CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-156

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

PHARMACOMETRICS REVIEW

NDA:	22-156
Drug name:	Cleviprex (Clevidipine)
Indication:	[redacted]
Proposed Regimen (Sponsor):	2-32 mg/hr (titration)
Applicant:	The Medicine's Company
Clinical Pharmacology Reviewer	Lydia V. Velazquez, Pharm. D.
Clinical Pharmacology Team Leader	Patrick J Marroum, Ph.D.
Pharmacometrics Reviewer:	Christoffer W. Tornoe, Ph.D.
Pharmacometrics Team Leader:	Yaning Wang, Ph.D.
Type of Submission:	Standard
Submission Date:	July 2, 2007
PDUFA Date:	May 2, 2008

TABLE OF CONTENTS

1 EXECUTIVE SUMMARY

The key pharmacometric findings from clevidipine NDA 22-156 submission for are:

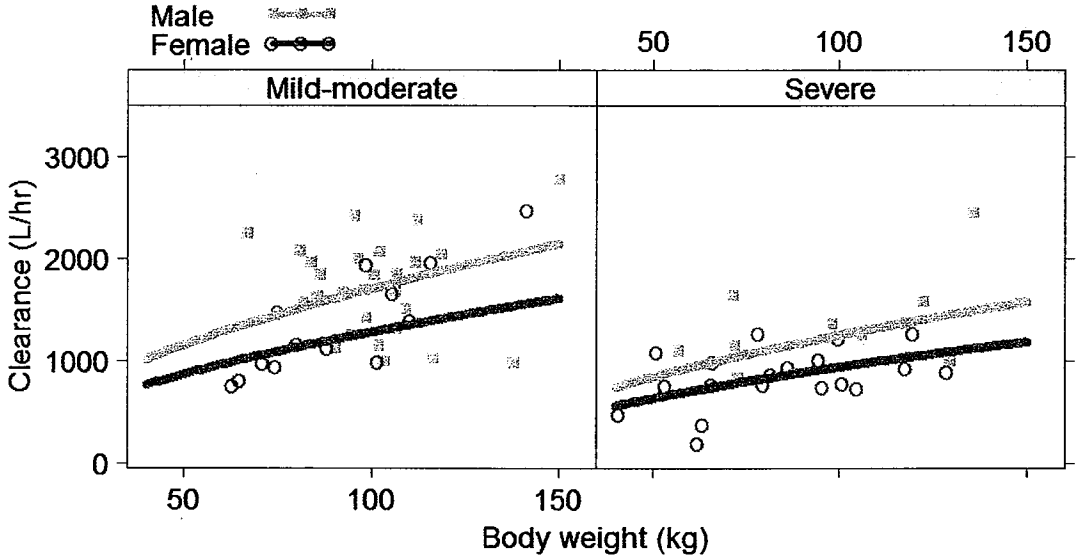
- The pharmacokinetics and pharmacodynamics (% change from baseline systolic blood pressure) of clevidipine was evaluated in 40 mild-moderate and 30 severe hypertension patients in clinical studies TMC-CLV-06-01 and TMC-CLV-06-02.
- A two-compartment pharmacokinetic model with first-order elimination adequately described the time-course of the observed clevidipine concentrations following constant 72 hour IV infusion (TMC-CLV-06-01) and titration to hemodynamic effect over 24 hours (TMC-CLV-06-02).
- A direct effect PK-SBP model with an E_{max} relationship (E_{max}=-25% and EC_{50}=7.1 ng/mL) was found adequate to describe the PK/PD relationship in mild-moderate hypertension patients. The PK-SBP relationship was different for severe hypertension patients with an apparently much lower EC_{50} but similar E_{max} (not estimated).
- Body weight, patient population (30% lower in severe compared to mild-moderate hypertension), gender (25% lower for females), and time (20% increase over 4 days) were found to be significant covariates for clevidipine clearance. The identified clearance covariates do not have any clinical impact since clevidipine has a very short half-life (2-3 min distribution and 1 hr terminal) and is easily titrated to blood pressure effect due to its clevidipine's direct hemodynamic effect. No dose adjustments based on the identified clearance covariates are thus warranted.
- There is evidence of rebound after end of the clevidipine infusion with a mean placebo-adjusted percent change from baseline systolic blood pressure (SBP) of 9.3 (90% CI 4.1-14.5) at 8 hours post a constant 72 hours IV infusion for the 16 mg/hr cohort in TMC-CLV-06-01. This corresponds to a rebound of 14 mm Hg in absolute systolic blood pressure for a patient with the mean baseline SBP of 150 mm Hg.
- The proposed dosing regimen of 2-32 mg/hr with a starting dose of 2 mg/hr was found adequate and safe. The dose may be doubled at 90 second intervals until the blood pressure —— goal blood pressure. Substantially smaller increase/decrease in dose rate (approx. ———————————— change from baseline SBP) and less frequent dose increases (every 5 min) are then warranted.
- Clevidipine was found to shorten the QT interval in a dose- and concentration-dependent manner with a mean change in ΔΔQTcF for 16 mg/hr and 60 mg/hr dose groups were -9.4 ms (90% CI -16, -3 ms) and -16 ms (90% CI -21, -11 ms). The TQT study had multiple deficiencies in the design (see IRT-QT review). As a result, the QT-IRT was not persuaded by the sponsor's data that quantification of the effect of administering clevidipine on the QT interval can be adequately assessed.

2 QUESTION BASED REVIEW

Is the sponsor's proposed dosing regimen of 2-32 mg/hr justified?
Body weight, patient population (mild-moderate/severe), and gender were found to be significant covariates for clevidipine clearance (see Figure below) with severe hypertension patients having 30% lower clearance compared to mild-moderate patients and females having 25% lower clearance compared to males. There was also an indication of time dependent clearance where the clearance increased by a total of 20% following 4 days continuous infusion due to unknown reasons.

These covariates (body weight, patient population, gender, and days since start of infusion) explain 15% of the unexplained inter-individual variability (IIV) in clevidipine clearance (IIV on clearance reduced from 51% to 36%).

The identified clearance covariates do not have any clinical impact since clevidipine has a very short half-life (2-3 min distribution and 1 hr terminal) and is easily titrated to effect. No dose adjustments based on the identified clearance covariates are thus warranted.



Clevidipine clearance vs. body weight. Mild-moderate (Left) and Severe (Right) hypertension patients. Male patients' individual clearance estimates are shown as grey filled squares and females are open red circles. The population mean predictions across body weights are illustrated as solid grey line for males and solid red line for females.

A dose of 2 mg/hr was shown to be the minimum effective dose (responders being classified as patients having a reduction in mean arterial pressure (MAP) ≥10% from baseline) in SAD-003 and thus appears to be an appropriate starting dose.

An E_{max} relationship exists between clevidipine dose, reduction of BP and clevidipine blood concentrations, including:

- A linear relationship between clevidipine dose and percent change in SBP at doses up to 20 mg/hr.

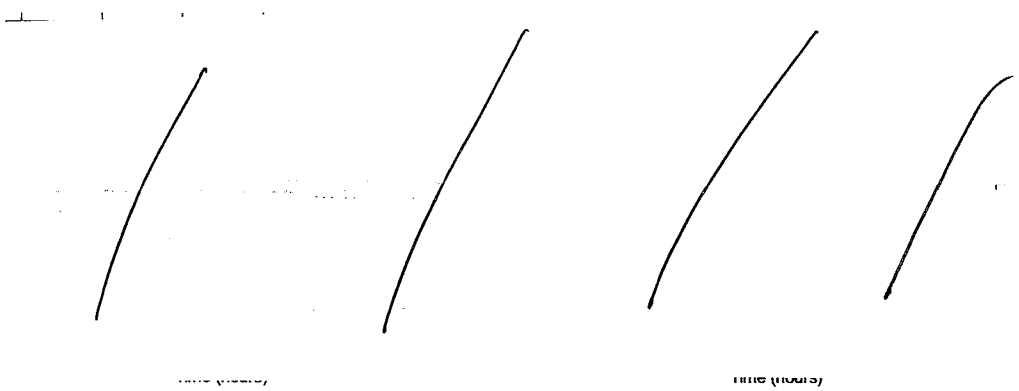
- A flattening of the dose-response relationship at doses greater than 20 mg/hr and up to 32 mg/hr.

The effective clevidipine dose range is 2-16 mg/hr and little additional blood pressure effect was observed at higher doses. Further decrease in SBP was obtained in 24 out of 38 patients (63.2%) who were up-titrated from 16 to 32 mg/hr in study SAD-003 (postcardiac surgical patients with perioperative hypertension) with a median decrease in SBP of 6.5 mm Hg. The highest dose rate of 46 mg/hr tested in study SAD-003 led to discontinuation of study therapy in 28% of patients due to hypotension. The proposed dosing regimen of 2-32 mg/hr is thus found to be adequate.

How should clevidipine be titrated to effect? (changed from Clin Pharm Review)
An alternative clevidipine dosing algorithm was derived using the following information:

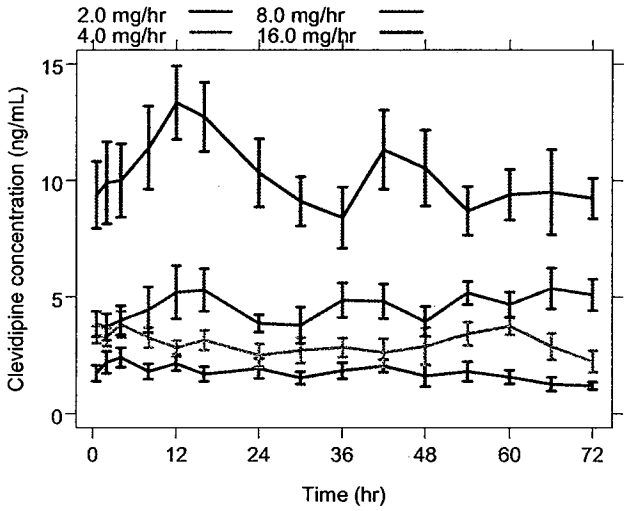
- Clevidipine concentrations reach 80% and 95% of steady-state 5 and 10 minutes after dose adjustments.
- The hemodynamic effect of clevidipine is direct (with an E_{max} relationship between clevidipine dose/exposure and blood pressure) and the reduction in blood pressure after dose adjustments will thus also reach 80% and 95% of steady-state after 5 and 10 min.
- A linear relationship with slope close to 1 (up to 16 mg/hr) between clevidipine infusion rates and % change from baseline in SBP was identified.

The dose may be doubled at 90 second intervals until the blood pressure [redacted] f goal blood pressure. Substantially smaller increase/decrease in dose rate [redacted], and less frequent dose adjustments (every 5 min) are then warranted. A simulation of the proposed dosing algorithm is shown in the figurer below.



Simulated median (10-90th percentile) mild-moderate hypertension patient's PK (left) and % change from baseline SBP (right) time profiles using alternative clevidipine dosing algorithm.

Do the kinetics change with short-term vs. long-term use?
The empirical mean (±SE) PK concentration-time profiles following 72 hour constant clevidipine IV infusions of 0-16 mg/hr appears to change over time with diurnal variations and a tendency towards lower concentrations over time. The mechanism behind the time dependent clevidipine PK is unknown. There was an indication of time dependent clearance with up to 20% increase over the 72 hour infusion. However, this has no clinical relevance since clevidipine is titrated to effect very fast due to its short half-life and direct SBP effect.



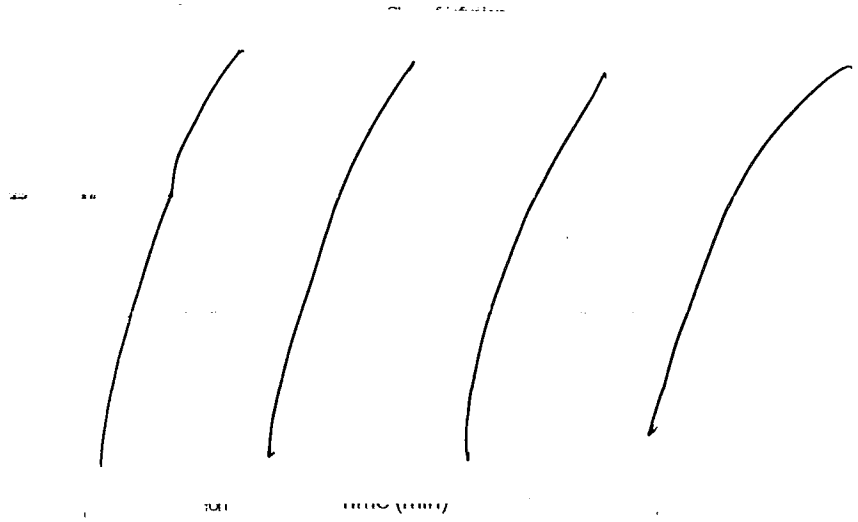
Mean (±SE) clevidipine concentration time profiles from 0-72 hours after start of the infusion for study TMC-CL-06-01.

APPEARS THIS WAY
ON ORIGINAL

Are the kinetics different in different patient populations (hypothermic vs. normothermic)?

The influence of body temperature on the PK of clevidipine was studied in patients in pre-bypass (normothermic) and bypass (hypothermic) stages of cardiac surgery in clinical study SH-SAD-0006.

The clearance of clevidipine was found to be slower in the hypothermic group (0.03 L/min/kg) compared to normothermic patients with a clearance of 0.06 L/min/kg.

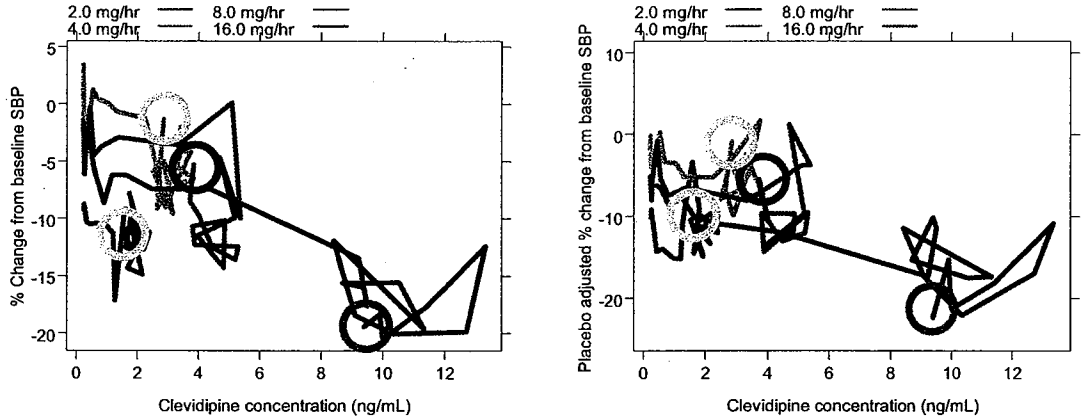


Concentrations of clevidipine in peripheral arterial blood and mixed venous blood during pre-bypass and concentration of clevidipine in peripheral arterial blood during bypass, following 10 min constant rate infusion (representative patient, dose rate of 2.05 μg/kg/min or 9.8 mg/hr).

(Source: Sponsor's Figure 29 in summary-clin-pharm.pdf)

Is there evidence of tolerance development?

There does not appear to be any tolerance development since no delay (hysteresis) was observed between clevidipine concentration and percent change from baseline SBP with or without placebo adjustment.



Relationship between time-matched mean percent change in SBP from baseline (left) and placebo-adjusted (right) and the mean clevidipine concentration over the 72 hour treatment period through 60 minutes post study drug infusion connected by lines in chronological order for study TMC-CL-06-01 (see appendix 10.4 for mean ±SE plots). The circles indicate the first time point with PK and SBP measurement.

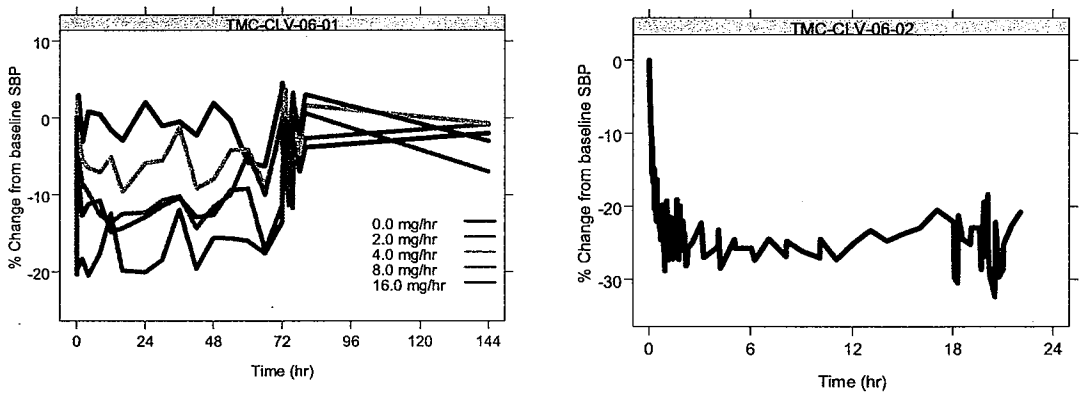
APPEARS THIS WAY
ON ORIGINAL

What is the onset/duration/offset of effect?

The time to onset of maximal systolic blood pressure effect in patients with mild to moderate hypertension in study TMC-CLV-06-01 was within 5-10 minutes of starting the constant clevidipine infusion approximately corresponding to the time of maximum concentration.

The duration of SBP effect appears to be as long as clevidipine is being infused evidenced by 72 hours constant infusion in mild to moderate hypertension patients.

The rapid clearance of clevidipine and direct effect on SBP result in a fast offset of SBP effect. In most patients, full recovery to baseline SBP is achieved in 5-15 minutes after end of clevidipine infusion. Any unintended hypotension may be easily reversed by down-titration or temporary discontinuation of the infusion.

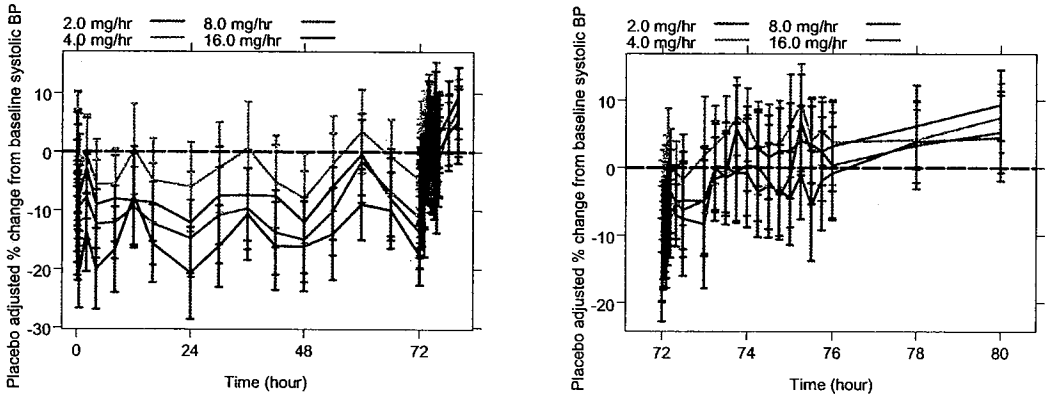


Mean percent change from baseline systolic blood pressure time profiles for mild to moderate hypertension patients following 72 hours constant clevidipine infusion (left) and 30 minutes forced titration followed by target SBP titration in patients with severe hypertension (right).

APPEARS THIS WAY
ON ORIGINAL

Is there rebound hypertension?

There is evidence of rebound after end of the clevidipine infusion when looking at placebo-adjusted percent change from baseline SBP at 8 hours post infusion (80 hours) for the 4 and 16 mg/hr cohorts in TMC-CLV-06-01 with a mean of 7.4 (90% CI 2.3-12.5) and 9.3 (90% CI 4.1-14.5) placebo-adjusted percent change from baseline (see orange and red lines in right graph in Figure 15). This corresponds to a rebound of 11 and 14 mm Hg in absolute systolic blood pressure for a patient with the mean baseline SBP of 150 mm Hg. The corresponding non-placebo adjusted mean percent change from baseline SBP for 4 and 16 mg/hr at 8 hours postdose is 2.2 (90% CI -1.7–6.0) and 4.1 (90% CI 0.15-8.0).



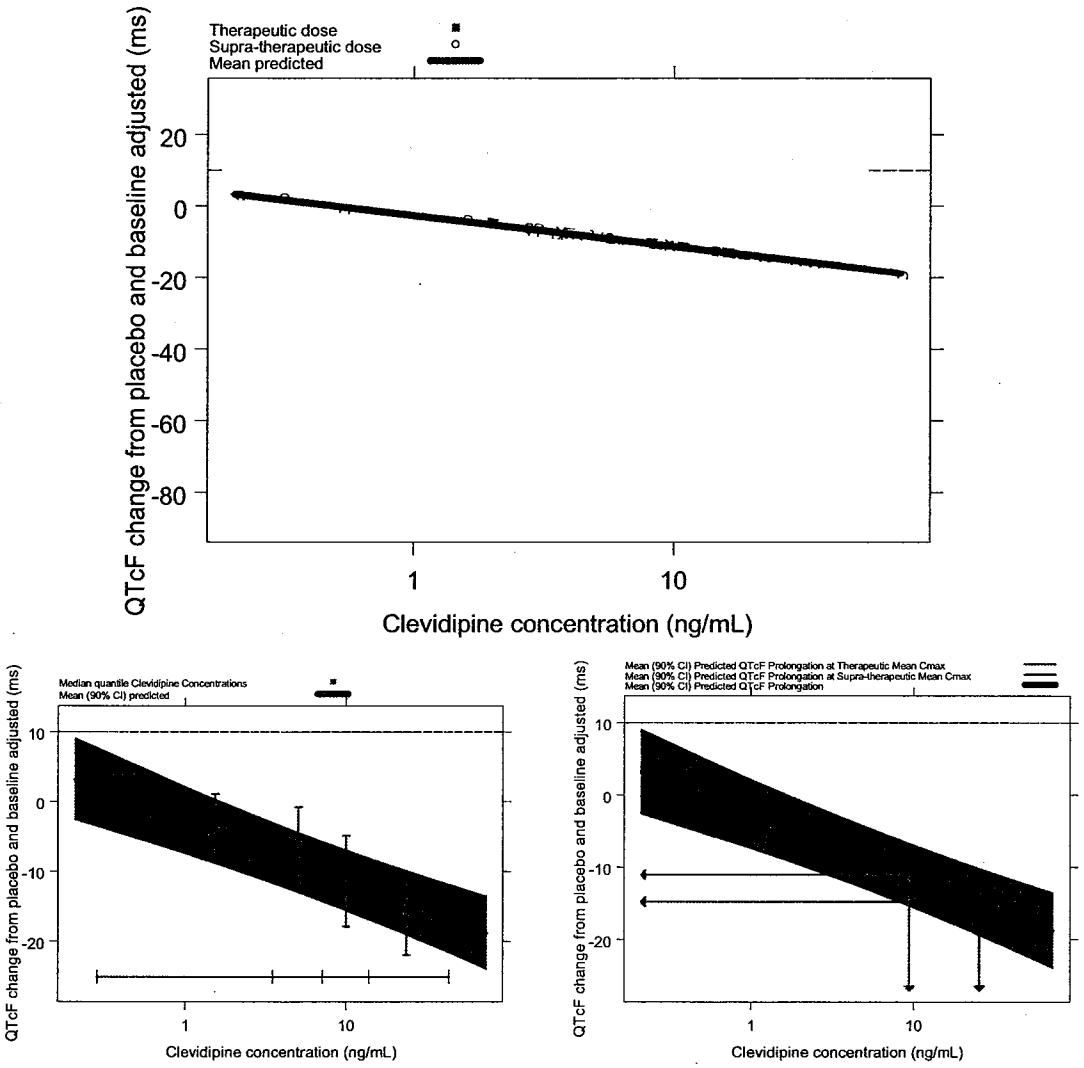
Mean (90% CI) placebo-adjusted percent change from baseline systolic blood pressure for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01.

Does clevidipine prolong QT?

The sponsor conducted a randomized, single-blind, vehicle (Intralipid®) and heart rate (fenoldapam) controlled 2-treatment crossover study in healthy volunteers, with an additional non-randomized, open-label moxifloxacin treatment with heart rate control.

Compared to the vehicle- and heart rate-control group, administration of clevidipine was found to shorten the QT interval in a dose- and concentration-dependent manner.

- The maximum decrease (and corresponding two-sided 90% CI) in the mean change in ΔΔQTcF for the 3.2 mcg/kg/min (~16 mg/hr) and 12 mcg/kg/min (~60 mg/hr) dose groups were -9.4 ms (-16, -3 ms) and -16 ms (-21, -11 ms).
- A log-linear model described the relationship between clevidipine concentrations and changes in ΔΔQTcF. Based on this relationship the expected ΔΔQTcF for a mean Cmax of 9 ng/ml was -11 ms (-15, -7 ms) and 25 ng/ml was -15 ms (-20, -10 ms) following 3.2 and 12 mcg/kg/min, respectively.
- The mean ΔΔQTcF for moxifloxacin was approximately 10 ms at t_{max} with lower 90% confidence interval greater than 5 ms at several timepoints. Since ten QT measurements were obtained over a short time, multiplicity adjustment may not be appropriate to compute confidence intervals.



(Top) ΔΔQTcF vs. Clevidipine concentration. (Bottom left) Mean (90% CI) predicted ΔΔQTcF (black line with shaded grey area) vs. Clevidipine concentration with observed median-quartile concentrations and associated mean ΔΔQTcF (90% CI) overlaid (blue). (Bottom right) Predicted ΔΔQTcF at mean Cmax after steady-state dosing of therapeutic dose (3.2 mcg/kg/min, blue line) and supra-therapeutic dose (12 mcg/kg/min, red line).

The study had multiple deficiencies in the design (see IRT-QT review). As a result, the QT-IRT was not persuaded by the sponsor's data that quantification of the effect of administering clevidipine on the QT interval can be adequately assessed.

3 RECOMMENDATIONS

The Office of Clinical Pharmacology finds that the NDA is acceptable.

The sponsor's recommended dosing regimen of 2-32 mg/hr is adequate. Clevidipine dose increments should only be administered 5-10 minutes after previous increments in order to reach [redacted] the new hemodynamic steady-state and no[redacted] as proposed by the sponsor.

Doubling dose increments (i.e. 2 to 4, 4 to 8, 8 to 16, 16 to 32 mg/hr) is adequate.

No dose adjustments based on patient factors (e.g. demographics) are warranted.

4 INTRODUCTION

4.1 BACKGROUND

Clevidipine is an ultrashort-acting 1-4 dihydropyridine calcium channel antagonist developed for [redacted] when the use of oral therapy is either not feasible or not desirable.

4.1.1 Pharmacokinetics

Clevidipine is metabolized by hydrolysis in blood and tissues by non-specific carboxyl esterases to an inactive metabolite, which in turn, is further metabolized (primarily 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.

Clevidipine is greater than 99.5% plasma protein bound. Clearance of clevidipine is extremely rapid, being approximately 5 L/min in arterial blood in both cardiac patients and healthy volunteers. The clearance of clevidipine is therefore approximately 10-20 times higher than that of other dihydropyridines. The rapid clearance results in a very short half-life. After reaching peak concentrations, clevidipine was found to decline in a triphasic manner in study SH-SAD-0018 in healthy volunteers with intensive sampling. The initial half-life (alpha phase) was approximately 0.6 to 0.8 minutes. The second half-life (beta phase) was approximately 2.2 to 2.3 minutes and accounts for approximately 10% of the area under the curve. The terminal half-life ranges between 16-22 minutes.

Clevidipine is intended for intravenous (IV) administration by infusion.

4.1.2 Pharmacodynamics

Since clinical effect on blood pressure (BP) is almost instantaneously achieved, the dosage and rate of clevidipine infusion is titrated to desired clinical effect.

Clevidipine reduces arterial BP in a dose/exposure dependent way by reduction of systemic vascular resistance (SVR). Clevidipine has no effect on central venous pressure (CVP). 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 (CO) is maintained or improved.

4.2 AIMS OF ANALYSIS

The objectives of this pharmacometrics review are:

- To develop a population pharmacokinetic model to describe concentration time data arising from TMC-CLV-06-01 and TMC-CLV-06-02 in patients with hypertension:
  - To identify and characterize patient factors which influence the pharmacokinetics and pharmacokinetic variability of clevidipine.
  - To estimate the magnitude of unexplained variability in clevidipine pharmacokinetics in this patient population.

- To develop a population pharmacodynamic model to describe the relationship between clevidipine concentrations and systolic blood pressure (SBP) data arising from TMC-CLV-06-01 and TMC-CLV-06-02 in patients with hypertension:
  - To identify and characterize patient factors which influence the pharmacodynamics and pharmacodynamic variability of clevidipine as determined for SBP
  - To estimate the magnitude of unexplained variability in clevidipine pharmacodynamics in this patient population.

- To explore exposure-response relationships for efficacy and safety.

5 COMMENTS ON SPONSOR'S PK/PD ANALYSIS

The reviewer's identified limitations of sponsor's population PK/PD analysis (see summary in Appendix section 12) include:

- PK data from both TMC-CLV-06-01 and 06-02 should have been used to develop the final PK model.
- The allometric model exponent parameters for clearance and central volume of distribution were fixed to 0.75 and 1 without verifying these assumptions with goodness-of-fit graphs.
- The PK-SBP analysis was performed using SBP instead of percent change from baseline which seems more relevant since it was the primary study endpoint.

6 STUDIES

6.1 TMC-CLV-06-01

This was a Phase IIb, randomized, single-blind, placebo-controlled, parallel-design trial in 52 patients with mild to moderate hypertension. The study occurred in three separate phases:

1. The screening/run-in period (up to 14 days),
2. The treatment period (72 hours) and
3. The follow-up period (4 days), representing a maximum study duration of 21 days.

The study population consisted of male and female patients, aged 18 to 80 years, with mild to moderate hypertension, either treated or untreated. All patients were allocated to one of the following four dosing cohorts:

- Cohort 1: Clevidipine 2.0 mg/hr or placebo (10:3 ratio)
- Cohort 2: Clevidipine 4.0 mg/hr or placebo (10:3 ratio)
- Cohort 3: Clevidipine 8.0 mg/hr or placebo (10:3 ratio)
- Cohort 4: Clevidipine 16.0 mg/hr or placebo (10:3 ratio)

Clevidipine was administered at an initial infusion rate of 2.0 mg/hr to patients in each cohort and force titrated in doubling increments every 3 minutes to the target dose in cohorts 2, 3 and 4. Once the target dose was achieved, it was maintained continuously for 72 hours. Placebo was administered intravenously in the same fashion. If the target dose was not tolerated, patients were withdrawn and replaced in order to ensure that a minimum of 10 clevidipine-treated and 3 placebo-treated patients per cohort completed the study.

6.2 TMC-CLV-06-02

This was a Phase III multi center, single-arm, open-label trial in patients who present with severe hypertension, defined as SBP >180 mmHg and/or diastolic blood pressure (DBP) >115 mmHg assessed on two successive occasions, 15 minutes apart. The patients may or may not have presented with evidence of acute or chronic end-organ injury. One hundred thirty six patients were enrolled in this study.

The treatment period consisted of three dosing paradigms for each patient:

1. Initial Dosing Phase in which clevidipine was infused at a fixed rate for 3 minutes,
2. Titration and Maintenance Phase in which clevidipine infusion rate could be titrated to effect and maintained for 18 to 96 hours, and
3. Transition Phase in which clevidipine was down-titrated starting approximately 1 hour after the administration of an oral antihypertensive agent.

During the Initial Dosing Phase patients received clevidipine via peripheral vein or by central venous infusion employing a volumetric pump. The initial rate of infusion was to be fixed at 2.0 mg/hr for 3 minutes.

During the Titration and Maintenance Phase, clevidipine could be up-titrated at the discretion of the investigator and as tolerated by the patient in doubling increments every

3 minutes until SBP is lowered to within the pre-specified target range. The clevidipine infusion rate may also be decreased at the discretion of the investigator in order to achieve an SBP within the target range. If the 30-minute target SBP range is achieved at any of the titration doses, that rate may be maintained for as long as necessary to maintain SBP within the desired target range. Additionally, at the discretion of the investigator, the clevidipine infusion rate could be titrated upwards or downwards to achieve/maintain an SBP within the target range. Beyond the first 30-minute treatment period, it may have been necessary to alter the desired SBP target range over the course of the remaining treatment period. Clevidipine infusion after the first 30 minutes could be maintained or further titrated to achieve the desired long-term reduction in SBP. Clevidipine infusion was to be administered continuously for a minimum duration of 18 hours and a maximum duration of 96 hours. The maximum infusion rate was not to exceed 32.0 mg/hr.

7 DATA

7.1 TMC-CLV-06-01

Pharmacokinetic sampling was conducted at the following nominal times: Pre-dose, 0.5, 2, 4, 8, 12, 16, 24, 30, 36, 42, 48, 54, 60, 66, 72 hours (end of infusion) and at 2, 4, 6, 8, 12, 20, 30 and 60 minutes post end of infusion.

Pharmacodynamic assessments of SBP were collected at the following nominal times: Pre-dose and then every 3 minutes during the titration phase to coincide with dose changes. Once the target dose was reached vital signs along with SBP were obtained at 5, 10, and 15 minutes and 0.5, 2, 4, 8, 12, 16, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours (end of infusion) and at 2, 4, 6, 8, 12, 20, 30 minutes and at 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 6, 8 and 96 hours post end of infusion. Change from baseline SBP was calculated based on the last predose SBP assessment.

Blood samples were analyzed for clevidipine and its major metabolite, (H152/81) in all patients. The lower limit of quantitation (LOQ) was set at 0.2 ng/mL for clevidipine and 20 ng/mL for the metabolite, H152/81.

7.2 TMC-CLV-06-02

Pharmacokinetic (PK) sampling was performed throughout the study in a subset of patients (n=30). Blood sample collections for PK analysis of plasma clevidipine concentrations were scheduled for the following time points:

- Prior to the initiation of clevidipine infusion (baseline sample)
- At any two time points during the maintenance phase.

The two samples were to have been collected at least 5 minutes apart and at least 5 minutes after a dose change.

Pharmacodynamic evaluations of SBP were taken on all patients throughout the study.

Blood samples were analyzed for clevidipine. The lower limit of quantification (LOQ) for clevidipine was 0.2 ng/mL.

Table 1 Summary Statistics of Demographics and Other Baseline Characteristics.

TMC-CLV-06-01:

Demographic (units)	**Mean (SD)**	**Median**	**Range**
Age (y)	52.93 (12.35)	53	21-77
Height (cm)	172 (8.75)	175	151-192.5
Weight (kg)	98.04 (19.53)	98.5	63.10-150
Sex	Males (N= 27); Females (N= 13)		
Race	Caucasian (N= 28); Non Caucasian (N= 12)		
Dose (mg/hr)	2 (N= 10); 4 (N= 10); 8 (N= 10); 16 (N= 10)		

TMC-CLV-06-02:

Demographic (units)	**Mean (SD)**	**Median**	**Range**
Age (y)	52.77 (17.73)	51	25-87
Height (cm)	167.7 (10.69)	167.6	138.4-188
Weight (kg)	88.35 (26.28)	84.1	40.9-136
Sex	Males (N= 10); Females (N=20)		
Race	Caucasian (N= 7); Non Caucasian (N= 23)		

8 RESULTS

8.1 POPULATION PK ANALYSIS

The empirical mean (±SE) PK concentration-time profiles following 72 hour constant clevidipine IV infusions of 0-16 mg/hr appears to change over time with diurnal variations and a tendency towards lower concentrations over time (see Figure 1).

The sponsor did not propose any mechanism or provide data to explain the time dependent clevidipine PK. The trend towards lower mean concentration over time might be attributed to an increase in clearance over time. One explanation for observing a high variability during the infusion (0-72 hours) could be due to difficulties in achieving a rapid and complete stop of the hydrolysis of the ester in the blood samples.

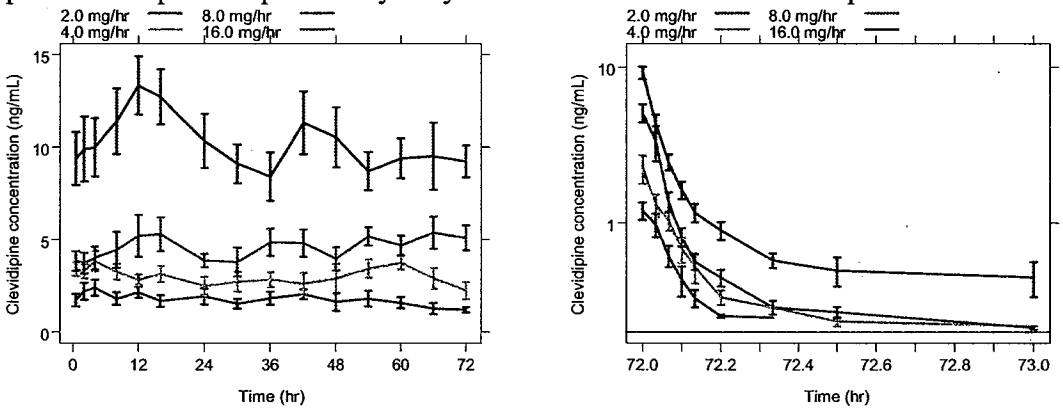


Figure 1. Mean (±SE) clevidipine concentration time profiles from 0-72 (left) and 72-73 (right) hours after start of the infusion for study TMC-CL-06-01.

8.1.1 Base PK Model

A two-compartment model was found adequate to describe the concentration-time profile of IV administered clevidipine.

The PK parameter estimates for the reviewer's base clevidipine PK model are shown in Table 2.

Table 2 Reviewer's Base PK Model Parameter Estimates.

		Population parameters		**Inter-individual variability**	
Parameter	**Unit**	**Estimate**	**%RSE**	**Estimate (CV%)**	**%RSE**
CL	[L/hr]	1360	7.57	50.7	38.3
Q	[L/hr]	146	11.8	-	-
V_1	[L]	83.5	10.6	57.4	28.2
V_2	[L]	160	14.6	-	-
Proportional residual error	[%]	42.7	4.92	-	-

8.1.2 Covariate PK Model

Body weight, sex, patient population/study, and study days since start of infusion were found to be significant covariates for clevidipine clearance (see Figure 29-Figure 30 for inter-individual random variable estimates vs. covariates for the base PK model).

The effect of study day on clearance is visualized in Figure 2 with an estimated percent change from day 1 of 10, 15, and 20% on study day 2, 3, and 4, respectively.

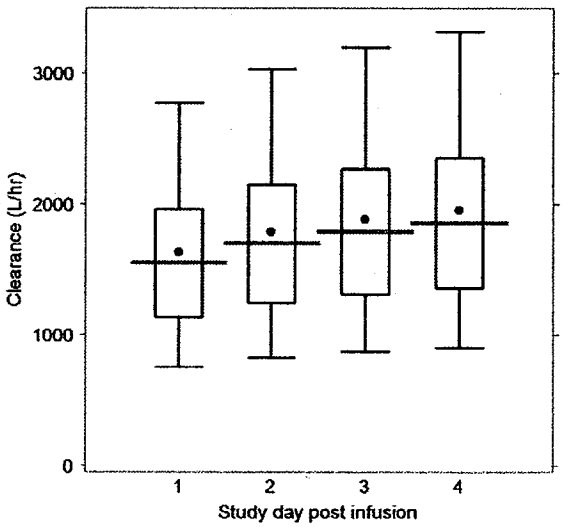


Figure 2. Clevidipine clearance vs. number of days since start of infusion in study TMC-CLV-06-01. The solid red lines are the population mean estimates and the box plots are based on empirical Bayes individual estimates.

Females were found to have 25% lower clearance compared to male patients and patients with severe hypertension were found to have approximately 30% lower clearance compared to mild-moderate hypertension patients (see Figure 3 and Figure 4).

No covariates were found to significantly influence clevidipine central volume of distribution (see Figure 5).

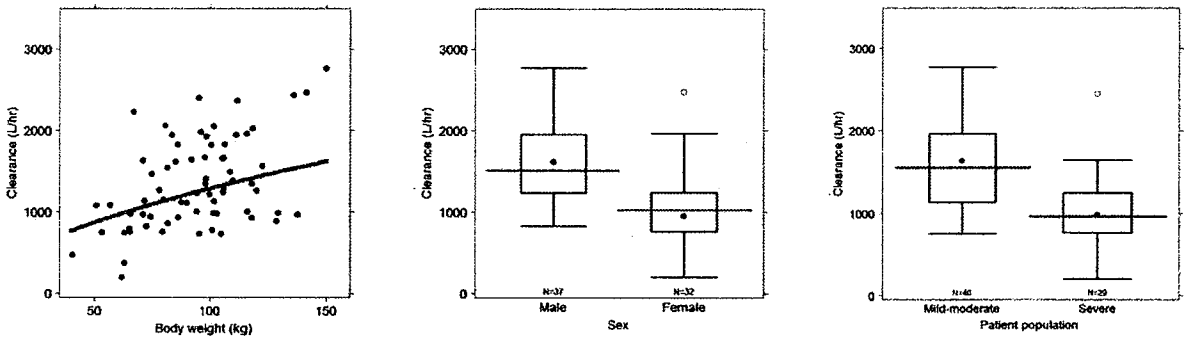


Figure 3. Identified covariate-PK parameter relationships. Clevidipine clearance vs. body weight (Left), sex (Middle), and patient population/study (Right). The solid red lines are the population mean estimates and the box plots and black dots are based on empirical Bayes individual estimates.

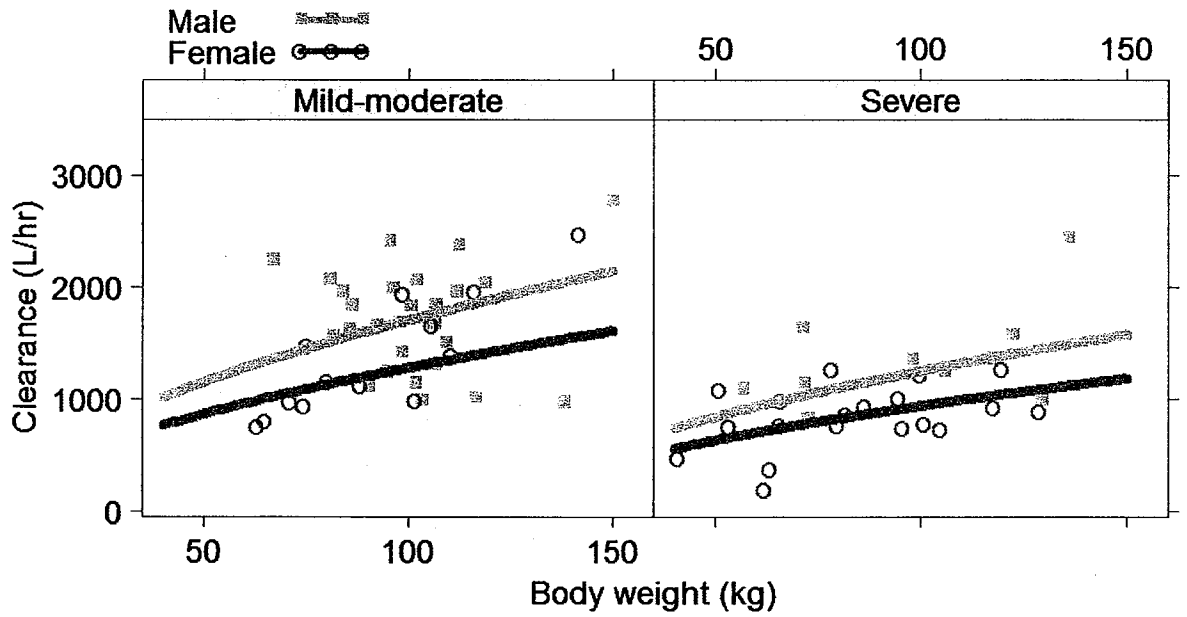


Figure 4. Clevidipine clearance vs. body weight for mild-moderate (Bottom Left) and severe (Bottom Right) hypertension patients. Male patients' empirical Bayes individual clearance estimates are shown as grey filled squares and females are open red circles. The population mean predictions across body weights are illustrated as solid grey line for males and solid red line for females.

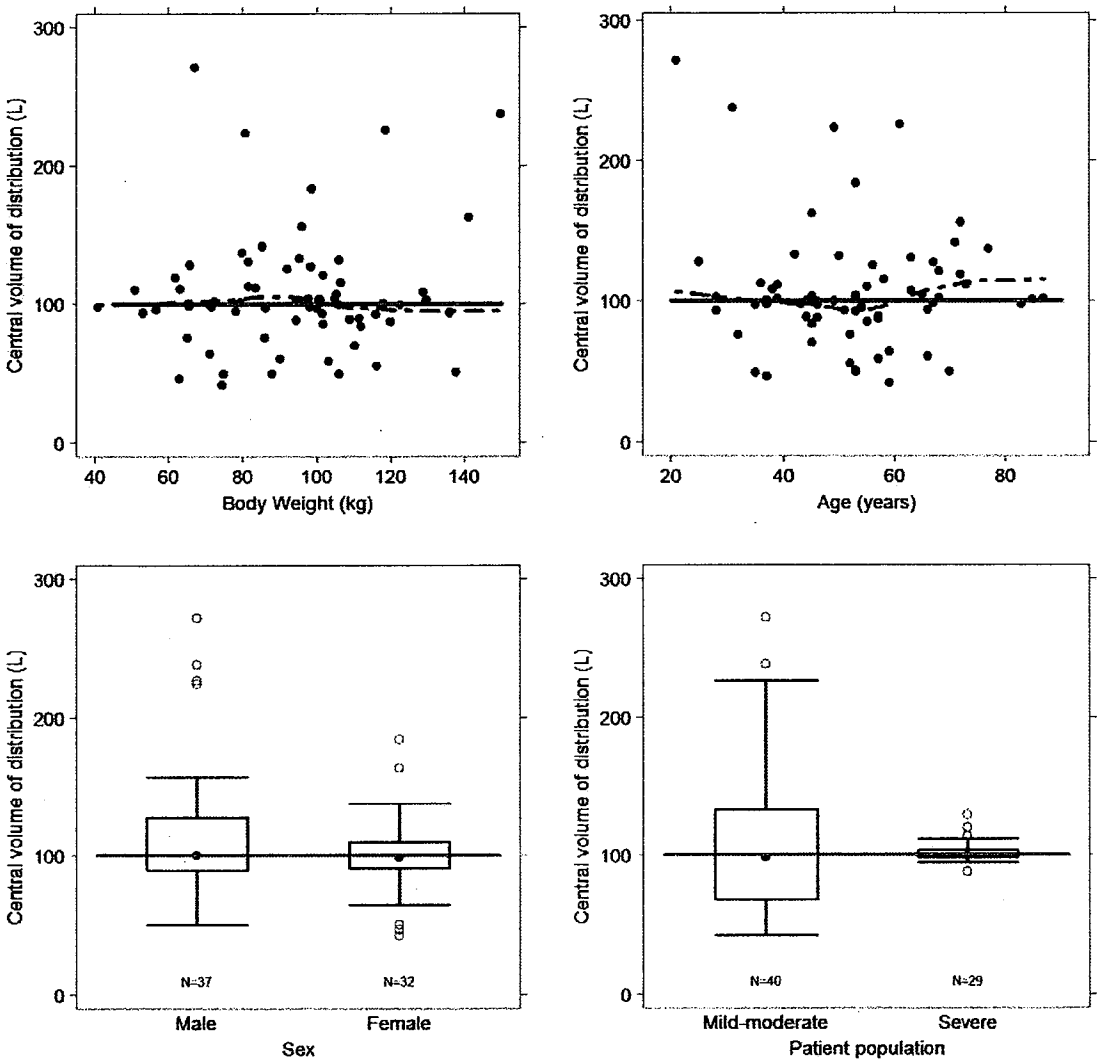


Figure 5. Clevidipine central volume of distribution vs. body weight (Top Left), age (Top Right), sex (Bottom Left), and patient population/study (Bottom Right). The solid red lines are the population mean estimates and the solid black circles are the individual predictions while the dashed blue lines are local regression smoothing lines. The box plots are based on empirical Bayes individual estimates.

8.1.3 Final PK Model

The PK parameter estimates for the reviewer's final clevidipine PK model using all available PK data from studies 06-01 and 06-02 are shown in Table 3 and the goodness-of-fit graphs are shown in Figure 31 - Figure 34.

Table 3 Reviewer's Final PK Model Parameter Estimates.

Parameter	Unit	Population parameters		Inter-individual variability	
		Estimate	%RSE	Estimate (CV%)	%RSE
Fixed-Effects Parameters					
CL (for 80 kg mild/moderate hypertension male patient)	[L/hr]	1500	8.40	36.3	18.4
Q	[L/hr]	169	12.8	56.4	15.0
V_1	[L]	100	11.2	-	-
V_2	[L]	213	17.5	-	-
Covariate-relationships					
CL-WT exponent	[-]	0.567	44.1	-	-
Female CL relative to males	[-]	0.750	9.64		
Severe hypertension CL relative to mild/moderate	[-]	0.733	11.9	-	-
CL-Day exponent	[-]	0.130	41.1		
Intra-Individual Variability					
Proportional error	[%]	42.5	4.75	-	-

The estimated distribution population half-life ($t_{1/2,\alpha}$) is 2-3 min and the terminal population half-life ($t_{1/2,\beta}$) is 1 hr with a steady-state volume of distribution (V_{ss}) estimate of 313 L indicating a high degree of tissue distribution.

The high intra-individual variability estimate of 42.5% is most likely due to difficulties in achieving a rapid and complete stop of the hydrolysis of the ester in the blood samples.

The population predictions 0-72 hours during the constant clevidipine infusion and 0-3 hours after end of the infusion are shown in Figure 6 while the individual observed clevidipine concentrations are overlaid in Figure 7.

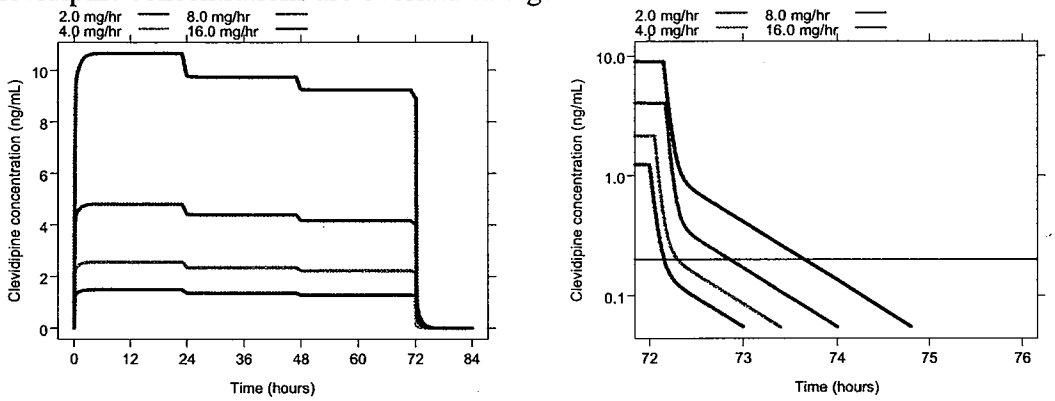


Figure 6. Population predicted clevidipine concentration-time profiles for 2 (black), 4 (blue), 8 (green), and 16 (red) mg/hr constant 72 hour clevidipine infusions from 0-84 hours after start of the infusion (left) and 0-4 hours after end of infusion (right) in study TMC-CLV-06-01. The dotted line represents the lower limit of quantification (LLOQ) of 0.2 ng/mL.

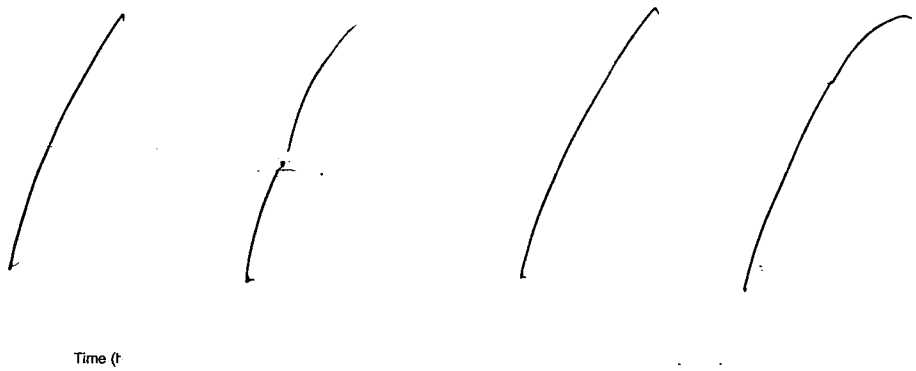


Figure 7. Individual observed (dots) and population predicted (solid lines) clevidipine concentration-time profiles for 2 (green), 4 (orange), 8 (blue), and 16 (red) mg/hr constant 72 hour clevidipine infusions from 0-84 hours after start of the infusion (left) and 0-4 hours after end of infusion (right) in study TMC-CLV-06-01. The dotted line represents the lower limit of quantification (LLOQ) of 0.2 ng/mL.

8.1.4 Body Temperature's Influence on Clevidipine PK

The effect of the blood temperature on the hydrolysis rate of clevidipine was studied in vitro and is shown in Figure 8 (left). The concentrations of clevidipine declined exponentially against time until approximately 90% of the added amount of drug had been hydrolyzed or at the lowest blood temperature (18°C) over a period of 60 minutes, which was the time the experiment ended.

The mean half-lives determined during this mono-exponential phase were 6 ± 1 min at 37°C, 11 ± 2 min at 30.5 °C and 40 ± 5 min at 18°C. In blood diluted with an equal volume of Ringer-glucose solution, the mean half-life was 11 ± 2 min at 30.5°C. The $t_{1/2}$ was linearly related to the temperature as seen in Figure 8 (right).

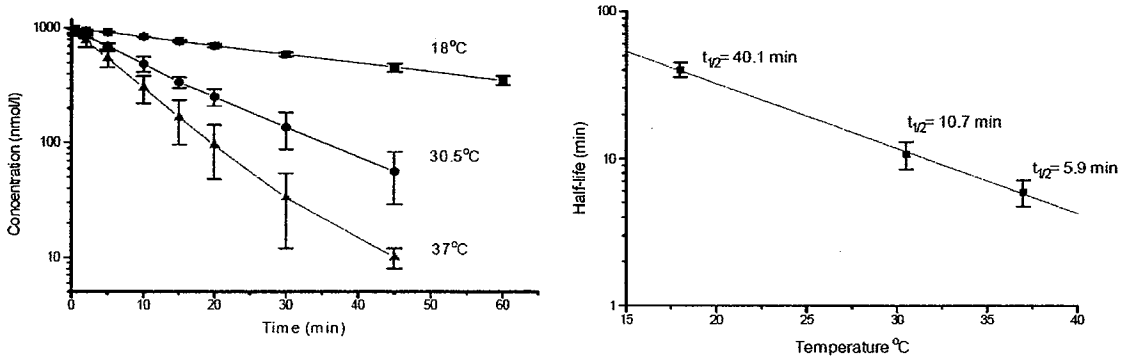


Figure 8. Clevidipine log concentration-time profiles at different temperatures (Left). Mean clevidipine half-life vs. temperature (Right). The bars indicate ±SD.
(Source: Sponsor's Figure 1 and 2 in summary-clin-pharm.pdf)

APPEARS THIS WAY
ON ORIGINAL

Pre-bypass (normothermic) and bypass (hypothermic)

The influence of body temperature on the PK of clevidipine was studied in patients in pre-bypass (normothermic) and bypass (hypothermic) stages of cardiac surgery in clinical study SH-SAD-0006.

The clearance of clevidipine was found to be slower in the hypothermic group (0.03 L/min/kg) compared to normothermic patients with a clearance of 0.06 L/min/kg (see Figure 9).

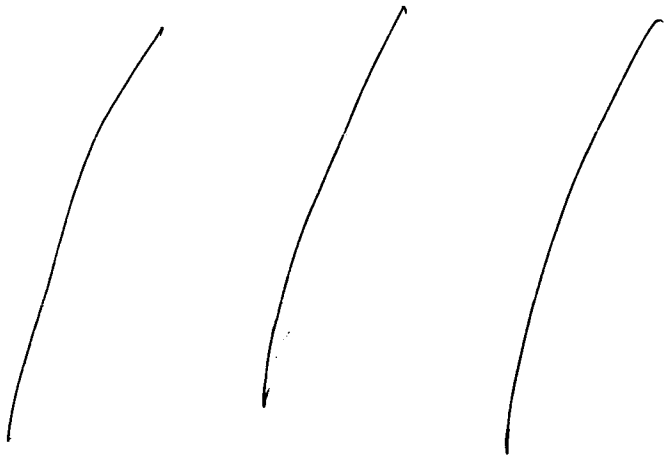


Figure 9. Concentrations of clevidipine in peripheral arterial blood and mixed venous blood during pre-bypass and concentration of clevidipine in peripheral arterial blood during bypass, following 10 min constant rate infusion (representative patient, dose rate of 2.05 µg/kg/min or 9.8 mg/hr).

(Source: Sponsor's Figure 29 in summary-clin-pharm.pdf)

Hypothermia and blood dilution had little effect on the volume of distribution (V_d), while $t_{½}$ of clevidipine increased during hypothermia due to a reduction in clearance of the drug rather than hemodilution.

Relationship between artial and venous blood concentrations

A clear difference in arterio-venous blood concentrations was obtained for blood concentrations during ongoing infusion in study SAD-0018.

The arterial concentration was approximately twice as high as the venous blood concentration following constant infusion to steady state blood levels. After the clevidipine infusion was stopped, the blood concentrations declined rapidly, and after a short time the arterial and venous blood concentrations merged into a common concentration-time profile (see Figure 10).

The differences between arterial and venous blood concentrations indicate an extensive and very rapid metabolism of clevidipine in the blood and tissues.

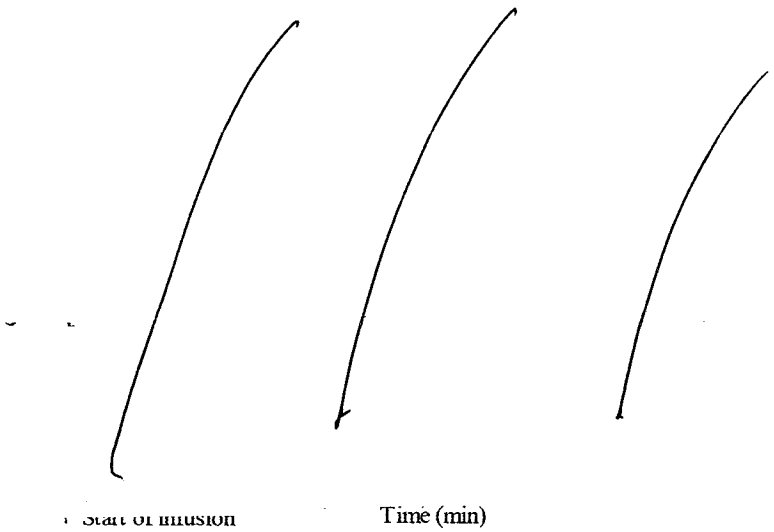


Figure 10. Blood concentrations of clevidipine in a representative subject following intravenous infusion at a target dose rate of 3.2 mcg/kg/min (16 mg/hr) over a 20-minute period.

(Source: Sponsor's Figure 12 in summary-clin-pharm.pdf)

8.2 SYSTOLIC BLOOD PRESSURE ANALYSIS

8.2.1 Exploratory SBP Data Analyses

The pharmacodynamic (PD) response to clevidipine, measured as percent change from baseline systolic blood pressure (SBP), shows dose dependence (except for the 2 mg/hr dose group), with higher doses of clevidipine resulting in greater reduction in SBP (see Figure 11).

The observed circadian rhythm in SBP with nadirs around 0, 24, 48, and 72 hours and peaks around 12, 36, and 60 hours postdose (see Figure 11) is strikingly similar to the observed fluctuations in clevidipine concentrations during 72 hours constant infusions with peaks around 12, 48, and 72 hours postdose (see Figure 1). However, the nadirs in SBP are expected to coincide with peak clevidipine concentrations due to clevidipine's mechanism of action lowering the blood pressure but the opposite is observed in TMC-CLV-06-01 for unknown reasons and might be due to random variations or diurnal effects the drug cannot suppress.

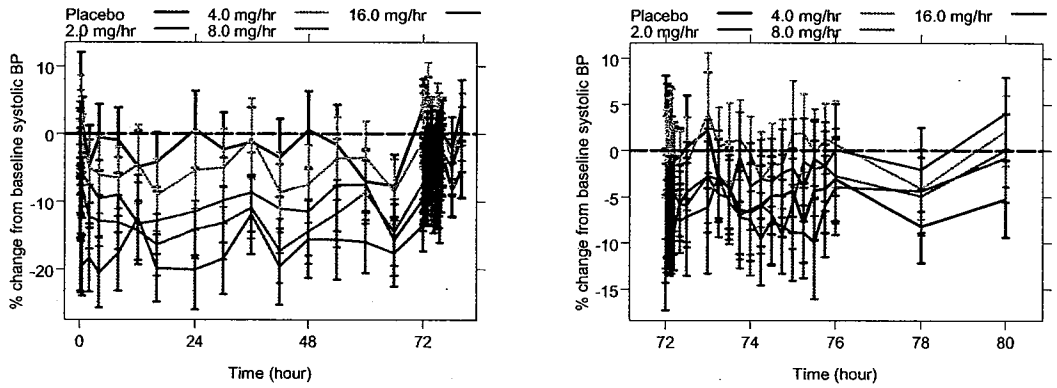


Figure 11. Mean (90% CI) percent change from baseline systolic blood pressure for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01 (Start of infusion occurred between 8 and 10 AM for all patients).

APPEARS THIS WAY
ON ORIGINAL

8.2.1.1 Tolerance

There does not appear to be any tolerance development since no delay (hysteresis) is observed between clevidipine concentration and percent change from baseline SBP with or without placebo adjustment (see Figure 12).

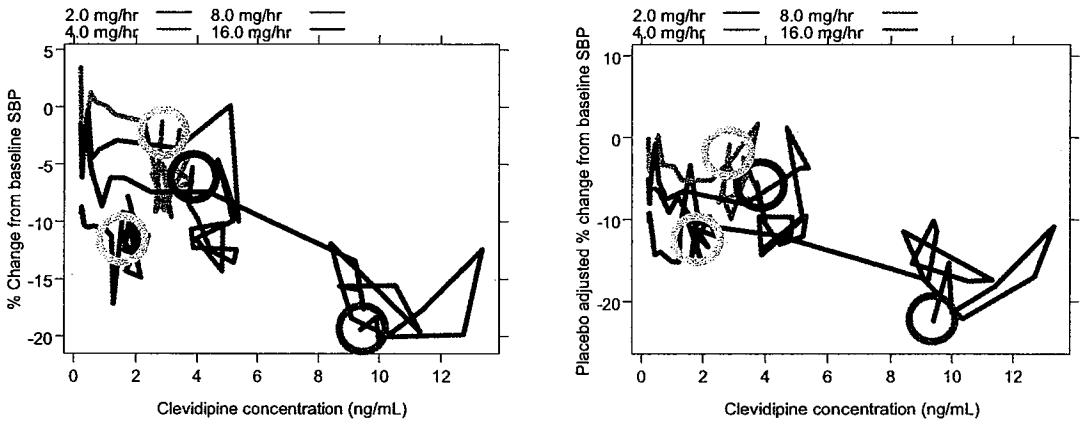


Figure 12. Relationship between time-matched mean percent change in SBP from baseline (left) and placebo-adjusted (right) and the mean clevidipine concentration over the 72 hour treatment period through 60 minutes post study drug infusion connected by lines in chronological order for study TMC-CL-06-01 (see appendix 10.4 for mean ±SE plots). The circles indicate the first time point with PK and SBP measurement.

8.2.1.2 Onset of SBP Effect

The time to onset of maximal systolic blood pressure effect in patients with mild to moderate hypertension in study TMC-CLV-06-01 appears to be within 5-10 minutes of starting the constant clevidipine infusion (see Figure 13).

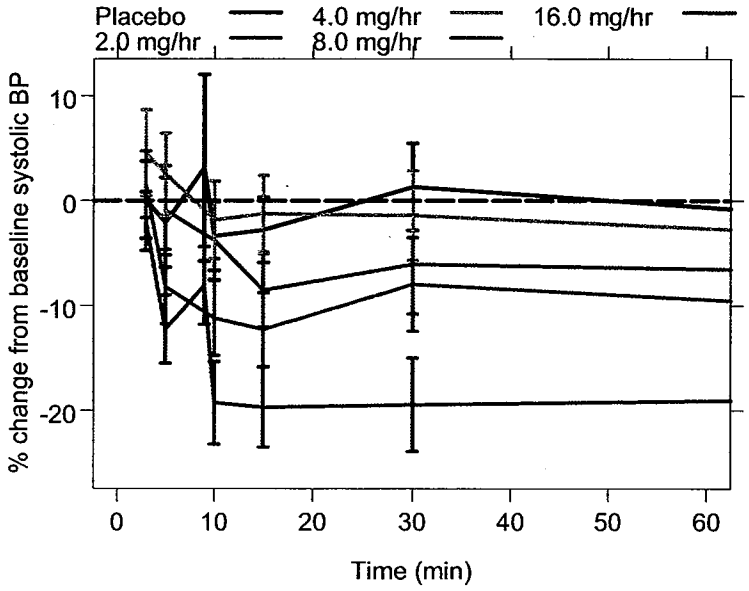


Figure 13. Mean percent change from baseline systolic blood pressure time profile for the first 60 minutes after start of infusion in patients with mild to moderate hypertension in study TMC-CLV-06-01.

8.2.1.3 Duration of SBP Effect

The duration of SBP effect appears to be as long as clevidipine is being infused evidenced by 72 hours constant infusion in mild to moderate hypertension patients (see left graph in Figure 14) and 30 minutes forced titration followed by target SBP titration in patients with severe hypertension for up to 24 hours (see right graph in Figure 14).

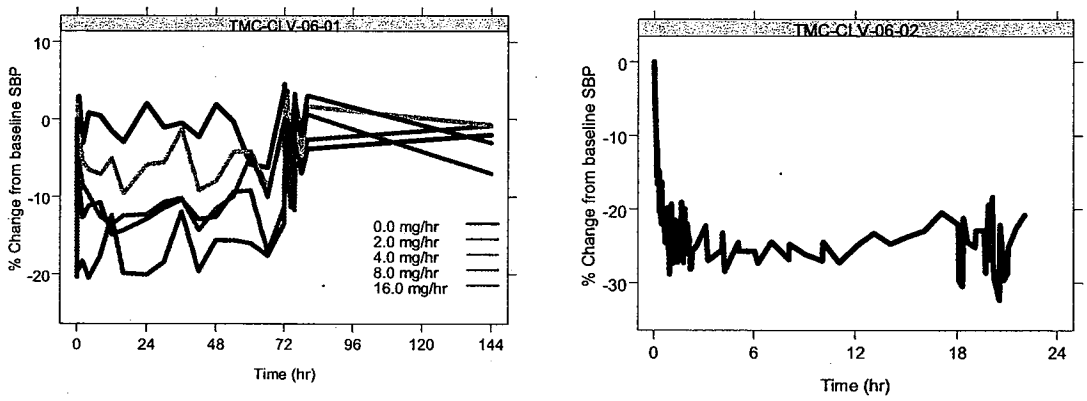


Figure 14. Mean percent change from baseline systolic blood pressure time profiles for mild to moderate hypertension patients following 72 hours constant clevidipine infusion

(left) and 30 minutes forced titration followed by target SBP titration in patients with severe hypertension (right).

8.2.1.4 Offset of SBP Effect

The rapid clearance of clevidipine results in a short offset of SBP effect due to its direct effect activity. In most patients, full recovery to baseline SBP is achieved in 5-15 minutes after end of clevidipine infusion. Any unintended hypotension may be easily reversed by down-titration or temporary discontinuation of the infusion.

However, there is evidence of rebound after end of the clevidipine infusion when looking at placebo-adjusted percent change from baseline SBP at 8 hours post infusion (80 hours) for the 4 and 16 mg/hr cohorts in TMC-CLV-06-01 with a mean of 7.4 (90% CI 2.3-12.5) and 9.3 (90% CI 4.1-14.5) placebo-adjusted percent change from baseline (see orange and red lines in right graph in Figure 15). This corresponds to a rebound of 11 and 14 mm Hg in absolute systolic blood pressure for a patient with the mean baseline SBP of 150 mm Hg.

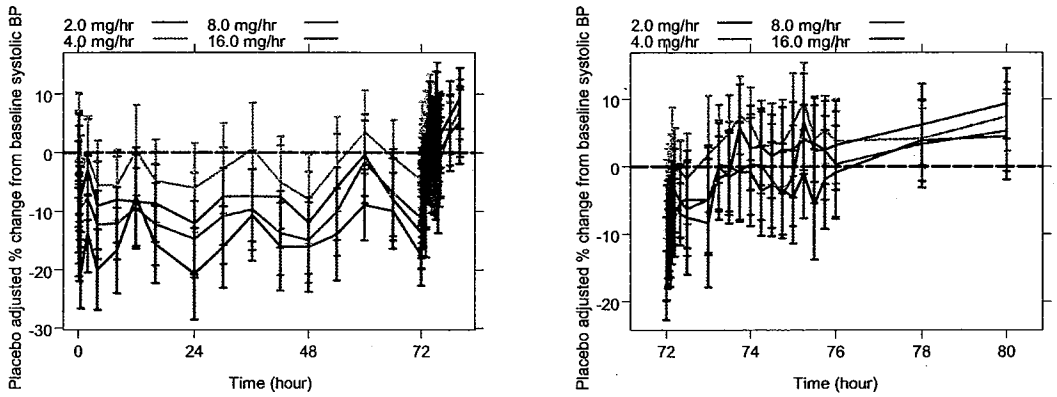


Figure 15. Mean (90% CI) placebo-adjusted percent change from baseline systolic blood pressure for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01.

The corresponding non-placebo adjusted mean percent change from baseline SBP for 16 mg/hr at 8 hours postdose is 4.1 (90% CI 0.15-8.0) (see Figure 11)

8.2.2 Population PK/SBP Analysis

Only PK/PD data from study TMC-CLV-06-01 in mild-moderate hypertension patients with intensive PK sampling were used for the model building while PK/PD data from TMC-CLV-06-02 in severe hypertension patients with sparse PK sampling was used for external validation.

8.2.2.1 Base SBP Model

The PK/PD relationship between clevidipine venous concentration and % change from baseline SBP was best described using a direct effect model using an E_{max} relationship, i.e.

$$\% \text{ change from baseline SBP} = \text{Intercept} + E_{max} * C_p/(EC_{50}+C_p)$$

where C_p is the individual predicted clevidipine concentration using the final PK model (see Section 8.1.3), E_{max} is the maximal SBP lowering effect of clevidipine, and EC_{50} is the clevidipine concentration needed to achieve half of that effect.

8.2.2.2 Covariate SBP Model

Only baseline SBP was found to be a significant covariate for the intercept (see Figure 16).

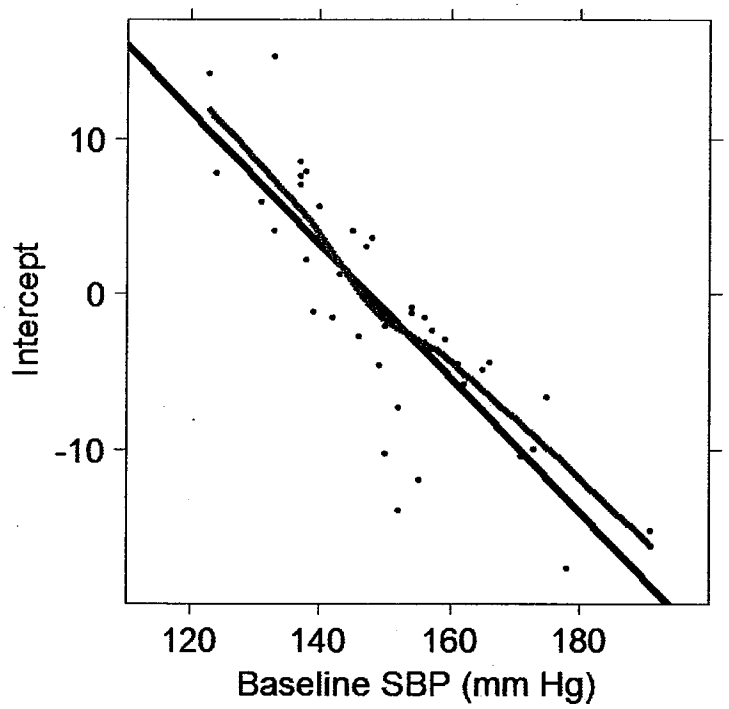


Figure 16 Identified covariate-SBP parameter relationships. Baseline SBP influence on intercept. The solid black line is the covariate model prediction, the solid red line is the smoothing local regression, and the dots are the empirical Bayes individual intercepts.

8.2.2.3 Final SBP Model

The parameter estimates for the reviewer's final SBP model using the individual predicted PK concentration at each time point where SBP measurements were taken in study 06-01 are shown in Table 4 and the goodness-of-fit graphs are shown in Figure 36-Figure 40.

Table 4 Reviewer's Final SBP Model Parameter Estimates.

		Population parameters		**Inter-individual variability**	
Parameter	**Unit**	**Estimate**	**%RSE**	**Estimate**	**%RSE**
Fixed-Effects Parameters					
Intercept for patient with 150 mm Hg baseline SBP	%	-1.34	67.2	4.37 (SD)	55.0
E_{max}	%	-24.7	26.0	5.86 (SD)	15.8
EC_{50}	ng/mL	7.10	51.8	2.18 (CV%)	39.4
Covariate-relationships					
Intercept-Baseline SBP		0.319	69	-	-
Intra-Individual Variability					
Additive error	[%]	6.82	4.35	-	-

The relative standard errors for the model parameters are generally high and some are above 50% indicating non-significant parameters. The confidence intervals around the population predictions are therefore expected to be very wide had they been calculated using e.g. bootstrapping techniques. The imprecision of parameter estimates is more likely due to lack of informative data rather than model misspecifications and the Emax model is therefore considered to be adequate for the purpose of understanding the PK-SBP relationship.

The maximal reduction in percent change from baseline SBP was estimated to be 25% corresponding to a 40 mm Hg drop in SBP for a patient with a baseline SBP of 150 mm Hg. The EC_{50} was estimated to be 7 ng/mL and the maximal effect is obtained at concentrations around 15 ng/mL and above (see Figure 17).

A direct effect PK/PD model seems to adequately describe the observed PK/PD data (see goodness-of-fit in Figure 17 (bottom)) thus indicating that clevidipine venous concentration is a good predictor of the antihypertensive activity.

Given clevidipine's rapid clearance and direct effect on SBP, a desired SBP effect can be achieved quickly by titration based on the SBP effect.

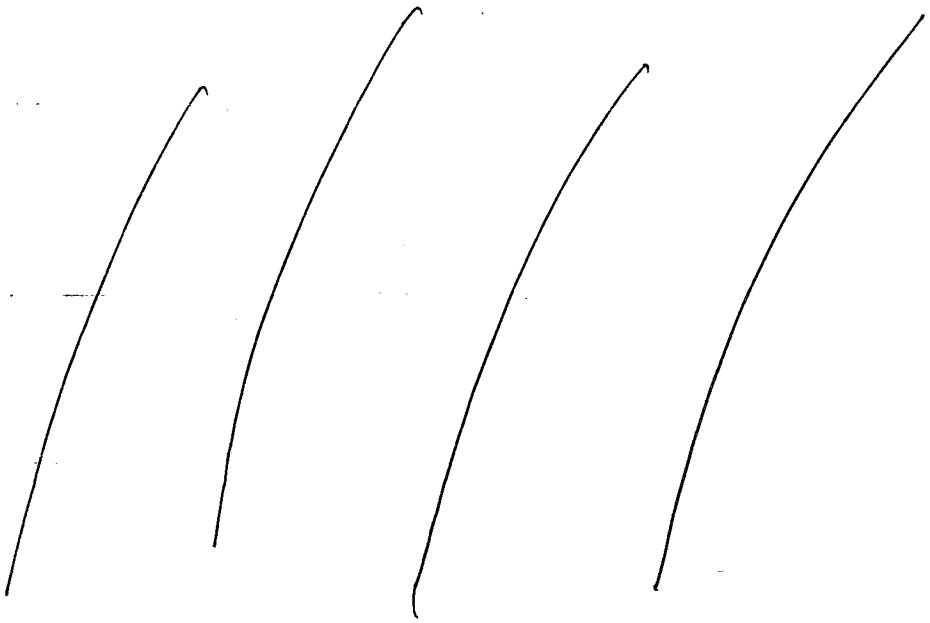


Figure 17. Population predicted (solid red line) and individual observed (solid black line) % change from SBP baseline vs. clevidipine concentration for study TMC-CL-06-01 (top).

The population predicted % change from baseline SBP time course is shown in Figure 18.

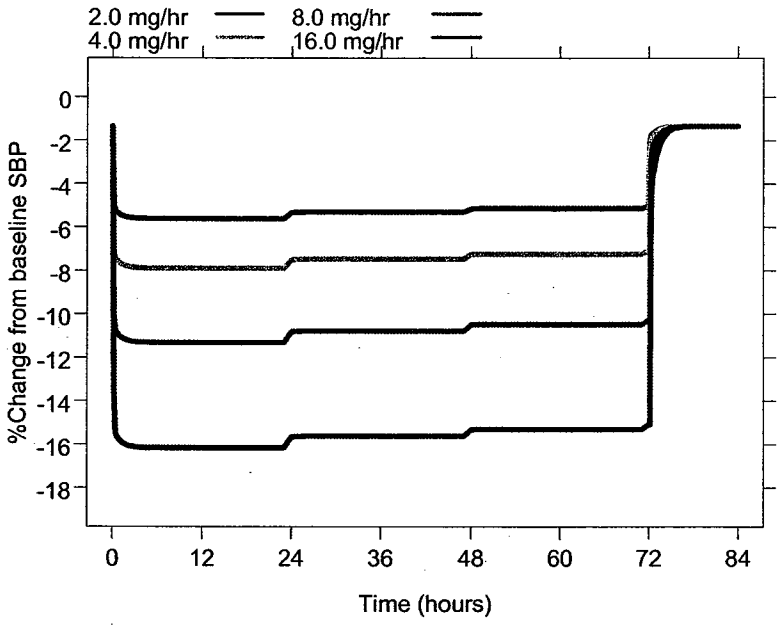


Figure 18. Population predicted percent change from baseline SBP for clevidipine doses of 2 (green), 4 (orange), 8 (blue), and 16 (red) mg/hr for an 80 kg male mild-moderate hypertension patient.

Patient population

The PK-SBP relationship for clevidipine appears to be different between patients with mild-moderate hypertension (TMC-CLV-06-01) and patients with severe hypertension (TMC-CLV-06-02) with a lower EC_{50} value for the severe hypertension patients but similar E_{max}.

This observation could be due to the following reasons:

- The systolic blood pressure effect in patients with severe hypertension is obtained with lower concentrations compared to mild-moderate hypertensive patients.
- The concomitant use of oral anti-hypertensive drugs as well as beta-blockers in the severe hypertensive patients (TMC-VLC-06-02) is having a synergistic effect when clevidipine is administered.

This difference in SBP response between patient populations was not explored further since clevidipine is titrated to effect very fast and can therefore be easily administered based on the observed response to clevidipine.

8.2.2.4 Dose limiting events

In the TQT study, a dose of 12 mcg/kg/min corresponding to 54 mg/hr was tolerated in healthy volunteers.

In study SAD-003 in postcardiac surgical patients with perioperative hypertension, the highest dose rate of 46 mg/hr led to discontinuation of study therapy in 28% of patients due to hypotension.

No dose limiting events were identified in TMC-CLV-06-01 and TMC-06-02 except for the apparent rebound SBP effect after end of infusion for the highest dose group of 16 mg/hr in TMC-CLV-06-01.

8.3 DIASTOLIC BLOOD PRESSURE ANALYSIS

The effect of clevidipine on diastolic blood pressure was also investigated. There also appears to be a dose-response relationship but unlike the systolic blood pressure, there does not seem to be an effect on diastolic blood pressure for clevidipine doses below 8 mg/hr (see Figure 19).

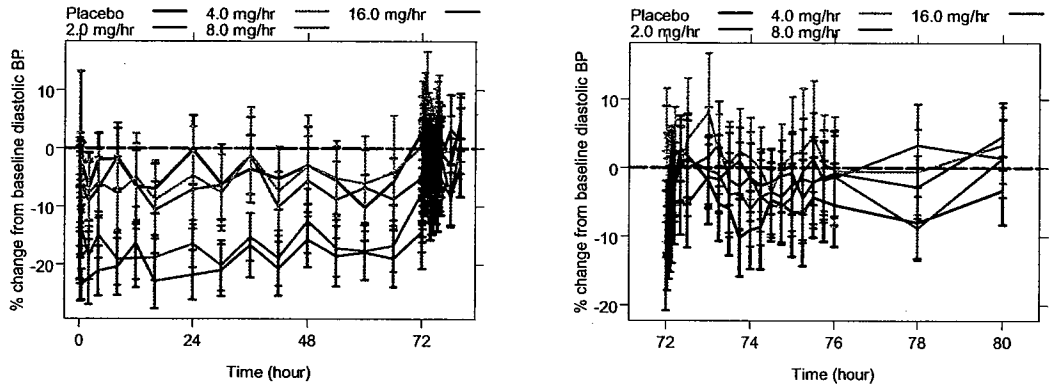


Figure 19. Mean (90% CI) percent change from baseline diastolic blood pressure for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01.

There is also slight evidence of rebound in placebo-adjusted percent change from baseline diastolic blood pressure from end of infusion (72 hours) to 8 hours post infusion (80 hours) (see right graph in Figure 20).

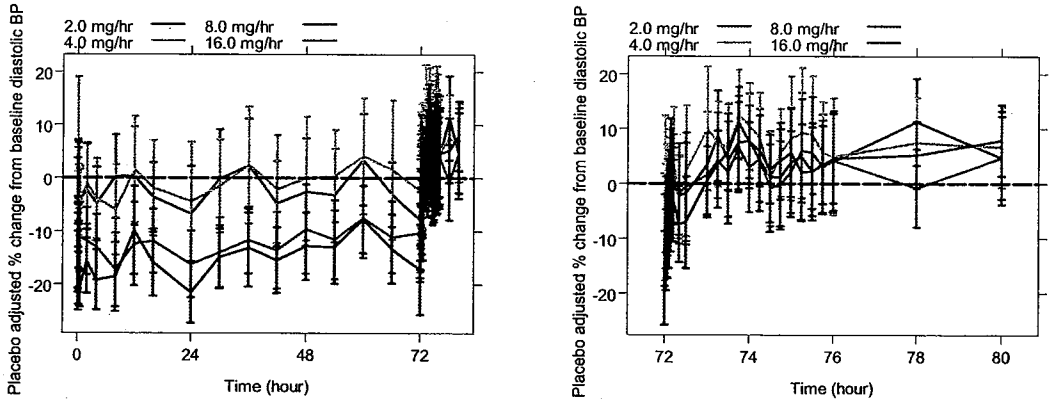


Figure 20. Mean (90% CI) placebo-adjusted percent change from baseline diastolic blood pressure for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01.

8.4 HEART RATE ANALYSIS

The heart rate is increased with clevidipine administration and it appears to be in a dose proportional manner except for the 4 mg/hr clevidipine dose group which is similar to placebo (see Figure 21 and Figure 22).

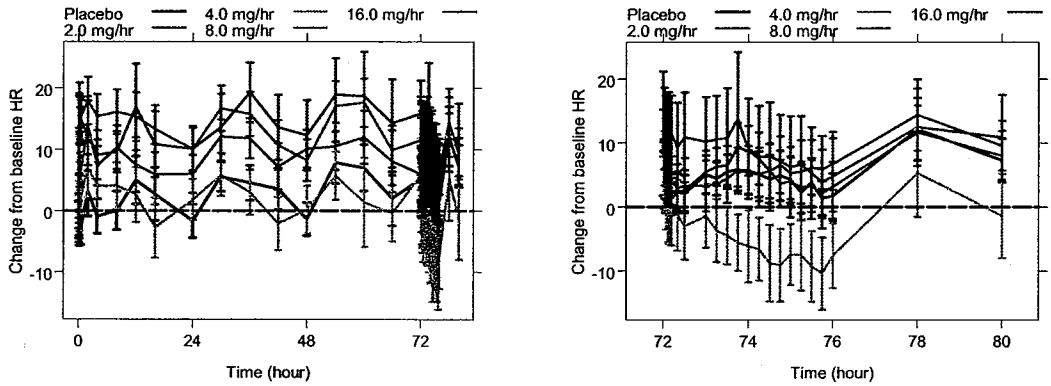


Figure 21. Mean (90% CI) change from baseline heart rate for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01.

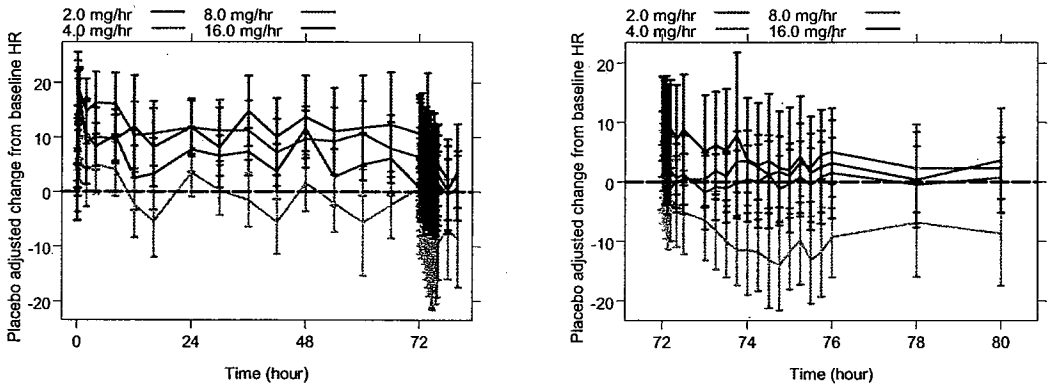


Figure 22. Mean (90% CI) placebo-adjusted change from baseline heart rate for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01.

APPEARS THIS WAY
ON ORIGINAL

8.5 MEAN ARTERIAL PRESSURE (MAP) ANALYSIS

The mean arterial pressure (MAP) is defined as the average arterial pressure during a single cardiac cycle and can be calculated by (2 x diastolic + systolic) / 3.

The ratio between MAP and heart rate (HR) (MAP/HR) is calculated as an indirect measure of the systemic vascular resistance.

The maximum reduction (% change from baseline) in MAP/HR is 40% for the two highest dose groups of 8 and 16 mg/hr and is maintained until end of infusion at 72 hours (see Figure 23-Figure 24).

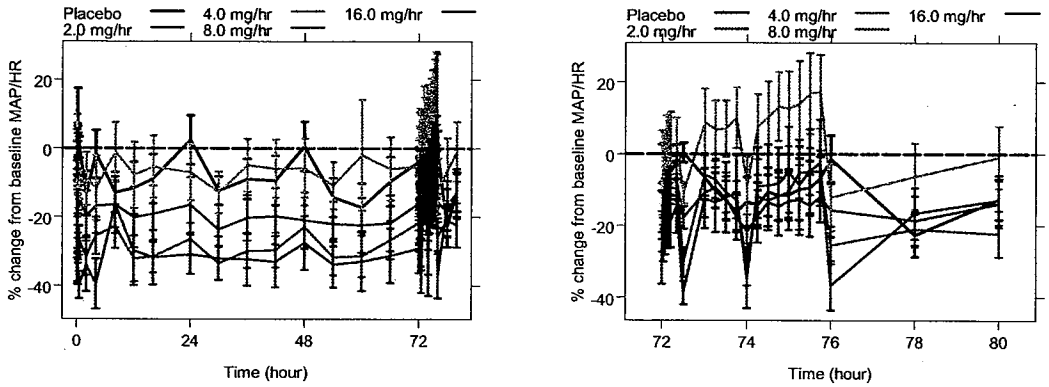


Figure 23. Mean (90% CI) percent change from baseline mean arterial pressure divided by heart rate (MAP/HR) for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01.

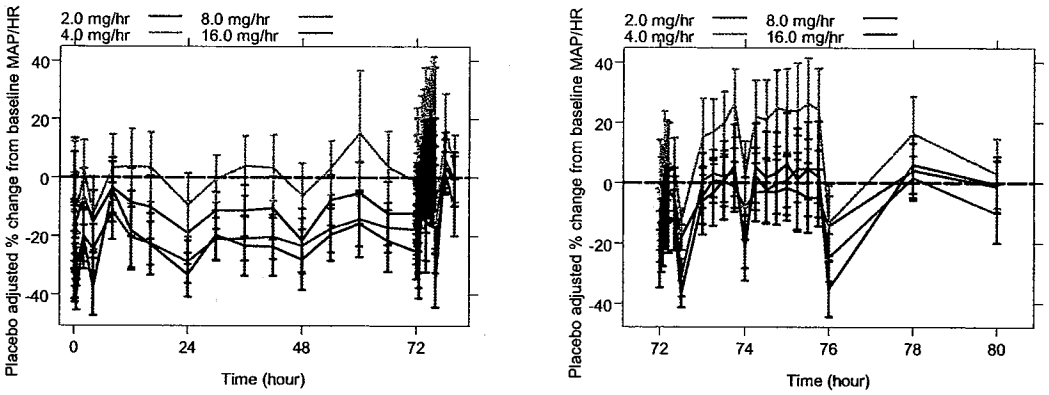


Figure 24. Mean (90% CI) placebo-adjusted percent change from baseline mean arterial pressure divided by heart rate (MAP/HR) for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01.

The sponsor also found an E_{max} relationship between the change in MAP/HR and blood concentration of clevidipine in healthy volunteers in Study SAD-0001. The estimated maximum reduction in MAP/HR (E_{max}) was 48.2% and the concentration to reach half-maximum effect (EC_{50}) was 21.7 nmol/L (see Figure 25).

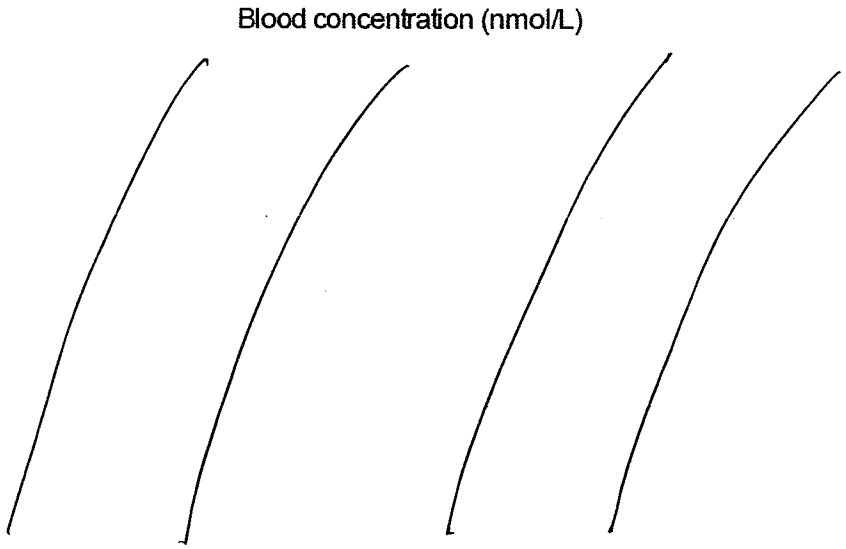


Figure 25. Relationship between blood concentration and effect expressed as reduction in the ratio of MAP/HR in healthy volunteers in study SAD-0001.
(Source: Sponsor's Figure 16 in SAD-0001 CSR)

8.6 DOSE-RESPONSE RELATIONSHIP

The Phase II dose-finding study (SAD-0003) in postcardiac surgical patients with perioperative hypertension demonstrated dose-dependent reductions in MAP between 0.24 to 46 mg/hr and that a dose of approximately 2 mg/hr (minimum effective dose) was an appropriate starting dose with responders being classified as patients having a reduction in MAP ≥10% from baseline (see Table 5 and Figure 26).

Table 5. Responder analysis from SAD-0003 according to randomized dose.

Randomized dose		Non-responders	Responders	
µg/kg/min	mg/h*	n (%)	n (%)	P value vs placebo
Placebo		11 (100)	0 (0)	NA
0.05	0.24	10 (91)	1 (9)	0.50
0.18	0.86	9 (69)	4 (31)	0.067
0.32	1.54	4 (40)	6 (60)	0.004
1.37	6.60	3 (25)	9 (75)	<0.001
3.19	15.31	1 (5)	19 (95)	<0.001
9.58	45.98	0 (0)	14 (100)	<0.001

Source: Final Study Report SAD-0003, Section 11.4.1.1, Table 6
* Based on a conversion for an 80 kg adult
NA = not applicable

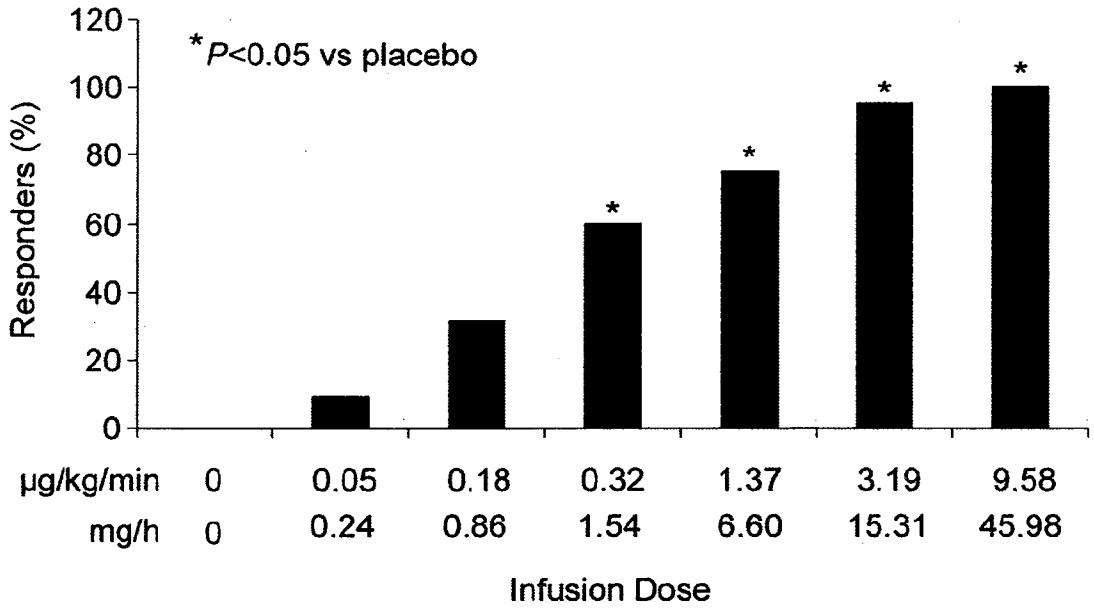


Figure 26. Effect of clevidipine on MAP as a function of infusion dose.
(Source: Figure 5 in sponsor's summary-clin-efficacy-acute-hypertension)

There was a statistical significant difference in MAP between all doses of clevidipine except for 0.05 mcg/kg/min (see Figure 27).

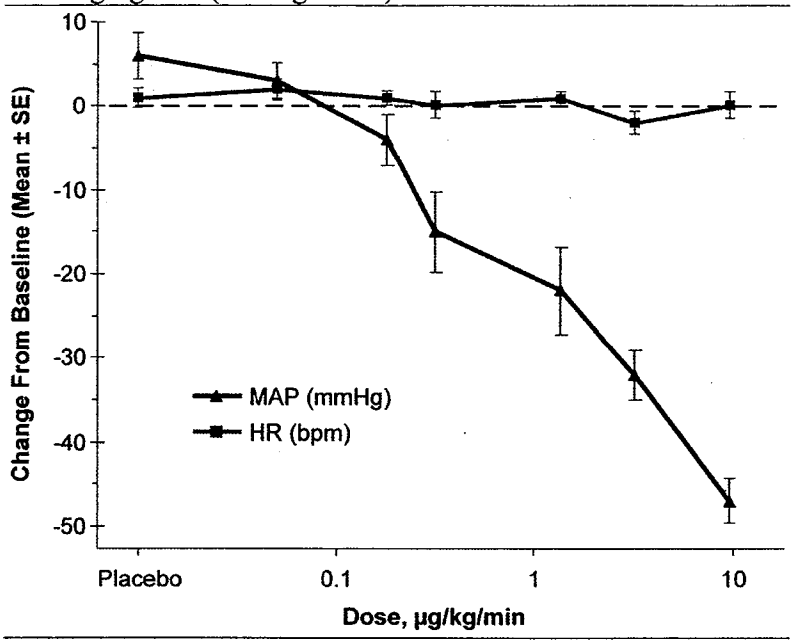


Figure 27. Mean change from baseline in mean arterial pressure (MAP) and heart rate as a function of clevidipine dose. *(Source: Figure 6 in sponsor's summary-clin-efficacy-acute-hypertension)*

Sponsor conducted a post-hoc regression analysis of Phase III studies supports an effective dose range of 2 mg/hr -32 mg/hr and a linear relationship between clevidipine dose and percent change in SBP at doses up to 20 mg/hr.

A regression analysis was constructed utilizing the modified intent-to-treat (mITT) population from the ESCAPE (Phase III perioperative studies TMC-CLV-03-01 and 03-02) and VELOCITY (severe hypertension study TMC-CLV-06-02) studies. The relationship between infusion rate and percent change in SBP was explored.

Only paired data (SBP and dose infusion rate) during the up-titration phase of treatment was included in the model. The ESCAPE and VELOCITY study designs included a rigorous period of hemodynamic data collection while clevidipine was titrated to a target SBP reduction. ECLIPSE studies were not included in the dose response analysis because most patients could only contribute one data point to the analysis and the majority of patients received doses at the lower end of the range.

A linear relationship was observed between clevidipine dose and percent change in SBP at doses up to 20 mg/hr where after the curve plateaus (see Figure 28). The dose-response relationship observed in the combined ESCAPE and VELOCITY studies predicts an approximate reduction in SBP of 1.0% per 1 mg/hr incremental increase in dose level.

According to the sponsor, further decrease in SBP was obtained in 24 out of 38 patients (63.2%) who were up-titrated from 16 to 32 mg/hr. The change in SBP observed

following up-titration from 8 to 16 mg/hr was subtracted from the change observed following up-titration from 16 to 32 mg/hr. The median value for this difference was 6.5 mm Hg which is the sponsor's argument for the proposed dose range of 2-32 mg/hr.

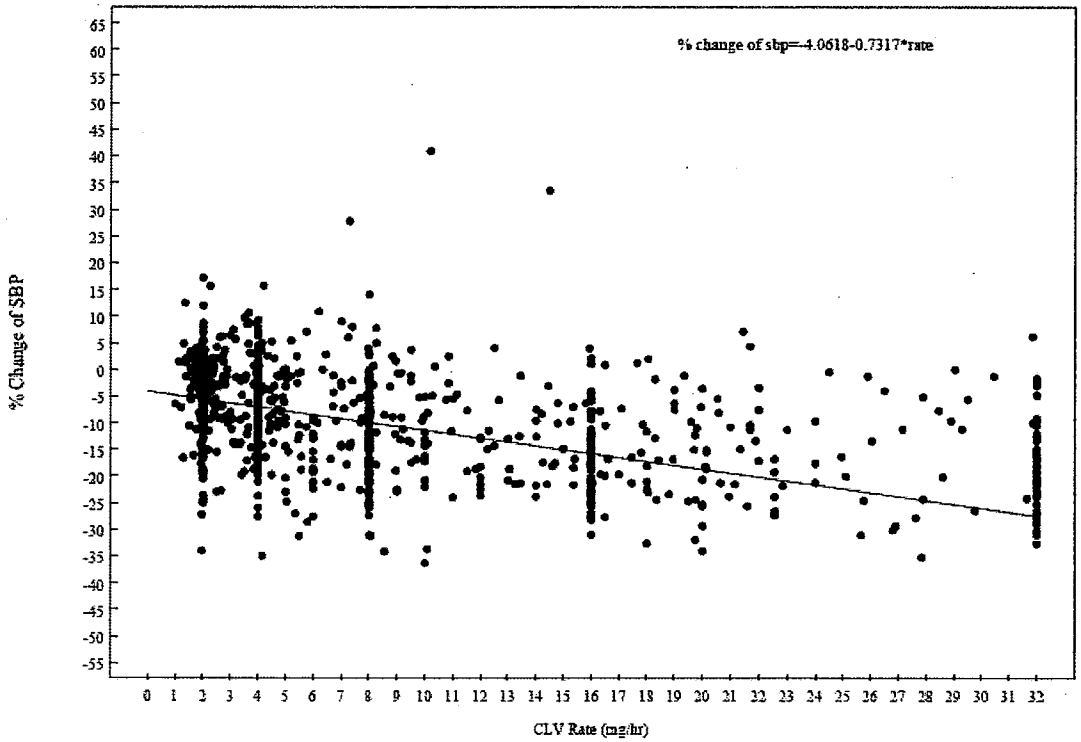


Figure 28. Linear regression of % change of SBP vs. clevidipine infusion by rate (ESCAPE and VELOCITY studies).
(Source: Figure 5.3 in sponsor's integrated summary of efficacy.

APPEARS THIS WAY
ON ORIGINAL

9 PHARMACOMETRICS REVIEW CONCLUSIONS

The overall conclusions for the Pharmacometrics review are:

Pharmacokinetic Conclusions

- A two-compartment pharmacokinetic model with first-order elimination adequately described the time-course of the observed clevidipine concentrations following a 72 hour constant IV infusion (TMC-CLV-06-01) and target SBP titration (TMC-CLV-06-02).
- The estimated distribution population half-life ($t_{1/2,\alpha}$) is 2-3 min and the terminal population half-life ($t_{1/2,\beta}$) is 1 hr with a steady-state volume of distribution (V_{ss}) estimate of 313 L indicating a high degree of tissue distribution.
- Clevidipine clearance was found to be influenced by body weight, body temperature, time since start of infusion, gender, and patient population.
    - There was an indication of time dependent clearance with up to 20% increase over the 72 hour infusion.
    - Females were found to have 25% lower clearance compared to male patients
    - Patients with severe hypertension were found to have approximately 30% lower clearance compared to mild-moderate hypertension patients.
    - The clearance of clevidipine was found to be slower in the hypothermic group (0.03 L/min/kg) compared to normothermic patients with a clearance of 0.06 L/min/kg.
- The identified clearance covariates do not have any clinical impact since clevidipine has a very short half-life (2-3 min distribution and 1 hr terminal) and is easily titrated to effect. No dose adjustments based on covariates are thus warranted.

Blood Pressure Conclusions

- There does not appear to be any tolerance development since no delay (hysteresis) was observed between clevidipine concentration and percent change from baseline SBP with or without placebo adjustment.
- The time to onset of maximal systolic blood pressure effect in patients with mild to moderate hypertension in study TMC-CLV-06-01 was within 5-10 minutes of starting the constant clevidipine infusion.
- The duration of SBP effect appears to be as long as clevidipine is being infused evidenced by 72 hours constant infusion in mild to moderate hypertension patients.
- The rapid clearance of clevidipine and direct effect on SBP results in a short offset of SBP effect. In most patients, full recovery to baseline SBP is achieved in

5-15 minutes after end of clevidipine infusion. Any unintended hypotension may be easily reversed by down-titration or temporary discontinuation of the infusion.

- There is evidence of rebound after end of the clevidipine infusion when looking at placebo-adjusted percent change from baseline SBP with a mean of 9.3% (90% CI 4.1-14.5%) for the 4 and 16 mg/hr group. This corresponds to a rebound of 11 and 14 mm Hg in absolute systolic blood pressure for a patient with the mean baseline SBP of 150 mm Hg.
- The maximal reduction in percent change from baseline SBP was estimated to be 25% corresponding to a 40 mm Hg drop in SBP for a patient with a baseline SBP of 150 mm Hg. The EC_{50} was estimated to be 7 ng/mL and the maximal effect was obtained at concentrations above 15 ng/mL.
- The PK-SBP relationship for clevidipine was different between patients with mild-moderate hypertension (TMC-CLV-06-01) and patients with severe hypertension (TMC-CLV-06-02) with a lower EC_{50} value in the severe hypertension patients but similar E_{max}.
- Clevidipine was found to have an effect on heart rate. The mean change from baseline heart rate increased by 20 bpm for the 16 mg/hr dose group.
- Similar dose-dependent effects were also observed for diastolic blood pressure and mean arterial pressure corrected by heart rate (measure of vascular resistance).

Dose-Response Conclusions

A regression analysis of clevidipine dose and % change from baseline SBP from the phase II and III studies suggest that:

- 2 mg/hr is an appropriate starting dose.
- An E_{max} relationship exists between clevidipine dose, reduction of BP and clevidipine blood concentrations, including:
    - A linear relationship between clevidipine dose and percent change in SBP at doses up to 20 mg/hr.
    - A flattening of the dose-response relationship at doses greater than 20 mg/hr and up to 32 mg/hr.
- The effective clevidipine dose range is 2-16 mg/hr and little additional blood pressure effect was observed at higher doses. Further decrease in SBP was obtained in 24 out of 38 patients (63.2%) who were up-titrated from 16 to 32 mg/hr in study SAD-003 (postcardiac surgical patients with perioperative hypertension) with a median decrease in SBP of 6.5 mm Hg.
- In study SAD-003 in postcardiac surgical patients with perioperative hypertension, the highest dose rate of 46 mg/hr led to discontinuation of study therapy in 28% of patients due to hypotension.

- The dose-response relationship observed in the combined ESCAPE and VELOCITY studies predicts an approximate reduction in SBP of 1% per 1 mg/hr incremental increase in dose level.

APPEARS THIS WAY
ON ORIGINAL

10 APPENDICES

10.1 COVARIATE-PK PARAMETER RELATIONSHIPS FOR BASE PK MODEL

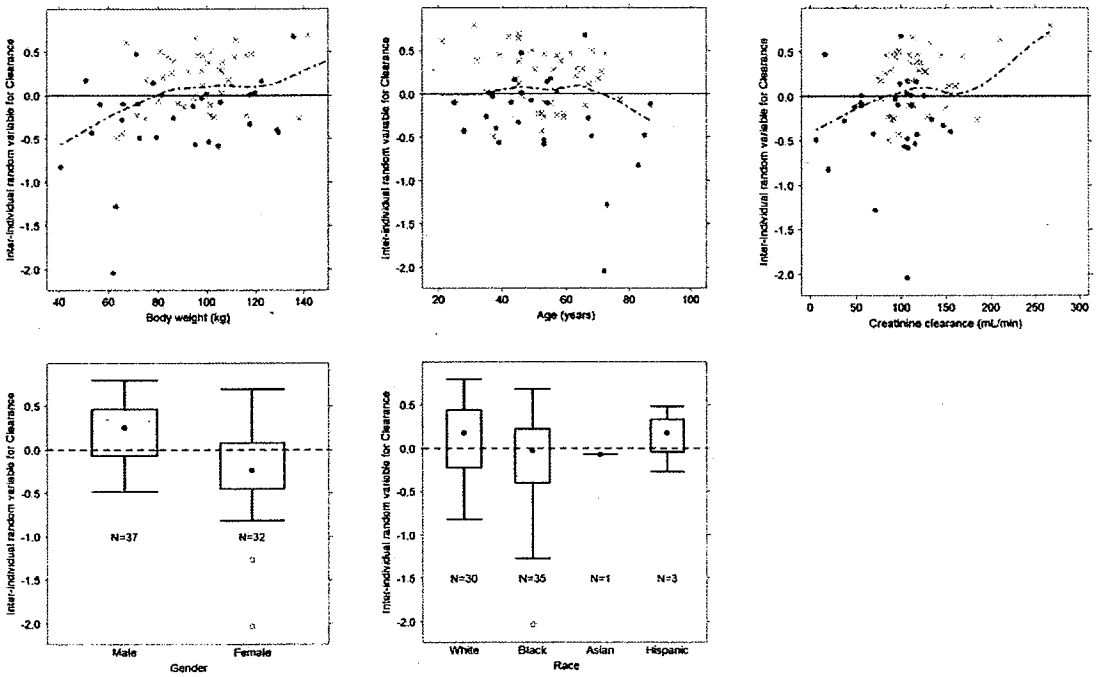


Figure 29 Graphical analyses of clearance-covariate relationships from base PK model.

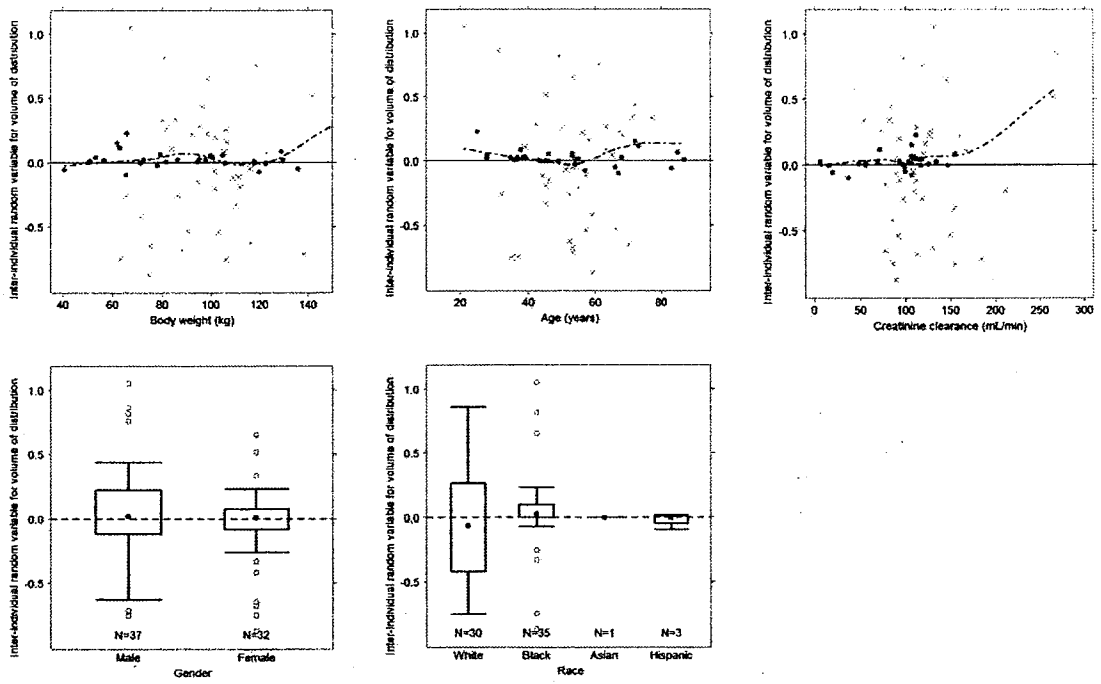


Figure 30 Graphical analyses of volume-covariate relationships from base PK model.

10.2 GOODNESS-OF-FIT GRAPHS FOR REVIEWER'S FINAL PK MODEL

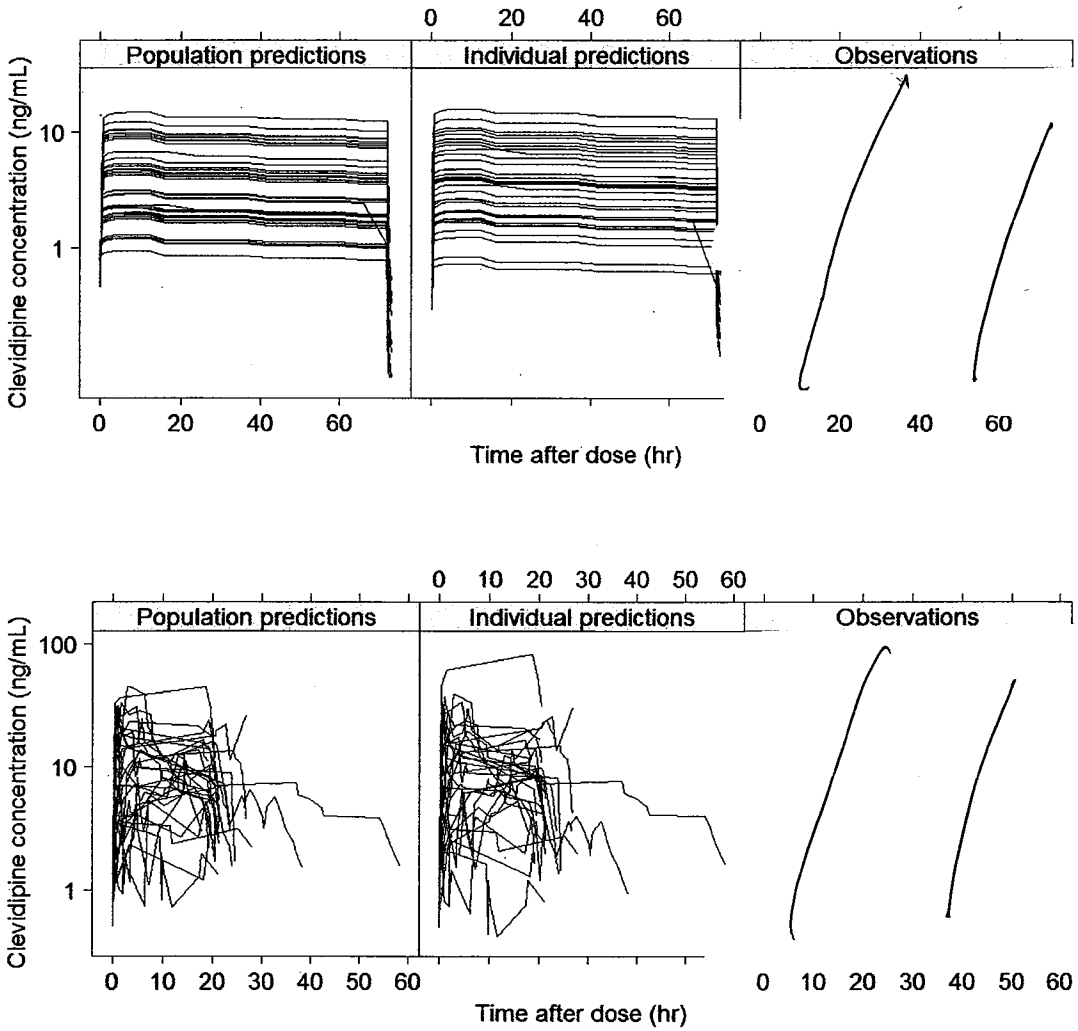


Figure 31 Clevidipine concentration-time profiles for population predicted (left), individual predicted (middle), and observed (right) clevidipine concentrations for study TMC-CLV-06-01 (Top) and TMC-CLV-06-02 (Bottom).

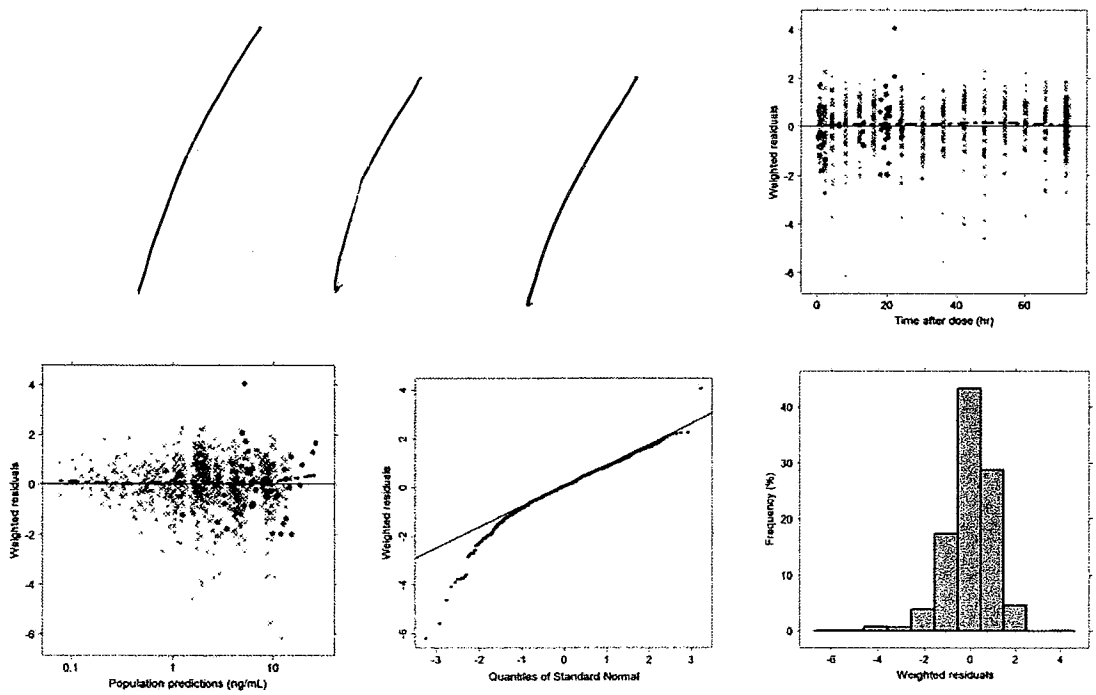


Figure 32 Goodness-of-fit graphs for reviewer's final PK model. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. time after dose (top right), population predictions (bottom left), quantiles of standard normal (bottom center), and a histogram of weighted residuals (bottom right). The solid black line is the line of unity/identity and the dashed blue line is a local smoothing regression line. The black crosses are subjects from study 601 and the red dots are from study 602.

10.3 COVARIATE-PK PARAMETER RELATIONSHIPS FOR FINAL PK MODEL

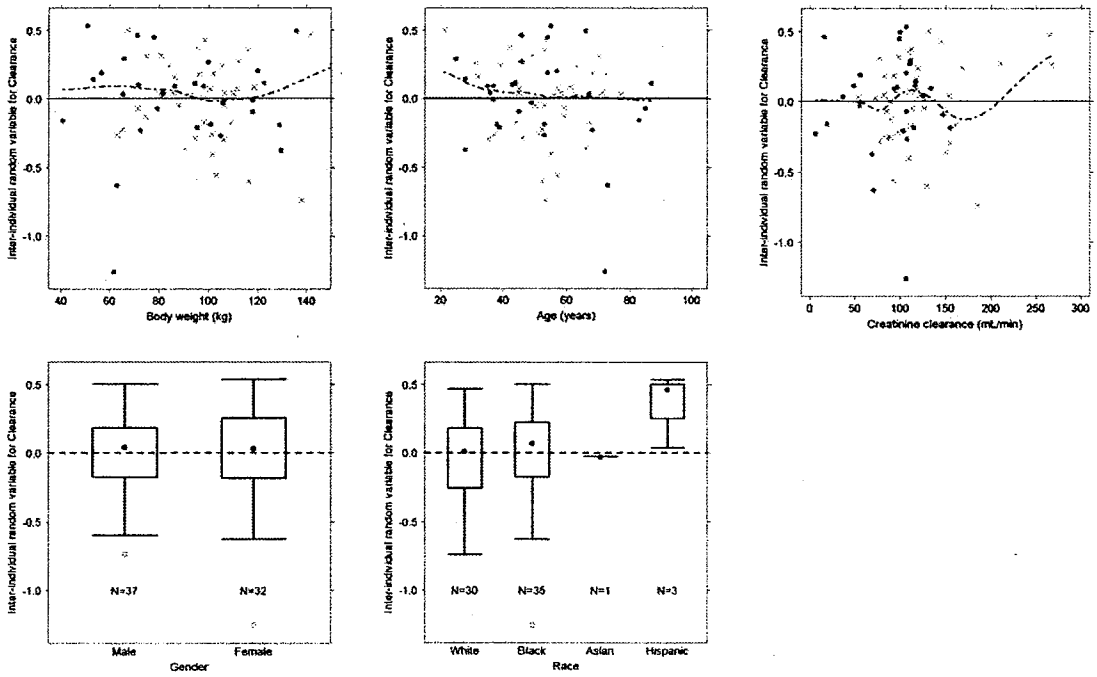


Figure 33 Graphical analyses of covariates vs. clearance inter-individual variability estimates.

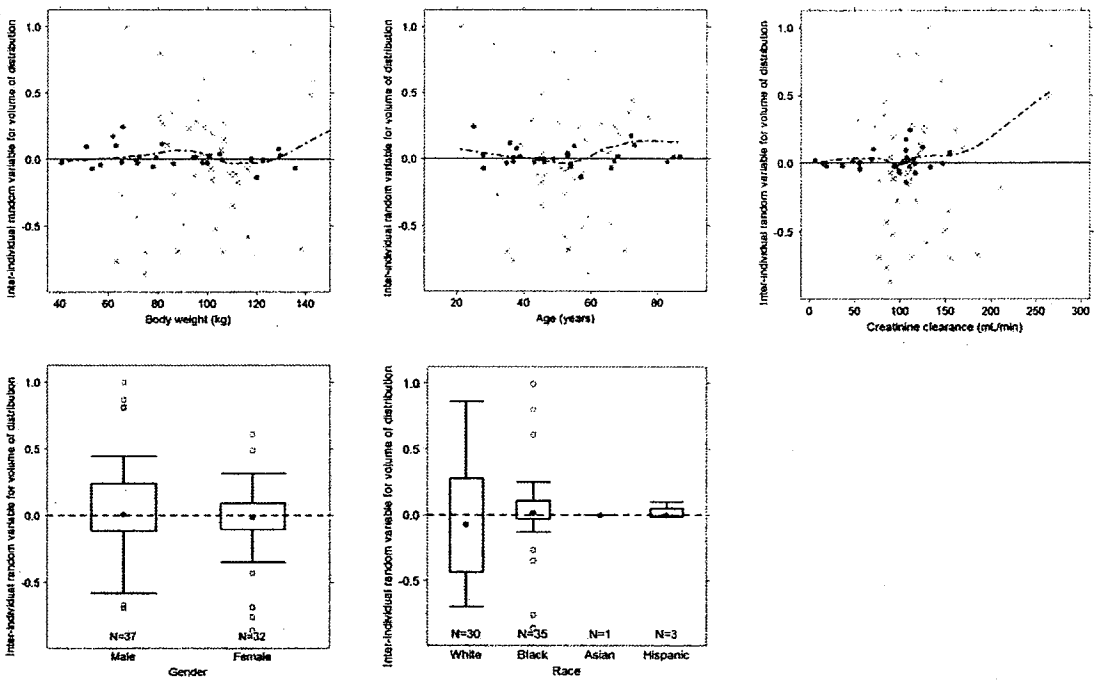


Figure 34 Graphical analyses of covariates vs. volume inter-individual variability estimates.

10.4 CLEVIDIPINE CONCENTRATION VS SYSTOLIC BLOOD PRESSURE

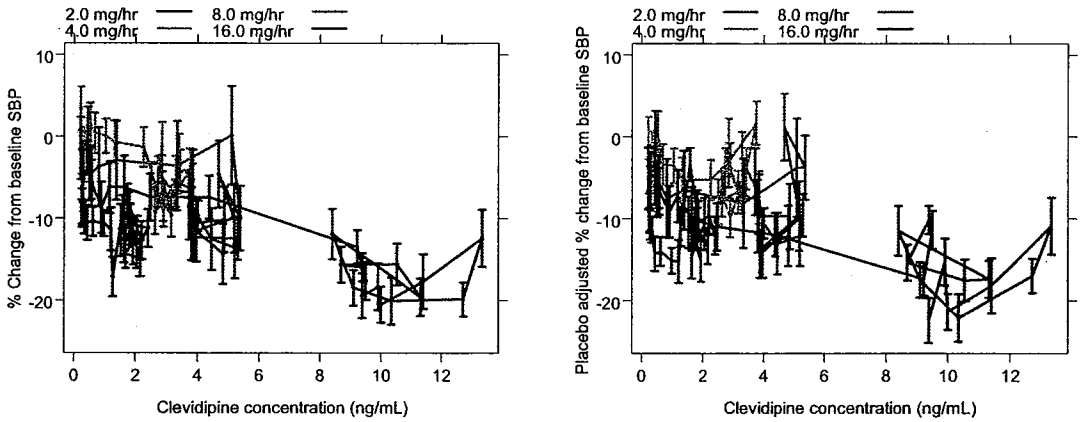


Figure 35. Relationship between time-matched mean (±SE) percent change in SBP from baseline (left) and placebo-adjusted (right) and the mean clevidipine concentration over the 72 hour treatment period through 60 minutes post study drug infusion connected by lines in chronological order for study TMC-CL-06-01.

APPEARS THIS WAY
ON ORIGINAL

10.5 GOODNESS-OF-FIT GRAPHS FOR REVIEWER'S FINAL PD MODEL

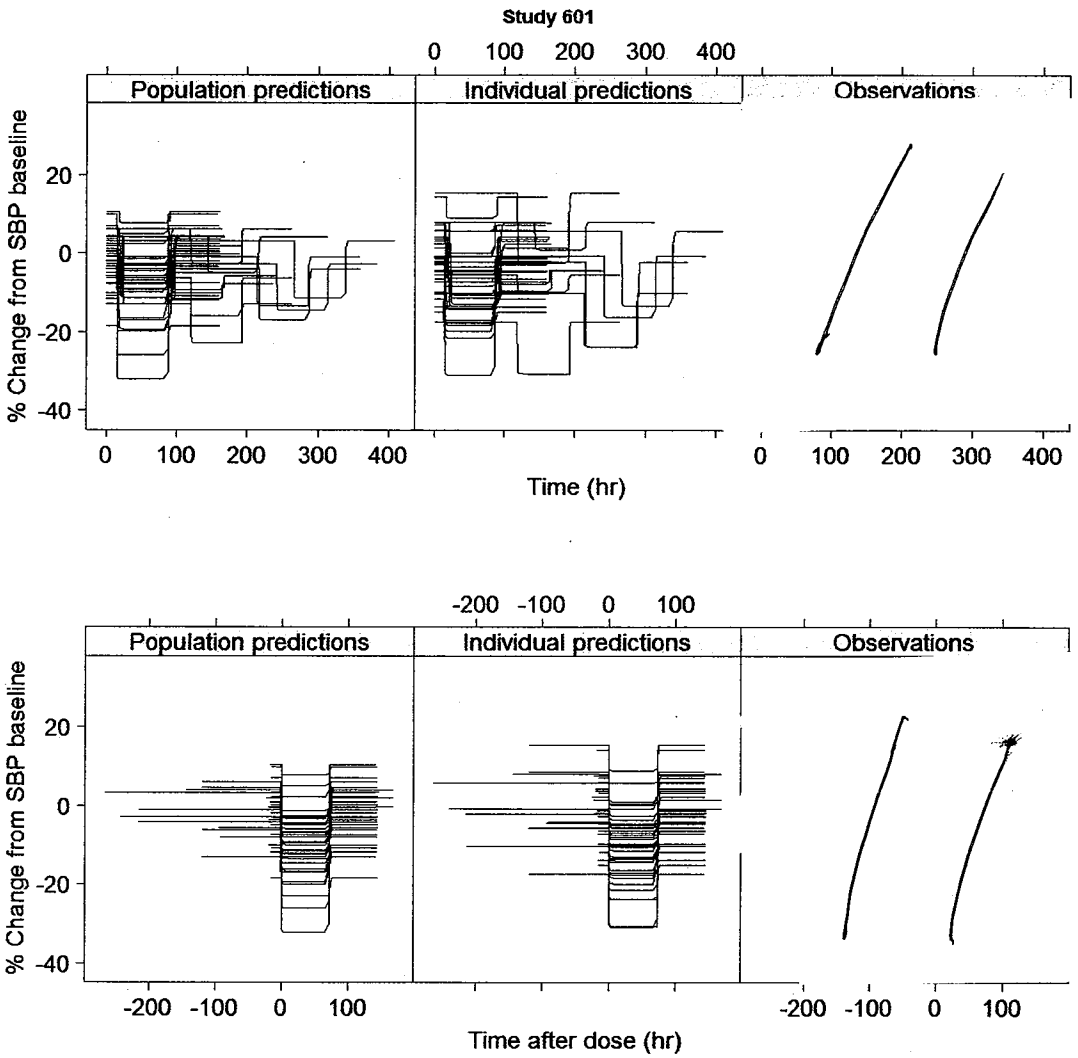


Figure 36 Percent change from baseline SBP time (top) and time after infusion (bottom) profiles for population predicted (left), individual predicted (middle), and observations (right) for study TMC-CLV-06-01.

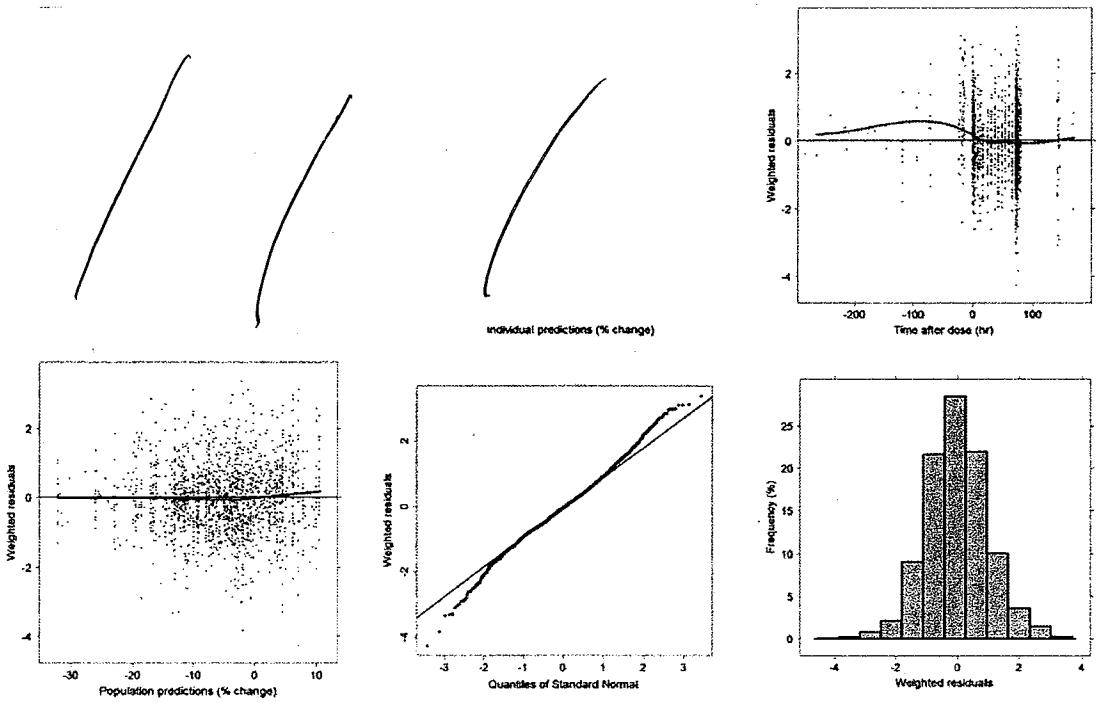


Figure 37 Goodness-of-fit graphs for reviewer's final SBP model. Observations vs. population (top left) and individual (top center) predictions, weighed residuals vs. time after dose (top right), population predictions (bottom left), quantiles of standard normal (bottom center), and a histogram of weighted residuals (bottom right). The solid black line is the line of unity/identity and the dashed blue line is a local smoothing regression line.

APPEARS THIS WAY
ON ORIGINAL

10.6 COVARIATE-PD PARAMETER RELATIONSHIPS FOR FINAL PD MODEL

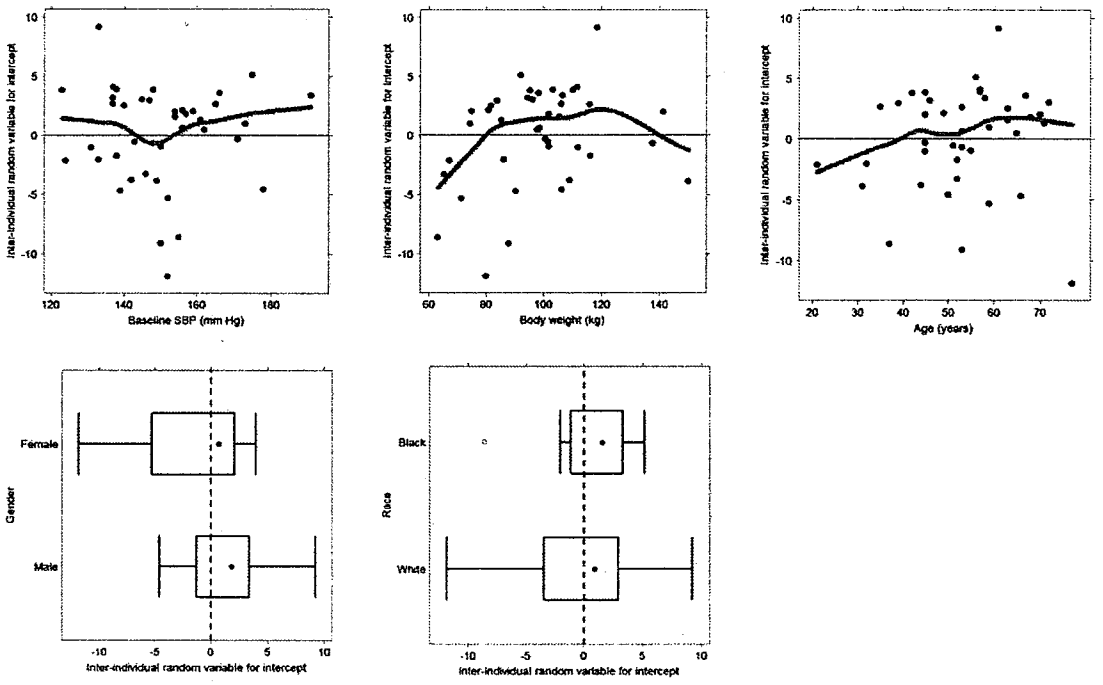


Figure 38 Graphical analyses of covariates vs. Intercept inter-individual variability estimates.

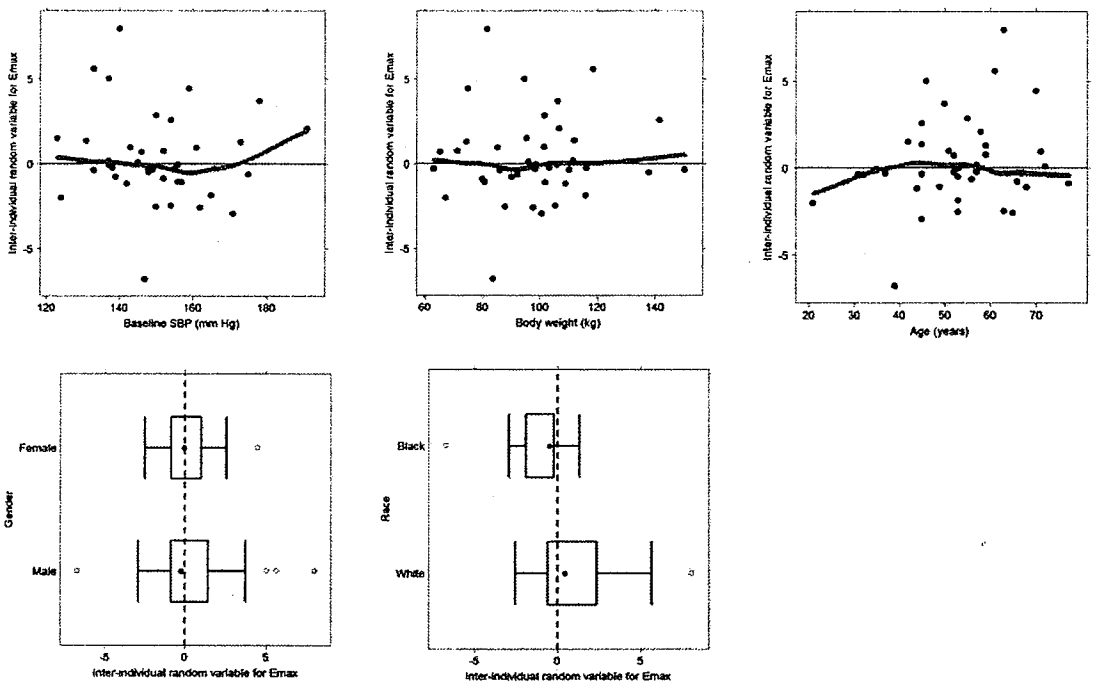


Figure 39 Graphical analyses of covariates vs. E_{max} inter-individual variability estimates.

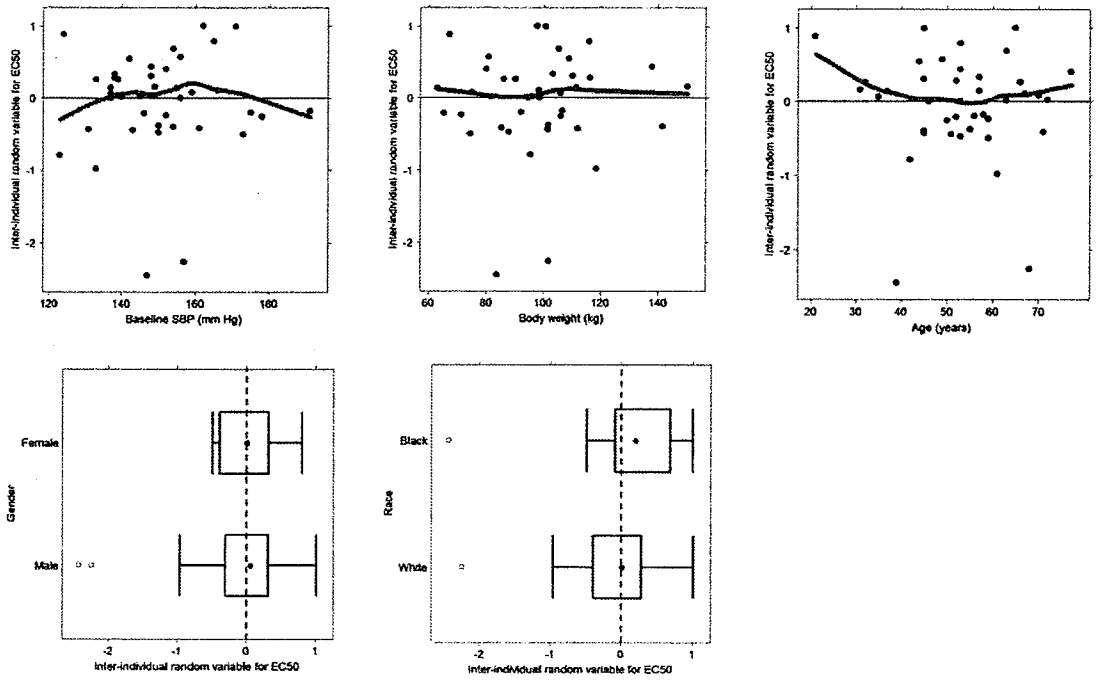


Figure 40 Graphical analyses of covariates vs. EC_{50} inter-individual variability estimates.

APPEARS THIS WAY
ON ORIGINAL

11 APPENDIX: ALTERNATIVE DOSING ALGORITHM

The following PK-SBP simulations were performed to investigate the adequacy of sponsor's proposed dosing with respect to SBP overshoot and fluctuations and alternatively propose a better dosing algorithm.

Sponsor's proposal is to start with 2 mg/hr and double the dose every 90 seconds

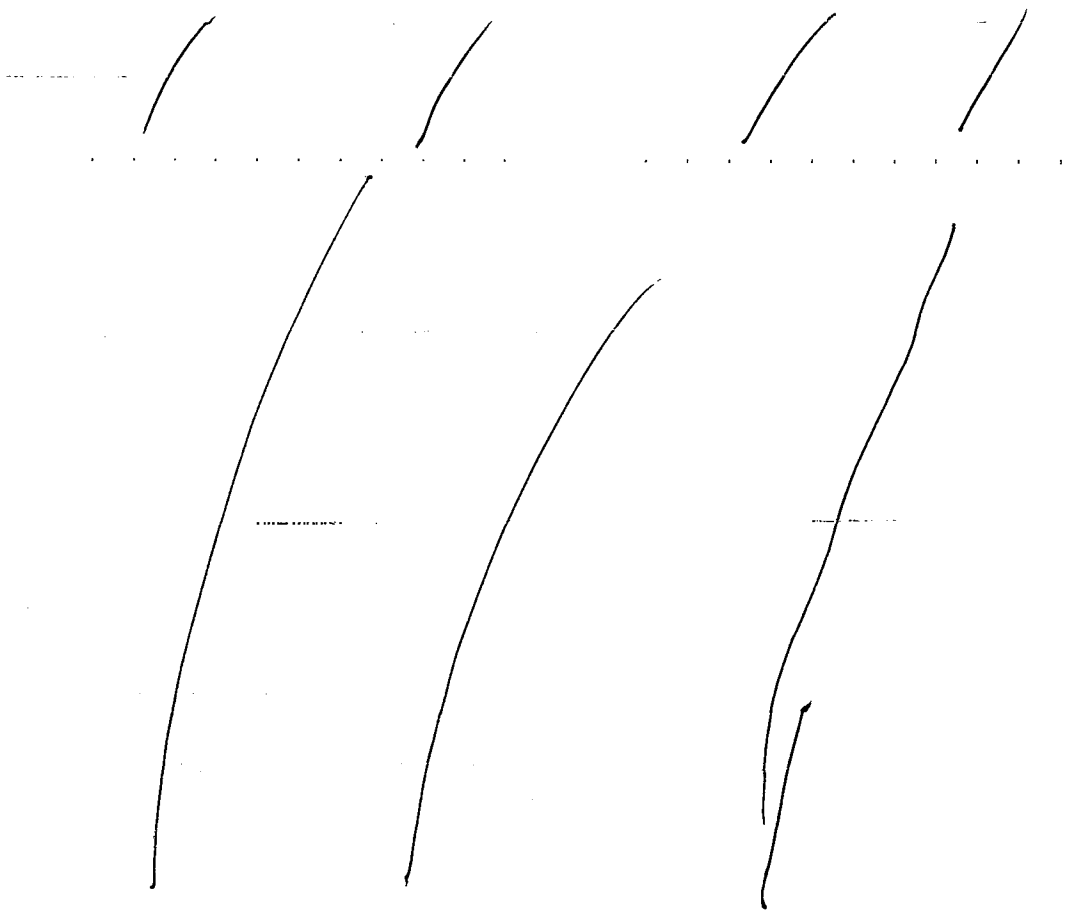


Figure 41. (Top) Typical mild-moderate hypertension patient's PK (top left) and % change from baseline SBP (top right) time profiles. (Bottom) Simulated median (10-90th percentile) mild-moderate hypertension patient's PK (bottom left) and % change from baseline SBP (bottom right) time profiles using sponsor's proposed dosing algorithm.

A more appropriate dosing algorithm which will get patients faster to target SBP and minimize SBP overshoot and fluctuations are explored in the following.

2 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

12 SPONSOR'S POPULATION PK/PD ANALYSIS

(Source: Section 2.7.2.2.4 in sponsor's summary of clinical pharmacology studies)

Population PK and PD analysis of clevidipine was performed using data from studies TMC CLV-06-01 and TMC CLV-06-02.

The main objective of this analysis was to develop a population PK and PD model to describe concentration time data arising from TMC CLV-06-01 in patients with hypertension, to identify and characterize patient factors which influence the PK, PD and their variability, and to estimate the magnitude of unexplained variability in clevidipine in this patient population. In addition, performance of the models developed for clevidipine in an external database TMC CLV-06-02 was evaluated.

The PK data used in the population PK analysis represent all available concentration data collected in TMC CLV 06-01. The primary metabolite (M1) information was not evaluated. The final database used for model building and evaluation consisted of 804 observations from a total of 40 subjects. Therefore, 83.8% of the original clevidipine observations and 100% of the original subjects were available for evaluation. Data from the PK database were merged with SBP data from all patients enrolled in TMC-CLV-06-01. For the PK/PD database, patients from all dose groups including placebo were included. The final database used for PD model building and evaluation consisted of 2380 SBP observations from a total of 53 subjects. Therefore, 99.3% of the original SBP observations and 100% of the original subjects were available for evaluation. Including the PK observations, there were a total of 3184 concentration and SBP records from a total of 53 subjects.

Pharmacokinetic results

The best final covariate pharmacokinetic model for clevidipine identified in the present analysis was a 2 compartment linear model with first order elimination. The model was parameterized Cl, the volumes of distribution of the central (V1) and peripheral (V2) compartments and the apparent inter-compartmental clearance (Q). The model included a time dependent clearance based on study day and weight. The addition of weight and day as a covariate on clearance decreased inter-individual variability in Cl from 32% to 28%. The variance for V1 reduced slightly from 58% to 55% and the variance for V2 decreased slightly from 58% to 57%.

For a subject weighing 70 kg, the model estimated Cl was 1220 L/h (0.29 L/kg/min). The expected typical predicted clearance values are presented in Table 28. Over a weight range from 50 to 100 kg, clearance changes substantially as compared to the reference subject.

Table 28: Effect of weight on typical values of clearance

Body Weight	Clearance	Percent change from reference
50	947.90	0.78
60	1086.80	0.89
70	1220.00	1.00
80	1348.51	1.11
90	1473.05	1.21
100	1594.18	1.31

The effect of day on Cl is presented in Table 29. In this evaluation, the apparent Cl of clevidipine increases by approximately 12% over the 3 day infusion.

Table 29: Effect of day on typical value of Cl

Day	Clearance	Percent change from reference
1	1220.00	1.00
2	1313.01	1.08
3	1370.68	1.12

The observed concentrations versus time were overlaid with the typical predicted concentrations for the final pharmacokinetic model. The agreement between observed and typical predicted concentrations was reasonable, and the typical predicted concentrations describe the central tendency of the data. However, due to intra- and interpatient variability, caution should be applied when interpreting this result.

Pharmacodynamic results

The best final pharmacodynamic model for clevidipine identified in the present analysis was parameterized for baseline SBP, and a slope term. The intercept value included an effect of age. There were some slight indications of a race effect on the slope term relating clevidipine concentration to SBP which may be further evaluated.

For a 55 year old subject, the model estimated SBP was 147 mmHg. The expected typical predicted baseline SBP values are presented in Table 30. Over an age range from 20 to 90 years, the expected baseline SBP changes only slightly as compared to the reference subject, although the magnitude of the change is approximately 20 mmHg over 70 years.

Table 30: Effect of age on typical value of SBP

Age	E0	Percent change from reference
20	135.93	0.92
30	140.26	0.95
40	143.42	0.98
55	147.00	1.00
60	147.99	1.01
70	149.77	1.02
80	151.33	1.03
90	152.71	1.04

The SBP values versus time were overlaid with the typical predicted SBP values for the final pharmacodynamic model. The agreement between observed and typical predicted concentrations was reasonable, and the typical predicted SBP values describe the central tendency of the data. Also, the typical predicted SBP values cover a greater range of the observed values, as might be expected given the addition of a covariate and the reduction of inter-individual variability.

PK/PD covariates

The evaluation of covariate effects in PK analysis showed an effect of body weight as the most important covariate. Over the range of body weights of 50 to 100 kg, the typical value of clearance changed from 948 to 1594 L/h and further examination of data suggested that height was also potentially important. Therefore, BSA may be a better descriptor of pharmacokinetic variability than weight. In addition, an effect of day was also identified. Over the three days of infusion, the typical value of clearance increased from 1220 to 1371 L/h for a 70 kg person. The cause of this effect is not known.

The evaluation of covariate effects in PD analysis showed an effect of age as the most important covariate. Over the age range in this present database, the typical value of SBP increased approximately 13%. There was some slight indication of a race effect on both SBP and slope. No other covariates were identified in this evaluation.

In general the PK of clevidipine subjects with mild to moderate hypertension were well described by a two-compartment open model with first order elimination from the central

compartment while the PD of clevidipine as measured by systolic blood pressure were best described using a direct effect linear model.

Body weight was found to significantly contribute to inter-individual variability in clearance and the central volume of distribution in this evaluation. There was an indication of time dependent clearance where the clearance increased with time and age was the only covariate to affect SBP.

However, the overall effect of covariance is small and should not affect dose of clevidipine planned to be used in the clinical setting since the drug is titrated to the desired hemodynamic effect.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Christoffer Tornoe
4/30/2008 11:00:30 AM
BIOPHARMACEUTICS

Yaning Wang
4/30/2008 12:32:17 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW
DIVISION OF CLINICAL PHARMACOLOGY I

NDA 22-156/N000	SUBMISSION DATE	July 2, 2007
QS000		September 6, 2007
BM000		September 6, 2007

TYPE: ORIGINAL NEW DRUG APPLICATION

BRAND NAME: Cleviprex® Intravenous Emulsion
GENERIC NAME: Clevidipine Intravenous Emulsion

DOSAGE STRENGTH: 0.5 mg/mL in 50 and 100 mL bottles

INDICATION: [redacted] when the use of oral therapy is not feasible or desirable

SPONSOR: The Medicines Company

PRIMARY REVIEWER: Lydia Velazquez, Pharm.D.
TEAM LEADER: Patrick Marroum, Ph.D.

PM REVIEWER: Christoffer Tornoe, Ph.D.
PM TEAM LEADER: Janing Wang, Ph.D.

QT REVIEWER: Christine Garnett, Pharm.D.

TABLE OF CONTENTS

Executive Summary

The Medicines Company is seeking approval of Cleviprex® (clevidipine IV emulsion). The sponsor is seeking an indication for [redacted] when the use of oral therapy is not feasible or not desirable. Clevidipine is being developed in one strength with a concentration of 0.5 mg/mL in 50 and 100 mL single use vials. In total, the sponsor has submitted 19 clinical studies to the NDA; which includes nine with pharmacokinetic data (Studies SAD-0004, SAD-0003, SAD-0010, CLV-06-01, SAD-0006, SAD-0001, SAD-0002, SAD-0018, and SAD-0003) and one QT study (CLV-05-01). One of the studies is focused on pharmacometrics analysis. Seven in-vitro studies were also submitted to the NDA containing metabolism and protein binding data of which all were reviewed. In total, this review will assess 17 studies from the Clinical Pharmacology perspective.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed NDA 22-156 original NDA submitted on July 2, 2007 and subsequent submissions to the NDA (see above) for Cleviprex® intravenous emulsion and has the following clinical pharmacology comments:

REVIEWER COMMENTS TO THE SPONSOR:

The following Comments should be addressed by the sponsor:

1. **Dosing Increments:**

The sponsor's recommended dosing regimen of 2-32 mg/hr is adequate. However, clevidipine dose increments should only be administered 5 minutes after previous increments in order to reach [redacted] the new hemodynamic steady-state and not [redacted] as proposed by the sponsor.

2. **Proposed Labeling:**

Please refer to label in Appendix I for details.

Lydia Velazquez, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary Reviewer

FT Initialed by Patrick Marroum, Ph.D. _____

OCPB Briefing was held March 11, 2008. Attendees were: L. Velazquez, C. Tornoe, M. Mehta, P. Marroum, B.N. Beasley, A. Karkowsky, N. Stockbridge, H.Y. Ahn, L.M. Lee, K. Estes, D. Hinton, Y. Wang, E. Hausner (telecon), E.D. Bashaw, P. Lee, J. Lazor, A. Rahman, F. Goodsaid, A. Adebowale, T.E. Ong, and J. Earp.

CC list: HFD-110: NDA 22-156 (HintonD, StockbridgeN); HFD-860: (VelazquezL, MarroumP, MehtaM); CDER Central Document Room

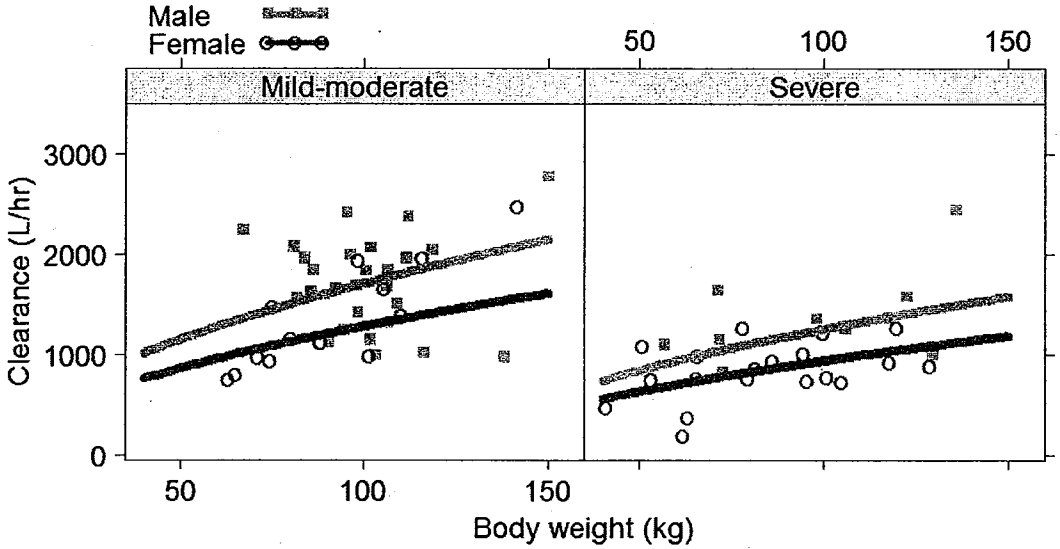
Summary of Important CPB Findings

Proposed Dosages of 2-32 mg/hr and Route of Administration: Cleviprex™ (clevidipine IV emulsion) is intended for intravenous use and should be titrated to achieve the desired blood pressure reduction. Dosage must be individualized depending on the severity of hypertension and the response of the patient. Blood pressure should be monitored during and after the infusion to avoid excessive reductions in systolic or diastolic blood pressure. Patients may be safely monitored with a blood pressure cuff or an arterial line.

Body weight, patient population (mild-moderate/severe), and gender were found to be significant covariates for clevidipine clearance (see Figure below) with severe hypertension patients having 30% lower clearance compared to mild-moderate patients and females having 25% lower clearance compared to males. There was also an indication of time dependent clearance where the clearance increased by a total of 20% following 4 days continuous infusion due to unknown reasons.

These covariates (body weight, patient population, gender, and days since start of infusion) explain 15% of the unexplained inter-individual variability (IIV) in clevidipine clearance (IIV on clearance reduced from 51% to 36%).

The identified clearance covariates do not have any clinical impact since clevidipine has a very short half-life (2-3 min distribution and 1 hr terminal) and is easily titrated to effect. No dose adjustments based on the identified clearance covariates are thus warranted.



Clevidipine clearance vs. body weight. Mild-moderate (Left) and Severe (Right) hypertension patients. Male patients' individual clearance estimates are shown as grey filled squares and females are open red circles. The population mean predictions across body weights are illustrated as solid grey line for males and solid red line for females.

A dose of 2 mg/hr was shown to be the minimum effective dose (responders being classified as patients having a reduction in mean arterial pressure (MAP) ≥10% from baseline) in SAD-003 and thus appears to be an appropriate starting dose with responders being classified as patients having a reduction in MAP ≥10%.
An E_{max} relationship exists between clevidipine dose, reduction of BP and clevidipine blood concentrations, including:

- A linear relationship between clevidipine dose and percent change in SBP at doses up to 20 mg/hr.
- A flattening of the dose-response relationship at doses greater than 20 mg/hr and up to 32 mg/hr.

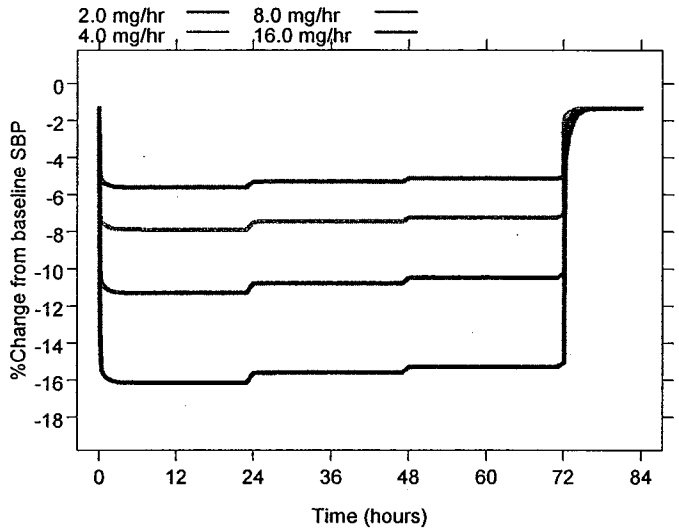
The effective clevidipine dose range is 2-16 mg/hr and little additional blood pressure effect was observed at higher doses. Further decrease in SBP was obtained in 24 out of 38 patients (63.2%) who were up-titrated from 16 to 32 mg/hr in study SAD-003 (postcardiac surgical patients with perioperative hypertension) with a median decrease in SBP of 6.5 mm Hg. The highest dose rate of 46 mg/hr tested in study SAD-003 led to discontinuation of study therapy in 28% of patients due to hypotension.

The proposed dosing regimen of 2-32 mg/hr is thus found to be adequate.

Transition to an oral hypertensive agent: Cleviprex can be discontinued or titrated to maintain blood pressure to the desired effect while appropriate oral therapy is established. If treatment includes transfer to an oral antihypertensive agent, continue blood pressure monitoring until desired effect is achieved.

Titration of Clevidipine to effect: Clevidipine concentrations reach 80% and 95% of steady-state 5 and 10 minutes after dose adjustments. The hemodynamic effect of clevidipine is direct (with an E_{max} relationship between clevidipine dose/exposure and blood pressure) and the reduction in blood pressure after dose adjustments will thus also reach 80% and 95% of steady-state after 5 and 10 min. Dose increments should thus only be allowed every 5 minutes to evaluate the blood pressure effect at a particular infusion rate.

Doubling dose increments (i.e. 2 to 4, 4 to 8, 8 to 16, 16 to 32 mg/hr) appear adequate because of the observed direct hemodynamic effect of clevidipine and the identified E_{max} relationship between clevidipine dose/exposure and blood pressure (see Figure below).



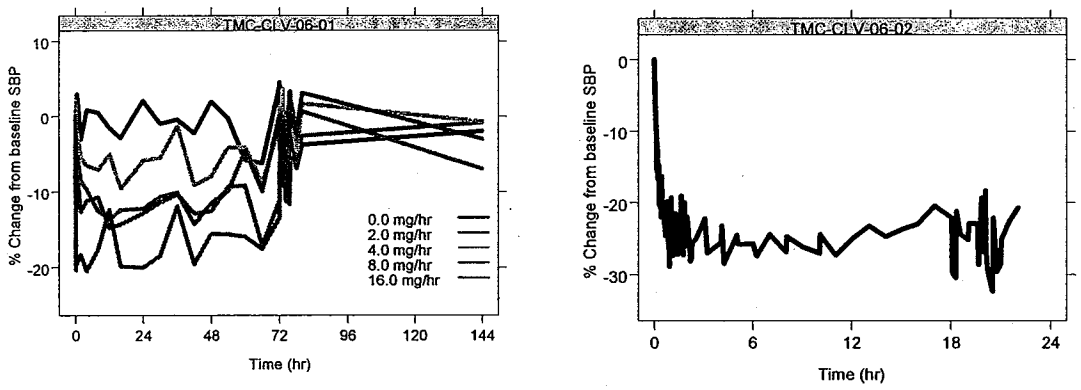
Population predicted percent change from baseline SBP for clevidipine doses of 2 (green), 4 (orange), 8 (blue), and 16 (red) mg/hr for an 80 kg male mild-moderate hypertension patient.

Onset/duration/offset of Effect?

The time to onset of maximal systolic blood pressure effect in patients with mild to moderate hypertension in study TMC-CLV-06-01 was within 5-10 minutes of starting the constant clevidipine infusion approximately corresponding to the time of maximum concentration.

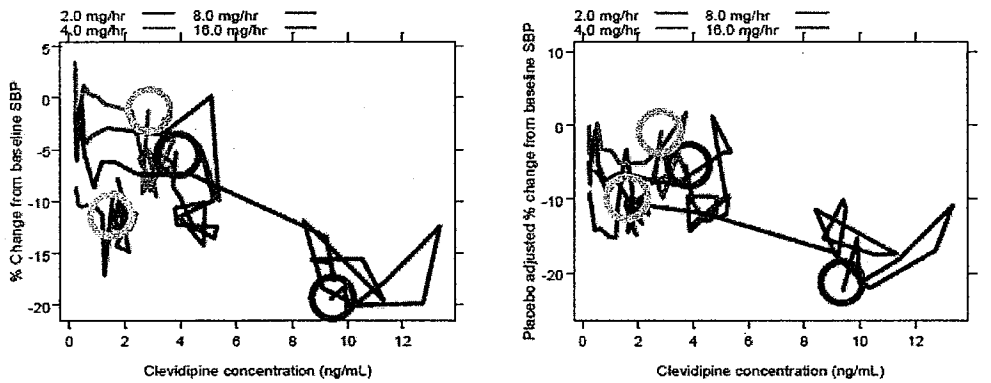
The duration of SBP effect appears to be as long as clevidipine is being infused evidenced by 72 hours constant infusion in mild to moderate hypertension patients.

The rapid clearance of clevidipine and direct effect on SBP result in a fast offset of SBP effect. In most patients, full recovery to baseline SBP is achieved in 5-15 minutes after end of clevidipine infusion. Any unintended hypotension may be easily reversed by down-titration or temporary discontinuation of the infusion.



Mean percent change from baseline systolic blood pressure time profiles for mild to moderate hypertension patients following 72 hours constant clevidipine infusion (left) and 30 minutes forced titration followed by target SBP titration in patients with severe hypertension (right).

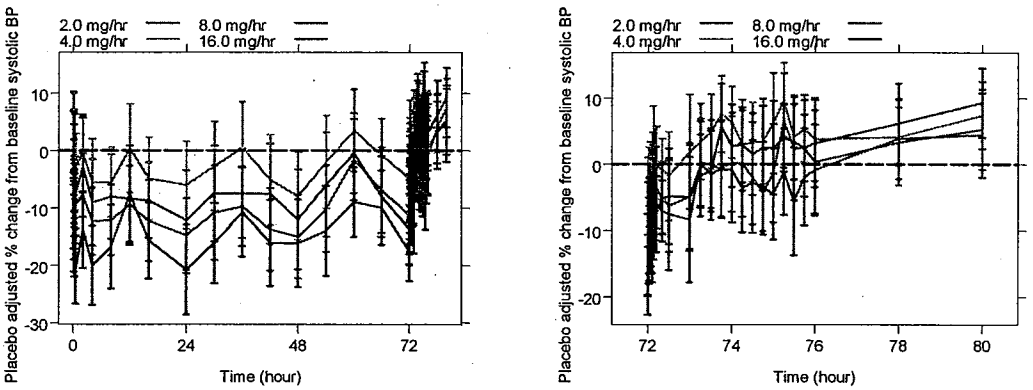
Tolerance Development: There does not appear to be any tolerance development since no delay (hysteresis) was observed between clevidipine concentration and percent change from baseline SBP with or without placebo adjustment.



Relationship between time-matched mean percent change in SBP from baseline (left) and placebo-adjusted (right) and the mean clevidipine concentration over the 72 hour treatment period through 60 minutes post study drug infusion connected by lines in chronological order for study TMC-CL-06-01 (see appendix 10.4 for mean ±SE plots). The circles indicate the first time point with PK and SBP measurement.

Rebound hypertension: There is evidence of rebound after end of the clevidipine infusion when looking at placebo-adjusted percent change from baseline SBP at 8 hours post infusion (80 hours) for the 4 and 16 mg/hr cohorts in TMC-CLV-06-01 with a mean of 7.4 (90% CI 2.3-12.5) and 9.3 (90% CI 4.1-14.5) placebo-adjusted percent change from baseline (see orange and red lines in right graph in Figure 15). This

corresponds to a rebound of 11 and 14 mm Hg in absolute systolic blood pressure for a patient with the mean baseline SBP of 150 mm Hg. The corresponding non-placebo adjusted mean percent change from baseline SBP for 4 and 16 mg/hr at 8 hours postdose is 2.2 (90% CI -1.7–6.0) and 4.1 (90% CI 0.15-8.0).



Mean (90% CI) placebo-adjusted percent change from baseline systolic blood pressure for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01.

Exposure-Response Relationship in terms of Efficacy and Safety: Please refer to the Pharmacometrics consult for appropriateness of the analysis of the submitted data. However, the sponsor did conduct several studies where efficacy related exposure-response relationships were explored:

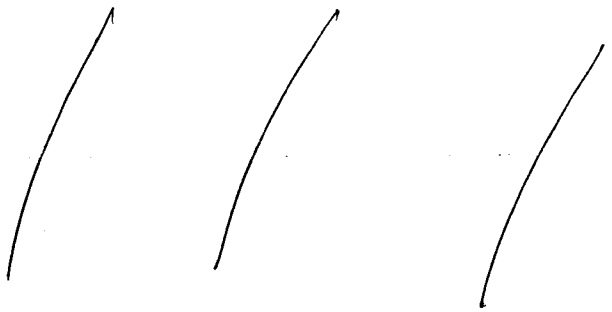
During study CLV-06-01, patients with mild to moderate hypertension receiving clevidipine for 72 hours, a correlation between steasy-state clevidipine concentrations and percent decrease from baseline in SBP was found across the four dose levels. The relationship was shallow suggesting changes in clevidipine concentrations will not result in substantial changes in SBP from baseline readings providing additional safety reassurance that changes in clevidipine concentrations should not result in substantial drops in blood pressure.

In patients with essential hypertension receiving beta-blocker treatment [Report SH-SAD-0004], the concentration-effect relationship shows that a 15% reduction in MAP is obtained at an infusion rate of 0.6 μg/kg/min (2.9 mg/h).

In patients not taking beta-blockers [Report SH-SAD-0010], the maximal reduction of MAP was about 30%, and the blood concentration producing half the maximal effect, i.e., EC_{50}, was approximately 25 nmol/L. The corresponding value for ED_{50}, i.e., the dose rate producing half the maximal effect, was 1.5 μg/kg/min (7.2 mg/h).

The effect on MAP (%) versus clevidipine arterial blood concentrations in patients with perioperative hypertension after cardiac surgery [Report SH-SAD-0003] is shown in the figure below. A dose rate of 3.2 µg/kg/min (16 mg/h), which was determined to be therapeutic in 95% of patients, corresponds to a steady-state clevidipine arterial blood concentration of approximately 100 nmol/L [Report SH-SAD-0003].

Reduction in MAP (%) versus arterial blood concentration of clevidipine in post-cardiac surgery patients

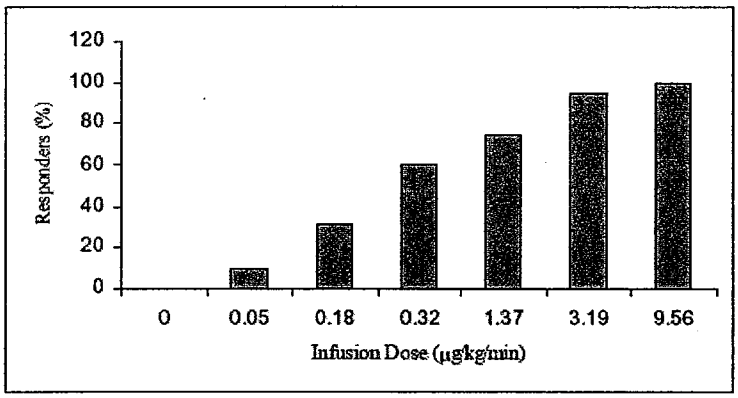


Arterial blood concentrations of clevidipine (nmol/L)

Source: Report SH-SAD-0003

In the placebo-controlled, dose-finding study [Study SH-SAD-0003] in 91 patients who developed perioperative hypertension following cardiac surgery, clevidipine was administered at six different doses ranging from 0.05-9.58 µg/kg/min (0.2-45.9 mg/h) with a run-in phase of 20 minutes, duration of treatment of 122 minutes and an optional maintenance phase of up to 12 hours. There was a clear dose-effect correlation (Figure below). At doses of 0.32 µg/kg/min (1.54 mg/h) and above (n=56), the response rates in lowering BP when compared to placebo were statistically and clinically significant.

Effect of clevidipine on MAP as a function of infusion dose



A positive response is defined as a decrease of MAP of 10% or more. A p-value of <0.01 was obtained for doses 0.32 µg/kg/min and above. 0.05 µg/kg/min = 0.2 mg/h, 0.18 µg/kg/min = 0.86 mg/h, 0.32 µg/kg/min = 1.54 mg/h, 1.37 µg/kg/min = 6.58 mg/h, 3.19 µg/kg/min = 15.3 mg/h, 9.56 µg/kg/min = 45.9 mg/h. Source: Report SH-SAD-0003

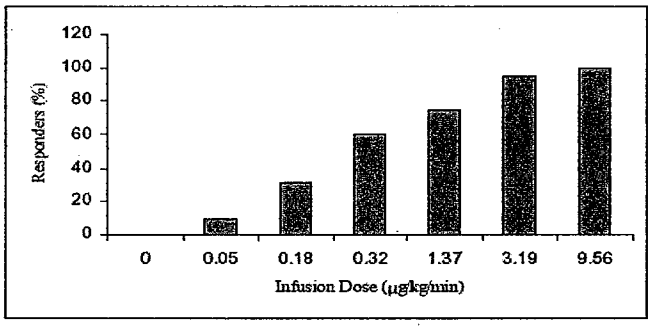
In all hypertensive patients, the first BP-loweing effect was within 3 to 10 minutes after starting the infusion. In the perioperative population, a 3 to 4% reduction in SBP was observed within 2 minutes following clevidipine administration. The median time to achieve target BP was 6.0 minutes. In patients with severe hypertension, SBP decreased by a mean of 5.9% within 3 minutes. The median time to achieve target BP was 10.9 minutes.

A short offset of BP-lowering effect is observed as well. A recovery to baseline SBP, MAP, and HR is achieved in 5 to 20 minutes.

Exposure-response relationship in terms of safety as mentioned earlier is of little concern regarding substantial drops in blood pressure. The medication is titrated to desired blood pressure and the half-life of the drug is short making clevidipine a relative safe drug.

Exposure-response support of dosing regimen: Clevidipine will be titrated to the desired effect. No dosing regimen is being proposed other than an appropriate starting dose would be

Effect of clevidipine on MAP as a function of infusion dose



A positive response is defined as a decrease of MAP of 10% or more. A p-value of <0.01 was obtained for doses 0.32 µg/kg/min and above. 0.05 µg/kg/min = 0.2 mg/h, 0.18 µg/kg/min = 0.86 mg/h, 0.32 µg/kg/min = 1.54 mg/h, 1.37 µg/kg/min = 6.58 mg/h, 3.19 µg/kg/min = 15.3 mg/h, 9.56 µg/kg/min = 45.9 mg/h. Source: Report SH-SAD-0003

Response Endpoints: The major endpoint is decrease in blood pressure since the indication is for [redacted]. The endpoints of interest that were measured are BP, mean arterial pressure (MAP) and heart rate (HR).

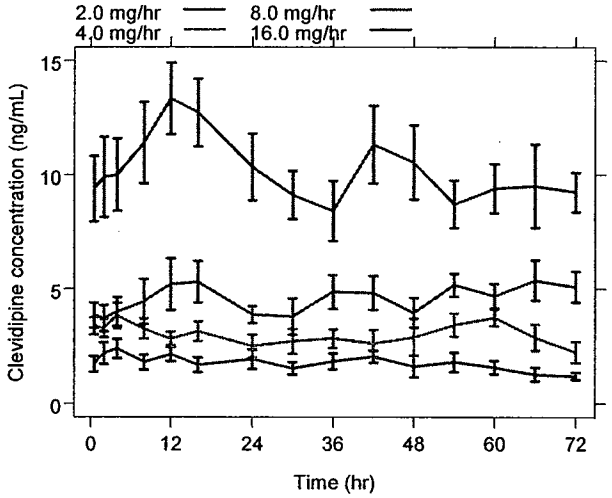
Short and Long Infusion Pharmacokinetic Parameters for Clevidipine: The pharmacokinetics of Clevidipine seem to change with prolonged infusion time. The terminal half-life seems to be prolonged with infusion time increases (20-minute infusion = terminal t1/2 16 to 25 minutes versus 72 hour infusion = t1/2 32-37 min). Clearance in normal subjects remains unchanged; but seems to increase with increasing infusion time in hypertensives.

The volume of distribution at steady state in arterial blood seems to be less with a slower clearance and a shorter half-life. The mean concentrations in venous blood were half of the concentrations in arterial blood.

Study	Infusion Time	Dose	C_{max} (ng/mL)	T_{max} (min)	C_{ss} (ng/mL)	AUC_{0-t} (ng.h/mL)	V_{ss} (L/kg)	$t^{1}/_{2\alpha}$ (min)	$t^{1}/_{2\beta}$ (min)	CL_b
SAD-0018 Venous Volunteers	20 min	3.2 µg/kg/min	NC	NC	NC	NC	0.67	4.3	25.6	0.147 L/min/kg
SAD-0018 Arterial Volunteers	20 min	3.2 µg/kg/min	NC	NC	NC	NC	0.14	2.3	16.3	0.07 L/min/kg
SAD-0002 Volunteers	60 min	12nmol (5.4µg) /kg/min	NC	NC	97.35 nmol/L (0.044 ng/mL)	5539.5 nmol*min/ mL	0.746	NC	11.65	0.136 L/min/kg
CLV-06-01 Mild-Mod HTN	72 hrs	33.0–266.7 µg/min (2-16 mg/h)	3.3-15.7	NC	1.37-9.20	122-724	NC	3-4	32-37	30 L/min

The empirical mean (±SE) PK concentration-time profiles following 72 hour constant clevidipine IV infusions of 0-16 mg/hr appears to change over time with diurnal variations and a tendency towards lower concentrations over time. The mechanism behind the time dependent clevidipine PK is unknown. There was an indication of time dependent clearance with up to 20% increase over the 72 hour infusion. However, this

has no clinical relevance since clevidipine is titrated to effect very fast due to its short half-life and direct SBP effect.



Mean (±SE) clevidipine concentration time profiles from 0-72 hours after start of the infusion for study TMC-CL-06-01.

Pharmacokinetic Parameters for Clevidipine metabolites: Clevidipine has one major metabolite (H152/81) M1, considered to be inactive. However, it does have Cytochrome P450 activity. Below are the pharmacokinetics of that metabolite in healthy subjects receiving 12 nmol/kg/min over a one hour infusion (SAD-0002):

Subject	CL (L/h/kg)	C_{max} (nmol/L)	t_{max} (h)	$t_{1/2\lambda z}$ (h)	$V_{\lambda z}$ (L/kg)
N	8	8	8	8	8
Mean	0.0306	3362.50	1.0359	9.1859	0.4041
SD	0.0034	218.55	0.0232	0.7715	0.0468
Max	0.0363	3730.00	1.0833	10.5126	0.4574
Median	0.0305	3330.00	1.0333	8.9586	0.4197
Min	0.0247	2990.00	1.0083	8.3195	0.3423

Pharmacokinetic Parameters for Clevidipine's enantiomers: The pharmacokinetics of clevidipine and its enantiomers (H190/90 and H190/91) were assessed in moderately hypertensive patients at doses of 0.18 to 5.48 µg/kg/min. There were no differences in concentrations at steady-state and blood clearances when assessed by compartmental (2-compartment) and non-compartmental methods. Concentrations at steady state for the enantiomers ranged from 2.2 to 49.7 nmol/L for dose rates of 0.18 to 5.48 µg/kg/min, respectively. Clevidipine concentrations at steady state ranged from 4.6 to 93.9 nmol/L, respectively. Corresponding blood clearances (non-compartmentally) for the enantiomers were in the range of 0.102 to 0.149 L/min/kg, respectively. Clevidipine clearances were 0.107 to 0.138 L/min/kg, respectively.

Compartmental analysis (2-compartment) revealed blood clearances ranging from 0.096 to 0.136 L/min/kg for the same respective dose ranges as stated above for the enantiomers. For clevidipine, the blood clearances ranged from 0.099 to 0.127 L/min/kg, respectively.

Pharmacokinetics in the Targeted Population versus Normal Volunteers: The pharmacokinetics seem to be the same between patients with essential hypertension and healthy volunteers. Below (Table 1) are pharmacokinetic parameters for subjects with essential hypertension (study SAD 0010- 120 min infusion) and Table 2 (study SAD 0002- 60 min infusion) are the pharmacokinetic parameters for healthy subjects. Clevidipine concentration at steady-state are essentially the same. However, it remains unclear if the pharmacokinetics between the two groups would be different with longer infusions (i.e., 72 hours).

Table 1 – 120 min infusion

	Dose rate 2.74 µg/kg/min (N=12)			Dose rate 5.48 µg/kg/min (N=8)		
	H 190/90	H 190/91	Clevidipine	H 190/90	H 190/91	Clevidipine
Dose rate (µg/kg/min)	1.37*	1.37*	2.74	2.74*	2.74*	5.48
Cl_b (l/min/kg)						
Mean	0.112	0.118	0.115	0.121	0.136	0.127
S.D	0.027	0.030	0.027	0.030	0.038	0.033
Median	0.108	0.113	0.111	0.129	0.132	0.127
V_1 (l/kg)						
Mean	0.31	0.30	0.31	0.39	0.38	0.38
S.D	0.14	0.14	0.14	0.15	0.17	0.16
Median	0.25	0.22	0.23	0.38	0.36	0.35
V_{ss} (l/kg)						
Mean	0.58	0.43	0.49	0.74	0.56	0.66
S.D	0.21	0.18	0.19	0.27	0.20	0.25
Median	0.54	0.39	0.46	0.75	0.57	0.64
$t_{1/2\lambda_1}$ (min)						
Mean	1.6	1.6	1.6	1.9	1.7	1.8
S.D	0.4	0.5	0.5	0.4	0.4	0.4
Median	1.5	1.5	1.6	2.0	1.8	1.9
$t_{1/2\lambda_2}$ (min)						
Mean	14.2	11.9	12.5	14.1	13.2	13.6
S.D	2.08	2.92	1.93	3.96	3.61	4.15
Median	14.5	12.4	12.8	16.0	14.5	15.6

* Since only clevidipine was infused, the estimated infusion rates of the two enantiomers were 50% of that of clevidipine.

Table 2 – 60 minute infusion

Study	Infusion Time	Dose	C_{max} (ng/mL)	T_{max} (min)	C_{ss} (ng/mL)	AUC_{0-t} (ng.h/mL)	V_{ss} (L/kg)	$t^1/_{2\alpha}$ (min)	$t^1/_{2\beta}$ (min)	CL_b
SAD-0002 Volunteers	60 min	12nmol (5.4µg) /kg/min	NC	NC	97.35 nmol/L (0.044 ng/mL)	5539.5 nmol*min/ mL	0.746	NC	11.65	0.136 L/min/kg

Bioavailability of Clevidipine: Since Clevidipine is administered intravenously, no bioavailability studies were performed.

Distribution Characteristics of Clevidipine: Protein binding of Clevidipine and its two enantiomers is about 99.5%.

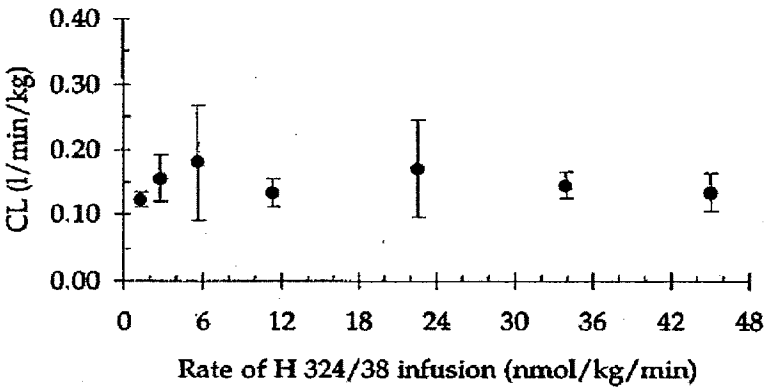
Characterization of the Metabolic Pathway: Metabolites were formed by four main routes: ester hydrolysis, oxidation of the dihydropyridine ring to the corresponding pyridine, glucuronidation and decarboxylation. Clevidipine was completely metabolized to the primary metabolite M1, which was the predominant peak in plasma. The main metabolites in urine were M3a and M3b, which were identified as the diastereomeric pair of M1 glucuronides. The predominant peak in the samples of faeces was the decarboxylated pyridine M5.

Routes of Elimination:

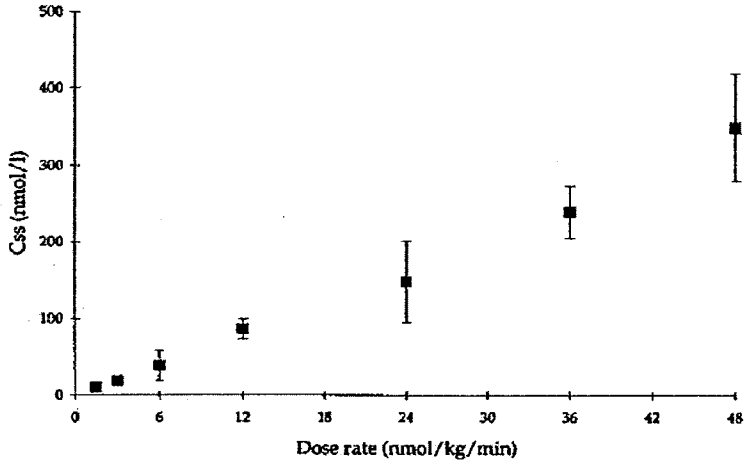
Inactive metabolite excreted predominantly in urine

In humans, a mean of 83% of a radiolabeled dose of clevidipine is excreted in urine and feces as inactive metabolite [Final Study Report SH-SAD-0002]. The major fraction of radioactivity, 63–74%, is excreted in the urine, with only 7–22% in the feces. More than 90% of the recovered radioactivity is excreted within the first 72 hours of collection. No intact parent compound is recovered in urine or feces, suggesting that clevidipine is completely and rapidly metabolized.

Dose Proportionality: CLss and Css were calculated for clevidipine in normal subjects receiving an infusion of 1.5 to 48 nmol/kg/min. Clearance remained constant:



Blood concentrations during steady state (mean of 10, 15, and 19 minutes) versus dose rate below, mean and SD (1.5 nmol/kg/min n=4, 3 nmol/kg/min n=4, 6 nmol/kg/min n=4, 12 nmol/kg/min n=4, 24 nmol/kg/min n=3, 36 nmol/kg/min n=4, 48 nmol/kg/min n=3):



There was a less than dose-proportional relationship between dose rate and C_{ss} in healthy volunteers. The same results are seen in hypertensive subjects. Clevidipine pharmacokinetic characteristics seems to be less than dose-proportional.

Clevidipine's Impact on the QT/QTc Interval:

The sponsor conducted a two-part study. Part I was an open-label, nonrandomized pilot study in 8 subjects to assess the effect of Intralipid® (20% IV fat emulsion) on ECG parameters; the effect of two fenoldopam infusion rates to attain prespecified heart rates; and the ability to detect the effect of moxifloxacin on uncorrected QT during heart rate control. The QT-IRT did not analyze these data.

The QT-IRT primarily focused on the data obtained in the main study phase. This phase was a randomized, single-blind, vehicle (Intralipid®) and heart rate (fenoldapam) controlled 2-treatment crossover study in healthy volunteers, with an additional nonrandomized, open-label moxifloxacin treatment with heart rate control.

Compared to the vehicle- and heart rate-control group, administration of clevidipine was found to shorten the QT interval in a dose- and concentration-dependent manner.

- The maximum decrease (and corresponding two-sided 90% CI) in the mean change in ΔΔQTcF for the 3.2 mcg/kg/min and 12 mcg/kg/min dose groups were -9.4 ms (-16, -3 ms) and -16 ms (-21, -11 ms).
- A log-linear model described the relationship between clevidipine concentrations and changes in ΔΔQTcF. Based on this relationship the expected ΔΔQTcF for a mean C_{max} of 9 ng/ml was -11 ms (-15, -7 ms) and 25 ng/ml was -15 ms (-20, -10 ms) following 3.2 and 12 mcg/kg/min, respectively.
- The mean ΔΔQTcF for moxifloxacin was approximately 10 ms at T_{max} with lower 90% confidence interval greater than 5 ms several timepoints (table below). Since ten QT measurements were obtained over a short time, multiplicity adjustment may not be appropriate to compute confidence intervals.

Evidence of Pharmacokinetic Changes in Renal or Hepatic Impairment:
A decision was made to not conduct a renal or hepatic study since clevidipine is intended to be given for a short duration of about 72 hours.

Pharmacokinetics of Clevidipine in Arterial versus Venous Blood: During CABG surgery, Clevidipine concentrations seem to be the same during the pre-bypass (hypothermic) phase:

Non-compartmental analysis of blood concentration during pre-bypass. Individual values and descriptive statistics.

Patient	R_0 (nmol/kg/min)*	Arterial blood		Mixed venous blood (pulmonary artery)	
		C_{ss} (nmol/l)	Cl_b (l/min/kg)	C_{ss} (nmol/l)	Cl_b (l/min/kg)
N	17	17	17	16	16
Mean	4.76	87.3	0.061	87.8	0.060
SD	1.87	50.0	0.019	54.1	0.019
Median	4.00	66.4	0.059	72.0	0.056
Min	2.49	26.5	0.032	25.4	0.028
Max	7.31	220.7	0.101	251.5	0.099

* molecular weight 456.3 g

However, during normothermic conditions, clevidipine arterial blood clearance seems to be slower (by about half) with shorter half-lives when compared to venous blood. The concentration of clevidipine in arterial blood is about twice as high as venous blood following constant infusion possibly due to extensive and rapid metabolism.

Evidence of a Drug Interaction between Clevidipine and Other Drugs: A decision was made that no drug interactions were to be explored since clevidipine will be administered for a short period time and has a short half-life.

Pharmacokinetic Differences with Differing Body Temperatures during Cardiac Surgery: Differences in the pharmacokinetics of clevidipine during hypothermia (pre-bypass) and normothermia (bypass) were explored during CABG:

Parameter	Estimate	Lower limit	Upper limit
R_0 (nmol/kg/min)	2.36	-0.26	4.86
C_{ss} (nmol/l)	5.8	-55.2	38.2
Cl_b (l/min/kg)	0.027	0.016	0.044

R_0 = infusion rate; Cl_b = Blood clearance

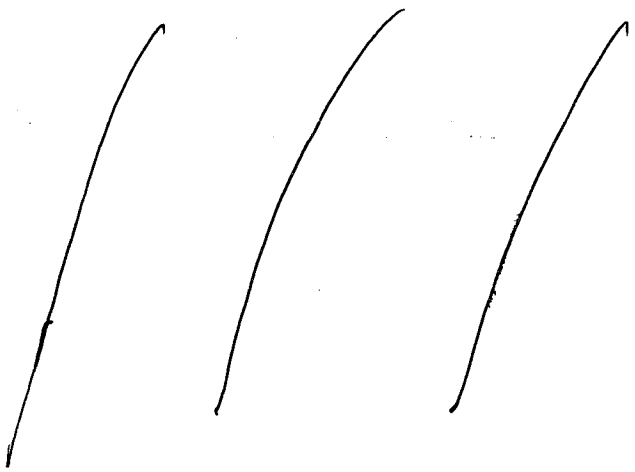
The confidence intervals indicate that Cl_b is higher during bypass compared to pre-bypass.

Difference between pharmacokinetic parameters during the pre-

bypass and the bypass. Hodges-Lehmann estimates of true median difference and 95 per cent confidence intervals based on data from patients treated during both pre-bypass and bypass (n=7). Pharmacokinetic parameters calculated by compartmental analysis.

Parameter	Estimate	Lower limit	Upper limit
A	-0,025	-0,040	-0,005
B	0,025	0,005	0,040
Cl_b (l/min/kg)	0.026	0.017	0.041
V_1 (l/kg)	0,01	-0,03	0,03
V_{ss} (l/kg)	0,01	-0,05	0,03
$t_{1/2\alpha}$ (min)	-0.5	-1.0	-0,2
$t_{1/2\alpha}$ (min)	-3,4	-9,8	-1,8

The confidence intervals indicate that model constant B and Cl_b are higher during bypass compared to pre-bypass, while model constant A, $t_{1/2\alpha}$ and $t_{1/2\alpha}$ are lower during bypass compared to pre-bypass.



The half-life of clevidipine increases during pre-bypass (hypothermia) possibly due to a decrease in clearance.

In-Vitro Metabolic Studies: In total, six in-vitro metabolic studies were performed for clevidipine and its metabolite (M1, H152/81).

Based on in-vitro data, clevidipine and it's major metabolite (H152/81) seem to have an induction potential to CYP 3A4, 2C9 and 1A2.

The inhibition potential of clevidipine and H152/81 to CYP 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 was evaluated in vitro as well. The therapeutic concentration of clevidipine given at 3.2 µg/kg/min (16 mg/hr) is about 50 nM. If the dose were to be doubled, as is allowed in the labeling one could assume a therapeutic concentration for clevidipine reaching approximately 100 nM. This scenario could potentially close in on inhibitory

concentrations for CYP P450 2C9 (150 nM). As a result, [redacted] In addition, clevidipine did inhibit CYP 2C19, and 3A4.

The metabolite, H152/81 did inhibit CYP 2C9, 2C19, and 3A4.

Assay Validation: Several Bioanalytical methods have been developed and used to support the non-clinical and clinical pharmacokinetic programs for clevidipine. The non-clinical and early clinical studies utilized a GC-MS method for clevidipine and an LC-Flur for the inactive metabolite H152/81 (M1). In more recent clinical studies, an LC/MS/MS assay was used for clevidipine and its metabolite M1 determination in blood that has a sensitivity of 0.2 ng/mL for clevidipine and 20 ng/mL for M1. Since clevidipine metabolizes rapidly, steps need to be taken to reduce the metabolism during sample collection and preparation. The GC-MS method and the LC-Flur were developed by Astra-Zeneca. Below are the different analytical methods and validation data summary:

Method	Compound	Recovery %	Repeatability	Reproducibility	Linearity	LOQ
GC-MS	H324/38	84.2-100.3%	2.0-15.6%	91.6-116.9%	linear	0.5-25.0 nmol/L
LC-Flur	H324/38	85.6-100.9%	3.0-4.1%	NE	linear	50 nmol/L
	H152/81	82.2-93.6%	0.9-7.5%	86.0-104.4%	linear	"
LC-MS	H324/38	82.4-92.8%	n/a	n/a	n/a	n/a
	H190/91	n/a	18.5-1.2%	92.8-104.0%	Linear-range	0.50 nmol/L
	H190/90	n/a	"	90.7-101.0%	0.5-700 nmol/L	"
GC/MS/ LC-Flur	H324/38	93.2-94.0%	3.1-4.3%	NE	linear	5.0 nmol/L
	H152/81	82.2-85.4%	1.4-4.7%	97.2-103.7%	linear	5.0-50.0 nmol/L
LC/MS/ MS	H324/38	71%	%Nom within 100±15%; %CV ≤ 15%	NE	linear	0.2 mg/mL
	H152/81	97.7%				20 mg/mL

NE = not evaluated;

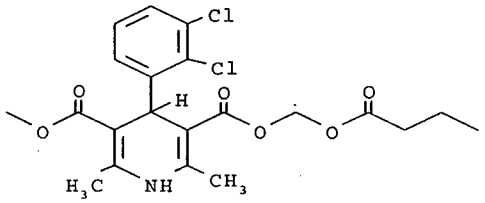
APPEARS THIS WAY
ON ORIGINAL

QUESTION BASED REVIEW

I. GENERAL ATTRIBUTES OF THE DRUG

A. WHAT ARE THE HIGHLIGHTS OF THE CHEMISTRY AND PHYSICAL-CHEMICAL PROPERTIES OF THE DRUG SUBSTANCE?

Cleviprex™ (clevidipine IV emulsion) is a rapidly acting, vascular and arterial selective dihydropyridine calcium antagonist with a very short half-life. Chemically, the active substance clevidipine is butyroxymethyl methyl 4-(2′,3′-dichlorophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate. It is a racemic mixture with a molecular weight of 456.3 g/mol. The structure and formula are:



Molecular formula: $C_{21}H_{23}Cl_2NO_6$

Clevidipine is practically insoluble in water and is formulated in an oil-in-water emulsion. Cleviprex contains clevidipine, soybean oil, glycerin, purified egg yolk phospholipids and sodium hydroxide to adjust pH. Cleviprex is a sterile, milky white, ready-to-use emulsion. Molecular weight of clevidipine is 456.3 g/mol.

B. WHAT ARE THE HIGHLIGHTS OF THE FORMULATION OF THE DRUG PRODUCT?

The sponsor has developed an intravenous product that is formulated as a lipid emulsion in 20% soybean oil (composition similar to the Intralipid® that is administered for parenteral nutrition) due to its negligible aqueous solubility. Cleviprex is a racemic mixture consisting of two enantiomers: H 190/90 and H 190/91 and contains approximately 0.2 g of fat per mL (2.0 kcal). It has been developed in one strength (0.5 mg/mL) with two vial sizes of 50 and 100 mL.

Composition of clevidipine emulsion 0.5 mg/mL:

Component	Reference to quality standard	Function	Quantity[a] mg/mL	Per 50 mL/ bottle	Per 100 mL/ bottle
Clevidipine	In-house standard	Active ingredient	0.5	25 mg	50 mg
Soybean oil	USP/Ph Eur	[redacted]	200	10 g	20 g
Glycerin	USP/Ph Eur	[redacted]	22.5	1.13 g	2.25 g
Purified egg yolk phospholipids	In-house standard	[redacted]	12	0.6 g	1.2 g
Sodium hydroxide	NF/Ph Eur	For pH adjustment		pH 6.0 to [redacted]	

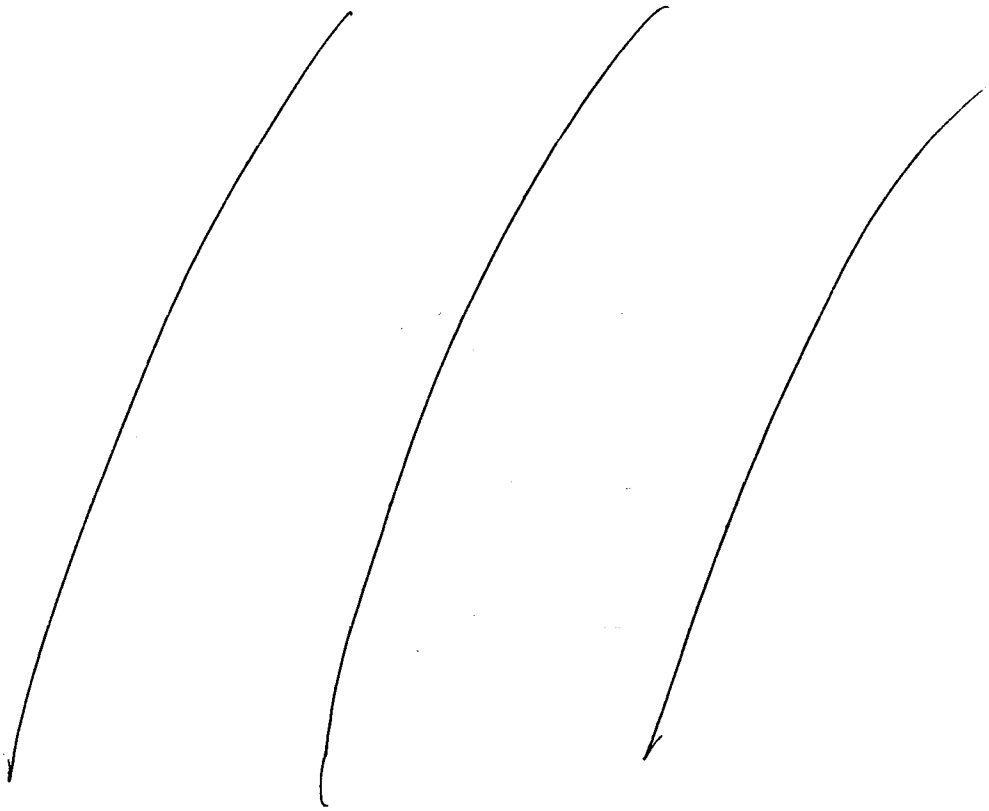
[a] Clevidipine Emulsion when filled in 100 mL bottles has an overfill volume of approximately [redacted] when filled in 50 mL bottles has an overfill volume of approximately [redacted]. See Section 3.2.P.2.2.2 Overages, for more information.
USP = United States Pharmacopeia; NF = National Formulary; Ph Eur = European Pharmacopoeia; q.s. = quantity sufficient

Of note, since Cleviprex contains phospholipids and can support the growth of microorganisms, it should not be used if contamination is suspected. Once the stopper is punctured, use within — hours and discard any unused portion.

C. WHAT IS THE PROPOSED MECHANISM OF ACTION AND THERAPEUTIC INDICATIONS?

L-type calcium channels mediate the influx of calcium during depolarization in vascular smooth muscle. Experiments in anesthetized rats and dogs show that clevidipine reduces mean arterial blood pressure by decreasing systemic vascular resistance, Clevidipine does not reduce cardiac filling pressure (pre-load), confirming lack of effects on the venous capacitance vessels.

D. WHAT ARE THE PROPOSED DOSAGES AND ROUTE OF ADMINISTRATION?



II. GENERAL CLINICAL PHARMACOLOGY

A. WHAT CLINICAL PHARMACOLOGY AND CLINICAL STUDIES WERE SUBMITTED TO SUPPORT DOSING OR CLAIMS?

In total, the sponsor submitted 19 clinical studies to the NDA; which includes eight with pharmacokinetic data and one QT study. Five studies were not reviewed because there was no pharmacokinetic data, the pharmacokinetic data was redundant in nature and offered no new information to the review, or was focused on pharmacometrics (PM) analysis (will be reviewed by PM under separate review; but results will be referenced in this review). An additional seven in-vitro studies were submitted to the NDA containing metabolism and protein binding data of which all were reviewed. In total, 14 studies were reviewed and are reported in this review.

B. WHAT IS THE BASIS FOR SELECTING THE RESPONSE ENDPOINTS AND HOW ARE THEY MEASURED IN CLINICAL PHARMACOLOGY STUDIES?

The major endpoint is decrease in blood pressure (BP) since the indication is for ———) when the use of oral therapy is not feasible or not desirable. The endpoints of interest that were measured are BP, mean arterial pressure (MAP) and heart rate (HR).

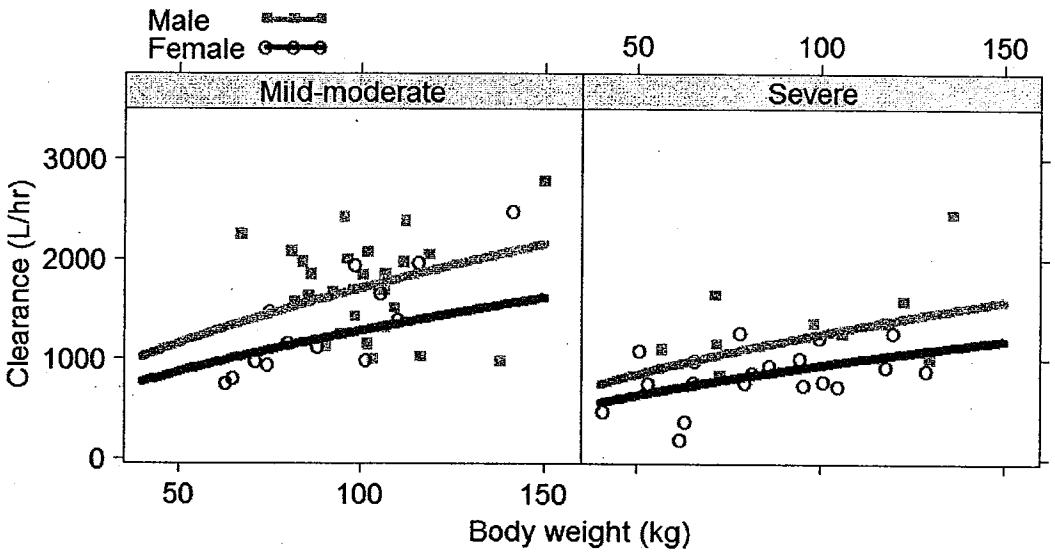
C. IS THE PROPOSED DOSAGES OF 2-32 MG/HR JUSTIFIED?

Cleviprex™ (clevidipine IV emulsion) is intended for intravenous use and should be titrated to achieve the desired blood pressure reduction. Dosage must be individualized depending on the severity of hypertension and the response of the patient. Blood pressure should be monitored during and after the infusion to avoid excessive reductions in systolic or diastolic blood pressure. Patients may be safely monitored with a blood pressure cuff or an arterial line.

Body weight, patient population (mild-moderate/severe), and gender were found to be significant covariates for clevidipine clearance (see Figure below) with severe hypertension patients having 30% lower clearance compared to mild-moderate patients and females having 25% lower clearance compared to males. There was also an indication of time dependent clearance where the clearance increased by a total of 20% following 4 days continuous infusion due to unknown reasons.

These covariates (body weight, patient population, gender, and days since start of infusion) explain 15% of the unexplained inter-individual variability (IIV) in clevidipine clearance (IIV on clearance reduced from 51% to 36%).

The identified clearance covariates do not have any clinical impact since clevidipine has a very short half-life (2-3 min distribution and 1 hr terminal) and is easily titrated to effect. No dose adjustments based on the identified clearance covariates are thus warranted.



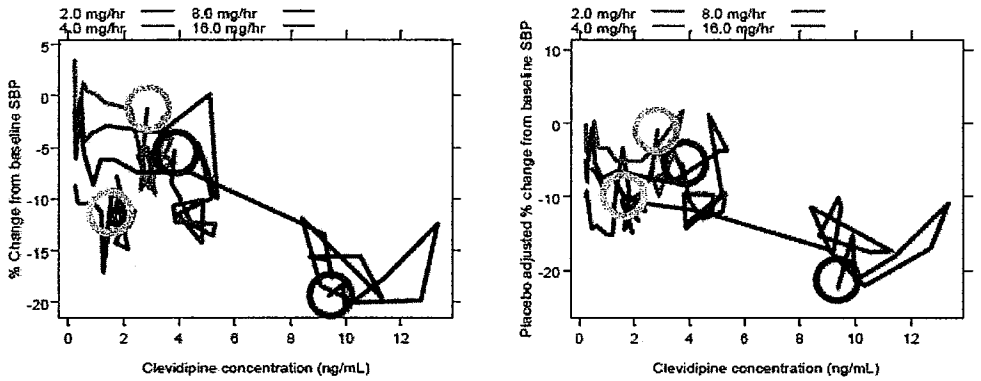
Clevidipine clearance vs. body weight. Mild-moderate (Left) and Severe (Right) hypertension patients. Male patients' individual clearance estimates are shown as grey filled squares and females are open red circles. The population mean predictions across body weights are illustrated as solid grey line for males and solid red line for females.

A dose of 2 mg/hr was shown to be the minimum effective dose (responders being classified as patients having a reduction in mean arterial pressure (MAP) ≥10% from baseline) in SAD-003 and thus appears to be an appropriate starting dose with responders being classified as patients having a reduction in MAP ≥10%.
An E_{max} relationship exists between clevidipine dose, reduction of BP and clevidipine blood concentrations, including:

- A linear relationship between clevidipine dose and percent change in SBP at doses up to 20 mg/hr.
- A flattening of the dose-response relationship at doses greater than 20 mg/hr and up to 32 mg/hr.

The effective clevidipine dose range is 2-16 mg/hr and little additional blood pressure effect was observed at higher doses. Further decrease in SBP was obtained in 24 out of 38 patients (63.2%) who were up-titrated from 16 to 32 mg/hr in study SAD-003 (postcardiac surgical patients with perioperative hypertension) with a median decrease in SBP of 6.5 mm Hg. The highest dose rate of 46 mg/hr tested in study SAD-003 led to discontinuation of study therapy in 28% of patients due to hypotension.

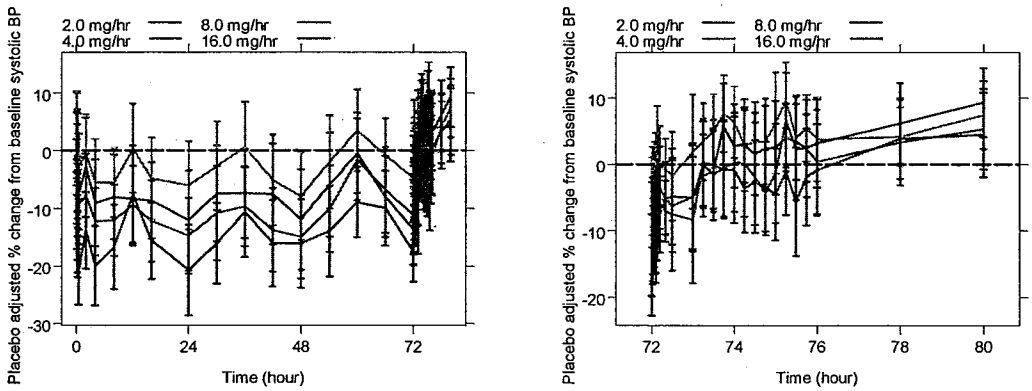
The proposed dosing regimen of 2-32 mg/hr is thus found to be adequate.



Relationship between time-matched mean percent change in SBP from baseline (left) and placebo-adjusted (right) and the mean clevidipine concentration over the 72 hour treatment period through 60 minutes post study drug infusion connected by lines in chronological order for study TMC-CL-06-01 (see appendix 10.4 for mean ±SE plots). The circles indicate the first time point with PK and SBP measurement.

F. Is there Rebound Hypertension?

There is evidence of rebound after end of the clevidipine infusion when looking at placebo-adjusted percent change from baseline SBP at 8 hours post infusion (80 hours) for the 4 and 16 mg/hr cohorts in TMC-CLV-06-01 with a mean of 7.4 (90% CI 2.3-12.5) and 9.3 (90% CI 4.1-14.5) placebo-adjusted percent change from baseline (see orange and red lines in right graph in Figure 15). This corresponds to a rebound of 11 and 14 mm Hg in absolute systolic blood pressure for a patient with the mean baseline SBP of 150 mm Hg. The corresponding non-placebo adjusted mean percent change from baseline SBP for 4 and 16 mg/hr at 8 hours post-dose is 2.2 (90% CI -1.7–6.0) and 4.1 (90% CI 0.15-8.0).



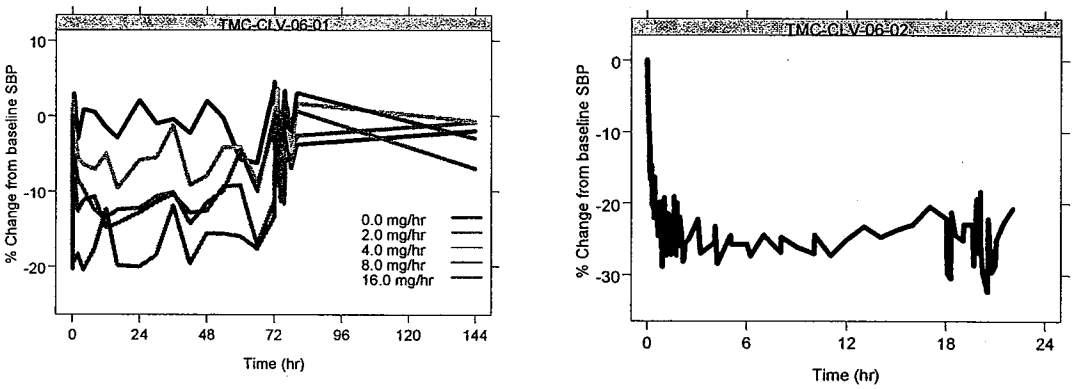
Mean (90% CI) placebo-adjusted percent change from baseline systolic blood pressure for 0-72 (left) and 72-80 (right) hours after start of the infusion for study TMC-CL-06-01.

G. What is the onset/duration/offset of effect?

The time to onset of maximal systolic blood pressure effect in patients with mild to moderate hypertension in study TMC-CLV-06-01 was within 5-10 minutes of starting the constant clevidipine infusion approximately corresponding to the time of maximum concentration.

The duration of SBP effect appears to be as long as clevidipine is being infused evidenced by 72 hours constant infusion in mild to moderate hypertension patients.

The rapid clearance of clevidipine and direct effect on SBP result in a fast offset of SBP effect. In most patients, full recovery to baseline SBP is achieved in 5-15 minutes after end of clevidipine infusion. Any unintended hypotension may be easily reversed by down-titration or temporary discontinuation of the infusion.



Mean percent change from baseline systolic blood pressure time profiles for mild to moderate hypertension patients following 72 hours constant clevidipine infusion (left) and 30 minutes forced titration followed by target SBP titration in patients with severe hypertension (right).

H. What are the characteristics of the exposure-response relationships for efficacy?

The sponsor did conduct several studies where efficacy related exposure-response relationships were explored:

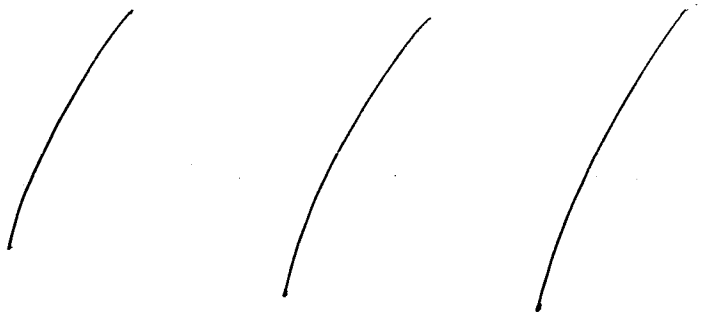
During the study in patients with mild to moderate hypertension receiving clevidipine for 72 hours [Report TMC-CLV-06-01] a general correlation between steady-state clevidipine concentrations and percent decrease from baseline in SBP across the four dose levels of clevidipine was found. The relationship was shallow, suggesting that changes in clevidipine concentrations will not result in substantial changes in change from baseline SBP. This observation provides additional safety reassurance since within-patient variability in blood concentrations of clevidipine achieved following dose adjustment should not result in unexpectedly large drops in blood pressure.

In patients with essential hypertension receiving beta-blocker treatment [Report SH-SAD-0004], the concentration-effect relationship shows that a 15% reduction in MAP is obtained at an infusion rate of 0.6 µg/kg/min (2.9 mg/h).

In patients not taking beta-blockers [Report SH-SAD-0010], the maximal reduction of MAP was about 30%, and the blood concentration producing half the maximal effect, i.e., EC_{50}, was approximately 25 nmol/L. The corresponding value for ED_{50}, i.e., the dose rate producing half the maximal effect, was 1.5 µg/kg/min (7.2 mg/h).

The effect on MAP (%) versus clevidipine arterial blood concentrations in patients with perioperative hypertension after cardiac surgery [Report SH-SAD-0003] is shown in the figure below. A dose rate of 3.2 µg/kg/min (16 mg/h), which was determined to be therapeutic in 95% of patients, corresponds to a steady-state clevidipine arterial blood concentration of approximately 100 nmol/L [Report SH-SAD-0003].

Reduction in MAP (%) versus arterial blood concentration of clevidipine in post-cardiac surgery patients



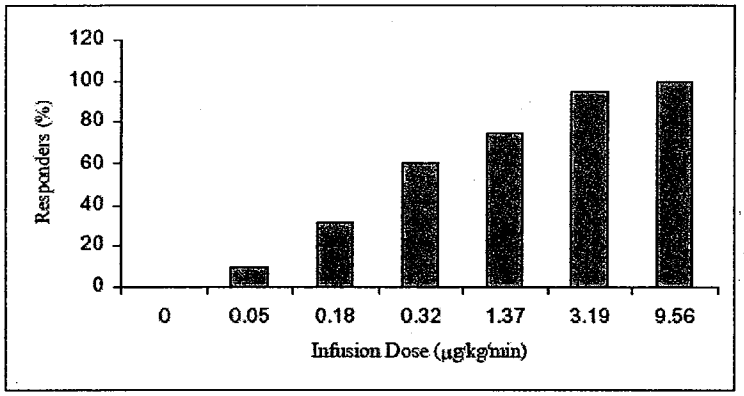
Arterial blood concentrations of clevidipine (nmol/L)

Source: Report SH-SAD-0003

In the placebo-controlled, dose-finding study [Study SH-SAD-0003] in 91 patients who developed perioperative hypertension following cardiac surgery, clevidipine was administered at six different doses ranging from 0.05-9.58 µg/kg/min (0.2-45.9 mg/h) with a run-in phase of 20 minutes, duration of treatment of 122 minutes and an optional maintenance phase of up to 12 hours. There was a clear dose-effect correlation (Figure

below). At doses of 0.32 µg/kg/min (1.54 mg/h) and above (n=56), the response rates in lowering BP when compared to placebo were statistically and clinically significant.

Effect of clevidipine on MAP as a function of infusion dose



A positive response is defined as a decrease of MAP of 10% or more. A p-value of <0.01 was obtained for doses 0.32 µg/kg/min and above. 0.05 µg/kg/min = 0.2 mg/h, 0.18 µg/kg/min = 0.86 mg/h, 0.32 µg/kg/min = 1.54 mg/h, 1.37 µg/kg/min = 6.58 mg/h, 3.19 µg/kg/min = 15.3 mg/h, 9.56 µg/kg/min = 45.9 mg/h. Source: Report SH-SAD-0003

In all hypertensive patients, the first BP-lowering effect was within 3 to 10 minutes after starting the infusion. In the perioperative population, a 3 to 4% reduction in SBP was observed within 2 minutes following clevidipine administration. The median time to achieve target BP was 6.0 minutes. In patients with severe hypertension, SBP decreased by a mean of 5.9% within 3 minutes. The median time to achieve target BP was 10.9 minutes.

A short offset of BP-lowering effect is observed as well. A recovery to baseline SBP, MAP, and HR is achieved in 5 to 20 minutes.

I. DOES CLEVIDIPINE HAVE AN IMPACT ON QT/QTC INTERVAL?

The sponsor conducted a two-part study. Part I was an open-label, nonrandomized pilot study in 8 subjects to assess the effect of Intralipid® (20% IV fat emulsion) on ECG parameters; the effect of two fenoldopam infusion rates to attain prespecified heart rates; and the ability to detect the effect of moxifloxacin on uncorrected QT during heart rate control. The QT-IRT did not analyze these data.

The QT-IRT primarily focused on the data obtained in the main study phase. This phase was a randomized, single-blind, vehicle (Intralipid®) and heart rate (fenoldapam) controlled 2-treatment crossover study in healthy volunteers, with an additional nonrandomized, open-label moxifloxacin treatment with heart rate control.

Compared to the vehicle- and heart rate-control group, administration of clevidipine was found to shorten the QT interval in a dose- and concentration-dependent manner.

- The maximum decrease (and corresponding two-sided 90% CI) in the mean change in ΔΔQTcF for the 3.2 mcg/kg/min and 12 mcg/kg/min dose groups were -9.4 ms (-16, -3 ms) and -16 ms (-21, -11 ms).
- A log-linear model described the relationship between clevidipine concentrations and changes in ΔΔQTcF. Based on this relationship the expected ΔΔQTcF for a mean C_{max} of 9 ng/ml was -11 ms (-15, -7 ms) and 25 ng/ml was -15 ms (-20, -10 ms) following 3.2 and 12 mcg/kg/min, respectively.
- The mean ΔΔQTcF for moxifloxacin was approximately 10 ms at T_{max} with lower 90% confidence interval greater than 5 ms several timepoints (table below). Since ten QT measurements were obtained over a short time, multiplicity adjustment may not be appropriate to compute confidence intervals.

Summary of Comparison of Moxifloxacin with Control

		ΔQTcF			
Ctrl Time	Moxi Time	Moxi	Ctrl	ΔΔQTcF	90% CI
21.5 h	40 min	5.08	-2.11	7.32	(2.29, 12.35)
22 h	1 h 0 min	6.95	-2.59	9.79	(4.38, 15.21)
22 h 20 min	1 h 20 min	9.61	-1.21	10.85	(6.39, 15.31)
22 h 28 min	1 h 28 min	8.23	-2.31	10.63	(6.50, 14.76)
22 h 36 min	1 h 36 min	8.95	-1.51	10.60	(6.77, 14.43)
22 h 42 min	1 h 42 min	8.14	-1.99	10.17	(5.79, 14.55)
22 h 50 min	1 h 50 min	8.55	0.69	8.04	(3.44, 12.63)
22 h 58 min	1 h 58 min	6.23	-3.20	9.32	(5.98, 12.66)
23 h 10 min	2 h 15 min	6.45	-4.44	10.96	(6.10, 15.82)
23 h 15 min	2 h 30 min	3.71	-4.73	8.35	(3.63, 13.07)

J. DOES THE EXPOSURE-RESPONSE DATA SUPPORT THE PROPOSED DOSING REGIMEN?

Clevidipine will be titrated to the desired effect. No dosing regimen is being proposed other than an appropriate starting dose would be b

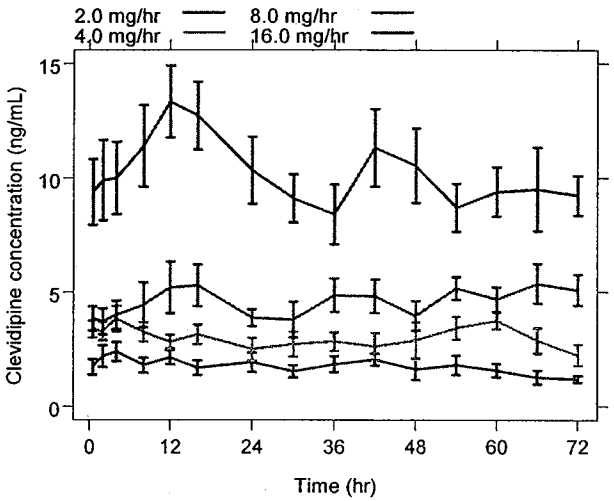
K. WHAT ARE THE LONG AND SHORT INFUSION PHARMACOKINETIC PARAMETERS FOR CLEVIDIPINE?

Study	Infusion Time	Dose	C_{max} (ng/mL)	T_{max} (min)	C_{ss} (ng/mL)	AUC_{0-t} (ng.h/mL)	V_{ss} (L/kg)	$t½_{\alpha}$ (min)	$t½_{\beta}$ (min)	CL_b
SAD-0018 Venous Volunteers	20 min	3.2 µg/kg/min	NC	NC	NC	NC	0.67	4.3	25.6	0.147 L/min/kg
SAD-0018 Arterial Volunteers	20 min	3.2 µg/kg/min	NC	NC	NC	NC	0.14	2.3	16.3	0.07 L/min/kg
SAD-0002 Volunteers	60 min	12nmol (5.4µg) /kg/min	NC	NC	97.35 nmol/L (0.044 ng/mL)	5539.5 nmol*min/ mL	0.746	NC	11.65	0.136 L/min/kg
CLV-06-01 Mild-Mod HTN	72 hrs	33.0–266.7 µg/min (2-16 mg/h)	3.3-15.7	NC	1.37-9.20	122-724	NC	3-4	32-37	30 L/min

The pharmacokinetics of Clevidipine seem to change with prolonged infusion time and the terminal half-life seem to be prolonged with infusion time increase. Clearance in normal subjects remained unchanged; but seems to increase with increasing infusion time in hypertensives.

The volume of distribution at steady state in arterial blood seems to be less with a slower clearance and a shorter half-life. The mean concentrations in venous blood were half of the concentrations in arterial blood.

In addition, the empirical mean (±SE) PK concentration-time profiles following 72 hour constant clevidipine IV infusions of 0-16 mg/hr appears to change over time with diurnal variations and a tendency towards lower concentrations over time. The mechanism behind the time dependent clevidipine PK is unknown. There was an indication of time dependent clearance with up to 20% increase over the 72 hour infusion. However, this has no clinical relevance since clevidipine is titrated to effect very fast due to its short half-life and direct SBP effect.



Mean (±SE) clevidipine concentration time profiles from 0-72 hours after start of the infusion for study TMC-CL-06-01.

L. WHAT ARE PHARMACOKINETIC PARAMETERS FOR CLEVIDIPINE METABOLITES?

Clevidipine has one major metabolite (H152/81) M1, considered to be inactive. Below are the pharmacokinetics of that metabolite in healthy subjects receiving 12 nmol/kg/min over a one hour infusion (SAD-0002):

Subject	CL (L/h/kg)	C_{max} (nmol/L)	t_{max} (h)	$t_{1/2\lambda z}$ (h)	$V_{\lambda z}$ (L/kg)
N	8	8	8	8	8
Mean	0.0306	3362.50	1.0359	9.1859	0.4041
SD	0.0034	218.55	0.0232	0.7715	0.0468
Max	0.0363	3730.00	1.0833	10.5126	0.4574
Median	0.0305	3330.00	1.0333	8.9586	0.4197
Min	0.0247	2990.00	1.0083	8.3195	0.3423

M. What are the pharmacokinetic Parameters for Clevidipine and its enantiomers?

The pharmacokinetics of clevidipine and its enantiomers were assessed in moderately hypertensive patients at doses of 0.18 to 5.48 μg/kg/min. There were no pharmacokinetic differences between enantiomers as demonstrated below.

Non-compartmental analysis for C_{ss} and CL_b

Dose rate 0.18 μg/kg/min (N=12) Dose rate 0.91 μg/kg/min (N=12)

	H 190/90	H 190/91	Clevidipine	H 190/90	H 190/91	Clevidipine
Dose rate (μg/kg/min)	0.09*	0.09*	0.18	0.46*	0.46*	0.91
R_0 (μg/kg/min)						
Mean	0.22	0.22	0.44	0.97	0.97	1.95
C_{ss} (nmol/l)						
Mean	2.4	2.2	4.6	9.9	9.2	19.4
SD	1.4	1.2	2.5	3.4	3.4	6.4
Median	2.0	1.9	3.9	9.4	9.1	18.5
CL_b (l/min/kg)						
Mean	0.102	0.112	0.107	0.111	0.124	0.112
SD	0.037	0.043	0.040	0.046	0.056	0.039
Median	0.098	0.104	0.101	0.105	0.108	0.106

Dose rate 2.74 μg/kg/min (N=12) Dose rate 5.48 μg/kg/min (N=8)

	H 190/90	H 190/91	Clevidipine	H 190/90	H 190/91	Clevidipine
Dose rate (μg/kg/min)	1.37*	1.37*	2.74	2.74*	2.74*	5.48
R_0 (μg/kg/min)						
Mean	2.91	2.91	5.83	6.00	6.00	11.99
C_{ss} (nmol/l)						
Mean	25.5	24.0	49.5	49.7	44.3	93.9
SD	6.2	6.3	12.5	14.4	13.6	27.7
Median	25.0	22.7	47.9	45.1	44.7	89.8
CL_b (l/min/kg)						
Mean	0.121	0.129	0.125	0.130	0.149	0.138
SD	0.030	0.034	0.031	0.037	0.053	0.043
Median	0.116	0.125	0.119	0.134	0.137	0.135

* Since only clevidipine was infused, the estimated infusion rates of the two enantiomers were 50% of that of clevidipine.

Pharmacokinetic parameters of clevidipine and its enantiomers calculated compartmental analysis (one-compartment for 0.18 and 0.91 μg/kg/min and two-compartment for 2.72 and 5.48 μg/kg/min).

Dose rate 0.18 μg/kg/min (N=12) Dose rate 0.91 μg/kg/min (N=12)

	H 190/90	H 190/91	Clevidipine	H 190/90	H 190/91	Clevidipine
Dose rate (μg/kg/min)	0.09*	0.09*	0.18	0.46*	0.46*	0.91
CL_b (l/min/kg)						
Mean	0.096	0.104	0.099	0.107	0.112	0.109
S.D	0.036	0.041	0.038	0.032	0.039	0.035
Median	0.092	0.097	0.094	0.104	0.107	0.109
V_{ss} (l/kg)						
Mean	0.46	0.47	0.44	0.60	0.43	0.48
S.D	0.29	0.35	0.32	0.28	0.31	0.29
Median	0.41	0.41	0.38	0.53	0.32	0.35
$t_{1/2}$ (min)						
Mean	3.3	3.1	3.1	3.8	2.5	2.9
S.D	1.6	1.5	1.6	1.0	1.1	1.0
Median	2.8	2.8	2.5	2.8	2.3	2.6

* Since only clevidipine was infused, the estimated infusion rates of the two enantiomers were 50% of that of clevidipine.

Below:

Pharmacokinetic parameters of clevidipine and its enantiomers calculated by compartmental analysis (one-compartment for 0.18 and 0.91 μg/kg/min and two-compartment for 2.72 and 5.48 μg/kg/min).

	Dose rate 2.74 μg/kg/min (N=12)			Dose rate 5.48 μg/kg/min (N=8)		
	H 190/90	H 190/91	Clevidipine	H 190/90	H 190/91	Clevidipine
Dose rate (μg/kg/min)	1.37*	1.37*	2.74	2.74*	2.74*	5.48
Cl_b (l/min/kg)						
Mean	0.112	0.118	0.115	0.121	0.136	0.127
S.D	0.027	0.030	0.027	0.030	0.038	0.033
Median	0.108	0.113	0.111	0.129	0.132	0.127
V_1 (l/kg)						
Mean	0.31	0.30	0.31	0.39	0.38	0.38
S.D	0.14	0.14	0.14	0.15	0.17	0.16
Median	0.25	0.22	0.23	0.38	0.36	0.35
V_{ss} (l/kg)						
Mean	0.58	0.43	0.49	0.74	0.56	0.66
S.D	0.21	0.18	0.19	0.27	0.20	0.25
Median	0.54	0.39	0.46	0.75	0.57	0.64
$t_{1/2\lambda_1}$ (min)						
Mean	1.6	1.6	1.6	1.9	1.7	1.8
S.D	0.4	0.5	0.5	0.4	0.4	0.4
Median	1.5	1.5	1.6	2.0	1.8	1.9
$t_{1/2\lambda_2}$ (min)						
Mean	14.2	11.9	12.5	14.1	13.2	13.6
S.D	2.08	2.92	1.93	3.96	3.61	4.15
Median	14.5	12.4	12.8	16.0	14.5	15.6

* Since only clevidipine was infused, the estimated infusion rates of the two enantiomers were 50% of that of clevidipine.

N. How does the pharmacokinetics of Clevidipine in healthy volunteers compare to patients with hypertension?

The pharmacokinetics seem to be the same between patients with essential hypertension and healthy volunteers when the infusions are for 120 minutes or less. Clevidipine concentration at steady-state and clearance are essentially the same. However, it remains unclear if the pharmacokinetics between the two groups would be different with longer infusions (i.e., 72 hours).

O. What is the distribution characteristic of Clevidipine and its enantiomers?

Clevidipine and its enantiomers are > 99.5% bound to plasma proteins.

P. Was the metabolic pathway for Clevidipine characterized?

Metabolites were formed by mainly four routes: ester hydrolysis, oxidation of the dihydropyridine ring to the corresponding pyridine, glucuronidation and decarboxylation. Clevidipine was completely metabolized to the primary metabolite M1, which was the predominant peak in plasma. The main metabolites in urine were M3a and M3b, which were identified as the diastereomeric pair of M1 glucuronides. The predominant peak in the samples of faeces was the decarboxylated pyridine M5.

Virtually all of the parent drug undergoes metabolism with no evidence of it in urine or faeces during the mass balance study.

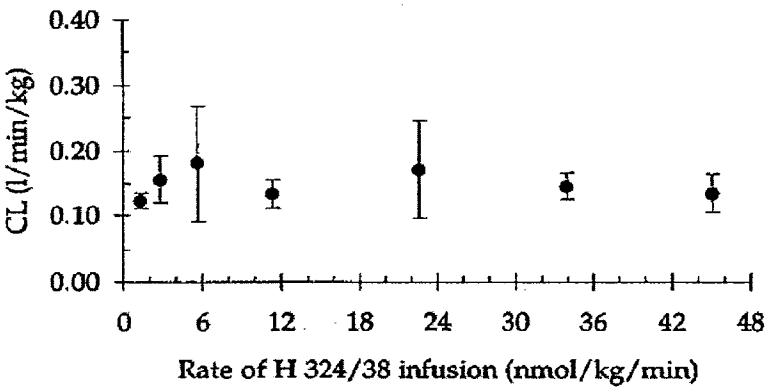
Q. What are the routes of elimination for Clevidipine?

Inactive metabolite excreted predominantly in urine

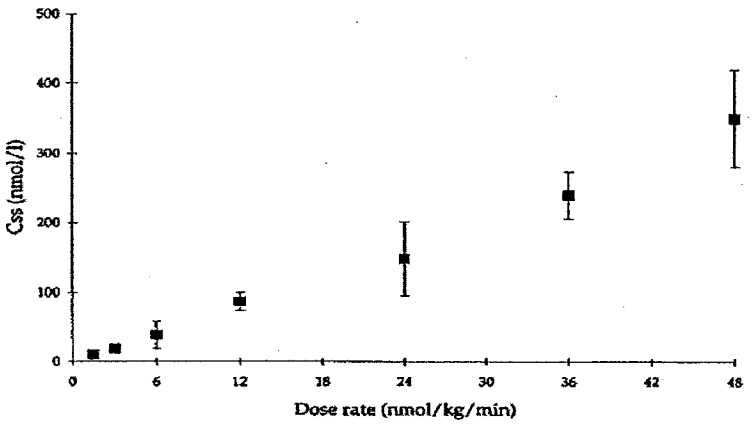
In humans, a mean of 83% of a radiolabeled dose of clevidipine is excreted in urine and feces as inactive metabolite [Final Study Report SH-SAD-0002]. The major fraction of radioactivity, 63–74%, is excreted in the urine, with only 7–22% in the feces. More than 90% of the recovered radioactivity is excreted within the first 72 hours of collection. No intact parent compound is recovered in urine or feces, suggesting that clevidipine is completely and rapidly metabolized.

R. Is Clevidipine dose proportional?

CLss and Css were calculated for clevidipine in normal subjects receiving an infusion of 1.5 to 48 nmol/kg/min. Clearance remained constant:



Blood concentrations during steady state (mean of 10, 15, and 19 minutes) versus dose rate below, mean and SD (1.5 nmol/kg/min n=4, 3 nmol/kg/min n=4, 6 nmol/kg/min n=4, 12 nmol/kg/min n=4, 24 nmol/kg/min n=3, 36 nmol/kg/min n=4, 48 nmol/kg/min n=3):



There was a less than dose-proportional relationship between dose rate and C_{ss} in healthy volunteers. The same results are seen in hypertensive subjects. Clevidipine seems to be less than dose-proportional.

S. INTRINSIC FACTORS

1. HEPATIC IMPAIRMENT

No hepatic impairment studies were performed since clevidipine is metabolized by hydrolysis in blood and in intravascular tissues and has a short half-life.

2. RENAL IMPAIRMENT

No renal impairment studies were performed since clevidipine will be administered for a short period of time (maximum 72 hours) and has a short half-life.

3. ARTERIAL VERSUS VENOUS BLOOD

During CABG surgery, Clevidipine concentrations seem to be the same during the pre-bypass (hypothermic) phase:

Non-compartmental analysis of blood concentration during pre-bypass. Individual values and descriptive statistics.

Patient	R_0 (nmol/kg/min)*	Arterial blood		Mixed venous blood (pulmonary artery)	
		C_{ss} (nmol/l)	Cl_b (l/min/kg)	C_{ss} (nmol/l)	Cl_b (l/min/kg)
N	17	17	17	16	16
Mean	4.76	87.3	0.061	87.8	0.060
SD	1.87	50.0	0.019	54.1	0.019
Median	4.00	66.4	0.059	72.0	0.056
Min	2.49	26.5	0.032	25.4	0.028
Max	7.31	220.7	0.101	251.5	0.099

* molecular weight 456.3 g

However, during normothermic conditions, clevidipine arterial blood clearance seems to be slower (by about half) with shorter half-lives when compared to venous blood. The concentration of clevidipine in arterial blood is about twice as high as venous blood following constant infusion possibly due to extensive and rapid metabolism.

Venous blood descriptive PK statistics:

		Low infusion rate	High infusion rate	Short infusion time
Cl (l/min/kg)	Mean	0.139	0.104	0.147
	SD	0.043	0.010	0.032
	Median	0.136	0.109	0.150
V_1 (l/kg)	Mean	0.45	0.31	0.39
	SD	0.21	0.15	0.11
	Median	0.47	0.28	0.38
V_{ss} (l/kg)	Mean	0.81	0.61	0.67
	SD	0.41	0.20	0.08
	Median	0.83	0.62	0.69
$t_{1/2\lambda1}$ (min)	Mean	2.1	1.7	1.6
	SD	0.4	1.0	0.4
	Median	2.1	1.6	1.6
$t_{1/2\lambda2}$ (min)	Mean	.*	9.5	4.3
	SD	.	2.7	0.5
	Median	.	9.8	4.4
$t_{1/2\lambda z}$ (min)	Mean	37.5	59.1	25.6
	SD	9.6	9.5	12.1
	Median	40.8	55.8	24.1

Arterial blood descriptive PK statistics:

		Low infusion rate	High infusion rate	Short infusion time
Cl (l/min/kg)	Mean	0.072	0.066	0.070
	SD	0.007	0.005	0.006
	Median	0.072	0.068	0.072
V_1 (l/kg)	Mean	0.10	0.08	0.07
	SD	0.02	0.02	0.01
	Median	0.10	0.09	0.07
V_{ss} (l/kg)	Mean	0.20	0.22	0.14
	SD	0.03	0.08	0.02
	Median	0.20	0.20	0.13
$t_{1/2\lambda1}$ (min)	Mean	0.7	0.8	0.6
	SD	0.1	0.3	0.1
	Median	0.7	0.7	0.6
$t_{1/2\lambda2}$ (min)	Mean	2.2	2.3	2.3
	SD	0.2	0.1	1.0
	Median	2.2	2.3	2.0
$t_{1/2\lambda z}$ (min)	Mean	18.4	21.7	16.3
	SD	2.8	1.6	2.8
	Median	18.0	21.1	15.6

T. EXTRINSIC FACTORS

1. WERE ANY DRUG INTERACTIONS EXPLORED?

No drug interactions were explored since clevidipine will be administered for a short period time and has a short half-life.

2. WERE PHARMACOKINETIC DIFFERENCES FOR BODY TEMPERATURE DURING CARDIAC SURGERY EXPLORED?

Yes, differences in the pharmacokinetics of clevidipine during hypothermia (pre-bypass) and normothermia (bypass) were explored during CABG:

Parameter	Estimate	Lower limit	Upper limit
R_0 (nmol/kg/min)	2.36	-0.26	4.86
C_{ss} (nmol/l)	5.8	-55.2	38.2
Cl_b (l/min/kg)	0.027	0.016	0.044

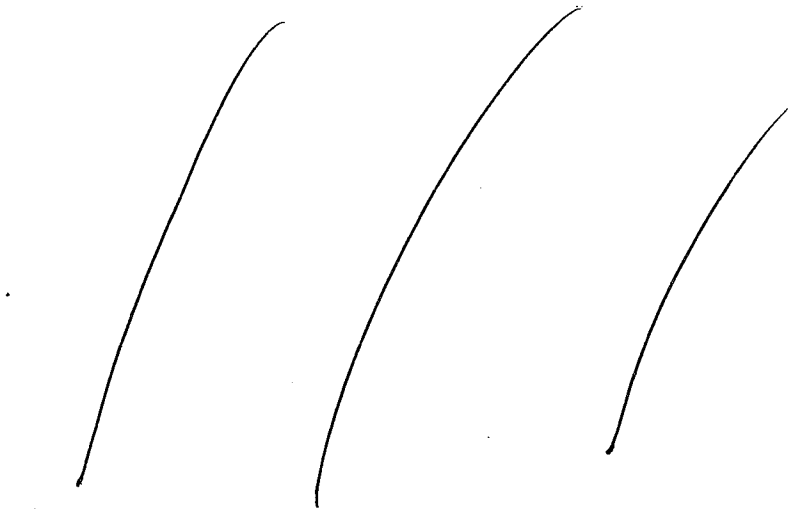
R_0 = infusion rate; Cl_b = Blood clearance

The confidence intervals indicate that Cl_b is higher during bypass compared to pre-bypass.

Difference between pharmacokinetic parameters during the pre-bypass and the bypass. Hodges-Lehmann estimates of true median difference and 95 per cent confidence intervals based on data from patients treated during both pre-bypass and bypass (n=7). Pharmacokinetic parameters calculated by compartmental analysis.

Parameter	Estimate	Lower limit	Upper limit
A	-0,025	-0,040	-0,005
B	0,025	0,005	0,040
Cl_b (l/min/kg)	0.026	0.017	0.041
V_1 (l/kg)	0,01	-0,03	0,03
V_{ss} (l/kg)	0,01	-0,05	0,03
$t_{1/2\alpha 1}$ (min)	-0.5	-1.0	-0,2
$t_{1/2\alpha 2}$ (min)	-3,4	-9,8	-1,8

The confidence intervals indicate that model constant B and Cl_b are higher during bypass compared to pre-bypass, while model constant A, $t_{1/2\alpha 1}$ and $t_{1/2\alpha 2}$ are lower during bypass compared to pre-bypass.



Concentrations of clevidipine in peripheral arterial blood and mixed venous blood during pre-bypass and concentration of clevidipine in peripheral arterial blood during bypass, following 10 min constant rate infusion (representative patient, dose rate of 2.05 µg/kg/min or 9.8 mg/hr).

(Source: Sponsor's Figure 29 in summary-clin-pharm.pdf)

The half-life of clevidipine increases during pre-bypass (hypothermia) possibly due to a decrease in clearance.

3. WERE ANY IN-VITRO METABOLIC STUDIES PERFORMED?

In total, six in-vitro metabolic studies were performed for clevidipine and its metabolite (M1, H152/81).

Based on in-vitro data, clevidipine and its metabolite, H152/81 seem to have an induction potential to CYP 3A4, 2C9 and 1A2.

The inhibition potential of clevidipine and H152/81 to CYP 1A2, 2C9, 2C19, 2D6, 2E1, and 3A4 was evaluated in vitro as well. The therapeutic concentration of clevidipine given at 3.2 µg/kg/min (16 mg/hr) is about 50 nM. If the dose were to be doubled, as is allowed in the labeling one could assume a therapeutic concentration for clevidipine reaching approximately 100 nM. This scenario could potentially close-in on inhibitory concentrations for CYP P450 2C9 (150 nM). As a result, _____ In addition, clevidipine did inhibit CYP 2C19, and 3A4.

For the metabolite, H152/81 did inhibit CYP 2C9, 2C19, and 3A4.

III. General Biopharmaceutics

A. Were the correct moieties identified and properly measured to assess the clinical pharmacology?

Clevidipine was identified and measured in all pharmacokinetic studies and several of the clinical studies as listed above in the summary tables addressing the design features of the clinical pharmacology and the clinical studies that were used to support dosing or claims. Clevidipine's enantiomers were also assessed in order to determine if the pharmacokinetics of the two enantiomers were different. In some studies as described above, H152/91 (M1) clevidipine's major metabolite was also assessed; which is considered to be inactive.

B. Where different formulations used throughout the development program of Clevidipine?

The only formulation used in the clinical studies is the formulation being marketed.

IV. Assay and Validation

Were all assays validated?

Several Bioanalytical methods have been developed and used to support the non-clinical and clinical pharmacokinetic programs for clevidipine. The non-clinical and early clinical studies utilized a GC-MS method for clevidipine and an LC-Flur for the inactive metabolite H152/81 (M1). In more recent clinical studies, an LC/MS/MS assay was used for clevidipine and its metabolite M1 determination in blood that has a sensitivity of 0.2 ng/mL for clevidipine and 20 ng/mL for M1. Since clevidipine metabolizes rapidly, steps need to be taken to reduce the metabolism during sample collection and preparation. The GC-MS method and the LC-Flur were developed by Astra-Zeneca. Below are the different analytical methods and validation data summary:

Method	Compound	Recovery %	Repeatability	Reproducibility	Linearity	LOQ
GC-MS	H324/38	84.2-100.3%	2.0-15.6%	91.6-116.9%	linear	0.5-25.0 nmol/L
LC-Flur	H324/38	85.6-100.9%	3.0-4.1%	NE	linear	50 nmol/L
	H152/81	82.2-93.6%	0.9-7.5%	86.0-104.4%	linear	"
LC-MS	H324/38	82.4-92.8%	n/a	n/a	n/a	n/a

	H190/91 H190/90	n/a n/a	18.5-1.2% "	92.8-104.0% 90.7-101.0%	Linear-range 0.5-700 nmol/L	0.50 nmol/L "
GC/MS/ LC-Flur	H324/38 H152/81	93.2-94.0% 82.2-85.4%	3.1-4.3% 1.4-4.7%	NE 97.2-103.7%	linear linear	5.0 nmol/L 5.0-50.0 nmol/L
LC/MS/ MS	H324/38 H152/81	71% 97.7%	%Nom within 100±15%; %CV ≤ 15%	NE	linear	0.2 mg/mL 20 mg/mL

NE = not evaluated;

V. LABELING

A. IS THE PROPOSED LABELING FOR CLEVIDIPINE ACCEPTABLE?

The proposed labeling is acceptable. The Reviewer Labeling Comments should be addressed by the sponsor. A copy of the proposed package insert is included in Appendix I with labeling comments by the reviewer.

APPEARS THIS WAY
ON ORIGINAL

DETAILED LABELING RECOMMENDATIONS

(Please refer to the Label in Appendix I for Recommendations)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Appendix I:
Proposed Package Insert
(June 4, 2007)

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL