In this patient, AF and tachycardia were assessed by the investigator as severe and not related to test medication but rather to the doxorubicin chemotherapy. Blood levels of doxorubicin were not reported.

TABLE 46
Study MCPR0048 (Report K-94-0929-CDS)

Serious AEs

Pt. ID/ age gender	Underlying Condition/ Chemotherapy	AE	SEV	Onset (h)	DUR (h)	Outcome/Relation to Test Med.
		50 mg (n=2)				
0384-0014 73 F	Large cell lymphoma with metastasis to the jugulodigastric lymph node. No prior Hx of seizures. Cyclophosph. 1250 mg vincristine 2 mg doxorubicin 85 mg	• Seizures + Headache	SEV	ca. 7d	3	• Re-hospitalization • Event resolved without sequelae • Unlikely (possible early sepsis)
0384-0025 47 F	Malignant lymphoma, well differentiated, lymphocytic type Cyclophosph. 1300 mg Vincristine 2 mg	• Abdominal Pain • Partial Obstruction of the bowel on CAT scan	SEV	ca. 6d	UNK	• Re-hospitalization • Event unsolved without sequelae • Not related (related to lymphoma causing a slight bowel obstruction)
		100 mg (n=2)				
0323-0007 77 M	Malignant lymphoma with metastasis to the lungs and liver Cyclophosph. 1400 mg (i.v.) doxorubicin 94 mg (i.v.) vincristine 2 mg (i.v.) prednisone 90 mg p.o.	• Neutropenia, sepsis	SEV	3d	58d	• Death • Not related • Death due to septic shock and related to progression of lymphoma
0384-0029 56 M	Follicular large cell lymphoma Cyclophosphamide 1425 mg Vinscristine 2 mg Doxorubicin 95 mg	• Atrial Fibrillation • Tachycardia	SEV	96	UNK	• Re-hospitalization • AF resolved without sequelae • [illegible] related (related to [illegible]

3) Severe AEs (Table 47)

In this study, the majority of AEs were mild to moderate in intensity. All in all, 16 pts. experienced one or more AEs whose intensity was rated "severe".

- Of the 16 pts. experiencing a SEV AE, 4 experienced AEs assessed as Tx-related by the investigator.

  - All 4 of these pts. experienced Tx-related, SEV headache:

DOLA•Mesyl (mg)	# of Pts. With SEV AEs
50	1
100	2
200	1
Total	4

- The remaining 12 pts. had SEV AEs which were not assessed to be related to test med. by the investigator. The distribution of these 12 pts. was

DOLA•Mesyl (mg)	# of Pts. With SEV AEs	SEV AE
25	3	diarrhea, n=1 weakness, n=1 N&V, n=1
50	2	seizure + headache*, n=1 int. obstruction*, n=1
100	4	headache, n=1 heartburn, n=1 dehydration, fever + sepsis*, n=1 AF + tachycardia*, n=1
200	3	insomnia, n=1 influenza-like symptoms, n=1 myalgia + arm pain, n=1
TOTAL	**12**	

* These 4 SEV AEs were also identified as serious (see Table 45)

TABLE 47
Study MCPR0048 (Report K-94-0929-CDS)

Severe AEs

Adverse Event		DOLA•Mesyl (mg)			
		25 [n=79]	50 [n=83]	100 [n=80]	200 [n=78]
Any AE	MILD MOD SEV	13 (16.5%)	11 (13.3%)	11 (13.8%)	10 (12.8%)
Central and Peripheral Nervous System AEs	MILD MOD SEV	5 (6.3%)	7 (8.4%)	5 (6.3%)	7 (9.0%)
Heart Rate and Rhythm AEs	MILD MOD SEV	0 (0.0%)	1 (1.2%)	0 (0.0%)	2 (2.6%)
Gastrointestinal System AEs	MILD MOD SEV	3 (3.8%)	4 (4.8%)	5 (6.3%)	0 (0.0%)
INDIVIDUAL TERMS					
Headache	MILD MOD SEV	4 (5.1%)	7 (8.4%)	5 (6.3%)	6 (7.7%)
Diarrhea	MILD MOD SEV	0 (0.0%)	2 (2.4%)	2 (2.5%)	0 (0.0%)
Sinus Bradycardia	MILD MOD SEV	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
T Wave Change or Abnormality	MILD MOD SEV	0 (0.0%)	1 (1.2%)	0 (0.0%)	0 (0.0%)

4) Overall Rate of AE Incidence (Table 48)

In this, as in trial 043, asymptomatic, treatment-emergent EKG interval changes were coded as AEs for signaling and tracking purposes.

As displayed in this Table, the overall rates of AEs by dose, were 59.5%, 55.4%, 66.3% and 71.8% for the 25, 50, 100 and 200 mg dose groups, respectively. There was a statistically significant trend with dose in the overall incidence of AEs (p=0.0492).

- There was no statistically significant trend with dose in the incidence of headache, diarrhea, sinus bradycardia and T-wave change or abnormality, the most frequently reported individual AEs (highlighted by a shadow in Table 48).

- The most frequently reported AEs by System Organ Class were those related to the CNS (96/320=30% of the patients), gastrointestinal system (56/320=17.5% of the patients), and heart rate and rhythm (72/320=22.5% of the patients), with sinus bradycardia and T-wave change or abnormality occurring in 20/320=6.3% of the patients each.

    - There was no statistically significant trend with dose in the incidence of AEs related to any of those three or any other System Organ Class.

- As already mentioned, the most frequently reported individual AEs were headache, diarrhea, sinus bradycardia and T wave change or abnormality (Table 48).

    - Headache was reported for 20/79 (25.3%) patients in the 25 mg dose group, 17/83 (20.5%) in the 50 mg dose group, 23/80 (28.8%) in the 100 mg dose group and 26/78 (33.3%) in the 200 mg dose group.

    - There was no statistically significant trend with dose in the incidence of headache.

    - Diarrhea was reported for 3/79 (3.8%) patients in the 25 mg dose group, 7/83 (8.4%) in the 50 mg dose group, 6/80 (7.5%) in the 100 mg dose group and 5/78 (6.4%) in the 200 mg dose group.

    - There was no statistically significant trend with dose in the incidence of diarrhea. The reported incidences of diarrhea do not include the relatively small number of additional patients who reported stools loose.

    - Sinus bradycardia was reported for 3/79 (3.8%) patients in the 25 mg dose group, 8/83 (9.6%) in the 50 mg dose group, 4/80 (5.0%) in the 100 mg dose group and 5/78 (6.4%) in the 200 mg dose group.

    - There was no statistically significant trend with dose in the incidence of sinus bradycardia.

    - T wave change or abnormality was reported for 4/79 (5.1%) patients in the 25 mg dose group, 5/83 (6.0%) in the 50 mg dose group, 3/80 (3.8%) in the 100 mg dose group and 8/78 (10.3%) in the 200 mg dose group.

    - There was no statistically significant trend with dose in the incidence of T wave change or abnormality.

- For treatment-related AEs, the overall [illegible] (38.6%), 38/80 (47.5%) and 42/78 (53.8%) [illegible] dose groups, respectively.

- There was a statistically significant trend with dose in the overall incidence of treatment-related AEs (p=0.0361).

- Of the 86 instances of headache, 78 were considered treatment-related by the investigator.

- 14 of the 21 instances of diarrhea were assessed as treatment-related by the investigator.

- Of the 20 instances of sinus bradycardia, 12 were assessed as treatment-related by the investigator.

- All 20 instances of T wave change or abnormality were considered treatment-related by the investigator.

TABLE 48
Study MCPR0048 (Report K-94-0929-CDS)

List of AEs and Treatment Emergent EKG Changes

I. Frequency (Percent) of All Adverse Events

System Organ Class and Included Term p-value*	DOLA•Mesyl Dose (mg)				Total [n=320]
	25 [n=79]	50 [n=83]	100 [n=80]	200 [n=78]	
Overall Rate (p=0.0492)	47 (59.6)	46 (55.4)	53 (66.3)	56 (71.8)	202 (63.1)
Centr & Periph Nervous System (p=N.S.)	23 (29.1)	20 (24.1)	25 (31.3)	28 (35.9)	96 (30.0)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Heart Rate & Rhythm (p=N.S.)	15 (19.0)	18 (21.7)	14 (17.5)	25 (32.1)	72 (22.5)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ST-T Change or Abnormality (p=N.S.)	5 (6.3)	1 (1.2)	3 (3.8)	4 (5.1)	13 (4.1)
Premature Ventricular Contraction (p=N.S.)	2 (2.5)	4 (4.8)	1 (1.3)	2 (2.6)	9 (2.8)
Sinus Tachycardia (p=N.S.)	2 (2.5)	2 (2.4)	1 (1.3)	0	5 (1.6)
EKG Abnormal Specific	0	1 (1.2)	2 (2.5)	1 (1.3)	4 (1.3)
Premature Atrial Contractions	0	1 (1.2)	0	3 (3.8)	4 (1.3)
Arrhythmia, Sinus	2 (2.5)	0	1 (1.3)	0	3 (0.9)
Fibrillation Atrial	0	0	2 (2.5)	0	2 (0.6)

Tachycardia	0	0	1 (1.3)	0	1 (0.3)
Gastrointestinal System (p=N.S.)	13 (16.5)	15 (18.1)	17 (21.3)	11 (14.1)	56 (17.5)
Diarrhea (p=N.S.)	3 (3.8)	7 (8.4)	6 (7.5)	5 (6.4)	21 (6.6)
Body As A Whole (p=N.S.)	6 (7.6)	5 (6.0)	10 (12.5)	2 (2.6)	23 (7.2)
Resistance Mechanism (p=N.S.)	5 (6.3)	3 (3.6)	8 (10.0)	3 (3.8)	19 (5.9)
Autonomic Nervous System (p=N.S.)	2 (2.5)	6 (7.2)	3 (3.8)	3 (3.8)	14 (4.4)
Cardiovascular, General (p=N.S.)	2 (2.5)	1 (1.2)	4 (5.0)	1 (1.3)	8 (2.5)
Skin & Appendages (p=N.S.)	2 (2.5)	3 (3.6)	2 (2.5)	1 (1.3)	8 (2.5)
Metabolic & Nutritional	2 (2.5)	0	3 (3.8)	1 (1.3)	6 (1.9)
Musculo-Skeletal System (p=N.S.)	1 (1.3)	2 (2.4)	2 (2.5)	1 (1.3)	6 (1.9)
Application Site	2 (2.5)	1 (1.2)	2 (2.5)	0	5 (1.6)
Special Senses, Other	1 (1.3)	0	2 (2.5)	2 (2.6)	5 (1.6)
Psychiatric	2 (2.5)	0	1 (1.3)	1 (1.3)	4 (1.3)
Respiratory System	2 (2.5)	0	2 (2.5)	0	4 (1.3)
Urinary System	3 (3.8)	0	0	1 (1.3)	4 (1.3)
Hearing & Vestibular	1 (1.3)	0	0	1 (1.3)	2 (0.6)
Liver & Biliary System	1 (1.3)	0	1 (1.3)	0	2 (0.6)
Platelet, Bleeding & Clotting	1 (1.3)	1 (1.2)	0	0	2 (0.6)
Vision	1 (1.3)	1 (1.2)	0	0	2 (0.6)
MYO-, ENDO-, Pericardial & Valve	1 (1.3)	0	0	0	1 (0.3)
White Blood Cells & RES	0	0	0	1 (1.3)	1 (0.3)

II. Frequency (Percent) of All Treatment-Emergent ECG Interval Changes

Overall Rate (p=N.S.)	24 (30.4)	29 (34.9)	[illegible]		
[illegible] (p=N.S.)	24 (30.4)	29 (34.9)	[illegible]		
[illegible] Prolongation (QT, >440) (p=N.S.)	21 (26.6)	[illegible] (28.9)	[illegible]		
[illegible] (p=N.S.)	3 (3.8)	[illegible]	[illegible]		

? QT not QTc

AV Block First Degree (PR≥220)	2 (2.5)	1 (1.2)	0	3 (3.8)	6 (1.9)
a) p-value for a linear trend with dose in the occurrence of the event calculated from a logistic regression model with dose as an explanatory variable.					

5) Treatment-emergent EKG Interval Changes by Severity and Dose

- All treatment-emergent EKG interval changes were mild in intensity.
- By dose, the overall rates of treatment-emergent EKG interval changes were 24/79 (30.4%), 29/83 (34.9%), 28/80 (35.0%) and 32/78 (41.0%) for 25, 50, 100 and 200 mg, respectively.
  - There was no statistically significant trend with dose in the overall incidence of treatment-emergent EKG interval changes.
- The most frequently reported individual change in this category was "QT interval prolongation", the coded term for QT_c prolongation (treatment-emergent increases in QT_c to ≥440 msec).
  - QT interval prolongation was reported for 21/79 (26.6%) patients in the 25 mg dose group, 24/83 (28.9%) in the 50 mg group, 25/80 (31.3%) in the 100 mg group and 26/78 (33.3%) in the 200 mg group.
  - There was no statistically significant trend with dose in the incidence of QT interval prolongation.
- "EKG abnormal specific" is the coded term that represents the number of patients with intraventricular conduction defect (IVCD; treatment-emergent increases in QRS width to ≥100 msec, but not complete BBB).
  - EKG abnormal specific was reported for 2/79 (2.5%) patients in the 25 mg dose group, 6/83 (7.2%) in the 50 mg dose group, 6/80 (7.5%) in the 100 mg dose group and 9/78 (11.5%) in the 200 mg dose group.
  - There was a statistically significant trend with dose in the incidence of EKG abnormal specific (p=0.0482).
- "AV block first degree" is the coded term that represents the number of patients with treatment-emergent increases in PR interval to ≥220 msec.
  - AV block first degree was reported for 2/79 (2.5%) patients in the 25 mg dose group, 1/83 (1.2%) in the 50 mg dose group, 0/80 (0.0%) in the 100 mg dose group and 3/78 (3.8%) in the 200 mg dose group.

- Of the 96 instances of QT interval prolongation, 95 were deemed treatment-related by the investigator.

- All 23 instances of EKG abnormal specific and all 6 instances of AV block first degree were assessed as treatment-related by the investigator.

6) AEs of Potential Concern (Table 49)

In an approach similar to that used for Study 043, this Table lists the patients that experienced chest pain, edema, hypo/hypertension or abnormal hepatic function/elevated serum enzymes. Included in this information is the DOLA•Mesyl dose, intensity (severity) of the AE and possible relationship to test medication. All in all, these data in individual patients are not reason for concern but they are the building blocks for the ISS, Cardiovascular Events, at the end of the review of the NDA for DOLA•Mesyl tablets.

TABLE 49
Study MDPR0048 (Report K-94-0929-CDS)

List of AEs of Potential Concern

CHEST PAIN [n=0]	EDEMA [n=6]	HYPO (↓) or HYPER (↑) - TENSION	ABNORMAL LFTs
	• MCST0381-0007 (25 mg) - generalized - mild - POSSIBLY • MCST0381-0025 (50 mg) - bilateral arm - MOD - unlikely • 3 patients (100 mg) - mild • 1 patient (200 mg) - mild The last 4 were attributed to pedal edema or Hx of [illegible]	• 1 patient (↓) (25 mg) - MOD - PROBABLY related • 1 patient (orthostatic ↓) (100 mg) - mild - unlikely	• 1 patient (25 mg) - mild - PROBABLY • 1 patient (100 mg) - mild - PROBABLY

7.) [illegible]

• [illegible] patients received a second full dose [illegible] (ondansetron or granisetron) during the [illegible]

- For 34 of these patients, ondansetron was administered as rescue medication; for the remaining patient, granisetron was administered as rescue medication.

- Of these 35 patients, the initial DOLA•Mesyl antiemetic treatment was 25 mg for 14 patients, 50 mg for 11 patients, 100 mg for 6 patients and 200 mg for 4 patients.

- In this sub-population, the overall rates of adverse events were 9/14 (64.3%), 7/11 (63.6%), 4/6 (66.7%) and 3/4 (75.0%) for 25, 50, 100 and 200 mg dose groups, respectively.

- The overall rates in this subgroup were slightly higher than the overall rates observed in all patients.

- Central and peripheral nervous system and gastrointestinal system adverse events occurred at a lower rate for this subgroup than for the overall population, but heart rate and rhythm AEs occurred at a slightly higher rate in this sub-population, 12/35 (34.3%) versus 72/320 (22.5%) for all patients. This was primarily due to increased incidences of sinus bradycardia and ST-T change or abnormality in this subgroup population.

- Overall incidence of treatment-emergent EKG interval changes were 14/35 (40.0%) in the subgroup, comparable to the incidence in all patients: 113/320 (35.3%).

- None of these 35 patients had a SAE.

  - 2 of the patients experienced AEs that were assessed by investigator as severe in intensity. Neither of these events was assessed to be study drug related by the investigator.

  - Patient MCST0314-0004 (25 mg) had severe diarrhea prior to rescue with ondansetron.

  - Patient MCST0323-0004 (also 25 mg) had severe nausea and vomiting prior to rescue with ondansetron.

- The reviewer agrees with the sponsor that although there were some small differences in incidence rates for some AEs in patients who received a 5-HT_3 receptor antagonist as rescue medication, the differences were minor and did not suggest any increased risk in this group of patients.

8) Clinical Laboratory Evaluation

There were no changes of concern.

- Analyses of laboratory data revealed statistically significant decreasing linear trends with increasing dose in

for serum albumin, serum total protein, hematocrit and hemoglobin. Administration of i.v. and oral fluids was considered the principal cause of these changes. But the dose relationship indicates that DOLA•Mesyl cannot be excluded as a possible contributor.

- Basophils also displayed a significant positive trend with dose, but the counts were so low this is not considered meaningful.

- Other laboratory abnormalities were common and were consistent with the patient's disease, chemotherapy or fluid administration.

- Treatment-emergent elevations in SGOT and SGPT, commonly observed after cancer chemotherapy, were mild (<2 x ULN), occurred at similar rates across treatment groups and were not associated with clinical sequelae.

  - There was a trend for total bilirubin to increase from baseline to 24-h post-treatment (independent of dose group).

9) <u>Descriptive Statistics for EKG Assessments</u>

Descriptive statistics for the six EKG measures, at Pre-Tx, hour 1-2 and hour 24, by dose, are given in Table 50. The associated changes from BL (median and mean) are also listed in this Table. The p-values for the test for linear trend in change from BL with dose are provided in the lower panel of this Table.

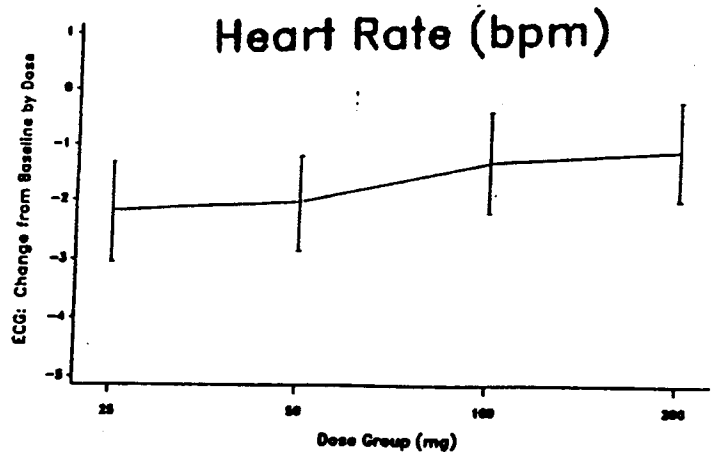
A graphic representation of the change from BL by Dose 1-2h POSTDOSE is given in Fig. 14, that for 24h POSTDOSE is depicted in Fig. 15. The average changes by time for those EKG parameters that showed a statistically significant trend in change from BL at 1-2h (PT, QRS and QTC) are shown in Fig. 16.

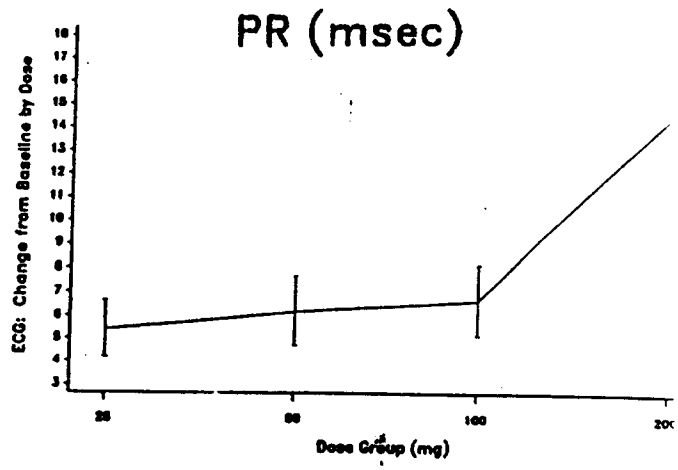
TABLE 50
Study MCPR0048 (Report K-94-0929-CDS)

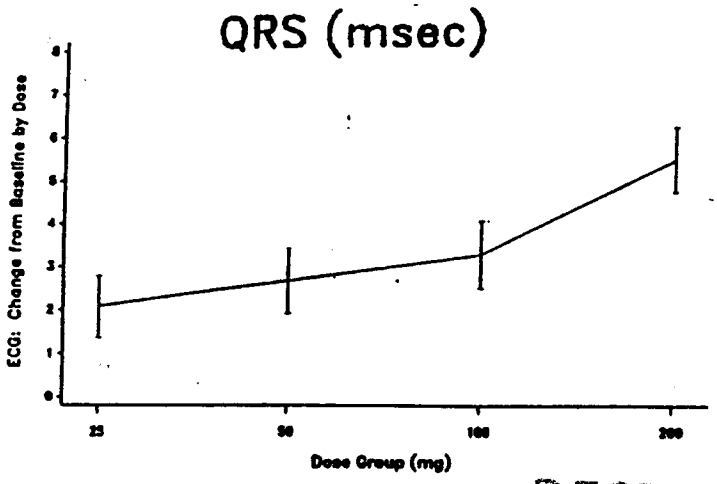
EKG Summary Measures (Mean of actual readings), Median and Mean Change from BL at Pre-Tx, 1-2h Post and 24-h Post-Tx as a Function of DOLA•Mesyl Dose
[All Patients]

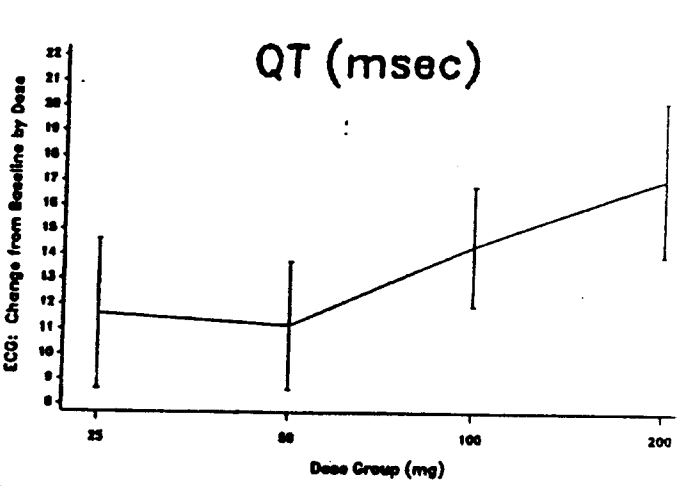
Dose (mg)	Evaluation	HR			PR			QRS			QT			QTc			JT		
		(bpm)	Change from BL		(msec)	Change from BL		(msec)	Change from BL		(msec)	Change from BL		(msec)	Change from BL		(msec)	Change from BL	
		Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean
25	PRE-BL	76.1			155.2			83.0			380.0			423.1			296.9		
	1-2h POST	73.4	-3	-2.2	161.2	4	5.4	85.1	2	2.1	392.3	10	11.6	429.7	5	7.3	307.2	10	9.5
	24h POST	78.5	3	2.4	159.4	3	4.2	83.1	0	0.1	380.0	0	0.0	430.3	11	7.3	296.9	0	-0.1
[illegible]	PRE-BL	79.9			160.3			85.8			382.5			424.8			296.7		
	1-2h POST	[illegible]	-2	-2.0	166.5	4	6.2	88.4	1	2.7	393.7	5	11.1	431.9	8	7.2	305.2	7	8.5
	24h POST	77.7	2	1.8	159.7	0	-0.6	85.7	0	-0.0	385.4	0	2.9	433.6	8	8.8	299.7	0	2.9
[illegible]	[illegible]	73.9			157.1			84.3			379.7			417.6			295.4		
	[illegible]	72.3	-2	-1.3	164.3	4	6.7	87.8	2	3.3	394.5	12	14.4	428.9	11	11.5	306.8	10	11.1
	[illegible]	[illegible]	0	1.7	157.9	0	0.4	85.1	0	0.7	384.7	5	4.1	428.7	9	10.4	299.6	5	3.5
[illegible]	[illegible]	[illegible]			158.1			86.6			386.1			428.1			299.5		
	[illegible]	[illegible]	-2	-1.1	173.1	15	14.6	92.3	4	5.5	403.2	16	17.2	443.1	16	15.3	310.9	12	11.7
	[illegible]	[illegible]	-1	-1.4	160.3	0	2.2	87.4	0	0.8	391.6	10	5.6	430.2	4	2.1	304.2	8	4.7
	[illegible]	[illegible]			<0.0001			0.0020			N.S.[a]			0.0049			N.S.		
	[illegible]	[illegible]			N.S.			N.S.			0.0992			N.S.			N.S.		

[a] [illegible] from a two-way rank analysis of variance F test for linear trend in change from BL with dose, controlling for investigator.









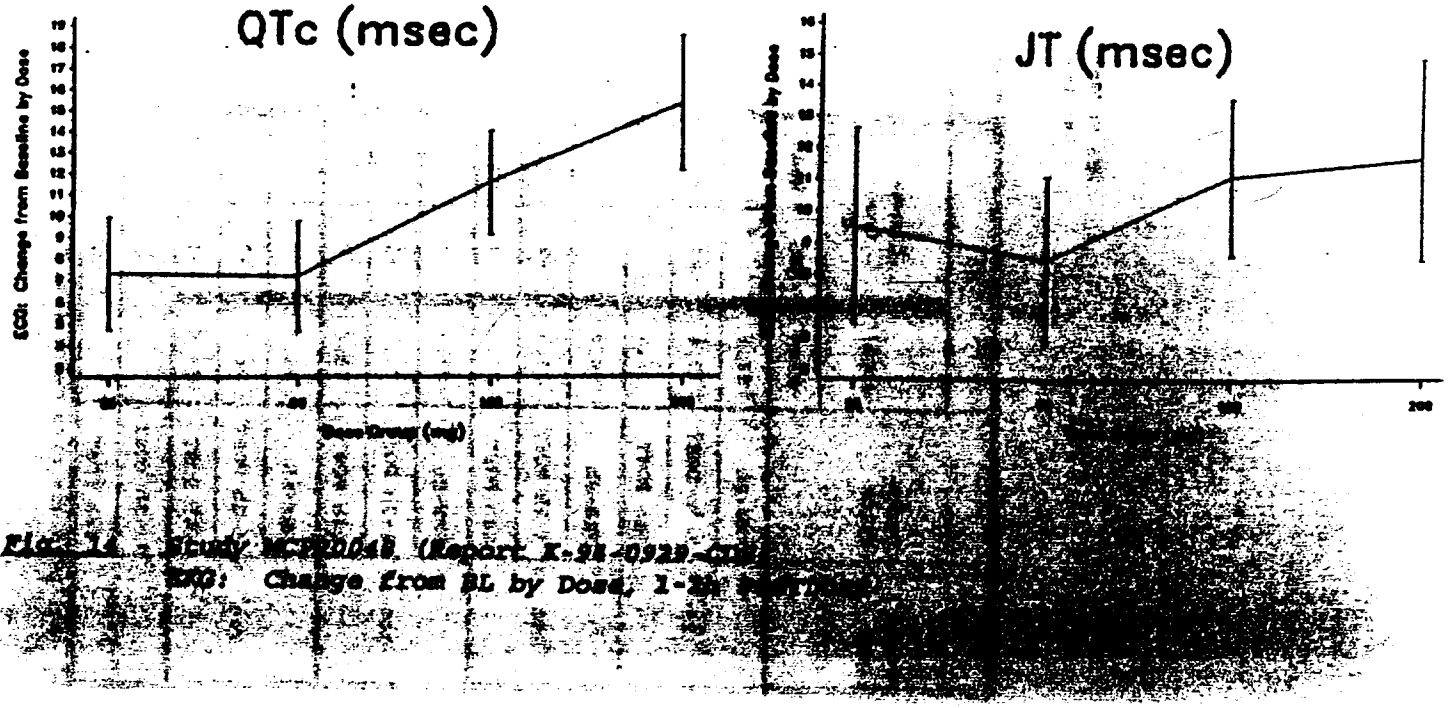


Fig. 14 - Study MCP20048 (Report X-98-0929-CN)
ECG: Change from BL by Dose, 1-2h

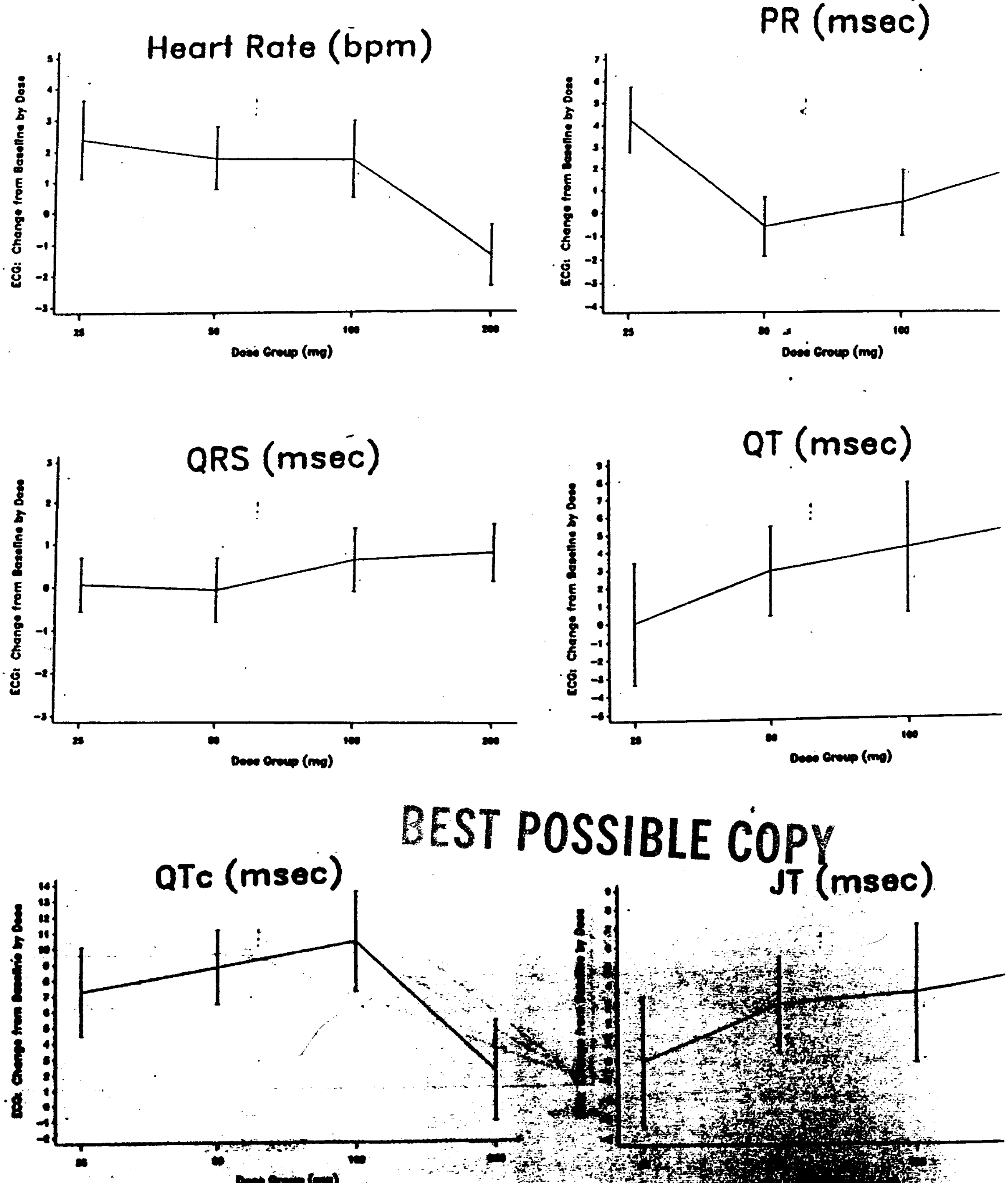
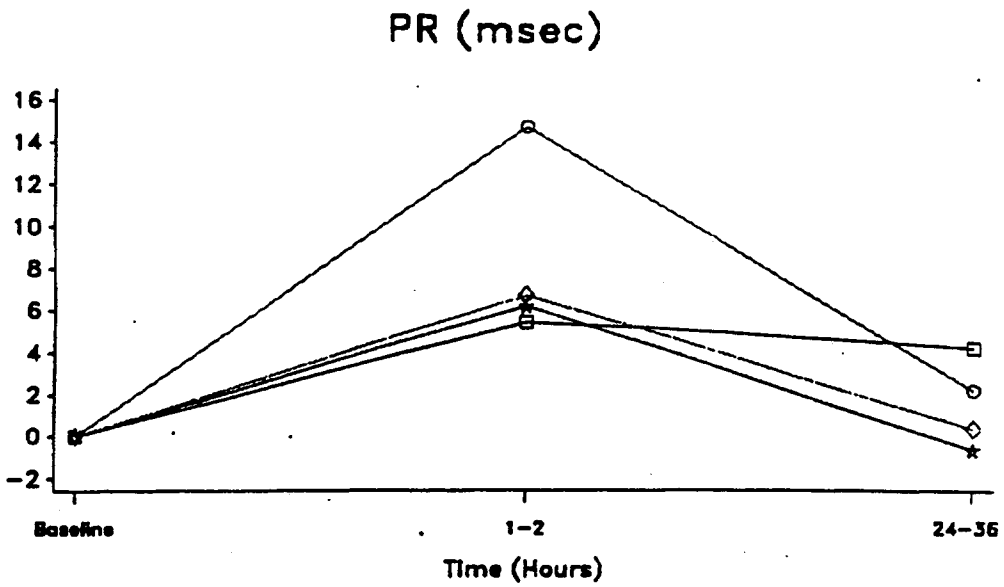
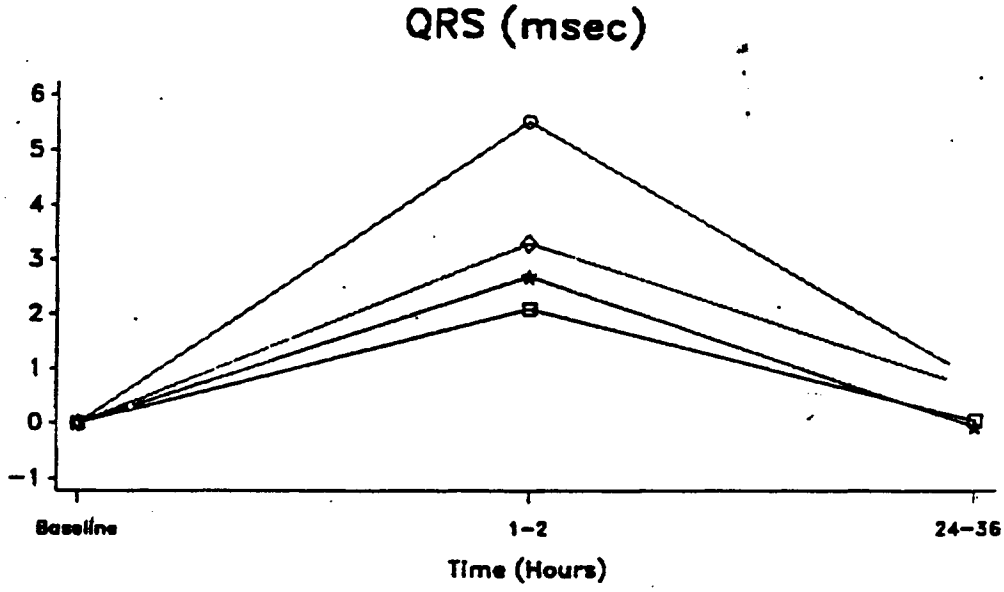
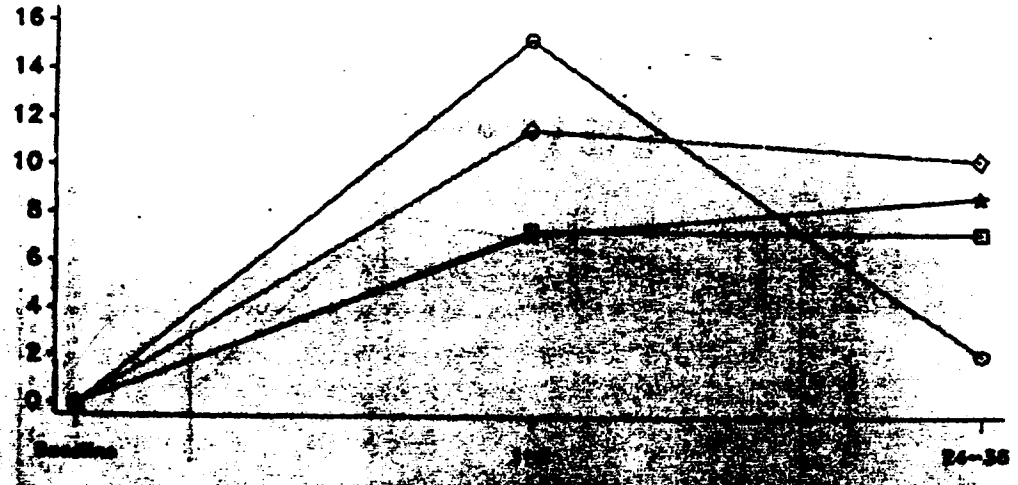


Fig. 15 - Study MCPR00[illegible] (Report [illegible]
ERG: Change from BL by Dose; [illegible]





Mean Change from Baseline



Drug
Group (mg) 25 50

(All Patients)

The frequency (%) of Tx-emergent changes at Acute (hour 1-2) and Exit (hour 24) are given in Table 51.

TABLE 51
Study MCPR0048 (Report K-94-0929-CDS)

Frequency (Percent) of Acute and Exit Treatment-Emergent EKG Changes
[All Patients]

Evaluation	Dose (mg)	n	HR Pre≤100 bpm and Post>100	HR Pre≥60 bpm and Post>60	PR Pre<220 msec and Post≥220	QRS Pre<100 msec and Post≥100	QT_c Pre<440 msec and Post≥440
Acute (Hour 1-2)	25	75	0 (0%)	2 (3%)	0 (0%)	2 (3%)	11 (15%)
	50	83	1 (1%)	6 (7%)	1 (1%)	5 (6%)	14 (17%)
	100	79	0 (0%)	3 (4%)	0 (0%)	5 (6%)	17 (22%)
	200	77	2 (3%)	4 (5%)	3 (4%)	9 (12%)	22 (29%)
Exit (Hour 24)	25	78	1 (1%)	2 (3%)	2 (3%)	1 (1%)	13 (17%)
	50	83	1 (1%)	4 (5%)	0 (0%)	3 (4%)	16 (19%)
	100	78	3 (4%)	4 (5%)	0 (0%)	4 (5%)	17 (22%)
	200	78	1 (1%)	5 (6%)	1 (1%)	3 (4%)	15 (19%)

The frequencies of treatment-emergent changes in EKG parameters, analyses of summary values and graphic representation of the mean change from BL by dose at 1-2h as well as 24h post-dose are considered in detail below.

i) Heart Rate (HR) (bpm)

Refer to Table 50.

- At hour 1-2, there was not a statistically significant trend in change from BL with dose: slight decreases in HR were seen for all four doses, ranging from -1.1 bpm in the 200 mg dose group to -2.2 bpm in the 25 mg dose group.
- There was a statistically significant trend with dose in change from baseline at hour 24 (p=0.0092). However, this trend was for larger increases from baseline for the lower dose groups: the mean changes from BL to hour 24 were 2.4 bpm, 1.8 bpm, 1.7 bpm and 1.4 bpm for the 25 mg, 50 mg, 100 mg and 200 mg dose groups.
- Fig 14 shows pronounced overlap among the mean changes in HR associated with the four DOLA-Neoyl doses at 1-2h Postdose. At 24-h Postdose, the response associated with 200 mg DOLA-Neoyl was distinct from that with the other three doses (Fig. 15).
- Refer to Table 51 (Tx-emergent changes in HR).

- 3 patients had acute ↑ in HR to above 100 bpm: 1 patient (1%) in the 50 mg dose group and 2 (3%) in the 200 mg dose group.

  - 2 of these patients also had exit increases in HR to above 100 bpm: 1 patient in the 50 mg dose group, and 1 in the 200 mg dose group.

- 15 patients had acute ↓ in HR to below 60 bpm: 2 patients (3%) in the 25 mg dose group, 6 (7%) in the 50 mg dose group, 3 (4%) in the 100 mg dose group and 4 (5%) in the 200 mg dose group.

  - 11 of these patients also had exit decreases in HR to below 60 bpm: 1 patient in the 25 mg dose group, 3 in the 50 mg dose group, 3 in the 100 mg dose group and 4 in the 200 mg dose group.

ii) PR Interval (msec)

Refer to Table 50.

- At hour 1-2 there was a statistically significant increasing trend in change from BL with dose ($p<0.0001$). Mean changes from BL were 5.4 msec, 6.2 msec, 6.7 msec and 14.6 msec for the 25, 50, 100, and 200 mg dose groups, respectively.

- There was not a statistically significant trend with dose in change from BL at hour 24: mean changes from BL ranged from 4.2 msec for the 25 mg dose group to -0.6 msec for the 50 mg dose group.

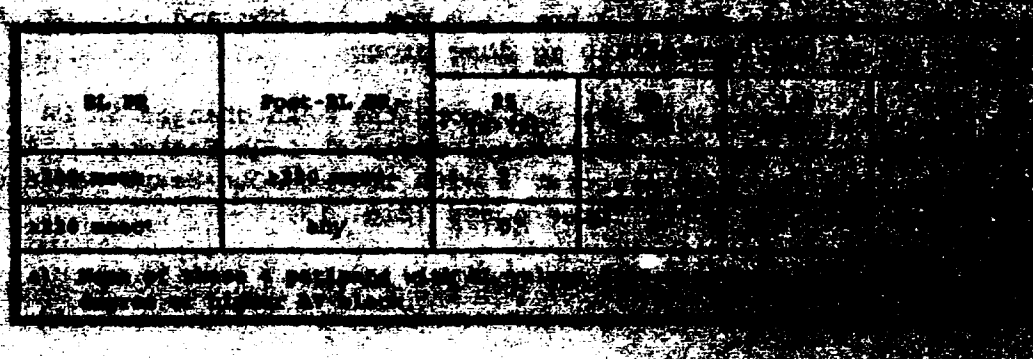
As seen in Fig. 14, for PR, the mean change from BL at hour 1-2 showed a clear difference between the 200 mg and the other three DOLA•Mesyl dose levels. But the four groups were not very dissimilar at hour 24 Postdose (Fig. 15).

Refer to Table 51 (Tx-emergent changes in PR).

- 4 patients had acute increases in PR interval to ≥220 msec: 1 patient (1%) in the 50 mg dose group and 3 (4%) in the 200 mg dose group.

  - 1 of these patients (200 mg dose) also had an acute increase in PR interval to ≥220 msec.

  - Overall, 6 patients experienced [illegible] in PR interval and 4 patients had BL values [illegible]



iii) ORS Duration (msec)

Refer to Table 50.

- At hour 1-2, there was a statistically significant increasing trend in change from BL with dose (p=0.0020).
  - Mean changes from baseline were 2.1 msec, 2.7 msec, 3.3 msec and 5.5 msec for the 25, 50, 100 and 200 mg dose groups, respectively.
- There was not a statistically significant trend with dose in change from baseline at hour 24: mean changes from baseline ranged from 0.8 msec for the 200 mg dose group to 0.0 msec for the 50 mg dose group.

Once again at hour 1-2, for QRS, the average change associated with the 200 mg dose was distinct from that seen with the other DOLA•Mesyl doses (Fig. 14). At hour 24, the change from BL was very similar for the 4 dose groups (almost a straight line) (Fig. 15).

Refer to Table 51 (Tx-emergent changes in QRS).

- 21 patients had acute increases in QRS duration to ≥100 msec: 2 patients (3%) in the 25 mg dose group, 5 (6%) in the 50 mg group, 5 (6%) in the 100 mg dose group and 9 (12%) in the 200 mg dose group.
  - 8 of these patients also had exit increases in QRS duration to ≥100 msec: 1 patient in the 25 mg dose group, 2 in the 50 mg dose group, 3 in the 100 mg dose group and 2 in the 200 mg dose group.
- Overall, 24 patients experienced treatment-emergent changes in QRS duration and 27 patients had BL values ≥100 msec.

BL QRS (msec)	Post-BL QRS (msec)	DOLA•Mesyl (mg)			
		25 (n=79)	50 (n=83)	100 (n=80)	200 (n=76)
<100	≥100	2	[illegible]	[illegible]	[illegible]
	100-109	1	[illegible]	[illegible]	[illegible]
	110-119	1	[illegible]	[illegible]	[illegible]
	≥120	0	0	0	0
100-119	any	3	12	[illegible]	[illegible]
	≥120	0	[illegible]	[illegible]	[illegible]
≥120	any	1	0	[illegible]	[illegible]

- There was no definitive pattern in increases in QRS duration for the patients having BL values ≥100 msec; all 27 such patients were safely treated.

iv) QT interval (msec)

Refer to Table 50.

- At hour 1-2, there was not a statistically significant trend in change from BL with dose: increases in QT interval were seen for all four doses, ranging from 11.1 msec in the 50 mg dose group to 17.2 msec in the 200 mg dose group.

- There was not a statistically significant trend with dose in change from BL at hour 24: mean changes from baseline ranged from 0.0 msec for the 25 mg dose group to 5.6 msec for the 200 mg dose group..

Per Fig. 14, at hour 1-2 post-dose, the QT changes associated with the 200 mg dose appear to be different (higher) than those associated with the 25 and 50 mg DOLA•Mesyl dose. At hour 24 Post-dose (Fig. 15) the response with the four DOLA•Mesyl groups was similar.

v) QT_c interval (msec)

Refer to Table 50.

- At hour 1-2, there was a statistically significant increasing trend in change from baseline with dose (p=0.0049).

  - Mean changes from baseline were 7.3 msec, 7.2 m sec, 11.5 msec and 15.3 msec for the 25, 50, 100 and 200 mg dose groups, respectively.

- There was not a statistically significant trend with dose in change from BL at hour 24: mean changes from BL ranged from 2.1 msec for the 200 mg dose group to 10.4 msec for the 100 mg dose group.

Fig. 14 demonstrates that, at hour 1-2 Postdose, the QT_c changes from BL associated with the two higher doses of DOLA•Mesyl (100 mg and especially 200 mg = no overlapping of SE with the lower doses) are higher than those associated with 25 or 50 mg of the drug. At hour 24 (Fig. 15) changes from BL with the 200 mg dose also differ from those with other doses of the drug, but actually the 25 mg dose group had smaller increases from BL than the three other dose groups.

Refer to Table 51 (Tx-emergent changes in QT

- 64 patients had events ≥ in QT, QTc ≥440 msec, with 25 mg dose group, 14 (11%) in the 50 mg dose group, 100 mg dose group and 28 (22%) in the 200 mg dose group.

  - 29 of these patients also had
  - 1 patient in the 25 mg dose group
  in the 100 mg dose group and 11

- Overall, 96 patients experienced treatment-emergent changes in QT_c interval, and 77 patients had BL values ≥440 msec.

BL QT_c [msec]	Post-BL QT_c [msec]	DOLA•Mesyl (mg)			
		25 [n=79]	50 [n=83]	100 [n=80]	200 [n=78]
<440	≥440	21	24	25	26
	440-449	10	8	7	10
	450-459	4	4	6	5
	460-469	4	8	8	7
	470-479	0	2	1	2
	480-489	0	2	2	0
	490-499	2	0	0	0
	≥500	1	0	1	2
440-499	any	22	21	11	23
	≥500	1	1	0	3
≥500	any	0	0	0	0

- No patients in this study developed torsades de pointes or any ventricular arrhythmias. All patients with baseline QT_c values ≥440 msec were safely treated.

vi) JT interval (msec)

Refer to Table 50.

- At hour 1-2, there was not a statistically significant trend in change from baseline with dose: increases in JT interval were seen for all four doses, ranging

- There was not a statistically significant trend with dose in change from baseline at hour 24: mean changes from baseline ranged from

Fig 14 and 15 illustrate little if any differences among the four DOLA•Mesyl doses in JT either at hour 1-2 or hour 24 Postdose.

10) Subgroup Analysis of Gender

There were no statistically significant gender main effects for any of the EKG parameters at 1-2h and 24-h Postdose. At both 1-2h and 24-h Postdose, there was evidence of an interaction between gender and dose for [illegible] interval change from BL (p=0.0294 and p=0.0126, respectively). At 24-h Postdose, there was a statistically significant interaction between gender and dose for JT interval change from BL (p=0.0073). Both the significant [illegible] and those in JT were apparently due to widely varying [illegible] the males, coupled with mean changes from BL in females [illegible] increasing trend with dose.

11) Subgroup Analysis by Chemotherapy (Table 52)

This Table depicts the descriptive statistics (p-values) for changes at 1-2h and 24-h for EKG measures in three subgroups of patients: those receiving DOX-containing chemotherapy, those receiving DOX-containing chemotherapy as continuous infusion[21] and those not receiving DOX-containing chemotherapy.

TABLE 52
Study MCPR0048 (Report K-94-0929-CDS)

Descriptive Statistics for the EKG Measures at hours 1-2 and hour 24 Postdose by Doxorubicin (DOX)-containing Chemotherapy

Subgroup	Evaluation	p-values[a]					
		HR	PR	QRS	QT	QT_c	JT
Patients receiving DOX-containing Chemotherapy [n=39 to 47][b]	1-2h POST	N.S.	0.0031	0.0364	N.S.	N.S.	N.S.
	24h POST	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Patients receiving DOX-containing Chemotherapy as Continuous Infusion[e] [n=8 to 10][c]	1-2h POST	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	24h POST	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
Patients Not Receiving DOX-containing Chemotherapy [n=23 to 30][d]	1-2h POST	0.0576	0.0007	0.0534	N.S.	0.0006	N.S.
	24h POST	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

a) All p-values were calculated from a two-way analysis of variance F-test for linear trend in change from BL with dose, controlling for investigator.
b,c,d) The n (per DOLA•Mesyl group) varied depending on the DOLA•Mesyl dose.
e) The total number of patients receiving DOX-containing chemotherapy as continuous infusion was 35. All 35 of these patients were female.

- In the first subgroup, increasing trends in change from BL with DOLA•Mesyl dose in PR and QRS (only) were seen at hour 1-2. There was no statistically significant difference in the changes for the other measures at hour 1-2 or any of the measures at hour 24.
- In the subgroup receiving DOX-containing chemotherapy as continuous infusion, changes from BL in EKG measures were not statistically significant at hour 1-2 nor at hour 24.
- At hour 1-2, in the subgroup of patients not receiving DOX-containing chemotherapy, the changes from BL in [illegible] significant and those in [illegible] significance. In this subgroup of patients, changes at hour 24 were apparently [illegible]

[illegible] All patients in this subgroup were treated at the [illegible]

Further analysis in the frequency of QT_c changes at hour 1-2 (Acute) and hour 24 (Exit) in the three subgroups of patients is given in Table 53.

- Marked differences between the 200 mg and the 25 mg DOLA•Mesyl groups are seen at hour 1-2. The Δ (200 mg - 25 mg), that is the difference in % of patients experiencing changes in QT_c was 30% in the subgroup of patients NOT receiving DOX-containing chemotherapy and 11% in those receiving DOX-containing chemotherapy. In the subgroup of patients who received DOX-containing chemotherapy as continuous infusion, 20% of the patients in the 25 mg dose had QT_c changes but none of the patients in the other three groups experienced QT_c alterations.

- QT_c changes at exit (hour 24) as a function of subgroup of chemotherapy and DOLA•Mesyl dose were not remarkable.

- It is worth reiterating that the number of patients in these subgroups, especially those in the subgroup receiving DOX-containing chemotherapy as continuous infusion, was small.

TABLE 53
Study MCPR0048 (Report K-94-0929-CDS)

QT_c
(Pre <440 msec and Post ≥440 msec)

DOLA•Mesyl Dose (mg)	SUBGROUP OF PATIENTS RECEIVING		
	DOX-Containing Chemotherapy[a]	DOX-Containing Chemotherapy as Continuous Infusion	Not Receiving DOX-Containing Chemotherapy
I. Acute (Hour 1-2)			
25	6/41 (15%)	2/20 (20%)	3/24 (13%)
50	11/47 (23%)	0/8 (0%)	3/28 (11%)
100	7/39 (18%)	0/9 (0%)	10/31 (32%)
200	12/46 (26%)	0/8 (0%)	[illegible]
II. Exit (Hour 24)			
25	9/42 (21%)	[illegible]	[illegible]
50	13/47 (28%)	[illegible]	[illegible]
100	11/38 (28%)	[illegible]	[illegible]
200	12/47 (26%)	[illegible]	[illegible]

a) Including patients receiving DOX-containing [illegible] infusion.

12) Vital Signs

- In their Table 44, page 238, the sponsor provided the descriptive statistics for the recumbent and standing pulse rate, systolic blood pressure, and diastolic blood pressure measurements and their associated changes from baseline by dose; p-values for the test for linear trend to change from BL with dose were also provided for each hour. Plots of mean change from BL to each time point over the entire study by dose for recumbent and standing pulse rate, systolic blood pressure and diastolic blood pressure are provided in Fig. 17.

  - There were no statistically significant trends with dose in recumbent or standing pulse rates at any time point. All four dose groups were associated with small median decreases (2 to 4 bpm) in pulse rate at hours 0.5 and 2.

  - At hour 0.5, all four dose groups had slight median decreases (2 to 4 mmHg) in recumbent systolic blood pressure, but there was no statistically significant trend with dose. Statistically significant trends with dose in change from baseline in recumbent systolic blood pressure were observed at hours 2 and 24-36 (p=0.0037 and p=0.0114, respectively). At hour 2, the median changes from BL in recumbent systolic blood pressure were -2 mmHg, -4 mmHg, -8 mmHg and -6 mmHg for the 25, 50, 100 and 200 mg dose groups, respectively. At hour 24-36, the median changes from baseline in recumbent systolic blood pressure were -3 mmHg, 0 mmHg, -6 mmHg and -6 mmHg for the 25, 50, 100 and 200 mg dose groups, respectively.

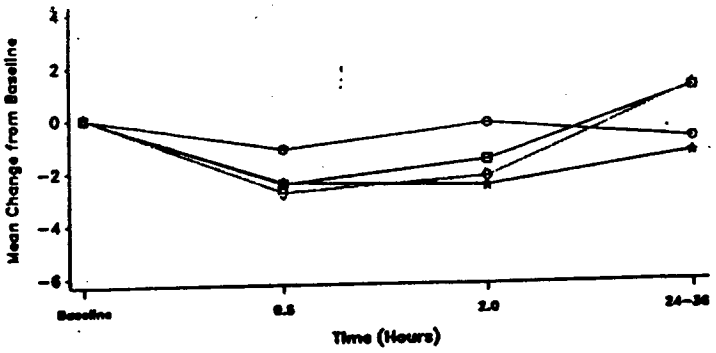
  - There were no statistically significant trends with dose nor any apparent treatment effects on recumbent diastolic blood pressure at hours 0.5 and 2. However, at hour 24-36, there was a statistically significant trend with dose in change from baseline (p=0.0137). At hour 24-36, the median changes from baseline in recumbent diastolic blood pressure were 0 mmHg, 0 mmHg, -2 mmHg and -4 mmHg for the 25 mg, 50 mg, 100 mg and 200 mg dose groups, respectively.

  - There were no statistically significant trends with dose nor any apparent Tx effects on standing systolic blood pressure at hour 0.5. However, at hours 2 and 24-36, there were statistically significant trends with dose in change from baseline (p=0.0105, respectively).

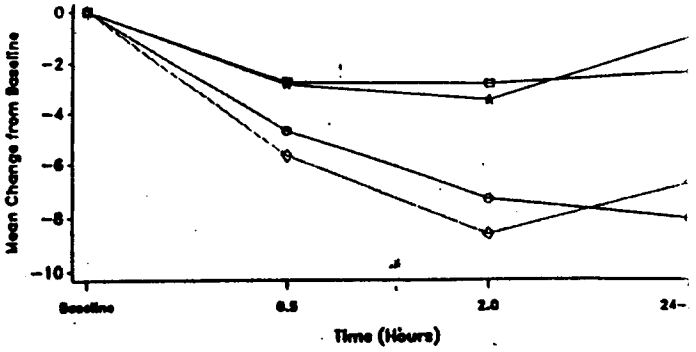
  - At hour 2, the median changes from baseline in standing systolic blood pressure were -2 mmHg, 0 mmHg, -6 mmHg and -6 mmHg for the 25, 50, 100 and 200 mg dose groups, respectively.

  - At hour 24-36, the median changes from baseline in standing systolic blood pressure were -4 mmHg, 0 mmHg, -6 mmHg and -6 mmHg for the 25, 50, 100 and 200 mg dose groups, respectively.

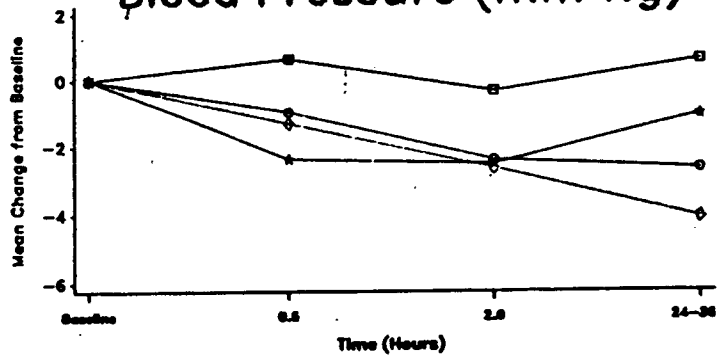
Recumbent Heart Rate (bpm)



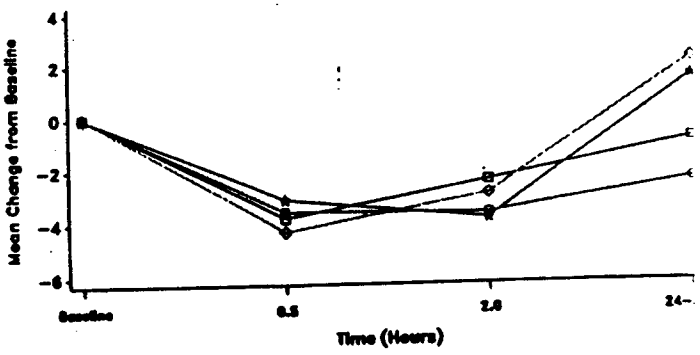
Recumbent Systolic Blood Pressure (mm Hg)



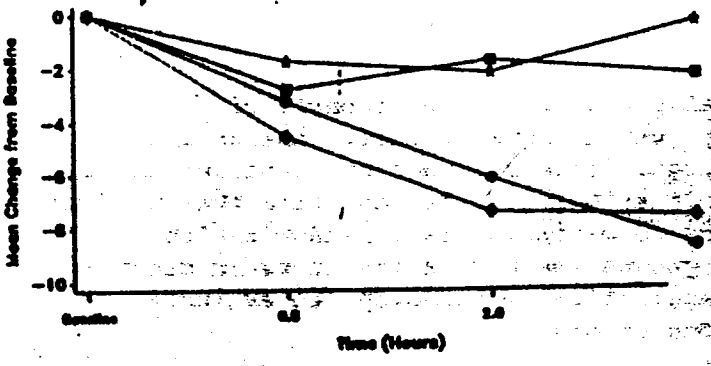
Recumbent Diastolic Blood Pressure (mm Hg)



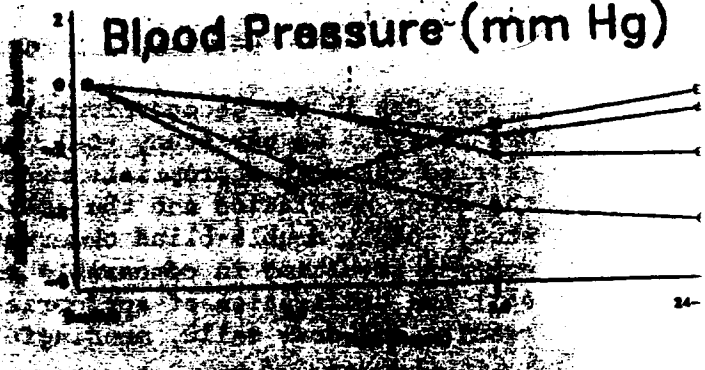
Standing Heart Rate (bpm)



Standing Systolic Blood Pressure (mm Hg)



Standing Diastolic Blood Pressure (mm Hg)



Dose Group (mg) 25 50

Fig. 17 - Study MCPR0048 (Report K-94-0929-CRI)
Vital Signs by Time

- There were no statistically significant trends with dose nor any apparent treatment effects on standing diastolic blood pressure at any time point.

- The results depicted in Fig. 17 are consistent with the median results presented above.

9. Sponsor's Conclusions

"The study objectives were met. Antiemetic efficacy of dolasetron mesylate was linearly related to dose, with maximal effectiveness achieved at 100 mg.

"Antiemetic efficacy of dolasetron mesylate was greatest in patients who were older, patients who received concomitant benzodiazepines, and in patients who received one of the primary chemotherapeutic agents (cyclophosphamide or doxorubicin) but not both. Expected differences in efficacy based upon gender, previous chemotherapy, history of heavy alcohol use, concomitant steroids or concomitant narcotics were not statistically significant.

"Pharmacokinetics and pharmacodynamics of PR interval and QRS duration increases, were comparable in cancer patients to results previously reported for healthy volunteers.

"Dolasetron mesylate, at the doses tested in this study, is safe in this patient population.

"While dolasetron mesylate elicted electrophysiologic effects that resulted in increases in measured 12-lead ECG intervals, there was no evidence of increased patient risk from this effect.

"There was no evidence of increased cardiovascular risk to patients who received dolasetron mesylate during doxorubicin therapy.

"Based on careful review of both safety and effectiveness data, there is little reason to select the 200 mg dolasetron mesylate dose over the 100 mg dose for this patient population. Although selecting the dose was a stated objective, the power for detecting differences between doses was limited."

10. Reviewer's Comments

Study -048 is the second pivotal trial submitted by the sponsor in NDA 20-623. As per study -041, study -048 employed a [illegible] was carried out with appropriate methodology. This [illegible] of the study population and the emetogenic stimulus [illegible] in study -048), double-blind observations to eliminate [illegible] schemes resulting in comparable test groups [illegible] 041) and utilization of appropriate statistical [illegible] results and draw valid, meaningful conclusions.

The study population (ITT-320; 60 M, 260 F) consisted of cyclophosphamide and doxorubicin naive patients (ca. 3% of the patients had received previous chemotherapy), ca. 54y old in age (on the average, 7 years younger than in study -043), mostly Caucasian, primarily (81%) female, in general without evidence of significant cardiovascular or hepatic disease. The site for primary neoplasm was breast (69% of the patients) and lymphoma (18%). As in study -043, the initial approach was to demonstrate - with respect to cardiovascular status - a dose of compound <3 mg/Kg (ca. 200 mg) was safe, with appropriate exclusions (Table 14). But eventually, the only patients that were routinely excluded were those with severe electrolyte abnormalities, those with poor ejection fractions and those with complete BBBs. So, these exclusions not withstanding, study -048 randomized a relatively broad spectrum of patients, thus mimicking clinical practice.

The randomization procedures used in this trial resulted in four populations of patients that were comparable (to each other) with respect to variables that may influence outcome. For the four test groups, the demographics, primary disease states, other significant medical conditions, physical examination, Karnofsky status (median score=100%) and prior medications were similar to each other.

The four test groups were also balanced with respect to concomitant medications in general and concomitant medications that may be confounding, such as concomitant chemotherapy (primarily 5-FU=53%, vincristine=24% and MTX=20% of the patients), narcotic analgesics (14% of the patients), benzodiazepines (11% of the patients), and steroids (11% of the patients).

The experimental groups were also well matched with regards to standardization of the emetic stimulus. This consisted primarily of cyclophosphamide (given to 58% of the patients, at a mean dose of 614 mg/m^2) and doxorubicin (given to 42% of the patients, at a mean dose of 44 mg/m^2). This regimen is best characterized as being of moderate emetogenic potential. The average duration of infusion of primary chemotherapy was 32 min. and the mean interval between test medication and the start of the primary chemotherapy was 32 min. also. Upon further examination, there were statistically significant imbalances among the four dose groups in DOX dose (p=0.0032) and cyclophosphamide dose (p=0.0321). The 200 mg had the lowest mean doses for both agents. For DOX, the mean doses (mg/m^2) were 45, 46, 43 and 41 for the 25, 50, 100 and 200 mg groups, respectively. For cyclophosphamide the corresponding mean doses (mg/m^2) were: 642, 624, 607 and 580.

Based on evaluations of complete and total [illegible] conclusions on efficacy are as follows: [illegible] Evaluable Population were consistent with [illegible] only the latter data are mentioned here. [illegible] demonstrated because there was a statistically [illegible] frequency of complete responders as well as [illegible] oral doses of the drug. Among complete responders, [illegible] dose groups were superior to the 25 mg group [illegible]

clinically important therapeutic gains of 31 and 28% (over the 25 mg dose) and of 20 and 18% (over the 50 mg dose), respectively. ITT analysis of total response showed statistical superiority therapeutic gains of 17% and 19% of the 100 and 200 mg doses over the 25 mg dose, but not over the 50 mg (therapeutic gains=11 and 13%, respectively, both N.S.). When the doses tested were converted into mg/Kg units, based upon the B_{wt} of the patient, a statistically significant increase in complete response, with increasing dose in mg (p=0.0011) was also demonstrated. The reviewer agrees with the sponsor that these findings suggest that a dosing regimen independent of B_{wt} is appropriate for this indication. Additional efficacy analyses demonstrated that investigator was not a significant predictor of complete response; there was no interaction between investigator and a linear dose response. Subgroup analyses indicated the following: age (p=0.0003) , concomitant use of benzodiazepines (p=0.042 50 mg=2; 100 mg=2 9), use of one primary chemotherapy agent (either cyclophosphamide or DOX but not both((p=0.0010) were all statistically significant predictor of complete response, but neither gender, previous Hx of chemotherapy, non-use of narcotic analgesics, concomitant use of steroids, nor Hx of heavy alcohol use were statistically significant predictors of complete response. When adjusting for age, use of benzodiazepines, number of primary chemotherapy agents, dose, dose by gender interaction, and investigator in the primary logistic regression model, there was still a statistically significant linear trend in complete response with dose (p=0.0001).

The reviewer's summary/conclusions on safety, using the same approach and emphasis as in study -043, are as follows:

Serious AEs (n=4, 50 mg=2; 100 mg=2), including one death in the 100 mg group - and three re-hospitalizations - were related to the underlying disease progression, septic complications or concomitant medications. One of these SAEs consisted of severe AF + tachycardia in a 56y old M with follicular large cell lymphoma who received cyclophosphamide, 1425 mg, vincristine, 2 mg and DOX, 95 mg. The investigator assessed the AF + tachycardia as not related to test med. and rather related to DOX therapy. But blood levels of DOX were not reported. The events resolved without sequelae. The majority of AEs were mild to moderate in intensity. Of the 16 pts. experiencing a severe AE, four (50 mg=1; 100 mg=2 and 200 mg=1) experienced AEs assessed as Tx-related by the investigator. The remaining 12 patients (25 mg=3; 50 mg=2; 100 mg=4 and 200 mg=3) had severe AEs that were not [illegible] related to test med. by the investigator. In this study, [illegible] significant trend with dose in the overall incidence [illegible] 25 mg=60%, 50 mg=55%, 100 mg=66% and 200 mg=71%). [illegible] occurring individual AEs were [illegible] wave change or abnormality but most [illegible] AEs by System Organ Class, showed a [illegible] incidence of the incidence of [illegible] 100 and 200 DOX dose groups was [illegible] incidence of T-wave change or abnormality [illegible] groups was 8%, 6%, 4% and 10%, respectively, [illegible] significant trend with dose in the overall [illegible]

(p=0.0361; 25 mg=39%, 50 mg=39%; 100 mg=48%; 200 mg=54%). The number Tx-related AEs from the overall incidence was

Total # of Cases	# Considered Tx-Related
86	78
21	14
20	12
20	All 20

There was no statistically significant trend with dose a) in the overall rate of Tx-emergent EKG interval changes or b) heart rate and rhythm. As per specific, most frequent Tx-emergent EKG interval changes, there were no statistically significant trends in the incidence of QT interval prolongation (QT_c ≥440 msec) or AV block first degree (PR ≥220 msec). But, for EKG abnormal specific (QRS ≥100 msec) a p-value of 0.0482 for a linear trend with dose was shown (25 mg=2.5%, 50 mg=7.2%, 100 mg=7.5% and 200 mg=11.5%). All Tx-emergent EKG interval changes were rated as mild in severity. Of the 96 instances of QT interval prolongation, 95 were deemed Tx-related by the investigator. All 23 instances of EKG abnormal specific and all 6 instances of AV block first degree were assessed as Tx-related by the investigator. There were no AEs of potential concern. One case of moderate hypotension (25 mg) and one case of mild abnormal LFTs (also in the 25 mg group) were assessed as probably related to test med. Although there were some small differences in incidence rates for some AEs in patients who received a 5-HT_3 receptor antagonist as rescue medication, the differences were minor. The reviewer agrees with the sponsor that these findings do not suggest any increased risk in this group of patients.

Clinical laboratory evaluations did not reveal changes of concern. There was a trend for total serum bilirubin to increase from baseline to 24-h Post-Tx. These findings, for which there is no plausible explanation, were independent of dose group.

As per study -043, a very detailed evaluation was carried out of the changes from BL in the six EKG measures assessed, which included graphic representation of the data to facilitate comparisons and conclusions.

At 1-2h Post-Tx, there was a statistically significant linear trend in PR interval, QRS width and QT_c interval. The graphic representation illustrates that the effects of the 200 mg dose are different (higher) from those of the other DOLA•Mesyl doses, especially the two lower doses (25 and 50 mg) and for PR, QRS, QT and QT_c. It is also clear that, for QRS, the effect of the 100 mg dose is also higher than that with the two lower doses. The 100 mg DOLA•Mesyl dose is not devoid of effects on EKG changes from baseline.

At 24-36h Post-Tx, there were no statistically significant linear trends with dose toward increases in any of the six EKG variables. The graphic representation reveals for QT and JT the 25 mg dose group had returned to baseline (0 change from BL) but there seemed to be a progressive albeit modest increase with dose in the change from BL for QT and JT. Oddly enough, for QT_c, the change from BL induced by the 200 mg was closer to zero (0) than that associated with the other three dose levels.

Pronounced specific changes from BL in the EKG variables, with emphasis in those assessed as Tx-emergent, are discussed next. Acute increases in PR interval to ≥220 msec were seen in 4 patients: 50 mg=1%, 200 mg=4%. The patient in the 200 mg dose group also had an exit increase in PR interval to ≥220 msec. Overall, 6 patients experienced Tx-emergent changes in PR interval. Acute increases in QRS to ≥100 msec were seen in 21 patients: 25 mg=3%, 50 mg=6%, 100 mg=6% and 200 mg=12%. Eight of these patients (25 mg, n=1, 50 mg, n=2, 100 mg, n=3 and 200 mg, n=2) also had exit increases in QRS duration to ≥100 msec. Overall, 24 patients experienced Tx-emergent changes in QRS duration. Acute increases in QT_c to ≥440 msec were seen in 64 patients: 25 mg=15%, 50 mg=17%, 100 mg=22% and 200 mg=29%. Twenty-nine of these patients also had exit increases in QT_c to ≥440 msec (25 mg, n=3, 50 mg, n=6, 100 mg, n=9 and 200 mg, n=11). Overall, 96 patients experienced Tx-emergent changes in QT_c interval.

It is to be noted that most of the QRS duration increases at both the acute and exit time points occurred in patients who received DOX. This suggests that DOX, either alone or in combination with DOLA•Mesyl, may have contributed to these increases. While this may have been true at the 24-h time point, increases in QRS duration at the acute time point represent a well-documented effect of DOLA•Mesyl. Furthermore, the incidence of Tx-emergent QT_c interval increases was nearly as great at study exit (hour 24) as at the acute time point. Comparing the incidences of QT_c interval increases in patients who received DOX vs those who did not shows that both groups had similar rates of QT_c interval increases at the acute time point, but the increases observed at hour 24 occurred primarily in patients receiving DOX. This suggests that the QT_c interval increases at 1-2h posttreatment were probably due to DOLA•Mesyl (consistent with the known pharmacology of the drug and its effects on QRS duration), while those observed at hour 24 may have been due to DOX alone or in combination with DOLA•Mesyl.

In Study -048, just as in Study -043, no clinically significant cardiac events were reported. The one case of AF + tachycardia [illegible] patient given 100 mg/[illegible] the drug had not [illegible] medication administration. Specifically, [illegible] torsades de pointes/hot were [illegible] therefore conclude that, [illegible] those patients with prolonged [illegible]

In Study -048, the following number of patients had [illegible] abnormally high at baseline:

Interval	BL Value (msec)	# of Pts.
PR[a]	≥220	4
QRS[b]	≥100	27
QTc[c]	≥440	77

a) The longest PR intervals recorded were for patient MCST0329-0018 (200 mg): 292 msec Pre-Tx, 312 msec at 1-2h Post-Tx and 304 msec at 24h Post-Tx. Neither this nor the other first degree AV block progressed to higher degree block.

b) None of the patients with Pre-Tx QRS duration <100 msec had a Tx-emergent increase to ≥120 msec.
- 4 patients (2 in the 50 and 2 in the 200 mg group) entered the study with Pre-Tx QRS duration of 100-119 msec, then had an acute or exit QRS duration ≥120 msec.
- In addition, 4 patients (1 in the 25 and 3 in the 200 mg group) were admitted to the study, and safely treated, with a Pre-Tx QRS duration ≥120 msec.
- The highest QRS durations recorded were for patient MCST0329-0018 (200 mg group); 152 msec Pre-Tx, 168 msec at 1-2h Post-Tx and 156 msec at study exit.

c) In 4 patients (1 each in the 25 and 100 mg groups, and 2 in the 200 mg group), QTc interval increased from <440 msec Pre-Tx to ≥500 msec at either the acute or the 24-h Post-Tx time point.
- An additional 5 patients (1 each in the 25 and 50 mg groups and 3 in the 200 mg group) had Post-Tx QTc intervals ≥500 msec after entering the trial with a QTc ≥440 msec at baseline.
- The highest QTc interval recorded in this study was for patient MCST0314-0019 (200 mg). This patient's QTc interval was 465 msec at study admission, 525 msec at the 1-2h Post-Tx, (an increase of 60 msec from BL) and 475 msec at study exit.
- All of these patients were safely treated and, as previously indicated, no ventricular arrhythmias occurred.

In conclusion, under the experimental conditions used in Study -048, the second pivotal trial in NDA 20-623, orally administered tablets of DOLA•Mesyl are effective in the prevention of nausea and emesis induced by cyclophosphamide/doxorubicin-based chemotherapeutic regimens of moderate emetogenic potential. Response is linearly related to dose, with 100 mg as effective as 200 mg. Electrophysiologic effects resulting in increases in 12-lead PR, QRS and QT_c EKG intervals were seen, especially in association with the 200 mg dose. These EKG changes from baseline were less frequently seen with the 100 mg dose and the latter is not devoid of these effects. Although clinically, there was no evidence of increased [illegible] these effects, the potential for seriousness of this [illegible] cannot be dismissed.