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 to 2h. as well as 24-36h post dose are considered in detail below.

i) Heart Rate (HR, bpm)

- There were no statistically significant trends with dose at 1 to 2h or 24 to 36h postdose in heart rate (Table 32). At 1 to 2h postdose, mean changes in heart rate ranged from -1.1 bpm in the 200 mg dose group to -4.2 bpm in the 25 mg dose group.
    - At 24 to 36h postdose, mean changes in heart rate ranged from -0.4 bpm in the 25 mg dose group to -1.6 bpm in the 100 mg dose group.
- Fig. 10 shows no overlap between the changes induced by 25 and 50 mg vs those induced by 100 and 200 mg DOLA•Mesyl. The latter showed very little decrease from BL.
- At the 24 to 36h observation, the four groups of DOLA•Mesyl doses showed similar changes from BL (Fig. 11).
- As seen in Table 33 (Tx-emergent changes in HR),
    - 3 patients had acute ↑s in HR to above 100 bpm: 1 patient (1%) in the 100 mg dose group and 2 (3%) in the 200 mg dose group.
    - One of these patients (200 mg dose group) also had exit increases in HR to above 100 bpm.
    - 13 patients had acute ↓ in HR to below 60 bpm: 7 patients (9%) in the 25 mg dose group, 2 (3%) in the 50 mg dose group, 2 (3%) in the 100 mg dose group, and 2 (3%) in the 200 mg dose group.
    - 2 of these patients (both in the 25 mg dose group) also had exit ↓ in HR to below 60 bpm.

ii) PR Interval (msec)

Refer to Table 32.

- At hour 1 to 2, there was a statistically significant increasing trend in change from BL with dose (p=0.0001). Mean changes from baseline were 6.3 msec, 5.7 msec, 10.8 msec and 13.2 msec for the 25 mg, 50 mg, 100 mg and 200 mg dose groups, respectively.

TABLE 32
Study MCPR0043 (Report K-95-0009-CDS)

EKG Summary Measures (Mean of Actual Readings), Median and Mean Change from BL at Pre-Tx, 1-2h Post- and 24-36 Post-Tx as a Function of DOLA•Mesyl Dose
[All Patients]

		H.R.			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	
Dose (mg)	Evaluation	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean
25	PRE-BL	81.7			158.7			89.2			368.5			421.8			279.2		
	1-2h POST	78.2	-4	-4.2	161.8	4	6.3	91.3	1	2.2	383.1	14	15.6	431.0	7	8.6	291.8	10	13.4
	24-36h POST	81.5	-1	-0.4	156.2	0	0.6	89.6	0	0.1	372.1	5	3.9	426.4	4	4.5	282.6	5	3.8
50	PRE-BL	81.7			156.9			87.1			367.2			421.9			280.1		
	1-2h POST	77.8	-2	-2.9	163.0	4	5.7	90.9	2	3.1	379.6	10	12.0	427.2	3	4.8	288.7	8	8.9
	24-36h	79.3	-1	-1.5	157.8	1	-0.1	87.4	0	-0.6	370.2	0	1.5	421.4	-3	-0.3	282.8	0	2.1
100	PRE-BL	84.6			159.1			87.0			370.4			418.3			283.4		
	1-2h POST	79.8	-3	-2.8	169.2	8	10.8	90.3	4	3.3	380.6	7	9.3	424.4	4	5.9	290.3	5	6.1
	24-36h	84.1	-1	-0.5	161.3	0	2.2	85.7	0	-1.0	372.4	0	2.2	417.4	-1	-0.9	286.6	0	3.2
	PRE-BL	81.1			154.1			86.3			363.5			417.2			277.3		
	1-2h POST	73.5	-7	-7.6	170.1	12	13.2	92.2	5	5.9	386.3	23	22.2	440.2	23	23.0	294.1	16	16.3
	24-36h	80.2	-1	-0.9	158.2	4	2.0	85.6	0	-0.5	370.2	5	7.4	421.7	-1	4.8	284.7	6	8.0
					0.0001			0.0002			N.S.			0.0001			N.S.		
			N.S.		N.S.			N.S.			N.S.			N.S.			N.S.		

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

- There was not a statistically significant trend with dose in change from baseline at hour 24-36: mean changes from BL ranged from -0.1 msec for the 50 mg dose group to 2.2 msec for the 100 mg dose group.

  - Once again, at hour 1 to 2 Post-dose (Fig. 10) changes seen in those patients receiving 100 and especially 200 mg of DOLA•Mesyl were well differentiated from those with 25 or 50 mg but the four groups were similar at 24-36h (Fig. 11).

Refer to Table 33 (Tx-emergent changes in PR)

- 10 patients had acute increases in PR interval to ≥220 msec: 1 patient (1%) in the 25 mg dose group, 1 (1%) in the 50 mg dose group, 4 (6%) in the 100 mg dose group and 4 (5%) in the 200 mg dose group.

- 3 of these patients also had an exit increase in PR interval to ≥220 msec; 1 in the 25 mg dose group, 1 in the 100 mg dose group and 1 in the 200 mg dose group.

- Overall 11 patients experienced treatment-emergent changes in PR interval, and 4 patients had BL values ≥220 msec.

BL PR	Post-BL PR	DOLA•Mesyl Dose (mg)			
		25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)
<220 msec	≥220 msec	1	2	4	4
≥220 msec[a]	any	2	1	1	0

a) None of these 4 patients developed second degree or higher AV block.

iii) QRS Duration (msec)

Refer to Table 32.

- At hour 1-2, there was a statistically significant increasing trend in change from BL with dose (p=0.0002).

  - Mean changes from BL were 2.2 msec, 3.1 msec, 3.3 msec, and 5.9 msec for the 25 mg, 50 mg 100 mg and 200 mg dose groups, respectively.

- There was not a statistically significant trend with dose in change from baseline at hour 24-36.

  - Mean changes from BL ranged from -1.0 msec for the 100 mg dose group to 0.1 msec for the 25 mg dose group.

- As seen in Fig. 10, at hour 1-2 Postdose, the response for the 200 mg DOLA•Mesyl group was distinct from that for the other groups. There is no overlapping of S.E. for the 200 mg dose vs the other three groups. The four groups were similar at 24-36h (Fig. 11).

TABLE 33
Study MCPR0043 (Report K-95-0009-CDS)
Frequency (Percent) of Acute and Exit Treatment-Emergent 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	QTc Pre<440 msec and Post ≥440
Acute (Hour 1-2)	25	75	0 (0%)	7 (9%)	1 (1%)	9 (12%)	9 (12%)
	50	77	0 (0%)	2 (3%)	1 (1%)	12 (16%)	16 (21%)
	100	70	1 (1%)	2 (3%)	4 (6%)	2 (3%)	11 (16%)
	200	78	2 (3%)	2 (3%)	4 (5%)	11 (14%)	32 (41%)
Exit (Hour 24-36)	25	74	4 (5%)	3 (4%)	1 (1%)	4 (5%)	10 (14%)
	50	76	2 (3%)	1 (1%)	1 (1%)	5 (7%)	6 (8%)
	100	70	0 (0%)	1 (1%)	1 (1%)	0 (0%)	7 (10%)
	200	78	2 (3%)	1 (1%)	1 (1%)	0 (0%)	10 (13%)

Refer to Table 33 (Tx-emergent changes in QRS)

- 34 patients had acute increases in QRS duration to ≥100 msec; 9 patients (12%) in the 25 mg dose group, 12 (16%) in the 50 mg dose group, 2 (3%) in the 100 mg dose group, and 11 (14%) in the 200 mg dose group.

- 4 of these patients also had exit increases in QRS duration to ≥100 msec: 1 patient in the 25 mg dose group and 3 in the 50 mg dose group.

- Overall, 39 patients experienced treatment-emergent changes in QRS duration, and 39 patients had baseline values [illegible]

BL QRS	Post-BL QRS	DOLA•Mesyl (mg)			
		25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)
<100 msec	≥100 msec	12	14	2	11
	100-109 msec	11	12	1	11
	110-119 msec	1	2	1	0
	≥120 msec	0	0	0	0
100-119 msec	any	9	3	7	14
	≥120 msec	1	1	0	0
≥120 msec	any	2	1	3	0

There was no definitive pattern in increases in QRS duration for the patients having baseline values ≥100 msec; all 39 such patients were safely treated.

iv) <u>QT interval (msec)</u>

Refer to Table 32.

- At hour 1-2, there was not a statistically significant trend in change from baseline with dose: mean increases in QT interval were seen for all four doses, ranging from 9.3 msec in the 100 mg dose group to 22.2 msec in the 200 mg dose group.

- There was not a statistically significant trend with dose in change from BL at hour 24-36: mean changes from baseline ranged from 1.5 msec for the 50 mg dose group to 7.4 msec for the 200 mg dose group.

- Nonetheless, at hour 1-2 Postdose, the response for the 200 mg DOLA•Mesyl group is different (higher) than that with the three other DOLA-Mesyl doses (Fig. 10). With an increase in the S.E., the four groups were similar at 24-36h (Fig. 11).

v) <u>QTc interval (msec)</u>

Refer to Table 32.

- At hour 1-2, there was a statistically significant increasing trend in change from baseline with dose *p=0.0001*.

  - Mean changes from baseline were 8.6 msec, 4.8 msec, 5.9 msec and 23.0 msec for the 25 mg, 50 mg, 100 mg and 200 mg dose groups, respectively.

- There was not a statistically significant trend with dose in change from baseline at hour 24-36.

  - Mean changes from baseline ranged from -0.9 msec for the 50 mg dose group to 4.8 msec for the 200 mg dose group.

- Fig. 10 could not be more demonstrative. At hour 1-2 Post dose, the 200 mg dose induced increases in QTc that clearly differentiated this DOLA•Mesyl dose from the other three. But, as per the other parameters, the four groups were similar at hour 24-36 Post dose (Fig. 11).

Refer to Table 33 (Tx-emergent changes in QTc).

- 68 patients had acute increases in QTc to ≥440 msec: 9 patients (12%) in the 25 mg dose group, 16 (21%) in the 50 mg dose group, 11 (16%) in the 100 mg dose group and 32 (41%) in the 200 mg dose group.

- 23 of these patients also had exit increases in QTc to ≥440 msec: 5 patients in the 25 mg dose group, 6 in the 50 mg dose group, 4 in the 100 mg dose group and 8 in the 200 mg dose group.

- Overall, 78 patients experienced treatment-emergent changes in QTc interval and 55 patients had baseline values ≥440 msec.

BL QT_c (msec)	Post BL QT_c (msec)	DOLA•Mesyl (mg)			
		25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)
<440	≥440	14	16	14	34
	440-449	5	7	8	14
	450-459	5	4	3	6
	460-469	3	2	1	5
	470-479	0	1	2	5
	480-489	1	1	0	3
	490-499	0	1	0	1
	≥500	0	0	0	0
440-499	any	20	14	10	11
	≥500	0	0	1	0
≥500	any	0	0	0	0

- **No patients in this study developed torsades de pointes or any ventricular arrhythmias.**

- **All patients with baseline QTc values ≥440 msec were safely treated.**

vi) JT interval (msec)

Refer to Table 32.

- **At hour 1-2, there was not a statistically significant trend in change from baseline with dose: mean increases in JT interval were similar for all four doses, ranging from 6.1 msec in the 100 mg dose group to 16.3 msec in the 200 mg dose group.**

- There was not a statistically significant trend with dose in change from baseline at hour 24-36: mean changes from baseline ranged from 2.1 msec for the 50 mg dose group to 8.0 msec for the 200 mg dose group.

- Refer to Figs. 10 and 11. Neither at 1-2 nor at 24-36h Postdose there were pronounced differences among the four groups in the mean change in JT from the BL.

10). Subgroup Analysis of Gender

As per sponsor's Tables 35 (response in males) and 36 (response in females), there were no statistically significant gender main effects, nor interactions between gender and dose, for any of the EKG parameters at 1-2 or 24-36h postdose.

11) Vital Signs

- In their Table 38, page 208, the sponsor provided the descriptive statistics for the recumbent and standing pulse rate, systolic blood pressure, and diastolic blood pressure measurements and for their associated changes from baseline by dose. P-values for the test for linear trend in change from baseline with dose were also provided for each hour. Plots of mean change from baseline to each time point over the entire study by dose for recumbent and standing pulse rate, systolic BP and diastolic BP are provided in Fig. 13.

  - 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 0.5 and 2h.

  - There were no statistically significant trends with dose in recumbent systolic or diastolic blood pressure at any time point. Recumbent systolic and diastolic blood pressures tended to decrease from baseline to posttreatment time points, independent of dose.

  - There were no statistically significant trends with dose in standing systolic or diastolic blood pressure at any time point. Standing systolic and diastolic blood pressures tended to decrease from baseline to posttreatment time points, independent of dose.

- The changes depicted in Fig. 13 seem inconsistent among the four doses and do not suggest dose-related treatment effects on the six parameters shown: on either recumbent or standing HR, or recumbent or standing diastolic or systolic BP.

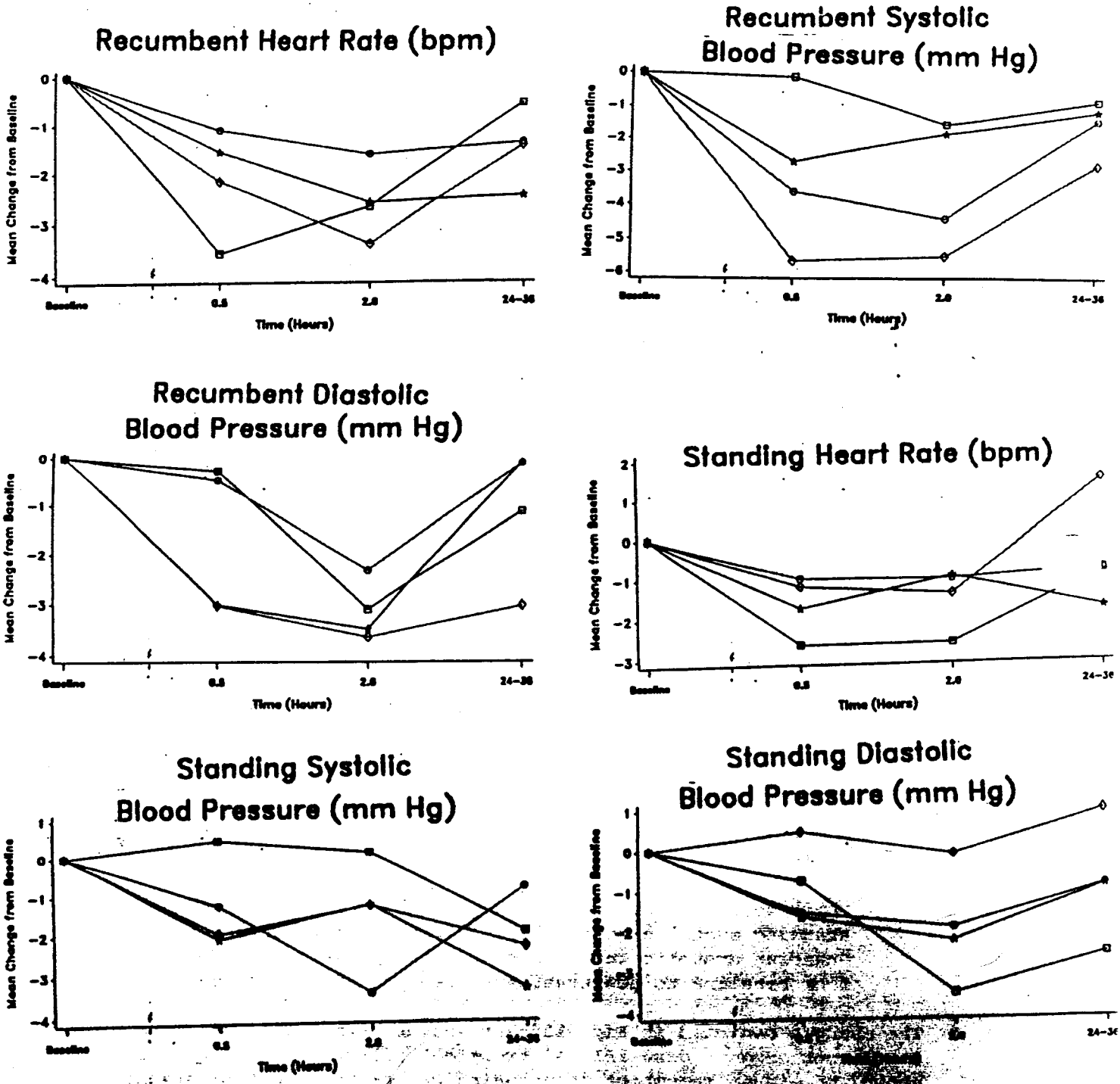

Fig. 11 - Study MCPR0043 (Report K-95-009-CDS)
Vital Signs by Time

trial, efficacy was to be demonstrated by showing a) that there was a trend toward decreasing acute emesis following chemotherapeutic regimens of moderate emetogenic potential with increasing doses of the orally administered DOLA•Mesyl and b) that there was statistical superiority of the proposed dose (200 mg) over the lowest dose (25 mg) in the proportion of complete responders. With the projected 75 patients per arm, calculations based on a 2-tail 0.05 significance level test and the use of a logistic regression model, a therapeutic gain (complete response with 200 mg - complete response with 25 mg) of 26% with a 93% power was expected.

The study population (ITT=307; 166 M, 142 F) consisted of platinum-naive (ca. 8% of the patients had received previous chemotherapy), ca. 61y old of age, mostly Caucasian, 54% female, 46% male, in general without evidence of significant cardiovascular hepatic disease. The site for primary neoplasm was lung (34%) and gynecological (18%). The initial intent was to demonstrate that - with respect to cardiovascular/EKG status - a dose of compound <3 mg/Kg (or 200 mg) was safe, with appropriate exclusions (Table 14). But the FDA called the sponsor's attention to the need not to exclude in Phase III trials types of patients likely to receive the drug following approval. 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 -043 included 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 state, other significant medical conditions, physical examination, Karnofsky status (median score=90%), and prior medications were similar to each other.

The groups were also balanced with respect to concomitant medication in general and concomitant medications that may be confounding, such as concomitant chemotherapy (primarily etoposide=53% and cyclophosphamide=11% of the patients), narcotic analgesics (28%) and benzodiazepines (10% of the patients). There was a statistically significant difference among the Tx groups in the concomitant use of steroids (p=0.0336), an imbalance due to a 16% with the 100 mg group. Although this imbalance is not expected to influence the response to 200 mg DOLA•Mesyl, it will be important to demonstrate that concomitant use of steroids did not contribute to the efficacy of the 100 mg dose.

In the present trial, the groups were well matched with [illegible] standardization of the emetic stimulus. This consisted [illegible] carboplatin (311 mg/m²), low-dose cisplatin (31 mg/m²) [illegible] of the patients, respectively. This regimen is [illegible] moderate emetogenic potential.

Also adequate were the clinical procedures and the [illegible] assess efficacy. In addition to complete response, [illegible]

parameter, total control of N&V was assessed. The latter differs from the former in the handling of mild nausea. Total Control is defined as NO nausea (of any severity), NO emesis (neither vomiting nor retching) and NO antiemetic rescue medication during the 24-h assessment interval. This is a very rigorous and convincing parameter of efficacy.

The reviewer's conclusions on efficacy - based on evaluations of complete response and total response - are as follows. Since results of analysis in the Evaluable Population were consistent with those given by the ITT analyses, only the latter data are mentioned. Efficacy for DOLA•Mesyl was demonstrated since there was a statistically significant trend in the frequency of complete responders as well as total responders with increasing oral doses of the drug. The 50, 100 and 200 mg dose groups were each statistically superior to the 25 mg dose group but neither the ITT nor the Evaluable Population analyses showed significant differences among the 50 vs 100 vs 200 mg DOLA•Mesyl groups. Although the highest therapeutic gain was attained with the 200 mg dose (38%), the therapeutic gains with both the 50 mg (27%) and the 100 mg (29%) were both clinically important and according to expectations based on the justification of sample size. As already mentioned, analysis of total response confirmed the efficacy of both the 200 and 100 mg doses. The 50 mg was also efficacious but the therapeutic gain of 16% was lower than that seen among complete responders (27%). In addition, the analysis of total response showed a therapeutic gain of 21% of the 200 over the 50 mg dose. But, for total response, the 200 mg dose could not be differentiated from the 100 mg dose. When the doses tested when 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 ($p=0.0006$) was also demonstrated. The reviewer agrees with the sponsor that these evaluations suggest that a dosing regimen independent of B_{wt} is appropriate for this indication.

Additional analyses of efficacy 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: no statistically significant differences in complete response rates in females vs males, chemotherapy-naive vs non-chemotherapy naive patients, patients receiving concomitant narcotic analgesics vs those not using these drugs, patients who received benzodiazepines or steroids vs those who did not, patients with a Hx of heavy alcohol use vs those with no such Hx and patients that were treated with carboplatin vs those that were treated with cisplatin. The complete response rates for older patients were statistically significantly higher than the complete response rates in younger patients. The significant linear trend with dose was maintained when adjusting for all subgroups.

The reviewer's summary/conclusions on safety are as follows. The reviewer's comments address general safety, cardiovascular AEs and [illegible] parameters. When present, differences between 200 mg (the dose proposed by the sponsor) and 100 mg (the dose proposed by the reviewer) are noted. Serious AEs (n=%), including 2 deaths (both in the 25 mg group, occurring >14 days after test medication) were related to disease progression.

patient's Hx. None of the severe AEs (25 mg, n=2; 100 mg, n=3; 200 mg=1) was Tx-related. The vast majority of AEs were mild to moderate in intensity. There was no statistically significant trend with dose in the overall incidence of AEs (25 mg=54%, 50 mg=48%, 100 mg=55%, 200 mg=60%), headache (18% across the four groups), sinus bradycardia (7% across all four groups; 15 out of 21 instances of sinus bradycardia were Tx-related), AEs related to the heart and rhythm (26% across all four groups), central and peripheral nervous system (20% across all four groups or gastrointestinal system (9% across all four groups).

There was no statistically significant trend with dose a) in the overall incidence of treatment-emergent EKG interval changes, although the incidence with the 200 mg was 18% higher than with the 25 mg dose and 27% higher than with the 100 mg dose or b) in the frequency of HR and rhythm changes, although the incidence with the 200 mg dose was 18% higher than with the 25 mg dose and 27% higher than with the 100 mg dose. As per specific, most frequent Tx-emergent EKG interval changes, there were no statistically significant trends in the incidence of AV block first degree (all were assessed as Tx-related) or EKG abnormal specific (intraventricular conduction deficit; 38 out of 39 of these IVCDs were Tx-related) but, for QT interval prolongation ($QT_c \geq 440$) a p-value of 0.0029, for a linear trend with dose was shown (77 out of 78 instances of QT interval prolongation were Tx-related). It is to be noted that the 200 mg dose was accompanied by a 24% and 23% higher incidence of QT_c interval prolongation than the 25 mg and 100 mg dose, respectively. It is also of interest to note that none of these Tx-emergent EKG changes were rated as severe. A few (n=5) were rated as moderate but the majority were mild in intensity.

Of a total of 12 AEs of potential concern, which included 2 cases of chest pain, 3 of edema, 5 of hypo or hypertension and 2 abnormal LFTs, 1 case of mild hypotension (50 mg) was assessed as possibly related and one case of mild orthostatic hypotension (200 mg) was considered as probably related to DOLA•Mesyl. An "additional" dose of 5-HT_3 receptor antagonist (ondansetron or granisetron over the dose of DOLA•Mesyl) during a 24-h period did not appear to have an unfavorable impact on the safety profile of DOLA•Mesyl.

Evaluation of laboratory data revealed no statistically significant positive linear trend with dose in change from BL for any variable. Some changes in laboratory variables were seen. These included statistically significant smaller increases in serum total bilirubin as the dose of DOLA•Mesyl increased. But these changes were not of concern. The [illegible] observed changes from baseline are puzzling since serum [illegible] one of the most stable parameters of liver function.

As concluded from Phase I-II studies, increases in PR interval, QRS width and QT_c interval have been reported in association with [illegible] to further characterise these EKG changes, [illegible] carried out of the changes from BL in the [illegible] evaluation included graphic representation of [illegible] comparison of effects among DOLA•Mesyl dose [illegible]

as a function of time. Emphasis is put on changes at 1 to 2h post-Tx, when plasma levels of MDL 74,156, the active metabolite of DOLA•Mesyl, were high. No marked changes are expected at study exit, approximately 24 to 36h posttreatment, when plasma levels of MDL 74,156 were low.

At 1-2h posttreatment there was a statistically significant linear trend in PR interval, QRS width and QT_c. The graphic representation leaves no doubt that the effects of the 200 mg are different (higher) from those with the other DOLA•Mesyl doses. It is also clear that, at least for PR interval, the effect of the 100 mg dose is also higher than that with 50 or 25 mg.

At 24-36 hours posttreatment, there were no statistically significant linear trends with dose toward increases in any of the six EKG variables. The graphic representation show that in those patients given either 100 or 200 mg, there are still some remnant effects on the PR and perhaps on QT in the 200 mg dose level. The sponsor stated that increases in QT_c interval at 24-36h posttreatment appear to primarily result from the increased QRS duration (ventricular depolarization, not repolarization as measured by the JT interval which showed no linear trend with dose). It is also stated that this is predictable based upon the documented relationship between QRS prolongation and plasma levels of MDL 74,156. However, the changes in JT are included when assessing changes in Q-T interval. In addition, although not statistically significant, in Study -048, the three DOLA•Mesyl doses produced increases in JT at 24-36h posttreatment. This contrasted to no changes from BL (=0) seen with the 25 mg dose.

At this point it is important to mention that what is being compared above is either the median or the mean change from baseline. But included in the average are changes much larger or smaller than the average. It is therefore important to mention the larger changes, because these are the more interesting from the clinical viewpoint. Since neither this nor the other two trials included a PL comparator, one does not know if the changes from BL seen with the lowest dose, 25 mg, are PL-like or whether all doses of compound induce changes, which are more frequent with the higher doses. Pronounced specific changes in the EKG variables, with emphasis on Tx-emergent changes are summarized below.

Acute increases in PR interval to ≥220 msec were seen in 10 patients: 25 and 50 mg=1% each; 100 mg=6%; 200 mg=5%. Three of these patients, one each in the 25, 100 and 200 mg dose group, respectively, also had an exit increase in PR interval to ≥220 msec. Overall, 11 patients experienced Tx-emergent changes in PR interval. Acute increases in QRS duration to ≥100 msec were seen in 34 patients: 25 mg=12%, 50 mg=16%, 100 mg=3% and 200 mg=14%. Four of these patients (25 mg, n=1; 50 mg, n=3) also had exit increases in QRS duration to ≥100 msec. Overall, 39 patients experienced Tx-emergent changes in QRS duration. Acute increases in QT_c to ≥440 msec were seen in 34 patients: 25 mg=12%, 50 mg=21%, 100 mg=16% and 200 mg=4%.

patients also had exit increases in QT_c to ≥440 msec (25 mg, n=5; 50 mg, n=6; 100 mg, n=4 and 200 mg, n=8). Overall, 78 patients experienced Tx-emergent changes in QT_c interval.

In this trial, the following numbers of patients had EKG interval values that were abnormally high at baseline:

Interval	BL Value (msec)	# of Pts
PR	≥220	4
QRS	≥100	39
QTc	≥440	55

- Eight of the ten pts. with first degree AV block at acute time point were in the 100 mg and 200 mg dose groups.
- Of the 4 pts. who entered the study with PR intervals ≥220 msec, one had an asymptomatic cardiovascular adverse event (sinus bradycardia) recorded for 1h.
- The longest PR intervals recorded were for Pt. MCST0156-0011 (50 mg): 248 msec Pre-Tx, 264 msec at 1-2h Post-Tx and 257 msec at 24-36h Post-Tx.
- None of the cases of first degree AV block progressed to a higher degree block.
- 2 pts. (1 in the 25 mg group and 1 in the 50 mg group entered the study with a Pre-Tx QRS of 100-119 msec, then had an acute QRS duration of 120 msec. 6 pts. (2 in the 25, 1 in the 50 and 3 in the 100 mg group) were admitted to the study with a premature QRS duration of ≥120 msec. Four of these pts. each reported one cardiovascular event:
  - 2 pts. had premature ventricular contractions
  - 1 had sinus bradycardia
  - 1 had T-wave change or abnormality
- Pt. MCST176-0002 (100 mg) entered the study with a QTc of 492 msec, which decreased to 470 msec 1-2h Post-Tx and then increased to 501 msec at 24-36h Post-Tx. This patient had sinus bradycardia on the 24-36h Post-Tx EKG.
- The highest QRS durations recorded in this study were for pt. MCST176-0002 (100 mg): 168 msec Pre-Tx, 166 msec at 1-2h Post-Tx, and 170 msec at study exit. This same Pt. had a 24-36h Post-Tx QTc interval of 501 msec.

In Study -043, other than those reported in the footnote above, no clinically significant cardiac events were reported. Specifically, [illegible] reports of SVT, VT or torsades de pointes nor were reports of [illegible] block. It is therefore concluded that, under the [illegible] this study, those patients with prolonged PR, QRS or QT [illegible] safely treated.

In conclusion, under the [illegible] administered tablets of DOLA-Mesyl are effective in the [illegible] and emesis induced by moderately emetogenic chemotherapy. [illegible] Response is linearly related to dose, with 100 mg [illegible]

this study population, graded oral doses of DOLA•Mesyl were well tolerated. 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, although less frequently with the 100 mg dose. Although clinically, there was no evidence of increased patient risk from these effects, the potential for seriousness of this toxicity with DOLA•Mesyl cannot be dismissed.

VIII. STUDY PROTOCOL MCPR0048 (REPORT K-94-0927-CDS)

1. Title

"A four-arm, double-blind, randomized, dose-response study of oral dolasetron mesylate with intravenous cyclophosphamide and/or doxorubicin-containing chemotherapy"

NOTE: The original protocol was amended to a) characterize the PKs in patients receiving i.v. cyclophosphamide and/or doxorubicin-containing chemotherapy (approved February 1, 1993) and b) to clarify several aspects of the exclusion criteria (approved September 23, 1993).

This study's proposed protocol design and excretion were very similar to those for Study 043. In the brief description that follows, only certain areas of Study 048 will be highlighted.

2. Objectives

1) Evaluate efficacy by showing that there was a trend toward decreasing acute emesis following i.v. cyclophosphamide- and/or doxorubicin-containing chemotherapy regimens with increasing oral doses of DOLA•Mesyl.

2) Provide recommended doses for the prevention of acute emesis due to cyclophosphamide- and/or doxorubicin-containing chemotherapy by estimating the nature of the dose response curve across 25, 50, 100 and 200 mg single oral doses of DOLA•Mesyl.

3) Evaluate the safety and tolerability of a single oral dose of DOLA•Mesyl in patients undergoing i.v. cyclophosphamide- and/or doxorubicin-containing chemotherapy regimens.

4) Compare the degree of patient satisfaction among the antiemetic dose levels.

5) By amendment, characterize the PKs of single oral doses of DOLA•Mesyl in patients receiving i.v. cyclophosphamide- and/or doxorubicin-containing chemotherapy.

NOTE: Data related to objective #5) were reviewed in Section [illegible]

3. Study Population

The characteristics of the study population were as is Study 043 (Table 14), with some modified inclusion-exclusion criteria to make them applicable to the different type of moderately emetogenic chemotherapy used in the present trial.

- Chemotherapy included cyclophosphamide in doses of mg/m² and/or doxorubicin in doses of mg/m² in combination chemotherapy or ≥40 mg/m² as a single agent administered over no more than 2 hours. The CHOP chemotherapy regimen [i.v. cyclophosphamide, doxorubicin and vincristine (Day 1) and oral prednisone (Days 1 through 5)] were permitted in the study. Cyclophosphamide or doxorubicin should have been the first chemotherapeutic agent given. If sites had patients for whom cyclophosphamide or doxorubicin was not designated the first chemotherapy agent, they contacted the sponsor by telephone. Waivers were granted in cases where the chemotherapy in question was considered to be minimally emetogenic.

- To be included, the patients had to a) be cyclophosphamide and doxorubicin naive (no previous cyclophosphamide- or doxorubicin-containing chemotherapy regimens) and b) meet the clinical and laboratory criteria required for the administration of cyclophosphamide or doxorubicin-containing chemotherapy regimens.

- Not included were those patients scheduled to receive carboplatin or cisplatin (at any dose), nitrogen mustard(s), DTIC (dacarbazine), CCNU (lomustine) >60 mg/m², BCNU (carmustine) >200 mg/m² or ifosfamide in doses >1.5 g/m² during the 24 hours following i.v. cyclophosphamide- or doxorubicin-containing chemotherapy regimens. Corticosteroids, with the exception of prednisone when used as a component of CHOP therapy, was not to be allowed during the trial.

The following exclusion criteria pertained to the cardiovascular status of the patient.

- Cardiomyopathy, congestive heart failure (CHF), or history of CHF.
- Arrhythmias requiring antiarrhythmic medication.
- Greater than first degree heart block.
- Preexisting complete bundle branch block, either left or right.
- Abnormal pretreatment potassium or calcium results which cannot be corrected prior to receiving chemotherapy.

While data were accumulating on the magnitude and frequency of 5-HT, antagonists, to protect patients from any potential sponsor elected to exclude from this study patients with abnormalities (ECG or CHF), concurrent

conduction blocks (greater than first degree heart block, complete bundle branch blocks). As safety data and preclinical data accumulated, the sponsor, with the advice of cardiology consultants, made exceptions on a case-by-case basis for several types of patients. Patients with history of CHF like symptoms were allowed to enroll and were safely treated. Patients with atrial arrhythmias (specifically atrial fibrillation and atrial flutter) with well-controlled ventricular rates were allowed to enroll. In addition, slightly abnormal pretreatment calcium or potassium levels were waived as exclusion criteria if they were unaccompanied by evidence of cardiovascular disease or abnormality. Eventually, the only patients who were routinely excluded on the basis of these criteria were those with severe electrolyte abnormalities, those with poor ejection fractions, and those with complete bundle branch blocks. Because excluded patients represented a very small fraction of the total patient population, and because the study was advanced nearly to the point of completion, it was elected not to formally address this issue via protocol amendment.

Any waiver of inclusion/exclusion criteria was approved by the investigator and the sponsor on a case-by-case basis. In addition, it was recognized that all concomitant medical conditions and nonstudy medications could not be listed in a single protocol; therefore, the advisability of entering or maintaining patients with unusual conditions or conditions not listed in the protocol was discussed on a case-by-case basis. A decision was reached between a representative of the sponsor's monitoring team and investigator prior to patient entry or participation.

- Also excluded were those patients with evidence of clinically significant liver disease--i.e., SGOT/SGPT ≥3 times the ULN (amended from ≥2 times the ULN) or serum BIL ≥2.0 mg/dl,

  - Patients were permitted to enter if they had documented liver metastasis with an SGOT or SGPT ≥3 times the ULNR provided they did not have signs or symptoms of hepatic failure, i.e., BIL of ≥2.0 mg/dl and/or abnormal coagulation tests.

4. Concomitant Medications: As per Study 043.

5. Test Medication:[19] As per Study 043.

6. Study Evaluations

   a. Efficacy Parameters: As per Study 043.

   b. Safety Parameters: As per Study 043.

EKG

As in Study 043, the sponsor used the following criteria to identify the treatment-emergent EKG interval changes. The AERF was used only as a tracking mechanism and these interval changes will not be found in the overall incidence tables of adverse events but are summarized separately.

PR interval ≥220 msec was the criteria for first degree AV block.

[19] DOXA-Mesyl was identified by lot numbers C-51687, C-51804, C-51844, C-51[illegible]

All QRS durations ≥100 msec were interpreted as intraventricular conduction delays. If a treatment-emergent QRS duration ≥120 msec was diagnosed as BBB by the cardiologist, it was reported as an AE.

A QTc interval ≥440 msec was interpreted as prolonged QT interval. QTc interval represents the QT interval corrected for heart rate and was calculated using Bazett's formula:

$$QT_C = \frac{QT}{\sqrt{RR}}$$

7. Statistical Methodology

a. Data Documentation: As per Study 043.

b. Sample Size Justification: As per Study 043.

c. Statistical Methods for Efficacy:

1) Primary Efficacy Analyses: As per Study 043.

2) Secondary Efficacy Analyses: As per Study 043.

3) Pooling of Sites

- 23 sites were group into six pooled sites to satisfy asymptotic considerations for main effects logistic regression and minimum information criteria for the secondary Mantel-Haenszel test.

  - The following pooled sites were created: MCST0312, 0316, 0321, 0324, 0331, 0379 and 0383; 0380, 0386, 0388, 0390 and 0391; 0322, 0332, 0382 and 0385; 0326 and 0333; 0328 and 0353; 0315, 0334 and 0335.

  - All analyses were performed using these pooled sites, together with the other 9 sites.

  - The exact method for pooling was as described for Study 043.

d. Safety Analyses

These were as per Study 043. It is worth reiterating that:

- Changes in recumbent and standing pulse rates, systolic [illegible] and diastolic blood pressures from Pre-Tx to [illegible] analyzed using a two-way rank ANOV controlling for [illegible]

- A test for linear trend with dose in the mean rank change of each vital sign was performed.

- The frequency of patients who had treatment-emergent vital sign changes were summarized by dose.

- A line plot of mean change from baseline representing each dose for each vital sign variable was constructed to compare doses and changes in vitals over the 24-h Tx period.

- Changes from prestudy to 1 to 2h and 24h poststudy in EKG measurements, HR, QT, QT_c, PR, QRS and JT, were also analyzed using a two-way rank AOV controlling for investigator.

  - A test for linear trend with dose in the mean rank change of each measurement was performed.

  - The frequency of patients who had acute (1-2h) and exit (24h) EKG changes was summarized by dose.

  - As a further analysis, the effect of gender was examined by testing for a gender by dose interaction as well as a gender main effect on change from baseline for all six EKG variables at the 1-2h and 24h evaluations.

8. Results

   a. Participating Investigators/Patient Accounting

From the information provided by the sponsor in the Clinical Report (vol. 1.237, p. 105-108 and 120-121), the following is noted.

- Of the 40 sites to which test med. was shipped:

  - 8 [Site # 311, 313, 318, 320, 330, 352, 387 and 389] did not randomize any patients.

  - 13 [Site # 312, 316, 321, 324, 331, 379, 380, 383, 385, 386, 388, 390 and 391] randomized 4 patients or less (each site).

  - 12 [Site # 315, 317, 322, 325, 326, 328, 332, 333, 334, 335, 353 and 382] randomized between 5 and 15 patients (each site).

  - The following 7 sites randomized 16 patients or more:

Site	Total # of Pts. Randomized
#314 (Grote; Winston-Salem, NC)	38
#319 (Hainsworth; Nashville, TN)	23
#323 (Eisenberg; Greenbare, CA)	18
#327 (Rubenstein; Houston, TX)	35
#329 (Khojasteh; Columbia, OH)	22
#381 (Modiano; Tucson, AZ)	29
#384 (Kalman; Miami, FL)	31

- A total of 320 patients were randomized to Tx, and received test medication. Patient MCST319-0019, in the 25 mg dose group, did not receive chemotherapy because she refused her chemotherapy treatment. Therefore, 319 patients received test medication, and underwent their first course of cyclophosphamide- and/or doxorubicin-containing chemotherapy. All 319 patients completed the study.

MAJOR PROTOCOL VIOLATIONS

- 7 patients (2%) had major protocol violations and were excluded from the efficacy evaluable dataset (see computation below). The actual protocol violations per dose group are listed at the footnote of this computation. Most of the violations were considered as minor (sponsor's listing 1, p. 410) and consisted of either missing EKGs or EKG out of timing stipulated in the protocol or potentially confounding medications given prior to the patient's randomization into the trial.

Frequency (Percent) of Dispositions by Dose

Disposition	DOSE (mg)				Total
	25 (n=79)	50 (n=81)	100 (n=80)	200 (n=79)	(n=320)
MAJOR VIOLATION	1* (1%)	5 (6%)	1 (1%)	[illegible]	[illegible]
NO CHEMOTHERAPY	1 (1%)	0	0	0	1 (0%)
EFFICACY EVALUABLE	77 (97%)	81 (100%)	79 (99%)	79 (100%)	[illegible]

*Actual Major Protocol Violations:

25 mg
#1: PT. 0116-0010 Cyclophosphamide dose < 450 mg/m²
doxorubicin (combination dose) < 35
doxorubicin (single agent dose) < 50

50 mg

b) PT. 0334-0005 Cyclophosphamide or doxorubicin infusion time > 6 h (for referenced emetogenic stimulus)

PT. 0379-0001 Not cyclophosphamide or doxorubicin naive

100 mg

c) Pt. 0314-0026 Fewer than 23.5 h of evaluation for efficacy parameter for patients with 0 emetic episodes and no rescue

200 mg

d) Pt. 0314-0034 Cyclophosphamide dose < 450 mg/m² or > 1320 mg/m² doxorubicin (combination dose) < 22.5 mg/m² or 82.5 mg/m², or doxorubicin (single agent dose) < 36 mg/m²

Pt. 0322-0004 Cyclophosphamide dose < 450 mg/m² or > 1320 mg/m² doxorubicin (combination dose) < 22.5 mg/m² or 82.5 mg/m², or doxorubicin (single agent dose) < 36 mg/m²

Pt. 0325-0001 Concomitant Meds: prior to/and or during: lorazepam (Ativan), prochlorperazine (Compazine), ondansetron (Zofran), promethazine (Phenergan), trimethobenzamide (Tigan), thiethylperazine (torecan), scopolamine

b. Comparability of Groups/Patient Baseline Characteristics

1) Demographics/Primary Disease (Table 34)

There were no statistically significant differences among the four doses with respect to gender, race, age, weight, height, Karnofsky performance status, and history of heavy alcohol use. The study population was predominantly female 260/320 (81.3%) and Caucasian 246/320 (76.9%). The median age was 54 y, the median weight was 72.6 kg; the median height was 162.6 cm; the median Karnofsky performance status was 100%[20]. Positive history of heavy alcohol use was reported in 24/317 (7.6%) of the patients (for three patients, Hx of heavy alcohol use was not obtained). As shown in Table 34 (lower panel), the most frequent sites of primary neoplasm were breast (221/320 = 69.1%), lymphoma (59/320 = 18.4%), and lung (13/320 = 4.1%).

2) Medical Hx and Physical Examination

There were no marked imbalances among the four Tx groups in organ system abnormalities, significant medical histories and Pre- and Post-Tx physical examination.

3) Distribution of Previous and Present Chemotherapeutic Regimens (Table 35)

There were no imbalances in previous cancer treatment Hx among the four dose groups. As shown in the upper panel of this Table, 11 patients (4.1%) had previously received chemotherapy (they were non-naive), 33 (10.3%) had

[20] 100%-normal (no evidence of disease). (Able to carry on normal activity; no special care needed).

previously undergone radiotherapy; and 184 (57.5%) had previously undergone surgery for cancer.

- In this trial, 39.5% of the patients used either doxorubicin or cyclophosphamide as single agents and 60.5% of the patients used both agents.

- During the present trial, 58% of the patients received cyclophosphamide and 42% received doxorubicin as the primary chemotherapy.

- In this study population,

  - 211 patients received doxorubicin in doses ranging with a mean of 43.6 mg/m². Of the patients receiving doxorubicin, 35 patients (all patients at site MCST0327) received continuous infusion doxorubicin in doses ranging .

  - 301 patients received cyclophosphamide; the doses ranged with a mean of 613.9 mg/m². Of these, three patients (MCST0323-0011, 0381-0008 and 0381-0012) received low-dose oral cyclophosphamide (115.5 mg/m², 31.0 mg/m² and 98.9 mg/m², respectively).

- There were no gross imbalances among the 4 Tx groups in the percentages of patients taking these chemotherapeutic agents taken either as single agent or both agents, the duration of the infusion of the chemotherapy and the interval (in min.) between test medication and primary chemotherapy.

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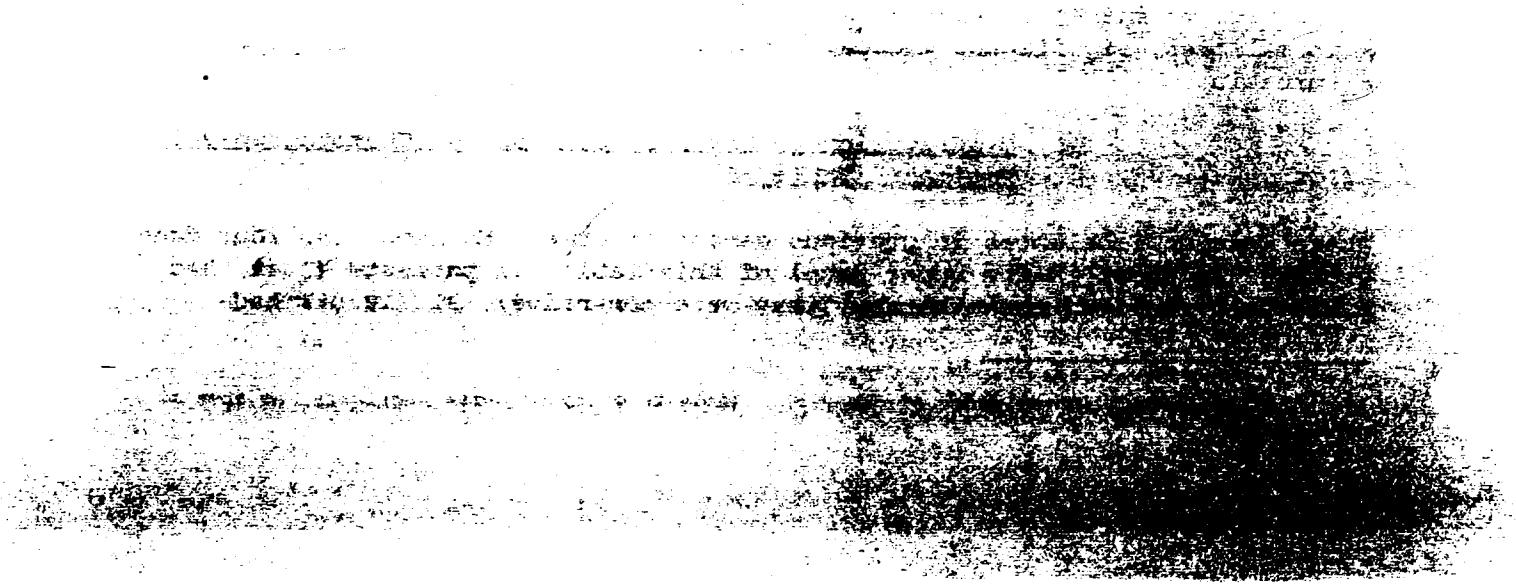

TABLE 34
Study MCPR0048 (Report K-94-0927-CDS)

Demographic and Primary Disease Baseline Characteristics
[ITT Population]

Variable	Dose (mg)				p-value
	25 [n=79]	50 [n=83]	100 [n=80]	200 [n=78	
Gender					
M	15.2%	18.1%	18.8%	23.1%	N.S.
F	84.8%	81.9%	81.3%	76.9%	
Race					
Caucasian	75.9%	75.9%	76.9%	6.9%	N.S.[a]
Black	13.9%	7.2%	8.8%	9.0%	
Hispanic	10.1%	15.7%	12.5%	14.1%	
Other	0.0%	1.2%	0.0%	0.0%	
Age (y)					
Mean	53.1	54.3	54.5	54.7	N.S.
Median	53.0	54.0	54.5	54.5	
Height (cm)					
Mean	163.6	164.3	164.4	164.9	N.S.
Median	162.6	162.6	163.0	165.0	
Weight (Kg)					
Mean	73.8	75.6	76.0	73.3	N.S.
Median	72.2	73.0	73.7	71.5	
Karnofsky Status (%)					
Mean	92.7	92.8	91.4	92.7	N.S.
Median	100.0	100.0	100.0	100.0	
HISTORY OF HEAVY ALCOHOL USE					
	3 (3.8%)	10 (12.0%)	4 (5.0%)	7 (9.0%)	N.S.
SITE OF PRIMARY NEOPLASM					
Breast	73.4%	69.9%	66.3%	66.7%	N.S.[b]
Lymphoma	13.9%	19.3%	21.3%	19.2%	
Other	6.3%	4.8%	10.0%	12.8%	
Lung	6.3%	6.0%	2.5%	1.3%	

a) Cauc. vs all others
b) Lung vs all others

TABLE 35
Study MCPR0048 (Report K-94-0927-CDS)

Distribution of Previous and Present Chemotherapeutic Regimens

Variable[a]	DOSE (mg)				p-value
	25 [n=79]	50 [n=83]	100 [n=80]	200 [n=78]	
PRIMARY CHEMOTHERAPY[b]					
Doxorubicin Cyclophosphamide	31 (39.7%) 47 (60.3%)	37 (44.6%) 46 (55.4%)	32 (40.0%) 48 (60.0%)	35 (44.9%) 43 (55.1%)	N.S.
DOXORUBICIN AND CYCLOPHOSPHAMIDE USE					
Single Agent Only Both Agents	30 (38.5%) 48 (61.5%)	30 (36.1%) 53 (63.9%)	33 (41.3%) 47 (58.8%)	33 (42.3%) 45 (57.7%)	N.S.
Doxorubicin Dose[c] (mg/m²) Mean Range n	 45.1 52	 45.7 55	 42.6 49	 40.8 55	0.0032
Cyclophosphamide Dose[d] (mg/m²) Mean Range n	 641.5 74	 623.8 81	 606.7 78	 580.4 68	0.0321
Duration of Primary Chemotherapy (min) Mean Range	33.3	29.1	33.8	31.4	N.S.
Interval Between Study Drug and Primary Chemotherapy (min) Mean Range	31.0	32.2	31.4	32.1	N.S.
PREVIOUS CANCER TREATMENT					
Chemotherapy	4 (5.1%)	3 (3.6%)	3 (3.8%)	1 (1.3%)	N.S.
Radiotherapy	9 (11.4%)	6 (7.2%)	11 (13.8%)	6 (7.7%)	N.S.
Surgery	48 (60.8%)	41 (49.4%)	51 (63.8%)	[illegible] (56.4%)	N.S.

a) For variables pertaining to current chemotherapy only 319 patients [illegible] (Pt. MCST0319-0019 did not receive chemotherapy).
b) Although some patients received both doxorubicin [illegible] agent which satisfied the dosage requirement specified [illegible] primary chemotherapy.
c) Summary statistics for doxorubicin dose (mg/m²) [illegible]
MEAN=48.8 STD=9.5 MIN=[illegible] [illegible]
d) Summary statistics for cyclophosphamide dose (mg/m²) [illegible]
MEAN=608.1 STD=131.3 MIN=[illegible]

- On the average, the doxorubicin dose was [illegible] mg/m² [illegible] administered at a mean dose of 613.9 mg/m² [illegible] of moderate emetogenic potential).

- The average duration of infusion of primary chemotherapy was 31.9 min and the mean interval between test medication and the start of the primary chemotherapy was 31.7 min.

- As shown in Table 35, there were statistically significant imbalances among the four dose groups in doxorubicin dose (p=0.0032) and cyclophosphamide dose (p=0.0321).

  - The 200 mg dose group had the lowest mean doses for both agents.

  - For doxorubicin, the mean doses were 45.1 mg/m², 45.7 mg/m², 42.6 mg/m² and 40.8 mg/m² for the 25 mg, 50 mg, 100 mg and 200 mg dose groups, respectively.

  - For cyclophosphamide, the mean doses were 641.5 mg/m², 623.8, 606.7 mg/m² and 580.4 mg/m² for the 25 mg, 50 mg, 100 mg and 200 mg dose groups, respectively.

The possible impact of these imbalances on outcome is discussed under the Comments section.

As seen in Table 36, the most frequent concomitant chemotherapies received during the 24-h treatment period were 5-FU (170/319=53.3%), vincristine (77/319=24.1%), MTX (63/319=19.7%) and prednisone (22/319=6.9%). There were no statistically significant imbalances among the four doses in use of concomitant chemotherapies or the use of potentially confounding benzodiazepines (10.9% of the patients in total), narcotic analgesics (13.8% of the patients) or steroids (10.6% of the patients).

TABLE 36
Study MCPR0048 (Report K-94-0927-CDS)

Concomitant Chemotherapy, Benzodiazepines, Narcotic Analgesics and Steroids

Concomitant[a] Use of:	DOSE (mg)				
	25 [n=79]	50 [n=83]	100 [n=80]	200 (n=78]	p-value
Chemotherapy					
5-FU W/BS	57.7%	55.4%	48.8%	51.3%	
VINCRISTINE	17.9%	26.8%	27.5%	24.4%	
MTX	20.5%	19.3%	23.8%	14.1%	
PREDNISONE	6.4%	8.4%	6.3%	6.4%	
Benzodiazepines	10.1%	10.8%	13.8%	8.9%	
Narcotic Analgesics	15.2%	24.1%	20.0%	11.5%	
Steroids	6.3%	13.3%	6.3%	11.5%	

a) For the variables summarized in this Table, all [illegible] patients

4) Previous/Concomitant Other Medications (Table 37)

There were no statistically significant imbalances among the four doses in the frequency (percent) of medications taken either Pre-Tx or concomitantly during the 24-h Tx period.

TABLE 37
Study MCPR0048 (Report K-94-0927-CDS)

Previous Concomitant Other Medications[a]

Non-Study Medication [p-value[b]]	DOSE (mg)				All Patients [n=320]
	25 [n=79]	50 [n=83]	100 [n=80]	200 [n=78]	
I. Frequency (Percent) of Concomitant Medications Taken Pretreatment					
LEVOTHYROXINE (p=0.714)	6 (8%)	6 (7%)	8 (10%)	4 (5%)	24 (8%)
PARACETAMOL	5 (6%)	3 (4%)	5 (6%)	5 (6%)	18 (6%)
ALLOPURINOL	7 (9%)	5 (6%)	2 (3%)	4 (5%)	18 (6%)
MULTI VITAMIN	4 (5%)	3 (4%)	4 (5%)	5 (6%)	16 (5%)
DYAZIDE	2 (3%)	4 (5%)	5 (6%)	3 (4%)	14 (4%)
IBUPROFEN	4 (5%)	3 (4%)	3 (4%)	3 (4%)	13 (4%)
TAMOXIFEN	3 (4%)	4 (5%)	1 (1%)	5 (6%)	13 (4%)
TYLOX	6 (8%)	2 (2%)	2 (3%)	3 (4%)	13 (4%)
II. Frequency (Percent) of Concomitant Medications Taken Posttreatment					
PARACETAMOL (p=0.633)	12 (15%)	9 (11%)	11 (14%)	14 (18%)	46 (14%)
LEVOTHYROXINE (p=0.714)	6 (8%)	6 (7%)	8 (10%)	4 (5%)	24 (8%)
TEMAZEPAM (p=0.931)	6 (8%)	5 (6%)	7 (9%)	6 (8%)	24 (8%)
IBUPROFEN (p=0.661)	6 (8%)	3 (4%)	6 (8%)	6 (8%)	[illegible]
[illegible] (p=0.688)	4 (5%)	4 (5%)	7 (9%)	6 (8%)	[illegible]
ALLOPURINOL	7 (9%)	5 (6%)	[illegible]	[illegible]	[illegible]

a) Listed in this table are the frequencies of [illegible] of the study population.
b) p-values were calculated using a [illegible]

5) Escape Medications (Table 38)

- The most frequent escape medications were prochloperazine 72/320 (23%), lorazepam 43/320 (13%), diphenhydramine 35/320 (11%) and ondansetron 34/320 (11%).

- There were statistically significant imbalances among the four test groups in escape medications. The incidence of the use of prochlorperazine (p=0.021), lorazepam (p-0.030) and ondansetron (0.053=borderline) were higher in the lower DOLA•Mesyl dose groups.

TABLE 38
Study MCPR0048 (Report K-94-0927-CDS)

ESCAPE MEDICATION

ESCAPE MEDICATION	DOLA•Mesyl Dose (mg)				All Patients [n=320]
	25 [n=79]	50 [n=83]	100 [n=80]	200 [n=78]	
PROCHLORPERAZINE (p=0.021)	26 (33%)	21 (25%)	11 (14%)	14 (18%)	72 (23%)
LORAZEPAM (p=0.030)	18 (23%)	11 (13%)	8 (10%)	6 (8%)	43 (13%)
DIPHENHYDRAMINE (p=0.159)	14 (18%)	7 (8%)	8 (10%)	6 (8%)	35 (11%)
ONDANSETRON (p=0.053)	14 (18%)	10 (12%)	6 (8%)	4 (5%)	34 (11%)
HALOPERIDOL (p=0.399)	8 (10%)	6 (7%)	4 (5%)	3 (4%)	21 (7%)
DEXAMETHASONE	6 (8%)	5 (6%)	2 (3%)	3 (4%)	16 (5%)
THIETHYLPERAZINE	4 (5%)	4 (5%)	4 (5%)	3 (4%)	15 (5%)
MCP	5 (6%)	1 (1%)	2 (3%)	3 (4%)	11 (3%)

c. Clinical Response

1) Analysis of Primary Efficacy Parameters

a) Complete Response (Table 39)

- In both the ITT (n=319) and the Evaluable Population (n=312), the test for linear trend in the proportion of Complete Responders with dose was statistically significant (p=0.0001 for both analyses).

- There was a trend toward decreasing acute emesis with increasing doses of DOLA•Mesyl. The response rate was similar for [illegible] and 200 mg (both population analyses) dose levels.

- There were statistically significant differences among the four dose groups. For both study populations, both the 100 mg and 200 mg dose groups were superior to the 25 mg group [p=0.0002 and 0.0004, respectively in the ITT population and 0.0001 and 0.0008 in the Evaluable population].

- Also, both the 100 mg and 200 mg dose groups were significantly different from the 50 mg dose group [p=0.0097 and 0.0209 in the ITT population and 0.0083 and 0.0441 in the Evaluable population].

- The therapeutic gains with the 100 and 200 mg DOLA•Mesyl (over 25 mg) were very similar (30.5% and 28.2%, respectively in the ITT population and 32.1% and 27.4%, respectively, in the Evaluable population] analyses.

- In this study, the 50 mg DOLA•Mesyl dose did not perform as well as in Study 043. The therapeutic gains with this dose level (over 25 mg) were only 10.2% in the ITT population and 10.8% in the Evaluable population analyses. None of these two therapeutic gains were statistically significant.

- In summary then, just as in Study 043, the results of analysis in the Evaluable population were consistent with those shown with the ITT analysis.

TABLE 39
Study MC:PR0048 (Report K-94-0927-CDS)

Clinical Response: Analyses of Primary Efficacy Parameter
Complete Response

Response by Dose (mg)				Therapeutic Gain (%)/p-value[a]					
I. Intent-to-Treat Analysis[b] (n=319)									
25 [n=78]	50 [n=83]	100 [n=80]	200 [n=78]	50 vs 25	100 vs 25	200 vs 25	100 vs 50	200 vs 50	200 vs 100
24 (30.8%)	34 (41.0%)	49 (61.3%)	46 (59.0%)	10.2% [N.S.]	30.5% [illegible]	28.2% [illegible]	20.3% [illegible]	18.0% (0.0309]	-2.3% [N.S.]
II. Efficacy Evaluable Analysis[c] (n=312)									
[n=77]	[n=81]	[N=74]	[illegible]						
22 (28.6%)	33 (40.7%)	48 (63.6%)	43 (57.3%)	10.8% [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	-6.7% [N.S.]

a) p-value was calculated from [illegible] a logistic regression model predicting complete response with [illegible] variables.
b) Primary Test, linear trend, p=0.0001
c) [illegible] p=0.0001

i) Complete Response Rates by Investigator and Dose (Table 40)

- Overall Complete Response rates by investigator ranged from 26.3% to 77.3% (right hand side column of Table 40).
- According to this information, investigator was not a significant predictor of Complete Response (p=N.S.).
- There was no interaction between investigator and a linear dose response (p=N.S.).
- When taking sample sizes into consideration, dose trends were consistent over investigators.

ii) Complete Response by Hour and Dose (mg) and by Dose in mg/Kg (Table 41)

- The data in this Table provide the proportion of Complete Responders over time (for hours 4, 8, 12, 18 and 24) for each dose group.
- By 4h, the four DOLA•Mesyl doses appeared to be equally effective.
- Some differences began at 8h, but from hour 18 onwards, the response with the two lower DOLA•Mesyl levels were lower than those with 100 mg and 200 mg of test med.
- As shown in the lower panel of Table 41, converting doses into mg/Kg units, based upon the body weight of each patient, also resulted in a statistically significant increase in complete response with increasing dose in mg/Kg (p=0.0011).
  - This Table shows the complete responders by dose in mg/Kg broken into four dose ranges, Each dose range includes a dose in mg/Kg (0.33, 0.67, 1.33, 2.67) that corresponds to the mg doses studied (25, 50, 100, 200) for a 75 Kg patient.
  - These results are driven by the observed response seen for dose in mg.
- Sponsor's *Figure 3, page 25* provided a graphical illustration in the form of a scatter plot of complete responders and non-responders by dose in mg and body weight. While this figure provides some evidence that response for the 25 mg and 50 mg doses may depend on the patient's body weight, the overlapping of weights of complete responders and non-responders for the 100 mg and 200 mg doses illustrate that response was not related to weight for these doses.
- The reviewer agrees with the sponsor that this supports a dosing regimen independent of body weight is appropriate for the [illegible]

TABLE 40
Study MCPR0048 (Report K-94-0927-CDS)

Complete Response by Investigator and Dose

Number of Complete Responders/Number of Patients in Investigator by Dose Cell (%)					
Investigator[a]	DOSE (mg)[b]				Total [n=319]
	25 [n=78]	50 [n=83]	100 [n=80]	200 [n=78]	
314 (n=38)	6/9 (66.7%)	3/10 (30.0%)	4/9 (44.4%)	5/10 (50.0%)	18/38 (47.4%)
317 (n=12)	2/3 (66.7%)	1/3 (33.3%)	2/3 (66.7%)	2/3 (66.7%)	7/12 (58.3%)
319 (n=22)	0/4 (0.0%)	2/6 (33.3%)	2/6 (33.3%)	4/6 (66.7%)	8/22 (36.4%)
323 (n=18)	0/4 (0.0%)	1/5 (20.0%)	2/4 (50.0%)	3/5 (60.0%)	6/18 (33.3%)
325 (n=15)	1/4 (25.0%)	2/4 (50.0%)	2/3 (66.7%)	3/4 (75.0%)	8/15 (53.3%)
327 (n=35)	1/10 (10.0%)	2/8 (25.0%)	4/9 (44.4%)	4/8 (50.0%)	11/35 (31.4%)
329 (n=22)	2/5 (40.0%)	4/5 (80.0%)	5/6 (83.3%)	6/6 (100%)	17/22 (77.3%)
381 (n=29)	0/8 (0.0%)	5/7 (71.4%)	6/7 (85.7%)	3/7 (42.9%)	14/29 (48.3%)
384 (n=31)	3/7 (42.9%)	3/8 (37.5%)	5/8 (62.5%)	5/8 (62.5%)	16/31 (51.6%)
312,316,321,324, 331,379,383[c] (n=11)	1/3 (33.3%)	1/2 (50.0%)	2/3 (66.7%)	2/3 (66.7%)	6/11 (54.5%)
380,386,388,390, 391[d] (n=14)	2/3 (66.7%)	1/5 (20.0%)	3/4 (75.0%)	1/2 (50.0%)	7/14 (50.0%)
322,332,382,385[e] (n=19)	0/6 (0.0%)	0/5 (0.0%)	2/4 (50.0%)	3/4 (75.0%)	5/19 (26.3%)
326,333[f] (n=12)	1/2 (50.0%)	2/4 (50.0%)	2/3 (66.7%)	1/3 (33.3%)	6/12 (50.0%)
328,353[g] (n=14)	2/3 (66.7%)	2/4 (50.0%)	3/4 (75.0%)	2/3 (66.7%)	9/14 (64.3%)
315,334,355[h] (n=27)	3/7 (42.9%)	5/7 (71.4%)	5/7 (71.4%)	2/6 (33.3%)	15/27 (55.6%)
Total (n=319)	24/78 (30.8%)	34/83 (41.0%)	[illegible]	[illegible]	183/319 (40.0%)

a) Investigator p=0.1413 from a 14 degree of freedom Chi-square test using a [illegible] regression model predicting complete response with dose and investigator as [illegible]

b) Linear Dose Response by Investigator interaction p=0.[illegible] from a [illegible] Chi-square test using Rao scores from a logistic [illegible] response with dose and investigator as [illegible]

c) through h) Investigators were pooled in order to [illegible] and Wagner modified Chi-square.

TABLE 41
Study MCPR0048 (Report K-94-0929-CDS)

Complete Response by Hour and Dose (mg)
and by Dose in mg/Kg
[ITT Population]

I. Complete Response by Hour and Dose (mg)

Number of Complete Responders through a Given Hour by Dose (%)

Hour	Dose (mg)[a]				Total [n=319]
	25 [n=78]	50 [n=83]	100 [n=80]	200 [n=78]	
4	73 (93.6%)	79 (95.2%)	77 (96.3%)	67 (85.9%)	296 (92.8%)
8	54 (69.2%)	68 (81.9%)	68 (85.0%)	56 (71.8%)	246 (77.1%)
12	43 (55.1%)	60 (72.3%)	67 (83.8%)	52 (66.7%)	222 (69.6%)
18	27 (34.6%)	46 (55.4%)	58 (72.5%)	51 (65.4%)	182 (57.1%)
24	24 (30.8%)	34 (41.0%)	49 (61.3%)	46 (59.0%)	153 (48.0%)

II. Complete Response by Dose (mg/Kg)

Number of Complete Responders by Dose Category (%)

Dose (mg/Kg)[b]			
≤0.6 [n=105]	>0.6 to ≤1.2 [n=80]	>1.2 to ≤1.8 [n=49]	>1.8 [n=85]
33 (31.4%)	39 (48.8%)	31 (63.3%)	50 (58.8%)

a) Dose (mg) p=0.0001 from the test for a linear contrast across doses in the hazard ratio estimated from Cox's Proportional Hazards Model of time to first emetic episode or escape medication, controlling for investigator.
b) Dose (mg/Kg) p=0.0011 from a one degree of freedom Chi-square test using a logistic regression model predicting complete response with dose entered directly, controlling for investigator.

2) Analysis of Secondary Efficacy Parameters

a) Total Response (Table 42)

Complete Response with no nausea rates, for the four dose groups, are summarized in this Table.

- The test for linear trend with dose in the proportion of complete responders with no nausea was statistically significant (p=0.0138).

- There were statistically significant differences among the four dose groups.

  - The 100 mg and 200 mg dose groups were significantly different from the 25 mg dose group (p=0.0181 and p=0.0079, respectively), with corresponding therapeutic gains of 17% and 19.2%.

- The therapeutic gains with the 100 and 200 mg over the 50 mg dose were modest at 11% and 13.2%; both were N.S.

- There were no other statistically significant differences in Total Responders.

TABLE 42
Study MCPR0048 (Report K-94-0929-CDS)

Clinical Response: Total Response[a]
[ITT Analysis]

Response by Dose (mg)				Therapeutic Gain (%)/p-value[b]					
25 [n=78]	50 [n=83]	100 [n=80]	200 [n=78]	50 vs 25	100 vs 25	200 vs 25	100 vs 50	200 vs 50	200 vs 100
16 (20.5%)	22 (26.5%)	30 (37.5%)	31 (39.7%)	6% [N.S.]	17% [0.0181]	19.2% [0.0079]	11% [N.S.]	13.2% [N.S.]	2.2% [N.S.]

a) Complete Response + No Nausea (defined as hour 24 nausea VAS score <5 mm).
b) p-value for linear trend (0.0028) was calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with no nausea using dose and investigator as explanatory variables.

b) Time to First Emetic Episode or Escape Medication (Table 43)

- The median time to the first emetic episode was 13h for the 25 mg dose group, 20h for the 50 mg dose group and >24h for the two higher dose groups. There was a statistically significant linear trend in the hazard ratios estimated from Cox's proportional hazards model of time to first emetic episode or escape medication (p=0.0001).

For this parameter (Table 43) there was substantial overlapping in the response with the four dose groups.

TABLE 43
Study MCPR0048 (Report K-94-0929-CDS)

Number and Timing of Emetic Episodes
[ITT Population]

Variable	DOLA•Mesyl Dose (mg)				Total [n=319]
	25 [n=78]	50 [n=83]	100 [n=80]	200 [n=78]	
Number of Emetic Episodes					
0 Complete Response	24 (30.8%)	34 (41.0%)	49 (61.3%)	46 (59.0%)	153 (48.0%)
1	4 (5.1%)	5 (6.0%)	3 (3.8%)	8 (10.3%)	20 (46.3%)
2	0	4 (4.8%)	0	2 (2.6%)	6 (1.9%)
1 or 2 Major Response	4 (5.1%)	9 (10.8%)	3 (3.0%)	10 (12.8%)	26 (8.2%)
0-2 Complete-Plus-Major Response[a]	28 (35.9%)	43 (51.8%)	52 (65.0%)	56 (71.8%)	179 (56.1%)
Received Escape Therapy	48 (61.5%)	37 (44.6%)	25 (31.3%)	21 (26.9%)	131 (41.1%)
Total Tx Fx[b]	50 (64.1%)	40 (48.2%)	28 (35.0%)	22 (28.2%)	140 (43.9%)
Median Emetic Episodes	>2	2	0	0	1
Range					
Median Time to First Emetic Episode or Escape ((h)	12.92	19.83	>24.00	>23.97	22.38
Range					

a) Complete-Plus-Major Response p=<0.0001 from a test for a linear contrast across doses in the parameter estimates obtained from a logistic regression model predicting complete-plus-major response with dose and investigator as explanatory variables; p-values for pairwise comparisons are as follows:

50 mg vs 25 mg p=0.0420 200 mg vs 25 mg p<0.0001 200 mg vs 50 mg p=0.0066
100 mg vs 25 mg p=0.0003 100 mg vs 50 mg N.S. 200 mg vs 100 mg N.S.

b) >2 emetic episodes and/or received escape therapy and/or monitored [illegible]

c) Nausea (Table 44)

- The median patient satisfaction VAS change from baseline to hour 24 was 49 mm, 10 mm, 11 mm, and 7 mm for the 25, 50, 100 and 200 mg [illegible] groups, respectively.

- There was a tendency toward decreased nausea with increasing doses of DOLA•Mesyl.

- The test for linear trend in nausea VAS change from baseline with dose was statistically significant (p=0.0006).

- There were statistically significant differences among the four dose groups.

    - The 50, 100 and 200 mg dose groups were significantly different from the 25 mg dose group.

    - There was no statistically significant difference among the 50, 100 and 200 mg dose groups.

- The proportions of patients with no nausea for the 25, 50, 100 and 200 mg dose groups were 21.9%, 37.8%, 40.5% and 44.9%, respectively.

- There was a tendency toward decreased nausea with increasing doses of DOLA•Mesyl.

- The test for linear trend in proportion of no nausea with dose was statistically significant (p=0.0028).

- There were statistically significant differences among the four dose groups.

    - The 50, 100 and 200 mg dose groups were significantly different from the 25 mg dose group.

    - There were no statistically significant difference among the 50, 100 and 200 mg dose groups.

TABLE 44
Study MCPR0048 (Report K-94-0929-CDS)

Nausea VAS

Scores Range 0="None" to 100="Nausea as bad as it can be"						
Dose [mg]	Evaluation	Actual Value			Change from Baseline	
		n	Median	% NO NAUSEA[a]	n	Median
25	Baseline	77	0.0	93.5		
	Hour 0	76	0.0	96.1	76	0.0
	Hour 24	73	50.0	21.9	73	49.0
50	Baseline	82	0.0	91.5		
	Hour 0	81	1.0	87.7	81	0.0
	Hour 24	82	11.5	37.8	82	10.0
100	Baseline	79	0.0	88.6		
	Hour 0	79	0.0	92.4	79	0.0
	Hour 24	79	11.0	40.5	79	11.0
200	Baseline	78	0.0	93.6		
	Hour 0	77	1.0	94.8	77	0.0
	Hour 24	78	7.0	44.9	78	7.0

a) "No Nausea" defined as VAS score <5 mm.
Hour 24 Change from Baseline p=0.0006 from a rank analysis of covariance F test for linear trend, controlling for investigator and baseline nausea VAS score; p-values for pairwise comparisons are as follows:

50 mg vs 25 mg p=0.0018	200 mg vs 25 mg p=0.0005	200 mg vs 50 mg p=N.S.
100 mg vs 25 mg p=0.0006	100 mg vs 50 mg p=N.S.	200 mg vs 100 mg p=N.S.

Hour 24 No Nausea p=0.0028 from a Chi-square test for linear trend calculated from a logistic regression model with treatment and investigator as explanatory variables; p-values for pairwise comparisons are as follows:

50 mg vs 25 mg p=0.0279	200 mg vs 25 mg p=0.0025	200 mg vs 50 mg p=N.S.
100 mg vs 25 mg p=0.0145	100 mg vs 50 mg p=N.S.	200 mg vs 100 mg p=N.S.

d) Patient Satisfaction

- The median scores were 48, 90, 95 and 91 mm, respectively, for the 25, 50, 100 and 200 mg dose groups.
- There was a tendency toward increased patient satisfaction with increasing doses of DOLA•Mesyl.

- The test for linear trend in patient satisfaction with dose was statistically significant (p=0.0009).

- There were statistically significant differences among the four dose groups.

  - The 50, 100 and 200 mg dose groups were significantly different from the 25 mg dose group.

  - There was no statistically significant difference among the 50, 100 and 200 mg dose groups.

3) Subgroup Analyses (Table 45)

This Table depicts the results of the subgroup analyses of Complete Response (eight variables). The effect of each variable on Complete Response is briefly described below.

- Age: Age was a statistically significant predictor of complete response (p=0.0003).

  - 46 of the 72 patients (63.9%) aged 65 y or older were complete responders, while 107 of the 247 patients (43.3%) aged less than 65 years were complete responders.

  - There was no significant interaction of age with a linear dose response.

  - When controlling for age together with dose and investigator in the primary logistic regression model, there was still a statistically significant linear trend in complete response with dose (p<0.0001).

- Gender: In this study, male gender was not a statistically significant predictor of complete response (p=0.0511), but there was a significant interaction of gender with a linear dose response (p=0.0195).

TABLE 45
Study MCPR0048 (Report K-94-0929-CDS)

Complete Response by Subgroups
[ITT Population]

Number of Complete Responders/Number of Patients in Dose by Subgroup Cell (Percent)						
Subgroup		DOLA•Mesyl Dose (mg)				p-values*
		25 [n=78]	50 [n=83]	100 [n=80]	200 [n=78]	
Age	<65 y (n=247)	14/60 (23.3%)	25/65 (38.5%)	36/63 (57.1%)	32/59 54.2%)	p(int)=N.S. p(m)=0.0003 p(lin)<0.0001
	≥65 y (n=72)	10/18 (55.6%)	9/18 (50.0%)	13/17 (76.5%)	14/19 (73.7%)	
Gender	M (n=60)	8/12 (66.7%)	8/15 (53.3%)	9/15 (60.0%)	10/18 (55.6%)	p(int)=0.0195 p(m)=0.0511 p(lin)=0.0001
	F (n=259)	16/66 (24.2%)	26/68 (38.2%)	40/65 (61.5%)	36/60 (60.0%)	
Previous Hx of Chemotherapy	NO (n=308)	21/74 (28.4%)	33/80 (41.3%)	47/77 (61.0%)	45/77 (58.4%)	p(int)=N.S. p(m)=N.S. p(lin)<0.0001
	YES (n=11)	3/4 (75.0%)	1/3 (33.3%)	2/3 (66.7%)	1/1 (100%)	
Use of Benzodiazepines	NO (n=284)	19/70 (27.1%)	28/74 (37.8%)	41/69 (59.4%)	39/71 (54.9%)	p(int)=N.S. p(m)=0.0429 p(lin)<0.0001
	YES (n=35)	5/8 (62.5%)	6/9 (66.7%)	8/11 (72.7%)	7/7 (100%)	
Use of Narcotic Analgesics	NO (n=275)	19/67 (28.4%)	31/71 (43.7%)	44/69 (63.8%)	42/68 (61.8%)	p(int)=N.S. p(m)=N.S. p(lin)<0.0001
	YES (n=44)	5/11 (45.5%)	3/12 (25.0%)	5/11 (45.5%)	4/10 (40.0%)	
Use of Steroids	NO (n=285)	22/73 (30.1%)	28/72 (38.9%)	44/71 (62.0%)	40/69 (58.0%)	p(int)=N.S. p(m)=N.S. p(lin)<0.0001
	YES (n=34)	2/5 (40.0%)	6/11 (54.5%)	5/9 (55.6%)	6/9 (66.7%)	
Hx of Heavy Alcohol Use	NO (n=292)	23/75 (30.7%)	29/72 (40.3%)	45/75 (60.0%)	45/72 (62.5%)	p(int)=N.S. p(m)=N.S. p(lin)<0.0001
	YES (n=24)	1/3 (33.3%)	4/10 (40.0%)	3/4 (75.0%)	[illegible]	
Cyclophosphamide and Doxorubicin Use	Single Agent (n=185)	15/70 (50.0%)	16/70 [illegible]	[illegible]	[illegible]	[illegible]
	Both Agents (n=193)	9/48 (18.8%)	[illegible]	[illegible]	[illegible]	[illegible]

Primary Test for Linear Trend adjusted for all significant subgroup [illegible] gender interaction, p*=0.0001 (Intent-to-Treat)

a) p values were calculated from a logistic regression model with dose and investigator as explanatory variables.
   - p(int) is the p value for testing the subgroup by linear dose response interaction.
   - p(m) is the p value for testing the subgroup as a main effect.
   - p(lin) is the p value for a linear dose response while controlling for the subgroup as a main effect.

b) p-value was calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose, investigator, age, concomitant use of benzodiazepines, cyclophosphamide and doxorubicin use, and gender by dose interaction as explanatory variables.

- 60 of the patients were M compared to 259 F.

- Complete response was recorded for 118/259 (45.6%) females, 16/66 (24.2%) in the 25 mg dose group, 26/68 (38.2%) in the 50 mg dose group, 40/65 (61.5%) in the 100 mg dose group and 36/60 (60.0%) in the 200 mg dose group.

- 35 of the 60 (58.3%) M patients were complete responders: 8/12 (66.7%) in the 25 mg dose group, 8/15 (53.3%) in the 50 mg dose group, 9/15 (60.0%) in the 100 mg dose group, and 10/18 (55.6%) in the 200 mg dose group.

- When controlling for a dose by gender interaction, together with dose and investigator in the primary logistic regression model, there was still statistically significant linear trend in Complete Response with dose (p=0.0001).

- Previous history of chemotherapy was not a significant predictor of complete response.

  - There was no significant interaction of previous Hx of chemotherapy with a linear dose response.

  - 11 patients had a previous Hx of chemotherapy compared to 308 patients who had no such history. In the latter subset, complete response was recorded for 146/308 (47.4%) patients compared to 7/11 (63.6%) patients in the former subset.

- Concomitant use of benzodiazepines (excluding those given as part of escape medication) during the 24-hour treatment period was a significant predictor of complete response (p=0.0429).

  - 97 of the 284 patients (41.7%) [illegible] were complete responders, whereas [illegible] who did receive benzodiazepines [illegible]

  - There was no significant interaction [illegible] benzodiazepines and a linear dose [illegible]

- When controlling for concomitant use of benzodiazepines together with dose and investigator in the primary logistic regression model, there was still a statistically significant linear trend in complete response with dose ($p<0.0001$).

- Non-use of narcotic analgesics during the 24-h treatment period was not a statistically significant predictor of complete response.

  - 44 patients received narcotic analgesics during the 24-h treatment period, of which 17 (38.6%) were complete responders, while 136 of the 275 patients (49.5%) not receiving narcotic analgesics were complete responders.

  - There was no significant interaction of use of narcotic analgesics with a linear dose response.

- Concomitant use of steroids (excluding those given as part of escape medication and non-systemic) prior to or during the 24-h treatment period was not a significant predictor of complete response.

  - 134 of the 285 patients (47.0%) who did not receive steroids were complete responders, whereas 19 of the 34 patients (55.9%) who did receive steroids were complete responders.

  - There was no significant interaction between concomitant use of steroids and a linear dose response.

- In this trial, Hx of heavy alcohol use was not a statistically significant predictor of complete response.

  - There was no significant intereaction of history of heavy alcohol use with a linear dose response.

  - 24 of the patients admitted to the study had a history of heavy alcohol use, compared to 292 patients with no such history (for 3 patients, no information was obtained and they were omitted from the subgroup analysis).

  - 13 of the 24 patients (54.2%) with a Hx of heavy alcohol use were complete responders, whereas 137 of the 292 (46.9%) patients with no Hx were complete responders.

- The use of one primary chemotherapy agent (i.e., cyclophosphamide or doxorubicin) was a statistically significant predictor of complete response ($p=0.0010$).

  - 80 of 126 patients (63.5%) receiving one primary agent were complete responders, while 73 of the 193 patients receiving both primary agents were complete responders.

- There was no significant interaction between number of primary agents used and a linear dose response.

- When controlling for the number of primary agents used together with dose and investigator in the primary logistic regression model, there was still a statistically significant linear trend in complete response with dose ($p<0.0001$).

It is important to note that 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 ($p=0.0001$).

d. Safety Results

1) Extent of Exposure

In Study MCPR0043, a total of 320 patients were treated with single oral doses of DOLA•Mesyl, with the following distribution:

25 mg (n=79) 50 mg (n=83) 100 mg (n=80) 200 mg (n=78)

All patients were compliant. Study medication was ingested under supervision of a trained staff member assuring 100% compliance.

2) Deaths, Dropouts, Due to AEs, and Other Serious AEs (Table 46)

- No patients dropped from the trial due to an AE.
- There were 4 SAEs, one of which resulted in death; the other in re-hospitalizations.
- All four events were due to worsening, progression of the underlying conditions, septic complications or to concomitant medications.
- The death, occurring 58 days after the patient received 100 mg DOLA•Mesyl was attributed to the patient's cancer.
- Additional information on Pt. 0364-0028 [illegible] tachycardia is given below.

One cannot assess temporal relationship to the [illegible] unknown. The patient had an ECG performed 2h after DOLA•Mesyl [illegible] apparent on a prestudy ECG) and non-specific ST-T wave changes. [illegible] 96h after DOLA•Mesyl, showed the patient was in AF with [illegible] 92 and 140 beats per minute. The patient was [illegible] hospitalized. Immediate treatment for [illegible] chemotherapy consisted during the [illegible] vincristine 2 mg and [illegible] 25 mg [illegible] vitamin C, d-alpha tocopherol, beta-carotene and [illegible].