

- Patient is terminally ill (death likely to occur within 48 hours)
- Use of methylphenidate, calcium channel blockers, aripiprazole and other atypical anti-psychotics and antihypertensive used for BP control within 2 hours prior to study drug initiation
- Positive serum or urine pregnancy test for any female of child bearing potential
- Participation in other clinical research studies involving the evaluation of other investigational drugs or devices within 30 days of enrollment
- Patients who, for any reason, are deemed by the investigator to be inappropriate for this study
- Patient is 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 may be re-screened for participation at any time if the exclusion characteristic has changed.

Test Product, Dose and Mode of Administration, Batch Number(s):

The investigational drug clevidipine will be administered intravenously as a slow infusion to all patients via a single dedicated peripheral venous line.

The investigator must pre-specify a target range for each patient prior to drug exposure for the desired reduction in systolic blood pressure (SBP) which includes a 15% reduction in SBP from baseline within the first 30 minutes. This patient-specific SBP range will be recorded in the electronic case report form (eCRF) 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 not be less than 20 mmHg and not more than 40 mmHg.

Adolescent patients (ages 12 up to 18 years) will receive initial weight based doses of CCI; this rate will be maintained for the first 1.5 minutes. The dosing to be used in subsequent cohorts will be based on data generated in the adolescent cohort.

If the target range of SBP is not achieved within 1.5 minutes of using the initial dose and additional blood pressure reduction is required, the clevidipine infusion rate may be doubled, progressing to CCI, CCI, CCI and the maximum dose of CCI every 1.5 minutes at the discretion of the investigator and as tolerated by the patient, to achieve an SBP within the prespecified target range. As the blood pressure approaches goal, dosing may be increased by less than doubling and lengthening the time between dose adjustments to greater than 1.5 minutes.

The clevidipine infusion rate may also be decreased as necessary at the discretion of the investigator to maintain SBP within the target range. If the target SBP range is achieved at any of the titration doses, that rate may be maintained for up to 96 hours at the discretion of the investigator to maintain the BP. Clevidipine infusion may be terminated at any time for safety reasons. Per protocol dosing reflects clinical experience to date (additional clinical utility is typically not observed at doses above CCI).

A DSMB will be set up to monitor the safety and dosing on an ongoing basis for all cohorts. Following completion of the adolescent cohort, the DSMB will evaluate safety data and make any safety recommendations to the Sponsor according to the DSMB Charter. The DSMB review of each completed cohort will be required before proceeding to the subsequent cohort to determine if it is appropriate to proceed with enrollment of subsequent cohorts and whether an adjustment in dosing scheme is required.

Duration of Treatment:

This study is comprised of three consecutive periods: a screening period, a treatment period, and a follow up period. The maximum duration of a patient's participation on study is approximately 18 days (screening up to 7 days, study drug administration up to 4 days and follow-up up to 7 days).

There will be 20 patients treated for each cohort but approximately 10-20 patients per pediatric age group are considered adequate to assess the pharmacokinetic (PK)/ pharmacodynamic (PD) model, based on prior clinical experience in adults. Collection of up to 10 blood samples for PK analysis is planned within the infusion period of 24 hours. The first PK sample will be collected during the screening period within 30 minutes before beginning clevidipine infusion, 4-5 samples will be collected following initiation of study drug infusion during the treatment period and 4 samples collected following cessation of clevidipine infusion during the follow-up phase of the study. To ensure precision of measurements, the actual time of the BP, heart rate (HR) and PK sample will be recorded and clocks used for these measurements will be synchronized.

The treatment period occurs from time the study drug administration is initiated for up to 96 hours. During the initial 30 minutes of the treatment period, clevidipine should be administered continuously as a monotherapy IV antihypertensive agent. Patients who receive rescue therapy along with clevidipine may continue in the study. It may be necessary to alter the desired SBP target range post the initial 30 minutes over the course of the treatment period. Any changes in the target range will be captured in the eCRF. 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. The alternative agent should be chosen per the institutional practice.

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 as determined by the principal investigator.

If transition from clevidipine to an oral antihypertensive agent is required, at any time following administration of the oral antihypertensive agent, the clevidipine infusion may be down-titrated or terminated in order to achieve the desired blood pressure level. If BP rises to an undesirable level upon cessation of clevidipine infusion, additional therapy may be administered or clevidipine infusion may be restarted (at initial infusion rate) until successful transition to an oral therapy has been achieved.

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

Rescue therapy with IV antihypertensive treatment will be determined by the principal investigator per the institutional treatment policy. If a patient is receiving rescue therapy with an IV antihypertensive treatment and transition to an oral antihypertensive agent is required, institutional practice must be followed.

Reference Therapy, Dose and Mode of Administration, Batch Number(s):

There will be no reference therapy in this trial.

Efficacy Endpoints:

The primary efficacy endpoints of this trial are:

- Median time and dose to attain the initial prespecified 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 prespecified target SBP range during the first 30 minutes of clevidipine infusion

Safety:

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

Pharmacology:

- Pharmacokinetic variables (half-life, area under the curve [AUC], volume

of distribution, clearance) established by noncompartmental analysis or sparse population methodology

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

The secondary efficacy endpoints of this trial are:

- The percentage of patients who reach the initial prespecified target SBP range without falling below the lower limit of the prespecified 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 prespecified target range at any time during the first 30 minutes and at any time during the entire study drug treatment period
- Percent change in SBP from baseline at each time point during the first 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 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 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 adverse events

Statistical Methods:

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. Statistical analyses will be performed using the following patient populations:

Safety population: all patients who are dosed with clevidipine. This will be the primary population used for the safety analyses.

Intent-to-Treat (ITT) population: all patients who have received clevidipine therapy, and have baseline and at least one post-baseline SBP measurements. This will be the primary population used for the efficacy analyses.

PK/PD population: all patients who are dosed with clevidipine and have at least one documented and evaluable blood concentration and/or SBP observation and documented dose records. Descriptive statistics and graphic display will be used to summarize the data collected in the case report form for overall and by cohort. Continuous variables will be summarized using mean, standard deviation, median, inter-quartile range, minimum and maximum. Categorical variables will be summarized using frequency and percentage. Time to event variables will be displayed using the Kaplan-Meier curve. The dose response relationship will be analyzed overall and by cohort. P-values and/or two-tailed 95% confidence intervals will be provided whenever appropriate to demonstrate the strength of the findings.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	adverse event
AHF	acute heart failure
ALT/SGPT	alanine aminotransferase/ serum glutamic-pyruvic transaminase
AST/SGPT	aspartate aminotransferase/ serum glutamic oxaloacetic transaminase
AUC	area under curve
AUC_{inf}	area under curve of the blood concentration to infinity
AUC_{last}	area under curve of the blood concentration to the last measurable concentration
BP	blood pressure
CH	controlled hypotension
C_{max}	maximum observed blood concentration
CL	total clearance
CL_{tot}	total clearance
CRF	case report form%
CV	coefficient of variation
DBP	diastolic blood pressure
DCF	data clarification form
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDL	high density lipoprotein
HR	heart rate
ICH	International Conference on Harmonization

ICU	Intensive Care Unit
IRB	Institution Review Board
ITT	intent-to-treat
IV	intravenous
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
kg	kilogram
LDL	low density lipoprotein
LC-MS/MS	liquid chromatography - mass spectrometry/ mass spectrometry
MAP	mean arterial pressure
max	maximum
MDCO	The Medicines Company
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
min	minimum
min.	minutes
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
MRT	mean residence time
n	number of patients
NDA	new drug application
NIC	nicardipine
NONMEM	nonlinear mixed-effect modeling
NTG	nitroglycerin
PCS	potentially clinical significant
PD	pharmacodynamics
CCI	CCI
CCI	CCI
PK	pharmacokinetics

Q	quartile
SAE	serious adverse events
SBP	systolic blood pressure
SD	standard deviation
SEM	standard error of mean
SNP	sodium nitroprusside
SVR	systemic vascular resistance
$t_{1/2}$	half-life
TBPR	target blood pressure range
TEAE	treatment emergent adverse event
T_{max}	time to reach $C_{max}\lambda_z$terminal rate
US	United States
VLDL	very low density lipoprotein
V_{SS}	volume distribution at a steady state
V_z	volume of distribution based in the terminal phase

1. INTRODUCTION

This protocol describes an open label dosing, efficacy and safety study evaluating the ability of clevidipine to rapidly control blood pressure in pediatric patients less than 18 years old, including adolescents, children, toddlers, and preterm and newborn infants.

Clevidipine has been studied in 22 completed clinical trials (4 Phase I, 10 Phase II, and 8 Phase III studies) [Clevidipine Investigator's Brochure, 2013[1]]. These studies included more than 2400 patients overall, of whom 1522 were clevidipine-treated patients.

To date, three case series [Towe and Tobias, 2010[5]] describing the use of clevidipine in the pediatric population have been carried out and published. These have included pediatric patients between 11 months and 18 years of age undergoing surgery for repair of congenital heart disease, excision of vasoactive tumors and spinal surgery. In the spinal surgery patients, clevidipine was used for controlled hypotension. In this series, clevidipine was shown to be effective in reaching and maintaining target blood pressure with minimal adverse events.

CCI [redacted]. This is the first study to investigate dosing, efficacy and safety of clevidipine in patients less than 18 years of age.

This study will be conducted in compliance with Good Clinical Practices (GCP) including the Declaration of Helsinki and all applicable regulatory requirements.

1.1. BACKGROUND

In patients undergoing surgery, persistent elevated blood pressure or sudden increases in systemic blood pressure perioperatively are important clinical problems. Anesthesiologists attempt to prevent, control and/or treat perioperative blood pressure (BP) elevations promptly in order to reduce the risk of perioperative mortality and morbidity. In general, perioperative BP elevations develop as a consequence of the activation of the sympathetic nervous system induced by stress of major surgery. The net effect of these autonomic adjustments is an increased systemic vascular resistance (SVR) and elevated arterial blood pressure.

Acute perioperative hypertension can cause a greater demand on the myocardium, an elevation in ventricular filling pressures, a reduction in subendocardial perfusion, and ischemia. In addition, surgical bleeding may be increased, with possible disruption of anastomotic sites. In adult patients certain types of surgery (e.g., coronary artery bypass surgery, aortic aneurysm repair, and carotid endarterectomy) are associated with high rates of postoperative hypertension. In patients undergoing elective general surgery, it was determined by Charlson et al[2] that intraoperative fluctuations in mean arterial pressure increased the probability of postoperative failure. They also reported that prolonged changes in perioperative blood pressure in patients undergoing elective non-cardiac surgery were

significantly related to increased complications. Basali et al[3] reported that patients who develop intracranial hemorrhage after craniotomy were more likely to have been hypertensive in the intraoperative and early postoperative periods. Therefore, the rationale for the treatment of hypertension perioperatively is based on the potential to reduce the risk of perioperative mortality and morbidity from both short- and long-term adverse effects.

Perioperative hypertension in the pediatric patient can be caused by renal failure or insufficiency, volume overload, or activation of the sympathetic nervous system. Patients with congenital heart disease and intracranial pathology may exhibit a higher likelihood of perioperative hypertension, and are more prone to have blood pressure problems with potentially more significant adverse outcomes. Once treatable and reversible causes of hypertension such as pain, hypercarbia, and hypoxemia are corrected, pharmacologic control of BP is indicated. This includes the use of intravenous antihypertensives that reverse the sympathetic system's increase in systemic vascular resistance by producing vasodilation. Additionally, controlled hypotension (CH), a deliberate reduction in blood pressure to reduce bleeding, transfusion therapy and better visualization of the surgical site, may also be utilized during surgery in children. Commonly used agents for both BP control and deliberate hypotension in infants and children include sodium nitroprusside (SNP), labetalol, and calcium channel antagonists, including nicardipine (NIC). These various pharmacologic strategies manifest a number of clinical limitations.

SNP dilates venous capacitance vessels and decreases preload, causing a decrease in cardiac output which predisposes patients to organ ischemia. It is frequently associated with tachyphylaxis, reflex tachycardia and, with renal insufficiency or renal failure especially with prolonged use, SNP may also cause cyanide toxicity. The potential for excessive hypotension and fluctuations in BP necessitate the use of invasive monitoring during administration. Labetalol is a mixed alpha and non-specific beta blocker. It has an onset of action of approximately 2 to 5 minutes, but also has a long duration of action; estimate from 2 to 4 hours. Labetalol's side effects include bradycardia, decreased ventricular function, bronchospasm and heart block. Nicardipine (NIC) is a calcium channel blocker with a long half-life that makes it difficult to titrate and its BP control action is difficult to reverse.

The pathophysiology of acute perioperative hypertension and control required during surgery require that an antihypertensive agent be arterial-selective, have a rapid onset and offset of action, be easy to titrate and have a predictable effect on the reduction of BP [Varon, 2008[4]]. Although these above mentioned agents possess some of these characteristics, none possess all of them.

Clevidipine was specifically and intentionally developed to address the limitations of other available IV antihypertensive therapies. Clevidipine is a rapidly-acting, vascular-selective, L-type calcium channel antagonist that lowers arterial blood pressure by reducing systemic vascular resistance. Its arterial selectivity allows for BP reduction with no adverse effects on heart rate or cardiac output. The quick offset of action is due to rapid metabolism by non-

specific blood and tissue esterases. Efficacy and safety have been well-documented in the adult population setting.

1.2. CLEVIDIPINE (CLEVIPREX®)

Clevidipine is a rapidly-acting, vascular-selective, L-type calcium channel antagonist that lowers arterial blood pressure by reducing systemic vascular resistance. It exerts a selective vasodilating action on arteriolar resistance vessels, but has no effect on venous capacitance vessels. Due to its fast onset and offset of effect on blood pressure, clevidipine can be easily titrated, allowing for effective, ongoing BP management.

1.2.1. Preclinical Studies

Clevidipine is classified as a short-acting, arterial-selective calcium channel antagonist since its primary effect is via inhibition of the calcium current in L-type calcium channels. Clevidipine is fifty times less potent in inhibiting myocardial contractility than in causing vascular smooth muscle relaxation, thereby illustrating that clevidipine is a vascular-selective calcium antagonist. At very high concentrations in vitro, clevidipine is more potent in inhibiting myocardial contractility than in depressing the spontaneous rate of depolarization in the sinus node or in prolonging atrioventricular conduction. Experiments in anesthetized dogs show that clevidipine reduces mean arterial pressure (MAP) due to a reduction in SVR, and that it does not exert any negative effects on cardiac contractility or conduction in the doses tolerated. Clevidipine causes a reflexogenic increase in heart rate in conscious rats and dogs but does not affect heart rate in anesthetized animals.

Clevidipine is rapidly hydrolyzed to its inactive metabolite in blood and extravascular tissues in the rat and dog. In experiments with rats, dogs and rabbits, clevidipine demonstrated a very short half-life, and reached steady-state blood concentrations within minutes after the start of infusion.

The general pharmacological studies of clevidipine have illustrated that it has a natriuretic/diuretic effect when given in a dose that only marginally lowers BP. This effect is similar to that of other dihydropyridines. At doses well above the therapeutic level, clevidipine inhibits gastrointestinal transport, which is also a characteristic of other calcium antagonists. Clevidipine is devoid of direct effects within the autonomic and central nervous systems and it does not interfere with neuromuscular transmission or skeletal muscle function. Clevidipine has no adverse pharmacological effects on respiratory, liver, or endocrine function or on bleeding time. It does not change body temperature.

In the animal toxicity studies, most findings could be attributed to the lipid content in the test formulation. The few effects related to exposure of clevidipine included small biochemical differences and organ weight deviations and a slight local irritative vascular effect. Most of these findings were related to the dose and/or duration of treatment and satisfactory safety

margins have been established. Study results indicate no clinically relevant risks of genotoxicity.

Further details on the preclinical studies with clevidipine are provided in the Investigator's Brochure [Clevidipine Investigator's Brochure, 2013[1]].

1.2.2. Clinical Studies

The clinical development program was comprised of 22 completed clinical studies (4 Phase I, 10 Phase II, and 8 Phase III studies) [Clevidipine Investigator's Brochure, 2013[1]]. These studies included over 2400 patients overall, of whom 1522 were clevidipine-treated healthy subjects or hypertensive patients including the following:

Four Phase I studies were conducted in 99 healthy volunteers to provide pharmacokinetic (PK), pharmacodynamic (PD), and safety/tolerability data. One of these studies, a QT/QTc study in 46 healthy volunteers was performed to establish the cardiac electrocardiogram (ECG) safety of clevidipine, and to provide further data documenting the tolerability and safety of a high therapeutic dose maintained continuously for approximately 24 hours.

Nine Phase II studies were conducted to obtain preliminary data on the effectiveness of clevidipine in 423 patients with hypertension treated in the setting of medical management (3 studies, 95 patients) or cardiac surgery (6 studies, 337 patients). One of these studies (TMC-CLV-06-01) was conducted in 61 medical patients with mild to moderate essential hypertension to investigate the PK/PD effects and safety of clevidipine during prolonged (≥72 hours) continuous infusion. Clinical safety and efficacy data were sufficient to permit the design of adequate and well-controlled Phase III studies.

An additional Phase II study, SPRINT (TMC-CLV-08-02) was completed post FDA marketing approval. This was an open-label, single-arm study that evaluated three different bolus doses of clevidipine (0.125 mg, 0.25 mg and 0.5 mg), in a total of 30 patients with hypertension undergoing elective cardiopulmonary bypass surgery. The study showed that clevidipine administered as an IV bolus was effective at rapidly reducing SBP in this population of cardiac surgery patients, with evidence of tolerability and a safety profile consistent with previous experience in other clinical settings.

Eight Phase III trials were conducted in a total of 1985 medical, surgical, neurocritical care and acute heart failure patients, 1078 of whom received clevidipine. All studies evaluated the overall benefit-risk relationship of clevidipine as follows:

- High-risk surgical patients (N=1720) with perioperative hypertension associated with cardiac surgery were treated with clevidipine (N=866), placebo (N=100), or the active comparators nitroglycerin (NTG), sodium nitroprusside (SNP), or nicardipine (NIC) (total comparator patients N=754) [ESCAPE-1 (TMC-CLV-03-01) and ESCAPE-2 (TMC-CLV-03-02); ECLIPSE-NTG (TMC-CLV-03-03), ECLIPSE-SNP (TMC-CLV-

03-04), and ECLIPSE-NIC (TMC-CLV-03-05)], all of which were submitted as part of the FDA New Drug Application (NDA) submission.

- High-risk medical patients with severe hypertension requiring BP lowering, most with evidence of end-organ dysfunction, presenting to the emergency department were treated with clevidipine (N=126) titrated to BP effect followed by at least 18 hours of continuous infusion in the VELOCITY trial (TMC-CLV-06-02).
- High-risk intracranial hemorrhage neurocritical care patients presenting to either the emergency department or neuro intensive care unit (ICU) with severe hypertension (N=35), and a subset of the total patients with intracranial pressure monitoring (N=7), were treated with clevidipine titrated to BP effect in the ACCELERATE trial (TMC-CLV-07-02).
- High-risk acute heart failure (AHF) patients presenting to the emergency department with severe hypertension and dyspnea (N=85) were treated with clevidipine titrated to BP effect in the PRONTO trial (TMC-CLV-08-01).

The clinical development program included mild-, moderate- and high-risk patient populations with respect to demographics, risk variables, and comorbidities. The duration of exposure to clevidipine is reflective of clinical practice in the management of patients with hypertensive urgencies/emergencies and perioperative hypertension. Patients enrolled in the program had high-risk features such as advanced age and comorbidities including myocardial ischemia due to coronary artery disease, heart failure, renal and hepatic dysfunction, peripheral vascular disease, chronic hypertension and diabetes.

The PK characteristics of clevidipine and the relationship between PK and PD have been studied. The findings demonstrate consistency of PK and PD behavior that is independent of infusion duration. Clevidipine has a direct effect and the rapid clearance determines ease and predictability of titration to desired effect as well as facilitates transition to oral therapy. No specific precautions are necessary with respect to patients with renal or hepatic impairment due to the route of metabolism.

The efficacy of clevidipine has been consistently established in all studies across all hypertensive patient populations. Rapid BP lowering effects were observed and a high success rate was achieved in titration to the desired BP targets. The appropriateness of the recommended dose range (2 mg/h up to 32 mg/h) is supported by the current prescribing information [Cleviprex Prescribing Information, December 08, 2011[8]].

Safety and tolerability has been examined in a large database of high-risk patients with multiple comorbidities and end-organ injuries. The safety of the starting dose was confirmed. The feasibility of safe use in the emergency room environment was established, in which clevidipine was administered by peripheral venous infusion with monitoring of effect by sphygmomanometer. No new issues were identified with respect to the incidence of

important clinical outcomes and adverse events (AEs). Subgroup analyses demonstrated consistent findings with the overall population analyses.

Evidence from the Phase III safety program in cardiac surgery patients with perioperative hypertension demonstrated an improvement in BP control achieved in patients managed with clevidipine compared to two agents commonly used in that setting (NTG and SNP). The additional post-hoc finding of an association between BP control and 30-day mortality suggests that a parenteral agent providing rapid and tight BP control may improve patient outcomes.

Further details of the clinical studies with clevidipine are provided in the Investigator's Brochure [Clevidipine Investigator's Brochure, 2013[1]].

1.2.3. Known and Potential Risks and Benefits

The lipid formulation of clevidipine has been well tolerated in all clinical studies to date. However, if strict aseptic precautions are not followed in the preparation and administration of clevidipine, accidental microbial contamination of the vial may occur. Septicemia may occur due to microbial growth within the vial contents followed by IV administration. This potential risk is mitigated by adherence with the recommended dosing and administration guidance provided to all investigators involved in the study.

Clevidipine contains approximately 0.2 g of lipid per mL (2.0 kcal/8.4 kJ). Lipid intake restrictions may be necessary for patients with significant disorders of lipid metabolism. For these patients, a reduction in the quantity of concurrently administered lipids may be necessary to compensate for the amount of lipid infused as part of the clevidipine formulation. Clevidipine is contraindicated in patients with defective lipid metabolism e.g., pathologic hyperlipemia, lipid nephrosis and acute pancreatitis if it is accompanied by hyperlipidemia. As part of monitoring of this clinical trial, blood chemistry for hepatic and pancreatic function will be performed to minimize these risks.

The most common adverse drug reactions (>2%) for clevidipine observed in patients were headache, nausea and vomiting [Cleviprex Prescribing Information, December 08, 2011[8]].

1.3. STUDY RATIONALE

Three previously conducted small case series in the perioperative setting have demonstrated the effectiveness and safety of clevidipine in the pediatric population aged 11 months to less than 18 years of age. These case series included infants and children undergoing surgery for repair of congenital heart disease and adolescents requiring controlled hypotension to minimize bleeding during spinal surgery. No significant adverse events during treatment were observed [Tobias et al[6]].

Given these favorable preliminary benefits and considering the limitations of other available IV antihypertensive, this study will sequentially determine the dosing including PK/PD,

efficacy, and safety of clevidipine for adolescents, children, toddlers and term and preterm infants.

1.4. DOSE RATIONALE

A population pharmacokinetic (PK) and pharmacodynamic (PD) model has been developed to describe the physiologic response (i.e., drop in systolic blood pressure, SBP [mmHg]) to clevidipine exposure in pediatric patients with moderate to severe acute hypertension.

Various dose regimens were simulated in pediatric patients with weights ranging from 2.5 kg up to 50 kg. CCI [redacted].

Adolescent patients (ages 12 to less than 18 years) will receive weight based doses ranging from CCI [redacted] to a maximum of CCI [redacted]. The appropriateness of lower starting weight-based doses of CCI [redacted] and CCI [redacted] and/or slower infusion rate of escalation will be considered as part of each DSMB review, which will be conducted after completion of each dosing cohort and prior to enrolling each subsequent cohort.

The above dosing rationale is supported by recently published case studies of the use of clevidipine in children [Tobias and Hoernschemeyer[7]].

1.5. STUDY POPULATION

The study population will be comprised of 80 pediatric male and female patients of any race undergoing an elective surgery requiring BP management with parenteral IV antihypertensive therapy. Patients will be enrolled in a stepwise approach according to the following age cohorts; 20 adolescent patients (12 to less than 18 years) and 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); 20 infants and toddlers (28 days to less than 24 months) and 20 preterm and newborn infants (0 to less than 28 days). To be eligible patients must be scheduled for a surgical procedure requiring a minimum of 1 hour of anesthesia, in which IV antihypertensive therapy to control BP is anticipated and an intra-arterial line for blood pressure monitoring is required. Written informed consent by parent or legal guardian and verbal assent by the patient as per institutional policy must be provided prior to initiating any study related procedures.

2. TRIAL OBJECTIVES AND PURPOSE

2.1. PRIMARY OBJECTIVES

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.

This will be accomplished by assessment of the median time and dose to attain a prespecified target SBP range during the first 30 minutes of clevidipine infusion, the percentage of patients achieving the prespecified range during the first 30 minutes of clevidipine infusion, as well as the pharmacokinetic variables established by sparse population methodology and pharmacodynamic variables. Safety will be assessed according to clinical laboratory parameters. Adverse events and serious adverse events (SAEs) will be assessed from time of consent through 7 days following termination of the study drug infusion.

2.2. SECONDARY OBJECTIVES

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

Additional assessments will include the percentage change in SBP from baseline at each time point during the first 30 minutes following initiation of clevidipine infusion.

Evaluation of efficacy after the initial 30 minute infusion period will include the percent change from baseline in SBP at each hour after the first 30 minutes of clevidipine infusion up to the cessation of infusion and the percentage of patients in whom the SBP is within target range at each hour after the first 30 minutes of clevidipine infusion.

Safety data will include:

- The percentage of patients who reach the initial prespecified target SBP range without falling below the lower limit of the prespecified 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 prespecified target range at any time during the first 30 minutes and at any time during the entire study drug treatment period
- The percent change from baseline in heart rate during the first 30 minutes of clevidipine infusion and during the rest of the treatment period; and
- The percentage of patients who require rescue therapy at any time during study drug treatment period

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. TRIAL DESIGN

3.1. TYPE/DESIGN OF TRIAL

This study is a Phase IV open-label trial in pediatric patients undergoing elective surgery requiring anesthesia ≥1 hour and for whom parenteral IV antihypertensive therapy for BP management is expected for at least 30 minutes. Approximately 80-100 patients are planned to be enrolled in a stepwise process at 2 centers within 24 months from initiation of the study. Patients will be screened between 0 and 7 days before their scheduled surgical procedure. Written informed consent by parent or legal guardian and verbal assent by the patient as per institutional policy must be provided prior to initiating any study related procedures. All eligible patients meeting all inclusion and none of the exclusion criteria will be enrolled to receive clevidipine.

This study will evaluate the dosing, efficacy and safety of clevidipine in 80 pediatric patients presenting for surgery and anticipated to require BP management with parenteral IV antihypertensive therapy during the surgical procedure.

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 remaining cohorts.

- 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).

A Data Safety Monitoring Board (DSMB) will be set up to monitor the safety and dosing on an ongoing basis for all cohorts. Following completion of the adolescent cohort, the DSMB will review the safety data and make any safety recommendations according to the DSMB Charter to the Sponsor prior to enrolling the remaining cohorts in a sequential order. The DSMB review of each completed cohort will be required before proceeding to the subsequent cohort to determine if it is appropriate to proceed with enrollment of subsequent cohorts and whether an adjustment in dosing scheme is required.

It is anticipated that there will be 10-20 enrolled patients per pediatric age group whose PK/PD parameters will be measured during the first 24-hour period. Up to 10 blood samples within the infusion window of 24 hours are planned for PK analysis, with samples taken prior to and shortly after infusion start, at least 4-5 samples taken during the infusion period, and 4 samples taken shortly following termination of infusion.

Multiple, timed BP measurements are required to be taken prior to and following PK sample collection. Accurate and well-timed BP readings will also be necessary to capture the

subject's response to infusion rate adjustments during the first 30 minute period and through study drug termination. To accommodate the frequency and precision required for this, blood pressure monitoring will be carried out using a peripheral arterial line, to allow for real-time heart rate and BP sampling while obtaining PK samples throughout the course of study drug titration and through the follow-up period. It is essential that the clock time of infusion pump devices, blood pressure monitors and clocks used to record the time of the PK sample be synchronized.

The investigator must pre-specify a target range for each patient prior to drug exposure for the desired reduction in SBP. This patient-specific target SBP range will be recorded in the electronic case report form (eCRF) and cannot be changed for the first 30-minute treatment period. The difference between the upper and lower limits of the prespecified target SBP range should be not less than 20 mmHg and not more than 40 mmHg.

Adolescent patients (ages 12 to less than 18 years) will receive an initial weight based dose of CCI ; 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 , CC , CCI , up to the maximum dose of CCI every 1.5 minutes until a SBP within the prespecified target range is reached. The initial dose for children, infant and toddler cohorts and the subsequent up-titration doses will be determined after an interim analysis of data from the preceding cohorts. 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. Per protocol dosing reflects clinical experience to date, additional clinical utility is typically not observed for doses above CCI .

Dosing in the remaining cohorts will be the same as adolescents unless information obtained from the previous cohorts suggests the need for modification of the starting dose and/or the incremental titration schema.

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 eCRF.

Patients who receive alternative intravenous rescue therapy after the first 30 minutes of 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). For 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, December 08, 2011[8]].

If treatment with an IV antihypertensive 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. Rescue therapy with IV antihypertensive treatment according to the standard of care will be determined by the investigator.

A DSMB will be set up to monitor the safety and dosing on an ongoing basis for all cohorts.

The DSMB will review the safety and dosing data from each cohort and make safety and dosing recommendations to the Sponsor according to the DSMB Charter prior to enrolling the remaining cohorts in sequential order. DSMB review of each completed cohort will be required before proceeding to the subsequent cohort.

In addition, an analysis to assess adequate precision of the efficacy findings will be performed at the end of each cohort to ensure that sample size for the following cohort is sufficient.

3.2. SCHEMATIC DIAGRAM OF TRIAL DESIGN

Screening Period (-7 to 0 days prior to enrollment)

- Informed consent and verbal assent of the patient per institutional policy
- Medical history, physical exam (including weight, height/length & prior medications)
- BP (SBP & DBP) and HR
- Labs: pregnancy test, hematology and serum chemistry (refer to Section 6.1 and Section 6.3)
- Pre-specified SBP Target Range, AE(s) and SAE(s) Reporting

↓

Treatment Period Phase 1: Initial Dosing Phase (0-1.5 minutes)

- BP (SBP & DBP) and HR (refer to Section 6.1 and Section 6.5.1)
- PK Samples 2, 3, 4 and PK Sample 5 (as applicable), taken immediately after BP and HR (refer to Section 6.5.1)
- Initiate Clevidipine infusion [redacted] for 1.5 minutes
- Concomitant Medications, AE and SAE Reporting

↓

Treatment Period Phase 2:
Titration & Maintenance Phase (>1.5–30 minutes & >30 minutes up to 96 hours)

- BP (SBP & DBP) and HR (refer to Section 6.1 and Section 6.5.2)
- PK Sample 4 and PK Sample 5 (as applicable), taken immediately after BP and HR (refer to Section 6.5.2)
- Serum Chemistry (refer to Section 6.1 and Sections 6.3 and Section 6.5.2)
- SBP Target Range changes after the first 30 minutes: any changes must be recorded (if applicable)
- Clevidipine titration schedule (Section 6.5.2)
- Concomitant Medications, AE and SAE Reporting

↓

Treatment Period Phase 3:
Transition & Termination Phase (Transition to oral to termination of infusion)

- BP (SBP & DBP) and HR (refer to Section 6.1 and Section 6.5.3)
- PK Sample 5 (as applicable) and PK Sample 6 taken immediately after BP and HR (refer to Section 6.5.3)
- Serum Chemistry (refer to Section 6.1, Section 4.4.1, Section 6.3 and Section 6.5.3)
- Termination of infusion or transition from clevidipine to oral antihypertensive approximately 1 hour prior to termination of study drug (refer to Section 6.5.3)
- Concomitant Medications, AE and SAE Reporting

↓

Follow-up Period (Post Study Drug Termination) 1 Hour (+30 minutes)

- BP (SBP & DBP) and HR (refer to Section 6.1 and Section 6.5.4)
- PK Samples 7, 8, 9, 10 each taken immediately after BP and HR (refer to Section 6.5.3 and Section 6.5.4)
- Serum Chemistry (refer to Section 6.1, Section 6.5.3 and Section 6.5.4)
- Concomitant Medications, AE and SAE Reporting

↓

Follow-up Period (Post Study Drug Termination) 12 Hour (+ 30 minutes)

- BP (SBP & DBP) and HR up to 12 hours (refer to Section 6.1 and Section 6.5.4)
- Concomitant Medications, AE and SAE Reporting

↓

Follow-up Period (Post Study Drug Termination) 24 hours (+ 30 minutes)

- Concomitant Medications, AE and SAE Reporting

↓

Follow-up Period (Post Study Drug Termination) 7 day (+1 day)

- AE and SAE Reporting

3.3. PRIMARY ENDPOINT(S)

The primary endpoint(s) of this trial are:

- Median time and dose to attain the initial prespecified 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 prespecified target SBP range during the first 30 minutes of clevidipine infusion
- Pharmacokinetic variables (half-life, area under the curve [AUC], volume of distribution, clearance) established by sparse population methodology
- Pharmacodynamic variables (relationship between change from baseline in SBP vs. blood concentration and infusion rate)
- Safety of a prolonged infusion of clevidipine (up to 96 hours) assessed according to clinical laboratory parameters, adverse events and serious adverse events (SAEs) will be assessed from time of consent through 7 days following termination of study drug infusion

3.4. SECONDARY ENDPOINT(S)

The secondary endpoints of this trial are:

- The percentage of patients who reach the initial prespecified target SBP range without falling below the lower limit of the prespecified 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 prespecified target range at any time during the first 30 minutes and at any time during the entire study drug treatment period
- Percentage change in SBP from baseline 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
- The percentage of patients in whom the SBP is within target range at each hour after the first 30 minute of clevidipine infusion
- Percent change from baseline in heart rate during the first 30 minutes of clevidipine infusion and the rest of the treatment period
- 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

- Percent change from baseline in SBP over the first 12 hours post study drug termination

3.5. EXPLORATORY ENDPOINT

Subgroup analysis of efficacy in patients with and without pre-existing hypertension. Additional analyses may be performed for efficacy and/or safety when applicable.

3.6. DATA SAFETY MONITORING BOARD

The safety information in clinical studies has demonstrated the safety of clevidipine in adults. A DSMB will monitor the safety and dosing on an ongoing basis for all patients. Following completion of each cohort, the DSMB will review the data and make safety recommendations according to the DSMB Charter to the Sponsor prior to enrolling the remaining cohorts in sequential order. DSMB review of each completed cohort will be required before proceeding to the subsequent cohort. The Sponsor will monitor the starting dose and titration schedule for each cohort. Details regarding data evaluation and process will be provided in the DSMB Charter.

3.7. MEASURES TO MINIMIZE/AVOID BIAS

3.7.1. Unblinded Study

This is an open label, single arm study. The primary endpoints are based on assessment of SBP and laboratory blood samples, which are measurements not likely to be subject to interpretation bias.

4. SUBJECT POPULATION

4.1. NUMBER OF PATIENTS

Approximately 80 pediatric patients scheduled for a surgical procedure who receive a minimum of 1 hour of anesthesia and are anticipated to require antihypertensive therapy to control BP will be studied at 2 centers located in the United States. It is anticipated that 80-100 patients (up to 20% overage) may need to be enrolled to achieve this goal.

4.2. INCLUSION CRITERIA

Patients may be included in the study if they meet all of the following criteria:

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

4.3. EXCLUSION CRITERIA

Patients will be excluded if they present with any of the following exclusion criteria:

1. Administration of an IV or oral antihypertensive agent within 2 hours prior to 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), hyperlipidemia, 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. Hemophilia or blood coagulation disorders
7. Any serious medical condition which, in the opinion of the investigator, is 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, is likely to interfere with study procedures or with the pharmacokinetics or pharmacodynamics of the study drug
10. Patient is 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 study drug initiation
12. Positive serum or urine pregnancy test for any female of childbearing potential
13. Participation in other clinical research studies involving the evaluation of other investigational drugs or devices within 30 days of enrollment
14. Patients who, for any reason, are deemed by the investigator to be inappropriate for this study
15. Patient is 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 may be re-screened for participation at any time if the exclusion characteristic has changed.

4.4. WITHDRAWAL CRITERIA

All patients or parent or legal guardian have the right to withdraw the patient at any point during treatment without prejudice. The investigator can discontinue any patient at any time if medically necessary. It will be documented whether or not each patient completed the clinical study. If, for any patient, study treatment or observations were discontinued, the reason will be recorded and the Sponsor should be notified promptly. Reasons for which a patient may discontinue participation in a clinical study are considered to constitute one of the following:

- Adverse event(AE)
- Death
- Patient or parent or legal guardian withdrew consent
- Physician decision
- Lost to follow-up
- Protocol violation
- Administrative problems

It is imperative to obtain complete follow-up data for all patients whether or not they receive their assigned treatment or have discontinued study drug. Every attempt should be made to collect follow-up information except for those patients who specifically withdraw consent to release of such information. All procedures and laboratory specimens or tests requested for evaluation following administration of the study drug should be carried out when possible, whether or not a patient continues to receive treatment according the protocol. Patients will not be replaced in this trial.

4.4.1. Withdrawal from Study Medication

The following data will be collected within 1 hour (+ 30 minutes) after the end of study drug infusion, provided the patient or parent or legal guardian did not withdraw the right for the Sponsor to use the patient's data:

- Physical examination
- Vital signs
- Serum chemistry including serum creatinine, triglycerides, lipase, total cholesterol, HDL, LDL, VLDL, ALT/SGPT, AST/SGOT, total bilirubin, lactate dehydrogenase, blood urea nitrogen, sodium, potassium, calcium, and magnesium
- AEs / SAEs
- Concomitant medications including oral and/or IV antihypertensive administration
- PK blood sample

In addition, any PK samples collected will be analyzed. The patient should continue to be followed through the follow-up phase of the study.

4.4.2. Withdrawal from Trial

If a study patient or parent or legal guardian withdraws informed consent or assent for the trial or is withdrawn from the trial by the investigator for any reason after termination of drug prior to discharge, an attempt should be made to collect the following safety information:

- Physical examination
- AEs/ SAEs
- Concomitant medications including oral and/or IV antihypertensive administration

Patients who are withdrawn during study drug IV infusion (treatment phase) should follow Section 4.4.1 above.

5. TREATMENT OF PATIENTS

5.1. STUDY MEDICATION

Clevidipine is being studied for the management of BP in pediatric patients less than 18 years of age through preterm and newborn infants undergoing an elective surgery requiring ≥ 1 hour of anesthesia.

Clevidipine injectable emulsion (hereafter referred to as clevidipine emulsion) is a single use parenteral product that contains a phospholipid emulsion. Clevidipine emulsion may be administered via peripheral vein or by central venous infusion employing a volumetric pump. The vial containing clevidipine emulsion should be gently inverted several times before use to ensure uniformity of the emulsion prior to connecting to the IV tubing. The infusion must be administered via a single dedicated line separate from any other medications. However, strict aseptic technique should always be used when administering clevidipine emulsion to reduce the risk of nosocomial infection. Consistent with the clinical development program to date, once the stopper is punctured, a vial must be used within 12 hours and any unused portion, including that which is currently being infused, should be discarded.

5.1.1. Clevidipine

Clevidipine is a dihydropyridine L-type calcium channel blocker developed for the reduction of blood pressure (BP) when rapid and predictable control is desired.

Clevidipine emulsion is intended for intravenous (IV) administration by infusion. Due to the rapidity with which clevidipine reduces BP, the dosage and rate of the clevidipine infusion is titrated to desired clinical effect.

Clevidipine is metabolized by hydrolysis in blood and tissues by non-specific carboxyl esterases to an inactive compound, which in turn is further, metabolized (mainly by glucuronidation) and excreted via the kidneys (~70%). No intact clevidipine is excreted. Thus, the metabolic degradation of clevidipine differs from that of other dihydropyridines, which are mainly metabolized by the cytochrome P450 system in the liver.

The high clearance and small volume of distribution result in very short half-lives for clevidipine. The half-lives of the two initial rapid phases that account for approximately 95% of the area under the curve (AUC) for blood concentration versus time after an IV bolus dose, ranged between 0.6 and 0.8 minutes and 2.2 and 2.3 minutes, respectively. The area under the terminal phase (half-life = 16–22 minutes) corresponded to between 3.3% and 5.7% of the total AUC after an IV bolus.

There is a linear relationship between dose rate and steady state blood concentration of clevidipine. The onset of effect is rapid after the start of a clevidipine infusion and the time required establishing steady state concentration and effect following an initial infusion or a change in administration rate is only 2 to 3 minutes. If the drug is discontinued, recovery of effect and return to baseline blood concentrations is rapid. In healthy volunteers, patients

with essential hypertension (with or without β-blockade) and post-cardiac surgery patients, more than a 50% recovery of effect (mean arterial pressure [MAP]) is achieved within 10 minutes following termination of the infusion.

Clevidipine reduces arterial BP dose-dependently by reduction of SVR. Clevidipine has no effect on central venous pressure. Stroke volume increases primarily as a result of afterload reduction with maintained cardiac preload. In post-cardiac surgical patients, a reflexogenic increase in heart rate (HR), typical of other antihypertensive therapies, has not been seen with clevidipine infusion. Cardiac output is maintained or improved.

5.1.2. Packaging and Labeling

The Medicines Company, Parsippany, NJ, USA will supply clevidipine emulsion to each investigative site packaged in boxes containing four single-use glass vials. Medication labels will comply with regulatory requirements. The storage conditions for the medication provided will be described on the medication label.

5.1.3. Storage

Clevidipine emulsion must be stored refrigerated in a secure enclosure at 2-8°C and should not be frozen, as specified in the Pharmacy Manual. Access should be strictly limited to the pharmacists and their designees or by investigators or designated study personnel if located outside of the pharmacy. Neither the pharmacists, investigators nor any designees may provide clevidipine to any subject not participating in this protocol and enrolled after full subject eligibility has been confirmed. Clevidipine emulsion will be stored in a secure cabinet in the Pharmacy or other hospital approved location under the appropriate conditions as specified in the Pharmacy Manual.

5.1.4. Accountability

The investigator or designee must maintain an inventory record of all vials of clevidipine emulsion received and all vials administered to assure the regulatory authorities and the Sponsor that the investigational drug labeled for use in the pediatric study will not be dispensed to any person who is not a patient under the terms and conditions set forth in this protocol. Drug accountability forms and/or specific instructions can be found in the Pharmacy Manual.

The clevidipine emulsion supplied for use in this study is to be prescribed only by the principal investigator or designated sub-investigators and may not be used for any purpose other than that outlined in this protocol.

During this study, all used (e.g., empty vials) and unused study drug containers will be kept until the study monitor has reviewed the drug accountability records.

Upon study drug inventory and review of the accountability records by the monitor at the end of the study, unused clevidipine emulsion will be destroyed onsite based on their drug

destruction policy OR returned to the packaging and labeling facility for destruction. In the event that clevidipine emulsion needs to be returned for any other reason, the site will receive a written request listing the drug lot number(s) to be returned and the reason for the return request.

5.2. CONCOMITANT MEDICATIONS

5.2.1. Required Concomitant Medication(s)

There are no required concomitant medications for this study. Concomitant medications, including anesthetic agents used as part of standard of care, will be recorded in the eCRF per the Schedule of Assessments (Section 6.1).

5.2.2. Prohibited Concomitant Medications

The following medications are prohibited and should not be administered to the patient within 2 hours prior to receiving treatment with clevidipine:

1. Methylphenidate
2. Aripiprazole and other atypical anti-psychotics
3. Calcium channel blockers
4. All other antihypertensive agents used for BP control

This is a study of an IV antihypertensive agent in a pediatric surgical population. Use of non-study drug medications and treatment procedures that affect the BP are discouraged during study drug administration, especially during the initial 30-minute period of study drug treatment. It is anticipated that an alternative antihypertensive agent(s) as rescue therapy will only be used if the study drug does not adequately lower BP. If a rescue therapy is used, it must be recorded in the eCRF, and the reason for such use must be documented.

5.2.3. Permitted Concomitant Medication(s)

1. Oral contraceptives will be permitted during the study for females of child-bearing potential
2. Beta-adrenergic blockers used specifically for reflex tachycardia
3. Ace inhibitors for volume overload

6. SCHEDULE AND SEQUENCE OF PROCEDURES

The Schedule of Assessments (Section 6.1 and Table 1) summarizes the study tests and procedures by time point. This study is comprised of three consecutive periods: a screening period, a treatment period, and a follow up period. The maximum duration of a patient's participation on study is approximately 18 days (screening up to 7 days, study drug administration up to 4 days and follow-up to 7 days).

The screening period begins from the time patients are consented for elective surgery to immediately prior to administration of study drug. The screening period consists of obtaining informed consent, confirming patient eligibility and collecting baseline assessments. During this period, a medical history (including all medications taken) and a physical examination (including height, length and weight) will be performed. Laboratory assessments (Section 6.3) including a pregnancy test for girls of childbearing potential will be performed. HR and BP measurements will be performed. With the exception of the pregnancy test, results of the laboratory tests are not required prior to administering study drug.

Prior to study drug administration, HR and BP measurements will be recorded. These will serve as the baseline HR and BP. Once a patient is deemed eligible a prespecified SBP target range must be identified prior to initiation of study drug treatment and recorded in the patient's medical record. The target range will later be entered into the eCRF.

The study drug infusion will commence following:

- Establishment of stable anesthetic condition (minimal change in anesthetic drug concentration and dose)
- Observation of stable vital signs following skin incision

The treatment period occurs from initiation of study drug up to 96 hours. This period is split into 3 phases for study drug administration. Initial dosing phase from 0 to 1.5 minutes; maintenance phase from > 1.5 to 30 minutes up to 96 hours and study drug transition phase defined as the transition and/or cessation of infusion.

BP and HR will be measured and PK samples will be obtained throughout this period. Multiple, timed BP measurements are required to be taken prior to and following PK sample collection. Accurate and well-timed BP readings will also be necessary to capture the patient's response to infusion rate adjustments during the first 30 minute period and through study drug termination. To accommodate the frequency and precision required for this, physiologic blood pressure monitoring will be carried out using a peripheral arterial line, to allow for real-time heart rate and BP sampling while obtaining PK samples throughout the course of study drug titration and through the follow-up period. It is essential that the clock time of infusion pump devices, blood pressure monitors and clocks used to record the time of the PK sample be synchronized.

Serum chemistry (Sections 6.1 and 6.3) will be assessed. Concomitant medications, AEs and SAEs will be monitored throughout the study period and concludes on day 7 in the follow-up period. If appropriate, patients will be transitioned to oral therapy one hour prior to termination of clevidipine (Section 6.5.3).

The follow-up period is divided into these time points following study drug termination: 1 hour follow-up, 12 hour follow-up, 24 hour follow-up and 7 day follow-up. The 1 hour time point starts from discontinuation of study drug until 1 hour (+ 30 minutes) post study drug termination. During this period, concomitant medications, serum chemistry, BP, HR and PK samples (PK Samples 7, 8, 9, 10 – Table 1) will be obtained and AE and SAEs will continue to be monitored and recorded. During the 12 hour time point (+ 30 minutes) period BP, concomitant medications, AEs and SAEs will continue to be monitored and recorded. During the 24 hour (+ 30 minutes) time point period, concomitant medications, AE and SAEs will be monitored and recorded. The 7 day (+1 day) follow-up time point period occurs on day 7 (+1 day) post study drug termination. The 7 days follow-up will occur by phone (if applicable) to monitor and record AE and SAEs.

6.1. 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 (Section 6.3)	X[2]							
Serum chemistry every 24 hours (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 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 1) 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 1 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 1: 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 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	1 hour (+30 minutes) post final termination of the clevidipine infusion

6.2. GENERAL CONDUCT OF THE TRIAL

Written informed consent will be obtained for this study by the principal investigator or sub-investigator from all patients or parent or legal guardian, with verbal assent obtained from children as per Institutional Review Board's (IRB's) policy before the performance of any protocol-specific procedures.

Multiple, timed BP measurements are required to be taken prior to PK sample collection. Accurate and well-timed BP readings will also be necessary to capture the patient's response to infusion rate adjustments during the first 30 minute period and through study drug termination. To accommodate the frequency and precision required for this, blood pressure monitoring will be carried out using a peripheral arterial line, to allow for real-time heart rate and BP sampling while obtaining PK samples throughout the course of study drug titration and through the follow-up period. It is essential that the clock time of infusion pump devices, blood pressure monitors and clocks used to record the time of the PK sample be synchronized.

6.3. SCREENING PERIOD (DAYS -7 TO 0)

The approved informed consent form may be signed up to two weeks prior to schedule screening procedures.

The following procedures will be performed within 0 to -7 days prior to enrollment:

- Informed consent and verbal assent: Written informed consent will be obtained for this study by the principal investigator or sub-investigator from all patients or parent or legal guardian, with verbal assent obtained from children as per IRB policy before the performance of any protocol-specific procedures are performed.
- Medical history
- Physical examination (including height/length and weight)
- Prior medications
- A pregnancy test for girls of childbearing potential only
- Hematology including red blood cells, hemoglobin, hematocrit, white blood cells, and platelets
- Serum chemistry including serum creatinine, triglycerides, lipase, total cholesterol, HDL, LDL, VLDL, ALT/SGPT, AST/SGOT, total bilirubin, lactate dehydrogenase, blood urea nitrogen, sodium, potassium, calcium, and magnesium

The following procedures are required to be performed *up to 30 minutes before* administration of study drug.

- Baseline PK Sample 1 (Table 1), taken up to 30 minutes prior to start of study drug infusion
    - BP and HR
    - PK Sample 1 (taken immediately following BP and HR measurements)

Note: The actual time of the BP, HR and PK sample should be recorded. The clocks used for these measurements should be synchronized (e.g., when the clock on the BP and HR device reads 13:01, the clock used to record the PK sample should also read 13:01).

The following procedures are required to be performed *just prior to* administration of study drug.

- Set prespecified SBP target range and document in patient's medical record
- Enrollment via IVRS/IWRS
- AE(s) and SAE(s)

6.4. ENROLLMENT

Enrollment should only occur once patient informed consent (and verbal assent, if applicable) is/are obtained and results of study specific laboratory tests listed in Section 6.3 have been reviewed. The site will enroll patients through an Interactive Voice/Web Response System (IVRS/IWRS), which will request specific information to confirm eligibility. Once eligibility is confirmed, the system will provide the site with the patient ID number that will be used as the patient's identifier throughout the trial.

6.5. TREATMENT PERIOD

The treatment period is split into 3 phases for study drug administration. An initial dosing phase is followed by a titration and maintenance phase. The final treatment phase is the transition/termination phase where patients may be switched to an oral medication prior to cessation of study drug.

6.5.1. Initial Dosing Phase, 0-1.5 minutes

During this phase of the treatment period, adolescent patients will receive clevidipine via IV infusion at an initial rate of CCI [redacted]. This initial rate will be maintained for the first 1.5 minutes. The initial dose for each of the subsequent age cohorts will be modified, if necessary, based on the recommendation of the DSMB. At 1.5 minutes after the first dose titration, BP and HR will be measured, immediately followed by PK Sample 3, which will be taken from the indwelling arterial line within a 30 second window after BP and HR are obtained (ie, 1.5 min. – 2.0 min.).

The following assessments will be performed during the Initial Dosing Phase of the treatment period:

- Baseline PK Sample 1 (Table 1), taken up to 30 minutes prior to start of study drug infusion
- 1.5 minutes *post-initiation* of clevidipine infusion
  - BP and HR
  - PK Sample 2 (Table 1), taken immediately following BP and HR measurements (+30 seconds)
- Concomitant medications

Note: The actual time of the BP, HR and PK sample should be recorded. The clocks used for these measurements should be synchronized (e.g., when the clock on the BP and HR devices reads 13:01, the clock used to record the PK sample should also read 13:01).

6.5.2. Dose Titration and Maintenance Phase, >1.5 minutes up to 96 hours

If the SBP range is not achieved within 1.5 minutes of the initial dose, the clevidipine IV infusion may be up-titrated (after PK Sample 2). At 1.5 minutes after this first dose titration, BP and HR will be measured, immediately followed by PK Sample 3, which will be taken from the indwelling arterial line within a 30 second window after BP and HR are obtained (ie, 1.5 min. – 2.0 min.). If the target SBP range is not achieved within 1.5 minutes of the first dose titration, the clevidipine IV infusion may be up-titrated (after PK Sample 3) per the proposed pediatric dosing schema, every 1.5 minutes (+ 30 second window where a PK sample is required). Dosing is at the discretion of the investigator and as tolerated by the patient, according to need, to achieve a SBP within the prespecified target range. Once the target range is achieved, BP and HR will be measured, immediately followed by PK Sample 4, taken from the indwelling arterial line within a 30 second window after BP and HR are obtained (ie, 1.5 min. – 2.0 min.).

The maximum clevidipine infusion rate of CCI cannot be exceeded. The clevidipine infusion rate may also be decreased as necessary at the discretion of the investigator to maintain SBP within the target range. 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.

After the initial 30 minutes, it may be necessary to alter the desired SBP target range over the course of the remaining treatment period. Any change in SBP target range must be recorded in the eCRF. It may also be necessary to adjust the dose titration up or down as needed at the discretion of the investigator to maintain SBP within the target range. BP and HR measurements are to be recorded according to the schedule below.

Clevidipine infusion may be administered continuously for up to a maximum duration of 96 hours. Clevidipine may also be terminated at any time for safety reasons. 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

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. Patients who receive rescue therapy along with clevidipine may continue in the study. The alternative agent should be chosen per the institutional practice. 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 as determined by the principal investigator.

If an additional/alternative IV antihypertensive agent is required, the clevidipine infusion may be down-titrated or terminated after initiation of the antihypertensive infusion in order to achieve the desired blood pressure level. If a patient is receiving rescue therapy with an IV antihypertensive treatment *and* transition to an oral antihypertensive agent is required, institutional practice must be followed. An alternative/additional IV antihypertensive agent that is administered as 'rescue therapy' will be recorded as rescue therapy in the eCRF. The following assessments will be performed during the titration and maintenance phase:

>1.5 Minutes – 30 Minutes Post Study Drug Initiation

- PK Sample 3: obtain 1.5 minutes after the first dose titration of study drug (taken in the order below)
  - BP and HR
  - PK Sample 3 (Table 1), taken immediately following BP and HR measurements
- Then, every 1.5 minutes for the remaining first 30 minutes post-study drug initiation:
  - BP and HR
- PK Sample 4: obtain once target range is achieved, or at 30 minutes if target range is not achieved (taken in the order below):
  - BP and HR
  - PK Sample 4 (Table 1), taken immediately following BP and HR measurements
  - BP and HR**,** taken every 1.5 minutes for the remaining first 30 minutes post-study drug initiation, as instructed above.

- PK Sample 5: only taken if transition to an additional antihypertensive is desired and concurrent administration is needed prior to the end of the first 30 minutes (taken in the order below)
  - BP and HR
  - PK Sample 5 (as applicable): taken immediately after BP and HR and before beginning administration of an additional antihypertensive agent
  - BP and HR, taken every 1.5 minutes, as instructed above, for the remaining first 30 minutes post-study drug initiation if the PK Sample 5 is obtained prior to the end of the first 30 minute period.

Note: The actual time of the BP, HR and PK sample should be recorded. The clocks used for these measurements should be synchronized (e.g., when the clock on the BP and HR devices reads 13:01, the clock used to record the PK sample should also read 13:01).

>30 Minutes (and up to 96 hours) Post-Study Drug Initiation

- BP and HR
  - every 10 minutes for the next 1 hour
  - every 30 minutes for the next 2 hours
  - once every hour until study drug is terminated (up to 96 hours)
  - 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.
- PK Sample 5: only taken if transition to an additional antihypertensive is desired and concurrent administration at any time >30 minutes and up to 96 hours (taken in the order below)
  - BP and HR
  - PK Sample 5 (as applicable): taken immediately after BP and HR and before beginning administration of an additional antihypertensive agent
  - BP and HR, taken as instructed above
  - BP and HR – to continue as instructed above
- Serum chemistry (Section 6.3) every 24 hours (+ 1 hour) from initiation of study drug infusion (up to 96 hours) or at the termination of study drug infusion if study drug is administered for less than the 24 hours
  - Concomitant medications
- AE(s) and SAE(s)

Note: The actual time of the BP, HR and PK sample should be recorded. The clocks used for these measurements should be synchronized (e.g., when the clock on the BP and HR devices reads 13:01, the clock used to record the PK sample should also read 13:01).

All assessments above (except PK) should be performed again if clevidipine is restarted for any reason.

6.5.3. Transition and Termination Phase, Transition to Oral to Study Drug Termination

For transition to oral therapy, approximately 1 hour prior to the anticipated cessation of clevidipine infusion, the oral antihypertensive agent may be administered. At any time following administration of the oral antihypertensive agent, the clevidipine continuous IV infusion may be down-titrated or terminated in order to achieve the desired blood pressure level.

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

If an additional/alternative IV antihypertensive agent is required, the clevidipine infusion may be down-titrated or terminated after initiation of the antihypertensive infusion in order to achieve the desired blood pressure level. An alternative/additional IV antihypertensive agent that is administered as 'rescue therapy' will be recorded as rescue therapy in the eCRF.

A PK sample will be taken just prior to discontinuation of study drug. Immediately before study drug termination, BP and HR will be measured, immediately followed by PK Sample 6, which will be taken from the indwelling arterial line within a 30 second window after BP and HR are obtained.

The following assessments will be performed during transition phase:

- BP and HR
  - at least every hour until study drug is terminated (up to 96 hours)
- PK Sample 5: only taken if transition to an additional antihypertensive is desired and concurrent administration at any time >30 minutes and up to 96 hours (taken in the order below)
  - BP and HR
  - PK Sample 5 (as applicable): taken immediately after BP and HR and before beginning administration of an additional antihypertensive agent
  - BP and HR, taken as instructed above

- PK Sample 6: obtain immediately prior to study drug termination (taken in the order below)
  - BP and HR
  - PK Sample 6, taken immediately after BP and HR
  - BP and HR – to continue, as instructed above, every hour until study drug is terminated
- Serum chemistry (Section 6.3) every 24 hours (+ 1 hour) during study drug administration (up to 96 hours).
- Concomitant medications
- AE(s) and SAE(s)

Note: The actual time of the BP, HR and PK sample should be recorded. The clocks used for these measurements should be synchronized (e.g., when the clock on the BP and HR devices reads 13:01, the clock used to record the PK sample should also read 13:01).

6.5.4. Follow-Up Period

The follow-up period is divided into these time points following study drug termination: The 1 hour time point is from study drug termination to 1 hour (+ 30 minutes) post study drug termination. The 12 hour, 24 hour and 7 day time points occur from 12 hours (+ 30 minutes), 24 hours (+ 30 minutes) and 7 days (+/- 1 day) post study drug termination, respectively. During this phase of the study, 4 PK samples will be taken: PK Sample 7 taken 0.5 minutes post study drug termination, PK Sample 8 taken at 3 minutes post study drug termination, PK Sample 9 taken at 15 minutes post study drug termination and PK Sample 10 taken 1 hour post study drug initiation. For all samples, BP and HR will be measured immediately followed by the PK blood draw, which will be taken from the indwelling arterial line within a 30 second window after BP and HR are obtained.

The following assessments will be performed during the Follow-up Period:

- BP and HR
  - measured at least every 15 min. until study drug has been stopped for 60 min. then at least every hour until study drug has been stopped for 12 hours post study drug termination
- PK Samples 7, 8, 9, 10: taken at 0.5 min. (PK Sample 7), 3 mins (PK Sample 8), 15 min (PK Sample 9) and 1 hours (+ 30 minutes) (PK Sample 10) post study drug termination (taken in the order below)
  - BP and HR
  - PK Sample

  - BP and HR – to continue at least every 15 min. until study drug has been stopped for 60 min. then at least every hour until study drug has been stopped for 12 hours post study drug termination, as instructed above

- Serum chemistry (Section 6.3) within 1 hour (+ 30 minutes) of termination of study drug.
- Concomitant medications through 24 hours post study drug termination (update if ongoing medications through day 7)
- AEs and SAEs through 24 hours post study drug termination (update if ongoing AEs through day 7 [+1 day])

Note: The actual time of the BP, HR and PK sample should be recorded. The clocks used for these measurements should be synchronized (e.g., when the clock on the BP and HR devices reads 13:01, the clock used to record the PK sample should also read 13:01).

Participation in the study is complete after day 7 follow-up visit is completed; all ongoing SAEs have been followed to resolution.

7. PROTOCOL ASSESSMENTS

7.1. ASSESSMENT OF SAFETY

7.1.1. Adverse Events

All patients with adverse events (AEs) will be carefully monitored for AE by the investigator during the entire study. All AEs and SAE information and the treatment provided during the study must be documented in source and will be captured in the electronic Case Report Form (eCRF).

All AEs and SAEs will be assessed and documented from time of consent through 7 days post study drug termination.

Those events that are serious in nature must be reported to The Medicines Company in an expedited manner (Section 8 for definitions and reporting requirements).

Patients experiencing adverse events should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the patient if necessary.

The AEs will be assessed and reported as detailed in Section 8. The investigator is responsible for evaluation and documentation of each AE or SAE occurring during the study. The investigator will inform the Sponsor about all AEs, independent of their relationship with the study medication. AEs being reported by the patient as well as laboratory findings outside normal ranges (e.g., serum chemistry, hematology, urinalysis) or other examination results deviating from normal values (e.g., blood pressure, pulse, 12-lead ECG, etc.), which are considered as clinically relevant by the investigator, must be reported to the principal investigator.

7.2. ASSESSMENT OF EFFICACY

7.2.1. Blood Pressure

7.2.1.1. Screening Period

Screening period is 0-7 days prior to surgery and BP (SBP, diastolic blood pressure [DBP]) measured using an intra-arterial catheter with electronic transducer. BP and other hemodynamic measurements will be obtained as specified in this protocol.

7.2.1.2. Screening Period immediately prior to study drug administration

BP (SBP, DBP) will be recorded at 60 sec, 45 sec, 30 sec, and 0 sec prior to study drug initiation. These BP measurements (SBP, DBP) will serve as the basis for determining target SBP range before the start of study drug.

7.2.1.3. Initial Dosing Phase 0-1.5 minutes

BP will be measured at 1.5 minutes post initiation of study drug and prior to the PK sample draw.

7.2.1.4. Titration and Maintenance Phase 1.5–30 minutes and >30 minutes up to 96 hours

BP will be measured every 1.5 minutes for a period of 30 minutes and prior to each PK sample draw.

BP will be measured every 10 minutes for the next 1 hour, then every 30 minutes for the next 2 hours, at least every 1 hour until the study drug is terminated (up to 96 hours) and prior to each PK sample draw.

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.

7.2.1.5. Transition and Termination Phase

BP will be measured every 1 hour until study drug is terminated (96 hour maximum duration of study drug).

7.2.1.6. Follow-up Phase 12 hours after first dose

BP will be measured at least every 15 minutes until study drug has been stopped for 60 mins, and then at least every hour until study drug has been stopped for 12 hours.

7.2.2. Concomitant Medication

The objective of monitoring concomitant medications to control BP is to determine the efficacy of clevidipine as monotherapy.

7.3. ASSESSMENT OF PHARMACODYNAMICS

BP will be measured at the time points specified in Section 7.2.1. Pharmacodynamic variables (the changes from baseline in SBP and its relationship with blood concentration of clevidipine and infusion rate) will be assessed.

7.4. ASSESSMENT OF PHARMACOKINETICS

7.4.1. Blood Sample Collection

Blood samples for determination of the blood concentrations of clevidipine and its inactive carboxylic acid metabolite M1 (H152/81) will be obtained from an intra-arterial catheter distant from the drug administration site, within 30 minutes before initiating clevidipine infusion; at 1.5 min post initiation of infusion before dose titration; right before the 2nd dose titration; once target BP is reached or at 30 minutes after the initial start of clevidipine infusion, whichever comes first; right before transitioning to another antihypertensive agent (if applicable); and at a time point just before the infusion

cessation. Blood samples will also be obtained at 0.5, 3 and 15 minutes, and 1 hour post end of clevidipine infusion for determination of the blood concentrations of clevidipine and M1 (Table 1 -).

Blood sample preparation, handling, storage and shipment will be carried out according to the PK manual provided by PPD . Briefly, an aliquot of 0.5 mL blood will be directly collected into the sample collection tube which contains the stabilizing reagents. After mixing, the blood samples will be stored at -70 ^{o}C or -20 ^{o}C.

The concentrations of clevidipine and M1 will be analyzed at PPD using validated liquid chromatography - mass spectrometry (LC-MS/MS) methods. PK variables (half-life, area under the curve [AUC], volume of distribution, clearance) will be established by sparse population methodology. Additional variables may be calculated if warranted by the data.

8. ADVERSE EVENTS

8.1. DEFINITIONS

8.1.1. Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Planned hospital admissions and/or surgical operations for an illness or disease that existed before the drug was given or the subject was randomized in a clinical study are not to be considered AEs.

Patients experiencing adverse events should be followed clinically until their health has returned to baseline status or until all parameters have returned to normal or have otherwise been explained. It is expected that the investigator will provide or arrange appropriate supportive care for the subject if necessary.

8.1.1.1. AE severity

The severity of an AE and the relationship to study drug will be assessed by the investigator. The investigator should ensure that any subject experiencing an AE receives appropriate medical support until the event resolves.

Adverse events (AE) will be graded on a 3-point scale and reported as indicated on the case report form. The intensity of an AE is defined as follows:

1 = Mild: Discomfort noticed, but no disruption to daily activity.

2 = Moderate: Discomfort sufficient to reduce or affect normal daily activity.

3 = Severe: Inability to work or perform normal daily activity.

8.1.1.2. Study drug causality

The relationship of an AE to study treatment will be assessed with consideration to the following criteria:

- Temporal relationship to the initiation of study medication
- Response of the event to withdrawal of study medication
- AE profile of concomitant therapies
- Clinical circumstances during which the AE occurred
- Patient’s clinical condition and medical history

Categorization* of causality will be designated by the investigator as stated below:

1. **Unrelated** - A clinical event, including laboratory test abnormality, reported as an adverse reaction, which lacks a reasonable time sequence between study drug administration and the occurrence of the event(s) or for which medical history, concomitant medications or other drugs provide a more likely explanation. Response to withdrawal of the study drug should not support a relationship between the study drug and the event.
2. **Unlikely related** - A clinical event, including laboratory test abnormality, with a temporal relationship to study drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
3. **Possibly related** - A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the study drug, which may possibly be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Information on study drug withdrawal may be lacking or unclear. Re-challenge information is not required to fulfill this definition.
4. **Definitely related** - A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to study drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study drug (de-challenge) should be clinically plausible. The event must be clinically definitive using a satisfactory re-challenge procedure if deemed necessary.

* For the purposes of regulatory reporting, categories '3' and '4' will be considered "related."

8.1.2. Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening, i.e., the subject was, in the opinion of the investigator, at immediate risk of death from the event as it occurred (it does not include an event that, had it occurred in a more severe form, might have caused death),
- Results in a significant, persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life,
- Requires in-subject hospitalization or prolongs hospitalization,

- Is a congenital anomaly/birth defect, or
- Is another medically significant event that, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above (e.g., allergic bronchospasm requiring intensive treatment in an emergency department or home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse).

A distinction should be drawn between serious and severe AEs. Severity is an estimate or measure of the intensity of an AE, while the criteria for serious AEs are indications of adverse subject outcomes for regulatory reporting purposes. A severe AE need not necessarily be considered serious and a serious AE need not be considered severe. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a myocardial infarction that may be considered minor could also be an SAE if it prolonged hospitalization.

When death occurs, the cause of death must be reported as an SAE. “Fatal” will be reported as the outcome for these events.

8.1.3. Additional Reporting Requirements

Occurrences of events of overdose, drug misuse and drug abuse are considered “important medical events” that should also be reported within 24 hours using appropriate reporting form. These events should be reported regardless of their association with other adverse events or serious adverse events.

- Abuse of a medicinal product: Persistent or sporadic, intentional excessive use of medicinal products which is accompanied by harmful physical or psychological effects [DIR 2001/83/EC Art 1(16)].
- Misuse: Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or not within the legal status of its supply (e.g., without prescription for medicinal products subject to medical prescription).
- Overdose: Administration of a quantity of a medicinal product given per administration or per day which is above the maximum recommended dose according to the reference safety information for the investigational product or comparator as applicable. This also takes into account cumulative effects due to overdose.

8.1.4. Reporting Events of Pregnancy

Occurrences of pregnancy in a study subject or study subject’s partner should also be reported within 24 hours using the Pregnancy Reporting Form. In cases where a

pregnancy occurs with a Serious Adverse Event, the SAE Report Form should be used to report the SAE and the Pregnancy Reporting Form should be used to report the pregnancy. When a pregnancy occurs without any intercurrent SAE, the Pregnancy Reporting Form may be submitted alone. The pregnancy must be followed through to conclusion. Any pregnancy discovered from the time of consent to follow-up need to be reported.

8.1.5. Complications of the Disease Under Study

Certain symptoms are considered typical outcomes of pediatric surgery and thus are expected side effects in pediatric surgery. Clinical events that are considered standard post-operative occurrences will be reported as AEs if they are considered untoward or unfavorable. In cases where the event is not considered as untoward or unfavorable it must be recorded as such in the source document. Consistency in reporting adverse events from all participating sites will be ensured through appropriate training and monitoring and investigators will be required to report all untoward or unfavorable events as adverse events based on their clinical judgment.

8.2. PROCEDURE FOR NON-SERIOUS ADVERSE EVENT RECORDING

All non-serious AEs that occur from the time of signing informed consent through 7 days post study drug termination must be recorded on the source documents and eCRF provided by the Sponsor, regardless of causal relationship to study drug.

8.3. PROCEDURE FOR SERIOUS ADVERSE EVENT REPORTING

All SAEs that occur from consent up to 7 days following study drug termination must be reported to The Medicines Company (MDCO) within 24 hours of awareness of the event using the provided study specific SAE Report Form. The completion and processing of the SAE Report Form (paper or electronic) should be per the instructions in the provided SAE Report Form completion guidelines. In addition to completing the SAE Report Form, each SAE must be entered on the appropriate page of the CRF.

The investigator must assess the causality for each SAE.

MDCO will contact the investigator, if necessary, to clarify any of the event information. The investigator should provide any follow-up information for the event to MDCO as soon as it becomes available.

If the investigator is notified of a SAE that occurs post-study period, that he or she wishes to report to the Sponsor (e.g., an event suspected to be causally related to study drug), the event should be reported through the process described above.

Where appropriate, if required by local regulations or procedures, the investigator should report these events to the Institutional Review Board (IRB)/Ethics Committee (EC) and/or national regulatory authority.

9. DATA COLLECTION

An electronic data capture (EDC) system will be used for this trial. All users will be trained on the technical features of the EDC as well as the content of the electronic case report form (eCRF) by qualified personnel prior to gaining access to the EDC. A UserID/Password will be granted after training. This ID is not to be shared amongst the study staff. All users must have a unique account to enter or review data. The eCRF should be filled out by the site within 5 days after completion of the 24 hour assessment. It is not expected that the eCRF will serve as source for any data collected in the trial. If there is a reason for a site to do so, it must be approved by the Sponsor and documented in the site files.

Prior to the database being locked, the investigator or designee will review, approve and electronically sign/date each completed eCRF. This signature serves as attestation of the Investigator's responsibility for ensuring that all data entered into the eCRF are complete, accurate and authentic. After the end of the trial, a copy of the data will be provided to the site. This copy will contain the final data, an audit trail of activity on the data, and any queries and answers that were posted for data clarification.

10. STATISTICAL PLAN

This study is a Phase IV, open-label trial in pediatric patients undergoing an elective surgery requiring anesthesia ≥ 1 hour and for whom parenteral IV antihypertensive therapy for BP management is expected. Approximately 80-100 patients of 4 cohorts are planned to be enrolled at 2 centers from initiation of the project to ensure 80 patients for efficacy evaluation. The primary objective of this study is to evaluate the efficacy, safety and dosing of an IV infusion of clevidipine for BP management in pediatric patients in the perioperative setting.

A separate Statistical Analysis Plan document will provide more detailed specifications in data analysis and presentation.

10.1. SAMPLE SIZE

The total sample size of 80 (20 per cohort) evaluable patients is considered primarily based on clinical judgment to provide adequate precisions 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.

10.2. DEFINITIONS

10.2.1. Patient Study Population

The following populations will be used for data analyses and/or presentation.

10.2.1.1. Safety Population

All patients who received any dose of clevidipine. This will be the primary population used for the safety analyses.

10.2.1.2. Intent-to-Treat (ITT) Population

All patients who have received clevidipine therapy and have baseline and at least one post-baseline SBP measurements. This will be the primary population used for the efficacy analyses.

10.2.1.3. Pharmacokinetics/Pharmacodynamics (PK/PD) Population

All patients who are dosed with clevidipine and 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.

10.2.2. Observational Period

The observational period for the study will be from the initiation of the study medication to 7 days following termination of the study drug. Adverse events and SAEs are to be reported from time of signing informed consent up to 7 days following termination of the study drug infusion. Any event occurring after the defined observational period, even if collected in the eCRF, will not be included in the planned statistical analysis. However, all data, including that reported before and after the defined observational period, will be included in the data listings.

10.2.3. Statistical Periods

The study will occur in three consecutive periods: a screening period, a treatment period, and a follow-up period. The Screening Period is 0 to 7 days prior to the initiation of study drug (IV clevidipine treatment).

The Treatment Period occurs from initiation of study drug administration up to 96 hours. This period can be split into 3 phases for study drug administration. Initial dosing phase from 0 to 1.5 minutes; titration and maintenance phase from >1.5 to 30 minutes and >30 minutes to 96 hours; transition and termination phase from end of study drug infusion to 12 hour follow-up.

The Follow-up Period is divided into 4 time points. The 1 hour time point (+ 30 minutes) is from discontinuation of study drug until 1 hour post study drug termination. The 12 hour time point (+ 30 minutes) is from study drug termination through12 hours post study drug termination. The 24 hour time point (+ 30 minutes) occurs from 12 hours post study drug termination until 24 hours post study drug termination. The 7 day time point (+ 1 day) is the final time point in the follow-up period, which occurs from 24 hours post study drug termination through day 7.

10.3. STATISTICAL ANALYSES

All study data will be summarized using descriptive statistics, graphs, and/or data listings. Descriptive statistics for continuous variables will include but not limited to number of patients (n), mean, standard deviation (SD), median, quartiles (Q1 and Q3), minimum (min) and maximum (max) values. Analysis of categorical variables will include frequency and percentage. Time to event variables will be analyzed using the Kaplan-Meier method.

No confirmatory hypothesis is established in this study; therefore 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.

Unless otherwise specified, missing data will not be imputed and will be excluded from the associated analysis.

Analyses will be presented for overall and by cohort.

10.3.1. Demographic and Background Characteristics

Patient demographic and background characteristics (including BP and HR recorded prior to the first dose of study drug) will be descriptively summarized. Separate analyses will be prepared for the safety, ITT, and PK/PD populations.

10.3.2. Efficacy Analysis

10.3.2.1. Primary Efficacy Endpoints

The primary efficacy endpoints of this trial are**:**

- **Median time and dose to attain the initial prespecified 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 prespecified target SBP range during the first 30 minutes of clevidipine infusion**

Median time is the median of the time in minutes between the initiation of study medication and time the patient first achieves the initial prespecified target SBP range (TBPR) during the first 30 minutes of clevidipine infusion. The median time will be summarized using the Kaplan-Meier method. Median time will be estimated with a two-tailed 95% confidence interval. If patients do not reach TBPR within 30 minutes from the initial treatment with study medication, or another intravenous antihypertensive agent is administered, the patient will be considered censored at 30 minutes or the time when another intravenous antihypertensive agent is given, whichever comes first.

The percentage of patients achieving TBPR will be calculated using the number of ITT patients achieving the endpoint divided by the total number of ITT patients, and multiplied by 100.

Number and percent of patients achieving TBPR during the first 30 minutes along with the calculated 95% confidence interval will be presented.

Analysis of the infusion rate, total dose infused, and total volume infused at the time of first achieving TBPR during the first 30 minutes will be summarized descriptively.

10.3.2.2. Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- **The percentage of patients who reach the initial prespecified target SBP range without falling below the lower limit of the prespecified 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 minute of clevidipine infusion**
- **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 reaching each endpoint above will be calculated for overall and within each cohort using the number of ITT patients achieving the endpoint divided by the number of total ITT patients, and multiplied by 100.

Number and percent of patients achieving each endpoint during the first 30 minutes along with the calculated 95% confidence interval will be presented.

- **Percent change in SBP from baseline 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**
- **Percent change from baseline in heart rate during the first 30 minutes of clevidipine infusion and the rest of the treatment period**

Percent change from baseline at each time point specified in above endpoints will be calculated for each ITT patient.

Descriptive statistics will be presented for overall and by cohort.

10.3.3. Safety Analysis

Safety of a prolonged infusion of clevidipine (up to 96 hours) will be assessed according to clinical laboratory parameters. Adverse events and serious adverse events (SAEs) will be assessed through 7 days following the termination of the study drug infusion.

10.3.3.1. Adverse Events

The Medical Dictionary for Regulatory Activities (MedDRA) will be used for coding adverse events (AEs). An AE (classified as preferred term) occurring during the treatment period 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 during the treatment period.

The number and percent 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.

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

10.3.3.2. Laboratory Tests

Laboratory values as well as changes and percent changes from baseline at each time point will be summarized. Analyses will also be performed for each laboratory parameter on incidence rates of potentially clinical significant (PCS) values for patients without PCS value at baseline.

10.3.3.3. Vital Signs

Change and percent change from baseline in vital signs will be summarized descriptively at each scheduled time point.

10.3.3.4. Pharmacokinetic Parameters

Blood concentration versus time data will be analyzed using non-compartmental analysis and/or Nonlinear Mixed-Effect Modeling (NONMEM). 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 comprise N, mean, geometric mean, SD, standard error of mean (SEM), median, percent coefficient of variation (%CV), minimum and maximum will be presented for the

pharmacokinetic variables (half-life, area under the curve [AUC], volume of distribution, clearance, etc.) established by sparse population methodology.

10.4. INTERIM ANALYSIS

Following completion of the adolescent cohort, the DSMB will review the safety data and make safety recommendations to the Sponsor according to the DSMB Charter prior to enrolling the remaining cohorts in sequential order. DSMB review of each completed cohort will be required before proceeding to the subsequent 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, an analysis to assess adequate precision of the efficacy findings will be performed at the end of each cohort to ensure that sample size for the following cohort is sufficient.

10.5. EXPLORATORY ANALYSIS

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

11. RECORDS RETENTION

FDA regulations require all investigators participating in clinical drug trials to maintain detailed clinical data for one of the following periods:

- At least two years following the date on which a New Drug Application is approved by the FDA, or
- Two years after the Sponsor notifies the investigator that no further application is to be filed with the FDA.

Similarly, International Conference on Harmonisation (ICH) guidelines require that essential documents be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

To comply with these requirements, the investigator will not dispose of any records relevant to this study without either (1) written permission from the Sponsor or (2) providing an opportunity for the Sponsor to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study, including any data clarification forms (DCFs) required for the study. Such documentation is subject to inspection by the Sponsor or its agents, the FDA and/or other regulatory agencies.

12. QUALITY CONTROL AND QUALITY ASSURANCE

12.1. MONITORING

The Sponsor has ethical, legal and scientific obligations to carefully follow this study in accordance with established research principles and applicable regulations. The investigator, as part of his responsibilities, is expected to cooperate with the Sponsor in ensuring that the study adheres to the protocol and GCP requirements.

As part of a concerted effort to fulfill these obligations, the Sponsor's monitor will visit the center(s) during the study in accordance with the Monitoring Plan set forth for this trial. The investigator will permit the Sponsor to monitor the study as frequently as is deemed necessary and provide access to medical records/source documents to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

12.2. AUDITING

The Sponsor may conduct audits at the study center(s). Audits will include, but not be limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRF with source documents. The investigator agrees to permit audits conducted at a reasonable time in a reasonable manner.

Regulatory authorities worldwide may also inspect the investigator during or after the study. The investigator should contact the Sponsor immediately upon notification of a site audit, and must permit regulatory authority inspections.

12.3. PROTOCOL DEVIATIONS

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the subject requires immediate intervention, based on the judgment of the investigator (or a responsible, appropriately trained professional designated by the investigator). In the event of a significant deviation from the protocol due to an emergency, accident, or mistake, the investigator or designee must contact the Sponsor, or their agent, at the earliest possible time by telephone. This will allow an early joint decision regarding the subject’s continuation in the study. The investigator and the Sponsor will document this decision. The IRB/EC will be informed of all protocol changes by the investigator in accordance with the IRB/EC established procedure. No deviations from the protocol of any type will be made without complying with all the IRB/EC established procedures.

The following will be classified as Major Protocol Deviations:

- Treatment of a patient who did not meet all inclusion criteria
- Treatment of a patient who met one or more exclusion criteria

- Any study procedure performed either prior to or without written informed consent obtained from a patient's guardian or legally authorized representative and without verbal assent performed as per institutional policy
- Any patient dosed at a rate higher than the protocol-defined starting rate
- Patient does not receive study drug as monotherapy for first 30 minutes of treatment
- PK sampling not obtained at their specified time points

13. ETHICS AND RESPONSIBILITY

This study will be conducted in compliance with the protocol, the Sponsor's standard operating procedures and/or guidelines, the United States Food and Drug Administration (FDA) regulations and local regulations, the International Conference on Harmonization (ICH) GCP guidelines, the Declaration of Helsinki and other local regulations, as applicable.

13.1. INFORMED CONSENT

Written informed consent will be obtained from all subjects' parent or legal guardian, and whenever possible, verbal assent will be obtained as per IRB or EC guidelines before any study-related procedures (including any pre-treatment procedures) are performed. The investigator(s) has both ethical and legal responsibility to ensure that each subject's parent or legal guardian, and the child where possible, are being considered for inclusion in this study is given a full explanation of the protocol. This shall be documented on a written informed consent form, which shall be approved by the same IRB or EC responsible for approval of this protocol. Each informed consent form shall include the elements required by ICH, Part E6, Section 4.8 and any applicable local regulations. The investigator agrees to obtain approval from the Sponsor of any written informed consent form used in the study, preferably prior to submission to the IRB or EC.

Once the appropriate essential information has been provided to the subject and fully explained by the investigators (or a qualified designee) and it is felt that the subject understands the implications of participating, the subject's guardian or legally authorized representative and the investigator (or designee) shall sign and date the IRB- or EC-approved written informed consent form. The subject's parent or legal guardian, and the subject whenever possible, shall be given a copy of the signed and dated informed consent form, and the original shall be filed appropriately, according to the institution. A second copy may be filed in the subject's medical record, if allowed by the institution.

13.2. INSTITUTIONAL REVIEW BOARD/ETHICS COMMITTEE

This protocol, the written informed consent form and any materials presented to patients shall be submitted to the IRB or EC identified with this responsibility. Notification in writing of approval must come from the IRB or EC chairman or secretary, to the investigator, either as a letter or as a copy of the appropriate Section of the IRB or EC meeting minutes where this protocol and associated informed consent form were discussed. The investigator will not participate in the decision. If the investigator is an IRB or EC member, the written approval must indicate such non-participation in the voting session. The investigator will submit status reports to the IRB or EC as required by the governing body. The IRB or EC must be notified by the investigator in writing of the interruption and/or completion of the study; the investigator must promptly report to the IRB or EC all changes in research (protocol amendments) and will not make such

changes without IRB or EC approval, except where necessary to eliminate apparent immediate hazards to human patients. In cases where it is necessary to eliminate immediate hazards to patients, the IRB or EC must then be notified of the change as per local requirements. The investigator is required to maintain an accurate and complete record of all written correspondence to and received from the IRB or EC and must agree to share all such documents and reports with the Sponsor.

14. CONFIDENTIALITY

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study without written prior permission from the Sponsor. However, authorized regulatory officials and Sponsor personnel will be allowed full access to the records. All medications provided and patient bodily fluids and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Only unique patient numbers in eCRF will identify patients. Their full names may, however, be made known to a product regulatory agency or other authorized official if necessary.

With respect to the clinical trial data that is received from countries in the European Economic Area and Switzerland, The Sponsor has certified adherence to the United States- European Union and the US-Swiss Safe Harbor Principles.

15. INVESTIGATOR AGREEMENT

I have read and understand the protocol (including the Investigator's Brochure) and agree that it contains all the ethical, legal and scientific information necessary to conduct this study. I will personally conduct the study as described.

I will provide copies of the protocol to all physicians, nurses and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the investigational drug clevidipine, the concurrent medications, the efficacy and safety parameters and the conduct of the study in general. I am aware that this protocol must be approved by the Institutional Review Board (IRB) or Ethics Committee (EC) responsible for such matters in the Clinical Study Facility where clevidipine will be tested prior to commencement of this study. I agree to adhere strictly to the attached protocol. I understand that this IRB or EC approved protocol will be submitted to relevant regulatory authorities by the Sponsor, as appropriate. I agree that clinical data entered on case report forms by me and my staff will be utilized by the Sponsor in various ways such as for submission to governmental regulatory authorities and/or in combination with clinical data gathered from other research sites, whenever applicable. I agree to allow Sponsor monitors and auditors full access to all medical records/source documents at the research facility for patients screened or randomized in the study.

I agree to provide all patients with informed consent forms, as required by government and ICH regulations. I further agree to report to the Sponsor any adverse experiences in accordance with the terms of this protocol, ICH guideline, Part E6, Section 4.11 and applicable local regulations.

Principal Investigator (Signature)	Date
Principal Investigator (Printed Name)	
Institution Name	

16. REFERENCES

1. Clevidipine Investigator's Brochure, Edition 11, 02 April 2013

2. Charlson, M.E., Mackenzie, C.R., Gold, J.P., et al. The Preoperative and Intraoperative Hemodynamic Predictors of Postoperative Myocardial Infarction or Ischemia in Patients Undergoing Noncardiac Surgery. Ann. Surg. 1989; 637-648.

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5. Towe, E. and Tobias, J. D. Preliminary Experience with Clevidipine in the Pediatric Population. J Intensive Care Med 2010; 25: 349-352.

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8. Cleviprex Prescribing Information, December 08, 2011

THE MEDICINES COMPANY®

Investigational New Drug

INTERNAL APPROVAL TEMPLATE

CLINICAL RESEARCH PROTOCOL AMENDMENT

STUDY DRUG: Clevidipine

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

PROTOCOL: VERSION 3 MDCO-CLV-12-01

PROTOCOL RELEASE DATE: 11 December 2013

Reviewed and approved by:

PPD

Senior VP & Global Launch Leader

PPD Date

Vice President Medical Director SCCP

PPD

Director Clinical Operations

PPD

Director GPV

PPD

VP, Development Operations

PPD

Statistical Operations

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Clinical Pharmacology Director

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Clinical Project Director – acting Regulatory, US

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