Table 69. Maximum percent change HR from baseline to 0-1 h after start of infusion

	Essential		Perioperative			Severe
Variable	**Clevidipine (N=82)**	**Placebo (N=26)**	**Clevidipine (N=968)**	**Placebo (N=102)**	**All active comparators (N=769)**	**Clevidipine (N=126)**
Number of patients with both baseline and post-baseline on treatment assessments	82 (100.0)	26 (100.0)	927 (100.0)	102 (100.0)	731 (100.0)	126 (100.0)
Maximum percent HR increase from baseline within 0-1 h post-infusion start[a]	71 (100.0)	13 (100.0)	682 (100.0)	78 (100.0)	542 (100.0)	115 (100.0)
≤ 10%	27 (38.0)	8 (61.5)	212 (31.1)	52 (66.7)	148 (27.3)	26 (22.6)
> 10% - 20%	18 (25.4)	5 (38.5)	173 (25.4)	18 (23.1)	98 (18.1)	29 (25.2)
> 20% - 30%	14 (19.7)	0 (0.0)	101 (14.8)	3 (3.8)	89 (16.4)	28 (24.3)
> 30% - 40%	3 (4.2)	0 (0.0)	59 (8.7)	2 (2.6)	66 (12.2)	10 (8.7)
> 40% - 50%	6 (8.5)	0 (0.0)	48 (7.0)	3 (3.8)	53 (9.8)	9 (7.8)
> 50%	3 (4.2)	0 (0.0)	89 (13.0)	0 (0.0)	88 (16.2)	13 (11.3)

Source: Table 9.7.2, Appendix 8.2.1
Note: Patients who received more than one treatment were counted in each of their treatment groups. Studies SH-SAD-0005, SH-SAD-0006, and SH-SAD-0017 were excluded.
[a] Values from the start of study drug infusion to permanent stop of infusion; on-pump values excluded as per SAP.

Taken from sponsor table 20, pg 56 of 6157 of ISS report

Table 70. HR (bpm): change from baseline to post-baseline on treatment assessment

	Essential		Perioperative			Severe
Variable	**Clevidipine (N=82)**	**Placebo (N=26)**	**Clevidipine (N=968)**	**Placebo (N=102)**	**All active comparators (N=769)**	**Clevidipine (N=126)**
Baseline						
n	82	26	927	102	731	126
Mean (SD)	68.1 (12.82)	66.8 (9.24)	76.9 (16.52)	84.4 (17.60)	76.1 (17.91)	81.2 (17.25)
Median	67.5	66.0	76.0	84.0	73.0	79.0
Q1, Q3	58, 76	62, 73	65, 89	69, 93	62, 88	69, 92
Minimum, Maximum	46, 114	47, 88	20, 142	53, 135	42, 172	47, 125

	Essential		Perioperative			Severe
Variable	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=968)	Placebo (N=102)	All active comparators (N=769)	Clevidipine (N=126)
Maximum of individual on-treatment post-baseline values[a]						
n	82	26	927	102	731	126
Mean (SD)	87.4 (14.76)	75.7 (7.75)	99.0 (18.88)	90.2 (19.34)	103.4 (19.34)	107.6 (21.55)
Median	90.0	75.5	98.0	89.5	102.0	105.0
Q1, Q3	78, 99	70, 83	87, 110	78, 101	90, 114	95, 118
Minimum, Maximum	55, 125	63, 88	47, 192	57, 150	53, 256	62, 177
Percentage change from baseline to maximum on-treatment assessment						
n	82	26	927	102	731	126
Mean (SD)	30.0 (19.18)	14.5 (13.53)	33.2 (34.49)	7.1 (9.40)	41.5 (36.39)	34.9 (24.24)
Median	26.5	14.5	25.0	3.7	36.8	29.5
Q1, Q3	14, 43	3, 26	6, 52	1, 10	13, 64	19, 49
Minimum, Maximum	3, 104	-5, 51	-30, 305	-10, 43	-32, 216	-7, 129

Source: Table 9.7.1, Appendix 8.2.1
Note: Patients who received more than one treatment were counted in each of their treatment groups. SH-SAD-0005, SH-SAD-0006, and SH-SAD-0017 were excluded.
[a] Values from the start of study drug infusion to permanent stop of infusion; on-pump values excluded as per SAP.

7.1.8.1 Overview of vital signs testing in the development program

The appropriateness of and measurements of BP and vital signs were discussed in Section 6.1.3.3.

In ESCAPE, HR was recorded every minute during treatment period and for a minimum of 30 minutes post study drug termination, or until induction of anesthesia. In ECLIPSE and VELOCITY, HR was recorded concomitantly with BP (ECLIPSE -for 24 hours following study drug initiation) (See Section 6.1.3.3 for details). Episodes of reflex tachycardia were recorded in ECLIPSE.

7.1.9 Electrocardiograms (ECGs)

A 12-lead ECG was scheduled at baseline and at discharge in the ECLIPSE trials (baseline only for ESCAPE and VELOCITY). Information on QT prolongation can be found in the thorough QT study (reviewed by the Interdisciplinary review team).

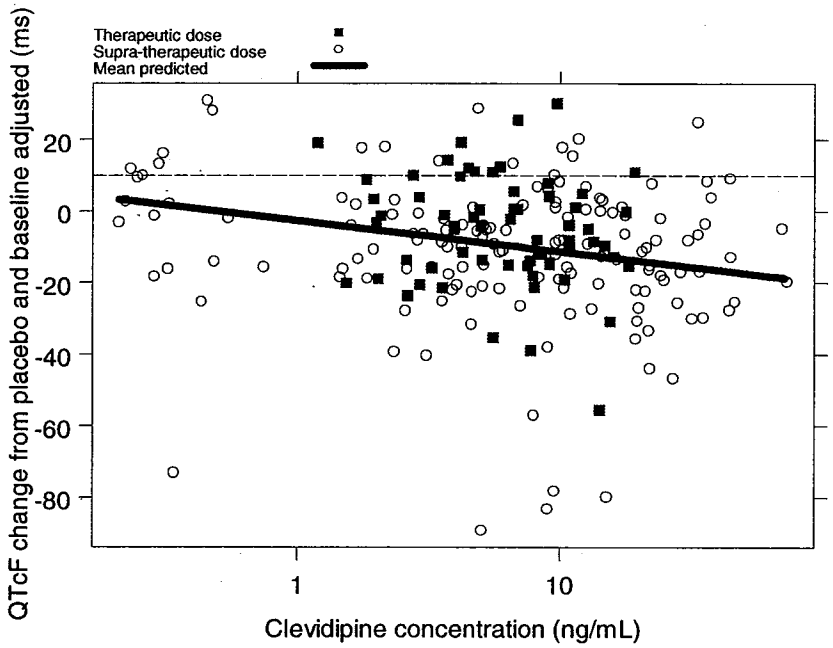
The sponsor conducted a randomized, single-blind, vehicle (Intralipid®) and heart rate (fenoldopam) controlled 2-treatment crossover study in healthy volunteers, with an additional non-randomized, open-label moxifloxacin treatment with heart rate control.

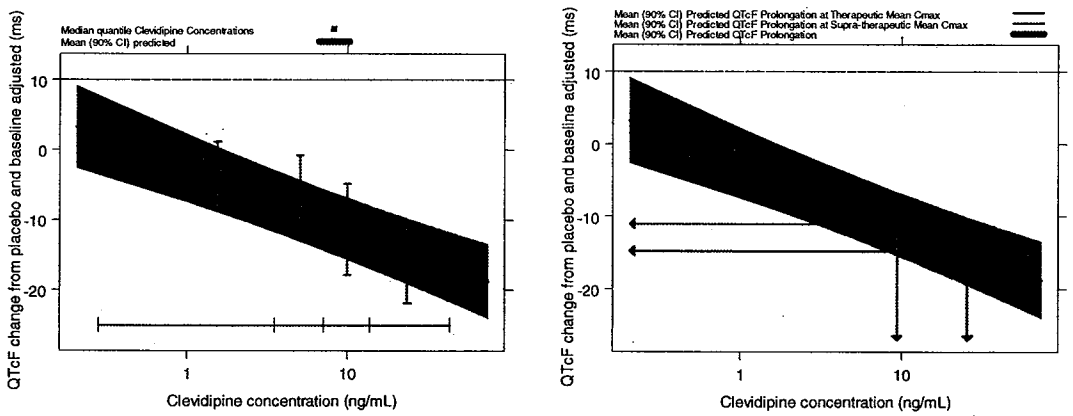
Compared to the vehicle- and heart rate-control group, administration of clevidipine was found to shorten the QT interval in a dose- and concentration-dependent manner.

- 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.

See the figures that follow for the effect of clevidipine on QTcF.

Figure 24. Effect on QTcf by CLV concentration





(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.

Nevertheless, there does not seem to be an increase in QTcF with clevidipine.

7.1.10 Immunogenicity

Not applicable.

7.1.11 Human Carcinogenicity

The development program was too short to detect any tumors.

7.1.12 Special Safety Studies

TMC-CLV-05-01 was a thorough QT study, although it had several design issues (use of fenoldopam for HR control) (see Section 7.1.9).

Although the ECLIPSE studies compared clevidipine to AC, none of the studies were designed or powered to detect a difference in safety over the AC.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable.

7.1.14 Human Reproduction and Pregnancy Data

According to the sponsor, there are no data on the use of clevidipine in women who are pregnant or lactating. The reviewer does have a potential concern that the formaldehyde could pose a potential threat to the fetus as there are anecdotal reports of women exposed to high levels of formaldehyde in the air who delivered premature babies. It is to be determined whether the formaldehyde concentrations from clevidipine are higher than "normal" levels seen in the body or more than that which can be removed from the body (and still be safe in the body).

7.1.15 Assessment of Effect on Growth

The drug is intended for short-term (72 hours) administration. Assessments of height and weight were not done.

7.1.16 Overdose Experience

No instances of clevidipine overdose were reported during the clinical development program. The maximum reported total clevidipine infusion dose was 1153 mg and the maximum infusion rate was 106 mg/h and 22 ug/kg/min for all studies. Patients (3 out of 4) that received 22 ug/kg/min experienced tachycardia. The longest continuous infusion was for 127.2 hours.

7.1.17 Postmarketing Experience

Not applicable.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See Table 4 in Section 4.2 for a description of studies, number of subjects for safety evaluation, patient groups, and dosing schedule.

7.2.1.1 Study type and design/patient enumeration

There were a total of 19 studies, with 99 healthy subjects (4 studies) and 1301 hypertensives patients who received at least one dose of clevidipine (1400 total clevidipine exposures). Fifteen studies evaluated clevidipine in hypertensives patients. There were 1093 perioperative hypertension, 82 essential hypertension, and 126 severe hypertension patients treated with clevidipine. The largest safety data come from the three ECLIPSE trials that compare clevidipine to an active comparator (SNP, NIC, or NTG). The ECLIPSE trials included a total of 752 clevidipine treated subjects. The breakdown by number of subjects is shown below. Table 4 includes all 19 studies.

Table 71. Total subjects treated by study

		TYPE	CLV	PBO	NTG	SNP	NIC	AC	TOTAL
Phase III	(study number)								
ESCAPE-1	(03-01)	**periop**	**53**	**51**					
ESCAPE-2	(03-02)	**Periop**	**61**	**49**					
ECLIPSE-NTG	(03-03)	**Periop**	**268**		**278**				
ECLIPSE-SNP	(03-04)	**Periop**	**296**			**283**			
ECLIPSE-NIC	(03-05)	**Periop**	**188**				**193**		
VELOCITY	(06-02)	**Severe**	**126**						
Phase I or II									
SH-SAD-0001		**Healthy**	**36**	**10**					
SH-SAD-0002 (mass)		**Healthy**	**8**						
SH-SAD-0003 (± BB in AM)		**Periop**	**83**	**2**					
SH-SAD-0004 (+ BB)		**essential**	**13**						
SH-SAD-0005		**Periop**	**14**			**14**			
SH-SAD-0006 (escape to SNP)		**Periop**	**18**						
SH-SAD-0010		**essential**	**21**	**13**					
SH-SAD-0013 (± BB)		**Periop**	**19**			**15**			
SH-SAD-0017		**Periop**	**39**	**31**					
SH-SAD-0018 (PK)		**Healthy**	**14**						
TMC-CLV-02-01		**Periop**	**54**		**56**				
TMC-CLV-05-01 (QT)		**Healthy**	**41**	**54**					
TMC-CLV-06-01 (72 h)		**essential**	**48**	**13**					

	CLV	PBO	NTG	SNP	NIC	AC	TOTAL
TOTAL Essential HTN	**82**	**26**					
TOTAL Healthy	**99**	**54**					
TOTAL ESCAPE	**114**	**100**					
TOTAL ECLIPSE	**752**					**754**	
TOTAL PERIOP PIII	**866**	**100**	**278**	**283**	**193**	**754**	**1720**
TOTAL PERIOP	**1093**	**133**	**334**	**312**	**193**	**839**	**2051**
TOTAL PATIENTS	**1301**	**159**	**334**	**312**	**193**	**839**	**2272**

BB=beta blocker
AM= morning
PK=pharmacokinetics
H=hour

7.2.1.2 Demographics

The demographics of the healthy subjects are shown in the table below. Most subjects were white, male, and less than 65 years old.

Table 72. Demographics of healthy subjects

Variable	Clevidipine (N=99)	Placebo (N=64)	Total Number of Subjects§ (N=122)
Sex			
Female	15 (15.2)	18 (28.1)	18 (14.8)
Male	84 (84.8)	46 (71.9)	104 (85.2)
Age (years)			
n	99	64	122
Mean (SD)	30.0 (8.20)	32.3 (10.02)	30.4 (8.06)
Median	28.0	31.0	28.5
Q1, Q3	24.0, 33.0	24.0, 38.5	24.0, 35.0
Minimum, Maximum	19.0, 60.0	19.0, 60.0	19.0, 60.0
Age Group			
<65 years	99 (100.0)	64 (100.0)	122 (100.0)
>=65 years	0 (0.0)	0 (0.0)	0 (0.0)

Note: Subjects who received more than one treatment are counted in each of their treatment groups.
§ Number of individual subjects (subjects from cross-over studies are only counted once).
^ Stage 1: 140<=SBP<160 and/or 90<=DBP<100, Stage 2: 160<=SBP<180 and/or 100<=DBP<115, Severe Stage 2: SBP>=180 and/or DBP>=115.
* Renal impairment: Creatinine Clearance (CL): Normal: CL > 80 ml/min, Mild: 50 < CL <= 80 ml/min,
Moderate: 30 < CL <= 50 ml/min, Severe: CL <= 30 ml/min,
Liver Function Status: Normal: Serum Bilirubin < 2 mg/dL and AST/SGOT <= 1.5 x ULN and ALT/SGPT <= 1.5 x ULN,
Abnormal: Serum Bilirubin >= 2 mg/dL and/or AST/SGOT > 1.5 x ULN and/or ALT/SGPT > 1.5 x ULN,
Program: t_demog.sas Output: T_02_2.lis Generated on: 27-APR-2007 17:34

Taken from sponsor's Table 2.2, pg 215 of 6157

Clevidipine-treated patients in the perioperative group were mostly white males (see table). Around half were ≥ 65 years old and the average BMI indicates that the average patient was overweight. More demographic information is available in the review for ESCAPE, ECLIPSE, and VELOCITY (Table 9, Table 10, Table 17, Table 18, Table 24, Table 25).

Table 73. Summary of demographics by type of hypertension

	Essential		Perioperative			Severe
Variable	**Clevidipine (N=82)**	**Placebo (N=26)**	**Clevidipine (N=1093)**	**Placebo (N=133)**	**All active comparators (N=839)**	**Clevidipine (N=126)**
Gender, n (%)						
Female	25 (30.5)	9 (34.6)	279 (25.5)	33 (24.8)	206 (24.6)	65 (51.6)
Male	57 (69.5)	17 (65.4)	814 (74.5)	100 (75.2)	633 (75.4)	61 (48.4)
Age (years)						
n	82	26	1093	133	839	126
Mean (SD)	55.0 (12.03)	57.7 (11.48)	64.6 (10.74)	62.7 (11.03)	64.8 (10.95)	53.5 (15.18)
Age group, n (%)						
<65 years	62 (75.6)	17 (65.4)	526 (48.1)	79 (59.4)	388 (46.2)	96 (76.2)
≥65 years	20 (24.4)	9 (34.6)	567 (51.9)	54 (40.6)	451 (53.8)	30 (23.8)
Race groups, n (%)						
Black	14 (17.1)	4 (15.4)	97 (8.9)	3 (2.3)	66 (7.9)	97 (77.0)
White	62 (75.6)	19 (73.1)	912 (83.4)	111 (83.5)	699 (83.3)	20 (15.9)
Other	6 (7.3)	3 (11.5)	84 (7.7)	19 (14.3)	74 (8.8)	9 (7.1)
Body mass index (kg/m²)						
n	82	26	1093	133	838	125
Mean (SD)	30.3 (5.64)	29.3 (5.46)	29.1 (5.73)	29.0 (5.58)	29.2 (5.89)	30.0 (7.56)

Source: Table 9.2 Appendix 8.2.1
Note: Patients who received more than one treatment are counted in each of their treatment groups.

Taken from sponsor Table 11, pg 41 of 6157

7.2.1.3 Extent of exposure (dose/duration)

Hypertensive patients received clevidipine doses up to 60 mg/h. The initial infusion rate was discussed earlier (Section 6.1.3.2). As noted earlier, the investigator could change the infusion (stop, restart, titrate up/down, add another antihypertensive) without noting the reason for the change. Thus it was difficult to make assessments of AE in relation to study drug. The dose is summarized by infusion rate, length of continuous infusion, total on-drug duration, and average and maximum rate in the following tables. Only study 06-01 included exposures of 72 hours.

Table 74. Summary of clinical trial exposure duration in hypertensives

Study	Duration of clevidipine continuous infusion		
	Clevidipine (N=1238) <48 hours	Clevidipine (N=51) ≥48 hours	Clevidipine (N=49) ≥72 hours[a]
	Overall clevidipine infusion		
All studies	1238 (100.0)	51 (100.0)	49 (100.0)
Essential hypertension			
SH-SAD-0004	13 (1.1)	0 (0.0)	0 (0.0)
SH-SAD-0010	21 (1.7)	0 (0.0)	0 (0.0)
TMC-CLV-06-01	1 (0.1)	47 (92.2)	47 (95.9)
Perioperative hypertension			
SH-SAD-0003	83 (6.7)	0 (0.0)	0 (0.0)
SH-SAD-0005	14 (1.1)	0 (0.0)	0 (0.0)
SH-SAD-0006	18 (1.5)	0 (0.0)	0 (0.0)
SH-SAD-0013	16 (1.3)	0 (0.0)	0 (0.0)
SH-SAD-0017	30 (2.4)	0 (0.0)	0 (0.0)
TMC-CLV-02-01	54 (4.4)	0 (0.0)	0 (0.0)
TMC-CLV-03-01	53 (4.3)	0 (0.0)	0 (0.0)
TMC-CLV-03-02	61 (4.9)	0 (0.0)	0 (0.0)
TMC-CLV-03-03	267 (21.6)	1 (2.0)	1 (2.0)
TMC-CLV-03-04	294 (23.7)	2 (3.9)	1 (2.0)
TMC-CLV-03-05	188 (15.2)	0 (0.0)	0 (0.0)
Severe hypertension			
TMC-CLV-06-02	125 (10.1)	1 (2.0)	0 (0.0)

Source: 14.1.1, Appendix 8.2.1

Note: Included are all hypertensive patients who received at least one dose of study drug. Patient data for 12 perioperative patients from SH-SAD-0013 (3 patients) and SH-SAD-0017 (9 patients) were not included.

[a] The ≥72 hours group is a subset of the ≥48 hours group.

Taken from sponsor table 5, pg 34 of 6157

Table 75. Longest continuous clevidipine infusion (hypertensive patients)

Variable	Essential Clevidipine (N=82)	Perioperative Clevidipine (N=1093)	Severe Clevidipine (N=126)
Duration (h)			
n	82	1080	126
Median	72.00	2.25	20.66
Q1,Q3	4.00, 72.10	0.58, 8.50	19.18, 22.52
Min, Max	1.04, 72.15	0.02, 127.20	0.12, 59.70
Duration (h), n (%)			
>0 - <6	34 (41.5)	745 (68.2)	5 (4.0)
≥6 - <12	1 (1.2)	135 (12.4)	0 (0.0)
≥12 - <18	0 (0.0)	113 (10.3)	4 (3.2)
≥18 - <24	0 (0.0)	58 (5.3)	98 (77.8)
≥24 - <48	0 (0.0)	26 (2.4)	18 (14.3)
≥48 - <72	0 (0.0)	1 (0.1)	1 (0.8)
≥72 - <96	47 (57.3)	1 (0.1)	0 (0.0)
≥96	0 (0.0)	1 (0.1)	0 (0.0)
Duration Groups (h), n (%)[a]			
<48	35 (42.7)	1077 (98.5)	125 (99.2)
≥48	47 (57.3)	3 (0.3)	1 (0.8)
≥72	47 (57.3)	2 (0.2)	0 (0.0)

Source: Table 9.3, Appendix 8.2.1
Note: Patient 00407 00006 (TMC-CLV-03-04) received a bolus dose of clevidipine and is excluded from the analysis.
[a] The ≥72 hours group is a subset of the ≥48 hours group.

Taken from sponsor table 9, pg 36 of 6157

In the Phase III perioperative studies, the average infusion rate was 3.5 mg/h, which is very low considering the initial infusion rate was 0.4 ug/kg/min (~2 mg/h). (The modeled EC50 dose is about 10-12 mg/h). In the severe HTN study, the average infusion rate was close to 8 mg/h.

Table 76. Clevidipine exposure by HTN type

	Essential	Perioperative	Severe
Variable	Clevidipine (N=82)	Clevidipine (N=1093)	Clevidipine (N=126)
Overall duration (h)			
N	82	1092	126
Median	72.05	4.41	20.66
Q1,Q3	52.00, 72.13	1.00, 13.35	19.18, 22.52
Min, Max	1.04, 196.00	0.02, 161.42	0.12, 59.70
On-drug duration (h)			
N	82	1080	126
Median	72.00	2.92	20.66
Q1,Q3	8.00, 72.10	0.75, 11.00	19.18, 22.52
Min, Max	1.04, 72.15	0.02, 127.20	0.12, 59.70
Total dose (mg)			
N	82	1026	126
Median	144.00	9.88	168.17
Q1,Q3	45.73, 576.30	2.55, 35.69	76.57, 292.56
Min, Max	0.43, 1152.70	0.01, 864.17	0.43, 731.82
Initial rate (mg/h)			
N	82	1080	126
Median	2.00	2.05	2.00
Q1,Q3	0.38, 2.00	1.72, 2.50	2.00, 2.00
Min, Max	0.02, 2.00	0.05, 52.32	1.00, 2.00
Average rate (mg/h)			
N	82	1026	126
Median	4.96	3.55	7.88
Q1,Q3	2.00, 7.99	2.23, 6.33	4.09, 13.32
Min, Max	0.37, 15.98	0.15, 46.19	1.01, 31.59

Variable	Essential Clevidipine (N=82)	Perioperative Clevidipine (N=1093)	Severe Clevidipine (N=126)
Maximum rate (mg/h)			
n	82	1026	126
Median	8.00	7.22	16.00
Q1,Q3	3.57, 16.00	3.60, 15.15	8.00, 32.00
Min, Max	0.50, 32.80	0.15, 60.00	2.00, 58.00

Source: Table 9.3, Appendix 8.2.1
Note: Patients who received more than one treatment are counted in each of their treatment groups.
Patient 00407 00006 (TMC-CLV-03-04) received a bolus dose of clevidipine and was excluded from the analysis.

Taken from sponsor table 7, pg 36 of 6157

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

There were no secondary source data as all studies used were conducted under the applicant's IND, and there were no postmarketing data since the drug is not approved elsewhere.

The reviewer referred to the 2004 ACC/AHA Practice Guidelines on the CABG to gauge the mortality and morbidity risk of CABG. The seven variables predictive of mortality after CABG were urgency of operation, age, prior heart surgery, sex, LVEF, percent stenosis of the L main, and number of major coronaries with more than 70% stenosis. Some of these data were not available on the patients. Level 1 (modest influence on predictive capability) variables included height, weight, PCI during index admission, MI within 1 week, history of angina, ventricular arrhythmias, CHF, MR, DM, CVD, PVD, renal dysfunction, and creatinine level.

7.2.3 Adequacy of Overall Clinical Experience

There are no ICH guidelines on extent and duration of exposure for short-term drugs. There were a total of 1400 subjects exposed to clevidipine (see section 7.2.1.1). Most subjects had perioperative HTN, while 82 had essential and 126 had severe HTN. The sponsor is seeking a 72 hour [redacted] in patients that cannot take oral medication. The number of patients exposed seems reasonable for this indication.

With respect to the 72 hour duration of use, very few subjects received clevidipine for 72 hours. Only 47essential HTN subjects received the drug for 72 hours (study 06-01). The mean dosing duration in severe HTN patients was 21 hours with a maximum infusion time of 60 hours. Patients (n=114) in ESCAPE received the drug for 30 minutes up to 1 hour. Mean actual infusion duration in the ECLIPSE studies was around 8 hours. Since most patients were exposed to clevidipine for 24 hours or less, with 5 of the 6 Phase III studies containing 8 hours or less of exposure, the reviewer feels the duration [redacted] should be 24 hours at the most.

There were 2 placebo controlled studies and 3 active control studies. These are adequate to answer critical questions; however the duration of use was very short in these studies.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The reader is referred to the Pharm/Tox review. The adequacy of the program is briefly summarized in Section 3.2.

7.2.5 Adequacy of Routine Clinical Testing

The frequency of laboratory testing in the Phase III trials was adequate to assess overall safety since the drug is only infused for a short duration. It is most likely inadequate to describe a transient change in lipids (if one existed). The 72 hour infusion study (06-01) with monitoring up to 8 hours after the infusion was adequate to assess rebound hypertension.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The reader is referred to the Clinical Pharmacology review. A cursory review appears adequate.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

AEs were included in the ISS from the start of the surgical procedure or start of drug infusion (whichever occurred first) until 7 days after this time. SAEs which started at any time up to 30 days post-surgery start for perioperative studies or 30 days post-study drug initiation for all other clinical studies were included in the safety analyses. The definition of an SAE was consistent with the ICH Guideline E2A.

Afib/flutter assessment

Enrollment in all three ECLIPSE trials was suspended on 25 March 2005 because of an excess incidence rate of afib/aflutter between treatment groups in ECLIPSE-SNP and ECLIPSE-NTG. This decision was made following a planned interim safety analysis after 680 patients were enrolled between all three ECLIPSE studies. The analysis showed that the incidence of afib was 25% in the clevidipine group, significantly higher than the 15% reported for NTG and 13% reported for SNP (see table).

Table 77. Afib/flutter reports up to March 2005 in ECLIPSE, n (%)

	CLV	NTG	SNP	NIC
ECLIPSE-all	88/348 (25)	32/218 (15)	9/72 (13)	11/42 (26)
ECLIPSE-NTG	52/213 (24)	32/218 (15)		
ECLIPSE-SNP	19/93 (20)		9/72 (13)	
ECLIPSE-NIC	17/42 (41)			11/42 (26)

Data from sponsor response IND 65,114, submission 043, 04 January 2006

Afib was captured as an AE by the investigator without a prospective, protocol specified definition. Thus the reported incidence varied (5-70%) between sites. The sponsor sent monitors to all sites to verify the source data for all subjects and capture afib related data on additional CRFs (15 more pages) *(Details can be found in the Sponsor's ECLIPSE studies, Section 16.1.3.6)*. The monitors were to look for clues that AF might have occurred (records in the ICU chart, treatment with drugs used to treat afib, DC cardioversion, multiple ECGs or rhythm strips). Sixty-six sites were monitored with 100% source document verification.

The CRFs collected data on episodes, number of episodes, duration, severity, treatment, concomitant medication, hemodynamics and fluid balance. The sponsor states that they verified 100% of the source data for all subjects that were enrolled until the study was stopped. They said that they implemented a change in the source data verification (SDV) on 6-16-05 (described in Section 16.1.3.6) whereby only 10% of subjects would have hemodynamic and lab data verified, but all other data would be verified in 100% of subjects.

The results of the investigation found no statistically significant difference in incidence of Afib between treatment groups (35% for clevidipine versus 30% for AC, p=0.11) (see table).

Table 78. Afib/flutter reports after sponsor review Sept 2005 ECLIPSE, n (%)

	CLV	NTG	SNP	NIC
ECLIPSE-all	153/441 (35)	90/278 (32)	25/112 (22)	16/50 (32)
ECLIPSE-NTG	90/268 (34)	90/278 (32)		
ECLIPSE-SNP	40/148 (31)		25/112 (22)	
ECLIPSE-NIC	23/45 (51)			16/50 (32)

Data from sponsor response IND 65,114, submission 043, 04 January 2006

The DSMB reviewed the unblinded data on 23 Sept 2005 and concluded that clevidipine did not pose any safety risk and that the ECLIPSE studies could be restarted. They recommended and approved the proposed changes to the protocols to prospectively capture AF events and related data. Sites and study monitors were given standard definitions of afib and flutter and defined the period between episodes to differentiate one continuous episode versus numerous episodes with short intervals of NSR between.

Amendment 2 was introduced to enable a detailed retrospective and prospective data collection (additional 15 CRF pages). It was decided that a sufficient number of patients had been enrolled in ECLIPSE-NTG, so no more patients were entered into the trial.

7.2.8 Assessment of Quality and Completeness of Data

Overall, the data quality and completeness were satisfactory. As noted earlier, the reviewer found more than 61 patients that were started on doses greater than or equal to 0.5 ug/kg/min. Most of these subjects were not described in the protocol deviations.

7.2.9 Additional Submissions, Including Safety Update

There have been no safety updates.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The drug related AE include reflex tachycardia (5-10%), rebound HTN (9% increase in SBP), headache (40%), nausea (7%), and hypotension (17% in perioperative). These AE were all discussed earlier. One limitation of the hypotension data is that hypotension that could be fixed by stopping clevidipine was not recorded as an AE. Thus, the incidence of hypotension is actually much more than the reported.

7.4 General Methodology

The sponsor's integrated analysis of safety (IAS) includes all data from 19 clinical trials (n=1400 clevidipine treated subjects). The sponsor's main IAS was based on pooled data from 15 Phase II and III studies of 1301 clevidipine treated subjects (excludes the 99 healthy volunteers in the four Phase I studies). The reviewer pooled the data for the two ESCAPE studies together and three ECLIPSE studies together since they were similar in design. The analysis of safety included all data.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Because most of the studies were designed to titrate to effect, information on true dose response at best comes from three studies. All of the perioperative studies were designed to titrate to effect, usually a MAP target, except for study SH-SAD-0003. This was the only dose ranging study that gave fixed dosed infusions. It also was a parallel study. In essential hypertensives, fixed doses were used in SH-SAD-0010, however it was a cross-over study and all patients were titrated up to reach their final dose. Probably the best assessment of dose response in essential hypertensives comes from study TMC-CLV-06-01, a parallel fixed dose, 72 hour infusion study. Except for the lowest dose of 2 mg/h, doses were titrated up to reach the final target dose. The PM reviewer used this study to model the PK/PD relationship.

Initial dose was based on the SH-SAD-0003 study, an open-label, randomized, dose ranging, placebo-controlled study where 60% of cardiac surgery patients had a MAP decreased of ≥ 10% with 0.32 ug/kg/min. This study evaluated doses from 0.05 to 9.58 ug/kg/min (~46 mg/h). At the highest dose, 28% of subjects discontinued due to hypotension.

In earlier dose ranging studies (SH-SAD-0001 in healthy volunteers), 22 ug/kg/min (~110 mg/h) was the highest tolerated dose and was limited by tachycardia (HR ≥ 120 bpm). The sponsor states that changes in BP were not a suitable measure of efficacy since BP lowering was countered by a reflex increase in HR. Because of this, the sponsor chose to examine the relationship between MAP/HR (to reflect changes in SVR) and the dose of clevidipine. The sponsor found that in a small study (SAD-0004) with concomitant beta blocker, a dose of 0.6 ug/kg/min provided a reduction of 15% in MAP from baseline. This study only had 10 patients treated with clevidipine and some patients were on other antihypertensives "by mistake". SAD-0010 examined the HD response in essential HTN patients not taking concomitant beta blockers and the EC 50 (25 nmol/L) was equivalent to 1.5 ug/kg/min or 7.5 mg/h. This is lower than our PM's analysis (7.1 ng/mL, ~10-12 mg/h).

The maximum infusion rate of 8 ug/kg/min was determined after consideration of systemic levels of drug based on nonclinical toxicity studies.

Overall, the doses used in the clinical program are justified. The starting dose in the 5 controlled Phase 3 studies was 0.4 ug/kg/min (~ 2mg/h). The starting dose in the severe hypertensives was 2 mg/h.

The quick titration scheme does not seem justified. In the 5 Phase III studies, the dose was doubled every 90 seconds. In the severe hypertensives, the dose was doubled every 3 minutes. This quick titration scheme has the potential to overshoot the BP resulting in hypotension. The true incidence of hypotension in the clinical program is unknown since it was not reported as an AE if hypotension could be controlled by stopping the infusion or decreasing the dose. The reasons for these dose changes were not recorded and there were no predefined directions for how to titrate the dose down or when to stop it. More discussion is devoted to the titration scheme in the PK/PD section 5.2.1. The time to maximal onset of effect is about 10-15 minutes after the start of the infusion. It seems reasonable to make dose titrations every 10 minutes to avoid the potential for hypotension.

8.2 Drug-Drug Interactions

Using human hepatocytes from several donors, clevidipine was found to be a significant inducer of CYP3A4, but not CYP1A2 or 2C9 at the 10 uM (1.2 fold induction) and 100 uM (7.3 fold induction) concentrations of clevidipine tested. The M1 metabolite also produced induction of the CYP3A4 of ~8.7 fold at a concentration of 100 uM.

Human hepatocyte studies showed that clevidipine had some inhibitory effect on CYP2C9, 2C19, 2D6, and 3A4 (see table).

Since the drug is intended to be used short-term, there are no dose adjustments recommended for clevidipine.

Table 79. Clevidipine IC50 values using cDNA-expressed CYP450

isozyme	Specific substrate	IC50 value(μM)
CYP2C9	Diclofenac4'-hydroxylase	4.4
CYP2C19	[(S)-mephenytoin 4'-hydroxylase	2.5
CYP2D6	Bufuralol 1'-hydroxylase	72
CYP3A4	Testosterone 6β-hydroxylase	8.4

8.3 Special Populations

In the pivotal efficacy studies (ESCAPE-1 and-2), there was no difference by gender, age or race with respect to onset of effect or bailout. With respect to race, there were only 12 blacks in the ESCAPE studies and 9 were on clevidipine. There are too few blacks in the perioperative patient population to determine if there are differences by rave. The severe HTN study contained mostly blacks. Modeling of these data seem to indicate that less clevidipine is required for its antihypertensive effect. But it is not known if this could be partly due to the allowed use of concomitant antihypertensives.

Specific studies in hepatic and renal insufficiency were not done due to the short-term use.

8.4 Pediatrics

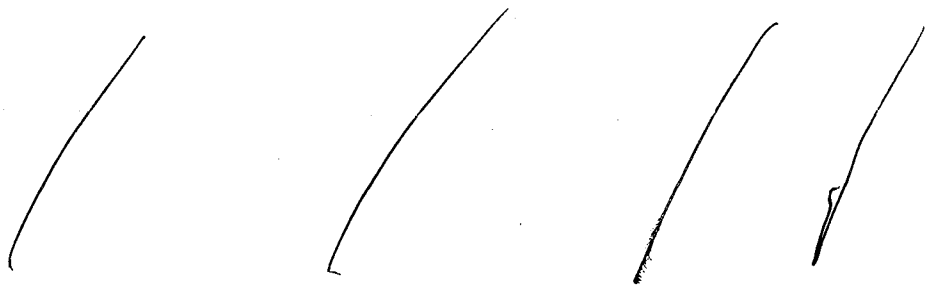
The sponsor submitted a request for deferral on May 2, 2007 (IND 65,114 submission number 072) to the statutory requirement to provide a pediatric assessment as described in the Pediatric Research Equity Act. The reason for the deferral request was because of the submission of the NDA later that month.

The sponsor expects to have an agreement with the Agency in place prior to the approval of the emulsion in adults. The sponsor is proposing to study the safety and efficacy of clevidipine in

in

- Adolescents 12- – years of age
- Children – 12 years of age
-
-

The sponsor proposes



This study and the pediatric development program will have to be reviewed in detail and discussed with the sponsor.

8.5 Advisory Committee Meeting

Not applicable.

8.6 Literature Review

None.

8.7 Postmarketing Risk Management Plan

Not submitted.

8.8 Other Relevant Materials

Consult comments from other Divisions have been placed in Sections 4.4, 9.4

9 OVERALL ASSESSMENT

9.1 Conclusions

Overall, clevidipine is an antihypertensive. It seems to be fairly safe, as evidenced by the AE profile. It does not seem to be any worse than the other IV antihypertensives. While the initial dose and dose increment seems acceptable, the reviewer recommends that the dose not be titrated as quickly as the sponsor proposes (every 90 seconds [redacted]. Based on the dose response study 06-01, the dose should be titrated every 10 minutes to avoid potential hypotension. Additionally, the reviewer recommends a shorter duration of infusion (form the sponsor's 72 hour proposal) to 24 hours since most patients were dose d for less than 8 hours.

9.2 Recommendation on Regulatory Action

The reviewer recommends that clevidipine be approved for [redacted] when oral medications are not feasible or desirable.

9.3 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions or Phase 4 commitments.

9.4 Labeling Review

The Division of Medication Errors and Technical Support Review dated 20-Dec 2007 have the following recommendations:

1. There are no objections to the use of the proprietary name, Cleviprex. However, a decision regarding approval must be made within 90 days of 20-Dec-2007. Otherwise, a re-review of the name, labels, and labeling must be made.
2. Consult Richard Lostritto, Chair of the CDER Labeling and Nomenclature Committee (LNC), Karl Stiller (the Project Manager assigned to the LNC), and the assigned ONDQA Chemist regarding the proper designation of the established name.
3. Delete rom the established name
4. The storage conditions for Cleviprex are unconventional and may be prone to error. The product should be protected from light. Since it must be used within 2 months after it is removed from the refrigerator and placed at room temperature, the potential exists for practitioners to forget to date the carton or vial once its removed from refrigeration. The medication may be sent to the ER or ICU, sit around, get sent back to the Pharmacy and returned to the refrigerator. The package insert
5. The dosage form should appear in conjunction with the established name. The complete established name should be at least ½ the size of the proprietary name per 21 CFR 201.10 (g)(2).
6. The strength should be expressed as total drug content and product strength (mg/mL) since it is not a single dose product.
7.
8.
9.
10. DMETS also has numerous comments regarding the carton labeling and container labels.

No patient package insert is needed since this will be given inpatient only and for less than 72 hours.

The reviewer will provide labeling recommendations in an addendum to this review.

9.5 Comments to Applicant

There are no comments from a clinical perspective. The reviewer was in constant contact with the sponsor during the review cycle.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 ECLIPSE studies (more information)

Primary endpoints
The definitions of the primary endpoints were as follows:

- Death: all- cause mortality; classified as cardiovascular or non-cardiovascular;

- Stroke: hemorrhagic or ischemic; diagnosed by a neurologist utilizing clinical signs and/ or radiological means of investigation, including arteriography, computed tomography (CT), or magnetic resonance imaging (MRI) scans and/ or carotid ultrasound;

- Myocardial infarction (MI): defined by symptomatic presentation, cardiac enzymes (such as CK-MB or CK, in the absence of CK- MB determination or troponin, as per institutional practice) and/ or new ECG changes;

- Renal dysfunction: defined as a postoperative (postrandomization), verified (i.e., the persistence of serum creatinine elevation 24 h following the initial acute serum creatinine elevation) serum creatinine level of ≥ 2.0 mg/dL (177 μmol/ L) and an increase of verified serum creatinine level of ≥ 0.7 mg/ dL (62 μmol/ L) from prerandomization to maximum postrandomization values and/ or the need for hemodialysis, venovenous or arterial venous hemofiltration, or peritoneal dialysis after surgery.

This definition of renal dysfunction is similar to that used in the first major multicenter study of renal dy7sfunction after CABG surgery referenced in the 2004 AHA/ACC CABG guidelines, except its definition of serum creatinine was the absolute value ≥ 2 mg/dL **OR** an increase of 0.7 mg/dL.

Protocol Amendment 1 (09 February 2005) changed the definition of renal dysfunction to that stated above. The CEC used the above definition for the entire adjudication process. The original definition of renal dysfunction was a 50% increase in peak postoperative serum creatinine from baseline. The original definition was used by investigators for the entire duration of the NTG study and for patients enrolled prior to 09 February 2005 for the SNP and NIC studies.

Renal function was calculated using Cockcroft-Gault equation with the following definitions of renal impairment (same definition as FDA Renal Guidance, 1998):

Mild	>50 – 80 mL/min
Moderate	>30 – 50 mL/min
Severe	≤30 mL/min

Myocardial infarction- enzyme level elevations:

Within 72 hours of CABG surgery, CK-MB greater than 5x upper limit of normal (ULN = 5 ng/ mL) and greater than 150% of the baseline (prerandomization) value. If more than 72 hours after CABG surgery, then CK-MB greater than 2x ULN and an increase of 50% or more over the previous value; Although other enzyme markers were collected, only CK-MB was used for cardiac event definitions.

Secondary
The secondary safety objectives were
The maximum increase in HR from the preoperative period (and prior to study drug administration) up to 24 hours after study drug initiation, was calculated; the intraoperative period was excluded from the analysis due to the use of cardioplegic arrest. Cardioplegia should not have been used in MIDCAB or OPCAB.

The following safety parameters were assessed: changes in HR, incidence of reflex tachycardia, incidence and duration of SVT including Afib and Aflutter (recorded until hospital discharge or Day 7), incidence of hypovolemia and total volume of fluids administered; incidence of AEs, and clinical laboratory parameters including hematology, biochemistry, and lipids. Clinical laboratory parameters were measured at baseline, 8 ± 2 hours after surgery, 24 ± 4 hours after surgery, and at hospital discharge or Day 7, whichever occurred first.

Although the effect of study drugs on ECG was listed as a secondary objective in the protocol, no ECG data wee collected in this study except to support the analyses associated with AF.

AMENDMENT
Amendment 1 – 9 February 2005 – changed definition of renal dysfunction.
Amendment 2 – 29 March 2005 – After a noted higher incidence of AF in the clevidipine (25%) groups in NTG (15%) and SNP (13%), enrollment was suspended (until Nov 2005; could be restarted on 23 September 2005) in the ECLIPSE studies until after a detailed retrospective and prospective data collection exercise of 680 subjects. The reported incidence varied among sites (5-70%). The sponsor sent monitors to all sites with additional CRF to capture AF-related data, ensuring that all the data entries had been made accurately and completely, and that all incidences of AF had been captured by the investigators for all patients at each of the sites. Results showed that there was no statistically significant difference in the incidence of AF between treatment groups (34.7 % CLV versus 32.4 % NTG). Outcomes as a result of AF were similar between groups. The duration and severity of AF episodes were similar. The DSMB gave approval to restart the program, however it was then decided that a sufficient number of patients were enrolled into ECLIPSE-NTG, so no further patients were entered

The incidence of AEs was assessed in the Day 7/discharge timeframe. Depending on when a patient was enrolled, SAEs were assessed in either the Day 7/Discharge timeframe (before 25 March 2005) or up to Day 30 following study drug administration (after 25 March 2005). For the ECLIPSE-NTG study, SAEs were assessed up to Day 7 only.

On Day 30 the incidence of all primary endpoints was assessed by telephone if the patient had been discharged.

10.1.1.1 Analysis

No formal statistical hypothesis testing was performed or study power calculated; 95% CI and p-values were provided to demonstrate the strength of the findings. The sample size was chosen based on clinical experience and in agreement with the FDA (EOP2, 25 March 2003).

Events were not censored. For example, if a patient had an MI and subsequently died, that patient was counted as an MI and a death.

Lost to follow- up and/ or missing values were not included in the derivation of incidence rates; if patient data was missing for the 30- day follow- up visit, that patient was removed from the denominator for all primary endpoint events. However, if the patient had experienced an endpoint event prior to Day 30, but had missing data for the 30- day follow- up visit, then the patient's data was included in the numerator and denominator for the incidence of that endpoint event but not in the denominator for the other endpoint events.

An AE that occurred after initiation of study drug was counted as a treatment emergent adverse event (TEAE) if it was not present at baseline or it increased in severity after initiation of study drug.

For repeat pre-baseline assessments, the results from the final assessment made prior to the start of the study drug infusion were used as baseline. Baseline BP was defined as the BP measured when the patient met the postrandomization criterion (had perioperative HTN – NTG). Immediately prior to study drug initiation.

Noteworthy is that the overall treatment infusion duration was calculated as the time between start of initial infusion and permanent stop of the study drug (hours).

The following pages contain brief summaries and details that may not be found elsewhere in the review. These pages are not intended to reiterate material that has been presented earlier in the review. The studies are for the most part presented in chronological order. All studies are randomized unless otherwise stated.

10.1.2 SH-SAD-0001: SB, PC, PK, X-over, CLV dose ranging and tolerability study in healthy males

10.1.2.1 Summary

This was the first study in man; a SB, PC, PK study in 25 healthy males. Twenty-one subjects were included twice (3 day acceptable washout in between), giving a total of 46 observations. The dose was infused over 20 minutes (see table). Placebo consisted of 20% Intralipid. For each of the first two dose steps, three subjects (2 active, 1 placebo) were included, and for each of the following consecutive dose steps, five subjects (four active, 1 placebo) were included. The highest tolerated dose 48 nmol/kg/min (22 ug/kg/min) was limited by tachycardia. A HR above 120 bpm was reached (predetermined safety endpoint) by 3 out of 4 subjects.

Table 80. Doses in study SH-SAD-0001

Part of the estimated therapeutic dose 2.7(38) µg/kg/min	Dose µg/kg/min	Dose nmol/kg/min
1/50	0.055	0.12
1/25	0.110	0.24
1/12	0.228	0.50
1/4	0.685	1.50
1/2	1.369	3.00
1	2.738	6.00
2	5.476	12.00
4	10.952	24.00
6	16.428	36.00
8	21.904	48.00
10	27.378	60.00

ECG, BP and HR were measured continuously during and for at least 4 hours after the infusion. Manual BP were obtained every 5th minute during the infusion and after the infusion starting at 25 minutes until 240 minutes after the start of the infusion. Clevidipine was analyzed by gas chromatography, and the metabolite H152/81 was analyzed by liquid chromatography. PK were measured for variable durations, with the longest being 12 hours after the highest dose. The effect on blood pressure is shown in the figure below.

Figure 25. BP response, SH-SAD-0001

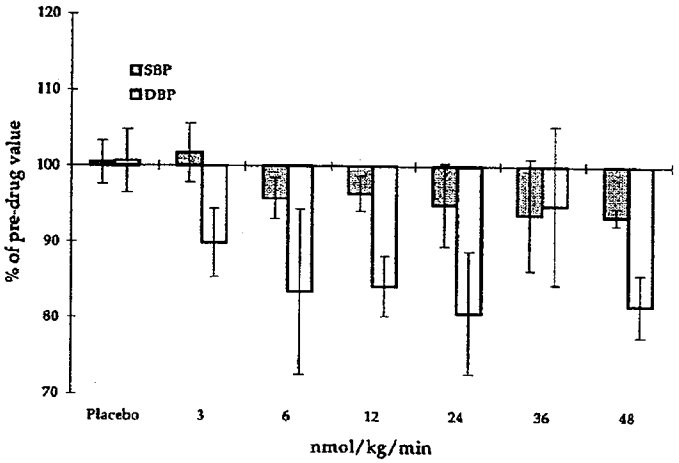
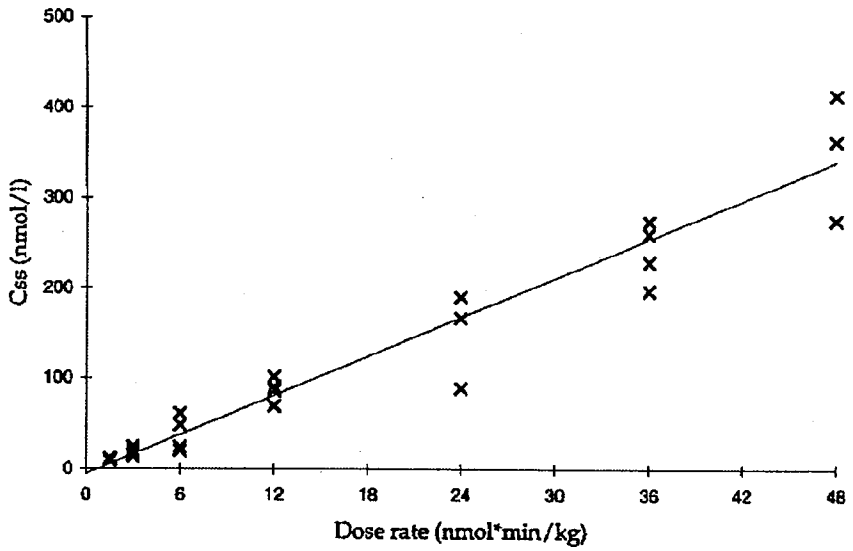


Figure 7. SBP and DBP, Steady-state value (mean of 10, 15 and 20 minutes), % of pre-drug value, Mean and SD (placebo n=10, 3 nmol/kg/min n=4, 6 nmol/kg/min n=4, 12 nmol/kg/min n=4, 24 nmol/kg/min n=3, 36 nmol/kg/min n=4, 48 nmol/kg/min n=3)

Taken from sponsor's Figure 7 on page 37 of 437.

The figure below shows the steady state concentration by dose rate, as fitted by a linear regression.

Figure 26. Css vs. dose rate as calculated by linear regression



Taken from Sponsor's Figure 15, pg 41 of 437

The most common AE was flushing (12/36) and headache (5/36). Clearance was high (0.1 – 0.2 L/kg/min) and independent of dose rate. The EC_{50} was 3 nmol/kg/min.

10.1.3 SH-SAD-0002: Mass balance study in healthy males

10.1.3.1 Summary

This was the mass balance study in 8 healthy males. Parent and radiolabeled concentrations were measured for 32 hours after the start of the 60 minute infusion. Urine and feces were collected up to 168 hours. Safety monitoring included ECG by oscilloscope for 2 hours after the start of the infusion, a 12 lead ECG 5 times around the infusion, and BP and HR for 8 hours after the start of the infusion (0, 15, 30, 45, 60, 75 and 90 minutes, 2, 3, 4, 5, 6, 7, and 8 hours after the start of the infusion).

The dose of 1030 nmol/min corresponded to 12-15 nmol/kg/min (weight range of 69 to 86 kg) or 5.5 ug/kg/min to 6.8 ug/kg/min. Clearance was 0.14 L/kg/min (high), the Vd was 0.5 L/kg, the initial T ½ was 1 minute and the terminal half-life ~ 12 minutes.

Figure 27. Median clevidipine concentration over time

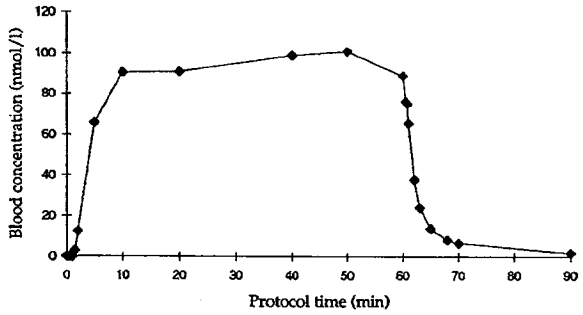
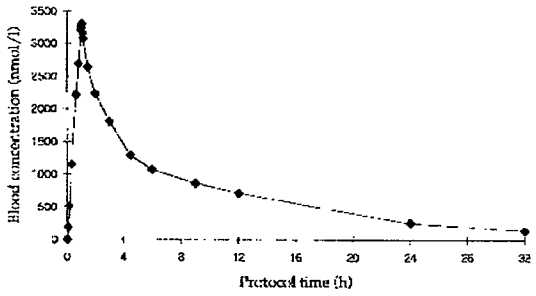


Figure 28. Median metabolite H 152/81 concentration over time



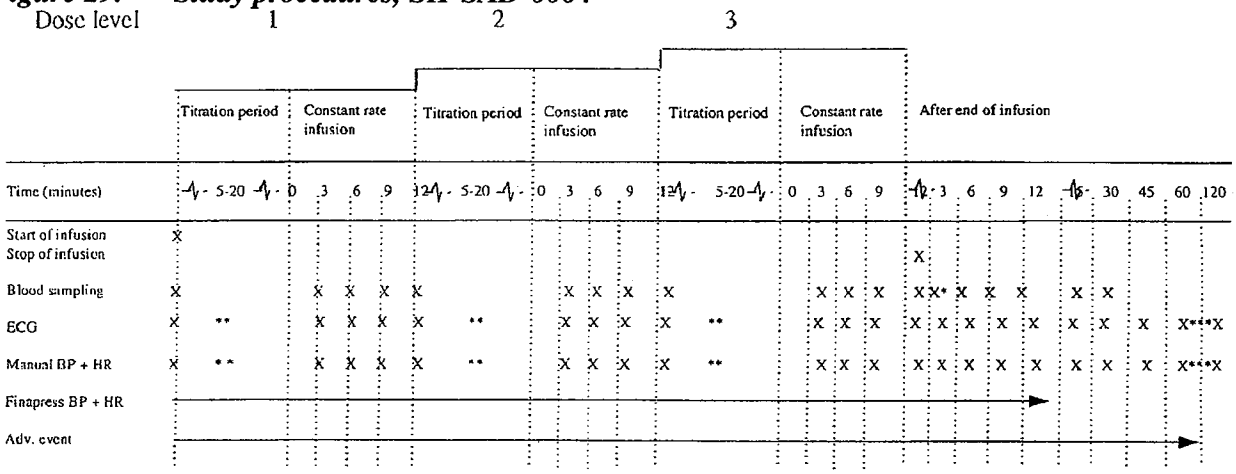
Approximately 70% of the radioactivity was recovered in the urine, and 15% in the feces with more than 90% of the dose excreted within 72 hours. The most common AE was flushing (n=7). Headache was reported in two males.

10.1.4 SH-SAD-0004: R, SB, PK study in essential hypertensives on beta blockers

10.1.4.1 Summary

The purpose of the study was to determine the dose –BP response of clevidipine in patients with essential hypertension taking concomitant beta blockers. Clevidipine was infused in 3 steps to obtain a MAP reduction of 5, 10, and 15 percent from baseline. The rate was adjusted (5-20 minutes) until the desired MAP was achieved, and then maintained for 12 minutes. Due to difficulties in finding the suitable concentration of clevidipine, the total infusion time varied from 67 to 174 minutes.

Figure 29. Study procedures, SH-SAD-0004



* Blood samples 0.5, 0.75, 1 and 3 minutes after the end of infusion
** ECG and BP every third minute
*** If the BP is not back to baseline after the first hour, continue with ECG and BP every 15 minutes until baseline BP has been reached

Thirteen patients were administered clevidipine, but three were excluded due to an exclusion criteria (1) and wrong inclusion pressures (2). Inclusion BPs were very high (moderate to severe), a supine SBP > 165 mmHg and DBP ≥ 100 mmHg after withdrawal of the calcium antagonist (if applicable). The starting dose was not allowed to exceed 0.5 nmol/kg/min and the maximum dose of 48 nmol/kg/min. Clevidipine emulsions was administered at different concentrations to different patients, ID 1 given 0.5 mg/mL, IDs 2-5 given 0.25 mg/mL, IDs 6, 8, and 10-15 given 0.1 mg/mL.

Being on drugs that could influence BP (other than beta blockers) was suppose to be an exclusion criteria, however, patients were allowed to be on other antihypertensives if their CCB was withdrawn. This was not stated in the protocol or in any amendments "by mistake". Three subjects were also taking other antihypertensives: ID 2, 6 and 13 also took a diuretic and an ACEI – all were withdrawn at least one week before the drug infusion.
The sponsor's linear regression showed that an average decrease in MAP of 5, 10, and 15 % would occur at dose rates of 0.06, 0.2, and 0.6 ug/kg/min, respectively. The corresponding blood concentrations were 1, 4, and 12 nmol/L. At the end of the constant infusion, MAP was decreased on average of 87 % from baseline. The clearance (mean ± SD) was 0.108 ± 0.045

L/kg/min (high). It is noted that the method of clevidipine analysis had improved and the limit of quantitation was now 0.5 nmol/L. No profound hypotension occurred. There was a transient increase in ALT within two times the baseline values in two patients.

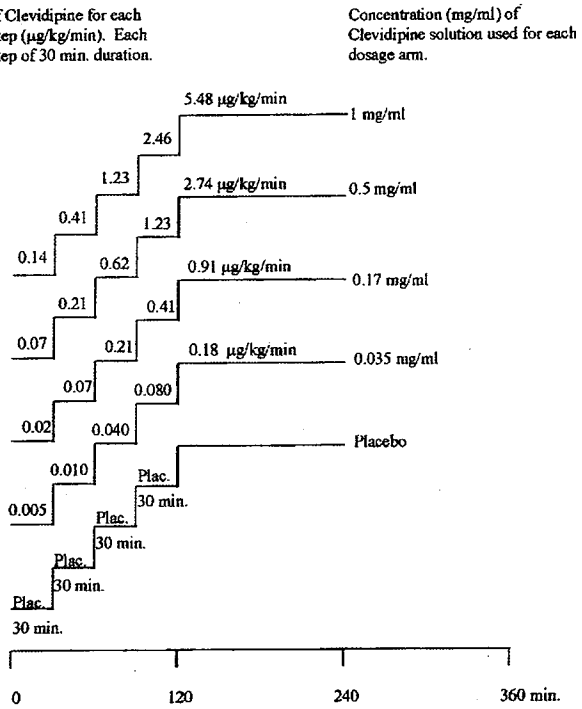
The sponsor only analyzed MAP data. Since this was a small study and the blood pressures were too high to discern if there were any detrimental effects of concomitant beta-blockers, the reviewer did not further analyze these data individually.

10.1.5 SH-SAD-0010: PK and PD of CLV in essential HTN: R, PC, SB, five-arm, three-way X-over

10.1.5.1 Summary

Twenty one patients with Stage II essential hypertension (by SBP AND DBP) were randomized. No antihypertensive medications were allowed at least 1 week prior to the first dose. Dosing was done as shown in the figure and was followed by a two hour washout period. Patients were crossed over to three arms out of five, and 2-7 days separated each arm.

Figure 30. Dosing scheme, SH-SAD-0010



Follow-up included a patient visit five days after the last study day.

Blood pressure was measured in the supine position during the study; however qualifying BP was taken while seated. SBP, DBP, and HR were recorded in conjunction with blood sampling.

- at enrolment, i.e. 1-4 weeks prior to the first dose of study drug
- at randomisation, i.e. 1-4 weeks after discontinuation of antihypertensive therapy (recorded in the seated position)
- immediately prior to the start of infusion (-10, -5, -1 min) and at the end of each dosage step during titration
- during study drug infusion at a constant rate, i.e. at 120, 230, 235 and 240 minutes after the start of infusion
- after the end of infusion i.e. at 280, 290, 315, 330, 345 and 360 minutes after the start of infusion

The following labs and 12-lead ECG were taken on six occasions (enrollment, prior to the first infusion, at 240 minutes after each infusion, and at 5 days after the last infusion):

Haematology:
Haemoglobin (Hb)
Leukocytes differential counts (WBC-diff):
neutrophil granulocytes
lymphocytes
eosinophils
monocytes
Platelets

Clin. chemistry:

ASAT (Aspartate aminotransferase)
ALAT (Alanine aminotransferase)
ALP (Alkaline phosphatase)
Bilirubin (total)

Sodium (Na^+)
Potassium (K^+)
Creatinine
Calcium
Creatinine kinase
Urea

ECG was monitored throughout the infusions. Patients were monitored for at least one hour after the last recording of blood pressure.

Patients were withdrawn by the investigator if their HR > 120 bpm or SBP ≥ 210 mmHg or ≤ 110 mmHg or DBP ≥ 115 mmHg or ≤ 60 mmHg or signs of myocardial ischemia.

Clevidipine emulsion concentration was 1, 0.05, 0.17, and 0.033 mg/mL for the 5.48, 2.74, 0.91, and 0.18 ug/kg/min arms. There were 10, 14, 13, and 12 patients exposed to each arm, respectively. Thirteen patients received placebo.
Patient no. 11 actually received 2.74 ug/kg/min at visit 4 instead of 5.48 ug/kg/min. Patient no. 1 actually received 0.36 ug/kg/min at visit 5 instead of 0.18 ug/kg/min. Patient 10 was excluded from the sponsor's PK analysis. Patient 9 had his/her infusion stopped due to the rapid SBP decline during study drug administration (5.48 ug/kg/min). She continued for the remaining

dose levels and visits. Patient no. 5 discontinued. Patient no. 01-0005 had drug stopped due to an AE. He received 2.74 ug/kg/min and it was decided to not expose him to a higher infusion rate. Two patients never received drug at the highest dose rate.

Table 4. Non-compartmental analysis for C_{ss} and CL_t

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)	(nmol/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_t (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)	(nmol/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_t (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.

PK

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_s (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~~ 0.093	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~~ 3.8	2.3	2.6

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

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	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
A** (nmol/l)						
Mean	0.98	0.98	0.98	0.96	0.98	0.97
S.D	0.02	0.02	0.01	0.03	0.02	0.03
Median	0.98	0.99	0.99	0.97	0.99	0.98
B **(nmol/l)						
Mean	0.02	0.02	0.02	0.04	0.02	0.03
S.D	0.02	0.02	0.01	0.03	0.02	0.03
Median	0.02	0.01	0.01	0.03	0.01	0.02
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.

The sponsor concludes that clevidipine is a high clearance compound (CLb=0.121 L/kg/min). The relationship between target dose rate and mean clevidipine concentration was linear. Dose dependent reductions in SBP, DBP, and MAP were observed. An increase in HR was observed. The clevidipine EC50 was 25 nmol/L. The dose rate producing half the maximal effect (ED50) was 1.5 ug/kg/min.

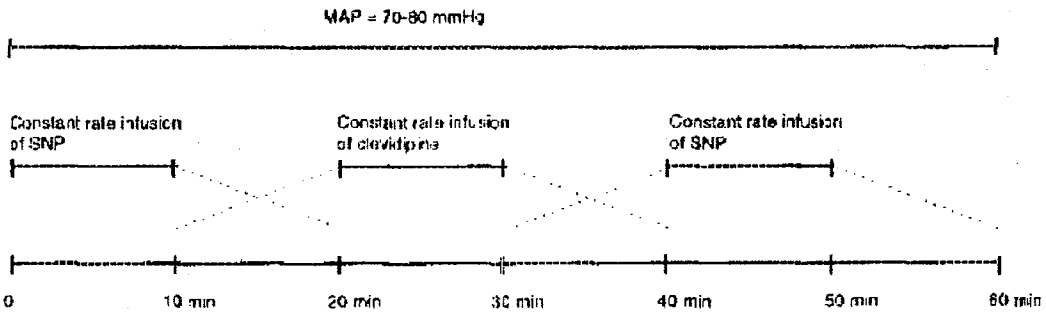
10.1.6 SH-SAD-0005: R, OL, CLV vs. SNP hemodynamics, myocardial blood flow and metabolism in postcardiac surgery patients

10.1.6.1 Summary

The objective of this study was to compare the effects of constant infusion clevidipine versus SNP on central hemodynamics, myocardial blood flow and metabolism after elective CABG. An amendment was made (1/1996) to also study four increasing dose rates of clevidipine and its effect on hemodynamics. Although 18 CABG patients perioperatively treated with SNP were recruited, 4 discontinued before study drug was given and one (ID 16) did not complete the study due to an MI. A beta-blocker was given preoperatively. No other inotropic or vasodilator treatment except SNP was allowed perioperatively. A HR $\geq$ 120 bpm qualified for exclusion. There were no BP criteria for inclusion or exclusion in this study.

Both drugs were administered by titration to achieve and maintain a MAP of 70-80 mmHg. SNP was dosed by manufacturer's instructions. The maximal clevidipine starting rate was 0.23 ug/kg/min, and the maximal infusion rate was 22 ug/kg/min. There were three 10 minute constant infusions with SNP, clevidipine, and SNP, with 10 minute washouts (n=13). See figure.

Figure 31. Study procedures, constant infusion phase, SH-SAD-0005

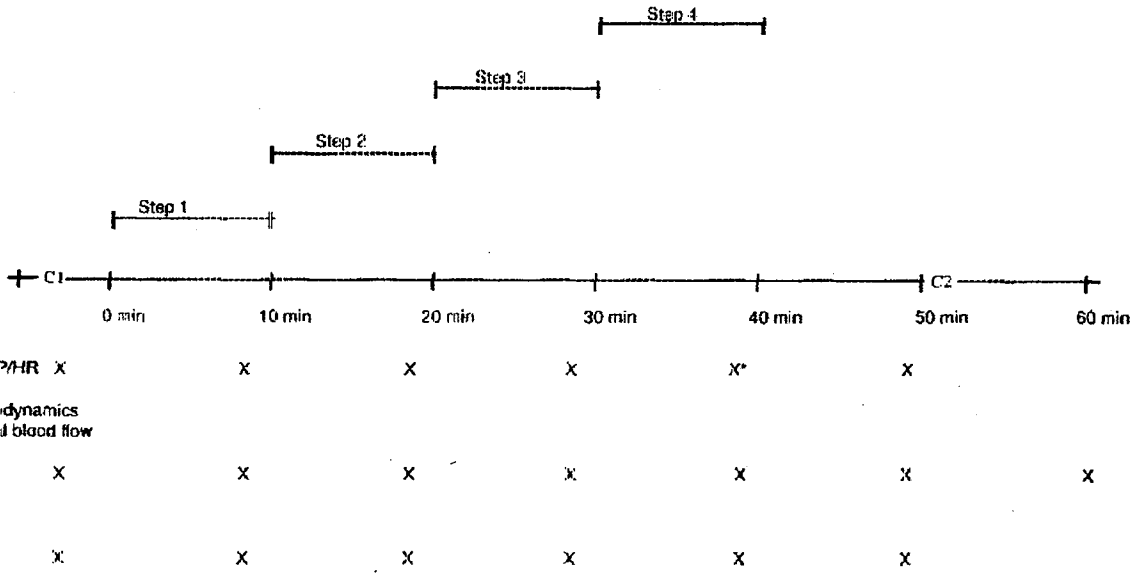


MAP/SBP/DBP/HR	X	X		X		X
Central haemodynamics and myocardial blood flow and metabolism	X	X		X		X
Phys. ex.	X*					
ECG	X	X		X		X
Lab.	X*					
AE		X		X		X
Medical history	X*					
Blood conc./clevidipine				X**		

* Preoperative
** Peripheral arterial and venous blood for determination of clevidipine were taken at 5 min. prior to start of infusion and after 8, 9 and 10 minutes during the constant rate infusion with clevidipine, and at 15, 30, 45 seconds 1, 3, 5, 7, 10 and 20 minutes after infusion stop of clevidipine.

After completion of the constant infusion phase, nine subjects received a controlled step-wise dose titration of four fixed doses of clevidipine (0.37, 0.75, 1.5, and 3.00 ug/kg/min) to evaluate the dose response. Patient 9 was unable to receive the highest dose.

Figure 32. Study procedures, dose response phase, SH-SAD-0005



* In 3 patients SBP/DBP and HR were recorded each 2nd minute between 40 and 60 minutes
All measurements were performed a few minutes before stop of each infusion step

The final dose rates (ug/kg/min) that maintain a MAP of 70-80 mm Hg are shown in the table below. The second dose of SNP was lower in 7 out of 13 patients, possibly suggesting that 10 minutes was too short of a washout after clevidipine or an effect of hemodynamics changing over time post CABG. The p-value for a difference between SNP infusion was barely not statistically different (p=0.0582).

Table 81. Final dose rates (ug/kg/min) to achieve and maintain a MAP of 70-80 mmHg, SH-SAD-0005

Patient	SNP 1	clevidipine	SNP 2
1	1.62	0.46	0.76
2	3.16	2.69	0.53
3	0.87	9.46	0.69
4	1.22	2.67	0.41
5	0.95	1.10	0.57
6	0.69	2.28	0.76
8	1.02	1.34	0.81
9	0.61	0.90	0.61
10	2.27	3.80	1.01
11	0.52	1.52	0.73
13	0.83	0.82	0.83
15	0.58	1.62	0.67
17	0.47	0.91	0.47

Mean	1.14	2.27	0.68
SD	0.79	2.36	0.16
Min	0.47	0.46	0.41
Median	0.87	1.52	0.69
Max	3.16	9.46	1.01

Clevidipine and SNP hemodynamics are shown in the table below. There was no statistical difference in the HD parameters between the two SNP doses. Statistical comparisons were done between the first SNP dose and clevidipine (see table). Clevidipine had a greater effect on preload (CVP and PCWP) compared to SNP. SVR was lower on clevidipine than on SNP. Left ventricular performance (SV) was higher with clevidipine than SNP. This may be attributed to lower SVR while filling pressures are maintained (CVP and PCWP). Thus, clevidipine may be a more efficient afterload reducing compound than SNP. The effect on PVRI was less pronounced with clevidipine, indicating that clevidipine is a less potent vasodilator of the pulmonary circulation compared to SNP.

Table 82. Central hemodynamics during the constant infusion phase, SH-SAD-0005

Variable	SNP 1	clevidipine	SNP 2
Heart rate (beats/min)			
N	13	10	13
Mean	83.5	81.5	83.5
SD	12.4	10.9	12.2
Systolic blood pressure (mmHg)			
N	13	10	13
Mean	106.0	107.6	105.5
SD	10.1	12.9	8.6
Diastolic blood pressure (mmHg)			
N	13	10	13
Mean	58.7	57.4	57.3
SD	5.8	4.5	5.4
Mean arterial pressure (mmHg)			
N	13	10	13
Mean	74.1	76.4	72.9
SD	5.2	4.3	5.3
Systolic pulmonary arterial pressure (mmHg)			
N	13	13	13
Mean	27.5	34.8	28.8
SD	4.9	5.3	4.7
Diastolic pulmonary arterial pressure (mmHg)			
N	13	13	13
Mean	13.7	15.7	14.2
SD	3.5	3.6	3.8
Mean pulmonary arterial pressure (mmHg)			
N	13	13	13
Mean	19.7	24.1	20.2
SD	3.7	3.6	4.1
Central venous pressure (mmHg)			
N	13	13	13
Mean	8.5	10.1	8.5
SD	3.0	3.5	3.3

Variable	SNP 1	clevidipine	SNP 2
Pulmonary capillary wedge pressure (mmHg)			
N	13	13	13
Mean	10.9	12.5	10.9
SD	3.3	3.3	3.2
Cardiac output (l/min)			
N	13	13	13
Mean	5.0	5.4	5.0
SD	0.8	1.0	0.9
Stroke volume (ml/min)			
N	13	13	13
Mean	61.4	69.4	60.8
SD	14.5	15.5	12.1
Pulmonary vascular resistance (dynes x sec x cm^{-5})			
N	13	13	13
Mean	139.8	174.2	151.3
SD	40.3	50.7	27.7
Systemic vascular resistance (dynes x sec x cm^{-5})			
N	13	13	13
Mean	1081.2	979.8	1067.7
SD	230.9	244.4	238.5
Cardiac index (l/min/m^2)			
N	13	13	13
Mean	2.4	2.6	2.4
SD	0.4	0.5	0.4
Stroke volume index (ml/beat/m^2)			
N	13	13	13
Mean	29.4	33.3	29.2
SD	6.3	6.8	5.4
Pulmonary vascular resistance index (dynes x sec cm^{-5} x m^2)			
N	13	13	13
Mean	291.4	360.8	314.9
SD	89.2	104.6	67.8

Variable	SNP 1	clevidipine	SNP 2
Systemic vascular resistance index			
(dynes x sec cm^{-5} x m^2)	13	13	13
N	2068.4	1873.3	2202.0
Mean	749.6	748.1	456.5
SD			
Arterial oxygen saturation (%)	13	13	13
N	98.9	98.8	98.9
Mean	1.8	1.8	2.1
SD			
Mixed venous oxygen saturation (%)	13	13	13
N	69.4	71.2	69.4
Mean	9.0	11.2	7.0
SD			
Whole body oxygen extraction (%)	12	12	12
N	29.4	27.3	30.4
Mean	7.8	9.1	7.0
SD			
Intrapulmonary shunt (%)			
N	13	13	13
Mean	14.9	16.1	14.1
SD	8.0	8.1	8.7
Arterial oxygen tension (kPa)			
N	13	13	13
Mean	17.2	17.3	18.5
SD	5.3	6.1	7.0
Oxygen delivery (ml/min)			
N	13	13	13
Mean	748.5	818.5	750.9
SD	147.9	184.3	149.4

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Taken from sponsor's Table 5, page 39 of 429

Table 83. Mean difference on central hemodynamics, SH-SAD-0005

SNP 1 *vs.* clevidipine		95% CI		
Variable	Mean difference	Lower	Upper	p-value
PCWP (mmHg)	1.62	0.53	2.71	0.0073
SV (ml/beat/m^2)	8.00	3.80	12.20	0.0014
SVR (dynes x sec x cm^{-5})	-101.46	-181.46	-21.46	0.0172
CVP (mmHg)	1.62	0.99	2.25	0.0001

Taken from Sponsor's Table 7, page 42 of 429

There was no difference between the two drugs in terms of myocardial lactate uptake or myocardial (see table).

Table 84. Myocardial metabolism comparison, SH- SAD-0005

Variable	SNP 1	clevidipine	SNP 2
Great cardiac vein flow (ml/min)			
N	11	11	11
Mean	90.4	92.8	89.4
SD	27.5	27.8	28.8
Coronary sinus flow (ml/min)			
N	11	11	11
Mean	189.6	216.7	193.9
SD	58.8	57.8	57.1
Myocardial oxygen extraction (%)			
N	13	13	13
Mean	50.3	49.4	50.8
SD	6.5	8.7	6.0
Regional myocardial oxygen consumption (ml/min)			
N	11	11	11
Mean	7.0	6.8	6.5
SD	2.2	1.8	1.4
Regional myocardial lactate extraction (%)			
N	13	13	13
Mean	2.1	3.9	4.2
SD	7.4	5.9	6.7
Regional myocardial lactate uptake (µmol/min)			
N	11	11	11
Mean	1.8	3.6	4.4
SD	6.1	5.7	6.7

Taken from Sponsor's Table 8 , page 43 of 429

During the dose response phase, there was no statistically significant difference in CVP or PCWP with increasing doses of clevidipine ($p > 0.05$) compared to Control 1 (C1), indicating maintained filling pressures due to lack of a vasodilating effect on the venous capacitance vessels. SVR significantly decreased with increasing doses. SV increased significantly with the Step 3 and 4 doses. Reflex tachycardia was not seen 10 minutes post infusion. See the following tables. C1 and C2 are control recordings prior to the start of the infusion and 10 minutes after stopping the infusion, respectively.

Table 85. Hemodynamics during dose response of clevidipine, SH-SAD-0005

Variable	C1	Step 1	Step 2	Step 3	Step 4	C 2
	N=9	N=9	N=9	N=9	N=8	N=9
Heart rate (beats/min)						
Mean	76.4	76.7	76.0	75.8	74.9	75.8
SD	8.4	8.4	8.4	7.4	8.0	8.2
Systolic blood pressure (mmHg)						
Mean	125.0	116.1	109.7	107.2	103.8	115.9
SD	15.2	13.1	11.0	10.1	6.7	7.7
Diastolic blood pressure (mmHg)						
Mean	63.4	59.3	56.1	54.2	51.4	58.4
SD	8.6	9.0	8.2	7.4	6.5	6.0
Mean arterial pressure (mmHg)						
Mean	85.7	79.7	75.1	73	69.8	78.6
SD	10.4	10.0	8.8	7.8	6.0	6.0
Systolic pulmonary arterial pressure (mmHg)						
Mean	36.0	34.7	33.6	33.9	33.5	33.0
SD	4.9	4.6	4.4	4.6	4.3	5.0
Diastolic pulmonary arterial pressure (mmHg)						
Mean	16.3	15.9	15.4	15.6	15.9	15.3
SD	3.6	4.3	4.1	4.4	3.9	4.0
Mean pulmonary arterial pressure (mmHg)						
Mean	24.6	23.7	23.1	23.3	23.4	22.4
SD	4.0	4.2	3.7	4.3	3.7	4.3
Central venous pressure (mmHg)						
Mean	10.7	10.9	11.0	11.4	11.4	10.0
SD	2.1	2.0	1.9	2.4	2.5	1.8

Variable	C1 N=9	Step 1 N=9	Step 2 N=9	Step 3 N=9	Step 4 N=8	C 2 N=9
Pulmonary capillary wedge pressure (mmHg)						
Mean	13.6	13.4	13.3	13.2	13.4	12.7
SD	1.6	2.2	2.0	2.6	2.7	2.2
Cardiac output (l/min)						
Mean	5.2	5.4	5.4	5.6	5.6	5.4
SD	0.8	0.7	0.9	0.9	1.2	1.1
Stroke volume (ml/min)						
Mean	68.9	71.0	71.4	74.3	75.6	71.1
SD	14.7	13.5	14.9	13.7	16.8	15.6
Pulmonary vascular resistance (dynes x sec cm^{-5})						
Mean	171.7	154.1	148.8	145.3	145.5	147.9
SD	56.3	37.9	36.8	33.6	26.8	37.8
Systemic vascular resistance (dynes x sec x cm^{-5})						
Mean	1197.1	1051.2	989.8	925.2	869.6	1058.9
SD	329.1	261.2	260.0	190.3	216.6	211.0
Cardiac index ($l/min/m^2$)						
Mean	2.5	2.6	2.6	2.7	2.7	2.6
SD	0.4	0.3	0.4	0.4	0.5	0.4
Stroke volume index ($ml/beat/m^2$)						
Mean	33.0	34.1	34.2	35.5	36.0	34.1
SD	6.8	6.0	6.4	6.2	7.4	6.9
Pulmonary vascular resistance index (dynes x sec x cm^{-5} x m^2)						
Mean	360.3	324.7	312.3	305.1	305.3	311.3
SD	129.0	98.4	91.0	84.2	62.5	94.2
Systemic vascular resistance index (dynes x sec cm^{-5} x m^2)						
Mean	2498.9	2192.3	2061.8	1933.2	1815.0	2205.9
SD	720.4	568.7	555.4	412.0	441.0	453.6

Variable	C1 N=9	Step 1 N=9	Step 2 N=9	Step 3 N=9	Step 4 N=8	C 2 N=9
Mixed venous oxygen saturation (%)						
Mean	70.4	68.8	68.5	68.2	67.8	67.9
SD	8.6	9.3	9.2	8.8	9.6	9.4
Whole body oxygen extraction (%)						
Mean	31.0	31.9	31.7	31.3	32.6	33.0
SD	8.2	9.3	9.5	9.1	10.1	9.5
Intrapulmonary shunt (%)						
Mean	10.6	13.6	14.2	17.0	19.8	12.2
SD	5.4	7.1	7.9	9.8	12.0	7.2
Arterial oxygen tension (kPa)						
N	9	9	9	9	8	9
Mean	21.6	18.3	16.9	15.4	14.1	19.5
SD	7.1	6.3	6.3	6.5	6.6	7.4
Whole body oxygen delivery (ml/min)						
N	9	9	9	9	8	9
Mean	768.2	791.6	788.2	808.9	826.5	794.2
SD	170.6	175.7	194.3	199.3	236.8	230.7

Taken from Sponsor's Table 11, page 45 of 429

Clevidipine is an arterial vasodilator (myocardial oxygen extraction decreased significantly). Mean values of myocardial lactate extraction decreased, but there were no lactate production (no negative mean value of myocardial lactate extraction) indicating that the coronary vasodilation with clevidipine did not induce ischemia.

Table 86. Myocardial metabolism during dose response, SH-SAD-0005

Variable	C1	Step 1	Step 2	Step 3	Step 4	C 2
Regional myocardial lactate extraction (%)						
N	9	9	9	9	8	9
Mean	5.0	4.0	2.7	1.2	0.3	2.3
SD	9.9	6.1	6.6	4.6	2.5	4.8
Regional myocardial lactate uptake (μmol/min)						
N	8	8	8	9	8	9
Mean	4.3	4.1	3.5	1.9	0.4	2.5
SD	9.6	7.1	7.5	4.0	2.1	3.9

Taken from Sponsor's Table 16, page 49 of 429

Similar to previous studies, clevidipine PK show that it is a high clearance drug, and arterial concentration were about twice that of venous concentrations. Following termination of infusion, concentrations declined rapidly, with the arterial concentrations declining faster. Arterial PK parameters (mean ± SD) were CL 0.046 ± 0.01 L/kg/min, T $1/2_{\alpha}$ 0.6 ± 0.3 min, ,T $1/2_{\beta}$ 4.1 ± 2.6 minutes, and Vdss 0.08 ± 0.04 L/kg. Venous PK parameters (mean ± SD) were CL 0.085 ± 0.03 L/kg/min, T $1/2_{\alpha}$ 0.9 ± 0.3 min, ,T $1/2_{\beta}$ 6.5 ± 2.9 minutes, and Vdss 0.27 ± 0.13 L/kg.

Patient 16 had clevidipine stopped after 6 minutes due to MAP of 68 mmHg. His BP remained low and was attributed to significant bleeding. It was treated with a blood transfusion and other volume therapy. There was no evidence of ischemia (labs nor ECG) during the measurements made with SNP or clevidipine, however the next day, his AST increased significantly and was accompanied by ECG changes suggestive of an AMI. An MI with afib, ventricular arrhythmias, and LV failure were verified. He was also on routine anesthesia, metoprolol, terbutaline, budesonide, bencylpenicillin and cloxacillan. He was treated with an ACE inhibitor, diuretics, and antiarrhythmic drugs and recovered after 6 days. He was 76 and had a history of angina and an MI 4 years and 1.5 months prior to enrollment. He was not included in any statistical analysis since he did not complete clevidipine.

Five patients reported a total of nine AE, all starting after completion of study drug infusion (see table).

Table 87. AEs in SH-SAD-0005

Patient No.	Start of Adverse event[1]	Adverse event	Intensity
02	Day 3	Atrial fibrillation	2
04	Day 3	Atrial fibrillation	2
10	Day 1	Atrial fibrillation	2
15	Day 3	Atrial fibrillation	1
16	Day 0	Postop. bleeding	0
	1	Myocardial infarction	3
	3	Atrial fibrillation	3
	3	Cardiac failure	3
	4	Ventricular arrhythmia	2

Intensity: 0=missing or not applicable, 1=mild, 2=moderate, 3=severe

Taken from Sponsor's Table 25, pg 60 of 429

Reviewer's comments:
Treatment order during the first phase was the same for all patients. It would have been better to change this up because of potential period effects following CABG. It is noted that the dose of SNP was not the same, in fact it was lower in the majority of patients, during the second SNP infusion (although no statistically significant difference was found).

10.1.7 SH-SAD-0003: R, PC, MC, OL dose ranging study in postcardiac surgery patients

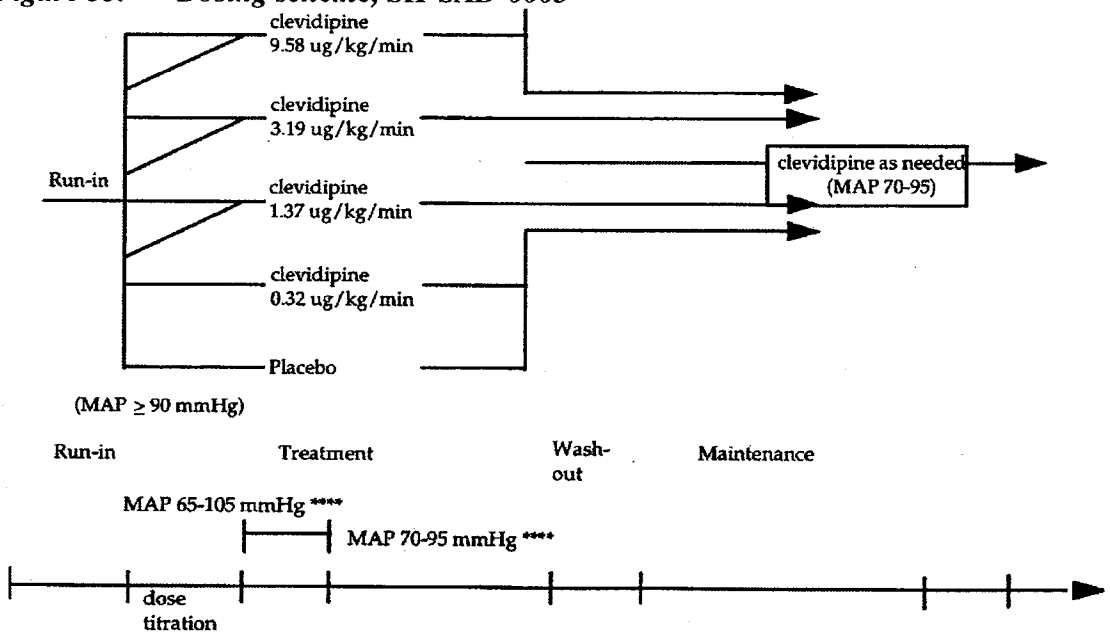
10.1.7.1 Summary

The purpose of this study was to determine the dose blood pressure response, PK and tolerability in post cardiac surgical patients (CABG, valve replacement or both). The primary endpoint was the response rate. A responder was defined as having at least a 10% reduction from baseline MAP during the first 22 minutes of treatment phase. The secondary endpoint was the mean change from baseline in MAP, SBP, DBP and HR 22 minutes after the start of the infusion.

Criteria for inclusion was a MAP ≥ 90 mmHg at two consecutive readings, separated by 5 minutes, at the end of the run-in period, ages 18-80 years, and EF ≥ 30%. There was no washout period for prior antihypertensives (merely had to be withdrawn for 5 minutes prior to randomization). Beta blockers were allowed the morning of surgery.

The study schematic is shown below. Study run-in lasted 20 minutes. Study drug was infused for 122 minutes (including titration over 12 minutes) Fixed dose infusion was defined as the first 10 minutes of constant infusion (during the 122 minutes). Study infusion was followed by a 20 minute washout. For safety reasons, MAP was to be between 65-105 mmHg during the dosing period. One dose change was allowed to either the next higher or lower dose arm during titration or fixed dose infusion for an excursion outside of this range. A dose change required HD measurements 10 minutes after the dose change. If MAP remained outside the safety parameters, the patient was discontinued from the study.

Figure 33. Dosing scheme, SH-SAD-0003



Placebo was administered at a rate corresponding to 1.37 ug/kg/min of clevidipine. There was a subsequent optional maintenance phase of up to 12 hours to maintain a MAP of 70-95 mmHg.

Because the initial lowest infusion rate of 0.32 ug/kg/min decreased MAP from baseline by ~20% and it was the anticipated no effect dose level, the study was amended 11/1996 to randomize an additional 30 patients into three dose groups (See Figure). The 0.05 ug/kg/min rate was chosen based on an Emax model performed on data from the first 30 patients enrolled in the trial and from post cardiac surgical patients in study SH-SAD-0005. The model estimated that 0.05 ug/kg/min would decrease MAP by less than 3-6%, and 0.18 ug/kg/min would decrease MAP by 6%.

Figure 34. Dosing scheme, extension phase, SH-SAD-0003

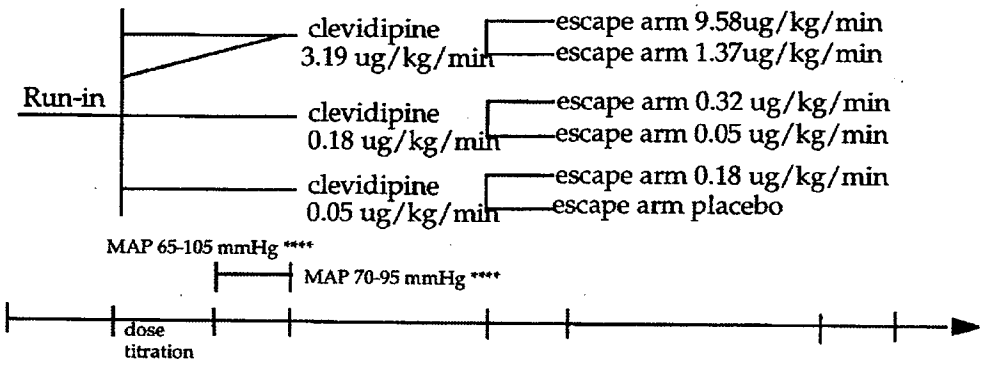
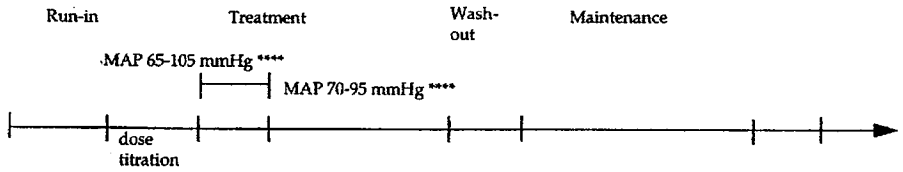


Figure 35. Study procedures, SH-SAD-0003

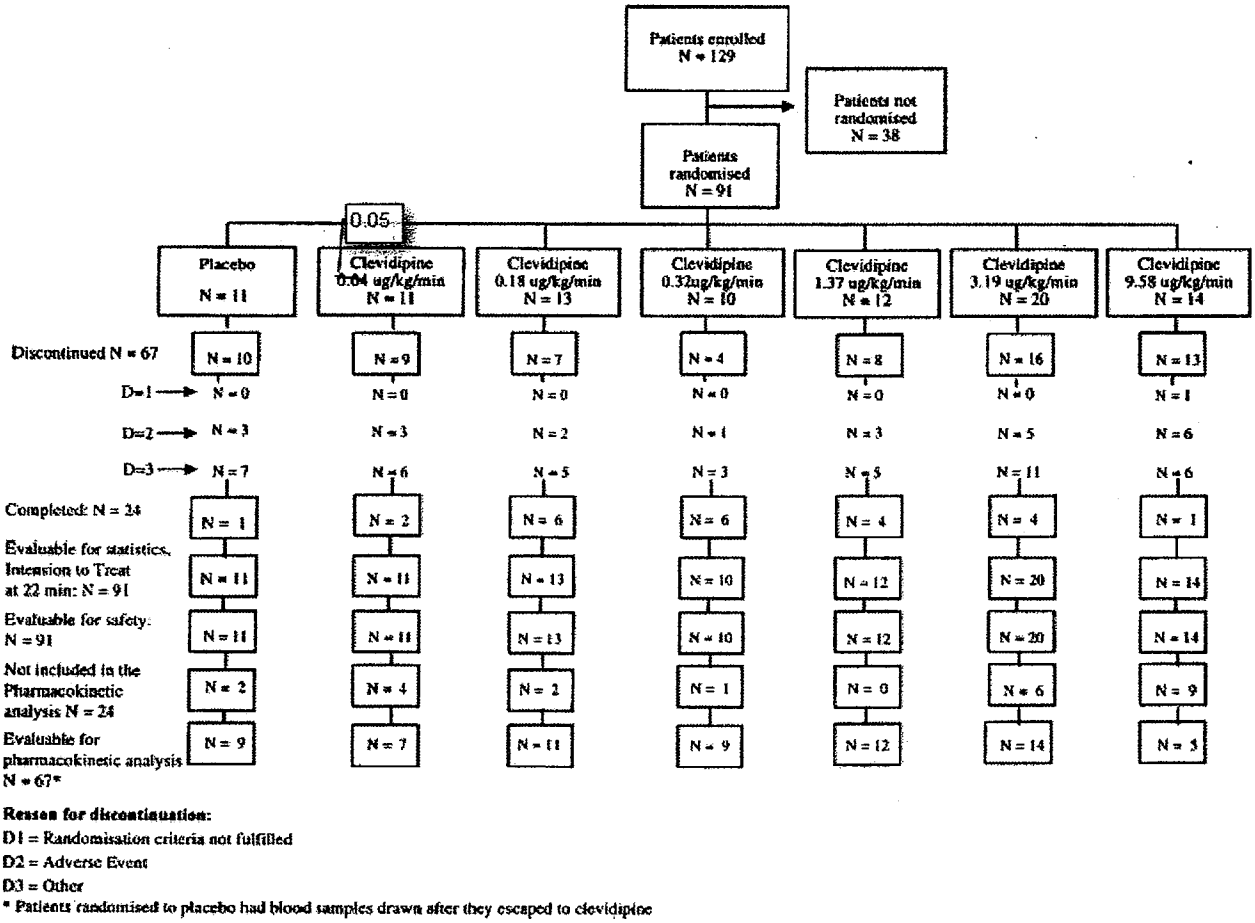


	-20 min	0 min	12 min	22 min	122 min	142 min	12 hrs	discharge from ICU	5-7 days
MAP	X	X*		X[1]	X*****		X	X	
SBP	X	X*		X[1]	X*****		X	X	
DBP	X	X*		X[1]	X*****		X	X	
HR	X	X*		X[1]	X*****		X	X	
Hemod.		X		X[1]	X	X	X		
Phys. exam.	X**							X	
Lab.	X**							X	X
ECG 12 lead	X**							X	X
ECG leads II and V5	X	X*		X[1]	X		X		
AE		X		X[1]	X		X	X	X
Med.history	X**								
Plasma conc.		X		X***[1]	X***	X***			

* Prior to infusion and at each dosage step.
** One day prior to the operation.
*** Blood samples taken at 10, 18, 33, 48, 68 and 88 min after start of fixed dose infusion (fixed dose infusion defined as the first 10 minutes of constant infusion) at 122 min after start of initial infusion and at 30 sec, 1, 1.5, 2, 3, 6, 12, 18 and 20 min after stop of infusion (i.e.during wash-out) and after re-start of infusion at 60 minutes' intervals during the maintenance phase. MAP, SBP, DBP and HR will be recorded in conjunction with blood sampling (except during wash-out phase).
1. Or 10 min after start of fixed dose.
**** Escape design - see 6.1
***** MAP, SBP, DBP and HR measured at each second minute during the wash-out period, and during each change of infusion during the maintenance phase.

A total of 91 patients were randomized to treatment and were included in the PD and safety analysis; 67 of these were included in the PK analysis. Patient flow chart is shown below.

Figure 36. Patient disposition, SH-SAD-0003



Taken from Sponsor's Figure 2, page 18 of 861

Safety endpoints for discontinuation included a HR ≥ 120 bpm, signs or symptoms of cardiac ischemia and a MAP outside of 65-105 mmHg. A MAP out of this range necessitated one dose change. If this change was insufficient to favorably affect the MAP, the patient was discontinued.

Baseline measurements were those taken prior to the infusion start. For efficacy assessments, if no dose change was required, the endpoint measurement was at 10 minutes after the start of the fixed dose infusion. If a dose change was required and the patient reached the randomized dose, the last measurement recorded while on the randomized dose during the first 22 minutes was used as the endpoint. If a dose change was required and the patient did not reach the randomized dose, the last measurement recorded during titration was used as the endpoint.

The sponsor modeled the PK and PK and percentage decrease in MAP.

The table below shows the treatment according to randomized dose versus actual dose, where the actual dose is either the randomized dose or the escape dose. N/A refers to those patients who had no MAP recorded at the 10 minute time point.

Table 88. Number of patients by randomized and actual dose, SH-SAD-0003

Randomised dose	Actual dose (µg/kg/min)								Total
	Placebo	0.05	0.18	0.32	1.37	3.19	9.58	N/A	
Placebo	2			9					11
0.05 µg/kg/min		6	5						11
0.18 µg/kg/min			11	2					13
0.32 µg/kg/min	1			6	3				10
1.37 µg/kg/min				4	7	1			12
3.19 µg/kg/min					12	6		2	20
9.58 µg/kg/min					1	8	1	4	14
Total	3	6	16	21	23	15	1	6	91

Taken from Sponsor's Table 5, pg 140 of 861

The lowest dose that had a statistically significant response rate compared to placebo was 0.32 ug/kg/min (see table).

Table 89. Response rates (defined as 10% reduction from baseline in MAP), SH-SAD-0003

Randomised dose	Non-responders n (%)	Responders n (%)	p-value, comparison with placebo
Placebo	11 (100)	0 (0)	
0.05 µg/kg/min	10 (91)	1 (9)	0.500
0.18 µg/kg/min	9 (69)	4 (31)	0.067
0.32 µg/kg/min	4 (40)	6 (60)	0.004
1.37 µg/kg/min	3 (25)	9 (75)	<0.001
3.19 µg/kg/min	1 (5)	19 (95)	<0.001
9.58 µg/kg/min	0 (0)	14 (100)	<0.001

There was a statistically significant difference in MAP, SBP, and DBP between placebo and all doses of clevidipine, except for 0.05 ug/kg/min (see tables for SBP and DBP). Thus, in this study, 0.18 ug/kg/min was the lowest effective BP lowering dose. There was no difference in HR between placebo and the six clevidipine doses (see table).

Table 90. $\Delta SBP_{10\ min}$, estimated mean difference by randomized dose, SH-SAD-0003

Comparison	Estimated difference	95% Confidence intervals lower	upper	p-value
0.05 vs placebo	-4.0	-17.7	9.6	0.558
0.18 vs placebo	-15.4	-28.4	-2.5	0.020
0.32 vs placebo	-26.7	-40.7	-12.6	<0.001
1.37 vs placebo	-39.2	-52.1	-26.2	<0.001
3.19 vs placebo	-53.3	-65.2	-41.4	<0.001
9.58 vs placebo	-68.9	-82.4	-55.4	<0.001

Taken from Sponsor's Table 11, pg 142 of 861

Table 91. $\Delta SBP_{10\ min}$, randomized dose, descriptive stats, SH-SAD-0003

Statistic	Randomised dose (µg/kg/min)						
	Placebo	0.05	0.18	0.32	1.37	3.19	9.58
N	11	11	13	10	12	20	14
Mean	8	3	-5	-24	-32	-47	-68
SD	13	10	14	20	21	18	14
Min	-13	-18	-21	-61	-88	-103	-94
Median	8	4	-8	-18	-31	-42	-70
Max	27	18	34	4	-1	-25	-40

Taken from Sponsor's Table 14, pg 143 of 861

Table 92. $\Delta SBP_{10\ min}$, actual dose, descriptive stats, SH-SAD-0003

Statistic	Actual dose (µg/kg/min)							
	Placebo	0.05	0.18	0.32	1.37	3.19	9.58	N/A*
N	2	6	15	21	20	10	1	1
Mean	-3	-1	-9	-23	-39	-47	-57	-42
SD	4	10	11	21	18	27		
Min	-5	-18	-30	-69	-100	-87	-57	-42
Median	-3	1	-9	-22	-38	-38	-57	-42
Max	0	12	10	16	-16	-7	-57	-42

Taken from Sponsor's Table 54, pg 171 of 861

Table 93. $\Delta DBP_{10\ min}$, estimated mean difference by randomized dose, SH-SAD-0003

Comparison	Estimated difference	95% Confidence intervals lower	upper	p-value
0.05 vs placebo	-1.5	-9.8	6.9	0.724
0.18 vs placebo	-8.7	-16.7	-0.7	0.033
0.32 vs placebo	-12.3	-20.6	-4.0	0.004
1.37 vs placebo	-21.0	-28.8	-13.1	<0.001
3.19 vs placebo	-26.9	-34.0	-19.8	<0.001
9.58 vs placebo	-38.2	-46.0	-30.5	<0.001

Taken from Sponsor's Table 15, pg 143 of 861

Table 94. $\Delta DBP_{10\ min}$, randomized dose, descriptive stats, SH-SAD-0003

Statistic	Randomised dose (µg/kg/min)						
	Placebo	0.05	0.18	0.32	1.37	3.19	9.58
N	11	11	13	10	12	20	14
Mean	5	3	-4	-9	-16	-21	-35
SD	6	6	7	14	13	11	9
Min	-5	-7	-15	-31	-47	-39	-50
Median	5	3	-4	-8	-16	-22	-34
Max	17	9	15	15	0	8	-24

Taken from Sponsor's Table 18, pg 144 of 861

Table 95. $\Delta DBP_{10\ min}$, actual dose, descriptive stats, SH-SAD-0003

Statistic	Actual dose (µg/kg/min)							
	Placebo	0.05	0.18	0.32	1.37	3.19	9.58	N/A*
N	2	6	15	21	20	10	1	1
Mean	4	-1	-6	-11	-19	-21	-26	-27
SD	8	5	6	12	8	15		
Min	-2	-7	-19	-36	-32	-47	-26	-27
Median	4	-2	-5	-11	-20	-18	-26	-27
Max	9	8	4	15	0	-2	-26	-27

Taken from Sponsor's Table 57, pg 172 of 861

Table 96. $\Delta HR_{10\ min}$, estimated mean difference by randomized dose, SH-SAD-0003

Comparison	Estimated difference	95% Confidence intervals lower	upper	p-value
0.05 vs placebo	0.2	-3.8	4.3	0.918
0.18 vs placebo	-0.8	-4.7	3.1	0.678
0.32 vs placebo	-0.6	-4.7	3.4	0.760
1.37 vs placebo	-0.6	-4.4	3.3	0.772
3.19 vs placebo	-3.1	-6.7	0.4	0.079
9.58 vs placebo	-1.7	-5.4	2.0	0.369

Taken from Sponsor's Table 19, pg 144 of 861

Table 97. $\Delta HR_{10\ min}$, randomized dose, descriptive stats, SH-SAD-0003

Statistic	Randomised dose (µg/kg/min)						
	Placebo	0.05	0.18	0.32	1.37	3.19	9.58
N	11	11	13	10	12	20	14
Mean	1	2	1	0	1	-2	-0
SD	4	4	3	5	3	6	6
Min	-6	-3	-3	-8	-4	-18	-10
Median	0	0	0	0	0	0	-1
Max	8	9	10	11	10	10	11

Taken from Sponsor's Table 22, pg 145 of 861

Table 98. $\Delta HR_{10\ min}$, actual dose, descriptive stats, SH-SAD-0003

Statistic	Actual dose (µg/kg/min)							
	Placebo	0.05	0.18	0.32	1.37	3.19	9.58	N/A*
N	2	6	15	21	20	10	1	1
Mean	0	1	1	1	-1	-2	-4	0
SD	3	2	3	5	8	9		
Min	-2	-2	-3	-8	-27	-18	-4	0
Median	0	0	0	0	0	1	-4	0
Max	2	4	7	14	10	10	-4	0

Taken from Sponsor's Table 60, pg 173 of 861

Clevidipine had no effect on PCWP, PAP, CVP, or CI at 10 minutes compared to baseline. There was not a dose dependent effect on PVR, but there was a dose dependent decrease in SVR (see tables).

Table 99. $\Delta PVR_{10\ min}$, (dynes_sec/cm5) randomized dose, descriptive stats, SH-SAD-0003

Statistic	Randomised dose (µg/kg/min)						
	Placebo	0.05	0.18	0.32	1.37	3.19	9.58
N	9	9	12	7	12	15	7
Mean	-23	20	-6	8	18	-14	22
SD	54	38	51	44	58	41	55
Min	-100	-44	-94	-28	-57	-74	-53
Median	-41	20	1	-7	3	-9	26
Max	63	80	63	102	147	70	88

Taken from Sponsor's Table 34, pg 148 of 861

Table 100. $\Delta SVR_{10\ min}$, (dynes_sec/cm5) randomized dose, descriptive stats, SH-SAD-0003

Statistic	Randomised dose (µg/kg/min)						
	Placebo	0.05	0.18	0.32	1.37	3.19	9.58
N	11	10	12	8	12	17	8
Mean	-275	-69	-141	-353	-382	-454	-659
SD	332	194	143	256	193	250	232
Min	-991	-439	-471	-950	-821	-1133	-1030
Median	-294	-61	-130	-273	-355	-504	-594
Max	170	296	139	-172	-84	-61	-359

Taken from Sponsor's Table 37, pg 1499 of 861

Similar to previous PK findings, clevidipine CL was high (0.05 L/kg/min) with a small Vd. The T ½ α was 0.4 minute and the T ½ β was 15 minutes.

There were 1256 AEs reported in 91 patients. Multiple occurrences of the same AE were counted once for each patient. See tables for most frequent AEs.

Table 101. Most frequent AEs by dose, SH-SAD-0003

	All study periods							
	Placebo	Randomised dose (µg/kg/min)						All treatments
No. of patients	n=11	0.05 n=11	0.18 n=13	0.32 n=10	1.37 n=12	3.19 n=20	9.58 n=14	n=91
Atelectasis	7	10	10	8	6	15	11	67 (73.6)
Pleural effusion	8	6	5	8	9	15	12	63 (69.2)
Rales	8	9	8	4	9	14	8	60 (65.9)
Constipation	3	6	11	4	4	10	6	44 (48.4)
Oedema generalized	2	8	6	5	5	5	7	38 (41.8)
Anaemia	5	6	4	3	5	6	7	36 (39.6)
Heart sound abnormal	6	2	3	6	6	7	6	36 (39.6)
Hypertension	4	8	5	3	2	8	6	36 (39.6)
Hypotension	5	4	5	3	3	5	8	33 (36.3)
Nausea	3	4	5	2	3	8	7	32 (35.2)
Fever	5	5	3	3	2	9	4	31 (34.1)
Respiratory disorder	3	6	8	1	4	6	3	31 (34.1)
Insomnia	3	2	4	6	3	6	5	29 (31.9)
Oliguria	4	4	7	2	1	7	2	27 (29.7)
Fibrillation atrial	3	2	4	5	1	4	5	24 (26.4)
Hypovolaemia	2	4	3	3	2	4	4	22 (24.2)
Oedema	3	2	3	1	2	6	4	21 (23.1)
Pulmonary infiltration	2	3	2	4	4	3	2	20 (22.0)
Rhonchi	3	4	3	5	2	2	1	20 (22.0)
Tachycardia	2	3	4	2	3	4	2	20 (22.0)

Taken from Sponsor's Table 46, pg 159 of 861

Table 102. All AEs by dose, SH-SAD-0003

		Active treatment period during open treatment						
	Placebo	Clevidipine (µg/kg/min)						All treatments
No. of patients	n=11	0.05 n=11	0.18 n=13	0.32 n=10	1.37 n=12	3.19 n=20	9.58 n=14	n=91
Atelectasis	2	7	6	5	4	7	4	35 (38.5)
Hypotension	2	0	4	1	1	3	6	17 (18.7)
Anaemia	3	1	0	1	2	3	5	15 (16.5)
Oedema generalized	2	2	3	2	0	3	3	15 (16.5)
Hypertension	1	6	1	1	1	1	1	12 (13.2)
Hyperglycaemia	1	2	2	0	1	3	0	9 (9.9)
Hypovolaemia	0	2	1	3	1	1	0	8 (8.8)
Oedema	2	0	2	0	1	2	1	8 (8.8)
Heart sound abnormal	0	0	1	1	1	1	2	6 (6.6)
Pleural effusion	1	0	0	1	1	1	2	6 (6.6)
Pulmonary infiltration	1	1	1	1	2	0	0	6 (6.6)
Hypokalaemia	0	0	0	1	0	4	0	5 (5.5)
Rales	0	2	2	0	1	0	0	5 (5.5)
Rigors (chills)	0	1	2	2	0	0	0	5 (5.5)
St changes	1	1	0	0	1	2	0	5 (5.5)
Bronchospasm	1	1	1	1	0	0	0	4 (4.4)
Diabetes mellitus	0	0	0	2	0	1	1	4 (4.4)
Hypocalcaemia	0	1	1	1	0	1	0	4 (4.4)
Cardiac disorder	0	1	0	0	2	0	0	3 (3.3)
Gastrointestinal symptoms nos	1	0	1	0	0	1	0	3 (3.3)
Hypomagnesaemia	0	2	0	0	0	1	0	3 (3.3)
Hypothermia	0	0	0	1	0	1	1	3 (3.3)
Pulmonary oedema	0	1	0	1	0	1	0	3 (3.3)
Respiratory disorder	0	1	2	0	0	0	0	3 (3.3)
St-t changes	0	0	2	1	0	0	0	3 (3.3)

Taken from Sponsor's Table 80b, pg 183 of 861

Fifteen patients reported 34 SAEs during (run-in, active treatment and follow-up) the study. Five patients report 8 SAEs after the study (5-6 days after surgery or hospital d/c, whichever came first) (001-0138, 003-0161, 003-0301, 001-0122, 003-0313).

During the open treatment, 21 patients discontinued due to AEs. Of these, the most common AEs leading to discontinuation were hypotension (n=10, with 4 on the highest dose) and hypertension (n=9,with 6 on the lowest dose). Other reasons included afib and bradycardia. The highest dose of 9.5 ug/kg/min was associated with hypotension resulting in discontinuation in 28 % of patients.

10.1.8 SH-SAD-0006: OL, dose titration to MAP, PK in pre-bypass and bypass HTN in elective CABG patients

10.1.8.1 Summary

This was an open label study to determine the dose rate of clevidipine required to lower MAP during the pre-bypass and bypass (hypothermic) period of CABG surgery. PK during pre-bypass and bypass was a secondary objective.

Clevidipine dose was titrated to reduce MAP from 90-95 mmHg to 70-75 mmHg during pre-bypass and mean perfusion pressure (MPP) from 75-80 mmHg to 55-60 mmHg during bypass, aiming at a 20% decrease of MAP and MPP. The protocol stated starting dose was 0.7 ug/kg/min, then titrated to goal MAP/MPP, then kept constant in order to achieve steady state for 10 minutes. The infusion was stopped when 15 minutes remained of the pre-bypass or hypothermic period. SNP was an alternative if the BP was too high (MAP $\geq$ 105 mmHg). Clevidipine was discontinued if MAP $\leq$ 65 mmHg (IV phenylephrine allowed). Beta-blockers were allowed the morning of surgery. Other antihypertensives were stopped prior to randomization. However, according to the sponsor's table 1.4.1, some patients were taking concomitant drugs that affected BP (nitrates, thiazides, other vasodilator (nicorandil)).

BP and HR were continuously monitored for 15 hours from the start of anesthesia. MAP, BP, and HR were documented before, during and after the infusion stop (for 20 minutes). Temperature, Hb and Hct were also followed.

Eighteen patients were randomized; 17 were evaluable prebypass and 8 during bypass. One (ID 9) discontinued due to intraoperative hypertension (but also had intraoperative bleeding). His infusion was titrated for 3 minutes during pre-bypass and prematurely stopped at a 2.7 ug/kg/min because his MAP was 109 mmHg and he was bleeding. He was then treated with SNP and an hour later was not hypertensive and his bleeding had stopped.

The mean dose of clevidipine required to control blood pressure during pre-bypass was 2.17 ± 0.85 ug/kg/min (1.1 – 3.3 ug/kg/min, range) and during hypothermia 1.26 ± 0.40 ug/kg/min (0.9 – 2.5 ug/kg/min). The starting dose ranged from 1.9 to 6.1 ug/kg/min, and the maximum dose was 16.8 ug/kg/min prebypass. During bypass the starting dose ranged from 2.2 to 5.1 ug/kg/min, and the maximum dose was 8.2 ug/kg/min.

Half-life prebypass was 4 h (terminal) and 0.7 hours (α). Half-life during bypass was 8.5 h (terminal) and 1.1 h (α). Arterial and venous CL was 0.06 L/kg/min prebypass (normothermic), during bypass it was 0.037 L/kg/min (hypothermic). Clevidipine T1/2 increased during hypothermia, mainly due to a reduction in clearance. Venous concentrations were lower than arterial.

10.1.9 SH-SAD-0013: R, DB, Parallel CLV vs. SNP dose titrate to MAP in postcardiac surgery patients

10.1.9.1 Summary

The primary objective of this study was to compare the efficacy of clevidipine and SNP to reduce and maintain a stable MAP and HR with few dose adjustments during a 3 hour infusion period in intravenously sedated patients status post elective CABG surgery. Primary variable was the number of dose adjustments required to maintain the MAP window, but there were no specific instructions for dosing.

Criteria for entry included a post-op SBP ≥ 145 mmHg or a MAP ≥ 90 mmHg. Patients were randomized to clevidipine/placebo or SNP/placebo for 3 hours. Infusions of clevidipine and SNP were given using a double dummy technique. Drug was titrated to reduce MAP to 70-80 mmHg. This was the first study to administer clevidipine blindly. Initial and maximum clevidipine dose was 0.3 ug/kg/min and 6 ug/kg/min. Initial and maximum SNP dose was 0.5 ug/kg/min and 10 ug/kg/min. A lower dose for both drugs was used if the patient weighed less than 83 kg. Patients on beta-blockers received metoprolol 50 mg the morning of surgery.

Figure 37. Study procedures, post surgery, SH-SAD-0013

Activity:	-5	0	10	30	60	90	120	150	180	240	360	720	leaving ICU
Infusion of clevidipine		start[1]							stop				
Ambulatory ECG monitoring	continuous recording[2]	------	--	--	--	--	----	----	-----	----	----	----	stop
		------	--	--	--	--	----	----	-----	----	----	----	
		------	--	--	--	--	----	----	-----	----	----	----	
			--	--	--	--	---	---		---	---	---	
			-	-	-	-							
MAP, SBP, DBP, and HR	start of continuous recording	------	--	--	--	--	----	----	stop				
		------	--	--	--	--	----	----					
		------	--	--	--	--	----	----					
			--	--	--	--	---	---					
			-	-	-	-							
CO, CVP, PAP, PCWP	X		X	X	X	X	X	X	X				
Fluid balance	X				X		X		X	X[3]			
AE									X[4]				
CKMB Troponin I	X										X[5]		

1 Start of continuous recording of the pump speed
2 A baseline monitoring starting the day before the operation and ending before surgery, starting again after entering the ICU and ending upon leaving the ICU, but not less than 12 hours postoperatively
3 Measure the fluid balance every hour until the patient was extubated
4 AE was recorded upon leaving the ICU, 24 hours after the end of infusion and at follow-up
5 CKMB and Troponin I were also drawn at pre-entry, 18, 24, 42 hours after the start of infusion and at follow-up

Escape to open treatment was allowed for MAP > 105 mmHg or HR ≥ 120 bpm (can add beta blockers). The infusion was discontinued if MAP ≤ 65 mmHg and AV pacing could be started if the HR ≤ 50 bpm. The study was terminated if the HR escapes were reached.

Thirty-one patients were randomized; 1 (CLV) excluded because he was paced (ID 32). This left 15 each on drug. Additionally, three pilot patients were given open label clevidipine.

Clevidipine was as effective as SNP in controlling MAP (no difference in number of dose adjustments). The average clevidipine and SNP dose was 0.76 and 0.58 ug/kg/min. The AUC outside the predefined HR window was significantly higher in the SNP group than in the clevidipine group.

Serious AEs and discontinuations due to AE were few and equally distributed between the two treatment groups. Drug was stopped prematurely in 13 patients; MAP < 65 mmHg (n=10), lack of study drug (n=1) and an AE (n=2).

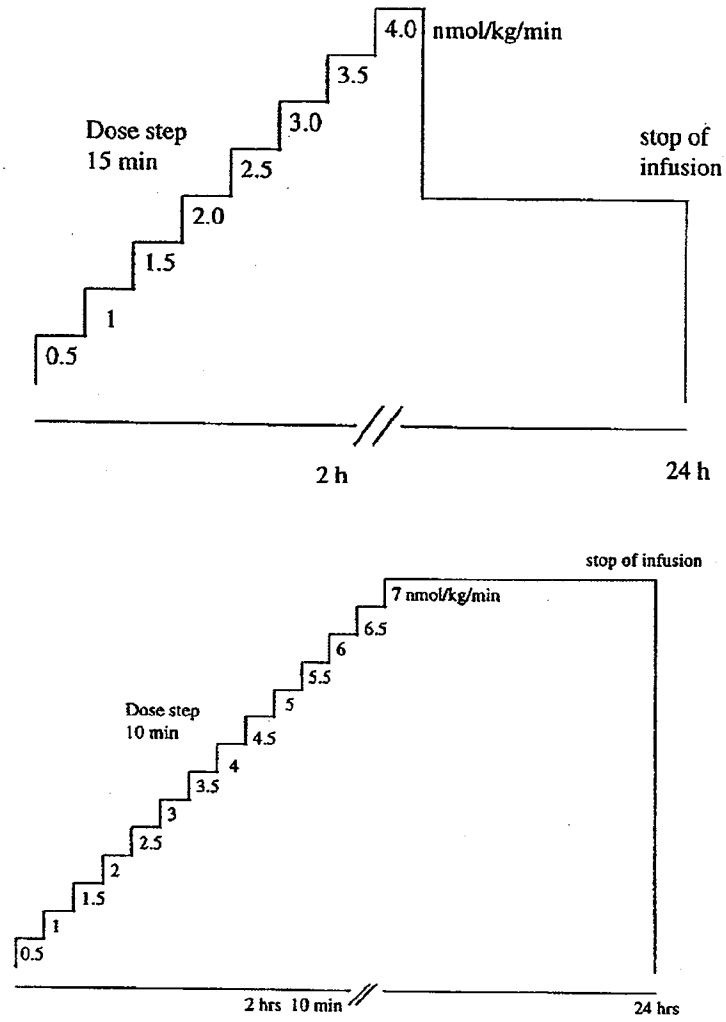
Reviewer comment: SNP was prepared by concentrating the solution and then diluting it with 98 mL of 5% glucose. This is slightly different than the instructions for reconstitution in the US label. If it is also different than the UK label, then this could impact the investigator's comfort with using SNP.

10.1.10 SH-SAD-0018: SD, PK study in healthy males

10.1.10.1 Summary

This was an OL, SD study in healthy males designed to study the PK of a 24 hour and 20 minute infusion. Four subjects each were to receive one of three infusions. The 24 hour infusion was dosed as shown below with a final dose rate of 0.91 ug/kg/min (2 nmol/kg/min, n=6) (each step lasted 15 minutes) and 3.2 ug/kg/min (7 nmol/kg/min, n=4) (each step lasted 10 minutes). The last infusion was 3.2 ug/kg/min for 20 minutes (n=4).

Figure 38. Dosing scheme, SH-SAD-0008



BP and HR were measured continuously in the finger and recorded before, the first 2.5 hours and from 23.5 hours after the start of the infusion to 1 hour after the end of the infusion. Manual BP were performed every hour after the final infusion rate had been reached, and at regular intervals until 8 hours after the end of the infusion. Twelve lead ECGs were recorded during the infusions, during each step, and at various times after the end of the infusion for up to 8 hours. Venous and arterial blood samples for clevidipine and metabolite were drawn several times at various dose steps.

Three subjects received Panodil for headache during the infusion. One subject discontinued due to nausea and vomiting (also experienced dizziness). He received the lowest infusion rate. The sponsor's BP illustrations all show MAP. The mean clevidipine concentration for the low infusion rate over time is shown in the figure below. Arterial concentrations were nearly twice as high as the venous concentrations during the infusion indicating rapid metabolism of clevidipine in the blood and tissues.

Figure 39. Mean clevidipine concentration in arterial and venous blood (0.91 ug/kg/min)

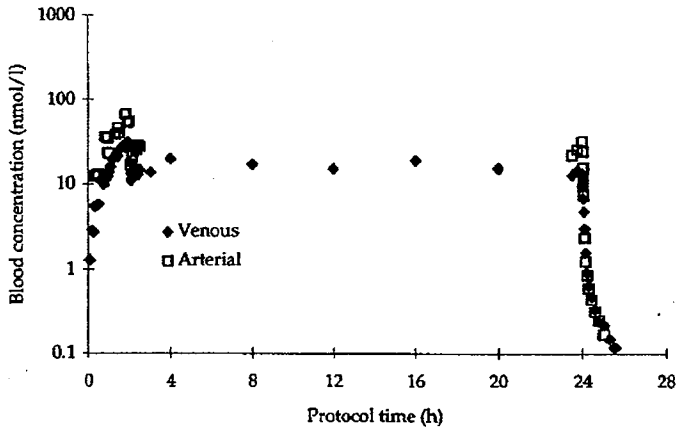
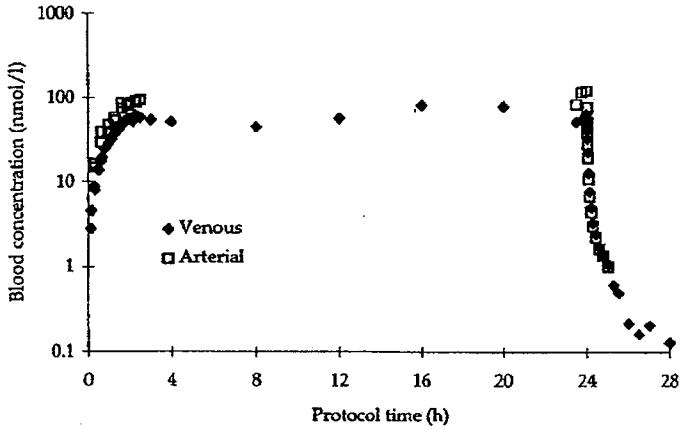


Figure 40. Mean clevidipine concentration in arterial and venous blood (3.2 ug/kg/min x 24 h)



PK parameters did not seem to vary with the dose or infusion time. For venous blood, CL was 0.1 L/kg/min, Vss 0.6 – 0.8 L/kg, and the T ½α 2 minutes. Terminal half-life varied by two fold between the three infusions, so the reviewer decided that it is most likely unreliable. Results of PK studies in more subjects are more reliable and will be reported.

10.1.11 SH-SAD-0017: R, DB, PC, MC, parallel clevidipine BP control with optional NTG in cardiac surgery patients

10.1.11.1 Summary

The primary objective of this study was to compare the reduction in MAP between clevidipine and placebo at 10 minutes after the start of the infusion in elective cardiothoracic surgery. The study start was during or after bypass. The goal MAP varied by the time of bypass: prebypass 70-80 mmHg, bypass 60-70 mmHg, post bypass and ICU 70-80 mmHg.

Clevidipine infusion ranged from 1.92 – 76.8 mL/h (16-640 ug/min) with a starting dose rate of 4.8 mL/h (40 ug/min corresponding to 0.5 ug/kg/min). Drug was adjusted within 2-3 minutes to achieve BP reduction and control. Dose rate between 42 and 76.8 mL/h (350 – 640 ug/min) were not administered for more than 120 minutes. The formulation was 0.5 mg/mL. A 20% lipid emulsion was used as a placebo solution and administered at the same dose rate as clevidipine. The maximum dose of lipid was 3 g/kg/24 h, with a maximal rate of 1.6 mL/minute. Patients were treated up to 12 hours.

Glyceryl trinitrate (NTG) was allowed (escape) if the MAP could not be kept at goal (see table). If NTG and drug failed, another antihypertensive could be added. The initial NTG dose was 0.2 – 0.5 ug/kg/min.

Table 103. MAP limits during study SH-SAD-0017

	Pre-bypass mmHg	Bypass mmHg	Post-bypass mmHg	ICU mmHg
Randomised MAP	≥ 90	≥ 80	≥ 90	≥ 90
Target MAP window	70-80	60-70	70-80	70-80
Escape MAP upper	105	100	105	105
Escape MAP lower	65	55	65	65

Taken from Sponsor's Table 9.1:1, page 24 of 706

Patients were randomized by blocks of two and by diagnosis of essential hypertension. Baseline hemodynamics was defined as the measurement at 2 and 1 minute prior and immediately prior to the start of the infusion. Survival at Day 30 post surgery was checked by telephone or follow-up visit on Day 30.

Clevidipine change from baseline in MAP at 10 minutes was significantly different (lower) than placebo. The mean difference was -17.7 mm Hg (95% CI: -23.1 to -12.3), $p<0.001$. BP even reduced in the placebo group. The number of patients needing NTG in the first 10 minutes was 1 in the placebo group and none in the NTG. See Sponsor's Table 16.2.6:2a for more information.

Twelve patients discontinued drug early; the most serious was for myocardial ischemia.

10.1.12 TMC-CLV-02-01: R, DB, parallel clevidipine vs. NTG for BP and preservation of renal function in CABG

10.1.12.1 Summary

The objective of this study was to compare BP control and preservation of renal function in patients undergoing CABG surgery and administered clevidipine or nitroglycerin intra- and postoperatively. The sponsor's primary objective was to show that clevidipine is not inferior to NTG in controlling BP. The analysis was of the AUC of MAP outside of the predefined target ranges prebypass. The secondary objective was to show that clevidipine is superior to NTG in preserving renal function. Glomerular filtration was estimated by measuring serum creatinine preoperatively, on entry into the ICU, at 12 and 24 hours postoperatively, and at daily intervals until discharge. Tubular function was determined by quantification of urinary N-acetyl-glucosaminidase.

This study consisted of an initial OL phase to determine dosing and dilution methods followed by a randomized, double-blind, parallel, multicenter phase in the US and New Zealand. The per protocol population consisted of all randomized patients who underwent CABG surgery with cardiopulmonary bypass (on-pump) and received at least one dose of study drug, classified by actual treatment. The safety population consisted of all those who received at least one dose of study drug.

Initial dose of clevidipine was 0.2 ug/kg/min and NTG was 0.4 ug/kg/min. Both drugs were infused by double dummy design after induction of anesthesia through 12 hours postoperatively with dose adjustment to maintain MAP mmHg. Clevidipine rates up to 4.4 ug/kg/min were allowed, rates between 4.4 – 8 ug/kg/min were allowed for no longer than 120 minutes. Instructions for NTG were that the maximum dose rate be consistent with normal clinical practice.

One-hundred patients were treated (49 clevidipine, 51 NTG, safety population); 93 received study drug (45 clevidipine, 48 NTG) and underwent on-pump surgery (per protocol).

Clevidipine was non-inferior to NTG in BP control. The ratio of geometric means of MAP AUC outside of the predefined range prebypass was 0.97; 95% CI 0.74 – 1.27.

There was no significant difference in renal function postoperatively in clevidipine-treated patients compared with NTG-treated patients. There were probably too few renal injuries to make any definitive statements about preservation of renal function.

Mean HR during study drug administration was higher in NTG-treated patients compared with clevidipine-treated patients.

One patient died in each group. SAEs were experienced by 12 (24.5%) on clevidipine and 9 (17.6%) on NTG. Five patients in each group discontinued due to an AE. Hypotension was the most frequent TEAE in both groups, 26.5% of clevidipine-treated and 15.7% of NTG-treated

patients. No patients in either group had hypertriglyceridemia (defined as TG before normalization of greater than 525 mg/dL).

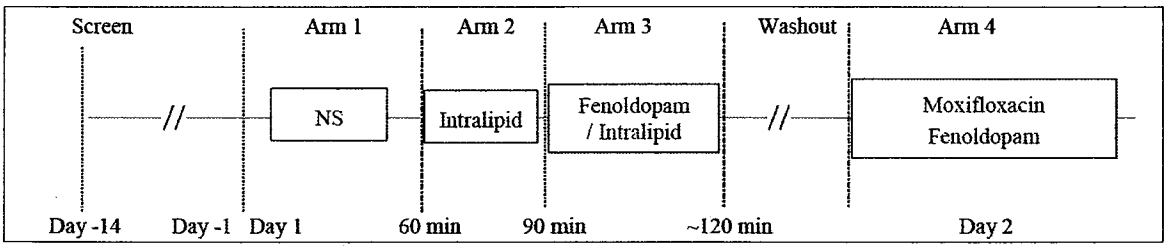
10.1.13 TMC-CLV-05-01: SB, R, moxifloxacin control to assess QT prolongation

10.1.13.1 Summary

This study was extensively reviewed by the QT IRT team. Thus it will only be briefly summarized here.

This was a two phase study. The first phase was OL in eight subjects to assess the effect of Intralipid (20% IV fat emulsion) on ECG parameters; the practicality of fenoldopam infusion at two rates to attain predetermined HR; and the ability to detect the effect of oral moxifloxacin on uncorrected QT during HR controlled infusion with fenoldopam. Each subject received treatment sequentially as shown in the figure below.

Figure 41. Phase I schematic of QT study

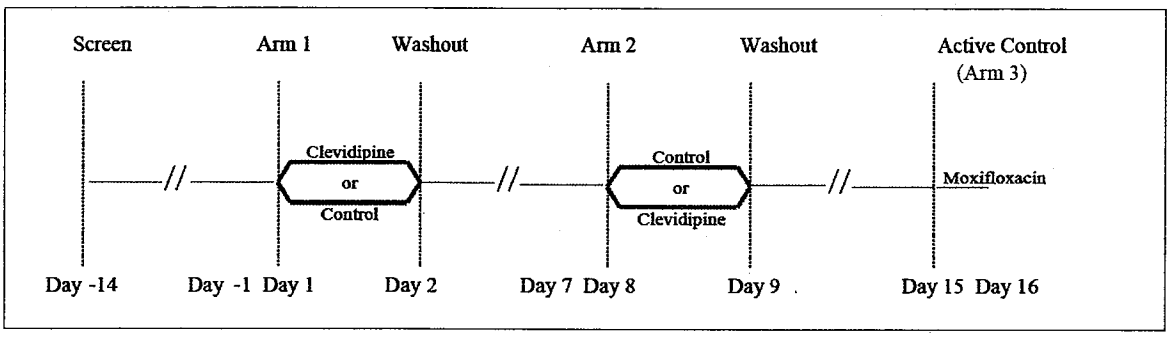


NS=normal saline infused over an hour

The main study was a randomized, single-blind, Intralipid- and HR-controlled (fenoldopam), 2 treatment crossover trial in 46 healthy volunteers, followed by an OL positive control (moxifloxacin 400 mg tablet) with HR control (fenoldopam) period. The purpose was to determine the ECG effects and PK of clevidipine.

The randomized part (clevidipine, intralipid, and fenoldopam) was divided into therapeutic, up-titration, and supratherapeutic periods. Subjects were randomized to one of two treatment sequences: 1) clevidipine IV infusion with accompanying plain NS infusion simulating fenoldopam infusions during the up-titration phase; and 2) Intralipid equal to the volume for that subject's clevidipine dose levels along with fenoldopam IV infusion titrated during the up-titration phase. Fenoldopam was infused (0.1, 0.3, or 0.5 ug/kg/min) to achieve HRs in the range expected during up-titration and supratherapeutic infusion of clevidipine. See the figure and table that follows for clarification.

Figure 42. Schematic of QT study



Clevidipine was administered over 3 consecutive infusion periods (total infusion time 23 hours 20 minutes) as follows:

- Therapeutic infusion period (22 hours 15 minutes) starting at 0.4 ug/kg/min increased by 1.1 ug/kg every 1.5 to 3 minutes, until reaching 3.2 ug/kg/min, then continuous infusion until 22 hours 15 minutes.
- Up-titration period (45 minutes) starting at 22 hours 15 minutes, rate was increased by 1.1 ug/kg every 5 minutes, until reaching 12 ug/kg/min or an intolerable dose.
- Supratherapeutic infusion period (20 minutes) – the highest tolerated dose or 12 ug/kg/min.

Table 104. Schedule of doses for main QT study

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Time Period	Time (hour:min)	Dose (µg/kg clevidipine or equivalent volume Intralipid®)
Therapeutic Infusion Period****	0:00	3.2
Up-Titration*** Infusion Period		
NS (Clevidipine arm) **or** Fenoldopam (Control arm) Level 1	22:15	4.3
		5.4
		6.5
Level 2*	22:30	7.6
		8.7
		9.8
Level 3*	22:45	10.9
		12.0**
Supra-therapeutic Infusion Period	23:00	12.0**
Postinfusion Period	23:20	0.0

* Maintained Level 1 if HR reached 100 bpm prior to 15 minutes or maintained Level 2 if HR reached 100 bpm prior to 30 minutes. Substituted NS if HR reached 125 bpm
** Or maximum tolerated dose.
*** NS was administered starting at 20 h 45 min (4 mL/min) until 22 h 15 min
**** Starting at 0.4 µg/kg/min, titrated dose to 3.2 µg/kg/min in increments of 1.1 µg/kg every 1.5 to 3 minutes

Table 105. Study flow chart of main QT Study

Study Assessment	Screening Period	Pre-Treatment (Night before)	Baseline (Saline infusion, -1.5 to 0 hours)				Therapeutic Infusion (0 to 22 h 15 min)									Up-Titration Infusion	Supra-therapeutic Infusion[3] (23 to 23.3 hours)					Post-Infusion[3] (23.3 to 36 hours)				
	-14 Days to -3 Days	Day 0 and Day 7	-1.5 h	-1.0 h	-30 min	-15 min	2 h	4 h.	8 h	12 h	22 h	20 h	21 h	21.5 h	22 h	(22 h 15 min to 23 hours)	23 h	23h 5 min	23h 10 min	23h 15 min	23h 20 min	23.5 h	24 h	27 h	28 h	36 h
Informed consent	X																									
Medical history	X																									
Chemistry and hematology[1]	X																									
Urine pregnancy[2]	X	X																								
Blood alcohol and urine drug screen	X	X																								
Normal Saline Infusion (4 mL/min)[7]													X	X	X											
12-lead ECG	X	X			X			X							X											X
Vital Signs	X	X			X	X	<----------									X[3]										>
Physical exam	X																									
Height and weight	X	X																								
Interim history		X																								
Holter[6]			<----------			X	---------->					<----------					X				>					
Extracted 12-lead ECG				X	X		X		X				X	X	X	X[5]			X	X		X	X	X		
Concomitant medications	X	X																								
Pharmacokinetic samples[4]						X	X		X				X	X	X		X			X			X	X		
AE and SAE reporting		<	----------									X									>					

1 As described in Section 9.7.3
2 Women of childbearing potential only
3 See Table 14 for the exact times for Therapeutic Infusion, Supra-therapeutic Infusion, and Post-infusion Periods BP and HR times.
4 The sampling timepoints were: -10 min, 2 h 20 min, 8 h 20 min, 20 h 50 min, 21 h 20 min, 21 h 50 min, 23 h 5 min, 23 h 18 min, 24 h 20 min, and 27 h 20 min. Sample should have been drawn to accommodate extraction of ECGs from Holter.
5 See Table 18 below for times of extracted ECGs.
6 Holter electrodes were to be applied and recording no later than 90 minutes prior to infusion start.
7 NS was administered at 4 mL/min starting 20 h 45 min until 22h 15 min when fenoldopam infusion was initiated.

Table 106. Study flow chart of main QT Study- Moxifloxacin arm

	Pre-treatment	Baseline			Moxifloxacin treatment								
					[illegible]								
Study Assessment[1]	Day -14	[illegible] h	-30 min	-15 min	0	1 h 15 min	1 h 30 min	1 h 45 min	2 h	3 h	4 h	6 h	8 h
Moxifloxacin drug administration					X								
NS (4 mL/min)[5]				X	X								
HR titration with fenoldopam[4]							<— X —>						
Informed consent													
Medical history													
Chemistry and hematology[1]	X												
Urine pregnancy[2]	X												
Blood alcohol and urine drug screen	X												
12-lead ECG	X		X									X	
Vital Signs	X		X	X			<— X[4] —>					X	
Physical exam													
Height and weight	X												
Medication history	X												
Holter						<— X —>							
Extracted 12-lead ECG from Holter							<— X[3] —>						
Concomitant medications	X												
Pharmacokinetic samples													
AE reporting							<— X —>						
SAE reporting							<— X —>						

Note – Dose time is 3 hours earlier, in relation to time of day, than start of clevidipine and control arm therapy

[1] As described in Section 9.7.3

[2] Women of child-bearing potential only

[3] See Table 13 below for times of extracted ECGs

[4] Continuous HR monitoring and BP was as necessary during fenoldopam infusion (See Table 14).

[5] NS was to be administered at 4 mL/min starting 15 minutes prior to dosing with moxifloxacin until 1h 15 min when fenoldopam was administered

The total planned maximum dose of clevidipine was equal to 4,876 ug/kg (3.2 ug/kg/min for 22 hours 15 minutes + 7.6 ug/kg/min (average of 3.2 and 12) for 40 minutes during titration + 12 ug/kg/min for 25 minutes if tolerated).

All definitive ECG measurements were derived from the continuous 12-lead Holter readings and were read by the central ECG laboratory cardiologists.

The QT IRT group reviewed the data and performed a concentration – QT analysis. Compared to the vehicle- and heart rate-control (fenoldopam) group, 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 ug/kg/min and 12 ug/kg/min dose groups were -9.4 ms (-16, -3 ms) and -16 ms (-21, -11ms). Based on the concentration ΔΔQTcF relationship (log-linear), 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 ug/kg/min, respectively.

The QT IRT review pointed out the many limitations of this study.

10.1.14 TMC-CLV-06-01: R, PC, SB, parallel PK and PD of CLV in essential mild to moderate HTN after 72 hour infusion

10.1.14.1 Summary

This study was extensively reviewed by the Pharmacometrics reviewer, Dr. Tornoe. Since it is critical for the understanding of clevidipine, his review will be discussed in the main body of this review. This section will only briefly discuss aspects not covered in the main review.

The objectives of this study were to determine the extent of any tolerance development during continuous prolonged clevidipine infusion (72 hours) at four different doses, evaluate the potential for rebound following termination of the infusion, determine the clevidipine concentration antihypertensive effect at four different doses, and to evaluate the safety.

Criteria for inclusion include medication-free for 8 days prior to administration of study drug, 3 consecutive average SBP and DBP (taken on separate days, one of which must be Day -1) that fall within eligibility range (140 mmHg ≤ SBP < 200 mmHg and/or 95 mmHg ≤ DBP < 115 mmHg), and HR < 120 bpm at every assessment. Treatments that affected BP were prohibited from 8 days prior to 4 hours following the infusion.

Sixty-one patients were allocated to 1 of 4 dosing cohorts and randomized 10 clevidipine to 3 placebo:
Cohort 1: clevidipine 2.0 mg/h or placebo
Cohort 2: clevidipine 4.0 mg/h or placebo
Cohort 3: clevidipine 8.0 mg/h or placebo
Cohort 4: clevidipine 16.0 mg/h or placebo

The initial infusion was 2.0 mg/h for 3 minutes for all cohorts. Patients were force titrated in doubling increment rates every 3 minutes to reach target dose where it was maintained for 72 hours. Placebo (Intralipid) was administered in the same fashion. Due to lipid load restrictions (maximum 2.5 g/kg/24 hours), patients weighing less than 64 kg were not enrolled in Cohort 4.

After 4 hours, patients switched to oral therapy as necessary.

PK sampling for the most part coincided with VS measurements. Both parent and metabolite were measured, but PK analysis was only performed on the parent. BP and HR were obtained at the following timepoints:

- During treatment: predose, every 3 minutes during the titration phase; after the target dose reached 5, 10, and 15 minutes, and 0.5, 2, 4, 8, 12, 16, 24, 30, 36, 42, 48, 54, 60, 66, and 72 hours,
- Following drug termination: 2, 4, 6, 8, 12, 20, 30, and 60 minutes, then every 15 minutes for the next 3 hours and then at 6 and 8 hours, Day 7

Patients were withdrawn if HR ≥ 120 bpm or MAP ≤ 73 mm Hg or ≥ 143 mmHg on 2 successive occasion at least 10 minutes apart, or for signs of myocardial ischemia. A withdrawal due to tachycardia or hypotension necessitated the infusion be down titrated in halving increments prior to discontinuation of treatment. A withdrawal due to hypertension called for the drug infusion to be maintained during the transition to oral antihypertensive medication. The need for an alternative antihypertensive was reason for study withdrawal.

Table 107. Patient disposition

	Treatment					
		Clevidipine				
	Placebo n (%) N=13	2.0 mg/h n (%) N=10	4.0 mg/h n (%) N=10	8.0 mg/h n (%) N=18	16.0 mg/h n (%) N=10	Total Clevidipine n (%) N=48
Enrolled	13 (100.0%)	10 (100.0%)	10 (100.0%)	18 (100.0%)	10 (100.0%)	48 (100.0%)
ITT Population	13 (100.0%)	10 (100.0%)	10 (100.0%)	18 (100.0%)	10 (100.0%)	48 (100.0%)
Replacement	0	0	0	1 (5.6%)	0	1 (2.1%)
Safety Population	13 (100.0%)	10 (100.0%)	10 (100.0%)	18 (100.0%)	10 (100.0%)	48 (100.0%)
PK Population	0	10 (100.0%)	10 (100.0%)	17 (94.4%)	10 (100.0%)	47 (97.9%)
PP Population	13 (100.0%)	10 (100.0%)	10 (100.0%)	10 (55.6%)	10 (100.0%)	40 (83.3%)
Withdrawal						
Patient Withdrew Consent	0	0	0	0	0	0
Lost to Follow-up	0	0	0	0	0	0
Adverse Experience	0	0	0	1 (5.6%)	0	1 (2.1%)
Patient Died	0	0	0	0	0	0
Other	0	0	0	0	0	0

Source: Table 14.1-1.
N = number of patients

Adapted from Sponsor's Table 7, page 41 of 2862

The sponsor states that there was no evidence of rebound hypertension following termination of the clevidipine infusion.

Mean half-life ranged from 3-4 minutes and mean beta half-life ranged from 32-37 minutes. Sampling was missed the first 2 minutes after clevidipine cessation, s the reported half lives are

more likely the beta and terminal half-lives as opposed to the true alpha and beta half-lives. Clearance was and similar across all dose groups. Over the range evaluated, there was no apparent Emax and the relationship between concentration and SBP effect was shallow.

There were no deaths or SAEs. The most common AEs were headache and infusion site reactions. There were two significant lab changes on Day 7; patient 203/030 (clevidipine 8 mg/h) had an ALT of 55 U/L on Day 7 (1.4x higher than the ULN and had progressively increased from baseline) and patient 203/055 (clevidipine 8.0 mg/h) had a serum K of 6.0 mEq/L (1.2x higher than the ULN). The K was repeated and WNL (4.2 mEq/L).

One patient (203/005) experienced AEs which led to discontinuation of drug and withdrawal. He was a 49 yo male with no relevant medical history who experienced generalized facial pressure starting 58 minutes after the start of the infusion (8 mg/h), which lasted for an hour. He also experienced mild headaches and nausea

Nine patients had one or more post-baseline normalized TG that were greater than 500 mg/dL, although two of these patients had elevated triglycerides at baseline. Of the remaining, Patient 203/045 (clevidipine 8.0 mg/h) had elevated TG on Day 4. Six patients had elevated levels on Day 7 or 8. The sponsor did not attribute these elevations to clevidipine since the infusion had ended 3 or 4 days prior to the sample.

	Mg/h	Mg/kg/h
201/053	4	
202/029	4	
203/019	8	
203/043	8	
203/058	8	
202/049	16	

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16 Page(s) Withheld

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10.3 References

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John Lawrence
3/10/2008 08:49:30 AM
BIOMETRICS

Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

NDA	22,156
Brand Name	Cleviprex
Generic Name	Clevidipine
Sponsor	The Medicines Company
Indication	[redacted]
Dosage Form	IV emulsion
Drug Class	Calcium Channel Antagonist
Therapeutic Dose	2-32 mg/hr (titration)
Duration of Therapeutic Use	Acute
Maximum Tolerated Dose	105 mg/h
Application Submission Date	July 2, 2007
Review Classification	Standard
Date Consult Received	August 23, 2007
Clinical Division	CDRP / HFD 110
PDUFA Date	May 2, 2008

1 SUMMARY OF FINDINGS

1.1 OVERALL SUMMARY OF FINDINGS

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 at several timepoints (Table 10). Since ten QT measurements were obtained over a short time, multiplicity adjustment may not be appropriate to compute confidence intervals.

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

Limitations of the Study

1. A precise estimate of the effect of administering clevidipine on the QT interval cannot be determined since the main study lacked a true placebo control group.
   - In the main study, the negative-control group contained two treatments that were not given to the clevidipine group: Intralipid® and fenoldapam. Intralipid® (20% fat emulsion) was administered by IV infusion for the same duration (23 hour 20 minutes) as clevidipine treatment. Fenoldapam was administered for 45 minutes during the up-titration period and discontinued 20 minutes prior to collecting ECGs for the supratherapeutic dose.
   - The sponsor attempted to assess the effect of administering Intralipid® on the QT interval in stage I of the study (Table 3). The sponsor concluded that there did not appear to be any effect of administering Intralipid® on the QTcF interval. However, this evaluation was descriptive only and definitive conclusions cannot be made.
   - The effect of administering fenoldapam on the QT interval is not known.
2. The assessment of assay sensitivity has the following limitations:
   - Administration of moxifloxacin was not blinded. Lack of blinding may result in changes in the conduct of the trial in the moxifloxacin arm (e.g. changes of the behavior of the investigators and/or the subjects), which may introduce bias and affect the QT interval.
   - The study design is a 2-period crossover part plus moxifloxacin arm at the 3rd period. Therefore, the effect of moxifloxacin is confounded with the period effect.
   - The timing of ECGs to determine assay sensitivity is inadequate. After moxifloxacin administration, ten ECGs were collected for 2.5 hours which coincide with T_{max}. We typically recommend that a full moxifloxacin profile since we also consider the time-course of QTc during our assessment of assay sensitivity.
   - Moxifloxacin was co-administered with fenoldapam for 45 minutes. Fenoldapam was administered starting from 1 hour 15 minutes to 2 hours after dosing moxifloxacin. The effect of administering fenoldapam on the QT interval is not known.

- Moxifloxacin treatments were compared with vehicle- and HR-control at analogous periods rather than actual time from administration as shown in Table 5.

3. The mean plasma concentrations achieved with the supratherapeutic dose are approximately 30% lower than the mean concentrations when the highest clinical dose is administered.
   - At the supratherapeutic dose (12 mcg/kg/min or 60 mg/hr for 83 kg patient), clevidipine plasma concentrations were 3-fold higher than concentrations following the therapeutic dose (3.2 mcg/kg/min or 16 mg/hr for 83 kg patient).
   - In the proposed label, subjects can be titrated to a maximum of 32 mg/hr with an expected mean C_{max} of 32 ng/mL (assuming linear PK and with a mean observed C_{max} was 16 ng/mL for 16 mg/hr in study TMC-CLV-06-01) which is not covered by the observed mean C_{max} of 25.4 ng/mL obtained in this study with 12 mcg/kg/min.

2 PROPOSED LABEL

The sponsor proposed the following description of study findings in Section 12.2 of the proposed label:

"Electrophysiologic Effects:

[redacted]

Reviewer's Comments: The mean plasma concentrations achieved with the supratherapeutic dose are approximately 30% lower than the mean concentrations when the highest clinical dose (32 mg/h) is administered.

3 BACKGROUND

Clevidipine is a short-acting dihydropyridine L-type calcium channel antagonist being developed fo[redacted] here an oral therapy is either not feasible or not desirable. The sponsor states that patients with hypertensive emergencies or acute elevations in blood pressure following major surgical procedures are the target population.

Reviewer's comment: The intended population is in-hospital and very likely having their heart rhythm continuously monitored.

3.1 MARKET APPROVAL STATUS

Not approved for marketing in the USA or elsewhere.

3.2 PRECLINICAL INFORMATION

The 15 Sept 2006 IB states:

"During cardiac pacing at a constant heart rate of 167 beats/min, anesthetized dogs (n=7) were given clevidipine at dose rates of: 6, 18 and 54 µmol/kg. Needle electrodes were placed subcutaneously for recording of ECGs ...made on a [redacted] polygraph and sampled by a computer. The data were transferred to a VAX 11/730 computer, and analyzed using the software BIOLAB V1.8.

There was no effect of either dose on the duration of the PQ-interval, the QRS-complex or the QT-interval."

Reviewer's comment: No hERG assay is cited.

3.3 PREVIOUS CLINICAL EXPERIENCE

Not reviewed in detail since the clinical data in the NDA is currently being reviewed by the Division of Cardiovascular and Renal products. The sponsor did not find any QT effects in a *post-hoc* analysis of two phase 1 studies. Systematic ECG analysis was not performed in the Phase III studies.

Clevidipine produces significant tachycardia in non-anesthetized subjects at higher doses.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of clevidipine's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 TQT STUDY

4.1.1 Title

A single-blind, prospective, randomized, crossover study of clevidipine in healthy volunteers to determine electrocardiographic safety.

4.1.2 Protocol Number

TMC-CLV-05-01

4.1.3 Objectives

- To assess the safety of clevidipine in terms of its effect on cardiac repolarization as measured by the electrocardiogram (ECG) at therapeutic and supratherapeutic concentrations

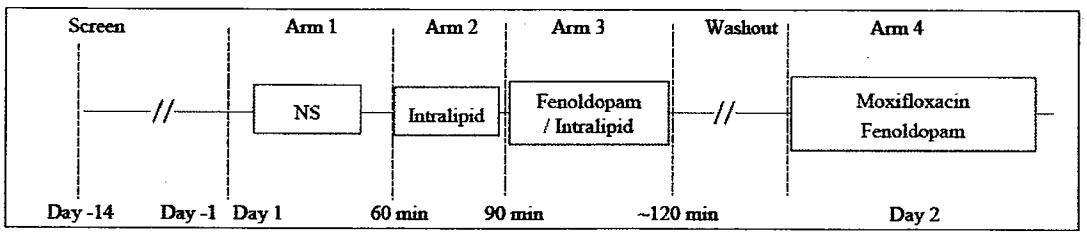
4.1.4 Study Description

4.1.4.1 Design

The study was conducted in 2 phases: a pilot study (Stage I) and the Main Study.

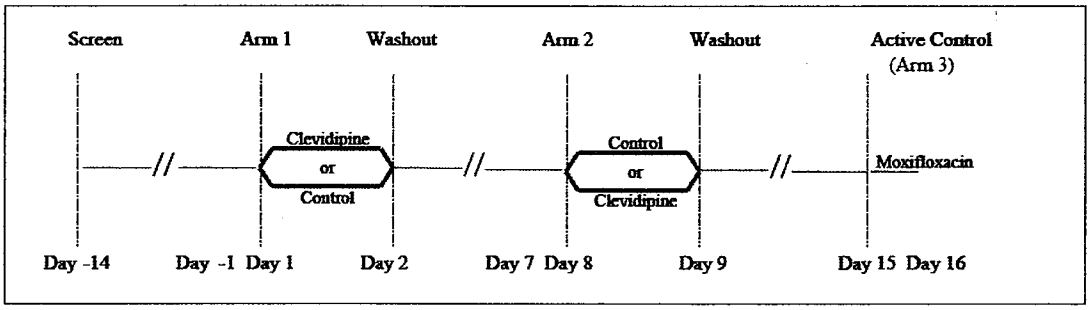
Stage I: An open-label, nonrandomized pilot study to assess: the effect of Intralipid® (20% intravenous [IV] fat emulsion) on ECG parameters.

Figure 1: Study Schematic of Stage I Treatment Arms



Main Study: A randomized, single-blind, vehicle (Intralipid®)- and heart rate-controlled, 2-treatment crossover trial in healthy volunteers, with an additional nonrandomized, open-label positive control treatment (moxifloxacin) with heart rate control, designed to determine the ECG effects and pharmacokinetics associated with IV administration of clevidipine.

Figure 2: Study Schematic of Main Study Treatment Arms



4.1.4.2 Controls

Rather than a standard placebo, a control arm was used. It consisted of Intralipid® infusion to coincide in time and approximate quantity to that given with clevidipine during therapeutic, up-titration, and supratherapeutic infusions and with fenoldopam for heart rate control during the equivalent time of the up-titration period.

Oral moxifloxacin was administered with fenoldopam infusion.

4.1.4.3 Blinding

The positive (moxifloxacin) control was not blinded.

4.1.5 Treatment Regimen

4.1.5.1 Treatment Arms

Clevidipine (0.5 mg/mL in 20% lipid emulsion), administered IV over a total infusion time of 23 hours 20 minutes, as follows:

- Therapeutic infusion period (22 hours 15 minutes) – starting at a dose of 0.4 μg/kg/min, with an up-titration to a continuous infusion of 3.2 μg/kg/min
- Up-titration period (45 minutes) – starting at 22 hours 15 minutes, infusion dose increased in increments of 1.1 μg/kg, every 5 minutes, until 12 μg/kg/min or a dose not tolerated by the subject was reached. If a dose was not tolerated the immediate previous lower dose was resumed.
- Supratherapeutic infusion period (20 minutes) – start at 12 μg/kg/min or highest tolerated dose.

Negative Control: Vehicle- and Heart Rate Control

1. Intralipid® was administered via a peripheral IV cannula in a volume equal to the volume of the dose of clevidipine, in the same manner as that described for clevidipine, for the total infusion period of 23 hours 20 minutes.

2. ——— (Fenoldopam) was provided as a 40.0 µg/mL solution in NS. (1 mL of 10.0 mg/mL in a solution of 250 mL NS). Fenoldopam infusion rates were 0.1 µg/kg/min, 0.3 µg/kg/min and 0.5 µg/kg/min.
   - At 20 hours 45 minutes, NS began at 4 mL/min via a separate peripheral IV cannula.
   - At 22 hours 15 minutes, into the NS cannula, fenoldopam was administered as follows:
     Fenoldopam infusion Level 1: 0.1 µg/kg/min 15 min duration
     Fenoldopam infusion Level 2: 0.3 µg/kg/min 15 min duration
     Fenoldopam infusion Level 3: 0.5 µg/kg/min 15 min duration
   - This infusion was discontinued at 23 hours

Positive-Control: Moxifloxacin 400 mg

——— tablets were available as film-coated tablets containing moxifloxacin hydrochloride (equivalent to 400 mg moxifloxacin). Subjects received a single oral dose of 400 mg moxifloxacin to swallow with water. Fenoldopam was administered as described in the Stage I treatment.

- On the treatment day at time 3 hours, in relation to the time of day, prior to start of dose in the infusion arms, subjects received a single oral dose of 400 mg moxifloxacin to swallow with water.
- Normal saline was administered at 4 mL/min starting 15 minutes prior to the time of moxifloxacin dosing until 1 hour 15 minutes.
- At 1 hour 15 minutes fenoldopam was administered as described above in this section under Vehicle- and Heart rate-control.
- Fenoldopam (or NS at 4 mL/min if fenoldopam was not tolerated) was administered until 2 hours after oral moxifloxacin then IV infusion was discontinued.

4.1.5.2 Sponsor's Justification for Doses

"The therapeutic dose, continuous infusion of 3.2 µg/kg/min for 22 hours 15 minutes, was intended to represent the dose at which a majority of patients demonstrate therapeutic response clinically. The supratherapeutic dose, upward titration to a maximally tolerated dose up to 12 µg/kg/min which was then continued for at least 20 minutes, was intended to achieve serum concentrations of clevidipine and its primary metabolite, H152/81, which are higher than those likely to be encountered clinically.

The presence of a metabolite with a longer half-life than the parent compound requires a long initial period of infusion to allow serum levels of the metabolite to approximate steady state. After the maintenance infusion, a period of up-titration to a maximally tolerated or maximal dose followed by continued administration of that dose for at least 20 minutes was used to increase levels of the parent compound and its metabolite to levels in excess of those likely to be encountered in clinical practice."

Reviewer's comment: The 12 mcg/kg/min dose (supra-therapeutic) corresponding to 60 mg/hr for a 83 kg patient is double the highest proposed clinical dose of 32 mg/hr.

However, in the proposed label, subjects can be titrated to a maximum of 32 mg/hr with an expected mean C_{max} of 32 ng/mL (assuming linear PK and with a mean observed C_{max} was 16 ng/mL for 16 mg/hr in study TMC-CLV-06-01) which is not covered by the observed mean C_{max} of 25 ng/mL obtained in this study with 12 mcg/kg/min.

4.1.5.3 Instructions with Regard to Meals

Subjects should have been given their morning meal at the usual time on Days 1 and 8 and after the discontinuation of the infusions on Days 2, 9, and 15.

4.1.5.4 ECG and PK Assessments

Table 1: Sampling Schedule for Main Stage — Clevidipine and Vehicle- and Heart Rate-Controlled Infusion Arms (Double Blind Phase)

Study Assessment	Screening Period	Pre-Treatment (Night before)	Baseline (Saline infusion, -1.5 to 0 hours)				Therapeutic Infusion (0 to 22 h 15 min)								Up-Titration Infusion	Supra-therapeutic Infusion[3] (23 to 23.3 hours)					Post-Infusion[3], (23.3 to 36 hours)				
	-14 Days to -3 Days	Day 0 and Day 7	-1.5 h	-1.0 h	-30 min	-15 min	2 h	4 h	8 h	12 h	22 h	20 h	21 h	21.5 h	22 h	(22 h 15 min to 23 hours)	23 h	23h 5 min	23h 10 min	23h 15 min	23h 20 min	23.5 h	24 h	27 h	28 h	36 h
Informed consent	X																									
Medical history	X																									
Chemistry and hematology[1]	X																									
Urine pregnancy[2]	X	X																								
Blood alcohol and urine drug screen	X	X																								
Normal Saline Infusion (4 mL/min)[7]													X	X	X											
12-lead ECG	X	X			X			X							X											X
Vital Signs	X	X			X	X	<-									X[3]										->
Physical exam	X																									
Height and weight	X	X																								
Interim history		X																								
Holter[6]			<-		X	->						<-				X	->									
Extracted 12-lead ECG				X	X		X		X				X	X	X	X[5]			X	X		X	X	X		
Concomitant medications	X	X																								
Pharmacokinetic samples[4]						X	X		X				X	X	X		X			X			X	X		
AE and SAE reporting		<-									X										->					

1 As described in Section 9.7.3

2 Women of childbearing potential only

3 See Table 14 for the exact times for Therapeutic Infusion, Supra-therapeutic Infusion, and Post-infusion Periods BP and HR times.

4 The sampling timepoints were: -10 min, 2 h 20 min, 8 h 20 min, 20 h 50 min, 21 h 20 min, 21 h 50 min, 23 h 5 min, 23 h 18 min, 24 h 20 min, and 27 h 20 min. Sample should have been drawn to accommodate extraction of ECGs from Holter.

5 See Table 18 below for times of extracted ECGs.

6 Holter electrodes were to be applied and recording no later than 90 minutes prior to infusion start.

7 NS was administered at 4 mL/min starting 20 h 45 min until 22h 15 min when fenoldopam infusion was initiated.

(Sponsor's Table 3, page 44 of Clinical Study Report TMC-CLV-05-01)

APPEARS THIS WAY
ON ORIGINAL

Table 2: Sampling Schedule for Main Stage — Moxifloxacin Arm (Open Label Phase)

	Pre-Treatment	Baseline			Moxifloxacin Treatment							
						HR titration							
Study Assessment	Day 14	-90 h	-30 min	-15 min	0	1 h 15 min	1 h 30 min	1 h 45 min	2 h	3 h	4 h	6 h	8 h
Moxifloxacin drug administration					X								
NS (4 mL/min)[5]				X	X								
HR titration with fenoldopam/NS						<-		X	->				
Informed consent													
Medical history													
Chemistry and hematology[1]	X												
Urine pregnancy[2]	X												
Blood alcohol and urine drug screen	X												
12-lead ECG	X		X									X	
Vital Signs	X		X	X		<-		X[4]	->			X	
Physical exam													
Height and weight	X												
Interim history	X												
Holter		<-			X					->			
Extracted 12-lead ECG from Holter			<-				X[3]			->			
Concomitant medications	X												
Pharmacokinetic samples													
AE reporting	<-				X								->
SAE reporting	<-				X								->

Note – Dose time is 3 hours earlier, in relation to time of day, than start of clevidipine and control arm therapy

[1] As described in Section 9.7.3

[2] Women of childbearing potential only

[3] See Table 19 below for times of extracted ECGs.

[4] Continuous HR monitoring and BP was as necessary during fenoldopam infusion (See Table 14).

[5] NS was to be administered at 4 mL/min starting 15 minutes prior to dosing with moxifloxacin until 1h 15 min when fenoldopam was administered

(Sponsor's Table 4, page 45 of Clinical Study Report TMC-CLV-05-01)

4.1.5.5 Baseline

The baseline ECGs were designated as all ECGs extracted during the time -1:30 to 0:00 in each of the clevidipine or control arms and all ECGs extracted during the time -0:30 to 0:00 for the moxifloxacin arm.

4.1.6 ECG Collection

Intensive 12-Lead Holter monitoring was used to obtain digital ECGs. Electrocardiogram data was recorded onto the flash memory cards, which were delivered to a core laboratory at the end of each treatment period. All definitive ECG measurements were derived from these continuous recordings. Subjects were supine and quiet from 5 minutes prior to the end of each recording period. Blood drawing, vital sign measurements, and other procedures followed the period of ECG acquisition.

The core ECG laboratory scanned all Holter recordings and identified arrhythmia, artifact, or signal loss preventing adequate interpretation of the recording. Each ECG was interpreted using digital, on-screen software allowing the placement of electronic markers at the beginning and end of each ECG interval. Three ECG complexes were marked on each ECG in the lead with the longest apparent QT interval. Three individual ECGs were extracted from each critical observation period and the results of these 3 averaged to comprise a single observation for statistical purposes.

A single cardiologist reader was assigned to each subject and was blinded to the treatment arms. The order of visits was randomly shuffled to minimize the possibility that

the blinded reviewers would be aware of sequencing of treatment in relation to effect on heart rate. In addition, reviewers were blinded to date and time of visits.

4.1.7 Sponsor's Results

4.1.7.1 Study Subjects

46 healthy male and female subjects 18 -60 years of age with normal baseline ECGs and blood pressure were enrolled. 14 subjects were terminated early. The reasons for withdrawal were:

- The protocol stipulated subjects with the following had to be withdrawn or dose of clevidipine or fenoldopam reduced if the blood pressure fell to less than 90 mmHg systolic or less than 45 mmHg diastolic on 2 vital sign readings repeated within 2 minutes; six subjects were discontinued for this reason.
- Two were discontinued due to AEs; both subjects had headaches.
- Three "withdrew consent."
- Two withdrew due to lack of transportation
- One withdrew due to work schedule conflicts

4.1.7.2 Statistical Analyses

4.1.7.2.1 Stage I Analysis

There is no effect seen during stable infusion of normal saline (NS), Intralipid infusion as seen in Table 3 were none of the comparison pairs are statistically significant.

Table 3 Paired Average Values by Subject

Pair	Int	Diff	Lower 95% two-sided CI	Upper 95% two-sided CI	N	p	significant
NS vs BL	HR	1.38	-2.87	5.62	8	0.469	
	QT	0.31	-5.53	6.16	8	0.903	
	QTcB	4.63	-5.48	14.73	8	0.315	
	QTcF	3.19	-2.76	9.14	8	0.246	
IL vs BL	HR	0.06	-1.72	1.84	8	0.936	
	QT	2.19	-3.03	7.40	8	0.354	
	QTcB	2.88	-0.92	6.67	8	0.117	
	QTcF	2.69	-0.96	6.36	8	0.127	
IL vs NS	HR	-1.31	-5.74	3.11	8	0.506	
	QT	1.86	-4.79	8.54	8	0.527	
	QTcB	-1.75	-13.30	9.80	8	0.731	
	QTcF	-0.50	-7.80	6.80	8	0.876	
IL vs NS and BL	HR	-0.63	-3.24	1.99	8	0.590	
	QT	2.03	-3.19	7.26	8	0.389	
	QTcB	0.56	-6.39	7.52	8	0.854	
	QTcF	1.09	-3.86	6.05	8	0.618	

NS=Normal saline, BL=Baseline,IL=Intralipid

(Sponsor's Table, page 753 of Clinical Study Report TMC-CLV-05-01)

The ability to detect the repolarization effect of moxifloxacin was assessed in 8 subjects. The estimated mean change in QTcF at 2 hours post moxifloxacin dosing was 10.4 ms (95% CI 1.9-18.9 ms) (see Table 4).

Table 4 Paired Analysis of All ECGs and Direct Comparison of Uncorrected QT

Interval	Time	Diff	Lower 95% two-sided CI	Upper 95% two-sided CI	N	p	significant
HR	1:20	3.25	0.00	6.50	8	0.050	
HR	1:35	1.13	-2.08	4.33	8	0.434	
HR	1:40	5.25	0.59	9.91	8	0.032	*
HR	1:45	4.63	2.06	7.19	8	0.004	**
HR	1:50	-0.25	-3.65	3.15	8	0.867	
HR	1:55	-0.13	-5.38	5.13	8	0.957	
HR	2:00	1.25	-3.90	6.40	8	0.584	
QT	1:20	-2.75	-15.23	9.73	8	0.618	
QT	1:35	-0.38	-6.90	6.15	8	0.896	
QT	1:40	-7.88	-16.12	0.37	8	0.059	
QT	1:45	-7.13	-18.20	3.95	8	0.172	
QT	1:50	0.38	-6.93	7.68	8	0.907	
QT	1:55	2.88	-11.36	17.11	8	0.648	
QT	2:00	6.88	-5.70	19.45	8	0.237	
QTcB	1:20	7.38	-4.66	19.41	8	0.191	
QTcB	1:35	4.63	-4.79	14.04	8	0.284	
QTcB	1:40	10.63	-1.71	22.96	8	0.081	
QTcB	1:45	6.63	-4.48	17.73	8	0.201	
QTcB	1:50	0.25	-14.90	15.40	8	0.970	
QTcB	1:55	4.38	-8.28	17.03	8	0.441	
QTcB	2:00	12.13	1.56	22.69	8	0.030	*
QTcF	1:20	3.88	-7.29	15.04	8	0.439	
QTcF	1:35	3.13	-3.70	9.95	8	0.315	
QTcF	1:40	4.25	-4.30	12.80	8	0.278	
QTcF	1:45	2.00	-8.34	12.34	8	0.661	
QTcF	1:50	0.13	-11.75	12.00	8	0.981	
QTcF	1:55	4.13	-6.59	14.84	8	0.393	
QTcF	2:00	10.38	1.86	18.89	8	0.024	*

(Sponsor's Table, page 755 of Clinical Study Report TMC-CLV-05-01)

Reviewer's comment: Stage I of the study does not demonstrate assay sensitivity. With only 8 subjects in phase 1, the data collected are descriptive only and any conclusions made by the sponsor should be viewed with caution.

4.1.7.2.2 Primary Analysis

The primary endpoint is the maximal mean difference in uncorrected QT between clevidipine and vehicle- and heart rate-control after baseline correction at each time point.

Reviewer's Comment: This pre-specified primary endpoint was not used. Instead, the sponsor relied on QTcF and exponential individual-correction (QTcEi). QTcB was presented for completeness.

Moxifloxacin treatments were compared with vehicle- and HR-control at analogous periods rather than actual time from administration as shown in Table 5.

Table 5. Pairing of Moxifloxacin Observations with Control Observations

Control Arm	Designation	Moxi Arm	Designation
-1 h	Baseline 1	- 30 min	MoxiBaseline 1
-30 min	Baseline 2	- 15 min	MoxiBaseline 2
21.5 h	Therapeutic concentration 2	40 min	Moxi 1
22 h	Therapeutic concentration 3	1 h 0 min	Moxi 2
22 h 20 min	Up-titration HR 1	1 h 20 min	MoxiFeno 1
22 h 28 min	Up-titration HR 2	1 h 28 min	MoxiFeno 2
22 h 36 min	Up-titration HR 3	1 h 36 min	MoxiFeno 3
22 h 42 min	Up-titration HR 4	1 h 42 min	Moxi/Feno 4
22 h 50 min	Up-titration HR 5	1 h 50 min	Moxi Feno 5
22 h 58 min	Up-titration HR 6	1 h 58 min	Moxi Feno 6
23 h 10 min	Supratherapeutic 1	2 h 15 min	Moxi Late 1
23 h 15 min	Supratherapeutic 2	2 h 30 min	Moxi Late 2

Source: Thorough QT Study Analysis Report for the Main Study, Appendix 16.1.12.2

(Sponsor's Table 29, page 99 of Clinical Study Report TMC-CLV-05-01)

Time-matched raw mean differences and upper bound of 95% one-sided CI between clevidipine and vehicle- and heart rate-control were estimated and listed in Table 6. Time-matched raw mean differences and lower bound of 95% one-sided CI between moxifloxacin and vehicle- and heart rate-control were estimated and listed in Table 7. Figure 3 details the complete results of paired t-testing for the control-subtracted changes from baseline for QTcF ($\Delta\Delta$QTcF).

Table 6. ΔΔQTcF Intervals – Clevidipine vs. Control

Time	dQTcF Clev	dQTcF Ctrl	Diff(ddQTcF)	StdErr	N	UB 95% one-sided CI	>10 msec
EI1	-8.1	-1.7	-6.4	3.24	32	-0.9	
EI2	-14	-9.1	-4.9	2.1	32	-1.3	
TC1	-9.2	-3.4	-5.8	3.256	33	-0.3	
TC2	-11.5	-2.1	-9.4	3.831	33	-2.9	
TC3	-10.6	-2.6	-8.1	3.785	33	-1.7	
UT1	-11.4	-1.2	-10.2	3.428	33	-4.4	
UT2	-13.2	-2.3	-10.9	3.07	33	-5.7	
UT3	-15	-1.5	-13.5	2.697	33	-8.9	
UT4	-18.4	-2	-16.4	3.126	32	-11.1	
UT5	-19.1	0.3	-19.4	3.173	31	-14.0	
UT6	-21.9	-3.4	-18.6	3.001	33	-13.5	
ST1	-20.4	-4.4	-15.9	2.967	33	-10.9	
ST2	-19	-4.7	-14.3	3.154	33	-9.0	
PI1	-9.8	-7.9	-1.9	3.347	33	3.8	
PI2	-11	-10.8	-0.3	3.226	31	5.2	
PI3	-15	-16.2	1.2	2.746	33	5.8	

UB = upper boundary.

(Sponsor's Table 10.3, page 812 of Clinical Study Report TMC-CLV-05-01)

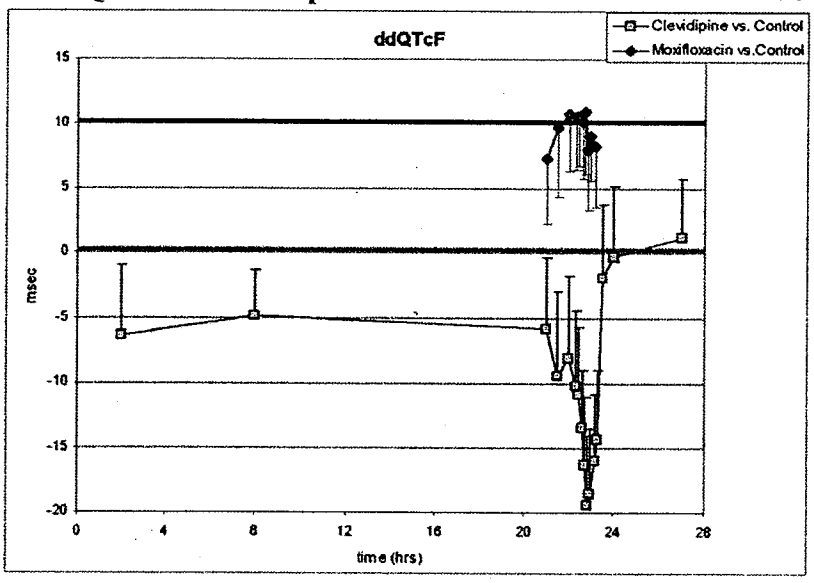
Table 7. ΔΔQTcF Intervals – Moxifloxacin vs. Control

Time	dQTcF Mox	dQTcF Ctrl	Diff(ddQTcF)	StdErr	N	LB 95% one-sided CI	>0 msec
M1	5.1	-2.2	7.3	2.970	32	2.3	***
M2	7.0	-2.8	9.8	3.193	32	4.4	***
MF1	9.6	-1.2	10.8	2.635	32	6.4	***
MF2	8.2	-2.4	10.6	2.437	31	6.5	***
MF3	9.0	-1.6	10.6	2.257	32	6.8	***
MF4	8.6	0.6	8.0	2.709	32	3.4	***
MF5	6.0	-3.3	9.3	1.967	31	6.0	***
MF6	6.4	-4.5	10.9	2.864	32	6.1	***
ML1	3.7	-4.6	8.3	2.781	32	3.6	***
ML2	8.1	-2.0	10.1	2.585	32	5.8	***

LB = lower boundary.

(Sponsor's Table 10.4, page 812 of Clinical Study Report TMC-CLV-05-01)

Figure 3. ΔΔQTcF for Clevidipine and Moxifloxacin with 1-sided 95% CI



(Sponsor's Figure 17, page 114 of Clinical Study Report TMC-CLV-05-01)

For the primary analyses, no values of mean for clevidipine exceeding 0 and all upper bounds considerably below 10 ms. The maximum of the means is at the last observation at 27 hours with a mean of 1.2 ms and the upper bound of the 95% CI one-sided of 5.8 ms.

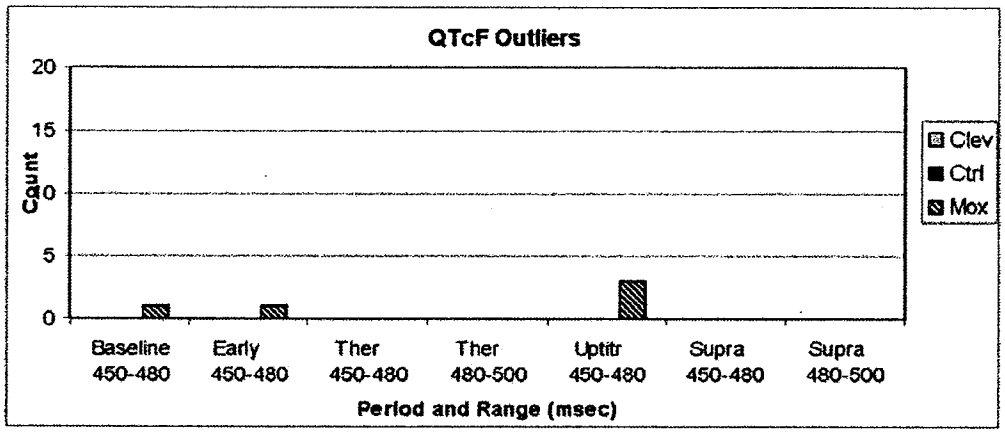
For moxifloxacin, each value of the ΔΔQTcF lower bounds exceeds 0. All ΔΔQTcF moxifloxacin values exceed the E14 threshold for adequate assay sensitivity. The maximal mean effect is 10.9 ms at the fifth up-titration time, 1 hour 50 minutes with a lower bound of the 95% CI one-sided of 6.1 ms. The minimum of the lower bounds is at the first observation at 40 minutes and is 2.3 ms.

Reviewer's comments: To establish assay sensitivity, at least one lower bound of 90% confidence interval with multiplicity justification should be greater than 5 ms. In this study moxifloxacin was measured 10 times over 2.5 hours, therefore, multiplicity adjustment may not be appropriate.

4.1.7.2.3 Categorical Analysis

Outliers for absolute values of QTcF were tabulated in Figure 4 according to the following ranges: >=450 to <480, >=480 to < 500, and >=500. The majority of outlier values are for moxifloxacin treatment. No trends are evident for QTcF for clevidipine outliers to be more prevalent than control at similar time points.

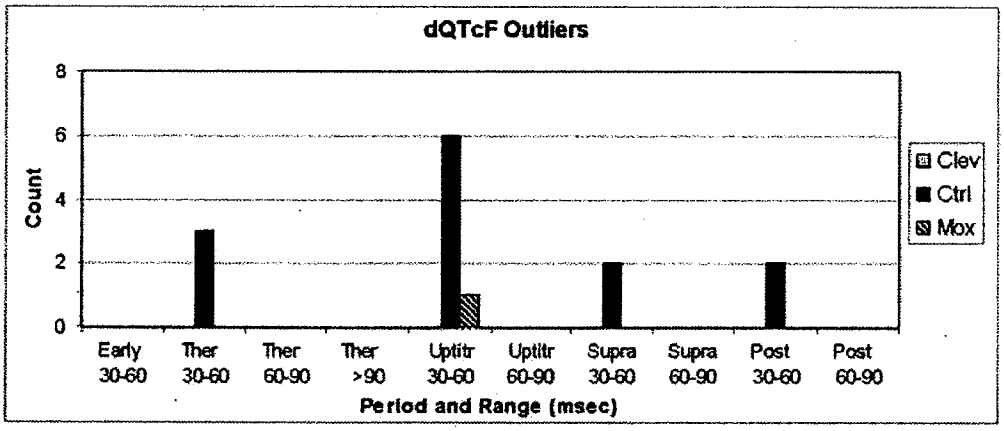
Figure 4. Intervals Outliers



(Sponsor's Figure 12.1, page 822 of Clinical Study Report TMC-CLV-05-01)

Outliers for delta values of QTcF were tabulated according to the following ranges: >=30 to <60, >=60 to <90, and >=90.

Figure 5. Delta Interval Outliers



(Sponsor's Figure 12.2, page 824 of Clinical Study Report TMC-CLV-05-01)

4.1.7.2.4 Additional Analyses

The sponsor also performed similar analysis for QTcB and individual (QTcEi) corrected QT using exponential equation. The results from QTcEi are similar to the results of QTcF. However, the results from QTcB were essentially uninterruptible. The maximal mean, control-subtracted change of QTcB, while in excess of the E14 criteria, was influenced by the heart rate changes associated with clevidipine. There were wide swings in the ΔΔQTcB response.

4.1.7.3 Safety Analysis

No deaths or SAEs were observed. Two AEs of headache led to subject discontinuation and six other subjects were discontinued for hypotension. No subjects were observed to

have syncope, seizure, or a ventricular arrhythmia. The sponsor concludes: "Overall, the changes in the clinical safety assessments were unremarkable."

4.1.7.4 Clinical Pharmacology

4.1.7.4.1 Pharmacokinetic Analysis

The time course of clevidipine and its major metabolite, H152/81, followed the predicted pattern with maximal values at the end of the supratherapeutic infusion. Clevidipine levels dropped rapidly after discontinuation (see Table 8 and Figure 6).

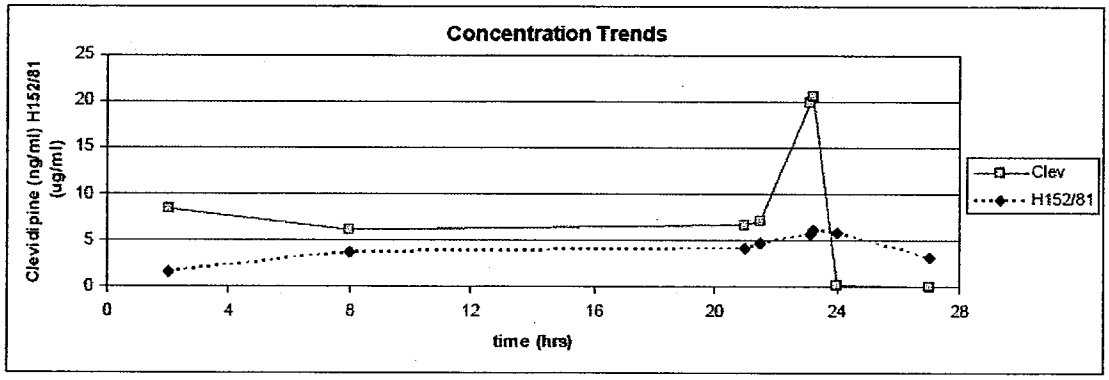
There was a rapid change in QTc findings immediately after discontinuation of clevidipine despite the persistence of levels of H152/81. The metabolite did not appear to have QT activity.

Table 8. Mean Maximum Concentration.

T_{max}	C_{max} Clevidipine (ng/mL)	C_{max} H152/81 (mcg/mL)
23h 15min from start of the 23h infusion	20.56	6.11

(Sponsor's Table 37, page 117 of Clinical Study Report TMC-CLV-05-01)

Figure 6. Concentration Time Course

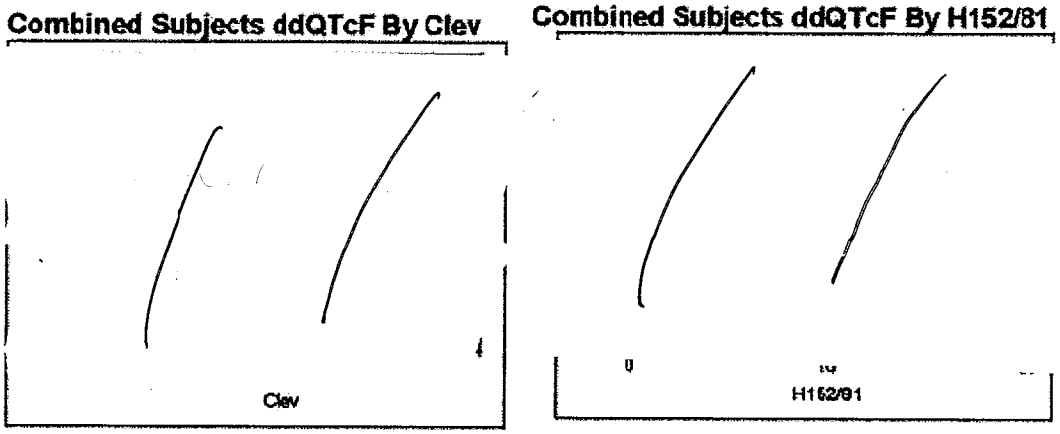


(Sponsor's Figure 19, page 117 of Clinical Study Report TMC-CLV-05-01)

4.1.7.4.2 Exposure-Response Analysis

The relationships for ΔΔQTcF and ΔΔQTcEi values for clevidipine and concentration showed a negative relationship and were statistically significant. All slope values were negative for H152/81 (see Figure 7).

Figure 7. DDQTcF vs. Clevidipine (left) and H152/81 (right) concentrations.



(Sponsor's Figures 25, page 882 of Clinical Study Report TMC-CLV-05-01)

5 REVIEWERS' ASSESSMENT

5.1 STATISTICAL ASSESSMENTS

Our evaluation is based on the sponsor's data and in accordance with ICH E14 guidelines on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. We used the following data set submitted in the NDA to carry out some of the independent analyses for statistical evaluation of the results:

http://eroom.fda.gov/eRoom/CDER1/CDERnterdisciplinaryReviewTeamQTGroup/0_b33f

This data set includes individual values of the 3 replicates ECG measurements. Forty six patients were enrolled in the main study. 32 patients completed the main study; 14 patients had early termination (1 patient completed the first 2 periods of the study). Therefore, the main analysis was based on the data from 33 patients (32 completers and the early withdrawn patient who completed the first 2 periods of the study). The assay sensitivity analysis was based on the data from the 32 completers. Categorical analysis was based on all the data from the 46 enrolled patients.

5.1.1 Inferential Analysis

We calculated the raw mean differences as well as the corresponding 90% CI between clevidipine/moxifloxacin and control at each time point. The QTcF of moxifloxacin treatment were measured at different time frame. We compared moxifloxacin treatments with the control using the time matching table provided by the sponsor (Table 5). QTcF change from baseline (for each subject the baseline is calculated as the average of all baseline values for that treatment) and the difference of QTcF change from baseline between control and clevidipine with the corresponding 90% CI at each time point are summarized in Table 9. Similar results for moxifloxacin and control are listed in Table 10. The results are similar to the sponsor's reported results. Figure 8 provides a time-matched mean ΔQTcF change from control values.

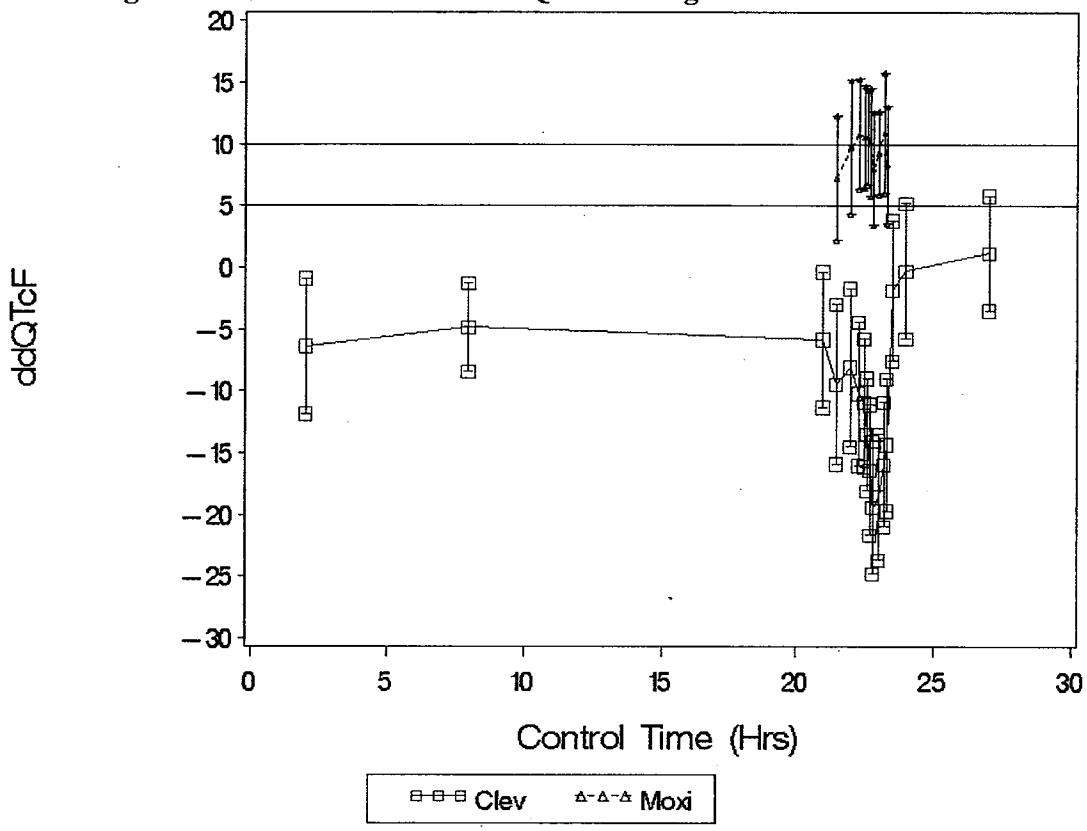
Table 9. Summary of Comparison of Clevidipine with Control

	ΔQTcF			
Time	Clev	Ctrl	ΔΔQTcF	90% CI
2 h	-8.06	-1.70	-6.36	(-11.85, -0.87)
8 h	-14.02	-9.27	-4.84	(-8.40, -1.28)
21 h	-9.25	-3.45	-5.79	(-11.30, -0.29)
21.5 h	-11.52	-2.11	-9.41	(-15.89, -2.92)
22 h	-10.62	-2.59	-8.04	(-14.44, -1.63)
22 h 20 min	-11.39	-1.21	-10.18	(-15.97, -4.38)
22 h 28 min	-13.23	-2.31	-10.91	(-16.10, -5.72)
22 h 36 min	-14.98	-1.51	-13.48	(-18.04, -8.92)
22 h 42 min	-18.35	-1.99	-16.36	(-21.65, -11.07)
22 h 50 min	-19.09	0.69	-19.37	(-24.75, -13.99)
22 h 58 min	-21.99	-3.20	-18.54	(-23.63, -13.44)
23 h 10 min	-20.36	-4.44	-15.91	(-20.94, -10.88)
23 h 15 min	-19.04	-4.73	-14.31	(-19.65, -8.97)
23.5 h	-9.75	-7.93	-1.82	(-7.50, 3.85)
24 h	-11.05	-10.81	-0.24	(-5.71, 5.23)
27 h	-14.83	-15.99	1.21	(-3.44, 5.86)

Table 10. 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)

Figure 8. Time-Matched Mean ΔQTcF Change from Control Values



Based on the above analysis, the statistical reviewer makes the following conclusions:

- All the upper bounds of the two-sided 90% confidence intervals on the mean difference in change from baseline between the clevidipine treatment group and control were less than 10 ms at all time points.
- The unadjusted largest 90% lower bound for moxifloxacin is 6.77 ms, which is above 5 ms.

5.1.2 Categorical Analysis

The statistical reviewer performed the categorical analysis on the individual triplicate readings. Since the collected data show some signals of QT shortening, the statistical reviewer also calculated the percentage of the observations less than -60 ms and between -60 ms to -30 ms after baseline correction (Table 15 and Table 16).

No observations have QTcF larger than 500 ms.

Table 11. Frequency for QTcF > 450 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	3	7.32%	242	5	2.07%

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Moxifloxacin	32	1	3.13%	192	3	1.56%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	2	5.26%	1588	2	0.13%
Moxifloxacin	32	5	15.63%	956	17	1.78%
Control	40	2	5.00%	1905	4	0.21%

Table 12. Frequency for QTcF > 480 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	0	0.00%	242	0	0.00%
Baseline - Moxifloxacin	32	1	3.13%	192	1	0.52%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	0	0.00%	1588	0	0.00%
Moxifloxacin	32	1	3.13%	956	1	0.10%
Control	40	0	0.00%	1905	0	0.00%

Table 13. Frequency for ΔQTcF between 30 ~ 60 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	0	0.00%	242	0	0.00%
Baseline - Moxifloxacin	32	0	0.00%	192	0	0.00%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	3	7.89%	1588	5	0.31%
Moxifloxacin	32	14	43.75%	956	25	2.62%
Control	39	4	10.26%	1857	36	1.94%

Table 14. Frequency for ΔQTcF > 60 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	0	0.00%	242	0	0.00%
Baseline - Moxifloxacin	32	0	0.00%	192	0	0.00%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	0	0.00%	1588	0	0.00%
Moxifloxacin	32	0	0.00%	956	0	0.00%
Control	39	1	2.56%	1857	5	0.27%

Table 15. Frequency for ΔQTcF between -60 ~ -30 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	1	2.44%	242	1	0.41%
Baseline - Moxifloxacin	32	1	3.13%	192	1	0.52%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	19	50.00%	1588	231	14.55%
Moxifloxacin	32	3	9.38%	956	5	0.52%
Control	39	16	41.03%	1857	55	2.96%

Table 16. Frequency for ΔQTcF <-60 ms

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Baseline - Clevidipine	41	0	0.00%	242	0	0.00%
Baseline - Moxifloxacin	32	0	0.00%	192	0	0.00%
Baseline - Control	39	0	0.00%	233	0	0.00%
Clevidipine	38	6	15.79%	1588	15	0.94%

Treatment	Total # of Subj.	# of Subj.	% of Subj.	Total # of Obs.	# of Obs.	% of Obs.
Moxifloxacin	32	1	3.13%	956	1	0.10%
Control	39	4	10.26%	1857	6	0.32%

5.2 CLINICAL PHARMACOLOGY ASSESSMENTS

5.2.1 Exposure-Response Modeling

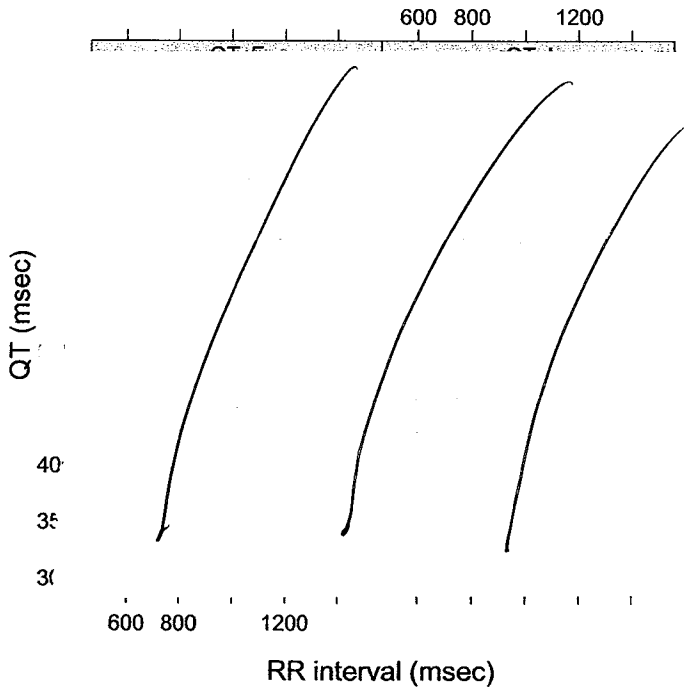
Only the subset of the ECG with corresponding clevidipine concentrations were used for the concentration-QT analysis (i.e. 9 out of 17 time points).

5.2.1.1 QTc Corrections

The observed QT-RR interval relationship is presented in Figure 9 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI) methods.

The QTcF appears to be the most reasonable QT correction method removing the heart rate effect in QT illustrated by a horizontal trend in the QTcF vs. RR relationship. The QTcF correction method was therefore used for the reviewer's concentration-QTcF analysis.

Figure 9. Baseline day QT, QTcB, QTcF, and QTcI vs. RR (Each Subject's Data Points are Connected with a Line).

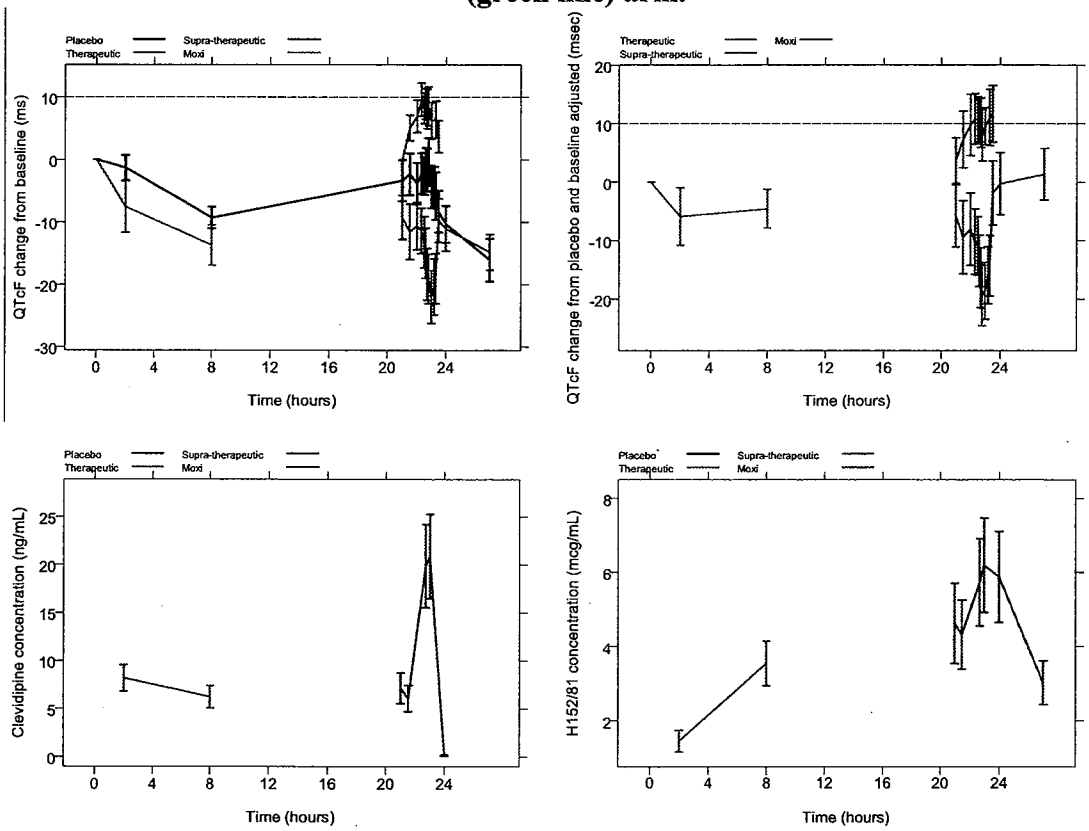


5.2.1.2 ΔΔQTcF and Concentration Time Profiles

The mean ΔQTcF (change from baseline), ΔΔQTcF (change from baseline and vehicle- and heart rate-control corrected), clevidipine and it's main metabolite H152/82 concentration profiles are shown in Figure 10.

The minimum ΔΔQTcF of -20 ms occurs around 23 hours postdose which coincide with the peak clevidipine concentration.

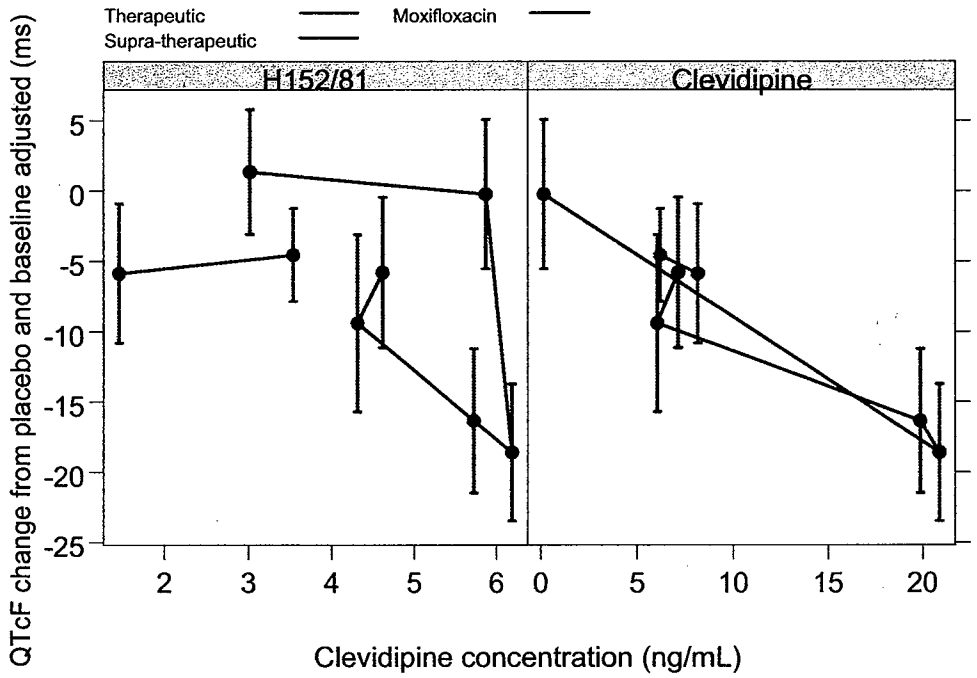
Figure 10. Mean (90% CI) ΔQTcF Change from Baseline (top left), ΔΔQTcF (top right), and Clevidipine concentration (bottom left), and H152/82 concentration (bottom right) profiles for control (black line), therapeutic dose of 3.2 mcg/kg/min (blue line), supra-therapeutic dose of 12 mcg/kg/min (red line), and moxifloxacin (green line) arm.



*Moxifloxacin was assessed 0- 2.5 hrs from baseline measurement but visualized around 21-23.5 hrs in order to subtract mean control ΔQTcF for moxifloxacin ΔΔQTcF calculations.

There was no delay observed between ΔΔQTcF and clevidipine concentrations while there was a delay between the metabolite H152/81 and ΔΔQTcF. The drug effect on the QT interval therefore appears to be caused by clevidipine and not the metabolite H152/81.

Figure 11. Mean (90% CI) ΔΔQTcF vs. H152/81 (Left) and Clevidipine (Right) concentrations



5.2.1.3 Concentration-QTcF Analysis

The relationship between ΔΔQTcF and clevidipine concentrations was investigated by linear mixed-effects modeling. Data collected from the 3.2 mcg/kg/min and 12 mcg/kg/min clevidipine dose groups was used for the clevidipine concentration-QTcF analysis.

Linear and log-linear models were initially tested with the log-linear models describing the data best.

The following three log-linear models were considered:

- Model 1 is a log-linear model with an intercept;
- Model 2 is a log-linear model with mean intercept fixed to 0 (with variability);
- Model 3 is a log linear model with no intercept.

Table 17 summarizes the results of the clevidipine-QTcF analyses. The intercept was not found to be statistical significant. However, model 1 was applied for further analysis due to better description of the observed data.

Table 17. Exposure-Response Analysis of Clevidipine associated ΔΔQTcF Prolongation

	Estimate (90% CI); p-value	Between-subject variability (SD)
Model 1: ΔΔQTcF = Intercept + slope*log(Clevidipine Concentration)		
Intercept, ms	-2.63 (-7.65,2.39) 0.38	14.4
Slope, ms per log ng/mL	-3.76 (-4.99, -2.53) <0.0001	0.0
Residual Variability, ms	12.2	--
Model 2: ΔΔQTcF = Intercept + slope*log(Clevidipine Concentration) (Fixed Intercept)		
Intercept, ms	0 (fixed)	14.7
Slope, ms per log ng/mL	-4.07 (-5.18, -2.96) <0.0001	0.0
Residual Variability, ms	12.2	--
Model 3: ΔΔQTcF = slope*log(Clevidipine Concentration) (No Intercept)		
Slope, ms per log ng/mL	-4.96 (-6.78, -3.13) <0.0001	5.38
Residual Variability, ms	15.4	--

Based on model 1, the predicted ΔΔQTcF interval at the mean peak clevidipine concentration after steady-state dosing of the therapeutic dose of 3.2 mcg/kg/min and single dose of 12 mcg/kg/min is presented in Table 18. The lower 90% CI of the mean ΔΔQTcF is -15.4 ms and -19.5 for the therapeutic and supra-therapeutic doses.

Table 18: Predicted Change of ΔΔQTcF Interval at Peak Clevidipine Concentration using a Log-Linear Model with Intercept.

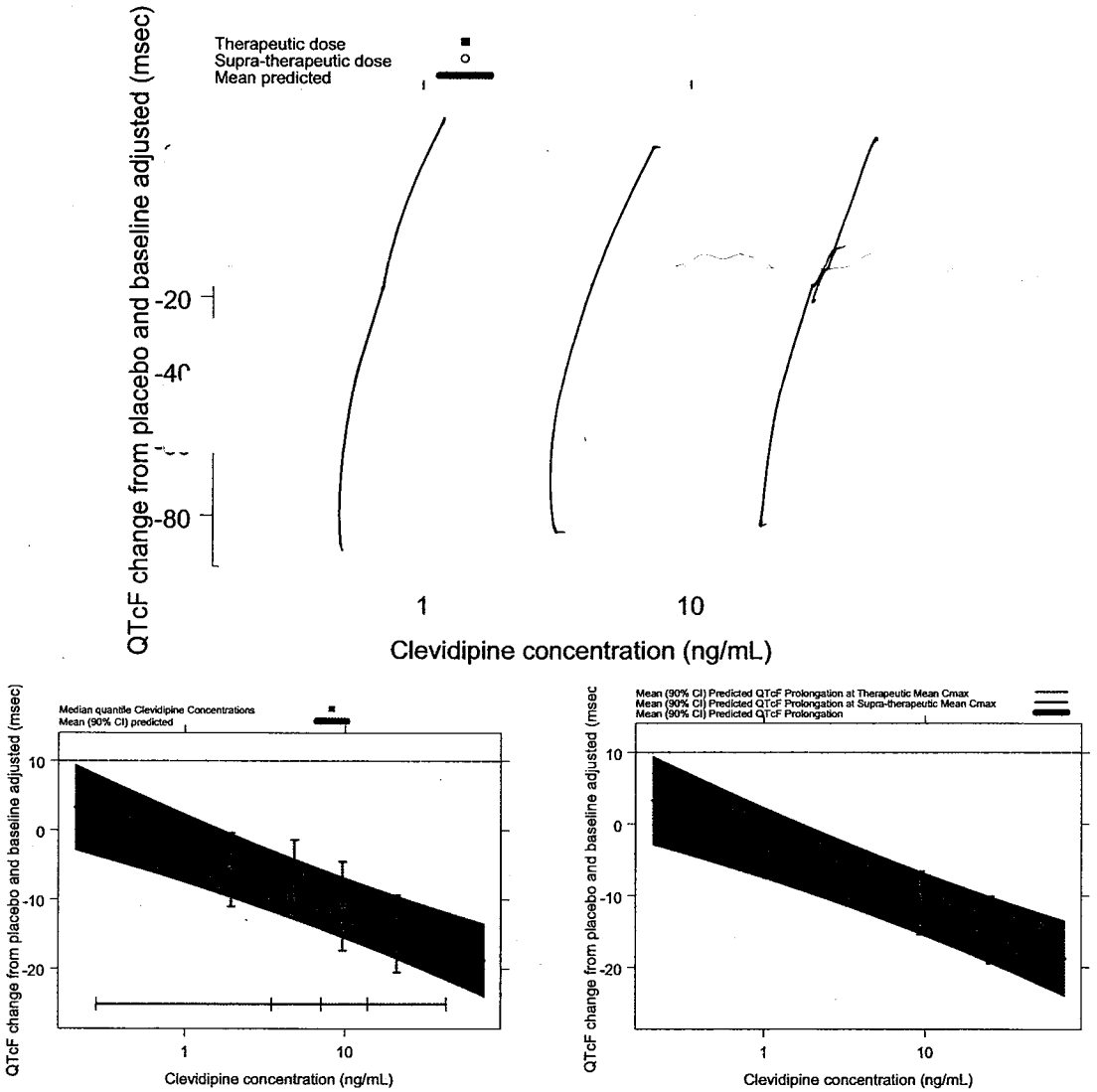
Dose Group	Predicted change in ΔΔQTcF interval (ms)	
	Mean	90% Confidence Interval
3.2 mcg/kg/min (steady-state)		
Mean C_{max} (9.33 ng/ml)	-11.0	(-15.4, -6.62)
12 mcg/kg/min (single dose)		
Mean C_{max} (25.4 ng/ml)	-14.8	(-19.5, -10.1)

The relationship between clevidipine concentrations and ΔΔQTcF is visualized in Figure 12 where the raw data is shown on top with the concentrations on the log-normal scale.

The goodness-of-fit is illustrated in the bottom left graph of Figure 12 showing the observed median-quartile concentrations and associated mean ΔΔQTcF (90% CI) within the mean (90% CI) predicted ΔΔQTcF (black line with shaded grey area).

The mean (90% CI) predicted ΔΔQTcF at mean C_{max} after steady-state dosing of 3.2 mcg/kg/min and single dose of 12 mcg/kg/min is shown in the bottom right graph of Figure 12.

Figure 12 (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 C_{max} after steady-state dosing of therapeutic dose (3.2 mcg/kg/min, blue line) and supra-therapeutic dose (12 mcg/kg/min, red line).



5.3 CLINICAL ASSESSMENTS

None of the events identified as significant in ICH E14 (i.e., death, SAE, seizure, syncope, and ventricular arrhythmia) are reported to have occurred in this study.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Clinical Pharmacology Information Request	Clinical Pharmacology Information
Therapeutic Dose	2 to 32 mg/hour for up to 72 hours.
Maximum Tolerated Dose	Clevidipine IV emulsion was safe and well tolerated up to a dose rate of 105.1 mg/h for 20 minutes in healthy volunteers.
Principal Adverse Events	Common adverse reactions: hypotension, tachycardia, dizziness, flushing, nausea, vomiting, headache, polyuria. Dose-limiting adverse reactions: hypotension, tachycardia, headache, nausea, vomiting (these were the common reasons for discontinuations in phase I/II).
Maximum Dose Level Tested	32 mg/h in patients with severe hypertension. 105.6 mg/h in patients with perioperative hypertension.
Maximum Exposure Achieved	Continuous infusion of 16 mg/h for 72 hours, Cmax = 15.8 ng/mL (SD = 4.0, % CV = 25.5); AUC0-t = 723.8 ng*h/mL (SD = 246.3, % CV = 34.0).
Range of Linear PK	In healthy volunteers, there is a linear relationship between dose rate and clevidipine blood concentrations following a 20 min infusion over a dose range of 3.2 to 105.1 mg/h. In patients with essential hypertension, there is a linear relationship between dose rate and blood concentration following a 2 hour infusion at doses of 0.86 to 26.3 mg/h. In patients with essential hypertension at doses of 2 to 16 mg/h administered for 72 hours, there is a linear and slightly less than dose proportional increase in mean Cmax, mean AUC0-t and mean Css.
Accumulation at Steady State	Clevidipine is administered by Intravenous infusion. Css occurs rapidly due to the short half-life.

Metabolites	Clevidipine is rapidly metabolized by hydrolysis in blood and in extravascular tissues by nonspecific carboxyl esterases to pharmacologically inactive carboxylic acid metabolite (M1).
Absorption	Not applicable because clevidipine is administered by intravenous infusion.
Distribution	Mean Vss = 0.504 L/kg (SD = 0.129). In a population pharmacokinetic evaluation of patients with essential hypertension, V1 was found to be 63.1 L (% CV = 16.5) and V2 was found to be 144 L (% CV = 30) for a 70 kg patient. Clevidipine is greater than 99.5% plasma protein bound.
Elimination Route	Clevidipine is rapidly metabolized to pharmacologically inactive metabolites. No intact drug is excreted in urine or feces. Mean cumulative dose (radioactivity) is excreted 68% in urine and 15% in feces over 7 days. The majority of radioactivity is excreted in 72 hours.
Elimination Half-life	The initial half-life is approximately 1 minute (SD=0.3) and accounts for approximately 85 – 90% of clevidipine elimination. The terminal half-life is about 12 minutes (SD= 2.9). In essential hypertensive patients receiving continuous infusion of 16 mg/h for 72 hours, the mean terminal half-life is 37 minutes (SD=21.7). The initial half-life of the major blood carboxylic acid metabolite (M1) is about 1 h (SD=0.02) and the terminal half-life is about 9.2 h (SD=0.8).
Elimination Clearance	Mean clearance values for venous samples for patients after cardiac surgery were 0.09 L/min/kg and for healthy volunteers 0.1-0.2 L/min/kg. In a population pharmacokinetic evaluation of patients with hypertension, the typical value of clearance for a 70 kg patient was 1220 L/h (% CV = 8).

Intrinsic Factors	In a population pharmacokinetic evaluation of patients with hypertension, the covariates of age, body weight, sex and race were examined. Given the rapid clearance exhibited by clevidipine together with the direct effect pharmacodynamic behavior, dose adjustments based on covariates are not warranted. As a result, and in agreement with the FDA, these factors were not examined in special population studies.
Extrinsic Factors	Pharmacokinetic drug interactions are unlikely since clevidipine is metabolized by plasma esterases. Clevidipine and its primary blood metabolite do not induce or inhibit cytochrome P450 isoenzymes at clinically relevant concentrations. As a result, and in agreement with the FDA, no drug interaction studies were performed. In clinical trials clevidipine has been administered with many concomitant medications before, during and after cardiac surgical procedures and in patients with severe hypertension without any observed drug interactions. Food effects were not studied because clevidipine is administered by intravenous infusion.
Expected High Clinical Exposure Scenario	Study TMC-CLV-05-01 (QTc evaluation) provides cardiac safety data on healthy volunteers exposed to the expected upper end of the recommended dosing regimen (16 mg/h) for most patients, although some patients may require dosing up to 32 mg/h. In this study, a 16 mg/h dose was maintained continuously for approximately 23 hours and then rapidly increased to supratherapeutic levels (58 mg/h) for 20 minutes to mimic an unintended overdose situation. At 16 mg/h the mean Css was approximately 6.5 ng/mL, while at the supratherapeutic dose of 58 mg/h the mean Css ranged from 18 – 21 ng/mL. Clevidipine will be administered in a highly monitored clinical setting. Unintended overdose is unlikely, but will be recognized immediately if it occurs, due to the hemodynamic effects of the drug. Due to its rapid clearance, high exposures can be rapidly titrated to lower levels.

6.2 TABLE OF STUDY ASSESSMENTS

Stage I

Study Assessment	Screening Period	Pre-Treatment (Night before infusion)	Pre-dose (–30 min)	Baseline Saline infusion (0-30 min)	Saline Infusion (30-60 min)	Intralipid® Infusion (60-90 min)	Intralipid®/ Fenoldopam (90~120 min)	Moxifloxacin / Fenoldopam (Day 2)[7]
Informed consent	X							
Medical history	X							
Chemistry and hematology[2]	X							
Urine pregnancy[2]	X	X						
Blood alcohol and urine drug screen	X	X						
12-lead ECG	X	X	X					X[3]
Vital signs	X	X			X[5]	X[5]	X[5]	X[5]
Physical exam	X	X						
Height and weight	X	X						
Interim history		X						
Study drug administration				X	X	X	X	X
Continuous 12-lead ECG (Holter)			<		X[6]		>	X
Extracted 12-lead ECG from Holter[4]				X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X
AE and SAE reporting		<			X			>

[1] As described in Section 9.7.3
[2] Women of childbearing potential only
[3] 4 hours post-administration of moxifloxacin
[4] See Table 17 below for times of extracted ECGs.
[5] See Table 13 for assessment schedule.
[6] Continuous 12 lead ECG (Holter) starts at -60 minutes
[7] NS administration prior to fenoldopam for 90 minutes to mimic day 1 NS infusion. HR and BP monitoring were to have mimicked Day 1 procedures during fenoldopam infusion.

Main Stage

Study Assessment	Screening Period	Pre-Treatment (Night before)	Baseline (Saline infusion, -1.5 to 0 hours)				Therapeutic Infusion (0 to 22 h 15 min)								Up-Titration Infusion	Supra-therapeutic Infusion[3] (23 to 23.3 hours)					Post-Infusion[3] (23.3 to 36 hours)				
	-14 Days to -3 Days	Day 0 and Day 7	-1.5 h	-1.0 h	-30 min	-15 min	2 h	4 h.	8 h	12 h	22 h	20 h	21 h	21.5 h	22 h	(22 h 15 min to 23 hours)	23 h	23h 5 min	23h 10 min	23h 15 min	23h 20 min	23.5 h	24 h	27 h	28 h	36 h
Informed consent	X																									
Medical history	X																									
Chemistry and hematology[1]	X																									
Urine pregnancy[2]	X	X																								
Blood alcohol and urine drug screen	X	X																								
Normal Saline Infusion (4 mL/min)[7]													X	X	X											
12-lead ECG	X	X			X			X							X											X
Vital Signs	X	X			X	X	<									X[3]										>
Physical exam	X																									
Height and weight	X	X																								
Interim history		X																								
Holter[6]			<		X	>						<			X	>										
Extracted 12-lead ECG				X	X		X		X				X	X	X	X[5]			X	X		X	X	X		
Concomitant medications	X	X																								
Pharmacokinetic samples[4]						X	X		X				X	X	X		X			X			X	X		
AE and SAE reporting		<													X											>

1 As described in Section 9.7.3
2 Women of childbearing potential only
3 See Table 14 for the exact times for Therapeutic Infusion, Supra-therapeutic Infusion, and Post-infusion Periods BP and HR times.
4 The sampling timepoints were: -10 min, 2 h 20 min, 8 h 20 min, 20 h 50 min, 21 h 20 min, 21 h 50 min, 23 h 5 min, 23 h 18 min, 24 h 20 min, and 27 h 20 min. Sample should have been drawn to accommodate extraction of ECGs from Holter.
5 See Table 18 below for times of extracted ECGs.
6 Holter electrodes were to be applied and recording no later than 90 minutes prior to infusion start.
7 NS was administered at 4 mL/min starting 20 h 45 min until 22h 15 min when fenoldopam infusion was initiated.

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