

Clinical and Statistical Review
B. Nhi Beasley, Pharm.D. and John Lawrence, Ph.D.
NDA 22-156, SN 000
Cleviprex™ (clevidipine butyrate)

TMC-CLV-03-01_00112_00004, was identified just after the study database was locked. The site was queried and confirmed that the starting dose was correct. Our SOP for unlocking databases typically allows changes for corrections related only to safety, primary endpoint or treatment assignment information. Since this one deviation was not considered to meet these criteria, the database was not unlocked to identify the patient as having a protocol deviation. Since no deviation was noted in the database, this event was not discussed in the CSR.

For the ECLIPSE studies, patient # TMC-CLV-03-04_00407_00006 was administered a bolus dose of clevidipine. This was reported as a protocol deviation in the CSR's patient listing. It was an oversight that this was not discussed in the text of the CSR.

During the ECLIPSE studies, dosing data were collected (in the eCRFs) in units of mL/hour and not in units of ug/kg/min. Units of mL/hour were chosen to provide consistency in reporting across the four different treatments (clevidipine, nicardipine, sodium nitroprusside and nitroglycerine) of the three ECLIPSE studies. Units of mL/hour, which were displayed by infusion pumps used in the hospital study sites, were chosen for data entry to minimize the potential for reporting errors that can occur with unit conversion. For the purpose of analyses, the dosing rate data (mL/hour) were converted to weight-based data (ug/kg/min).

Because of the focus on data entry in the form of mL/hour, edit checks for the units of ug/kg/min were not programmed. As a result, we were not aware of the additional cases of starting weight-based doses ≥ 0.5 ug/kg/min until you brought them to our attention.

The minimum infusion time in the ESCAPE trials was 30 minutes, or until bailout if needed. The maximum infusion time was one hour (or in ESCAPE-1 until induction of anesthesia, whichever occurred first).

Since the ECLIPSE studies infused drug for longer than 1 hour more restrictions were placed on the dose. Rates between 4.4 – 8.0 ug/kg/min were only allowed for 2 hours during a 24 hour period. The maximum infusion rate was not to be exceeded for any reason. Due to lipid load restrictions, no more than 500 mL of clevidipine infusion (formulated in 20% lipid) was to be administered in the first 24 hour period, and the maximum amount of lipid that may be administered was 2.5 g/kg/24h. Clevidipine, placebo or active control could be interrupted, restarted, or titrated up or down as required, to attain the desired BP effect.

In the ECLIPSE trials clevidipine or active control were subjectively initiated by the investigator (no predefined hypertension definition set) with treatment maintained as long as deemed necessary until discharge from the ICU. The active control was administered "per institutional practice". No specific instructions were given.

The dose used in severe hypertension (VELOCITY) was 2 mg/h doubled every 3 minutes to a maximum dose of 32 mg/h. If target BP was not reached after 30 minutes, an antihypertensive could be added with or without clevidipine. After 30 minutes, the desired SBP target could be altered, and the clevidipine infusion rate could be titrated to achieve the desired target. The total amount of lipid (placebo) administered was not to exceed 2.5 g/kg per 24 hours. The infusion

duration minimum and maximum were 18 and 96 hours. ID TMC-CLV-06-02_00101_00004 received an initial dose of 1 mg/hr, otherwise 125 subjects received an initial dose of 2 mg/hr.

6.1.3.3 BP measurements

In the ESCAPE studies blood pressure was measured before study drug administration (SDA), every minute during SDA (via arterial line), and for at least 30 minutes post study drug termination, or induction of anesthesia, whichever occurred first.

In the ECLIPSE trials, blood pressure (and HR) was recorded for 24 h following study drug initiation. Preoperatively, BP (and HR) measurements were taken every 15 minutes; intraoperatively BP (and HR) was recorded (cuff) every five minutes; postoperatively BP (and HR) was measured every 15 minutes for four hours, and then once every hour through 24 hours. These data were used to calculate the AUC. While these recorded measurements are sufficiently spaced to determine AUC, with clevidipine titration occurring every 90 seconds, **these records of BP are too infrequent to make appropriate assessments of investigator dosing.**

In the VELOCITY severe hypertension trial, BP was measured every 3 minutes until SBP was within the target range, then every 15 minutes for the next 2 hours, then hourly until initiation of transition to oral therapy. During the transition, BP (and HR) was measured every 15 minutes until 30 minutes after cessation of clevidipine infusion, and then at least hourly until study drug had been stopped for 6 hours.

6.1.3.4 Concomitant medications

In the ESCAPE studies, non-study medications and procedures for the treatment of hypertension were prohibited during the first 30 minutes of the study drug administration unless bailout was required. Drugs with antihypertensive properties were permitted during study drug administration if used for a condition other than hypertension. Use of sedatives, anesthetics, vasodilators, and beta blockers was recorded on the CRFs from the start of the procedure through 1 hour post study drug initiation.

In the ECLIPSE studies, the use of non-study drug medications and treatment procedures to specifically treat hypertension were discouraged, however the investigator could administer an alternative antihypertensive agent to lower BP as per institutional practice if a patient's BP was not uncontrolled with treatment drug, or if there was a safety concern.

In VELOCITY, use of an agent to treat hypertension within the 2 hours prior to clevidipine administration was not allowed. Use of non-study drug medications and treatment procedures to treat hypertension were strongly discouraged during study drug administration, especially during the first 30 minutes of the infusion. An alternate IV antihypertensive was allowed if the study drug did not adequately lower BP. During the 18 to 96 hour infusion period patients were to be transitioned to oral antihypertensive treatment as necessary. The oral antihypertensive agent was initiated approximately 1 hour before the anticipated cessation of clevidipine infusion, but no earlier than the 18 hour time point. The reason for oral antihypertensive agents was not captured.

6.1.3.5 Analysis

For the ESCAPE primary efficacy analysis (incidence of bailout in the first 30 minutes in the mITT population), missing bailout records were imputed with yes for clevidipine and no for placebo. No bailout was considered treatment success. While it is highly likely that an antihypertensive will easily show an effect with this endpoint when compared to placebo, it does not quantify the effect. All quantification of efficacy was done by the reviewer. For the secondary endpoint of time to target BP lowering effect, Kaplan-Meier survival curves for time to target effect were presented according to treatment. Change from baseline in MAP was compared by analysis of covariance (ANCOVA) for absolute changes with baseline MAP as the covariate, and by analysis of variance for percent changes from baseline. Reasons for bailout were summarized by treatment group and compared using the Chi-square test. Missing causalities were not imputed.

Dr. John Lawrence reviewed the sponsor's primary and secondary analysis for the ESCAPE trials and found them to be acceptable.

For the ECLIPSE studies, the effect of study drug on BP control was compared in the two treatment groups by calculating AUC related to the time (min) that each patient's SBP was outside the target range of SBP 65 – 135 mmHg intraoperatively and 75-145 mmHg pre- and post-operatively. AUC was calculated based on data collected from the initiation of study drug infusion through the permanent removal of the arterial line or 24 hours post study drug initiation, whichever occurred first. If the time of last removal of arterial line was missing, it was imputed by ICU discharge time. AUC was normalized per hour and expressed as mmHg*min/h and abbreviated as AUC_{SBP-D}. Individual AUC_{SBP-D} values were ranked, regardless of treatment group, in order to define patient quartiles. The prevalence of patients from each treatment group within each quartile was compared using the Cochran Mantel-Haenszel row mean modified-relative to an identified distribution scores test.

The VELOCITY study was designed without formal calculation of sample size. No statistical hypothesis testing was planned. The final SAP was approved after study conclusion. All analyses were descriptive. The last observation prior to the start of study drug infusion was used as baseline. The initial target range was used in all calculations. Patients not reaching the target within the first 30 minutes were censored at 30 minutes.

Randomized patients were all patients who met pre-randomization inclusion/exclusion criteria and who were randomized to a treatment group in the study.

The modified intent-to-treat (mITT) population consisted of all patients who were randomized and met the post-randomization criterion (if applicable) of hypertension prior to the initiation of study drug. This was the primary population for efficacy. Comparisons were performed according to the randomized treatment, regardless of which treatment a patient actually received. For the VELOCITY (06-02) trial, the mITT population was defined as all patients who were enrolled into the trial via interactive voice response system (IVRS) whose SBP was above the pre-specified target range at the time of study drug initiation. The mITT population was used for the efficacy endpoint. The dose-response population consisted of mITT patients who were

treated with clevidipine and had at least one BP measurement during infusion. The extended exposure subset (EES) included all patients who received continuous study drug for at least 18 hours.

The safety population included all randomized patients who were administered study drug. This was the primary population for the safety analysis; comparisons were performed according to the actual treatment received.

6.1.4 Efficacy Findings

6.1.4.1 ESCAPE

6.1.4.1.1 Disposition

Most subjects were male and White. There was an under representation of Blacks in the ESCAPE studies. (The severe hypertension group (VELOCITY study) was mostly Blacks). Usually the distribution of patient characteristics is well balanced between groups in randomized trials. This trial had some imbalances that are probably partly due to the post-randomization criteria. The placebo patients had higher mean BP, more OPCAB surgeries, normal renal function, severe renal function, diabetes and PVD. The clevidipine treated patients included more elderly, valve replacements and repairs, mild renal impairment, and CHF. The mean BMI indicates that the average subject was overweight (BMI ≥ 30 kg/m² defines obese.).

Table 9. ESCAPE patient disposition, n (%)

Demo & Baseline	CLV N=114	Pbo N=101	Total N=215
Male, n (%)	84 (73.7)	74 (73.3)	158 (73.5)
Female, n (%)	30 (26.3)	27 (26.7)	57 (26.5)
Age yrs, mean (SD)	64.7 (22.4)	62.0 (11.03)	63.4 (11.30)
Age ≥ 65 years, n (%)	66 (57.9)	35 (34.7)	101 (47.0)
Race, n (%)			
White	91 (79.8)	78 (77.2)	169 (78.6)
Black	9 (7.9)	3 (3.0)	12 (5.6)
Other	14 (12.3)	20 (19.8)	34 (15.8)
Weight kg, mean (SD)	85.7 (18.02)	86.9 (20.43)	86.3 (19.15)
BMI kg/m², mean (SD)	29.3 (6.37)	29.3 (5.75)	29.3 (6.07)
SBP mmHg, mean (SD)	161.9 (21.80)	174(21.58)	162.9 (21.67)
DBP mmHg, mean (SD)	72.6 (10.50)	75.2 (11.68)	73.8 (11.12)

Table 10. ESCAPE patient disposition (continued)

Demographics/Baseline characteristics	Clevidipine (N=114)	Placebo (N=101)	Total (N=215)
Hypertensive Severity[^], n (%)			
Stage 1	55 (48.2)	39 (38.6)	94 (43.7)
Stage 2	36 (31.6)	41 (40.6)	77 (35.8)
Severe Stage 2	20 (17.5)	20 (19.8)	40 (18.6)
Initiation of Infusion#, n (%)			
Pre-operative	52 (45.6)	51 (50.5)	103 (47.9)
Intra-operative	0 (0.0)	0 (0.0)	0 (0.0)
Post-operative	61 (53.5)	49 (48.5)	110 (51.2)
Unknown	1 (0.9)	1 (1.0)	2 (0.9)
Renal Impairment[*], n (%)			
Normal	65 (57.0)	62 (61.4)	127 (59.1)
Mild	39 (34.2)	25 (24.8)	64 (29.8)
Moderate	8 (7.0)	6 (5.9)	14 (6.5)
Severe	0 (0.0)	4 (4.0)	4 (1.9)
Liver Function Status[*], n (%)			
Normal	94 (82.5)	85 (84.2)	179 (83.3)
Abnormal	8 (7.0)	7 (6.9)	15 (7.0)
Perioperative Procedure Type#, n (%)			
CABG	64 (56.1)	62 (61.4)	126 (58.6)
MIDCAB	1 (0.9)	1 (1.0)	2 (0.9)
OPCAB	13 (11.4)	18 (17.8)	31 (14.4)
Valve Replacement	19 (16.7)	9 (8.9)	28 (13.0)
Valve Repair	2 (1.8)	0 (0.0)	2 (0.9)
Combination	14 (12.3)	11 (10.9)	25 (11.6)
Surgery Not Classified	0 (0.0)	0 (0.0)	0 (0.0)
No Surgery	1 (0.9)	0 (0.0)	1 (0.5)

Continued

Demographics/Baseline characteristics	Clevipidine (N=114)	Placebo (N=101)	Total (N=215)
Disease Subgroup[§], n (%)			
Diabetes	40 (35.1)	42 (41.6)	82 (38.1)
CHF	18 (15.8)	11 (10.9)	29 (13.5)
Stroke	13 (11.4)	10 (9.9)	23 (10.7)
Peripheral Vascular Disease	16 (14.0)	19 (18.8)	35 (16.3)

Source: Table 6.1, Appendix 6.2

Individual study data come from the TMC-CLV-03-01 and TMC-CLV-03-02 studies.

Percentages are relative to the total number of patients who were to undergo cardiac surgery (perioperative hypertension).

^ Stage 1: 140<=SBP<160 mmHg and/or 90<=DBP<100 mmHg, Stage 2: 160<=SBP<180 mmHg and/or 100<=DBP<115 mmHg, Severe Stage 2: SBP>=180 mmHg and/or DBP>=115 mmHg.

* 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.

§ A patient can belong to more than one disease subgroup.

Adapted from Sponsor's Table 3, pg 26 of 264 of ISE

6.1.4.1.2 Bailout (Efficacy endpoint)

For the ESCAPE primary endpoint, clevidipine had a higher success rate compared to placebo, 92.1 % vs. 18.8%, respectively (see table).

Table 11. Primary and secondary efficacy endpoints (ESCAPE-1 and -2)

Parameter	Randomized treatment		Treatment difference (%)		
	Clevipidine N=114, n (%)	Placebo N=101, n (%)	Estimate	95(%) CI	p value
Number of Patients with Success (Patients who did not bailout)	105 (92.1)	19 (18.8)	73.3	64.2 – 82.4	<0.001
Number of Patients with Bailout	9 (7.9)	82 (81.2)			
Reason for Bailout					
Lack of efficacy	0 (0.0)	55 (67.1)			
Safety reasons	3 (33.3)	0 (0.0)			
Treatment failure	6 (66.7)	27 (32.9)			

Source: Table 6.3, Appendix 6.2.

Individual study data come from the TMC-CLV-03-01 and TMC-CLV-03-02 studies.

P values are based on Chi-square test.

Adapted from Sponsor's Table 5, pg 31 of 264 of ISE

6.1.4.1.3 Study drug exposure

Because the investigator could start, stop, and titrate at his discretion and all Phase III studies were titration to effect studies, the assessment of dose - BP effect was complicated. Additionally, reasons for dose changes were not noted in the CRF. A summary of study drug exposure in the ESCAPE trials are shown below. The reviewer did not find any major discrepancies in the table.

Table 12. Study drug exposure in ESCAPE -1 and -2

Parameter	Treatment	
	Clevidipine (N=114)	Placebo (N=101)
Overall infusion duration (h)		
Mean (SD)	0.53 (0.227)	0.36 (0.165)
Minimum, Maximum	0.07, 1.00	0.05, 0.83
On-drug infusion duration (h)		
Mean (SD)	0.50 (0.224)	0.35 (0.158)
On-drug infusion duration (h)		
Minimum, Maximum	0.07, 1.00	0.05, 0.80
Total Infusion volume (mL)		
Mean (SD)	10.3 (10.28)	14.6 (11.02)
Average volume infusion rate (mL/h)		
Mean (SD)	19.7 (17.59)	38.9 (18.60)
Total Infusion dose (mg)		
Mean (SD)	5.13 (5.141)	

Adapted from Sponsor's Table 4, pg 30 of 264 of ISE

Table 13. Reviewer's summary of clevidipine exposure in ESCAPE (not reported in previous table)

	ESCAPE
Ave infusion rate, mg/hr (mean , 90% CI)	9.84 (8.47, 11.21)
Ave infusion rate, mg/hr (min)	1.35
Ave infusion rate, mg/hr (max)	40.25
Ave infusion rate, ug/kg/min (mean , 90% CI)	1.88 (1.63, 2.13)
Ave infusion rate, ug/kg/min (min)	0.37
Ave infusion rate, ug/kg/min (max)	6.47

In contrast to the mean infusion rate, the median was 5.95 mg/hr.

6.1.4.1.4 Effect on BP over time

The reviewer used a random effects model to find the mean change from baseline in BP over time in both groups. The predicted means at each time point for each group are shown in the figures that follow.

Figure 12. Change in SBP over 30 minutes, ESCAPE-1(periop)

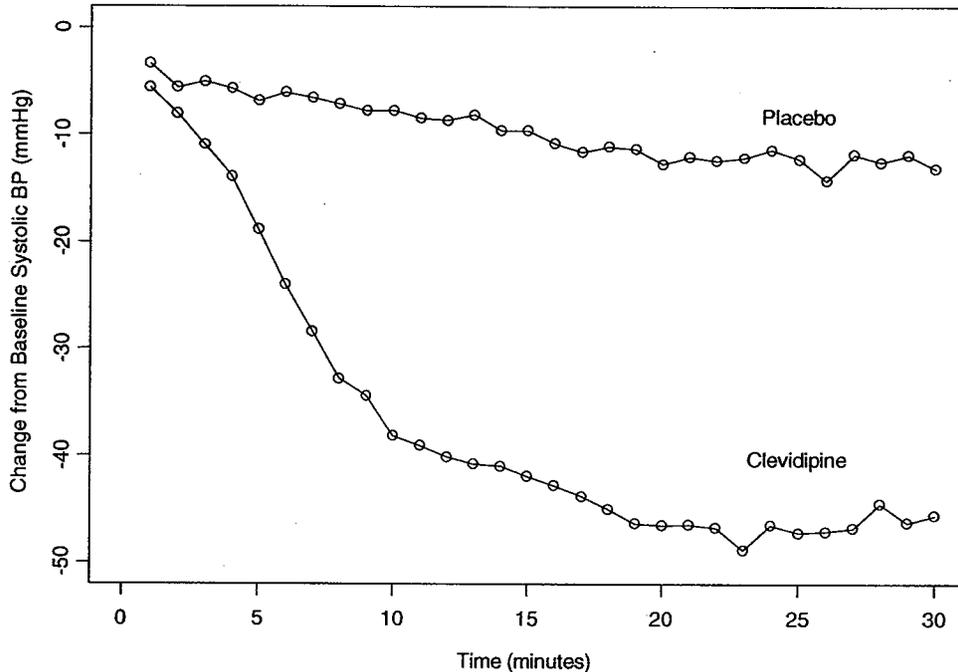
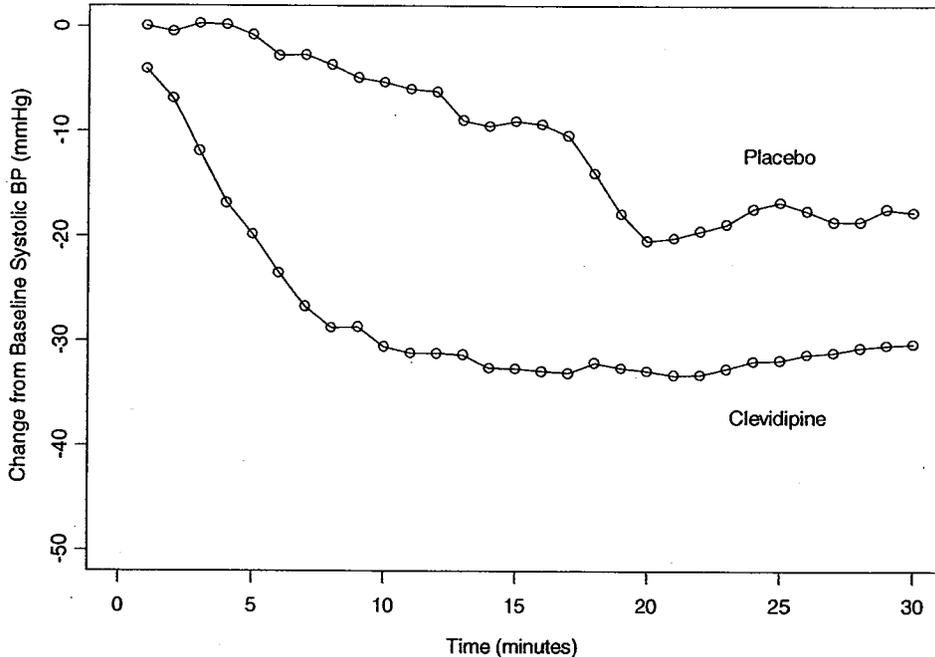


Figure 13. Change in SBP over 30 minutes, ESCAPE-2 (postop)



There was a statistically significant difference in mean effect of 4 % at 2 minutes in the postoperative setting (ESCAPE-2) and of 5% at 4 minutes in the perioperative setting (ESCAPE-1) (see table). The maximal mean effect on SBP was about 20% perioperative and 17% postoperative, however the ESCAPE studies were titration to effect studies (15% reduction in SBP).

Table 14. Clevidipine Effect on SBP – ESCAPE-1 and -2

Minutes After Baseline	ESCAPE-1 Estimated Mean Difference Between Groups (%) ¹	P-value ²	ESCAPE-2 Estimated Mean Difference Between Groups (%) ³	P-value ⁴
1	-2.2 (-1)	0.499	-4.1 (-3)	0.196
2	-2.4 (-1)	0.449	-6.4 (-4)	0.044
3	-5.9 (-3)	0.066	-12.2 (-8)	<0.001
4	-8.2 (-5)	0.009	-17.1 (-11)	<0.001
5	-12.0 (-7)	<0.001	-19.1 (-13)	<0.001
6	-17.9 (-10)	<0.001	-20.8 (-14)	<0.001
7	-21.9 (-12)	<0.001	-24.0 (-16)	<0.001
8	-25.6 (-14)	<0.001	-25.1 (-17)	<0.001
9	-26.6 (-15)	<0.001	-23.8 (-16)	<0.001
10	-30.4 (-17)	<0.001	-25.2 (-17)	<0.001
11	-30.6 (-17)	<0.001	-25.2 (-17)	<0.001
12	-31.4 (-18)	<0.001	-25.0 (-17)	<0.001
13	-32.6 (-18)	<0.001	-22.4 (-15)	<0.001
14	-31.4 (-18)	<0.001	-23.1 (-15)	<0.001
15	-32.3 (-18)	<0.001	-23.6 (-16)	<0.001
16	-32.0 (-18)	<0.001	-23.6 (-16)	<0.001
17	-32.2 (-18)	<0.001	-22.7 (-15)	<0.001
18	-33.9 (-19)	<0.001	-18.1 (-12)	<0.001
19	-35.0 (-20)	<0.001	-14.7 (-10)	<0.001
20	-33.8 (-19)	<0.001	-12.4 (-8)	0.001
21	-34.4 (-19)	<0.001	-13.1 (-9)	0.001
22	-34.3 (-19)	<0.001	-13.7 (-9)	0.001
23	-36.7 (-21)	<0.001	-13.8 (-9)	0.001
24	-35.1 (-20)	<0.001	-14.6 (-10)	0.001
25	-35.0 (-20)	<0.001	-15.1 (-10)	<0.001
26	-32.8 (-18)	<0.001	-13.7 (-9)	0.002
27	-34.9 (-20)	<0.001	-12.5 (-8)	0.005
28	-31.9 (-18)	<0.001	-12.1 (-8)	0.009
29	-34.4 (-19)	<0.001	-13.0 (-9)	0.006
30	-32.4 (-18)	<0.001	-12.6 (-8)	0.009

¹Estimates from a random effects model with time as a categorical variable, treatment, and the interaction (a total of 60 fixed effect terms), intercept and time (continuous) effects are random (each subject has a random intercept and slope). Percent is relative to the average baseline systolic blood pressure.

²From the random effects model assuming the linear combination of fixed effects parameters have a t-distribution with 101 degrees of freedom under the null hypothesis that the treatment effects are 0.

³Estimates from a random effects model with time as a categorical variable, treatment, and the interaction (a total of 60 fixed effect terms), intercept and time (continuous) effects are random (each subject has a random intercept and slope). Percent is relative to the average baseline systolic blood pressure.

⁴From the random effects model assuming the linear combination of fixed effects parameters have a t-distribution with 108 degrees of freedom under the null hypothesis that the treatment effects are 0.

The data are shown for DBP on the following pages.

Figure 14. *Change in DBP over 30 minutes, ESCAPE-1(periop)*

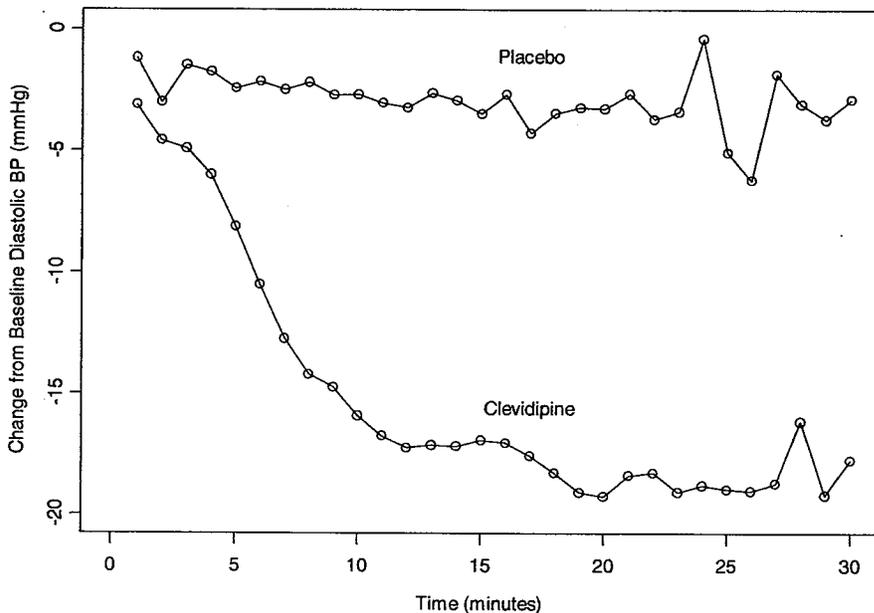
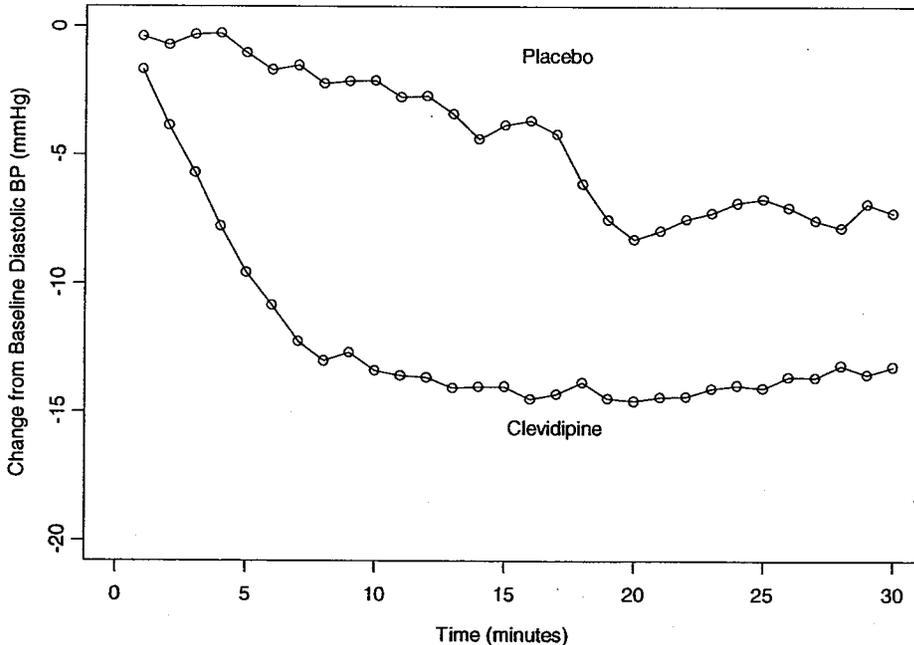


Figure 15. *Change in DBP over 30 minutes, ESCAPE-2(postop)*



There was a statistically significant difference in mean effect of 8 % at 3 minutes in the postoperative setting (ESCAPE-2) and of 5% at 4 minutes in the perioperative setting (ESCAPE-1) (see table). The maximal mean effect on DBP was about 15-20%. Similar to SBP, the maximal effect was smaller in the ESCAPE-2 study. It is noted that ESCAPE-2 subjects only needed a SBP \geq 140 mmHg within 4 hours of arrival in the postop setting to qualify (vs. a preop SBP \geq 160 mmHg in ESCAPE-1).

Table 15. Clevidipine Effect on DBP – ESCAPE-1 and -2

Minutes After Baseline	ESCAPE-1 Estimated Mean Difference Between Groups (%) ¹	P-value ²	ESCAPE-2 Estimated Mean Difference Between Groups (%) ³	P-value ⁴
1	-1.9 (-2)	0.312	-1.3 (-2)	0.391
2	-1.6 (-2)	0.407	-3.2 (-4)	0.040
3	-3.4 (-4)	0.067	-5.4 (-8)	0.001
4	-4.2 (-5)	0.023	-7.5 (-11)	<0.001
5	-5.7 (-7)	0.002	-8.6 (-12)	<0.001
6	-8.4 (-11)	<0.001	-9.2 (-13)	<0.001
7	-10.3 (-13)	<0.001	-10.8 (-15)	<0.001
8	-12.0 (-15)	<0.001	-10.8 (-15)	<0.001
9	-12.0 (-16)	<0.001	-10.6 (-15)	<0.001
10	-13.2 (-17)	<0.001	-11.3 (-16)	<0.001
11	-13.7 (-18)	<0.001	-10.9 (-15)	<0.001
12	-14.0 (-18)	<0.001	-11.0 (-15)	<0.001
13	-14.5 (-19)	<0.001	-10.7 (-15)	<0.001
14	-14.3 (-18)	<0.001	-9.6 (-14)	<0.001
15	-13.5 (-17)	<0.001	-10.2 (-14)	<0.001
16	-14.4 (-18)	<0.001	-10.8 (-15)	<0.001
17	-13.3 (-17)	<0.001	-10.1 (-14)	<0.001
18	-14.8 (-19)	<0.001	-7.7 (-11)	<0.001
19	-15.9 (-20)	<0.001	-7.0 (-10)	<0.001
20	-16.0 (-21)	<0.001	-6.3 (-9)	0.002
21	-15.7 (-20)	<0.001	-6.5 (-9)	0.002
22	-14.6 (-19)	<0.001	-6.9 (-10)	0.001
23	-15.7 (-20)	<0.001	-6.8 (-10)	0.001
24	-18.4 (-24)	<0.001	-7.1 (-10)	0.001
25	-13.9 (-18)	<0.001	-7.4 (-10)	0.001
26	-12.8 (-17)	<0.001	-6.6 (-9)	0.004
27	-16.9 (-22)	<0.001	-6.1 (-9)	0.008
28	-13.1 (-17)	<0.001	-5.4 (-8)	0.024
29	-15.5 (-20)	<0.001	-6.6 (-9)	0.006
30	-14.9 (-19)	<0.001	-6.0 (-8)	0.016

¹Estimates from a random effects model with time as a categorical variable, treatment, and the interaction (a total of 60 fixed effect terms), intercept and time (continuous) effects are random (each subject has a random intercept and slope). Percent is found by dividing by the average baseline diastolic values.

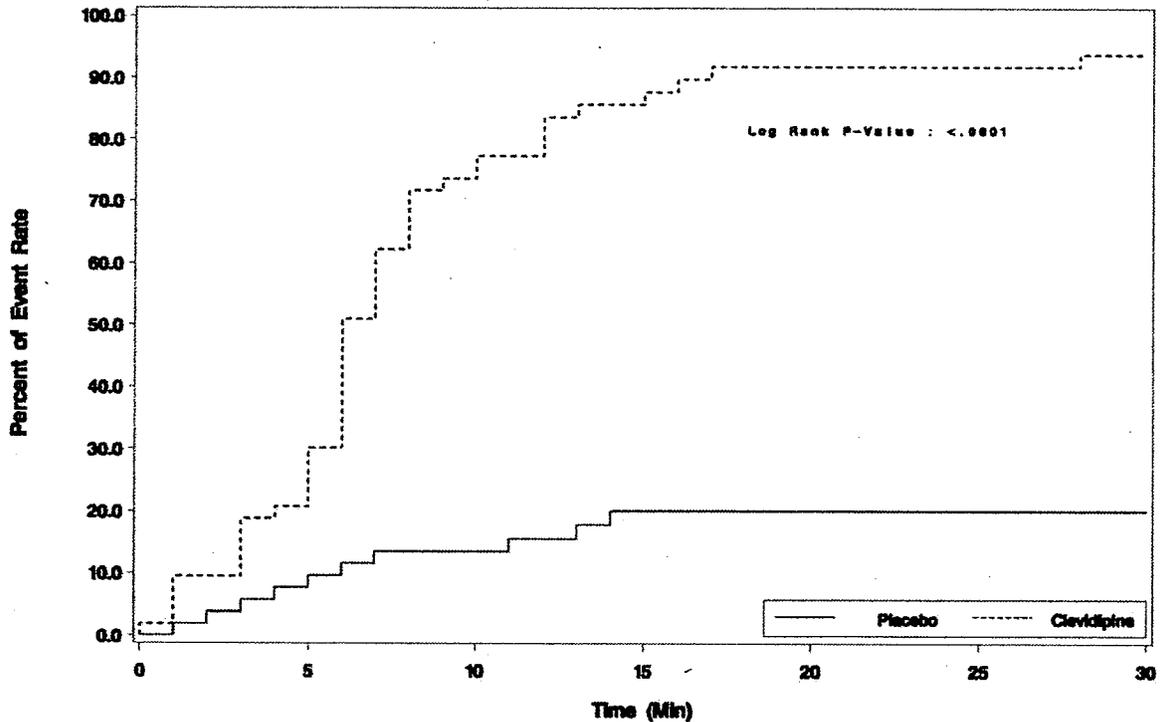
²From the random effects model assuming the linear combination of fixed effects parameters have a t-distribution with 101 degrees of freedom under the null hypothesis that the treatment effects are 0.

³Estimates from a random effects model with time as a categorical variable, treatment, and the interaction (a total of 60 fixed effect terms), intercept and time (continuous) effects are random (each subject has a random intercept and slope). Percent is found by dividing by the average baseline diastolic values.

⁴From the random effects model assuming the linear combination of fixed effects parameters have a t-distribution with 108 degrees of freedom under the null hypothesis that the treatment effects are 0.

A median time of 6 minutes (95% CI, 6 to 7 min) was the time to reach target SBP reduction of 15% (sponsor's secondary endpoint) in the ESCAPE studies (see figures). The time in the placebo group was not estimable.

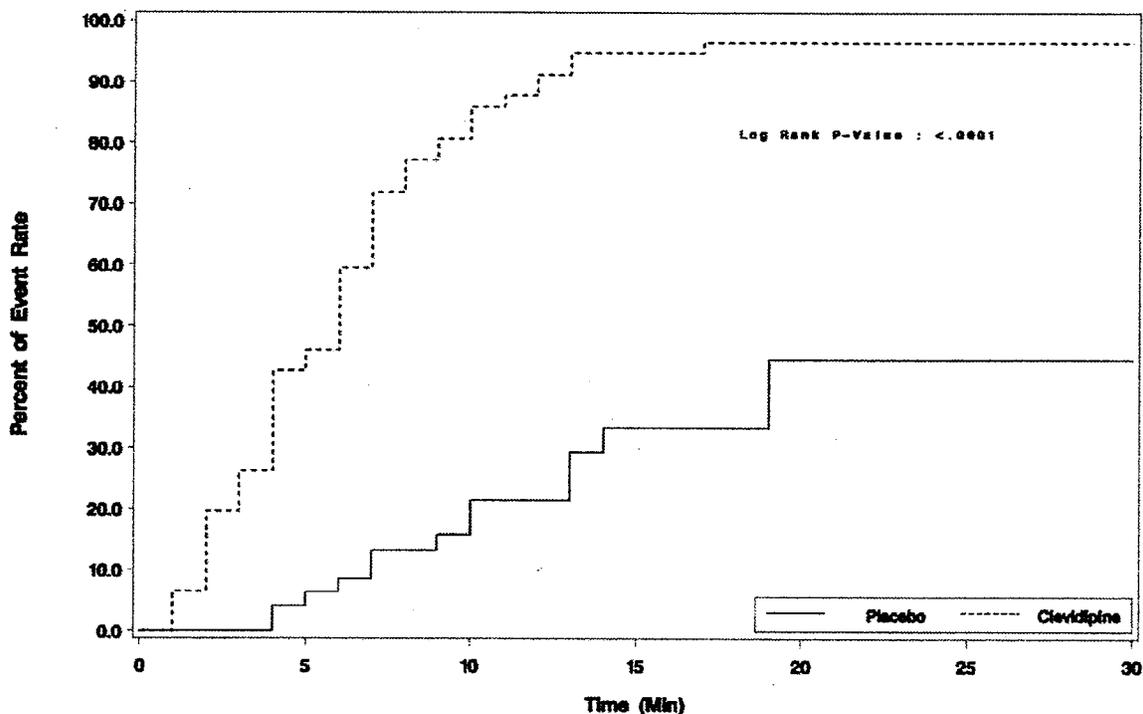
Figure 16. Event rate estimate of time to 15% SBP reduction ESCAPE-1



Kaplan Meier, mITT population

Taken from Sponsor's Figure 3, pg 43 of 1827, ESCAPE-1 study report

Figure 17. Event rate estimate of time to 15% SBP reduction ESCAPE-2



Kaplan Meier, mITT population

Taken from Sponsor's Figure 3, pg 44 of 2183, ESCAPE-2 study report

6.1.4.1.5 Concomitant medications that affect BP

The use of sedatives and vasodilator/beta blockers were recorded from the start of the operation through 1 hour post study drug initiation. Drugs with antihypertensive properties were permitted during SDA if used for an indication other than hypertension. The most common sedative taken during this period for both clevidipine and placebo was versed (ESCAPE-1) and propofol (ESCAPE-2). The most common vasodilator or beta blocker taken for both groups was nitroglycerin. Very few subjects took beta-blockers.

Table 16. Concomitant sedative or vasodilator during SDA (30 min), safety population, n (%)

	ESCAPE-1		ESCAPE-2	
	Pbo (n=51)	CLV (n=53)	Pbo (n=49)	CLV (n=61)
Patients ¹	17	11	56	52
Patients on VD	10 (19.6)	2 (3.8)	20 (40.8)	27 (44.3)
Patients on sedative	7 (13.7)	9 (17)	36 (73.5)	25 (41.0)
Nitroglycerin	9 (17.6)	1 (1.9)	22 (44.9)	22 (36.1)
Beta blocker	0 (0)	2 (3.8)	3 (6.1)	0 (0)
CCB	1 (2.0)	0 (0)	1 (2.0)	0 (0)
Versed	7 (13.7)	3 (5.7)	2 (4.1)	1(1.6)

Morphine	0 (0)	2 (3.8)	10 (20.4)	10 (16.4)
Other sedative	1 (2.0)	4 (7.6)	16 (33)	27 (44)

One patient may be counted twice in table

1 – sum of those on vasodilators and sedatives.

VD=vasodilator

Taken from sponsor Tables 4.1.2 and 4.2.2, ESCAPE-1 and -2

6.1.4.2 ECLIPSE

6.1.4.3 Disposition

For the most part, patient disposition in the ECLIPSE trials was similar to the ESCAPE study patients. There were a few notable differences. The elderly are more balanced in these trials compared to ESCAPE which had more elderly in the CLV group. The baseline BP were lower in these cardiac surgery patients (by about 20-40 mm Hg SBP), and there were less severe Stage 2 patients in the ECLIPSE studies. Some ECLIPSE patients were dosed intraoperatively, when clevidipine clearance is slower, while ESCAPE patients were dosed pre- or post-operatively. The degree of renal impairment, disease subgroups, and type of surgery were more balanced with the exception of more valve repairs in the clevidipine group.

Table 17. ECLIPSE patient disposition, n(%)

Demo & Baseline	CLV N=755	AC N=757	Total N=1512
Male, n (%)	545 (72.2)	564 (74.5)	1109 (73.3)
Female, n (%)	210 (27.8)	193 (25.5)	403 (26.7)
Age yrs, mean (SD)	64.7 (10.7)	65.0 (10.9)	64.8 (10.8)
Age ≥ 65 years, n (%)	389 (51.9)	408 (53.9)	797 (52.7)
Race, n (%)			
White	618 (81.9)	629 (83.1)	1247 (82.5)
Black	76 (10.1)	65 (8.6)	141 (9.3)
Other	61 (8.1)	63 (8.3)	124 (8.2)
Weight kg, mean (SD)	87.5 (19.3)	87.4 (20.0)	87.4 (19.7)
BMI kg/m², mean (SD)	29.4 (5.9)	29.4 (6.0)	29.4 (5.9)
SBP mmHg, mean (SD)	141.4 (22.7)	139.6 (25.8)	140.5 (24.3)
DBP mmHg, mean (SD)	70.2 (13.4)	69.8 (15.2)	70.0 (14.3)

AC=active control, either SNP, NTG or NIC

Table 18. ECLIPSE patient disposition (continued)

Variable	Clevipidine (N=755)		All Active Comparators (N=757)		Total Number of Patients (N=1512)	
Hypertensive Severity[^], n (%)						
Stage 1	267	(35.4)	236	(31.2)	503	(33.3)
Stage 2	110	(14.6)	96	(12.7)	206	(13.6)
Severe Stage 2	41	(5.4)	53	(7.0)	94	(6.2)
Perioperative Procedure Type[#], n (%)						
CABG	475	(62.9)	485	(64.1)	960	(63.5)
MIDCAB	0	(0.0)	0	(0.0)	0	(0.0)
OPCAB	106	(14.0)	99	(13.1)	205	(13.6)
Valve Replacement	80	(10.6)	78	(10.3)	158	(10.4)
Valve Repair	24	(3.2)	10	(1.3)	34	(2.2)
Combination	67	(8.9)	84	(11.1)	151	(10.0)
Surgery Not Classified	2	(0.3)	1	(0.1)	3	(0.2)
No Surgery	1	(0.1)	0	(0.0)	1	(0.1)
Initiation of Infusion[#], n (%)						
Pre-operative	144	(19.1)	153	(20.2)	297	(19.7)
Intra-operative	306	(40.6)	290	(38.3)	596	(39.4)
Post-operative	301	(39.9)	311	(41.1)	612	(40.5)
Unknown	3	(0.4)	3	(0.4)	6	(0.4)
Renal Impairment[*], n (%)						
Normal	402	(53.2)	391	(51.7)	793	(52.4)
Mild	229	(30.3)	244	(32.2)	473	(31.3)
Moderate	56	(7.4)	58	(7.7)	114	(7.5)
Severe	16	(2.1)	13	(1.7)	29	(1.9)
Liver Function Status[*], n (%)						
Normal	616	(81.6)	613	(81.0)	1229	(81.3)
Abnormal	43	(5.7)	56	(7.4)	99	(6.5)

Variable	Clevipine (N=755)	All Active Comparators (N=757)	Total Number of Patients (N=1512)
Disease Subgroup[§], n (%)			
Diabetes	269 (35.6)	272 (35.9)	541 (35.8)
CHF	143 (18.9)	136 (18.0)	279 (18.5)
Stroke	93 (12.3)	84 (11.1)	177 (11.7)
Peripheral Vascular Disease	117 (15.5)	112 (14.8)	229 (15.1)

Source: Table 7.1, Appendix 6.2

Individual study data come from the TMC-CLV-03-03, TMC-CLV-03-04, and TMC-CLV-03-05 studies.

Percentages are relative to the total number of patients who were to undergo cardiac surgery (perioperative hypertension).

^ Stage 1: 140 ≤ SBP < 160 mmHg and/or 90 ≤ DBP < 100 mmHg, Stage 2: 160 ≤ SBP < 180 mmHg and/or 100 ≤ DBP < 115 mmHg, Severe Stage 2: SBP ≥ 180 and/or DBP ≥ 115 mmHg.

* 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.

§ A patient can belong to more than one disease subgroup.

6.1.4.3.1 Efficacy Endpoint

The drug effect on BP was analyzed as the AUC of SBP outside of a predefined range, AUC_{SBP-D}, of 65-135 mmHg intraoperatively and 75-145 mmHg pre- and post-operatively. Overall, the AUC_{SBP-D} was lower for clevidipine than for active comparator (see table). Similar observations were observed for whites, males and age ≥ 65 years. This does not suggest a race or gender effect, there just weren't many subjects for differences to be found.

Table 19. AUC SBP outside of the predefined range, ECLIPSE (Mean ± SD)

Variable	CLV	All active comparators	p-value
AUC _{SBP-D} outside	22.45 (57.0)	40.41 (100.9)	< 0.001
AUC _{SBP-D} above	20.45 (56.4)	36.12 (92.4)	< 0.001
AUC _{SBP-D} below	1.99 (9.1)	4.29 (42.1)	0.037

AUC_{SBP-D} = AUC SBP outside of a predefined range

Adapted from sponsor's Table 10, pg 42 of 264, ISE

A comparison by study showed no statistically significant differences between clevidipine and NIC-treated patients with regard to the median duration of AUC_{SBP-D} normalized per hour, or AUC_{SBP-D} above or below the target range. Clevidipine had a significantly lower AUC_{SBP-D} than SNP (4.37 vs. 10.5 mmHg x min/h, respectively, p=0.0027) and NTG (4.14 vs. 8.87 mmHg x min/h, respectively, p=0.0006).

Although not an endpoint, the percentage of time in the prespecified BP range was slightly greater for the clevidipine treated subjects compared to active controls, (95.7 ± 7.8% vs. 93.5% ± 11.1%) respectively.

For the other secondary efficacy endpoint, an alternative IV antihypertensive was not needed in 52.5% of patients versus 49.1% of all active comparators. The most frequently used classes of antihypertensives are shown in the table below.

Table 20. Top five alternative antihypertensive class, ECLIPSE

	ECLIPSE-SNP (%)		ECLIPSE-NTG (%)		ECLIPSE-NIC (%)	
	CLV (%) n=297	SNP (%) n=284	CLV (%) n=270	NTG (%) n=278	CLV (%) n=188	NIC (%) n=195
Patients taking ≥ 1 med	42.8	52.8	57.8	56.8	40.4	39.5
Beta blockers selective	30	31	35.6	34.9	22.9	39.5
Organic nitrates	10.1	16.9	15.2		7.4	6.7
ACE inhibitors	5.1	11.6	6.7	8.3	10.1	8.2
SNP	3.4			10.8		2.6
dihydropyridines	3.0	6.0	5.6	7.2	4.8	
Alpha, beta blocker					4.3	
Hydralazine		2.1				2.6
Beta blocker nonselective			3.7	6.8		

Data from Sponsor's Table 6.2.2. –SNP report, NTG report and NIC report

The reasons for use are shown in the table below. Between 40-60% of patients treated with CLV required an alternative antihypertensive agent for the treatment of hypertension in ECLIPSE. The use of an alternative antihypertensive was more common with SNP, but was similar between clevidipine and the other active comparators. (It is noted that the sponsor's written conclusion on pg 47 of 264 of the ISE differs from this reviewer's observation. The sponsor states that the use of alternative antihypertensives was more common in the SNP, NTG and combined AC groups.) The use of an agent for ischemia was more common with clevidipine.

Table 21. Reasons for alternative antihypertensive agent, ECLIPSE

	ECLIPSE-SNP (%)		ECLIPSE-NTG (%)		ECLIPSE-NIC (%)	
	CLV (%) n=297	SNP (%) n=284	CLV (%) n=270	NTG (%) n=278	CLV (%) n=188	NIC (%) n=195
hypertension	45.1	55.3	57.8	56.8	40.4	39.5
ischemia	13.5	12.7	9.3	5.4	9.0	6.7
Anti-spasmodic	10.4	12.0	5.2	3.2	3.2	2.1
other	10.4	9.2	5.2	4.3	5.9	5.1
Anti-arrhythmic	6.7	7.0	8.1	6.5	3.7	4.1
tachycardia	4.4	5.3	5.2	3.2	3.7	3.1

Data from Sponsor's Table 6.2.3. –SNP report, NTG report and NIC report

6.1.4.3.2 Drug exposure

The sponsor states that clevidipine has a shorter median overall infusion duration and on-drug infusion duration than all the active comparators combined. However, there were no specific dosing instructions given for the other active treatments. Nitroglycerin could have also been

used as an anti ischemic. The sponsor reports a lower infusion volume for clevidipine, but asserts that this probably due to the differences in reconstitution. In the sponsor's ISE, section 4.3.2., the sponsor reports an initial infusion rate of 2.4 mg/hr (mean) with a min of 0.05 and a max of 31.2 mg/hr. This is different than what the reviewer found in her analysis of the data. Patient TMC-CLV-03-04_00407_00006) received a bolus dose of 125 mg/hr and was excluded from this analysis per the sponsor. The average infusion rate was 4.49 mg/hr with a min of 0.2 and a max of 34.1 mg/h. The maximum reported infusion rate was 56 mg/hr.

The reviewer's summary statistics are shown in the table below (mean data). The sponsor shows median data in their exposure tables in the individual study reports. The ISE, Table 8 (pg 38 of 264) also contains mean data. The reviewer did not find any major discrepancies with the sponsor's summary statistics on exposure compared to her own analysis. No comparisons were done with the active comparators since it is not known if differences between clevidipine and the active comparators weren't due to the fact that investigators were not given explicit instructions on appropriate dosing of the active comparators.

Table 22. Reviewer's summary of clevidipine exposure in ECLIPSE

	ECLIPSE-all	ECLIPSE-SNP	ECLIPSE-NTG	ECLIPSE-NIC
Ave infusion rate, mg/hr (mean, 90% CI)	4.5 (4.3, 4.7)	4.4 (4.0, 4.7)	4.20 (3.9, 4.5)	5.1 (4.6, 5.6)
Ave infusion rate, mg/hr (min)	0.2	0.2	0.9	0.2
Ave infusion rate, mg/hr (max)	34.1	34.1	20.7	31.2
Ave infusion rate, ug/kg/min (mean, 90% CI)	0.9 (0.8, 0.9)	0.8 (0.8, 0.9)	0.81 (0.7, 0.9)	1.0 (0.9, 1.1)
Ave infusion rate, ug/kg/min (min)	0.03	0.05	0.14	0.03
Ave infusion rate, ug/kg/min (max)	5.0	4.9	4.2	5.0
Total actual infusion duration, hr (mean, 90% CI)	8.2 (7.6, 9.0)	8.2 (7.1, 9.2)	7.5 (6.3, 8.7)	9.4 (8.1, 10.7)
Total actual infusion duration, hr (min)	0.02	0.02	0.05	0.08
Total actual infusion duration, hr (max)	127.2	89.2	127.2	73.9

6.1.4.3.3 Concomitant medications that affect BP

These were discussed in Section 6.1.4.3.1.

6.1.4.4 VELOCITY

6.1.4.5 Disposition

A total of 131 patients were enrolled (ITT). The mITT consisted of 117 patients in whom the baseline SBP was above the prespecified initial target range and was derived from the ITT by disqualifying 14 patients (13 patients reached their prespecified target range by the time of dosing and one patient did not have a baseline SBP to assess (ID 104-002)). Of the 117, 105 completed the study because 12 patients did not complete their Day 7 follow-up visit.

The safety population consisted of 126 patients (131 minus 5 that did not receive study drug) of which 102 had end organ damage. Of the 126, 114 completed the study (12 did not complete the Day 7 follow-up visit).

The Extended Exposure Subset (EES) consisted of all patients that received at least 18 hours of continuous infusion (n=117). Of this group, 110 patients completed the study. Thirty patients provided blood samples for PK.

More protocol deviations were reported for this study compared to the other Phase III studies (see table). However, it should be noted that the dosing protocol deviation in ECLIPSE and ESCAPE were not reported by the sponsor.

Table 23. Summary of protocol deviations

Protocol deviation	Safety (N=126)
Exclusion criteria	
SBP ≤ 180 mmHg and DBP ≤ 115 mmHg	10 ^a
Concomitant antihypertensive medication <2 hours prior to study drug	2 ^b
Study drug administration	
Incorrect starting dose	1 ^c
Study drug discontinued prior to 18 hours	9 ^d
SBP target range	
Predefined range too narrow (<20 mmHg) or too wide (>40 mmHg)	6 ^e
SBP within target range prior to start of study drug	9 ^f

Source: Appendix 16.2.2.

^a Patients who had SBP ≤180 mmHg and DBP ≤115 mmHg: 101001, 102002, 102008, 102019, 102021, 102036, 104006, 114001, 114002, 114012

^b Patients on antihypertensive medication <2 hours prior to clevidipine initiation: 114003 and 116013

^c Patient 101004 received initial infusion rate of 1 mg/h

^d Patients who received <18 hours of clevidipine and excluded from EES population: 101002, 102007, 102020, 104012, 111005, 111006, 112001, 114002, 116015

^e Patients with SBP target range too narrow or too wide: 102032, 114014, 116001, 116002, 116008, 116020

^f Patients with SBP within target range before clevidipine initiated and excluded from mITT analysis: 101001, 102021, 106003, 111004, 114001, 116015, 116020, 116026, 116029

Taken from Sponsor's VELOCITY report, pg 48 of 2725

Notable difference between this severe HTN population and the cardiac surgery patients are the following: balanced distribution of sex, mostly Blacks, higher baseline BP, history of hypertension, slightly less diabetes, more heart failure (only compared to ECLIPSE), and less peripheral vascular disease were all characteristic of the severe HTN population.

Table 24. VELOCITY patient disposition

Demo & Baseline	CLV N=126
Male, n (%)	61 (48.4)
Female, n (%)	61 (51.6)
Age yrs, mean (SD)	53.5 (15.2)
Age ≥ 65 years, n (%)	
Race, n (%)	
White	20 (15.9)
Black	97 (77.0)
Other	9 (7.1)
Weight kg, mean (SD)	86.4 (24.6)
BMI kg/m², mean (SD)	30.0 (7.6)
SBP mmHg, mean (SD)	202.1 (21.8)
DBP mmHg, mean (SD)	111 (21.0)

Adapted from sponsor table 5, pg 49 of 2725, VELOCITY report

The reviewer examined if there was a difference between qualifying and baseline SBP. The average value of {baseline-qualifying} is -6.07 and 2/3 of them are less at baseline compared to the qualifying values (see figure).

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Figure 18. Qualifying and baseline SBP, VELOCITY

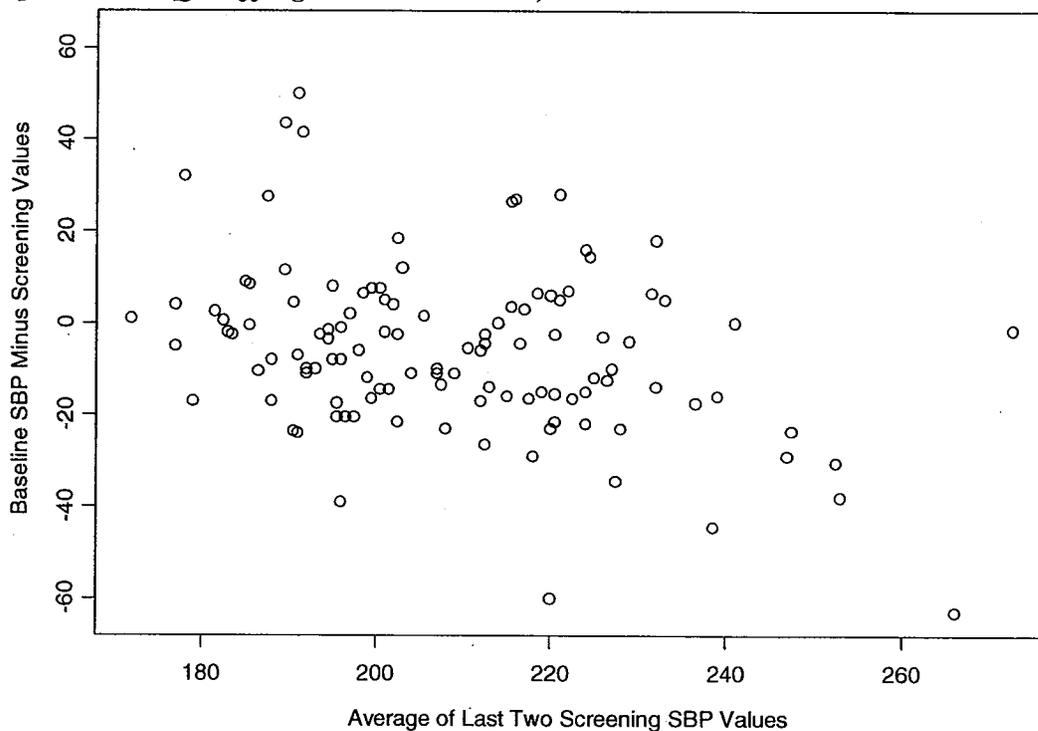


Table 25. VELOCITY patient disposition (continued)

Parameter	End-Organ Injury		All Patients (N=126) n (%)	
	Yes (N=102)	No (N=24)		
	n (%)	n (%)		
Hypertension	99 (97.1)	23 (95.8)	122 (96.8)	
History of Renal Disease	Total	32 (31.4)	0 (0.0)	32 (25.4)
	Dialysis - dependent	14 (13.7)	0 (0.0)	14 (11.1)
	Not Dialysis - dependent	18 (17.6)	0 (0.0)	18 (14.3)
Diabetes	Total	32 (31.4)	7 (29.2)	39 (31.0)
Congestive Heart Failure		21 (20.6)	1 (4.2)	22 (17.5)
Stroke	Total	14 (13.7)	0 (0.0)	14 (11.1)
Peripheral Vascular Disease		10 (9.8)	2 (8.3)	12 (9.5)

Adapted from sponsor's Table 6 of VELOCITY report, pg 51 of 2725

End organ injury was present in 102 patients, with the most prevalent being left ventricular hypertrophy (see table).

Table 26. Summary of end organ injury, VELOCITY

Parameter	System Organ Class	End-Organ Injury	Statistic	All Patients (N=126)
Did Not Have End-Organ Injury			n (%)	24 (19.0)
Had End-Organ Injury			n (%)	102 (81.0)
	Brain	Acute focal neurological signs	n (%)	10 (7.9)
	Eye	Retinal changes consistent with HTN	n (%)	27 (21.4)
	Heart	Acute congestive heart failure	n (%)	19 (15.1)
		Ischemic ECG changes	n (%)	4 (3.2)
		Left ventricular hypertrophy(total)	n (%)	64 (50.8)
		Left ventricular hypertrophy alone	n/N (%)	26/64 (40.6)
		Positive CK-MB	n (%)	0 (0.0)
		Positive troponin	n (%)	2 (1.6)
		Unstable angina	n (%)	2 (1.6)
	Kidney	Hematuria	n (%)	6 (4.8)
		Proteinuria	n (%)	18 (14.3)
		Renal dysfunction	n (%)	24 (19.0)

Source: Table 2.3.2, Section 14.1

Patient may have more than one end-organ injury.

Left ventricular hypertrophy alone percentage is based on the number of patients with left ventricular hypertrophy without concurrent end-organ injuries.

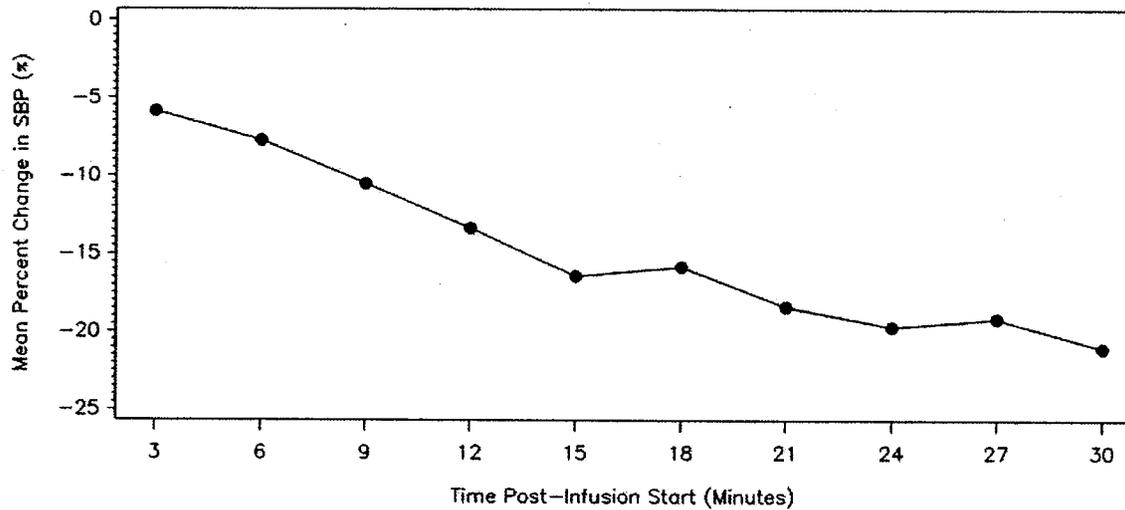
Taken from sponsor's Table 7, pg 52 of 2725 VELOCITY report

6.1.4.5.1 Efficacy Endpoint

The SBP was successfully decreased to the prespecified initial SBP target range within 30 minutes of starting the clevidipine infusion in 89% (104/117) of patients (primary efficacy endpoint); approximately 76% of patients reached their prespecified target range within 20 minutes. There were five subjects in the mITT population whose prespecified target ranges were too narrow (< 20 mmHg) or too wide (> 40 mmHg). Excluding these five subjects changes the percent of subjects reaching target to 90.2% (102/112).

The effect on SBP is shown in Figure 8 and was modeled by the PM reviewer (see Section 5.3). The next figure shows the mean percent change in SBP during the first 30 minutes of infusion (mITT).

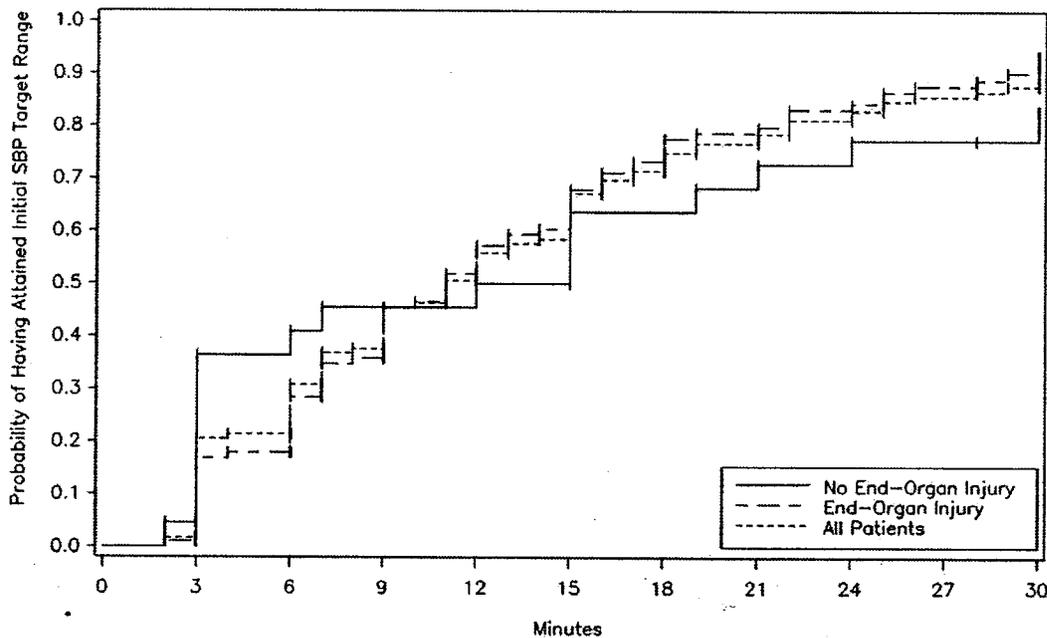
Figure 19. Mean percent change in SBP during the first 30 minutes of infusion (mITT), VELOCITY



Taken from sponsor figure 3, pg 56 pf 2725, VELOCITY report

The secondary endpoint results are described as follows. The median time to achieve the prespecified 30 minute target range was 10.9 minutes (n=104). Thirteen patients were censored for time; 3 patients never reached SBP target range.

Figure 20. Time to attain initial SBP target range, VELOCITY



Taken from sponsor's figure 5, pg 59 of 2725 VELOCITY report

After about 9.5 minutes, a 15% reduction in SBP was achieved.

The average of the mean clevidipine infusion rate was 9.52 mg/h. The average of the median clevidipine infusion rate was 7.48 mg/h. Transition to oral therapy within 6 hours of discontinuing clevidipine was successful in 91.3% of patients.

Up titration to 32 mg/h further decreased SBP in 24 of 38 subjects (mean effect of - 6 mmHg) (see table).

Table 27. Change in SBP with increasing dose, VELOCITY

Change in SBP (mmHg)	Mean ± SD
From 8 to 16 mg/h (n=38)	-6.42 ± 10.11
From 16 to 32 mg/h (n=38)	-12.42 ± 9.43

Taken from sponsor table 13.1, section 14.1, pg 394 of 2725 VELOCITY report

6.1.4.5.2 Drug exposure

The median duration of clevidipine exposure was 20.7 hours, and 92.9% of patients received at least 18 hours of therapy. The table below summarizes clevidipine exposure. The reviewer did not find any major discrepancies between her results and the sponsor's.

Table 28. Reviewer's summary of clevidipine exposure in VELOCITY

	VELOCITY
Ave infusion rate, mg/hr (mean, 90% CI)	9.52 (8.47, 10.57)
Ave infusion rate, mg/hr (min)	1.01
Ave infusion rate, mg/hr (max)	31.59
Ave infusion rate, ug/kg/min (mean, 90% CI)	1.95 (1.71, 2.19)
Ave infusion rate, ug/kg/min (min)	0.26
Ave infusion rate, ug/kg/min (max)	10.07
Total actual infusion duration, hr (mean, 90% CI)	21.26 (20.28, 22.24)
Total actual infusion duration, hr (min)	0.12
Total actual infusion duration, hr (max)	59.7

The average infusion rate was approximately double that of ECLIPSE, but is similar to ESCAPE.

6.1.4.5.3 Concomitant medications

Other IV antihypertensives were used concurrently with clevidipine in 8.7% of patients (n=11) and used without clevidipine in 6.3% (n=8). This is a small percentage compared to the ECLIPSE (40-60%) and ESCAPE studies (ESCAPE-2 at least 36%). The most common medication was selective beta blockers, followed by hydralazine. It is possible that the reason for less use of concomitant medications was due to the higher absolute target (142.9 ± 20.1 to 174.7±19.8, mean ± SD).

Of patients that received 18 hours continuous IV clevidipine (EES population), 92.3% were managed without the use of additional IV antihypertensive agents.

The reason for oral antihypertensive use was not documented. However, a criterion of 2 hours before clevidipine cessation to define agents used for transition results in 75.4% of patients with oral use as a transition, and 34.1 % with oral use as supplementary. The most common medications used during the transition period were imidazoline receptor agonists (32.5%), ACE inhibitors (28.6%), dihydropyridine derivatives (23.8%), selective beta blockers (20.6%), and alpha beta blockers (7.1%). The most common medication used as an oral supplement were imidazoline receptor agonists (12.7%), selective beta blockers (11.9%), ACE inhibitors (10.3%), and dihydropyridine derivatives (7.1%). The imidazoline receptor agonists include moxonidine and clonidine.

6.1.5 Clinical Microbiology

Not applicable since this is not an antimicrobial.

6.1.6 Efficacy Conclusions

The sponsor studied two distinctly different patient populations; the perioperative cardiac surgery patient with a desired SBP range of 65-135 mmHg intraoperatively, 75-145 mmHg pre and postoperatively (ECLIPSE) or 15% reduction in SBP from baseline (ESCAPE), and the severe hypertension patient with a "target" SBP reduction of 15% from baseline (VELOCITY). Patients with preoperative SBP \geq 160 mmHg were enrolled in ESCAPE-1, postoperative SBP \geq 140 mmHg were enrolled in ESCAPE-2, and SBP > 180 mmHg were enrolled in VELOCITY. The ECLIPSE studies were primarily for safety assessments and are not emphasized in the reviewer's analysis of efficacy for reasons already stated.

In the sponsor's pivotal efficacy studies (ESCAPE-1 and -2), there were less bailouts in the clevidipine group compared to the placebo group (primary endpoint), 7.9% vs. 81.2%, respectively. The VELOCITY study showed 89% of subjects reaching target SBP range within 30 minutes of the infusion.

In ESCAPE, the time to 15% SBP lowering (not placebo adjusted) was ~ 5-6 minutes using a dosing scheme of 0.4 ug/kg/min increased every 90 seconds until 3.2 ug/kg/min reached. The average infusion rate was 1.88 ug/kg/min (maximum average of 6.47 ug/kg/min); in mg/hr this was 9.8 mg/hr, with a maximum average infusion rate of 40.3 mg/hr. Mean drug exposure was 0.5 hours with a maximum of 1 hr.

In VELOCITY, where the dose titration occurred more gradually, the time to 15% SBP lowering was about 10 minutes using a dosing scheme of 2 mg/hr doubled every 3 minutes to a maximum dose of 32 mg/h. The average infusion rate was 1.95 ug/kg/min (maximum average of 10.07 ug/kg/min); in mg/hr this was 9.5 mg/hr, with a maximum average infusion rate of 31.6 mg/hr. The mean drug exposure was 21 hours.

The effect on BP was significantly different from placebo by ~ 4 minutes after the dose. The maximum effect on BP with this dosing scheme was reached around 10 minutes postoperatively and 20 minutes perioperatively after the start of the infusion.

The use of concomitant medications that could confound the results was fairly sparse in ESCAPE-1 (3.8% on beta blockers), but in ESCAPE-2 up to 36% were also taking nitroglycerin. Approximately 15% of subjects took additional IV antihypertensives in VELOCITY.

The majority of patients in ESCAPE were white. No meaningful differences by race, age, or gender could be found.

These Phase III efficacy studies demonstrate that clevidipine lowers BP and can be used in the perioperative and postoperative setting as well as in severe hypertensives (although the severe HTN study was uncontrolled and open-label). Given that clevidipine dose could be titrated or stopped and restarted at the investigators' discretion, as well as the nondiscriminatory use of additional IV antihypertensives, the assessment of dose response was difficult. These studies do not provide complete information regarding the best dosing titration scheme (drug onset, offset, tolerance, etc.). This information was gathered from studies TMC-CLV-06-01 and SH-SAD-0003.

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7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

All 19 studies (see Table 4) were used in the sponsor (and reviewer's) analysis of safety. However, the ECLIPSE studies were three large, open-label, Phase III trials whose primary objective was to establish the safety of clevidipine in the treatment of perioperative (postoperative for NIC) hypertension by comparing the incidences of death, stroke, MI and renal dysfunction in the clevidipine and active comparator groups from the initiation of study drug infusion through postoperative Day 30. A blinded Clinical Events Committee (CEC) adjudicated the occurrence of the primary endpoint events. These endpoints are defined in the Appendix, Section 10.1.1. An independent DSMB reviewed safety data in an open-label manner. There was no prespecified alpha for these endpoints, combined or individually. In addition to these studies being underpowered to detect a meaningful difference in these endpoints, changes in dose (stop, restart, reduce) were subjective. The mean study drug duration in ECLIPSE was 8 hours. Given that the elimination half-life is 1 hour, most of the drug is gone by 5 hours after the dose. Thus, relating causality to safety assessments made out to 30 days does not make much sense. The reviewer will undertake an assessment of all AEs up to 24 hours after the infusion is stopped. This will be included in an addendum

Deaths in the clevidipine program occurred mostly in cardiac surgery patients. There was only one death (study 02-01, ID 1004_132) that could have been attributable to clevidipine causing hypotension and setting off a cascade of deleterious events with no recovery. There was no difference in death, stroke, MI or renal dysfunction at 30 days between clevidipine and active comparators (SNP, NIC, and NTG).

There were no SAEs in essential HTN or healthy volunteers that received clevidipine. The most common SAE in the perioperative patient was cardiac disorders, with Afib being the most common cardiac disorder. The rate was no different than that in active comparators. Cardiac disorders was the most common SAE across the five perioperative studies, except for ECLIPSE-NIC (respiratory, thoracic and mediastinal disorders was more common). Nervous system disorders were more common in severe HTN, however only 12 patients total had SAEs. Five had nervous system disorders.

The most common reason for an AE leading to discontinuation was headache in healthy subjects, and hypotension and hypertension in hypertensive subjects. The most common AE in essential HTN was headache (40%), polyuria (7%), infusion site reaction (7%), and nausea (7%). The most common AE for clevidipine in perioperative patients were incision site complications (51%), atelectasis (41%), and atrial fibrillation (33%). Headache (7%) was the most common AE in the severe HTN group.

The only AE that seemed to be related to dose was headache.

Clevidipine causes a reflex tachycardia of about 5-12%. There is not extensive experience with its use with beta blockers. In the severe HTN study, where 46 subjects were also taking beta blockers, there were no incidences of hypotension, but the BP were very high, so this is not surprising.

Atrial fibrillation was the most common cardiac disorder in perioperative patients (30%). The ECLIPSE studies were temporarily stopped due to a greater incidence of afib in clevidipine treated patients compared to AC. An extensive retrospective review of the data was done, resulting in similar incidence rates of afib between the 4 treatments (CLV, SNP, NTG, and NIC).

Rebound HTN seems to be dose related, with a placebo adjusted mean change from baseline SBP of 9% for the 16 mg/h dose group.

Clevidipine does not prolong the QTc interval.

7.1.1 Deaths

There were a total of 55 (25 clevidipine, 29 AC, 1 placebo) deaths that occurred within 30 days of study drug administration in the clevidipine development program; 22 (10 clevidipine, 12 AC) deaths occurred within 7 days and 59 total were reported (see tables). Deaths occurred mostly in cardiac surgery patients (primarily CABG, many with concurrent valve repairs or replacements). There were three deaths in severe hypertensive patients who also had end organ damage. An independent, blinded, Clinical Events Committee (CEC) adjudicated the deaths in the ECLIPSE studies. None of the deaths were attributable to treatment and all seem to be related to the nature and risk of the surgery and patient. Total reported deaths are shown in the table below.

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Table 29. Total reported deaths

Study	CLV	AC	PBO
	27/1400 (1.9) n (%)	30/839 (3.6) n (%)	1/223 (0.4) n (%)
02-01 (NTG)	1/54 (1.9)	1/56 (1.8)	---
ESCAPE-1 (03-01)	2/53 (3.8)	---	0
ESCAPE-2 (03-02)	0	---	1/49 (2.0)
ECLIPSE-NTG (03-03)	8/268 (3.0)	9/278 (3.2)	---
ECLIPSE-SNP (03-04)	5/296 (1.7)	14/283 (4.6)	---
ECLIPSE-NIC (03-05)	8/188 (4.3)	7/193 (3.6)	---
VELOCITY (06-02)	3/126 (2.4)	---	---

The following four subjects died (difference bolded in above table), but were not included in the sponsor's ISS report of deaths table because the death occurred after 30 days. The day of the operation was Day 0.

ID TMC-CLV-03-05_00507_00019 was a 72 yo WF with a hx of CHF, IDDM, HTN, prior afib, and TIA randomized to nicardipine who **died from sepsis on Day 31** s/p 4 vessel CABG and MV repair. Beginning 8 hours after surgery end (Day 1), she received nicardipine IV for 44 hours (Day 2). Her recovery was complicated by an ischemic stroke on Day 4, and numerous complications including heparin induced thrombocytopenia, reintubation, right arm ischemia (requiring thrombectomy), afib, PE, pneumonia, and sepsis that ended in death on Day 31 after the operation. Time of death was either — per d_ae.xpt file) or — (per CRF and narrative). The sponsor counted her as “stroke”, but not “death”. Concomitant antihypertensives included metoprolol and lasix. Reviewer attribution of death: not drug.

ID TMC-CLV-03-03_00363_00032 was a 76 yo WM with a hx of USA, NIDDM, dyslipidemia, prior afib, and recent MI (within 6 months) randomized to clevidipine who **died from sepsis on Day 35** s/p 4 vessel CABG. Beginning 13 minutes prior to surgery, clevidipine was infused for 1.5 hours. His course was complicated by an intraoperative AMI, hypotension on Day 0 due to significant chest tube drainage, afib and flutter, chest reopening for additional two bypasses, acute renal failure (Day 1) requiring hemodialysis, sepsis (Day 11), bradycardia and reintubation with subsequent death. Concomitant antihypertensives included esmolol, levophed, diuril, and lasix. Reviewer attribution: not drug.

ID TMC-CLV-03-01_00101_00014 was a 68 yo WF with a hx of HTN, NIDDM, and angina randomized to clevidipine who **died of multiorgan system failure on Day 36** s/p CABG and AV replacement. Clevidipine was infused on Day 0 preoperatively for 8 minutes. Her initial starting dose was 0.4 ug/kg/min and her maximum dose was 3.2 ug/kg/min. Her average infusion dose was 2.1 ug/kg/min. Her doses were doubled every 2-3 minutes for three doses; the last dose is recorded as being administered for 5 minutes, however the CRF states that drug was stopped after 8 minutes. Her SBP decreased from 171 mmHg to 125 mmHg while on clevidipine. Clevidipine was discontinued prior to surgery. Her postop recovery was complicated by severe GI bleeding, thrombocytopenia, and multi-system organ failure. The

CEC attributed the death to family withdrawal of life support. Concomitant antihypertensives were valsartan and isosorbide mononitrate. Reviewer attribution: not drug

ID TMC-CLV-03-04_00424_00019 was a 83 yo AM with a hx of angina, CHF, dyslipidemia, recent MI, and HTN randomized to sodium nitroprusside who **died of ischemic bowel on Day 97**. He had a 3 vessel CABG and AV replacement. Beginning 26 hours after the start of surgery, SNP was infused for ~ 72 hours. The actual infusion duration was 69.5 hours. On Day 0, 30 minutes after the start of the infusion, he developed excessive chest tube drainage subsequently causing hypotension and reduced cardiac index. The source of bleeding was the retrograde cannulation site. It was repaired in the OR, but he also developed acute renal failure on Day 0 eventually needing hemodialysis. He was extubated on Day 2, but subsequently required a feeding tube and remained hospitalized. Other postop complications included afib and bradycardia. He died on Day 97 after developing rectal ulcer and/or ischemic bowel. The CEC attributed the death to family withdrawal of life support. Concomitant antihypertensive included NTG, lasix, diuril, and metolazone. Reviewer attribution: not drug

The deaths that occurred within 30 days (sponsor follow-up period) are shown in the table.

Table 30. Deaths within 30 days (n=55)

Study	CLV	AC	PBO
	25/1400 (1.8) N (%)	29/839 (3.5) n (%)	1/223 (0.4) n (%)
02-01 (NTG)	1/54 (1.9)	1/56 (1.8)	---
ESCAPE-1 (03-01)	1/53 (1.9)	---	0
ESCAPE-2 (03-02)	0	---	1/49 (2.0)
ECLIPSE-NTG (03-03)	7/268 (2.6)	9/278 (3.2)	---
ECLIPSE-SNP (03-04)	5/296 (1.7)	13/283 (4.6)	---
ECLIPSE-NIC (03-05)	8/188 (4.3)	6/193 (3.1)	---
VELOCITY (06-02)	3/126 (2.4)	---	---

The reviewer analyzed all deaths and decided on drug attribution based on the information contained in the narratives and labs. An overall comparison between clevidipine, active control and placebo should not be done since clevidipine was also studied in healthy individuals. Deaths within study between clevidipine and active control or placebo were similar except for the ECLIPSE-SNP study. The 18 deaths in ECLIPSE-SNP are individually summarized below since there were differences between treatments. None of the deaths were attributed to drug. There were 7 and 3 deaths that occurred by Study Day 7 in the SNP and clevidipine groups, respectively. Deaths in other studies that occurred within 30 days were reviewed and summarized in the table that follows with the reviewer's assessment of drug attribution to death.

ECLIPSE-SNP
Clevidipine
Died by Study Day 7

1. ID 455019 was a 68yo WF with a hx of CHF, dyslipidemia, AI, and HTN randomized to clevidipine who **died of complete system shutdown (per investigator) on Day 2** s/p CABG and AV replacement. Beginning 9 minutes after the start of surgery, clevidipine was infused for ~ 5 hours. The initial dose was 0.4 ug/kg/min, and the average dose was 0.67 ug/kg/min. The dose was doubled twice and then reduced back to the initial starting dose for the remainder of the study. The actual infusion duration was 0.5 hours. Her surgery was complicated by difficulty weaning from bypass. She left the OR with her chest open, subsequently returned for sternal closure, but it was unsuccessful due to heart swelling and persistent bleeding. Her postop recovery was complicated by development of renal failure and cardiac arrest with unsuccessful resuscitation. The CEC attributed the death to family withdrawal of life support. Reviewer attribution: not drug
2. ID 405007 was a 82 yo WM with a hx of dyslipidemia, HTN, and PVD randomized to clevidipine who **died of an ischemic stroke on Day 6** s/p single vessel CABG, MV repair, and AV replacement. Beginning 7 minutes after the start of surgery, he received IV clevidipine for 30 minutes (initial dose 0.4 ug/kg/min, double to 0.8 after 21 minutes). His course was complicated by a prolonged bypass (4 hrs) requiring inotropic support for postoperative hypotension, renal insufficiency, afib, and ischemic stroke (on Day 0). The ischemic stroke was said to be due to surgical manipulation of the calcified aorta and extended pump time. His condition persisted and the family withdrew life support. Concomitant antihypertensives included amlodipine and metoprolol. Reviewer attribution: not drug
3. ID 418007 was a 69 yo WM with a hx of dyslipidemia, HTN, and PVD randomized to clevidipine who **died of a pulmonary embolism on Day 7** s/p AV replacement. Beginning 30 minutes prior to surgery he started clevidipine for 12 hours and 20 minutes. The actual infusion duration was about 9 hours. The initial and average dose was ~ 0.4 ug/kg/min. On Day 7 he experienced a pulmonary embolism and cardiac arrest and never regained consciousness. Concomitant antihypertensives included atenolol. Other postop complications included afib, renal insufficiency, and anemia. The investigator considered PE the cause of death. Reviewer attribution: not drug

Died after Day 7

4. ID 471004 was a 81yo WF with a hx of CHF, dyslipidemia, and HTN randomized to clevidipine who **died of respiratory failure on Day 18** s/p AV replacement. Beginning 9 minutes after the start of surgery, clevidipine was infused for ~ 33 hours. The initial and average dose was ~0.4 ug/kg/min. The actual infusion duration was 25 hours. Her postop recovery was complicated by development of bradycardia and sick sinus syndrome on Day 3 (2 days after clevidipine infusion stopped), subsequent respiratory failure, HF, afib, acute renal insufficiency and reintubation (x2). The CEC attributed the death to family withdrawal of life support. Reviewer attribution: not drug
5. ID 445012 was a 78 yo WF with a hx of CHF and HTN randomized to clevidipine who **died of respiratory failure and renal insufficiency on Day 23** s/p MV replacement. Beginning 11 minutes after the start of surgery, clevidipine was infused for ~ 23 hours. The initial dose was 0.09 ug/kg/min, and the average dose was 0.23 ug/kg/min. The actual infusion duration

was 7 hours. Her postop recovery was complicated by respiratory failure on Day 1, colonic obstruction due to ischemic colitis on Day 4, failure to successfully extubate, afib, flutter, tachycardia, decreased Hg and platelets, renal failure with oliguria, and urosepsis. The CEC adjudicated the cause of death to withdrawal of life support. Reviewer attribution: not drug

Sodium nitroprusside Died on Study Day 0

1. ID 403006 was a 67 yo WM with a hx of CABG, CHF, chronic afib, severe AS, and chronic renal failure randomized to clevidipine who **died of cardiogenic shock on Day 0** s/p CABG and AV replacement. Beginning 2 hours after the start of surgery, SNP was infused over ~ 6.5 hours. The actual infusion duration was 3.75 hours. He experienced hemorrhagic pulmonary edema during surgery (and during the infusion). Drug was withdrawn 3 hours after the pulmonary edema. His course was complicated by difficulty weaning from bypass, significant inotropic support, and cardiogenic shock. The CEC adjudicated the cause of death to be cardiac in nature and due to pulmonary edema. Concomitant antihypertensive included esmolol. Reviewer attribution: not drug
2. ID 471019 was a 72 yo HM with a hx of recent MI, USA, dyslipidemia, NIDDM, and HTN randomized to SNP who **died of RV rupture on Day 0** s/p 4 vessel CABG. Beginning 30 minutes prior to the start of surgery, SNP was infused over ~ 3.5 hours. The actual infusion duration was 1.3 hours. Her postop recovery was complicated by hypotension and asystole occurring 2 hours after surgery and the last dose of medication. He was found to have RV rupture and subsequently died. The CEC attributed the death as cardiac. Concomitant antihypertensive included IV NTG and verapamil. Reviewer attribution: not drug
3. ID 473012 was a 83 yo WF with a hx of USA, dyslipidemia, prior percutaneous coronary intervention, and HTN randomized to SNP who **died of left atriotomy resulting in exsanguination and cardiac arrest on Day 0** s/p 2 vessel CABG and MV replacement. Beginning 36 minutes prior to the start of surgery, SNP was infused for ~ 5 hours. The actual infusion duration was 0.5 hours. Immediately postop she developed excessive chest tube bleeding and became severely hypotensive. After chest reopening, a tear in the left atriotomy site was discovered. She lost a significant amount of blood and died due to cardiac arrest from postop hemorrhage. The CEC attributed the death to left atriotomy resulting in exsanguination. Concomitant antihypertensive included IV NTG. Reviewer attribution: probably not drug
4. ID 418058 was a **41 yo** WM with a hx of USA, dyslipidemia, recent MI, and HTN randomized to SNP who **died of catastrophic hemorrhage on Day 0** s/p 3 vessel CABG. Beginning 2 hours after the start of surgery, SNP was infused for 3 minutes. He suffered a cardiac arrest during sternal closure (~ 4 hours after the last dose of medication), was defibrillated for Vfib and resuscitated. His postop recovery was further complicated by the emergent bypass requiring an IABP and L and RVAD, massive transfusions for severe coagulopathy, hypotension and acidosis. Life support was discontinued. The CEC attributed the death to catastrophic hemorrhage during cardiac surgery. Concomitant antihypertensive included diltiazem. Reviewer attribution: not drug

Died by Study Day 7

5. ID 400004 was a 71 yo WF with a hx of dyslipidemia and HTN randomized to SNP who **died of probably pulmonary thromboembolism on Day 1** s/p 2 vessel CABG. Beginning 31 minutes prior to the start of surgery, SNP was infused for ~ 22 hours. The actual infusion duration was 19 hours. Her postop recovery was complicated by back pain, a smothering sensation, bradycardia and subsequent cardiac arrest. The CEC attributed the death to cardiac arrest. Concomitant antihypertensive included atenolol and micardis. Reviewer attribution: not drug
6. ID 418004 was a 74yo WM with a hx of AS, angina randomized to SNP who **died of LV failure on Day 1** s/p CABG and AV replacement. Beginning 1 hour prior to the end of surgery, SNP was infused for ~ 1.2 minutes. At 23 minutes after the end of surgery, he experienced LV failure and ventricular tachycardia and subsequent vfib. His postop was complicated by chest reopening, emergent bypass needing an IABP, hypotension and cardiogenic shock. The CEC attributed the death to LV failure. Reviewer attribution: not drug
7. ID 455048 was a 77yo WF with a hx of USA, dyslipidemia, prior afib, stroke, and HTN randomized to SNP who **died of cardiac arrest on Day 4** s/p 2 vessel CABG. Beginning 40 minutes after the start of surgery, SNP was infused for ~ 20 minutes around ——— Later that evening she had a Q-wave MI. Her postop recovery was further complicated by vfib on Day 3 with resuscitation, continued bradycardia, hypotension, afib, another MI, and fatal cardiac arrest. The CEC attributed the death to cardiac arrest. Concomitant antihypertensive included sotalol. Reviewer attribution: not drug

Died after Study Day 7

8. ID 443044 was a 82yo WM with a hx of USA, NIDDM, recent MI, and HTN randomized to SNP who **died of probable CAD on Day 11** s/p 4 vessel CABG. Beginning 18 minutes after the end of surgery, SNP was infused for ~ 9 hours. The actual infusion duration was 9.25 hours. She recovered from surgery and was discharged home on O₂ on Day 8. On Day 11 the patient died. The CEC attributed the death to CAD. Concomitant antihypertensive included IV NTG and toprol XL. Reviewer attribution: not drug
9. ID 471028 was a 75yo HM with a hx of USA, dyslipidemia, prior afib, and HTN randomized to SNP who **died of cardiac arrest on Day 12** s/p 3 vessel CABG with IABP. Beginning 3 minutes after the start of surgery, SNP was infused for ~ 8 hours. The actual infusion duration was 2.6 hours. His postop recovery was complicated by respiratory failure on Day 1, a NQWMI (Day 2), failure to ween from ventilator, afib, CHF, and ischemic stroke (Day 5) of cardioembolic origin probably occurring on Day 0. He was transferred to hospice care and had a fatal cardiac arrest on Day 12. The CEC attributed the death to family withdrawal of support. Concomitant antihypertensive included IV NTG, oral lopressor, NTG patch, and verapamil. Reviewer attribution: not drug

10. ID 455036 was a 74yo WF with a hx of CHF, recent MI, AI, severe aortic regurgitation, and HTN randomized to SNP who **died of respiratory arrest on Day 21** s/p 2 vessel CABG and AV replacement. Beginning 3 hours after the start of surgery, SNP was infused for ~ 1.5 hours. The actual infusion duration was 0.5 hours. Her postop recovery was complicated by the development of acute renal failure secondary to IV contrast on Day 3 requiring hemodialysis and recurrent afib. She was discharged on Day 15. On Day 20 she presented to the ER with HTN and absent L lung sounds due to a pneumothorax. She later developed cardiac arrest during dialysis (resuscitated), multi-organ system failure, hemodynamic instability and subsequent respiratory arrest. The CEC attributed the death to family withdrawal of life support. Reviewer attribution: not drug

11. ID 460008 was a 69 yo AM with a hx of USA, dyslipidemia, and HTN randomized to SNP who **died of aortic rupture on Day 25** s/p 3 vessel CABG. Beginning 10 minutes after the start of surgery, SNP was infused for ~ 1.5 hours. The actual infusion duration was 1.7 hours. Her postop recovery was complicated by the development of acute renal failure (and sinus tachycardia) on Day 1 requiring hemodialysis, a sternal wound infection on Day 13, massive bleeding from the sternal incision with hypotension, subsequent death from a presumed aortic rupture. The CEC attributed the death to sudden massive hemorrhage. Concomitant antihypertensive included clonidine, diltiazem, enalapril, IV NTG, lopressor, and nitro-dur patch. Reviewer attribution: not drug

12. ID 473002 was a 74yo WM with a hx of USA, dyslipidemia, PVD, and HTN randomized to SNP who **died of ARDS and respiratory failure on Day 25** s/p 3 vessel OPCAB. Beginning 5 minutes prior to the start of surgery, SNP was infused for ~ 30 minutes. Her postop recovery was complicated by bronchitis (Day 3), recurrent afib/flutter, pneumonia, ARDS requiring reintubation (Day 19), acute renal failure (Day 21), and heparin induced thrombocytopenia. The CEC attributed the death to family withdrawal of life support. Concomitant antihypertensive included diltiazem, IV NTG, metoprolol, lasix, and propranolol. Reviewer attribution: not drug

13. ID 418044 was a 76yo WM with a hx of angina, dyslipidemia, PVD, and recent MI randomized to SNP who **died of ischemic colitis on Day 26** s/p 2 vessel CABG. Following surgery, but prior to SNP, he developed postoperative bleeding and required re-exploration. Beginning 5 hours after the end of surgery, SNP was infused for ~ 6.4 hours. His postop recovery was complicated by failed extubation, afib, acute respiratory failure, acute renal insufficiency (Day 5) requiring hemodialysis, and fatal ischemic colitis. The CEC attributed the death to family withdrawal of life support. Concomitant antihypertensive included diamox, diuril, and lasix. Reviewer attribution: not drug

This table lists the deaths in chronological order by study for studies other than ECLIPSE-SNP. Below the table are comments on selected IDs.

Table 31. Death attributions

#	Study	ID	Treat	Day	Cause	Attribution to drug	
						PI	Reviewer
1	02-01	1004_132	CLV	10	MSOF	no	probable
2	02-01	1002_148	NTG	11	Card. shock	no	no
3	ESCAPE-1 (03-01)	114_001	CLV	1	Mediastinal hemorrhage	no	undetermined
4	ESCAPE-2 (03-02)	216_008	PBO	11	Cardiac tamponade	no	no
5	ECLIPSE-NTG (03-03)	346_007	CLV	1	Vfib	no	no
6	ECLIPSE-NTG (03-03)	340_002	CLV	4	Card shock	no	no
7	ECLIPSE-NTG (03-03)	334_011	CLV	6	Cardiac arrest	no	no
8	ECLIPSE-NTG (03-03)	335_007	CLV	8	Bronchopneumonia	no	no
9	ECLIPSE-NTG (03-03)	363_028	CLV	9	Cardiac arrest	no	no
10	ECLIPSE-NTG (03-03)	363_043	CLV	13	Mediastinitis, Cardiopulmonary arrest	no	no
11	ECLIPSE-NTG (03-03)	352_004	CLV	18	unknown	unk	Probably no
12	ECLIPSE-NTG (03-03)	365_008	NTG	3	Cardiac arrest	no	no
13	ECLIPSE-NTG (03-03)	339_036	NTG	5	RV heart failure 2° MI	no	no
14	ECLIPSE-NTG (03-03)	339_021	NTG	9	3° AVB, card shock	no	no
15	ECLIPSE-NTG (03-03)	339_003	NTG	16	end stage COPD	no	no
16	ECLIPSE-NTG (03-03)	357_007	NTG	18	Cardiac arrest	no	no
17	ECLIPSE-NTG (03-03)	342_014	NTG	20	Unknown	unk	Probably no
18	ECLIPSE-NTG (03-03)	335_034	NTG	26	Ischemic stroke	no	no
19	ECLIPSE-NTG (03-03)	357_002	NTG	26	Respiratory failure	no	no
20	ECLIPSE-NTG (03-03)	365_030	NTG	29	Ischemic stroke	no	No
21	ECLIPSE-NIC (03-05)	557_014	CLV	2	Cardiac arrest, hypotension	no	No
22	ECLIPSE-NIC (03-05)	560_022	CLV	6	Cardiac arrest	no	No
23	ECLIPSE-NIC (03-05)	503_015	CLV	8	Respiratory & renal failure, hypotension	no	No
24	ECLIPSE-NIC (03-05)	546_029	CLV	10	Renal failure, respiratory distress	no	No
25	ECLIPSE-NIC (03-05)	503_029	CLV	11	MSOF	no	No
26	ECLIPSE-NIC (03-05)	560_012	CLV	14	Respiratory failure	no	No
27	ECLIPSE-NIC (03-05)	526_027	CLV	26	renal failure, cardiac arrest	no	No
28	ECLIPSE-NIC (03-05)	525_014	CLV	27	MSOF	no	No
29	ECLIPSE-NIC (03-05)	507_011	NIC	2	Metabolic acidosis, mesenteric infarct	no	Possible
30	ECLIPSE-NIC (03-05)	544_002	NIC	2	Bleeding, cardiac arrest	no	No
31	ECLIPSE-NIC (03-05)	546_027	NIC	2	Respiratory failure	no	No
32	ECLIPSE-NIC (03-05)	557_001	NIC	12	Respiratory failure, cardiac arrest	no	No
33	ECLIPSE-NIC (03-05)	556_008	NIC	17	Pulmonary embolism	no	No
34	ECLIPSE-NIC (03-05)	556_007	NIC	28	Cardiac arrest	no	No
35	VELOCITY (06-02)	102_020	CLV	2	Card shock	no	No
36	VELOCITY (06-02)	102_013	CLV	9	hemorrhagic stroke & neurologic deterioration	no	No
37	VELOCITY (06-02)	102_027	CLV	11	End stage COPD	no	no

MSOF = multisystem organ failure

1 – infusion stopped due to hypotension and bradycardia, setting off a cascade of deleterious events. Never recovered.

3 – experienced hypotensive episode probably related to blood loss, but it is unclear when the hypotensive episode occurred in relation to the CLV infusion.

11- died at home four days after discharge from hospital; details of death unknown because he was lost to follow-up

Clinical and Statistical Review

B. Nhi Beasley, Pharm.D. and John Lawrence, Ph.D.

NDA 22-156, SN 000

Cleviprex™ (clevidipine butyrate)

17 – Discharged on Day 8. In ER on Day 20 in cardiac arrest, unsuccessful resuscitation. Cause of death unclear. Death omitted from d_ae.xpt ISS dataset.

18 – Discharged on Day 10. Suffered ischemic stroke on Day 26. Death and stroke omitted from d_ae.xpt in ISS.

21 – received CLV from Day 0 – Day 1 (18.75 hours), 26 hours after the infusion stopped, patient experiences hypotension with subsequent cardiac arrest and death. Patient also taking metoprolol

23 – received CLV on Day 0 for almost 6 hours. ~15 hours after the infusion stopped, pt experiences respiratory failure with hypotension, hemodynamically unstable, progressed to renal failure.

29 – 78 yo male underwent OPCAB. Received nicardipine for 4 hours (ended on Day 1 at → ; developed metabolic acidosis on Day 1 with abdominal pain which was later determined to be mesenteric infarct with small and large bowel necrosis. Patient died on day 2 from the intestinal infarct.

35 - received clevidipine for almost 14 hours, during which time she required intubation and suffered an AMI.

Drug was stopped due to lack of effect at the highest dose of 32 mg/h. Patient then had a cardiac arrest, was cathed and received a drug eluting stent. The next day (Day 2), she developed pulmonary edema, cardiogenic shock and arrested.

7.1.2 Other Serious Adverse Events (SAEs)

The incidence and type of SAEs observed were comparable to that expected in perioperative and severe hypertensive patients. There were no SAEs in essential hypertension patients or healthy volunteers who received clevidipine or placebo. The sponsor's calculations for the SAE table by system organ class (SOC) in the ISS include all subjects treated with clevidipine (i.e., also healthy subjects), making the denominator larger and the SAE seem smaller. However, there were no clinically relevant differences between clevidipine, placebo, and all active comparators treatment groups with respect to the incidence of SAEs categorized by (SOC) in hypertensive patients. Cardiac disorders and respiratory, thoracic and mediastinal disorders were the SOCs with the highest incidence of SAEs in all treatment groups.

The following table shows the SAEs by type of hypertension, which is a better depiction than by treatment. The incidence of SAEs was similar between the clevidipine and all active comparators group. It is also noted that there should be 77 (not 76) on clevidipine with cardiac disorders. Drug for ID SH-SAD-0003_00001_00422 was listed as unknown, but review of the CRF shows that she received clevidipine. The incidence of SAEs was different for the severe HTN group, with nervous system disorders, and respiratory, thoracic, and mediastinal disorders being the top ranked.

**APPEARS THIS WAY
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Table 32. SAEs by system organ class by type of hypertension

System Organ Class	Essential		Perioperative		All active comparators (N=839)	Severe Clevidipine (N=126)
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)		
Patients with at least one adverse event, n (%)	0 (0.0)	0(0.0)	222 (20.3)	21 (15.8)	183 (21.8)	12 (9.5)
Cardiac disorders	0 (0.0)	0 (0.0)	76 (7.0)	9 (6.8)	68 (8.1)	3 (2.4)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	61 (5.6)	4 (3.0)	56 (6.7)	4 (3.2)
Renal and urinary disorders	0 (0.0)	0 (0.0)	34 (3.1)	2 (1.5)	22 (2.6)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	30 (2.7)	1 (0.8)	11 (1.3)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	29 (2.7)	1 (0.8)	25 (3.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	21 (1.9)	6 (4.5)	20 (2.4)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	18 (1.6)	0 (0.0)	20 (2.4)	5 (4.0)
Gastrointestinal disorders	0 (0.0)	0 (0.0)	12 (1.1)	1 (0.8)	15 (1.8)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	12 (1.1)	0 (0.0)	7 (0.8)	2 (1.6)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	9 (0.8)	0 (0.0)	3 (0.4)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	8 (0.7)	1 (0.8)	2 (0.2)	0 (0.0)

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Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	5 (0.5)	0 (0.0)	5 (0.6)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	4 (0.4)	2 (1.5)	5 (0.6)	1 (0.8)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	1 (0.1)	1 (0.8)
Surgical and medical procedures	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	4 (0.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)	0 (0.0)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)

Source: Table 9.4.4, Appendix 8.2.1

Note: Patients who received more than one treatment were counted in each of their treatment groups.

From sponsor's table 32, pg 80 of 6157 ISS

The SAEs for the five Phase III studies are shown in the tables that follow. The investigator judged the SAEs in ESCAPE-1 to be unrelated to study drug.

Table 33. ESCAPE-1 SAE by SOC by Day 7

MedDRA System Organ Class	Treatment	
	Clevipidine N=53, n (%)	Placebo N=51, n (%)
Patients with at least one SAE	13 (24.5)	10 (19.6)
Cardiac disorders	3 (5.7)	6 (11.8)
Infections and infestations	1 (1.9)	0 (0.0)
Injury, poisoning and procedural complications	1 (1.9)	3 (5.9)
Nervous system disorders	2 (3.8)	0 (0.0)
Renal and urinary disorders	1 (1.9)	1 (2.0)
Respiratory, thoracic and mediastinal disorders	4 (7.5)	1 (2.0)
Vascular disorders	2 (3.8)	0 (0.0)

Source: Table 7.3, Section 14.1

Protocol- specified SAE reporting period was from start of study drug administration up until seven days after permanent stop of study drug administration or hospital discharge, whichever occurred first.

Taken from sponsor table 15, pg 56 of 1827, ESCAPE-1 report

The investigator judged 1 SAE in ESCAPE-2 to be related to clevidipine. It was a thrombophlebitis occurring 2 days after receiving clevidipine.

Table 34. ESCAPE-2 SAE by SOC by Day 7

MedDRA System Organ Class	Treatment	
	Clevipine (N=61),n (%)	Placebo (N=49),n (%)
Patients with at least one SAE	10 (16.4)	6 (12.2)
Cardiac disorders	2 (3.3)	3 (6.1)
Gastrointestinal disorders	0 (0.0)	1 (2.0)
Infections and infestations	2 (3.3)	0 (0.0)
Injury, poisoning, and procedural complications	2 (3.3)	1 (2.0)
Psychiatric disorders	1 (1.6)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (2.0)
Respiratory, thoracic, and mediastinal disorders	4 (6.6)	1 (2.0)
Vascular disorders	1 (1.6)	0 (0.0)

Source: Table 7.3, Section 14.1

Protocol- specified SAE reporting period was from start of study drug administration up until 7 days after permanent stop of study drug administration or hospital discharge, whichever occurred first.

Taken from sponsor table 15, pg 56 of 2183, ESCAPE-2 report

The investigator judged 3 SAE in ECLIPSE-NTG to be possibly related to clevidipine and none in the NTG treated patients. These included afib, blurred vision, and pulmonary HTN.

Table 35. ECLIPSE-NTG SAEs by SOC by Day 7

System organ class/ Preferred Term	Clevipine (N=268), n (%)	Nitroglycerin (N=278), n (%)
Patients with at least one SAE	43 (16.0)	51 (18.3)
Cardiac disorders	19 (7.1)	22 (7.9)
Renal and urinary disorders	11 (4.1)	5 (1.8)
Respiratory, thoracic and mediastinal disorders	9 (3.4)	19 (6.8)
Infections and infestations	6 (2.2)	4 (1.4)
Blood and lymphatic system disorders	3 (1.1)	1 (0.4)
Gastrointestinal disorders	2 (0.7)	2 (0.7)
Injury, poisoning and procedural complications	2 (0.7)	4 (1.4)
Nervous system disorders	2 (0.7)	6 (2.2)
Eye disorders	1 (0.4)	0 (0.0)
General disorders and administration site conditions	1 (0.4)	1 (0.4)
Metabolism and nutrition disorders	1 (0.4)	2 (0.7)
Vascular disorders	1 (0.4)	1 (0.4)
Investigations	0 (0.0)	1 (0.4)
Psychiatric disorders	0 (0.0)	1 (0.4)
Surgical and medical procedures	0 (0.0)	2 (0.7)

Source: Table 7.7, Section 14.1

Taken from sponsor table 22, pg 73 of 8452, ECLIPSE-NTG report

This table shows the SAEs with more than 1% incidence. The investigator judged 7 SAEs (AF, vfib, ileus, hepatic enzyme increased and ARF) in 4 clevidipine treated patients in ECLIPSE-SNP to be possibly related to study drug and 3 SAEs (AF, cardiac arrest) in 2 patients in the NTG treated patients.

Table 36. ECLIPSE-SNP SAE by SOC by Day 7

System organ class/ Preferred Term	Clevipine (N=296) n (%)		Sodium nitroprusside (N=283) n (%)	
Patients with at least one SAE	57	(19.3)	66	(23.3)
Cardiac disorders	19	(6.4)	22	(7.8)
Renal and urinary disorders	14	(4.7)	10	(3.5)
Respiratory, thoracic and mediastinal disorders	13	(4.4)	20	(7.1)
Injury, poisoning and procedural complications	6	(2.0)	5	(1.8)
Gastrointestinal disorders	5	(1.7)	6	(2.1)
Nervous system disorders	4	(1.4)	5	(1.8)
Psychiatric disorders	4	(1.4)	0	(0.0)

Taken from table 23, pg 77 of 10485 of ECLIPSE-SNP report

The investigator judged 4 SAEs (CHF, MI, vfib, and hypoxia) in clevidipine treated patients in ECLIPSE-NIC to be possibly related to study drug and 1 SAE (vfib) in a NTG treated patient.

Table 37. ECLIPSE-NIC SAEs by SOC by Day 7

System organ class/	Clevipine (N=188) n (%)		Nicardipine (N=193) n (%)	
Patients with at least one SAE	33	(17.6)	34	(17.6)
Respiratory, thoracic, and mediastinal disorders	12	(6.4)	9	(4.7)
Cardiac disorders	9	(4.8)	10	(5.2)
Vascular disorders	5	(2.7)	2	(1.0)
General disorders and administration site conditions	4	(2.1)	0	(0.0)
Infections and infestations	4	(2.1)	4	(2.1)
Nervous system disorders	4	(2.1)	6	(3.1)
Gastrointestinal disorders	2	(1.1)	2	(1.0)

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Renal and urinary disorders	2 (1.1)	4 (2.1)
Injury, poisoning, and procedural complications	1 (0.5)	3 (1.6)
Psychiatric disorders	1 (0.5)	1 (0.5)
Endocrine disorders	0 (0.0)	1 (0.5)
Investigations	0 (0.0)	1 (0.5)
Metabolism and nutrition disorders	0 (0.0)	1 (0.5)
Skin and subcutaneous tissue disorders	0 (0.0)	1 (0.5)

Source: Table 7.7, Section 14.1

Serious adverse events reported in this table are from first study drug initiation to discharge or seven days postoperation, whichever occurred first.

Taken from sponsor table 23, pg 75 of 7102, ECLIPSE-NIC report

When analyzed by individual study the events are few. In the following table the reviewer analyzed the top SOCs by type of hypertension. The cardiac disorders recorded over 30 days are shown in the table below. The reviewer's sum of cardiac disorders are more for clevidipine (97 vs. 76-sponsor), active control (98 vs. 68-sponsor), and placebo (10 vs. 9-sponsor). Comparison of reviewer's cardiac disorders by Day 7 to the Sponsor's individual tables (previously shown) also finds differences between all three groups: clevidipine (81 vs. 52-sponsor), active control (75 vs. 54-sponsor), and placebo (10 vs. 9-sponsor). The reason for the discrepancy is because if a patient had more than one cardiac disorder, the sponsor counted the patient only once.

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Table 38. Cardiac disorders in perioperative hypertension patients

	CLV N=1093	(%)	Nic N=193	(%)	Ntg N=334	(%)	Snp N=312	(%)	Pbo N=133	(%)
Afib	33	3.02	8	4.15	10	2.99	13	4.17	1	0.75
AMI/MI	9	0.82	0	0.00	1	0.30	1	0.32	3	2.26
A flutter	9	0.82	0	0.00	1	0.30	4	1.28	0	0.00
Vfib	8	0.73	1	0.52	5	1.50	5	1.60	0	0.00
cardiac arrest/failure/CR arrest	7	0.64	5	2.59	4	1.20	8	2.56	0	0.00
CHF/LV or RV failure/ventricular dysfunction	7	0.64	2	1.04	2	0.60	2	0.64	0	0.00
cardiogenic shock	3	0.27	1	0.52	1	0.30	0	0.00	0	0.00
cardiac tamponade	3	0.27	0	0.00	1	0.30	1	0.32	2	1.50
Vtach	3	0.27	0	0.00	1	0.30	5	1.60	1	0.75
pericardial effusion	3	0.27	0	0.00	0	0.00	0	0.00	0	0.00
sick sinus syndrome	3	0.27	0	0.00	0	0.00	0	0.00	0	0.00
bradyarrhythmia/cardia	2	0.18	0	0.00	2	0.60	1	0.32	0	0.00
pericarditis	2	0.18	0	0.00	0	0.00	0	0.00	0	0.00
AV block complete	1	0.09	1	0.52	3	0.90	1	0.32	0	0.00
SVT	1	0.09	1	0.52	0	0.00	0	0.00	0	0.00
low cardiac output syndrome	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
nodal rhythm	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
pericardial hemorrhage	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
AV block	0	0.00	1	0.52	0	0.00	0	0.00	1	0.75
sinus tach	0	0.00	0	0.00	2	0.60	0	0.00	0	0.00
MV incompetence	0	0.00	0	0.00	1	0.30	0	0.00	0	0.00
USA	0	0.00	0	0.00	0	0.00	1	0.32	0	0.00
AV block 2 degree	0	0.00	0	0.00	0	0.00	0	0.00	1	0.75
CAD	0	0.00	0	0.00	0	0.00	1	0.32	0	0.00
ventricular rupture	0	0.00	0	0.00	0	0.00	1	0.32	0	0.00
Sum Cardiac disorders	97	8.9	20	10.4	34	7.2	44	14.1	10	7.5
Sponsor sum Cardiac disorders	76		68	11.7	68	(AC)			9	

Data from d_ae.xpt in ISS

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Table 39. Cardiac disorders in perioperative hypertension patient by Day 7

	CLV N=1093		Nic N=193		Ntg N=334		Snp N=312		Pbo N=133	
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
afib	27	2.47	5	2.59	9	2.69	11	3.53	1	0.75
Vfib	8	0.73	1	0.52	5	1.50	5	1.60	0	0.00
AMI/MI	8	0.73	0	0	1	0.30	1	0.32	3	2.26
a flutter	7	0.64	0	0	1	0.30	3	0.96	0	0.00
cardiac arrest/failure/CR arrest	6	0.55	2	1.04	2	0.60	1	0.32	0	0.00
cardiogenic shock	3	0.27	1	0.52	1	0.30	0	0.00	0	0.00
cardiac tamponade	3	0.27	0	0.00	1	0.30	1	0.32	2	1.50
Vtach	3	0.27	0	0	1	0.30	5	1.60	1	0.75
pericardial effusion	3	0.27	0	0.00	0	0.00	0	0.00	0	0.00
sick sinus	3	0.27	0	0.00	0	0.00	0	0.00	1	0.75
bradyarrhythmia/cardia	2	0.18	0	0.00	2	0.60	1	0.32	0	0.00
pericarditis	2	0.18	0	0.00	0	0.00	0	0.00	0	0.00
SVT	1	0.09	1	0.52	0	0.00	0	0.00	0	0.00
AV block complete	1	0.09	0	0.00	3	0.90	1	0.32	0	0.00
CHE/LV or RV failure/ventricular dysfunction	1	0.09	0	0.00	2	0.60	1	0.32	0	0.00
low cardiac output syndrome	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
nodal rhythm	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
pericardial hemorrhage	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
AV block	0	0.00	1	0.52	0	0.00	0	0.00	1	0.75
sinus tach	0	0.00	0	0.00	2	0.60	0	0.00	0	0.00
MV incompetence	0	0.00	0	0.00	1	0.30	0	0.00	0	0.00
AV block 2 degree	0	0.00	0	0.00	0	0.00	0	0.00	1	0.75
CAD	0	0.00	0	0.00	0	0.00	1	0.32	0	0.00
USA	0	0.00	0	0	0	0.00	1	0.32	0	0.00
ventricular rupture	0	0.00	0	0.00	0	0.00	1	0.32	0	0.00
Sum Cardiac disorders	81	7.4	11	5.7	31	9.3	33	10.6	10	7.5

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The top reasons for respiratory disorders SAEs are shown in the table below.

Table 40. Respiratory disorders in perioperative hypertension patients

	CLV N=1093	(%)	Nic N=193	(%)	Ntg N=334	(%)	Snp N=312	(%)	Pbo N=133	(%)
respiratory failure/arrest	22	2.01	5	2.59	9	2.69	9	2.88	2	1.50
pleural effusion	8	0.73	2	1.04	0	0.00	0	0.00	0	0.00
respiratory distress	7	0.64	3	1.55	0	0.00	0	0.00	0	0.00
pulmonary edema	7	0.64	0	0.00	1	0.30	1	0.32	0	0.00
mediastinal hemorrhage	5	0.46	1	0.52	2	0.60	3	0.96	0	0.00
dispend/hypoxia	4	0.37	1	0.52	0	0.00	2	0.64	0	0.00
pulmonary embolism	4	0.37	1	0.52	0	0.00	3	0.96	1	0.75
pneumothorax	3	0.27	2	1.04	3	0.90	3	0.96	1	0.75
atelectasis	3	0.27	0	0.00	0	0.00	0	0.00	0	0.00
dependent on respiratory	2	0.18	0	0.00	0	0.00	1	0.32	0	0.00
ARDS	1	0.09	0	0.00	3	0.90	1	0.32	0	0.00
pulmonary HTN	1	0.09	0	0.00	1	0.30	0	0.00	0	0.00
apnea	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
bronchospasm	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
chylothorax	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
respiratory gas exchange disorder	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
tracheal edema	1	0.09	0	0.00	0	0.00	0	0.00	0	0.00
COPD	0	0.00	0	0.00	1	0.30	0	0.00	0	0.00
wheezing	0	0.00	0	0.00	1	0.30	0	0.00	0	0.00
pulmonary hemorrhage	0	0.00	0	0.00	0	0.00	1	0.32	0	0.00
Sum respiratory disorder	72	6.6	15	7.8	21	6.3	24	7.7	4	3.1
Sponsor sum respiratory disorder	61	5.6	56	8.1(AC)	4	3.0	4	3.0	4	3.0

Data from d_ae.xpt in ISS

The incidence of death, stroke, MI and renal dysfunction (defined in Appendix, Section 10.1.1) occurring from the initiation of study drug infusion through postoperative Day 30 was the primary endpoint in the ECLIPSE safety trials. These endpoints were adjudicated by a blinded Clinical Endpoints Committee (CEC). The table below shows the CEC adjudicated events for those other than death. There were slightly more strokes in the Active Comparator arm and slightly more AMI and renal dysfunction in the clevidipine arm.

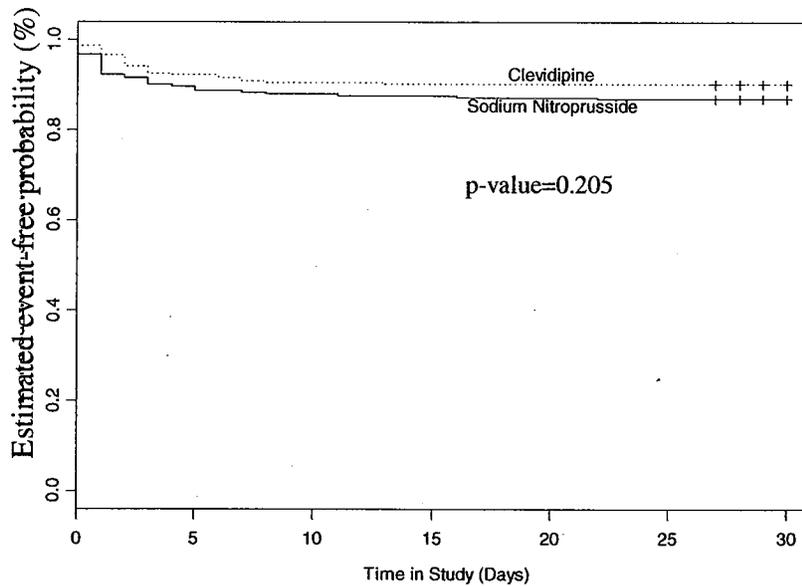
Table 41. CEC adjudicated events in ECLIPSE trials, (%)

	Total (n=1506)	CLV (n=752)	AC (n=754)	NIC (n=193)	NTG (n=278)	SNP (n=283)
Stroke	34	10 (1.4)	17 (2.3)	8	6	3
Died	4	2	2		1	1
AMI	90	47(6.3)	43 (5.7)	11	10	22
Died	14	7	7	2	2	3
Renal dysfunction¹	312	168 (22.3)	144 (19.1)	35	52	57
Died	12	8	4	0	1	3

Stroke for ID TMC-CLV-03-03_00335_00034 was not coded in sponsor d_ae.xpt

Although the intent of the ECLIPSE trials was to assess safety, there was no prespecified alpha priori for these endpoints combined or individually. Sample size in all three trials was arbitrarily chosen, and there was no study power calculation. Only the ECLIPSE-SNP study hinted at a nominally significant mortality benefit of clevidipine compared to SNP. The reviewer's analysis of the combined endpoint through 30 days shows that there is no difference between clevidipine and SNP (see figure). There were 37 primary endpoint events in the SNP group and 29 in the clevidipine group. The log-rank p-value is not significant (p=0.205).

Figure 21. Kaplan Meier event free curves through 30 days- ECLIPSE-SNP



The sponsor's CEC adjudicated endpoints table is shown below. The sponsor acknowledges that there were no clinically meaningful differences between clevidipine and active comparators.

Table 42. CEC adjudicated events – ECLIPSE

Term	Clevipidine (N=752)	All Active Comparators (N=754)
Any CEC-adjudicated event, n (%)	77 (10.7)	86 (11.8)
Death	20 (2.8)	28 (3.8)
Stroke	8 (1.1)	12 (1.7)
Myocardial infarction	16 (2.3)	17 (2.4)
Renal dysfunction	56 (7.9)	56 (7.9)
Death or stroke	27 (3.8)	36 (4.9)
Death or MI	35 (4.9)	38 (5.2)
Death or stroke or MI	41 (5.7)	46 (6.3)

Source: Table 4.1, Appendix 8.2.1

Note: Losses to follow-up and missing values are not included in the calculation of incidence rates. See IAS Section 2.1.4.1 for definitions of events.

Taken from Sponsor's table 14, pg 49 of 6157, ISS

The clinical events rates at Day 30 from cardiac surgery patients in the Society of Thoracic Surgeons National database are shown below. The higher incidence rates of MI may be due to the definition of AMI in the ECLIPSE studies (subclinical infarcts based on enzyme elevations and/or ECG changes alone).

Table 43. Clinical event rates at Day 30 for cardiac surgery patients

Clinical Event	Primary ON Pump (%) N= 564,275	Primary OFF Pump (%) N= 140,981	Primary Valve Surgeries (%) N= 124,683	Range for all cardiac surgeries ^b (%) 870,671-1,018,755	Table no. in STS database
Death	2.7	2.1	4.47 ^c	1.84-9.61	15
MI	0.90	0.90	0.44	0.37-2.35	14
Stroke	1.1	1.1	1.90	1.10-3.48	14

^a Source: Society of Thoracic Surgeons Database: data analysis 2000-2004 [STS database] Tables 14 and 15. Rates of reported incidence of events are for only Primary CABG and Primary valve surgery patients.

^b Including mitral valve repair, mitral and/or aortic valve replacement, primary or reop on- or off-pump CABG surgery.

^c For aortic valve replacement only, N=71,575

Taken from Table 15, pg 50 of 6157 of ISS

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

The table below includes an overall profile of dropouts for the TMC conducted studies. The * for the "other" dropouts in the VELOCITY study included 7 that did not complete the study and 9 that had less than 18 hours of clevidipine. The "other" in ECLIPSE-SNP was a patient that did not have CABG due to a new diagnosis of cancer. The reviewer could not find information on completers in ESCAPE-2. The discontinuations due to AE are described in the next section.

Table 44. Overall profile of dropouts in TMC studies

Study	number	Drug	n	n complete	n withdraw	lost	died	other	w/d consent	physician decision	d/c AE
ESCAPE-1	03-01	CLV	53	52			1				1
		PBO	51	51			0				1
ESCAPE-2	03-02	CLV	61	61			0				2
		PBO	49	49		1					
ECLIPSE-NTG	03-03	CLV	268	253	15	8	7				13
		NTG	278	265	13	4	9				4
ECLIPSE-SNP	03-04	CLV	296	286	10	4	5	1			7
		SNP	283	268	15	1	13		1		6
ECLIPSE-NIC	03-05	CLV	188	176	12	3	8			1	13
		NIC	193	186	7	1	6				11
VELOCITY	06-02	CLV	126	110	16		3	*			6
TMC-CLV	02-01	CLV	49	48	1		1			1	
		NTG	51	49	2		1			1	1
TMC-CLV	05-01	CLV	46	32	14	0	0	9	3	0	2
TMC-CLV	06-01	CLV	48	47	1	0	0	0	0	0	1
		PBO	13	13	0	0	0	0	0	0	0

7.1.3.2 Adverse events associated with dropouts

Most of the AEs leading to discontinuation occurred in the perioperative setting. The most common AE leading to discontinuation was hypotension (true for both clevidipine and active comparators). The second most common AE leading to discontinuation in the clevidipine group was hypertension. The AE of hypoxia occurred twice in the active comparator arms, while all other AEs leading to discontinuation occurred only once. Hypotension and hypertension were further explored by the reviewer.

Of the healthy volunteers, 3 treated with clevidipine and 1 treated with placebo discontinued due to headache, nausea and vomiting (see table).

Table 45. AE leading to discontinuation in healthy subjects

SOC preferred term	CLV (n=99), n (%)	Pbo (n=64), n (%)
Patients with ≥ 1 AE	3 (3.0)	1 (1.6)
Nervous system disorders	3 (3.0)	1 (1.6)
headache	3 (3.0)	0
dizziness	0	1 (1.6)
GI disorders	2 (2.0)	0
nausea	2 (2.0)	0
Vomiting	2 (2.0)	0

Taken from Sponsor Table 2.4.5., pg 234 of 6157, ISS

The clevidipine group had more patients (5.5% vs. 3.2%) discontinuing treatment due to an AE compared to the active comparator. Yet, it should be kept in mind that specific dosing instructions were not given for the active comparator, as they were for clevidipine. Whether the clevidipine dosing instructions were appropriate is debatable and discussed later. The sponsor's table below should read n=74 with at least 1 AE for clevidipine instead of n=72. There were two subjects (001_123 and 001_422) from study SH-SAD-0003 with study drug listed as unknown, but review of their narrative shows that the received clevidipine (randomized to 9.58 ug/kg/min).

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Table 46. AE leading to discontinuation in hypertensive patients

System Organ Class Preferred Term	Clevipidine (N=1301)	Placebo (N=159)	Nitroglycerin (N=334)	Sodium Nitroprusside (N=312)	Nicardipine (N=193)	All Active Comparators (N=839)
Patients with at least one adverse event, n (%)	72 (5.5)	1 (0.6)	9 (2.7)	7 (2.2)	11 (5.7)	27 (3.2)
Vascular disorders	39 (3.0)	1 (0.6)	5 (1.5)	4 (1.3)	6 (3.1)	15 (1.8)
Hypotension	25 (1.9)	0 (0.0)	4 (1.2)	4 (1.3)	6 (3.1)	14 (1.7)
Hypertension	11 (0.8)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemorrhage	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Flushing	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pallor	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiac disorders	16 (1.2)	0 (0.0)	1 (0.3)	1 (0.3)	2 (1.0)	4 (0.5)
Atrial fibrillation	3 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Ventricular fibrillation	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)
Bradycardia	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Supraventricular tachycardia	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Atrial flutter	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block complete	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block second degree	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure congestive	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardio-respiratory arrest	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Low cardiac output syndrome	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial ischaemia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Supraventricular extrasystoles	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ventricular tachycardia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiogenic shock	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Cardiac tamponade	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)

continued

System Organ Class Preferred Term	Clevidipine (N=1301)	Placebo (N=159)	Nitroglycerin (N=334)	Sodium		All Active Comparators (N=839)
				Nitroprusside (N=312)	Nicardipine (N=193)	
Investigations	6 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Blood pressure systolic decreased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood triglycerides increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood urea increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Haemoglobin decreased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oxygen saturation decreased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary arterial pressure increased	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram ST segment depression	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	4 (0.3)	0 (0.0)	0 (0.0)	2 (0.6)	3 (1.6)	5 (0.6)
Hypoxia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)	2 (0.2)
Acute respiratory failure	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary hypertension	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory arrest	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Atelectasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Pulmonary haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Pulmonary oedema	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Respiratory gas exchange disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)
Psychiatric disorders	3 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Confusional state	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Restlessness	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	Clevodipine (N=1301)	Placebo (N=159)	Nitroglycerin (N=334)	Sodium Nitroprusside (N=312)	Nicardipine (N=193)	All Active Comparators (N=839)
Injury, poisoning and procedural complications	2 (0.2)	0 (0.0)	3 (0.9)	1 (0.3)	0 (0.0)	4 (0.5)
Incision site complication	2 (0.2)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Post procedural haemorrhage	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Post procedural pain	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Venous Injury	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
General disorders and administration site conditions	2 (0.2)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.2)
Chest discomfort	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Chest pain	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Oedema	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Anasarca	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Blood and lymphatic system disorders	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Thrombocytopenia	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Renal and urinary disorders	1 (0.1)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Renal insufficiency	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure acute	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)
Gastrointestinal disorders	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Nausea	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.1)
Nervous system disorders	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)
Headache	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 3.4.5, Appendix 8.2.1

Note: Patients who received more than one treatment are counted in each of their treatment groups.

In hypertensive patients, the most common reason for discontinuation due to an AE was for a vascular disorder (SOC) with hypotension and hypertension the most common of the vascular disorders (see table).

Only 1 patient in the essential hypertension group (treated with clevidipine) discontinued due to an AE. This patient experienced nausea and headache.

Table 47. AE leading to discontinuation by type of hypertension

System Organ Class Preferred Term	Essential		Perioperative		All active comparators (N=839)	Severe Clevidipine (N=126)
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)		
Patients with at least one adverse event, n (%)	1 (1.2)	0 (0.0)	65 (5.9)	1 (0.8)	27 (3.2)	6 (4.8)
Vascular disorders	0 (0.0)	0 (0.0)	37 (3.4)	1 (0.8)	15 (1.8)	2 (1.6)
Hypotension	0 (0.0)	0 (0.0)	24 (2.2)	0 (0.0)	14 (1.7)	1 (0.8)
Hypertension	0 (0.0)	0 (0.0)	11 (1.0)	1 (0.8)	0 (0.0)	0 (0.0)
Haemorrhage	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Pallor	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Ischaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Flushing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Cardiac disorders	0 (0.0)	0 (0.0)	14 (1.3)	0 (0.0)	4 (0.5)	2 (1.6)
Atrial fibrillation	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	1 (0.1)	0 (0.0)
Ventricular fibrillation	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)
Bradycardia	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Atrial flutter	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block complete	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Atrioventricular block second degree	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Continued

System Organ Class Preferred Term	Essential		Perioperative			Severe
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)	All active comparators (N=839)	Clevidipine (N=126)
Cardiac failure congestive	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Low cardiac output syndrome	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Myocardial ischaemia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Supraventricular extrasystoles	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Tachycardia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.8)
Ventricular tachycardia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiogenic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cardiac tamponade	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Cardio-respiratory arrest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	4 (0.4)	0 (0.0)	5 (0.6)	0 (0.0)
Hypoxia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	2 (0.2)	0 (0.0)
Acute respiratory failure	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pulmonary hypertension	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory arrest	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Atelectasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Pulmonary haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Pulmonary oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Respiratory gas exchange disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Investigations	0 (0.0)	0 (0.0)	4 (0.4)	0 (0.0)	1 (0.1)	2 (1.6)
Blood urea increased	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Haemoglobin decreased	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Oxygen saturation decreased	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Continued

System Organ Class Preferred Term	Essential		Perioperative			Severe
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)	All active comparators (N=839)	Clevidipine (N=126)
Blood pressure systolic decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Blood triglycerides increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Pulmonary arterial pressure increased	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Electrocardiogram ST segment depression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Confusional state	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Restlessness	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	4 (0.5)	0 (0.0)
Incision site complication	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)
Post procedural haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Post procedural pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Venous Injury	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	0 (0.0)
Renal insufficiency	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Renal failure acute	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)

Continued

System Organ Class Preferred Term	Essential		Perioperative			Severe
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)	All active comparators (N=839)	Clevidipine (N=126)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Erythema	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.2)	2 (1.6)
Oedema	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Anasarca	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Chest discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Chest pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Gastrointestinal disorders	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Nausea	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)
Headache	1 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Source: Table 9.4.5, Appendix 8.2.1

Note: Patients who received more than one treatment are counted in each of their treatment groups.

Take from Sponsor's table 34, pg 85 of 6157

7.1.3.2.1 Hypotension leading to discontinuation

Most of the clevidipine treated patients with vascular disorder AEs leading to discontinuation were in study SH-SAD-0003 (see table). This was the force titration, dose finding study in cardiac surgery patients with prespecified BP criteria for withdrawal. These withdrawals were recorded as AEs. The sponsor listed one subject (TMC-CLV-06-02_00111_00005) in the severe HTN study under Investigations while the event was hypotension. The reviewer placed this 53 yo BF in the "hypotension" preferred term in her table. **In the ECLIPSE and ESCAPE trials, hypotension was not recorded as an AE during study drug administration unless it could not be corrected with titration or cessation of the study drug or reversed by standard treatment procedures. AEs were to be recorded according to ICH standards of an AE, which meant that the event had to untoward medical occurrence or unfavorable and unintended sign, symptom or disease. Subjects that had hypotension reversed by stopping or lowering the infusion rate were not considered AEs in the absence of untoward medical occurrence or unfavorable and unintended sign, symptom or disease.**

Table 48. Hypotension leading to discontinuation in all studies

Study	CLV, other,		CLV							
	n	n	%	NIC	%	NTG	%	SNP	%	pbo
SH-SAD-0003	89	2	10	11.2						0
SH-SAD-0013	16	15	0	0.0				1	6.7	
TMC-CLV-02-01	49	51	5	10.2		3	5.9			
ECLIPSE-NTG (03-03)	268	278	2	0.7		1	0.4			
ECLIPSE-SNP (03-04)	296	283	1	0.3				3	1.1	
ECLIPSE-NIC (03-05)	188	193	8	4.3	6	3.1				
VELOCITY (06-02)	126		2	1.6						
Total			26		6		4		4	

Data from d_ae.xpt in ISS

Dosing information for the active comparators was not available. The table below shows the mean for the initial infusion rate, average infusion rate, and maximum infusion rate by study. Assuming that hypotension is related to dose, the range of the maximum infusion rate was wide, 0.18 to 8.3 ug/kg/min. The average infusion rate is relatively low, considering the initial starting dose in the ECLIPSE and ESCAPE studies was 0.4 ug/kg/min. On average, patients were also receiving clevidipine for several hours before experiencing hypotension leading to dropout (see Infusion duration in table).

Table 49. Mean clevidipine dose in subjects discontinuing due to hypotension

Study	Ave infusion rate, ug/kg/min	Infusion duration, h	Initial infusion rate, ug/kg/min	Maximum infusion rate, ug/kg/min
SH-SAD-0003 (n=8)*	1.3 ± 1.4 (0.18 - 3.42)	0.8 ± 0.5 (0.28 - 1.65)	1.2 ± 0.8 (0.18 - 2.38)	2.1 ± 1.7 (0.18 - 4.54)
TMC-CLV-02-01 (n=5)	Not available	6.3 ± 3.5 (3.3 - 10.9)	0.3 ± 0.1 (0.2 - 0.4)	Not available
ECLIPSE-NTG (03-03) (n=2)	0.9 ± 0.8 (0.3 - 1.4)	6.1 ± 0.5 (5.8 - 6.5)	0.4 ± 0.0 (0.4 - 3.2)	2.0 ± 1.7 (0.8 - 3.2)
ECLIPSE-SNP (03-04) (n=1)	0.5	9.6	0.3	8.3
ECLIPSE-NIC (03-05) (n=8)	1.2 ± 1.1 (0.3 - 3.3)	4.8 ± 4.1 (0.1 - 16.5)	0.6 ± 0.4 (0.4 - 1.4)	2.7 ± 2.7 (0.4 - 7.9)
VELOCITY (06-02) (n=2)	1.1 ± 0.3 (0.8 - 1.3)	10.3 ± 10.2 (3.1 - 17.5)	0.4 ± 0.1 (1.4 - 1.5)	1.5 ± 0.1 (1.4 - 1.5)

Mean ± SD (min - max)

*Note that study SH-SAD-0003 is missing dosing information in the SAS dataset for the two IDs that were randomized to 9.58 ug/kg/min. ID 001_0422 was a 46 yo BF who had her infusion prematurely stopped 7 minutes after the start of the infusion due to hypotension. Concomitant medications included anesthesia, **nitroglycerin**, insulin, **nitroprusside**, sodium and propofol. ID 001_0123 was a 50 yo M who escaped to the next lower dose arm (3.19 uk/kg/min) (reason not stated, but most likely hypotension) and had the infusion stopped at 6 minutes after the start of the initial infusion. Concomitant medication was anesthesia, **glyceryl trinitrate**, sodium lactate compound injection, **nitroprusside** and propofol.

Most of the hypotensive events leading to discontinuation occurred on Day 0 (n=35), 6 occurred on Day 1 and 1 occurred on Day 4.

7.1.3.2.2 Hypertension leading to discontinuation

Hypertension leading to discontinuation occurred in 11 clevidipine treated subjects and 1 placebo treated subject out of all hypertensive subjects. (This was the only discontinuation due to an AE in the placebo arm.) There were no hypertension cases leading to discontinuation in the active comparator arms. Of the clevidipine treated cases, 9 were in study SH-SAD-0003, 1 was in SH-SAD-0006, and 1 was in SH-SAD-0013. Six of the nine subjects in study SH-SAD-0003 were randomized to the lowest dose of 0.05 ug/kg/min. ID SH-SAD-0006_00001_00009 was started at 0.9 ug/kg/min and titrated up to 2.7 ug/kg/min. The infusion was stopped after 3 minutes due to hypertension and bleeding. The subject was also on glyceryl trinitrate and isosorbide mononitrate. The subject was switched to nifedipine which was able to control the blood pressure and bleeding after an hour. ID SH-SAD-0013_00002_00044 was started at 0.3 ug/kg/min and titrated up to 5.5 ug/kg/min. The infusion was stopped after 48 minutes due to inadequate BP control. The subject was also on glyceryl trinitrate and metoprolol. The subject was switched to nifedipine which was able to control the blood pressure. **In the ECLIPSE and ESCAPE trials, hypertension occurring during study drug administration was not recorded as an AE.**

7.1.3.2.3 AE leading to discontinuation by dose

Other than hypotension and hypertension, there were not enough AEs for other preferred terms to make any meaningful analysis by dose.

7.1.3.3 Other significant adverse events

7.1.3.3.1 Hypotension

There were a total of 368 AE reports of hypotension (219 on clevidipine) in the ISS, occurring from Day -9 to Day 30. Examination of those from Day -1 to Day 7 resulted in 361 events (214 on clevidipine), with 54% (n=197) occurring on Day 0 and 22% occurring on day 1. The dose was examined for possible trends between hypotension and dose. There was no apparent trend as the initial infusion rate as well as average and maximum infusion rates were relatively low (see table). Of the clevidipine hypotensive cases (n=214), clevidipine dose was adjusted in 6, dose was not changed in 41, dose was temporarily interrupted in 3, drug was withdrawn in 28, action taken was "not applicable" in 117, and unknown or missing in 16.

Table 50. Mean dose in clevidipine subjects with hypotension occurring from day -1 to day 7

Study	Ave infusion rate, ug/kg/min	Infusion duration, h	Initial infusion rate, ug/kg/min	Maximum infusion rate, ug/kg/min
SH-SAD-0003 (n=24)*	1.0 ± 1.1 (0.04 – 3.42)	1.0 ± 0.8 (0.22 – 2.78)	0.8 ± 0.8 (0.04 – 2.38)	1.5 ± 1.4 (0.04 – 4.55)
TMC-CLV-02-01 (n=15)	Not available	12.6 ± 5.3 (3.3 – 19.2)	0.3 ± 0.1 (0.2 – 0.5)	Not available
ESCAPE -1 (03-01) (n=3)	2.7 ± 2.1 (0.6 – 4.8)	0.5 ± 0.0 (0.4 – 0.4)	0.4 ± 0.0 (0.4 – 0.4)	3.5 ± 2.7 (0.8 – 6.2)
ESCAPE-2 (03-02) (n=1)	0.4	1.0	--	--
ECLIPSE-NTG (03-03) (n=39)	0. ± 0.5 (0.2 – 3.1)	5.8 ± 8.3 (0.1 – 37.9)	0.5 ± 0.5 (0.2 – 3.2)	1.5 ± 1.5 (0.4 – 8.1)
ECLIPSE-SNP (03-04) (n=51)	0.9 ± 0.8 (0.2 – 4.9)	7.3 ± 10.5 (0.2 – 66.0)	0.7 ± 2.1 (0.1 – 15.3)	2.0 ± 2.5 (0.4 – 15.3)
ECLIPSE-NIC (03-05) (n=50)	0.9 ± 0.8 (0.3 – 4.0)	8.3 ± 8.9 (0.1 – 32.1)	0.5 ± 0.6 (0.2 – 4.0)	1.9 ± 1.9 (0.4 – 7.9)
VELOCITY (06-02) (n=2)	1.1 ± 0.3 (0.8 – 1.3)	10.3 ± 10.2 (3.1 – 17.5)	0.4 ± 0.1 (1.4 – 1.5)	1.5 ± 0.1 (1.4 – 1.5)

Mean ± SD (min - max)

*Again, IDs 001_0422 and 001_0123 were not included in the calculations.

The sponsor's table below shows the incidence of hypotension through Day 7.

Table 51. Hypotension

System Organ Class Preferred Term	Essential		Perioperative			All active comparators (N=839)	Severe Clevipidine (N=126)
	Clevipidine (N=82)	Placebo (N=26)	Clevipidine (N=1093)	Placebo (N=133)			
Hypotension	0 (0.0)	0 (0.0)	184 (16.8)	3 (2.3)	130 (15.5)	2 (1.6)	
Hypotension	0 (0.0)	0 (0.0)	169 (15.5)	2 (1.5)	124 (14.8)	1 (0.8)	
Blood pressure decreased	0 (0.0)	0 (0.0)	11 (1.0)	0 (0.0)	4 (0.5)	0 (0.0)	
Orthostatic hypotension	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	
Blood pressure systolic decreased	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	1 (0.1)	1 (0.8)	
Procedural hypotension	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.8)	0 (0.0)	0 (0.0)	

Taken from sponsor table 35, pg 89 of 6157

7.1.4 Other Search Strategies

None.

7.1.5 Common Adverse Events

The most common (≥ 5%) adverse events for clevidipine in the entire clinical program are shown in the following table by type of hypertension. The most common AE in essential hypertensive patients was **headache** (40.2% vs. placebo rate of 15.4%) followed by **polyuria** (7.3% vs.

placebo rate of 0%), **infusion site reaction** (7.3% vs. placebo rate of 15.4%), and **nausea** (7.3% vs. placebo rate of 0%). The common AEs in the perioperative patients were for the most part similar between clevidipine and active comparator. There were a few exceptions, clevidipine had less sinus tachycardia, incision site complications (and other AE associated with this), hyperglycemia, fluid overload, anemia, thrombocytopenia, and more insomnia. The most common AE in the severe hypertension group was headache (7.1%) and **nausea** (4.8%). **Edema** is a known consequence of excessive intravascular volume replacement. Its overall occurrence (see table) was less compared to AC (incidence somewhat higher for lower clevidipine doses). However, there was no difference between clevidipine and AC for “edema” and “peripheral edema”.

Table 52. Edema

System Organ Class Preferred Term	Essential		Perioperative			Severe
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)	All active comparators (N=839)	Clevidipine (N=126)
Edema	0 (0.0)	0 (0.0)	459 (42.0)	15 (11.3)	385 (45.9)	2 (1.6)
Oedema peripheral	0 (0.0)	0 (0.0)	144 (13.2)	3 (2.3)	107 (12.8)	1 (0.8)
Oedema	0 (0.0)	0 (0.0)	118 (10.8)	6 (4.5)	98 (11.7)	0 (0.0)
Anasarca	0 (0.0)	0 (0.0)	109 (10.0)	2 (1.5)	92 (11.0)	1 (0.8)
Fluid overload	0 (0.0)	0 (0.0)	63 (5.8)	1 (0.8)	73 (8.7)	0 (0.0)
Pulmonary congestion	0 (0.0)	0 (0.0)	61 (5.6)	2 (1.5)	56 (6.7)	0 (0.0)
Pulmonary oedema	0 (0.0)	0 (0.0)	59 (5.4)	5 (3.8)	64 (7.6)	0 (0.0)
Fluid retention	0 (0.0)	0 (0.0)	9 (0.8)	0 (0.0)	1 (0.1)	0 (0.0)
Pitting oedema	0 (0.0)	0 (0.0)	8 (0.7)	0 (0.0)	4 (0.5)	0 (0.0)
Gravitational oedema	0 (0.0)	0 (0.0)	5 (0.5)	0 (0.0)	1 (0.1)	0 (0.0)
Acute pulmonary oedema	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)
Generalised oedema	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Taken from sponsor table 36, pg 91 of 6157 of ISS report

Table 53. Common (≥5%) AE

System Organ Class Preferred Term	Essential		Perioperative		All active comparators (N=839)	Severe Clevipidine (N=126)
	Clevipidine (N=82)	Placebo (N=26)	Clevipidine (N=1093)	Placebo (N=133)		
Cardiac disorders						
Atrial fibrillation	0 (0.0)	0 (0.0)	332 (30.4)	20 (15.0)	258 (30.8)	1 (0.8)
Sinus tachycardia	0 (0.0)	0 (0.0)	230 (21.0)	1 (0.8)	231 (27.5)	0 (0.0)
Ventricular extrasystoles	0 (0.0)	0 (0.0)	117 (10.7)	0 (0.0)	97 (11.6)	1 (0.8)
Ventricular tachycardia	1 (1.2)	0 (0.0)	99 (9.1)	6 (4.5)	72 (8.6)	0 (0.0)
Supraventricular extrasystoles	1 (1.2)	0 (0.0)	78 (7.1)	0 (0.0)	55 (6.6)	0 (0.0)
Respiratory, thoracic and mediastinal disorders						
Atelectasis	0 (0.0)	0 (0.0)	403 (36.9)	7 (5.3)	318 (37.9)	0 (0.0)
Pleural effusion	0 (0.0)	0 (0.0)	299 (27.4)	8 (6.0)	254 (30.3)	0 (0.0)
Breath sounds decreased	0 (0.0)	0 (0.0)	119 (10.9)	0 (0.0)	101 (12.0)	0 (0.0)
Rhonchi	0 (0.0)	0 (0.0)	96 (8.8)	0 (0.0)	78 (9.3)	0 (0.0)
Dyspnoea	0 (0.0)	0 (0.0)	87 (8.0)	0 (0.0)	60 (7.2)	1 (0.8)
Wheezing	0 (0.0)	0 (0.0)	70 (6.4)	2 (1.5)	65 (7.7)	0 (0.0)
Pulmonary congestion	0 (0.0)	0 (0.0)	61 (5.6)	2 (1.5)	56 (6.7)	0 (0.0)
Pulmonary oedema	0 (0.0)	0 (0.0)	59 (5.4)	5 (3.8)	64 (7.6)	0 (0.0)
Pneumothorax	0 (0.0)	0 (0.0)	56 (5.1)	3 (2.3)	49 (5.8)	0 (0.0)
Injury, poisoning and procedural complications						
Incision site complication	0 (0.0)	0 (0.0)	442 (40.4)	3 (2.3)	438 (52.2)	0 (0.0)
Post procedural pain	0 (0.0)	0 (0.0)	121 (11.1)	1 (0.8)	113 (13.5)	0 (0.0)
Post procedural discharge	0 (0.0)	0 (0.0)	60 (5.5)	0 (0.0)	52 (6.2)	0 (0.0)

continued

System Organ Class Preferred Term	Essential		Perioperative			Severe
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)	All active comparators (N=839)	Clevidipine (N=126)
General disorders and administration site conditions						
Pyrexia	3 (3.7)	0 (0.0)	150 (13.7)	13 (9.8)	123 (14.7)	0 (0.0)
Oedema peripheral	0 (0.0)	0 (0.0)	144 (13.2)	3 (2.3)	107 (12.8)	1 (0.8)
Oedema	0 (0.0)	0 (0.0)	118 (10.8)	6 (4.5)	98 (11.7)	0 (0.0)
Anasarca	0 (0.0)	0 (0.0)	109 (10.0)	2 (1.5)	92 (11.0)	1 (0.8)
Asthenia	0 (0.0)	0 (0.0)	100 (9.1)	0 (0.0)	99 (11.8)	0 (0.0)
Crepitations	0 (0.0)	0 (0.0)	95 (8.7)	0 (0.0)	63 (7.5)	0 (0.0)
Pain	0 (0.0)	0 (0.0)	93 (8.5)	0 (0.0)	89 (10.6)	1 (0.8)
Infusion site reaction	6 (7.3)	4 (15.4)	4 (0.4)	0 (0.0)	4 (0.5)	0 (0.0)
Infusion site swelling	5 (6.1)	1 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Feeling hot	5 (6.1)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)	1 (0.8)
Gastrointestinal disorders						
Nausea	6 (7.3)	0 (0.0)	292 (26.7)	13 (9.8)	249 (29.7)	6 (4.8)
Constipation	0 (0.0)	1 (3.8)	175 (16.0)	5 (3.8)	136 (16.2)	1 (0.8)
Vomiting	1 (1.2)	0 (0.0)	95 (8.7)	7 (5.3)	83 (9.9)	4 (3.2)
Bowel sounds abnormal	0 (0.0)	0 (0.0)	61 (5.6)	0 (0.0)	52 (6.2)	0 (0.0)
Investigations						
White blood cell count increased	0 (0.0)	0 (0.0)	143 (13.1)	2 (1.5)	126 (15.0)	2 (1.6)
Haematocrit decreased	0 (0.0)	0 (0.0)	121 (11.1)	2 (1.5)	113 (13.5)	0 (0.0)
Haemoglobin decreased	0 (0.0)	0 (0.0)	111 (10.2)	1 (0.8)	104 (12.4)	0 (0.0)
Body temperature increased	0 (0.0)	0 (0.0)	96 (8.8)	1 (0.8)	84 (10.0)	3 (2.4)
Platelet count decreased	0 (0.0)	0 (0.0)	88 (8.1)	0 (0.0)	71 (8.5)	1 (0.8)
Blood calcium decreased	0 (0.0)	0 (0.0)	79 (7.2)	0 (0.0)	69 (8.2)	0 (0.0)
Red blood cell count decreased	0 (0.0)	0 (0.0)	75 (6.9)	0 (0.0)	67 (8.0)	0 (0.0)

continued

System Organ Class Preferred Term	Essential		Perioperative			Severe
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)	All active comparators (N=839)	Clevidipine (N=126)
Blood lactate dehydrogenase increased	0 (0.0)	0 (0.0)	74 (6.8)	0 (0.0)	65 (7.7)	0 (0.0)
Urine output decreased	0 (0.0)	0 (0.0)	71 (6.5)	2 (1.5)	52 (6.2)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	67 (6.1)	1 (0.8)	45 (5.4)	0 (0.0)
Blood glucose increased	0 (0.0)	0 (0.0)	63 (5.8)	0 (0.0)	47 (5.6)	0 (0.0)
Blood creatinine increased	0 (0.0)	0 (0.0)	63 (5.8)	0 (0.0)	43 (5.1)	0 (0.0)
Blood urea increased	1 (1.2)	0 (0.0)	60 (5.5)	0 (0.0)	51 (6.1)	0 (0.0)
Protein total decreased	0 (0.0)	0 (0.0)	60 (5.5)	0 (0.0)	47 (5.6)	0 (0.0)
Blood albumin decreased	0 (0.0)	0 (0.0)	56 (5.1)	0 (0.0)	49 (5.8)	0 (0.0)
Psychiatric disorders						
Anxiety	0 (0.0)	1 (3.8)	121 (11.1)	4 (3.0)	95 (11.3)	0 (0.0)
Confusional state	0 (0.0)	0 (0.0)	106 (9.7)	6 (4.5)	70 (8.3)	1 (0.8)
Insomnia	0 (0.0)	0 (0.0)	85 (7.8)	4 (3.0)	53 (6.3)	3 (2.4)
Agitation	0 (0.0)	0 (0.0)	83 (7.6)	3 (2.3)	68 (8.1)	0 (0.0)
Metabolism and nutrition disorders						
Hyperglycaemia	0 (0.0)	0 (0.0)	126 (11.5)	3 (2.3)	122 (14.5)	0 (0.0)
Hypokalaemia	0 (0.0)	0 (0.0)	75 (6.9)	0 (0.0)	74 (8.8)	2 (1.6)
Fluid overload	0 (0.0)	0 (0.0)	63 (5.8)	1 (0.8)	73 (8.7)	0 (0.0)
Blood and lymphatic system disorders						
Anaemia	0 (0.0)	0 (0.0)	232 (21.2)	8 (6.0)	238 (28.4)	2 (1.6)
Thrombocytopenia	0 (0.0)	0 (0.0)	79 (7.2)	2 (1.5)	87 (10.4)	0 (0.0)
Leukocytosis	0 (0.0)	0 (0.0)	79 (7.2)	2 (1.5)	74 (8.8)	0 (0.0)

continued

System Organ Class Preferred Term	Essential		Perioperative		All active comparators (N=839)	Severe Clevidipine (N=126)
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)		
Vascular disorders						
Hypotension	0 (0.0)	0 (0.0)	169 (15.5)	2 (1.5)	124 (14.8)	1 (0.8)
Nervous system disorders						
Headache	33 (40.2)	4 (15.4)	27 (2.5)	3 (2.3)	28 (3.3)	9 (7.1)
Renal and urinary disorders						
Polyuria	6 (7.3)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.8)

Source: Table 9.4.1 and Table 9.4.2, Appendix 8.2.1

Note: Patients who received more than one treatment were counted in each of their treatment groups.

7.1.5.1 Eliciting adverse events data in the development program

Adverse events information was collected until Day 7 or discharge from the hospital whichever occurred first in the ECLIPSE and ESCAPE trials. In VELOCITY, AE information was collected until 6 hours post study drug termination and SAE information until 7 days. The reviewer's issue with how the sponsor elicited for the AE of hypertension (see 7.1.3.2.2) and hypotension (see 7.1.3.2.1) were previously mentioned.

SAEs which started at any time up to 30 days post surgery start for perioperative or 30 days post-study drug initiation for all other clinical studies were included in the ISS.

The primary endpoints of death, stroke, MI, and renal dysfunction (in ECLIPSE) were assessed at Day 30 by telephone.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor's classification seemed appropriate. Events were categorized by system organ class (highest category) then preferred term, then AE term.

7.1.5.3 Incidence of common adverse events

The most common AE in the Phase III trials for clevidipine were incision site complications (51%), atelectasis (41%), and atrial fibrillation (33%). (See table). Headache (7%) was the most common AE in the severe HTN group.

Table 54. Common (≥5%) AE from Phase III studies

System Organ Class Preferred Term	Perioperative Hypertension			
	Clevipidine (N=866)	Placebo (N=100)	All Active Comparators (N=754)	Severe Hypertension Clevipidine (N=126)
Cardiac disorders				
Atrial fibrillation	284 (32.8)	12 (12.0)	248 (32.9)	1 (0.8)
Sinus tachycardia	221 (25.5)	0 (0.0)	230 (30.5)	0 (0.0)
Ventricular extrasystoles	105 (12.1)	0 (0.0)	96 (12.7)	1 (0.8)
Ventricular tachycardia	91 (10.5)	6 (6.0)	72 (9.5)	0 (0.0)
Supraventricular extrasystoles	71 (8.2)	0 (0.0)	55 (7.3)	0 (0.0)
Tachycardia	48 (5.5)	4 (4.0)	41 (5.4)	2 (1.6)
Respiratory, thoracic and mediastinal disorders				
Atelectasis	352 (40.6)	5 (5.0)	314 (41.6)	0 (0.0)
Pleural effusion	241 (27.8)	5 (5.0)	254 (33.7)	0 (0.0)
Breath sounds decreased	94 (10.9)	0 (0.0)	100 (13.3)	0 (0.0)
Rhonchi	78 (9.0)	0 (0.0)	78 (10.3)	0 (0.0)
Dyspnoea	78 (9.0)	0 (0.0)	60 (8.0)	1 (0.8)
Wheezing	57 (6.6)	2 (2.0)	64 (8.5)	0 (0.0)
Pulmonary congestion	55 (6.4)	2 (2.0)	55 (7.3)	0 (0.0)
Pulmonary oedema	52 (6.0)	4 (4.0)	63 (8.4)	0 (0.0)
Pneumothorax	47 (5.4)	2 (2.0)	49 (6.5)	0 (0.0)
Cough	46 (5.3)	2 (2.0)	40 (5.3)	2 (1.6)
Injury, poisoning and procedural complications				
Incision site complication	440 (50.8)	3 (3.0)	433 (57.4)	0 (0.0)
Post procedural pain	120 (13.9)	1 (1.0)	113 (15.0)	0 (0.0)
Post procedural discharge	56 (6.5)	0 (0.0)	51 (6.8)	0 (0.0)

Continued

System Organ Class Preferred Term	Perioperative Hypertension			
	Clevipidine (N=866)	Placebo (N=100)	All Active Comparators (N=754)	Severe Hypertension Clevipidine (N=126)
General disorders and administration site conditions				
Oedema peripheral	128 (14.8)	3 (3.0)	107 (14.2)	1 (0.8)
Pyrexia	123 (14.2)	10 (10.0)	116 (15.4)	0 (0.0)
Oedema	98 (11.3)	6 (6.0)	98 (13.0)	0 (0.0)
Asthenia	98 (11.3)	0 (0.0)	98 (13.0)	0 (0.0)
Anasarca	98 (11.3)	2 (2.0)	92 (12.2)	1 (0.8)
Pain	89 (10.3)	0 (0.0)	83 (11.0)	1 (0.8)
Crepitations	48 (5.5)	0 (0.0)	63 (8.4)	0 (0.0)
Gastrointestinal disorders				
Nausea	257 (29.7)	11 (11.0)	241 (32.0)	6 (4.8)
Constipation	137 (15.8)	4 (4.0)	136 (18.0)	1 (0.8)
Vomiting	81 (9.4)	5 (5.0)	79 (10.5)	4 (3.2)
Bowel sounds abnormal	55 (6.4)	0 (0.0)	52 (6.9)	0 (0.0)
Investigations				
White blood cell count increased	141 (16.3)	2 (2.0)	125 (16.6)	2 (1.6)
Haematocrit decreased	121 (14.0)	2 (2.0)	113 (15.0)	0 (0.0)
Haemoglobin decreased	109 (12.6)	1 (1.0)	104 (13.8)	0 (0.0)
Platelet count decreased	88 (10.2)	0 (0.0)	71 (9.4)	1 (0.8)
Body temperature increased	86 (9.9)	0 (0.0)	84 (11.1)	3 (2.4)
Blood calcium decreased	79 (9.1)	0 (0.0)	69 (9.2)	0 (0.0)
Red blood cell count decreased	74 (8.5)	0 (0.0)	67 (8.9)	0 (0.0)
Blood lactate dehydrogenase increased	72 (8.3)	0 (0.0)	65 (8.6)	0 (0.0)
Blood glucose increased	63 (7.3)	0 (0.0)	47 (6.2)	0 (0.0)

Continued

System Organ Class Preferred Term	Perioperative Hypertension			
	Clevidipine (N=866)	Placebo (N=100)	All Active Comparators (N=754)	Severe Hypertension Clevidipine (N=126)
Aspartate aminotransferase increased	63 (7.3)	0 (0.0)	44 (5.8)	0 (0.0)
Protein total decreased	60 (6.9)	0 (0.0)	47 (6.2)	0 (0.0)
Blood urea increased	59 (6.8)	0 (0.0)	51 (6.8)	0 (0.0)
Blood creatinine increased	59 (6.8)	0 (0.0)	43 (5.7)	0 (0.0)
Blood albumin decreased	56 (6.5)	0 (0.0)	49 (6.5)	0 (0.0)
Urine output decreased	50 (5.8)	1 (1.0)	51 (6.8)	0 (0.0)
Neutrophil count increased	46 (5.3)	0 (0.0)	41 (5.4)	0 (0.0)
Lymphocyte count decreased	43 (5.0)	0 (0.0)	38 (5.0)	0 (0.0)
Psychiatric disorders				
Anxiety	114 (13.2)	4 (4.0)	94 (12.5)	0 (0.0)
Confusional state	97 (11.2)	5 (5.0)	70 (9.3)	1 (0.8)
Agitation	79 (9.1)	3 (3.0)	67 (8.9)	0 (0.0)
Insomnia	60 (6.9)	4 (4.0)	52 (6.9)	3 (2.4)
Blood and lymphatic system disorders				
Anaemia	214 (24.7)	5 (5.0)	238 (31.6)	2 (1.6)
Thrombocytopenia	78 (9.0)	2 (2.0)	87 (11.5)	0 (0.0)
Leukocytosis	75 (8.7)	2 (2.0)	74 (9.8)	0 (0.0)
Metabolism and nutrition disorders				
Hyperglycaemia	114 (13.2)	3 (3.0)	120 (15.9)	0 (0.0)
Hypokalaemia	61 (7.0)	0 (0.0)	73 (9.7)	2 (1.6)
Fluid overload	55 (6.4)	1 (1.0)	72 (9.5)	0 (0.0)
Vascular disorders				
Hypotension	131 (15.1)	1 (1.0)	112 (14.9)	1 (0.8)

Continued

System Organ Class Preferred Term	Perioperative Hypertension			
	Clevidipine (N=866)	Placebo (N=100)	All Active Comparators (N=754)	Severe Hypertension Clevidipine (N=126)
Nervous system disorders				
Dizziness	47 (5.4)	1 (1.0)	39 (5.2)	2 (1.6)
Headache	26 (3.0)	3 (3.0)	28 (3.7)	9 (7.1)
Musculoskeletal and connective tissue disorders				
Back pain	48 (5.5)	0 (0.0)	35 (4.6)	1 (0.8)

Source: Table 5.4.2, Appendix 8.2.1

7.1.5.4 Common adverse event tables

See table in section 7.1.5. and section 7.1.5.3.

7.1.5.5 Identifying common and drug-related adverse events

Analysis of common AE by average infusion rate did not reveal any relationships. Pyrexia and headache trended towards a dose response relationship, however there no incidences of headache in the highest dose group.

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Table 55. Common AE by dose

System Organ Class Preferred Term#	<= 2 mg/h (N=232)	> 2 mg/h and <= 4 mg/h (N=398)	> 4 mg/h and <= 8 mg/h (N=363)	> 8 mg/h and <= 16 mg/h (N=175)	> 16 mg/h (N=67)
Patients with at Least one Adverse Event	205 (88.4)	371 (93.2)	321 (88.4)	140 (80.0)	45 (67.2)
Cardiac disorders					
Atrial fibrillation	67 (28.9)	120 (30.2)	99 (27.3)	29 (16.6)	13 (19.4)
Sinus tachycardia	48 (20.7)	88 (22.1)	62 (17.1)	26 (14.9)	6 (9.0)
Ventricular extrasystoles	29 (12.5)	39 (9.8)	39 (10.7)	9 (5.1)	2 (3.0)
Ventricular tachycardia	27 (11.6)	33 (8.3)	29 (8.0)	8 (4.6)	1 (1.5)
Supraventricular extrasystoles	14 (6.0)	20 (5.0)	36 (9.9)	9 (5.1)	0 (0.0)
Pericardial rub	14 (6.0)	15 (3.8)	11 (3.0)	4 (2.3)	0 (0.0)
Tachycardia	13 (5.6)	20 (5.0)	14 (3.9)	7 (4.0)	1 (1.5)
Sinus bradycardia	13 (5.6)	10 (2.5)	6 (1.7)	4 (2.3)	1 (1.5)
Bundle branch block right	12 (5.2)	21 (5.3)	7 (1.9)	3 (1.7)	1 (1.5)
Atrial flutter	12 (5.2)	18 (4.5)	14 (3.9)	1 (0.6)	3 (4.5)
Supraventricular tachycardia	3 (1.3)	18 (4.5)	14 (3.9)	5 (2.9)	4 (6.0)
Respiratory, thoracic and mediastinal disorders					
Atelectasis	78 (33.6)	156 (39.2)	119 (32.8)	36 (20.6)	9 (13.4)
Pleural effusion	64 (27.6)	114 (28.6)	82 (22.6)	33 (18.9)	5 (7.5)
Breath sounds decreased	24 (10.3)	35 (8.8)	43 (11.8)	15 (8.6)	2 (3.0)
Rhonchi	24 (10.3)	27 (6.8)	23 (6.3)	20 (11.4)	2 (3.0)
Dyspnoea	20 (8.6)	34 (8.5)	23 (6.3)	10 (5.7)	1 (1.5)
Pulmonary congestion	17 (7.3)	18 (4.5)	19 (5.2)	3 (1.7)	2 (3.0)
Wheezing	16 (6.9)	23 (5.8)	19 (5.2)	9 (5.1)	3 (4.5)
Pulmonary oedema	15 (6.5)	16 (4.0)	18 (5.0)	8 (4.6)	1 (1.5)
Cough	13 (5.6)	17 (4.3)	9 (2.5)	9 (5.1)	3 (4.5)
Pneumothorax	10 (4.3)	25 (6.3)	13 (3.6)	5 (2.9)	1 (1.5)
Rales	9 (3.9)	18 (4.5)	19 (5.2)	5 (2.9)	0 (0.0)
Productive cough	7 (3.0)	15 (3.8)	10 (2.8)	12 (6.9)	1 (1.5)
General disorders and administration site conditions					
Oedema peripheral	35 (15.1)	51 (12.8)	38 (10.5)	15 (8.6)	5 (7.5)

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System Organ Class Preferred Term#	<= 2 mg/h (N=232)	> 2 mg/h and <= 4 mg/h (N=398)	> 4 mg/h and <= 8 mg/h (N=363)	> 8 mg/h and <= 16 mg/h (N=175)	> 16 mg/h (N=67)
(SOC continued ...)					
General disorders and administration site conditions					
Oedema	26 (11.2)	46 (11.6)	32 (8.8)	11 (6.3)	3 (4.5)
Crepitations	25 (10.8)	30 (7.5)	23 (6.3)	12 (6.9)	4 (6.0)
Pyrexia	21 (9.1)	46 (11.6)	44 (12.1)	22 (12.6)	13 (19.4)
Asthenia	15 (6.5)	45 (11.3)	28 (7.7)	8 (4.6)	3 (4.5)
Pain	15 (6.5)	41 (10.3)	28 (7.7)	5 (2.9)	2 (3.0)
Anasarca	15 (6.5)	35 (8.8)	46 (12.7)	10 (5.7)	4 (6.0)
Injury, poisoning and procedural complications					
Incision site complication	86 (37.1)	174 (43.7)	132 (36.4)	40 (22.9)	8 (11.9)
Post procedural pain	21 (9.1)	52 (13.1)	37 (10.2)	6 (3.4)	5 (7.5)
Post procedural discharge	7 (3.0)	29 (7.3)	17 (4.7)	5 (2.9)	1 (1.5)
Gastrointestinal disorders					
Nausea	59 (25.4)	113 (28.4)	87 (24.0)	34 (19.4)	8 (11.9)
Constipation	36 (15.5)	63 (15.8)	52 (14.3)	18 (10.3)	7 (10.4)
Vomiting	15 (6.5)	41 (10.3)	21 (5.8)	15 (8.6)	3 (4.5)
Bowel sounds abnormal	9 (3.9)	23 (5.8)	23 (6.3)	5 (2.9)	1 (1.5)
Investigations					
White blood cell count increased	18 (7.8)	61 (15.3)	49 (13.5)	14 (8.0)	3 (4.5)
Body temperature increased	17 (7.3)	38 (9.5)	28 (7.7)	12 (6.9)	4 (6.0)
Haemoglobin decreased	16 (6.9)	42 (10.6)	43 (11.8)	4 (2.3)	6 (9.0)
Haematocrit decreased	15 (6.5)	52 (13.1)	44 (12.1)	5 (2.9)	5 (7.5)
Platelet count decreased	15 (6.5)	38 (9.5)	31 (8.5)	4 (2.3)	1 (1.5)
Urine output decreased	15 (6.5)	25 (6.3)	19 (5.2)	8 (4.6)	2 (3.0)
Aspartate aminotransferase increased	13 (5.6)	28 (7.0)	22 (6.1)	4 (2.3)	0 (0.0)
Blood lactate dehydrogenase increased	12 (5.2)	33 (8.3)	19 (5.2)	9 (5.1)	1 (1.5)
Blood creatinine increased	12 (5.2)	26 (6.5)	13 (3.6)	8 (4.6)	4 (6.0)
Blood glucose increased	10 (4.3)	31 (7.8)	16 (4.4)	3 (1.7)	3 (4.5)

Note: CEC adjudicated terms are not included but will be reported separately.
 # Sorted by most frequent SOCs and descending order of preferred term frequencies.
 Only TEAEs reported from first study drug initiation to 7 days post-operation or study drug initiation, whichever occurs first are presented.
 Program: t_taeom.sas Output: T_15_4_2.lis Generated on: 27-APR-2007 18:57

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continued

System Organ Class Preferred Term#	<= 2 mg/h (N=232)	> 2 mg/h and <= 4 mg/h (N=398)	> 4 mg/h and <= 8 mg/h (N=363)	> 8 mg/h and <= 16 mg/h (N=175)	> 16 mg/h (N=67)
(SOC continued ...)					
Investigations					
Blood albumin decreased	9 (3.9)	23 (5.8)	19 (5.2)	4 (2.3)	1 (1.5)
Blood calcium decreased	8 (3.4)	36 (9.0)	29 (8.0)	5 (2.9)	1 (1.5)
Red blood cell count decreased	8 (3.4)	35 (8.8)	28 (7.7)	2 (1.1)	2 (3.0)
Blood urea increased	8 (3.4)	24 (6.0)	23 (6.3)	4 (2.3)	2 (3.0)
Protein total decreased	7 (3.0)	29 (7.3)	18 (5.0)	5 (2.9)	1 (1.5)
Neutrophil count increased	5 (2.2)	24 (6.0)	14 (3.9)	4 (2.3)	1 (1.5)
Lymphocyte count decreased	3 (1.3)	24 (6.0)	13 (3.6)	3 (1.7)	1 (1.5)
Metabolism and nutrition disorders					
Hyperglycaemia	31 (13.4)	51 (12.8)	28 (7.7)	10 (5.7)	3 (4.5)
Fluid overload	15 (6.5)	27 (6.8)	18 (5.0)	1 (0.6)	1 (1.5)
Hypokalaemia	14 (6.0)	25 (6.3)	23 (6.3)	10 (5.7)	2 (3.0)
Psychiatric disorders					
Anxiety	22 (9.5)	42 (10.6)	39 (10.7)	14 (8.0)	4 (6.0)
Confusional state	21 (9.1)	42 (10.6)	31 (8.5)	8 (4.6)	3 (4.5)
Insomnia	20 (8.6)	33 (8.3)	22 (6.1)	11 (6.3)	2 (3.0)
Agitation	16 (6.9)	30 (7.5)	25 (6.9)	8 (4.6)	3 (4.5)
Blood and lymphatic system disorders					
Anaemia	50 (21.6)	97 (24.4)	59 (16.3)	25 (14.3)	3 (4.5)
Thrombocytopenia	20 (8.6)	35 (8.8)	18 (5.0)	4 (2.3)	1 (1.5)
Leukocytosis	16 (6.9)	35 (8.8)	22 (6.1)	5 (2.9)	1 (1.5)
Vascular disorders					
Hypotension	29 (12.5)	68 (17.1)	37 (10.2)	14 (8.0)	7 (10.4)
Hypertension	14 (6.0)	15 (3.8)	15 (4.1)	6 (3.4)	3 (4.5)
Nervous system disorders					
Dizziness	20 (8.6)	18 (4.5)	14 (3.9)	6 (3.4)	2 (3.0)
Headache	13 (5.6)	16 (4.0)	26 (7.2)	14 (8.0)	0 (0.0)
Musculoskeletal and connective tissue disorders					
Back pain	14 (6.0)	22 (5.5)	12 (3.3)	5 (2.9)	2 (3.0)

Taken from sponsor's Table 15.4.2, pg 5737 of 6157, ISS

Examination by duration of infusion was also not helpful in eliciting a total dose AE relationship. This was because the majority of subjects were dosed for less than 48 hours (n=1238), only 51 were dose for more than 48 hours and of those 51, 49 were dosed for more than 72 hours. Dividing the total dose in quartiles found a relationship between dose quartile and headache. This AE probably is dose related.

Table 56. Most common (≥5%) clevidipine AE by total infusion dose quartile

System Organ Class Preferred Term	Total clevidipine dose (mg)			
	≤3.6 (N=308)	>3.6 to ≤15.0 (N=311)	>15.0 to ≤67.4 (N=308)	>67.4 (N=308)
Cardiac disorders				
Atrial fibrillation	87 (28.2)	105 (33.8)	90 (29.2)	46 (14.9)
Sinus tachycardia	62 (20.1)	65 (20.9)	63 (20.5)	40 (13.0)
Ventricular extrasystoles	37 (12.0)	27 (8.7)	35 (11.4)	19 (6.2)
Ventricular tachycardia	32 (10.4)	21 (6.8)	34 (11.0)	11 (3.6)
Supraventricular extrasystoles	18 (5.8)	18 (5.8)	26 (8.4)	17 (5.5)
Tachycardia	18 (5.8)	13 (4.2)	15 (4.9)	9 (2.9)
Bundle branch block right	16 (5.2)	15 (4.8)	10 (3.2)	3 (1.0)
Pericardial rub	15 (4.9)	18 (5.8)	8 (2.6)	3 (1.0)
Atrial flutter	14 (4.5)	16 (5.1)	15 (4.9)	3 (1.0)
Respiratory, thoracic and mediastinal disorders				
Atelectasis	114 (37.0)	112 (36.0)	110 (35.7)	62 (20.1)
Pleural effusion	87 (28.2)	82 (26.4)	86 (27.9)	43 (14.0)
Breath sounds decreased	34 (11.0)	29 (9.3)	37 (12.0)	19 (6.2)
Rhonchi	31 (10.1)	19 (6.1)	22 (7.1)	24 (7.8)
Dyspnoea	22 (7.1)	20 (6.4)	27 (8.8)	19 (6.2)
Wheezing	22 (7.1)	18 (5.8)	19 (6.2)	11 (3.6)
Pulmonary oedema	16 (5.2)	18 (5.8)	13 (4.2)	11 (3.6)
Pneumothorax	16 (5.2)	14 (4.5)	16 (5.2)	8 (2.6)
Rales	16 (5.2)	9 (2.9)	16 (5.2)	10 (3.2)
Pulmonary congestion	15 (4.9)	17 (5.5)	19 (6.2)	8 (2.6)
Cough	15 (4.9)	11 (3.5)	17 (5.5)	8 (2.6)

System Organ Class Preferred Term	Total clevidipine dose (mg)			
	≤3.6 (N=308)	>3.6 to ≤15.0 (N=311)	>15.0 to ≤67.4 (N=308)	>67.4 (N=308)
Productive cough	12 (3.9)	7 (2.3)	17 (5.5)	9 (2.9)
General disorders and administration site conditions				
Oedema	52 (16.9)	29 (9.3)	23 (7.5)	14 (4.5)
Oedema peripheral	50 (16.2)	28 (9.0)	33 (10.7)	33 (10.7)
Crepitations	37 (12.0)	28 (9.0)	18 (5.8)	11 (3.6)
Pyrexia	33 (10.7)	40 (12.9)	47 (15.3)	26 (8.4)
Anasarca	24 (7.8)	28 (9.0)	40 (13.0)	18 (5.8)
Pain	23 (7.5)	26 (8.4)	29 (9.4)	13 (4.2)
Asthenia	22 (7.1)	27 (8.7)	34 (11.0)	16 (5.2)
Injury, poisoning and procedural complications				
Incision site complication	111 (36.0)	120 (38.6)	124 (40.3)	85 (27.6)
Post procedural pain	32 (10.4)	40 (12.9)	34 (11.0)	15 (4.9)
Post procedural discharge	12 (3.9)	13 (4.2)	22 (7.1)	12 (3.9)
Gastrointestinal disorders				
Nausea	76 (24.7)	87 (28.0)	82 (26.6)	56 (18.2)
Constipation	56 (18.2)	43 (13.8)	47 (15.3)	30 (9.7)
Vomiting	26 (8.4)	28 (9.0)	23 (7.5)	18 (5.8)
Abdominal distension	16 (5.2)	7 (2.3)	10 (3.2)	3 (1.0)
Bowel sounds abnormal	13 (4.2)	18 (5.8)	20 (6.5)	10 (3.2)
Investigations				
White blood cell count increased	28 (9.1)	36 (11.6)	44 (14.3)	37 (12.0)
Body temperature increased	25 (8.1)	32 (10.3)	29 (9.4)	13 (4.2)
Haemoglobin decreased	22 (7.1)	30 (9.6)	34 (11.0)	25 (8.1)
Urine output decreased	22 (7.1)	18 (5.8)	20 (6.5)	9 (2.9)
Haematocrit decreased	19 (6.2)	35 (11.3)	36 (11.7)	31 (10.1)
Aspartate aminotransferase increased	19 (6.2)	10 (3.2)	26 (8.4)	12 (3.9)
Blood calcium decreased	16 (5.2)	25 (8.0)	23 (7.5)	15 (4.9)
Platelet count decreased	16 (5.2)	23 (7.4)	29 (9.4)	21 (6.8)
Red blood cell count decreased	16 (5.2)	22 (7.1)	22 (7.1)	15 (4.9)
Blood lactate dehydrogenase increased	14 (4.5)	15 (4.8)	29 (9.4)	16 (5.2)

System Organ Class Preferred Term	Total clevidipine dose (mg)			
	≤3.6 (N=308)	>3.6 to ≤15.0 (N=311)	>15.0 to ≤67.4 (N=308)	>67.4 (N=308)
Blood glucose increased	13 (4.2)	17 (5.5)	19 (6.2)	14 (4.5)
Blood albumin decreased	12 (3.9)	13 (4.2)	20 (6.5)	11 (3.6)
Blood creatinine increased	10 (3.2)	19 (6.1)	19 (6.2)	15 (4.9)
Protein total decreased	10 (3.2)	15 (4.8)	23 (7.5)	12 (3.9)
Blood urea increased	8 (2.6)	17 (5.5)	22 (7.1)	14 (4.5)
Neutrophil count increased	7 (2.3)	11 (3.5)	16 (5.2)	14 (4.5)
Psychiatric disorders				
Anxiety	32 (10.4)	30 (9.6)	38 (12.3)	21 (6.8)
Confusional state	30 (9.7)	24 (7.7)	27 (8.8)	24 (7.8)
Insomnia	27 (8.8)	25 (8.0)	26 (8.4)	10 (3.2)
Agitation	19 (6.2)	24 (7.7)	21 (6.8)	18 (5.8)
Vascular disorders				
Hypotension	60 (19.5)	35 (11.3)	39 (12.7)	21 (6.8)
Hypertension	25 (8.1)	14 (4.5)	11 (3.6)	3 (1.0)
Blood and lymphatic system disorders				
Anaemia	70 (22.7)	66 (21.2)	59 (19.2)	39 (12.7)
Thrombocytopenia	29 (9.4)	23 (7.4)	17 (5.5)	9 (2.9)
Leukocytosis	16 (5.2)	27 (8.7)	26 (8.4)	10 (3.2)
Metabolism and nutrition disorders				
Hyperglycaemia	38 (12.3)	38 (12.2)	28 (9.1)	19 (6.2)
Hypokalaemia	21 (6.8)	18 (5.8)	20 (6.5)	15 (4.9)
Fluid overload	15 (4.9)	26 (8.4)	15 (4.9)	6 (1.9)
Nervous system disorders				
Dizziness	21 (6.8)	14 (4.5)	16 (5.2)	9 (2.9)
Headache	11 (3.6)	6 (1.9)	20 (6.5)	32 (10.4)
Musculoskeletal and connective tissue disorders				
Back pain	17 (5.5)	10 (3.2)	18 (5.8)	10 (3.2)

Source: Table 16.4.2, Appendix 8.2.1

Note: Patient data for 12 perioperative patients from SH-SAD-0013 (3 patients) and SH-SAD-0017 (9 patients) were not included.

Taken from sponsor's Table 28, pg. 74 of 6157, ISS report

7.1.5.6 Additional analyses and explorations

7.1.5.6.1 Use with beta blockers

In the VELOCITY trial, 46 patients received a beta blocker during the clevidipine infusion, nine patients (19.6%) had at least one AE from the time the beta blocker was added. These incidences were lower than or no greater than those observed in patients who did not receive a beta blocker with clevidipine. It is noted that blood pressures were very high in these subjects. Thus it was not surprising that hypotension was not an AE with concomitant antihypertensive use in this severe HTN population.

Table 57. AE in subjects also treated with a beta blocker, VELOCITY

System Organ Class/ Preferred Term	Patients Who Used Beta-blocker (N=46)	
	n	(%)
Number of Patients with at least one TEAE	9	(19.6)
Cardiac disorders	1	(2.2)
Cardiac arrest	1	(2.2)
Cardiogenic shock	1	(2.2)
Myocardial infarction	1	(2.2)
Gastrointestinal disorders	1	(2.2)
Vomiting	1	(2.2)
General disorders and administration site conditions	1	(2.2)
Chest pain	1	(2.2)
Investigations	2	(4.3)
Blood pressure increased	1	(2.2)
Troponin increased	1	(2.2)
Metabolism and nutrition disorders	1	(2.2)
Hypomagnesaemia	1	(2.2)
Nervous system disorders	2	(4.3)
Dyskinesia	1	(2.2)
Headache	1	(2.2)
Respiratory, thoracic and mediastinal disorders	1	(2.2)

Taken from sponsor Table 12.1, pg 389 of 2725, VELOCITY report

Totaling all types of beta blockers in the perioperative patients results in 801 of 866 perioperative patients that received a beta blocker (see table). In two studies (SH-SAD-0004 and -0005), patients were pretreated with beta blockers. Again there were no reports of hypotension,

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however the addition of clevidipine occurred after the beta blocker was already given and the clevidipine dose was titrated to effect.

Table 58. Concomitant beta blockers in Phase III studies

ATC Class	All Hypertensive Patients										Severe Hypertension Clevidipine (N=126) n %
	Clevidipine (N=866) n %	Placebo (N=100) n %	Sodium Nitroprusside (N=283)				Nicardipine (N=193) n %	All Active Comparators (N=754)			
			Nitroglycerin (N=278) n %	Nitroglycerin (N=278) n %	Nitroglycerin (N=278) n %	Nitroglycerin (N=278) n %		n %	n %		
ALPHA AND BETA BLOCKING AGENTS	93 (10.7)	1 (1.0)	50 (18.0)	29 (10.2)	13 (6.7)	92 (12.2)	16 (12.7)				
BETA BLOCKING AGENTS	3 (0.3)	0 (0.0)	1 (0.4)	4 (1.4)	0 (0.0)	5 (0.7)	2 (1.6)				
BETA BLOCKING AGENTS, NON-SELECTIVE	47 (5.4)	0 (0.0)	27 (9.7)	21 (7.4)	5 (2.6)	53 (7.0)	0 (0.0)				
BETA BLOCKING AGENTS, SELECTIVE	655 (75.6)	12 (12.0)	230 (82.7)	234 (82.7)	166 (86.0)	630 (83.6)	51 (40.5)				
BETA BLOCKING AGENTS, SELECTIVE, AND THIAZIDES	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)				

Taken from Sponsor's Table 5.9, pg 747 and 750 of 6157, ISS report

Patients taking beta-blockers with clevidipine did not have a greater incidence of hypotension compared to those not taking beta blockers (see two tables). There was also no difference in incidence of Afib, but the table does not show who was taking beta-blockers prior to surgery. The table also does not specify when during the course of treatment with clevidipine that the patient received the beta blocker. So these tables may not be reliable assessments of the safety of concomitant beta blocker use.

Table 59. Selected AEs in patients on concomitant beta blockers

System Organ Class/ Preferred Term	Patients Who Used Beta-blocker										Severe Hypertension Clevidipine (N=46) n %
	All Hypertensive Patients					All Active Comparators (N=213)					
	Clevidipine (N=212) n %	Placebo (N=3) n %	Nitroglycerin (N=96) n %	Nitroglycerin (N=71) n %	Nitroglycerin (N=71) n %	Nicardipine (N=46) n %	Nicardipine (N=46) n %	Nicardipine (N=46) n %	Nicardipine (N=46) n %	Nicardipine (N=46) n %	
Number of Patients with at least one TEAE	210 (99.1)	1 (33.3)	94 (97.9)	69 (97.2)	45 (97.8)	208 (97.7)	13 (28.3)				
Atrial fibrillation	68 (32.1)	0 (0.0)	34 (35.4)	23 (32.4)	15 (32.6)	72 (33.8)	0 (0.0)				
Hypotension	26 (12.3)	0 (0.0)	6 (6.3)	11 (15.5)	3 (6.5)	20 (9.4)	1 (2.2)				

Taken from Sponsor's Table 5.10.1, pg 763 and 789 of 6157, ISS report

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Table 60. Selected AEs in patients not on concomitant beta blockers

System Organ Class/ Preferred Term	Patients Who Did not Use Beta-blocker													
	Clevipipine (N=654)		Placebo (N=97)		Nitroglycerin (N=182)		Nitroprusside (N=212)		All Active Comparators (N=541)		Severe Hypertension Clevipipine (N=80)			
	n	%	n	%	n	%	n	%	n	%	n	%		
Atrial fibrillation	214	(32.7)	12	(12.4)	53	(29.1)	67	(31.6)	49	(33.3)	169	(31.2)	0	(0.0)
Hypotension	101	(15.4)	1	(1.0)	22	(12.1)	37	(17.5)	26	(17.7)	85	(15.7)	0	(0.0)

Taken from Sponsor's Table 5.10.2, pg 791 and 828 of 6157, ISS report

7.1.5.6.2 Reflex tachycardia

This was discussed earlier in the PK/PD section, and is discussed in Section 7.1.8 (Vital signs).

7.1.5.6.3 Atrial fibrillation

The reader is referred to Section 7.2.7 for a discussion on how afib/flutter was assessed and why the ECLIPSE studies were stopped and restarted. The table that follows shows the sponsor's afib incidence by study type was similar between clevidipine and AC.

Table 61. Atrial fibrillation events

System Organ Class Preferred Term	Essential		Perioperative			Severe
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)	All active comparators (N=839)	Clevidipine (N=126)
Atrial Fibrillation	1 (1.2)	0 (0.0)	412 (37.7)	25 (18.8)	316 (37.7)	2 (1.6)
Atrial fibrillation	0 (0.0)	0 (0.0)	332 (30.4)	20 (15.0)	258 (30.8)	1 (0.8)
Supraventricular extrasystoles	1 (1.2)	0 (0.0)	78 (7.1)	0 (0.0)	55 (6.6)	0 (0.0)
Atrial flutter	0 (0.0)	0 (0.0)	48 (4.4)	1 (0.8)	38 (4.5)	0 (0.0)
Supraventricular tachycardia	0 (0.0)	0 (0.0)	44 (4.0)	2 (1.5)	47 (5.6)	0 (0.0)
Arrhythmia supraventricular	0 (0.0)	0 (0.0)	16 (1.5)	3 (2.3)	15 (1.8)	1 (0.8)
Atrial tachycardia	0 (0.0)	0 (0.0)	9 (0.8)	0 (0.0)	3 (0.4)	0 (0.0)

Taken from sponsor Table 36, pg 91 of 6157, ISS report

7.1.5.6.4 Rebound hypertension

The sponsor calculated the maximum increase in SBP within 1 hour post-termination of study drug infusion to evaluate the incidence of rebound hypertension. Of the perioperative patients, only data for patients who received study drug for the postoperative treatment of hypertension were included. The following studies were excluded: SH-SAD-0005 (intraoperative and could not exclude on-pump data), SH-SAD-0006 (could not exclude on-pump data), TMC-CLV-03-01 (ESCAPE-1) (preoperative only), and TMC-CLV-02-01 (SBP data not in a form suitable for analysis). The sponsor concludes that 57% of perioperative patients who received clevidipine postoperatively had a maximum increase of no more than 10% in SBP from the last measurement on study drug to one hour after termination of study drug. About 10% of patients had a maximum increase of greater than 30%.

Rebound hypertension analysis was conducted by the PM reviewer and was discussed in Section 5.2.4. The placebo adjusted percent change from baseline SBP was around 9% for the 16 mg/hr dose group (lower for lower doses and occurring around 8 hours after the stop of a 72 hour infusion).

7.1.6 Less Common Adverse Events

Hypovolemia

This is an expected AE because the use of agents that cause dilation of venous capacitance vessels may result in hypovolemia due to the necessity to replenish intravascular volume for effective maintenance of systemic BP.

Table 62. Hypovolemia

System Organ Class Preferred Term	Essential		Perioperative			All active comparators (N=839)	Severe Clevidipine (N=126)
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)			
Hypovolemia	0 (0.0)	0 (0.0)	25 (2.3)	1 (0.8)	8 (1.0)	0 (0.0)	

Taken from sponsor table 36, pg 92 of 6157 of ISS report

Blood borne infections

Since clevidipine is formulated in lipid emulsion, there is a theoretical risk of blood borne infection if care is not taken to maintain sterility. The incidence (3.8%) was slightly higher than AC (3.0%).

Table 63. Blood borne infections

System Organ Class Preferred Term	Essential		Perioperative			All active comparators (N=839)	Severe Clevidipine (N=126)
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)			
Blood-borne Infections	0 (0.0)	0 (0.0)	41 (3.8)	2 (1.5)	25 (3.0)	0 (0.0)	
Pneumonia	0 (0.0)	0 (0.0)	16 (1.5)	0 (0.0)	9 (1.1)	0 (0.0)	
Wound infection	0 (0.0)	0 (0.0)	6 (0.5)	0 (0.0)	5 (0.6)	0 (0.0)	
Cellulitis	0 (0.0)	0 (0.0)	4 (0.4)	0 (0.0)	3 (0.4)	0 (0.0)	
Lung infection pseudomonal	0 (0.0)	0 (0.0)	3 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	
Sepsis	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	5 (0.6)	0 (0.0)	
Bacteraemia	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	2 (0.2)	0 (0.0)	
Bacterial infection	0 (0.0)	0 (0.0)	2 (0.2)	0 (0.0)	1 (0.1)	0 (0.0)	
Candidiasis	0 (0.0)	0 (0.0)	2 (0.2)	1 (0.8)	0 (0.0)	0 (0.0)	
Aspergillosis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Enterococcal sepsis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Escherichia sepsis	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Fungal infection	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Sepsis syndrome	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Serratia bacteraemia	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	
Septic shock	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	
Clostridial infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	
Staphylococcal bacteraemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	
Pneumonia fungal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)	0 (0.0)	

Taken from sponsor table 36, pg 92 of 6157 of ISS report

7.1.7 Laboratory Findings

There were no clinically relevant changes in laboratory parameters.

There was an observed increase in triglycerides with longer infusions of clevidipine, but these increases were transient and were not associated with clinical sequelae. The laboratory parameters where the incidence of potentially significant values was greater than 5% were hematocrit, elevated WBC, AST, and serum creatinine. These increases were also observed in the AC group.

Table 64. Potentially clinically significant lab findings

	PCS Criteria		Clevidipine (N=1301)	Placebo (N=159)	Nitroglycerin (N=334)	Sodium Nitroprusside (N=312)	Nicardipine (N=193)	All Active Comparators (N=839)
	Non- surgical	surgical						
Hematocrit (%)	<= 30	<= 24	69/1239 (5.6)	0/135 (0.0)	22/331 (6.6)	22/288 (7.6)	4/192 (2.1)	48/811 (5.9)
Hemoglobin (g/dL)	<= 10	<= 8	55/1275 (4.3)	0/149 (0.0)	13/331 (3.9)	16/304 (5.3)	7/193 (3.6)	36/828 (4.3)
Platelets (K/uL)	<= 100	<= 75	61/1270 (4.8)	1/147 (0.7)	19/331 (5.7)	28/306 (9.2)	6/191 (3.1)	53/828 (6.4)
WBC (K/uL)	>= 20	>= 20	108/1233 (8.8)	0/149 (0.0)	29/276 (10.5)	32/304 (10.5)	21/192 (10.9)	82/772 (10.6)
	<= 3	<= 2.8	0/1230 (0.0)	0/149 (0.0)	0/277 (0.0)	0/301 (0.0)	0/192 (0.0)	0/770 (0.0)
ALT/SGPT (U/L)	>= 2*ULN	>= 3*ULN	40/1159 (3.5)	3/135 (2.2)	6/267 (2.2)	9/293 (3.1)	8/186 (4.3)	23/746 (3.1)
AST/SGOT (U/L)	>= 2*ULN	>= 3*ULN	77/1176 (6.5)	5/130 (3.8)	24/321 (7.5)	22/291 (7.6)	15/184 (8.2)	61/796 (7.7)
HDL (mg/dL)	<= 20	<= 20	4/152 (2.6)	0/13 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
LDL (mg/dL)	>= 200	>= 200	4/146 (2.7)	0/11 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)
Lactate	>= 2*ULN	>= 3*ULN	26/881 (3.0)	0/71 (0.0)	8/295 (2.7)	6/234 (2.6)	5/177 (2.8)	19/706 (2.7)
Dehydrogenase (U/L)								
Serum Creatinine (mg/dL)	>= 2.5	>= 2	85/1245 (6.8)	3/152 (2.0)	25/319 (7.8)	24/286 (8.4)	16/186 (8.6)	65/791 (8.2)
Total Bilirubin (mg/dL)	>= 1.5*ULN	>= 1.5*ULN	55/1151 (4.8)	4/132 (3.0)	16/261 (6.1)	22/290 (7.6)	12/187 (6.4)	50/738 (6.8)
Total Cholesterol (mg/dL)	>= 300	>= 300	1/1043 (0.1)	2/131 (1.5)	0/291 (0.0)	0/263 (0.0)	0/179 (0.0)	0/733 (0.0)
Triglycerides (mg/dL)	>= 500	>= 300	28/1039 (2.7)	2/126 (1.6)	2/276 (0.7)	3/246 (1.2)	2/168 (1.2)	7/690 (1.0)
VLDL (mg/dL)	>= 100	>= 100	0/33 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)	0/0 (0.0)

Taken from sponsor table 3.5.3.1 and 3.5.3.2, pg 474-475 of 6157 of ISS report

Note: Patients who received more than one treatment are counted in each of their treatment groups. Counts refer to number of patients who had a non-potentially clinically significant (PCS) measurement at baseline and who had at least one PCS post-baseline assessment.

PCS limits are compared to local laboratory values in standardized units.

Program: t_labpcs.sas Output: T_03_5_3_2.lis Generated on: 29-APR-2007 10:47

Program: t_labpcs.sas Output: T_03_5_3_1.lis Generated on: 29-APR-2007 10:47

A small rise in LFT's is expected after cardiac surgery. The rise in LFT's was greater than that seen in the essential or severe hypertensive group.

More clevidipine treated patients had elevations in triglycerides compared to AC (see previous table). Triglycerides are examined more closely. Eight patients had increased TG reported as an AE and one patient discontinued due to the event. TG assessments in the Phase II studies were only done at baseline and Day 7 or last assessment. It is likely that more people had elevated TG, however, it was not tested more frequently. The mean changes from baseline actually decreased on clevidipine (-10%) and placebo (-4%). AC mean change was 0.3%. There was a mean increase in TG level of 43% in the severe HTN study. The mean baseline was 215 mg/dL and the mean Day 7 value was 304 mg/dL.

There were no infusion rate, duration or total infusion related changes in serum creatinine, LFTs and triglyceride (TG) concentrations, except that longer infusion durations were associated with an increase in TG (see table).

Table 65. Change from baseline to Day 7/last TG (mg/dL) assessment by CLV continuous infusion duration

Variable	Duration of clevidipine continuous infusion		
	<48 hours (N=1238)	≥48 hours (N=51)	≥72 hours ^b (N=49)
Baseline			
N	953	49	48
Median	201.7	201.0	196.0
Q1, Q3	135.9, 300.0	127.5, 288.3	122.8, 286.8
Min, max	40.0, 4137.5	40.2, 1533.3	40.2, 1533.3
Day 7/Last assessment^a			
N	1068	51	49
Median	180.1	206.6	206.6
Q1, Q3	130.0, 246.7	123.8, 428.8	129.4, 410.8
Min, max	11.7, 4715.0	41.5, 1645.0	41.5, 1645.0
Percentage change from baseline			
N	903	49	48
Median	-8.5	16.4	14.2
Q1, Q3	-36.8, 25.1	-9.4, 81.3	-10.2, 81.8
Min, max	-91.4, 841.9	-55.1, 410.1	-55.1, 410.1

Source: Table 14.5.1.2.2, Appendix 8.2.1

Note: Patient data for 12 perioperative patients from SH-SAD-0013 (3 patients) and SH-SAD-0017 (9 patients) were not included.

^a Last post-treatment measurement before/on Day 7.

^b The ≥72 hours group is a subset of the ≥48 hours group.

Taken from sponsor table 47, pg 107 of 6157 of ISS

The table below shows no associated between total clevidipine dose and TG level.

Table 66. Change from baseline to Day 7/last TG (mg/dL) assessment by total CLV infusion dose

Variable	Total clevidipine dose (mg)			
	≤3.6 (N=308)	>3.6 to ≤15.0 (N=311)	>15.0 to ≤67.4 (N=308)	>67.4 (N=308)
Baseline				
N	246	235	235	233
Median	203.3	215.0	204.5	187.5
Q1, Q3	145.0, 340.5	141.3, 305.2	135.0, 291.7	126.7, 285.2
Min, max	40.0, 1963.1	51.3, 1231.3	60.5, 4137.5	40.2, 1533.3
Day 7/Last assessment^a				
N	267	266	264	268
Median	173.4	178.5	182.8	181.7
Q1, Q3	126.9, 236.1	133.3, 245.0	125.4, 248.3	131.8, 270.4
Min, max	38.8, 544.7	38.8, 1132.5	11.7, 507.5	41.5, 4715.0
Percentage change from baseline				
N	236	225	229	209
Median	-13.7	-14.2	-13.0	5.6
Q1, Q3	-43.5, 16.5	-36.2, 21.1	-36.8, 22.1	-24.7, 48.5
Min, max	-80.7, 185.9	-91.4, 330.2	-90.4, 290.2	-82.6, 841.9

Source: Table 16.5.1.2.2, Appendix 8.2.1

Note: Patient data for 12 perioperative patients from SH-SAD-0013 (3 patients) and SH-SAD-0017 (9 patients) were not included.

^a Last post-treatment measurement before/on Day 7.

Taken from sponsor table 53, pg 113 of 6157 of ISS

7.1.7.1 Overview of laboratory testing in the development program

In the ECLIPSE trials, clinical laboratory parameters including hematology, biochemistry, and lipids were measured within 24 hours of randomization (baseline) and at 8 ± 2 hours, 24 ± 4 hours after surgery, and at hospital discharge or Day 7, whichever occurred first.

In VELOCITY, chemistry, hematology, and lipid panel were drawn at screening, every 24 hours during the infusion, and 6 hours after cessation.

In ESCAPE, serum creatinine, total cholesterol and triglycerides were evaluated at baseline, 24 ± 4 hours after surgery, and at hospital discharge (or Day 7).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

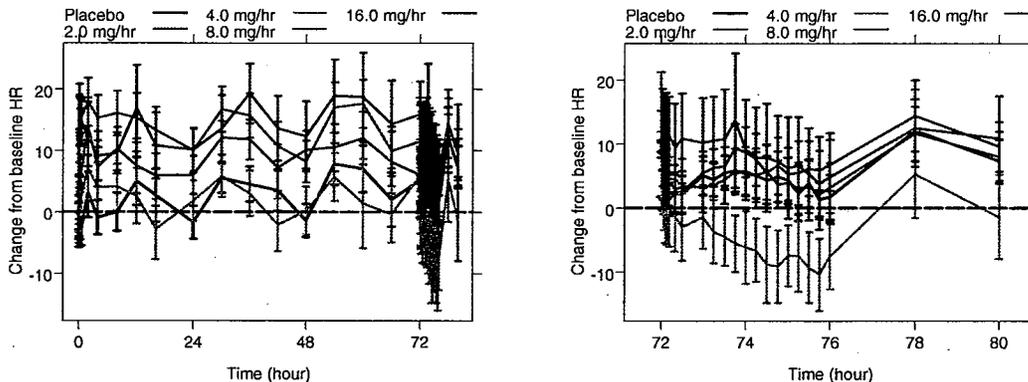
The selection of studies for analysis of laboratory findings (as well as overall safety) was difficult. The ESCAPE studies were placebo controlled, but very short in duration (30 – 60 minutes drug infusion). The ECLIPSE studies were longer duration, but most patients were still treated for less than 48 hours. This study had an AC for comparison, although the dosing of the AC was not controlled. That leaves VELOCITY as the last Phase III trial for safety data. The duration of continuous infusion in most patients was less than 48 hours and there was no control, however more patients received higher doses than patients in ECLIPSE and ESCAPE.

Laboratory finds were assessed overall and by HTN type since the patient population differed.

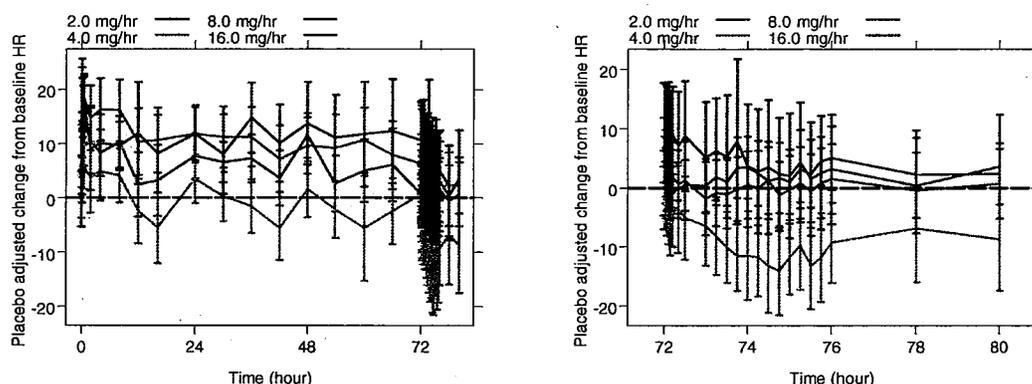
7.1.8 Vital Signs (other than BP)

Reflex tachycardia

Heart rate is increased with clevidipine administration and it appears to be in a dose proportional manner except for the 4 mg/hr clevidipine dose group which is similar to placebo.



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



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

Reflex tachycardia is an expected phenomenon due to activation of the baroreceptor-mediated response to a reduction in BP. There seems to be a lower incidence of it compared to active comparators.

Table 67. Reflex tachycardia events

System Organ Class Preferred Term	Essential		Perioperative		All active comparators (N=839)	Severe Clevidipine (N=126)
	Clevidipine (N=82)	Placebo (N=26)	Clevidipine (N=1093)	Placebo (N=133)		
Reflex Tachycardia	0 (0.0)	0 (0.0)	230 (21.0)	1 (0.8)	231 (27.5)	0 (0.0)
Sinus tachycardia	0 (0.0)	0 (0.0)	230 (21.0)	1 (0.8)	231 (27.5)	0 (0.0)

Taken from sponsor Table 36, pg 91 of 6157, ISS report

Changes in HR from baseline to post-baseline on treatment were assessed in all hypertensive patients. The maximum percent change at 0-1 and 1-4 hours after the study drug infusion started were analyzed by the sponsor. Excluded studies included SH-SAD-0005, SH-SAD-0006, and SH-SAD-0017 because on-pump data could not be excluded. The reviewer examined the individual study reports for the Phase III trials for the incidence of reflex tachycardia by study. It was a secondary safety endpoint in the ECLIPSE trials. Reflex tachycardia was not reported for any patients in the ESCAPE-1, -2 or VELOCITY. It is unclear why there seem to be big differences in the reported cases. The reviewer did not check the SAS dataset for “reflex tachycardia” preferred term reports.

Table 68. Reflex tachycardia in ECLIPSE report

	CLV	NIC	NTG	SNP
ECLIPSE-NTG (03-03)	2 (0.7) ¹		1 (0.4)	
ECLIPSE-SNP (03-04)	4 (1.4)			4 (1.4) ²
ECLIPSE-NIC (03-05)	1 (0.5) ³	0		4

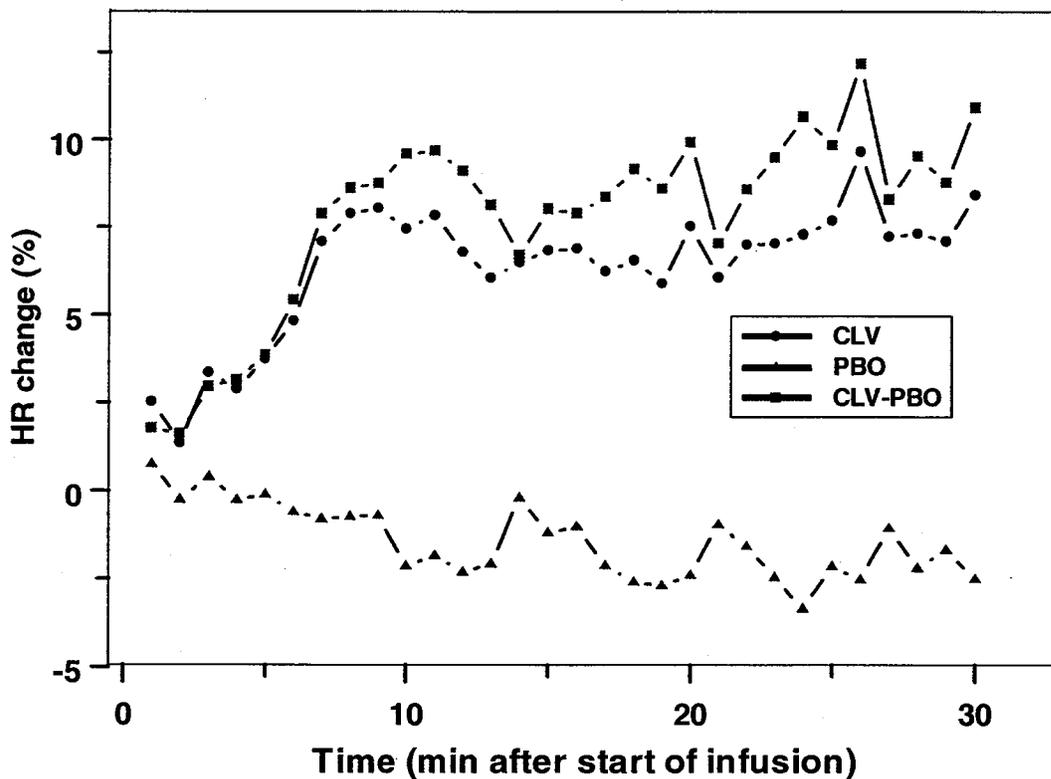
- 2 Additional ID 342_018 experienced reflex tach 97 hour after the en of the study drug infusion
 3 Additional ID 466_010 experienced reflex tach 4 hours after the end of the study drug infusion
 4 Additional ID 564_004 experienced reflex tach 45 hours after the end of the study drug infusion
 5 Additional ID 535_002 experienced reflex tach 1 hour after the end of the study drug infusion & ID 507_006 had multiple episodes (6, 12, 109, 133, 161, and 174 hours after the end of the study drug infusion).

VELOCITY reported 2 patients with “tachycardia” and 2 patients with “heart rate increased”.

HR

ESCAPE examined the change in HR (safety secondary endpoint) from baseline and compared it to placebo. In ESCAPE-1 the mean HR at baseline was 73.1 bpm for clevidipine versus 78.3 bpm for placebo treated patients. The mean highest HR was 86.1 bpm for clevidipine and 84.3 bpm for placebo treated patients within the 30 minute efficacy evaluation. The maximum increase in HR was 12.2% (occurring around 26 minutes after the start of the infusion) (see figure).

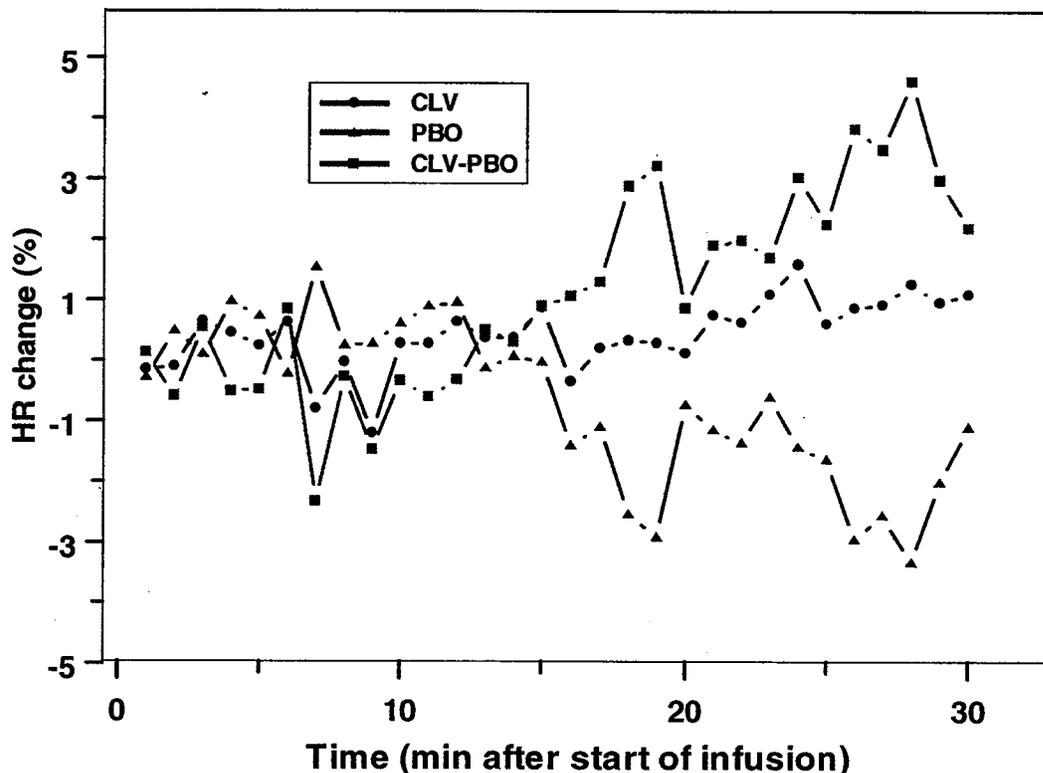
Figure 22. ESCAPE-1 HR change from baseline, CLV, PBO and CLV-PBO



Data from d_hdhr.xpt in ISS

In ESCAPE-2, the mean HR at baseline was higher than in ESCAPE-1 (87.9 bpm) for clevipidine and placebo (94.0 bpm). The mean highest HR was 94.0 bpm for clevipidine and 95.1 bpm for placebo treated patients within the 30 minute evaluation period. In ESCAPE-2 the maximum increase in HR was almost 5% (occurring around 28 minutes after the start of the infusion) (see figure).

Figure 23. ESCAPE-2 HR change from baseline, CLV, PBO and CLV-PBO



In summary, the reviewer found that the data do support that clevipidine causes reflex tachycardia, somewhere in the range of about 5-10% mean change from baseline (placebo adjusted).

The sponsor examined the maximum increase in HR within 1 hour after start of the infusion. Almost 30% of clevipidine treated patients had more than a 30% maximum HR increase. See next table. The sponsor's results for change from baseline to post baseline (0-1 hour) by HTN type are shown in the table that follows.