EKG

The sponsor used the following criteria to identify the Tx-emergent EKG interval changes. The AERF was used as a tracking mechanism and these interval changes were summarized separately.

- PR interval ≥220 msec was the criterion for first degree AV block.
- All QRS durations ≥100 msec were interpreted as intraventricular conduction delays (IVCD).
  - If a treatment-emergent QRS duration ≥120 msec had been diagnosed as BBB[14] by the cardiologist, it would have been reported as an AE.
- A QT_c interval ≥440 msec was interpreted as prolonged QT interval.
  - QT_c interval represents the QT interval corrected for HR and was calculated using Bazett's's formula:

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

HR

- Defined criteria for HR changes were:
  - Sinus tachycardia as defined by a HR ≥100 beats per min.
  - Sinus bradycardia as defined by HR <60 beats per min.

7. Statistical Methodology

a. Data Documentation

From the information provided by the sponsor in the Clinical Report (S8, vol. 1.253, p. 59-60) I have concluded that the procedures used by the sponsor were adequate. Following a Pre-entry review of the data, as the data were entered, a previously developed computerized exception criteria were executed against the database. An electronic audit log was maintained to document changes made to the database, including old value, new value, date and time of change, who made the change, reason for change. Also adequate were procedures related to QC of the database for verification, correction of program errors, and study audit and database finalization. Following finalization of the database, the drug code was unblinded and applied to the database. A 100% verification of the randomization schedule to the patient number in the database was

[14] No patients in the trial were diagnosed by the cardiologist as meeting criteria for [illegible] BBB.

performed. This unblinding occurred on 01 Dec. 1994. Listing of all CRF data were incorporated in the CRF Tabulations (Report K-95-0010-S).

b. Sample Size Justification

The sample size determination was based on establishing a trend in Complete Response (the primary efficacy parameter) with dose, using a logistic regression model. The power calculations listed below are based on a 2-tail 0.05 significance level test, and 75 patients per dose group. With the sponsor's approach, there is little power for detecting differences between doses.[15]

Sponsor's Hypothesized Complete Response Percentages by Dose (mg)

25	50	100	200	Power
25%	33%	42%	51%	93%
25%	31%	38%	45%	77%
35%	43%	52%	61%	91%
35%	41%	48%	55%	73%

NOTE: The reviewer reiterates that, since this is an "active-active", dose response study, the "active dose" needs to be statistically superior to the 25 mg. If the response to 25 mg is 25%, the power for detecting the proposed 26% therapeutic gain 200 mg >25 mg is 93%.

c. Statistical Methods

1) Primary Analyses

- The primary endpoint for studying the efficacy of DOLA•Mesyl was complete response (0 emetic episodes, no rescue medication, and monitored for emesis at least 23.5 h).
- Patients not monitored for emesis at least 23.5 h were categorized as treatment failures.
- Logistic regression with a test for linear trend in the proportion of complete responders with dose, controlling for investigator as a main effect, was the primary test for efficacy.

[15] For example, if two doses had true Complete Response rates of 70% and 80%, then with 75 patients in each dose group, the power for detecting this difference is only [illegible]

- Subgroups [age, gender, previous Hx of chemotherapy, use of benzodiazepines, narcotic analgesics, steroids, Hx of heavy alcohol use, and primary chemotherapy (carboplatin vs cisplatin)] were added one at a time to the logistic model to test for any impact on complete response.

2) Secondary Analyses

These are listed below; these analyses were conducted controlling for investigator as a main effect.

Total Response[16]

Logistic regression techniques were used to test for a linear trend with dose in the proportion of Total Responders.

Complete plus major response

(same model as per primary analysis)

Time to first emetic episodes or escape medication

whichever occurred first [Cox Regression Model (SAS PHREG procedure)]

- Patients who did not experience emesis or did not receive escape medication were treated as being censored at 24 h or the duration the patient was monitored after initiation of chemotherapy, whichever was less. The trend in hazard ratios was examined, controlling for investigator.

Nausea VAS

- The nausea VAS was completed at three time points: hour -0.75 (baseline), hour 0 (just prior to chemotherapy infusion) and hour 24. Two analyses were conducted.

  - First, the mean change from baseline to hour 24 was analyzed for a trend in dose using a rank analysis of covariance, controlling for investigator, and baseline nausea.

  - Second, the proportion of no nausea was compared. No nausea was defined as an hour 24 VAS less than 5 mm. The proportion of patients with no nausea was analyzed using a logistic regression model controlling for dose and investigator.

[16] A patient was considered a total responder (Complete [illegible]) if the patient experienced no emetic episodes in the 24-h Tx period, received [illegible] was monitored for emesis for at least 23.5 h after initiation of [illegible] hour 24 nausea VAS less than 5 mm.

24-h Patient Satisfaction VAS

This was analyzed using a two-way rank AOV, controlling for investigator, with a test for linear trend with dose in patient satisfaction.

4) Safety Analyses

In general, a test for linear trend in response with dose using a Rank Analysis of Variance, controlling for investigator, was used to analyze data from EKGs, clinical laboratories and vital signs. It is important to add further information on vital signs and EKG analyses.

- As stated, changes in recumbent and standing pulse rates, systolic blood pressures and diastolic blood pressures from Pre-Tx to Post-Tx time points were analyzed using a two-way rank AOV controlling for investigator.
  - 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 was 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 24-36 h Tx period.
- Changes from prestudy to 1 to 2 h and 24-36 h poststudy in electrocardiogram measurements, heart rate, 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 (24-36h) 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 1-2 h and 24-36 h evaluations.

3. Pooling of Sites[17]

[17] According to the explanation given by the sponsor (Appendix [illegible]) in the protocol, all "small" sites were grouped together into pooled site(s). A site was considered to have [illegible] to be a candidate for pooling if it failed to have at least five [illegible] (major responders or Tx failures) (asymptotic considerations for [illegible]

- 24 sites were grouped into 8 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: MCST0152, 0154, 0157, 0175, 0186 and 0190; 0153, 0155, 0179 and 0188; 0160, 0163, 0184 and 0185; 0169 and 0394; 0183 and 0189; 0167 and 0173; 0176 and 0178; 0171 and 0174.

  - All analyses were performed using these pooled sites, together with the other 8 sites.

  - The exact method for pooling was described in sponsor's Appendix E1: Analysis Plan, page 2206.

NOTE: It is of interest to note that a strategy of pooling sites was developed which assured that the assumptions for validity of the main effects logistic regression and minimum information criteria for the secondary Mantel-Haenszel analyses were satisfied. Such strategy such not lead to a single, large pool site which may drive the analysis results. Sites were pooled with sizes of like size, so as to maintain any effect due to size of investigative site.

8. Results

a. Participating Investigators/Patient Accounting

From the information provided by the sponsor in the Clinical Report (vol. 1.253, p. 119-121), the following is noted.

- Of the 41 sites to which test medication was shipped:

  - 9 [Site #161, 162, 164, 168, 177, 180, 181, 182 and 189] did not randomize any patients.

  - 11 [Site #152, 153, 154, 155, 157, 175, 179, 184, 186, 188 and 190] randomized 4 patients or less (each site).

  - 15 [Site #151, 156, 160, 163, 166, 167, 169, 173, 174, 176, 178, 183, 185, 189 and 394] randomized between 5 and 15 patients (each site).

  - The following six sites randomized 16 patients or more (each site):

Site	Total # of Patients Randomized
#153 (Grote, Winston-Salem, NC)	31
#159 (Figlin, Los Angeles, CA)	24
#165 (Pineda, Birmingham, AL)	28
#170 (Porter III, Nashville, TN)	18
#171 (Reeves Jr., Fort Myers, FL)	16
#172 (Modiano, Tucson, AZ)	25

- A total of 307 patients were randomized to Tx and received test medication. All 307 patients completed the trial.

Major Protocol Violations

- 31 patients (10%) were considered to have major protocol violations and were excluded from the efficacy evaluable dataset. As computed below, the proportion of patients with major protocol violations per group was very similar.

Frequency (Percent) of Dispositions by Dose

Disposition	Dose (mg)				Total (n=307)
	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)	
MAJOR VIOLATION	8 (11%)	9 (11%)	5 (7%)	9 (11%)	31 (10%)
EFFICACY EVALUABLE	68 (90%)	71 (89%)	66 (93%)	71 (90%)	276 (90%)

- The actual protocol violations in patients given 25 mg and those receiving 200 mg DOLA•Mesyl are listed in Table 15. In these two groups, as well as in the 50 and 100 mg groups (data not shown), patients are being excluded from the evaluable population efficacy analysis for valid reasons prospectively stipulated in the protocol. Among these reasons were the administration of chemotherapeutic agents at doses different from those listed in the protocol and the use of potentially confounding concomitant medications.

TABLE 15
Study MCPR0043 (Report K-95-0009-CDS)

List of Major Protocol Violations

25 mg	200 mg
0159-004 Carboplatin dose <247.5 mg/m^2 >440 mg/m^2 or Cisplatin dose <18 mg/m^2 of >55 mg/m^2	0151-0003 Concomitant meds: prior to and/or during: lorazepam (Ativan), prochlorperazine (Compazine), ondansetron (Zofran), promethazine (Phenergan), trimethobenzamide (Tigan), thiethylperazine (torecan), scopolamine
0159-0021 Carboplatin dose <247.5 mg/m^2 >440 mg/m^2 or Cisplatin dose <18 mg/m^2 of >55 mg/m^2	0159-0006 Concomitant meds: prior to and/or during: lorazepam (Ativan), prochlorperazine (Compazine), ondansetron (Zofran), promethazine (Phenergan), trimethobenzamide (Tigan), thiethylperazine (torecan), scopolamine, Steroids (i.v. or oral) prior to and/or during study period in doses >=30 mg prednisone or >=30 mg prednisolone or >=5 mg dexamethasone or >=130 mg hydrocortisone, or >=24 mg solumedrol
0160-0002 Concomitant meds: prior to and/or during: lorazepam (Ativan), prochlorperazine (Compazine), ondansetron (Zofran), promethazine (Phenergan), trimethobenzamide (Tigan), thiethylperazine (torecan), scopolamine	0160-0003 Carboplatin dose <247.5 mg/m^2 >440 mg/m^2 or Cisplatin dose <18 mg/m^2 of >55 mg/m^2
0166-0003 Concomitant meds: prior to and/or during: lorazepam (Ativan), proclorperazine (Compazine), ondansetron (Zofran), promethazine (Phenergan), trimethobenzamide (Tigan), thiethylperazine (torecan), scopolamine	0165-0013 Steroids (i.v. or oral) prior to and/or during study period in doses >=30 mg prednisone or >=30 mg prednisolone or >=5 mg dexamethasone or >=130 mg hydrocortisone, or >=24 mg solumedrol
0166-0015 Carboplatin dose <247.5 mg/m^2 >440 mg/m^2 or Cisplatin dose <18 mg/m^2 of >55 mg/m^2	0165-0020 Concomitant meds: prior to and/or during: lorazepam (Ativan), prochlorperazine (Compazine), ondansetron (Zofran), promethazine (Phenergan), trimethobenzamide (Tigan), thiethylperazine (torecan), scopolamine
0170-0007 Steroids (i.v. or oral) prior to and/or during study period in doses >=30 mg prednisone or >=30 mg prednisolone or >=5 mg dexamethasone or >=130 mg hydrocortisone, or >=24 mg solumedrol	0166-0014 Carboplatin dose <247.5 mg/m^2 >440 mg/m^2 or Cisplatin dose <18 mg/m^2 of >55 mg/m^2
0171-0014 Carboplatin dose <247.5 mg/m^2 >440 mg/m^2 or Cisplatin dose <18 mg/m^2 of >55 mg/m^2	0170-0018 Study medication error (<4 tablets taken)
0196-0008 Concomitant meds: prior to and/or during: lorazepam (Ativan), prochlorperazine (Compazine), ondansetron (Zofran), promethazine (Phenergan), trimethobenzamide (Tigan), thiethylperazine (torecan), scopolamine	0172-0013 Concomitant meds: prior to and/or during: lorazepam (Ativan), [illegible], ondansetron (Zofran), [illegible], trimethobenzamide (Tigan), [illegible], (torecan), scopolamine
[illegible]	0172-0015 Carboplatin dose [illegible] Cisplatin dose [illegible]

b. Comparability of Groups/Patient Baseline Characteristics

1) Demographics/Primary Disease (Table 16)

There were no statistically significant differences among the four groups in demographic characteristics or the most frequent site of primary neoplasm. The study population was 54% male and 46% female and predominantly Caucasian (88%), with a median age of 64y, median height of 170 cm and median weight of 73 Kg. The median Karnofsky status was 90% and ca. 9% of the patients had a Hx of heavy alcohol use. As shown in the lower panel of Table 16, the most frequent sites of primary neoplasm were lung (54%), gynecological (18%), gastrointestinal (7%) and head/neck (4%).

TABLE 16
Study MCPR0043 (Report K-95-0009-CDS)

Demographic and Primary Disease Baseline Characteristics

[ITT Population]

Variable	Dose (mg)				p-value
	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80	
Gender:					
M	(56.6%)	(55.0%)	(57.7%)	(46.3%)	N.S.
F	(43.4%)	(45.0%)	(42.3%)	(53.8%)	
Race					
Caucasian	(90.8%)	(87.5%)	(91.5%)	(81.3%)	N.S.[a]
Black	(2.6%)	(10.0%)	(5.6%)	(7.5%)	
Hispanic	(2.6%)	(2.5%)	(2.8%)	(6.3%)	
Other	(3.9%)	(0.0%)	(0.0%)	(5.0%)	
Age (y)					
Mean	61.6	59.0	61.7	62.2	N.S.
Median	65.5	61.0	65.0	64.0	
Height (cm)					
Mean	170.1	170.0	169.8	168.4	N.S.
Median	170.2	168.5	170.2	167.6	
Weight (Kg)					
Mean	75.1	75.1	74.9	72.1	N.S.
Median	75.0	73.8	72.2	72.7	
Karnofsky Status (%)					
Mean	86.2	84.8	84.0	83.4	N.S.
Median	90.0	90.0	90.0	87.5	
Hx of Heavy Alcohol Use					
	9.2%	10.0%	8.5%	7.5%	N.S.
Site of Primary Neoplasm					
Lung	56.6%	55.0%	59.7%		
Gynecologic	15.8%	16.3%	15.5%		
Gastrointestinal	3.9%	7.5%	7.0%		
Head/Neck	2.6%	3.8%	4.2%		
Other	21.1%	17.5%	13.6%		

a) Test, vs all others
b) Lung vs all others

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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 17)

There were no gross imbalances in previous cancer treatment Hx among the four study groups: 10% of the patients had previously received chemotherapy; 19% had previously undergone radiotherapy and 36% of the patients had previously undergone surgery for their malignant condition.

- 60% of the patients received carboplatin, at a mean dose of 311 mg/m²
- 40% of the patients received cisplatin, at a mean dose of 36 mg/m²
- The mean duration of the infusion of the primary chemotherapy was 75 min.
- The mean interval between test medication and primary chemotherapy was 32 min.
- None of the above-described differences were statistically significant.
- As shown in Table 18, the most frequent concomitant chemotherapies received during the 24-h treatment period were:

etoposide	(53.4%)	
cyclophosphamide	(11.4%)	and
5-FU	(8.1%)	

The associated p-values for these concomitant chemotherapies among the four Tx groups, were not statistically significant. The groups were also well-balanced in the concomitant use of benzodiazepines (10.4% of patients) and narcotic analgesics (27.7%). There was, however, a statistically significant difference among the Tx groups in the concomitant use of steroids (p=0.0336) (7.2% of the patients). But this imbalance due to a 15.5% with the 100 mg dose is not expected to influence the response to 200 mg Ondansetron.

TABLE 17
Study MCPR0043 (Report K-95-0009-CDS)

Distribution of Previous and Present Chemotherapeutic Regimens

Variable	DOLA●Mesyl Dose (mg)				p-value
	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)	
Previous Cancer Treatment					
Chemotherapy	7.9%	16.3%	7.0%	8.8%	N.S.
Radiotherapy	15.8%	28.8%	14.1%	16.3%	N.S.
Surgery	27.6%	45.0%	36.6%	32.5%	N.S.
Primary Chemotherapy					
Carboplatin	64.5%	63.8%	50.7%	60.0%	N.S.
Cisplatin	35.5%	36.3%	49.3%	40.0%	
Mean Carboplatin Dose (mg/m^2)	308.1	310.8	312.1	313.8	N.S.
Range					
Mean Cisplatin Dose (mg/m^2)	34.7	41.4	31.6	38.8	N.S.
Range					
Mean Duration of Primary Chemotherapy (min.)	74.4	72.9	77.9	76.2	N.S.
Range					
Mean Interval Between Study Drug and Primary Chemotherapy (min.)	32.1	31.9	30.8	31.5	N.S.
Range					

- 5 patients were excluded from the efficacy evaluable analysis due to receiving doses of carboplatin considered to be too low to constitute a moderate emetogenic stimulus (<247.5 mg/m² carboplatin): patient MCSTO159-0004 = 168.32 mg/m²; patient MCSTO159-0021 = 232.56 mg/m²; patient [illegible] 247.25 mg/m²; patient MCSTO146-0014 = 205.88 mg/m²; and patient MCSTO[illegible] of these patients were complete responders, with the exception of patient [illegible] emetic episodes (major response).

- 6 patients were excluded from the efficacy evaluable analysis due to receiving [illegible] or cisplatin considered (by the sponsor) to be too high to constitute a [illegible] (>448 mg/m² carboplatin or >53 mg/m² cisplatin). [Patient MCSTO[illegible] patient MCSTO146-0015 carboplatin = 463.48 mg/m²; patient MCSTO171-0015 [illegible] patient MCSTO171-0015 cisplatin = 74.71 mg/m²; patient MCSTO172-0025 [illegible] patient MCSTO169-0009 cisplatin = 98.68 mg/m².] These patients were [illegible] exceptions of patients MCSTO171-0015 and MCSTO172-0025, both of whom [illegible]

NOTE: Administration of high dose cisplatin was the exception, not the rule, [illegible] cisplatin (98.68 mg/m²) given to a single patient (MCSTO169-0009) [illegible] of high emetogenic potential.

TABLE 18
Study MCPR0043 (Report K-95-0009-CDS)

Concomitant Chemotherapy, Benzodiazepines, Narcotic Analgesics and Steroids

Concomitant Use of	DOLA•Mesyl Dose (mg)				p-value
	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)	
Chemotherapy:					
5-FU	6.6%	11.3%	9.9%	5.0%	N.S.
Cyclophosphamide	11.8%	10.0%	8.5%	15.0%	N.S.
Etoposide	55.3%	53.8%	56.3%	48.8%	N.S.
Benzodiazepines	7.9%	13.8%	9.9%	10.0%	N.S.
Narcotic Analgesics	36.8%	23.8%	25.4%	25.0%	N.S.
Steroids	5.3%	3.8%	15.5%	5.0%	0.0336

4) Previous/Concomitant Other Medications (Table 19)

There were no statistically significant imbalances among the four Tx groups in medications used prior to test medication (for meds. that were used in >2% of the study population) or the incidence of concomitant medication use during the 24-h Tx period (for meds. that were used in >2% of the study population).

TABLE 19
Study MCPR0043 (Report K-95-0009-CDS)

Previous Concomitant Other Medications

Non-Study Medication (p-value)	DOLA®Mesyl Dose (mg)				All Patients (n=307)
	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)	
I. Frequency (Percent) of Concomitant Medications Taken Pretreatment					
MANNITOL (p=0.438)	13 (17%)	17 (21%)	19 (27%)	14 (18%)	63 (21%)
PARACETAMOL[a] (p=0.241)	11 (14%)	13 (16%)	15 (21%)	21 (26%)	60 (20%)
FUROSEMIDE (p=0.165)	13 (17%)	17 (21%)	6 (8%)	11 (14%)	47 (15%)
POTASSIUM (p=0.365)	12 (16%)	16 (20%)	7 (10%)	11 (14%)	46 (15%)
MAGNESIUM SULFATE (p=0.775)	10 (13%)	9 (11%)	12 (17%)	12 (15%)	43 (14%)
VICODEN[b] (p=0.775)	10 (13%)	7 (9%)	7 (10%)	7 (9%)	31 (10%)
RANITIDIN[c] (p=0.370)	3 (4%)	9 (11%)	7 (10%)	6 (8%)	25 (8%)
TYLOX[c] (P=0.996)	6 (8%)	6 (8%)	6 (8%)	6 (8%)	24 (8%)
SALBUTAMOL[d] (P=0.510)	7 (9%)	4 (5%)	3 (4%)	7 (9%)	21 (7%)
II. Frequency (Percent) of Concomitant Medications Taken During 24-h Treatment Period					
POTASSIUM (p=0.294)	10 (13%)	9 (11%)	3 (4%)	9 (11%)	31 (10%)
RANITIDIN[c] (p=0.242)	2 (3%)	8 (10%)	7 (10%)	5 (6%)	22 (7%)
SALBUTAMOL (p=0.386)	8 (11%)	3 (4%)	4 (6%)	6 (8%)	21 (7%)
FUROSEMIDE (P=0.257)	6 (8%)	8 (10%)	4 (6%)	2 (3%)	20 (7%)
PARACETAMOL (p=0.973)	5 (7%)	6 (8%)	4 (6%)	5 (6%)	20 (7%)
ALPRAZOLAM	1 (1%)	3 (4%)	2 (3%)	2 (3%)	8 (3%)
DILTIAZEM	1 (1%)	3 (4%)	4 (6%)	3 (4%)	11 (4%)
IPRATROPIUM	5 (7%)	1 (1%)	6 (8%)	5 (6%)	17 (6%)
MAGNESIUM SULFATE	2 (3%)	2 (3%)	2 (3%)	4 (5%)	10 (3%)
MORPHINE	5 (7%)	3 (4%)	3 (4%)	3 (4%)	14 (5%)
TEMAZEPAN	2 (3%)	2 (3%)	2 (3%)	2 (3%)	[illegible]
TYLOX	3 (4%)	5 (6%)	4 (6%)	2 (3%)	[illegible]

a) acetaminophen
b) acetaminophen and hydrocodone bitartrate
c) acetaminophen and oxycodone
d) albuterol

* Listed in this Table are the frequencies of non-study medication taken by [illegible] of the patients.
# The p-values were calculated using a 3 degree of freedom [illegible]

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5) Escape Medications (Table 20)

There were statistically significant imbalances among the four test groups in the use of escape medications. The incidence of the use of the benzodiazepine lorazepam (p=0.011) or prochlorperazine (p=0.0139) was highest in the 25 mg dose group.

TABLE 20
Study MCPR0043 (Report K-95-0009-CDS)

Escape Medication

	DOLA•Mesyl Dose (mg)				All Patients (n=307)
	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)	
DEXAMETHASONE	9 (12%)	1 (1%)	6 (8%)	2 (3%)	18 (6%)
DIPHENHYDRAMINE	6 (8%)	3 (4%)	1 (1%)	2 (3%)	12 (4%)
LORAZEPAM (p=0.011)	11 (14%)	3 (4%)	4 (6%)	2 (3%)	20 (7%)
METOCLOPRAMIDE	4 (5%)	1 (1%)	2 (3%)	0	7 (2%)
ONDANSETRON	7 (9%)	2 (3%)	5 (7%)	2 (3%)	16 (5%)
PROCHLORPERAZINE (p=0.0139)	12 (16%)	5 (6%)	5 (7%)	6 (8%)	28 (9%)
PROMETHAZINE	3 (4%)	1 (1%)	2 (3%)	1 (1%)	7 (2%)
p-values are calculated using a 3 degree of freedom Chi-square test.					

c. Clinical Response

1) Analysis of Primary Efficacy Parameters

a) Complete Response (Table 21)

- In both, the ITT (n=307) and the Evaluable Population (n=276) analyses there was a statistically significant trend in Complete Response with DOLA•Mesyl dose (p<0.0001 for both analyses).
- There were statistically significant differences among the four dose groups. The 50, 100 and 200 mg dose groups were statistically superior to the 25 mg dose group (both study populations).
- The therapeutic gains with 50 and 100 mg (over the 25 mg dose) were very similar (26.6% and 28.5% in the ITT and 27.6% and 25.6% in the Evaluable population).
- The therapeutic gain with the 200 mg (over the 25 mg) was 38% and this was higher than those with 50 (27%) and 100 mg (29%).

- In spite of the above, statistically, neither the ITT nor the Evaluable Population analyses showed significant differences among the 50, 100 and 200 mg DOLA•Mesyl groups.

- In summary then, the results of analysis in the Evaluable Population were consistent with those given by the ITT analysis.

i) Complete Response Rates by Investigator and Dose (Table 22)

- Overall Complete Response rates (right hand side column in this Table) by investigator (and pooled sites) ranged from

- According to this information, investigator was not a significant predictor of Complete Response.

- There was no interaction between investigator and a linear response.

- When taking sample sizes into consideration dose trends were consistent over investigators.

TABLE 21
Study MCPR0043 (Report K-95-0009-CDS)

Clinical Response: Analysis of Primary Efficacy Parameter
Complete Response

RESPONSE BY DOSE (mg)				THERAPEUTIC GAIN (%)/p-value[a]					
I. Intent-to-Treat Analysis[b] (n=307)									
25 [n=76]	50 [n=80]	100 [n=71]	200 [n=80]	50 vs 25	100 vs 25	200 vs 25	100 vs 50	200 vs 50	200 vs 100
34 (44.7%)	57 (71.3%)	52 (73.2%)	66 (82.5%)	26.6% [0.0006]	28.5% [0.0005]	37.8% [<0.0001]	1.9% [N.S.]	11.2% [N.S.]	9.3% [N.S.]
II. Efficacy Evaluable Analysis[c] (n=276)									
[n=68]	[n=71]	[n=66]	[n=71]						
31 (45.6%)	52 (73.2%)	47 (71.2%)	59 (83.1%)	27.6% [0.0009]	25.6% [0.0031]	37.5% [<0.0001]	-2.0% [N.S.]	9.9% [N.S.]	11.9% [N.S.]

a) Primary Test: Linear Trend ($p<0.001$).
   • Mantel-Haenszel Test for Non-Zero Correlation, $p<0.001$.
b) The p-value was calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting Complete Response with dose and investigator as explanatory variables.
c) Test for Linear Trend, $p<0.0001$.

TABLE 22
Study MCPR0043 (Report K-95-0009-CDS)

Complete Response by Investigator and Dose[a]
ITT Analysis

Investigator[b] or Pooled Site	DOLA●Mesyl Dose (mg)[c]				Total (n=307)
	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)	
151 (n=10)	1/3 (33.3%)	1/3 (33.3%)	2/2 (100%)	1/2 (50.0%)	5/10 (50.0%)
156 (n=11)	0/3 (0.0%)	2/3 (66.7%)	2/2 (100%)	1/3 (33.3%)	5/11 (45.5%)
158 (n=31)	6/8 (75.0%)	6/8 (75.0%)	6/7 (85.7%)	8/8 (100%)	26/31 (83.9%)
159 (n=24)	3/6 (50.0%)	4/6 (66.7%)	6/6 (100%)	3/6 (50.0%)	16/24 (66.7%)
165 (n=28)	2/5 (40.0%)	5/7 (71.4%)	5/7 (71.4%)	8/9 (88.9%)	20/28 (71.4%)
166 (n=15)	0/4 (0.0%)	3/4 (75.0%)	2/3 (66.7%)	4/4 (100%)	9/15 (60.0%)
170 (n=18)	1/4 (25.0%)	5/5 (100%)	2/4 (50.0%)	5/5 (100%)	13/18 (72.2%)
172 (n=25)	2/6 (33.3%)	5/6 (83.3%)	6/6 (100%)	7/7 (100%)	20/25 (80.0%)
(152, 154, 157, 175, 186, 190[d]) (n=10)	0/3 (0.0%)	2/4 (50.0%)	0/0 (0.0%)	3/3 (100%)	5/10 (50.0%)
(153, 155, 179, 188[d]) (n=14)	0/4 (0.0%)	1/2 (50.0%)	3/4 (75.0%)	2/4 (50.0%)	6/14 (42.9%)
(160, 163, 184, 185[d]) (n=19)	3/4 (75.0%)	4/5 (80.0%)	2/5 (40.0%)	5/5 (100%)	14/19 (73.7%)
(169, 394[d]) (n=12)	2/2 (100%)	1/3 (33.3%)	2/4 (50.0%)	2/3 (66.7%)	7/12 (58.3%)
(183,189[d]) (n=16_	1/4 (25.0%)	4/5 (80.0%)	2/4 (50.0%)	1/3 (33.3%)	8/16 (50.0%)
(167, 173[d]) (n=22)	4/6 (66.7%)	5/7 (71.4%)	2/4 (50.0%)	5/5 (100%)	16/22 (72.7%)
(176, 178[d]) (n=23)	4/6 (66.7%)	4/5 (80.0%)	4/6 (66.7%)	4/6 (66.7%)	16/23 (69.6%)
(171, 174[d]) (n=29)	5/8 (62.5%)	5/7 (71.4%)	6/7 (85.7%)	7/7 (100%)	23/29 (79.3%)
TOTAL (n=307)	34/76 (44.7%)	57/80 (71.3%)	52/71 (73.2%)	66/80 (82.5%)	209/307 (68.1%)

a) This Table depicts the number of Complete Responders/Number of Patients in investigator or Pooled site by Dose Cell (%)

b) Investigator p=0.1559 from a 15 degree of freedom Chi-square test using a logistic regression model predicting complete response with dose and investigator as explanatory variables.

c) Linear Dose Response by Investigator interaction (p=0.8736) from a 15 degree of freedom Chi-square test using Rao scores from a logistic regression model predicting complete response with dose and investigator as explanatory variables.

d) Investigators were pooled in order to estimate parameters for logistic regression and Mantel-Haenszel Chi-square.

ii) Complete Response by Hour and Dose (mg) and by Dose in mg/Kg (Table 23)

- The data in this Table provide the proportion of Complete Responders over time (for hours 4, 8, 12, 18 and 24) for each experimental group. By 4 hours, the four DOLA•Mesyl dose groups appeared to be equally effective. From 8 to 24h, the effectiveness of the lower dose is gradually decreasing but that of the other doses, especially the 200 mg dose after 18h, appeared to be maintained.

TABLE 23
Study MCPR0043 (Report K-95-0009-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 (Percent)					
Hour	DOLA•Mesyl Dose (mg)[a]				Total (n=307)
	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)	
4	72 (94.7%)	78 (97.5%)	70 (98.6%)	78 (97.5%)	298 (97.1%)
8	55 (72.4%)	74 (92.5%)	66 (93.0%)	75 (93.8%)	270 (87.9%)
12	43 (56.6%)	66 (82.5%)	61 (85.9%)	73 (91.3%)	243 (79.2%)
18	35 (46.1%)	61 (76.3%)	56 (78.9%)	72 (90.0%)	224 (73.0%)
24	34 (44.7%)	57 (71.3%)	52 (73.2%)	66 (82.5%)	209 (68.1%)

II. COMPLETE RESPONSE BY DOSE (mg/Kg)			
Number of Complete Responders by Dose Category (Percent)			
DOLA•Mesyl Dose (mg/Kg)[b]			
≤0.6 (n=101)	>0.6 to ≤1.2 (n=75)	>1.2 to ≤1.8 (n=43)	>1.8 (n=88)
51 (50.5%)	57 (76%)	29 (67.4%)	72 (81.8%)

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=0.0006 from a one degree of freedom Chi-square test using a logistic regression model predicting complete response with dose entered directly, controlling for investigator.

- Table 23, lower panel, shows the Complete Responders by dose in mg/Kg broken into dose ranges from ≤0.6 through >1.8 mg/Kg. Each dose range included a dose in mg/Kg (0.33, 0.67, 1.33, 2.67) that corresponds to the mg doses tested (25, 50, 100, 200) for a 75 Kg patient. These results are driven by the observed response seen for dose in mg.

Converting doses into mg/Kg units, based upon the B_{wt} of each patient, also resulted in a statistically significant increase in Complete Response with increasing dose in mg (p=0.0006). In their Figure 3 (page 226) the sponsor provided a graphical illustration in the form of a scatter plot of complete responders and nonresponders by dose in mg and body weight. The overlapping of weights of complete responders and nonresponders for all doses illustrated that response was not related to weight. The reviewer agrees with the sponsor that these evaluations suggest that a dosing regimen independent of B_{wt} is appropriate for this indication.

2) Analysis of Secondary Efficacy Parameters

a) Total Response (Table 24)

Complete Response with no nausea rates, for the four dose groups, is summarized in this Table. The test for linear trend with dose in the proportion of Total Responders was statistically significant (p<0.0001). Each of the higher dose groups was statistically superior to the 25 mg group, with therapeutic gains of 15.9%, 29.1% and 37.1% for the 50, 100 and 200 mg groups, respectively, over the 25 mg group. In addition, the 200 mg dose group was significantly different from the 50 mg dose group (therapeutic gain = 21.2%; p=0.0058).

TABLE 24
Study MCPR0043 (Report K-95-0009-CDS)

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

Response by Dose (mg)				Therapeutic Gain (%)/p-value[b]					
25 [n=76]	50 [n=80]	100 [n=71]	200 [n=80]	50 vs 25	100 vs 25	200 vs 25	100 vs 50	200 vs 50	200 vs 100
25 (32.9%)	39 (48.8%)	44 (62.0%)	56 (70.0%)	15.9% [0.0462]	(29.1%) [0.0004]	(37.1%) [<0.0001]	(13.2%) [N.S.]	(21.2%) [0.0058]	(8.0%) [N.S.]

a) Complete Response + No Nausea (defined as hour 24 nausea VAS score <5 mm).
b) p-value 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 25)

The median times to first emetic episode or escape medication, whichever occurred first, were 15.38, >24, >24 and >24h for the 25, 50, 100 and 200 mg dose groups, respectively. There was a statistically significant linear trend in the hazard ratios estimated from Cox's proportional hazards model for time to first emetic episode or escape medication (p=0.0001).

TABLE 25
Study MCPR0043 (Report K-95-0009-CDS)

Number and Timing of Emetic Episodes
[ITT Population]

Variable	DOLA©Mesyl Dose (mg)				Total (n=307)
	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)	
Number of Emetic Episodes:					
0 (Complete Response)	34 (44.7%)	57 (71.3%)	52 (73.2%)	66 (82.5%)	209 (68.1%)
1	5 (6.6%)	3 (3.8%)	3 (4.2%)	4 (5.0%)	15 (4.9%)
2	3 (3.9%)	2 (2.5%)	0	0	5 (1.6%)
1 or 2 Major Response	8 (10.5%)	5 (6.3%)	3 (4.2%)	4 (5.0%)	20 (6.5%)
0 to 2 Complete-Plus-Major Response[a]	42 (55.3%)	62 (77.5%)	55 (77.5%)	70 (87.5%)	229 (74.6%)
Received Escape Therapy	31 (40.8%)	15 (18.8%)	16 (22.5%)	9 (11.3%)	71 (23.1%)
Total Tx Fx[b]	34 (44.7%)	18 (22.5%)	16 (22.5%)	10 (12.5%)	78 (25.4%)
Median Emetic Episodes	1	0	0	0	0
Range	0 to ≥7	0 to ≥8	0 to ≥6	0 to 9	0 to 9
Median Time to First Emetic Episode or Escape (h)	15.38	>24.00	>24.00	>24.00	>24.00
Range	1.83 to >24.00	1.00 to >24.00	4.00 to >24.00	2.00 to >24.00	1.00 to >24.00

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=0.0030 | 200 mg vs 25 mg p<0.0001 | 200 mg vs 50 mg p=N.S.
100 mg vs 25 mg p=0.0048 | 100 mg vs 50 mg p=N.S. | 200 mg vs 100 mg p=N.S.

b) Total Treatment Failure = >2 emetic episodes and/or received escape therapy and/or monitored less than 23.5 (h)

c) Nausea (Table 26)

- The median VAS change from baseline to hour 24 was 12, 5 mm, 1 mm, 0 mm and 0 mm for the 25 mg, 50 mg, 100 mg and 200 mg dose 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=0.0034).

- There were statistically significant differences among the four dose groups. The 50 mg, 100 mg and 200 mg dose groups were significantly different from the 25 mg dose group.

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

- The proportions of patients with no nausea for the 25 mg, 50 mg, 100 mg and 200 mg dose groups were 40.3%, 55.7%, 63.4% and 72.5%, respectively.

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

  - The test for linear trend in proportion of patients with no nausea with dose was statistically significant (p=0.0001).

  - 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. In addition, the 200 mg dose group was significantly different from the 50 mg dose group.

  - There was no statistically significant difference between the 25 mg and 50 mg dose groups, nor between the 50 mg and 100 mg dose groups, or between the 100 mg and 200 mg dose groups.

d) Patient Satisfaction

- The median patient satisfaction VAS scores were 81 mm, 98 mm, 98 mm and 99 mm, respectively, for the 25 mg, 50 mg, 100 mg 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=0.0023).

  - There were statistically significant differences among the four dose groups. The 50 mg, 100 mg and 200 mg dose groups were significantly different from the 25 mg dose group.

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

TABLE 26
Study MCPR0043 (Report K-95-0009-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	76	0.0	90.8		
	Hour 0	76	0.0	94.7	76	0.0
	Hour 24	72	16.0	40.3	72	12.5
50	Baseline	80	0.0	91.3		
	Hour 0	80	0.0	90.0	80	0.0
	Hour 24	79	2.0	55.7	79	1.0
100	Baseline	69	0.0	94.2		
	Hour 0	68	0.0	92.6	68	0.0
	Hour 24	71	1.0	63.4	69	0.0
200	Baseline	79	0.0	97.5		
	Hour 0	79	0.0	97.5	79	0.0
	Hour 24	80	1.0	72.5	79	0.0

a) "No Nausea" defined as VAS score <5 mm.

Hour 24 Change from Baseline, p=0.0034, from a rank analysis of covariance F test for linear trend, controlling for investigator and baseline nausea VAS score. p value for pairwise comparisons are as follows:

50 mg vs 25 mg p=0.0264	200 mg vs 25 mg p=0.0026	200 mg vs 50 mg p=N.S.
100 mg vs 25 mg p=0.0163	100 mg vs 50 mg p=N.S.	200 mg vs 100 mg p=N.S.

Hour 24 No Nausea, p=0.0001, from a Chi-square test for linear trend calculated from a logistic regression model with dose and investigator as explanatory variables; p values for pairwise comparisons are as follows:

50 mg vs 25 mg p=N.S.	200 mg vs 25 mg p=0.0001	200 mg vs 50 mg p=0.0289
100 mg vs 25 mg p=0.0062	100 mg vs 50 mg p=N.S.	200 mg vs 100 mg p=N.S.

3) Subgroup Analyses (Table 27)

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

- Age was a statistically significant predictor of complete response (p=0.0013).

- 112 of the 149 patients (75.2%) aged 65 y or older were complete responders, while 97 of the 158 patients (61.4%) aged less than 65 y 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 was not a statistically significant predictor of Complete Response.

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

  - Complete Response was recorded for 93/142 (65.5%) females and 116/165 (70.3%) males.

- Previous Hx of chemotherapy was not a significant predictor of Complete Response.

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

  - 31 patients had a previous Hx of chemotherapy compared to 276 patients who had no such history. In the latter subset, complete response was recorded for 186/276 (67.4%) patients compared to 23/31 (74.2%) patients in the former subset.

- Concomitant use of benzodiazepines (excluding those given as part of escape medication) during the 24-h treatment period was not a significant predictor of complete response.

  - 186 of the 275 patients (67.6%) who did not receive benzodiazepines were complete responders, whereas 23 of the 32 patients (71.9%) who did receive benzodiazepines were complete responders.

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

  - 85 patients received narcotic analgesics during the 24-h treatment period, of which 53 (62.4%) were complete responders, while 156 of the 222 patients (70.3%) 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 or those administered by non-systemic routes) prior to or during the 24-h treatment period was not a significant predictor of complete response.

  - 192 of the 285 patients (67.4%) who did not receive steroids were complete responders, whereas 17 of the 22 patients (77.3%) who did receive steroids were complete responders.

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

  - 27 of the patients admitted to the study had a Hx of heavy alcohol use, compared to 280 patients with no such Hx.

  - 19 of the 27 patients (70.4%) with a Hx of heavy alcohol use were complete responders, whereas 190 of the 280 (67.9%) patients with no Hx of heavy alcohol intake were complete responders.

- The primary chemotherapy agent (i.e., carboplatin or cisplatin) was not a statistically significant predictor of complete response.

  - 129 of 184 patients (70.1%) receiving carboplatin as the primary agent were complete responders, while 80 of the 123 patients (65.0%) receiving cisplatin as the primary agent were complete responders.

  - There was no significant interaction between primary agent and a linear dose response.

d. Safety Results

1) Extent of Exposure

In Study MCPR0043, a total of 307 patients took single oral doses of DOLA•Mesyl, with the following distribution:

25 mg (n=76) 50 mg (n=80) 100 mg (n=71) 200 mg (n=80)

All patients were compliant because when they took test medication, they were in the Hospital or Research Unit, being prepared to receive the intravenously administered chemotherapy.

TABLE 27
Study MCPR0043 (Report K-95-0009-CDS)

Complete Response by Subgroups

Number of Complete Responders/Number of Patients in Treatment by Subgroup Category Cell (Percent)						
Subgroup		DOLA®Mesyl Dose (mg) 25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)	p-values[a]
Age	<65 y (n=158)	11/35 (31.4%)	33/50 (66.0%)	22/32 (68.8%)	31/41 (75.6%)	p (int) = N.S. p (m) = 0.0013 p (lin) = <0.0001
	≥65 (n=149)	23/41 (56.1%)	24/30 (80.0%)	30/39 (76.9%)	35/39 (89.7%)	
Gender	M (n=165)	22/43 (51.2%)	29/44 (65.9%)	33/41 (80.5%)	32/37 (86.5%)	p (int) = N.S. p (m) = N.S. p (lin) = <0.0001
	F (n=142)	12/33 (36.4%)	28/36 (77.8%)	19/30 (63.3%)	34/43 (79.1%)	
Previous History of Chemotherapy	NO (n=276)	32/70 (45.7%)	46/67 (68.7%)	48/66 (72.7%)	60/73 (82.2%)	p (int) = N.S. p (m) = N.S. p (lin) = <0.0001
	YES (n=31)	2/6 (33.3%)	11/13 (84.6%)	4/5 (80.0%)	6/7 (85.7%)	
Use of Benzodiazepines	NO (n=275)	31/70 (44.3%)	50/69 (72.5%)	46/64 (71.9%)	59/72 (81.9%)	p (int) = N.S. p (m) = N.S. p (lin) = <0.0001
	YES (n=32)	3/6 (50.0%)	7/11 (63.6%)	6/7 (85.7%)	7/8 (87.5%)	
Use of Narcotic Analgesics	NO (n=222)	22/48 (45.8%)	46/61 (72.1%)	42/53 (79.2%)	48/60 (80.0%)	p (int) = N.S. p (m) = N.S. p (lin) = <0.0001
	YES (n=85)	12/28 (42.9%)	13/19 (68.4%)	10/18 (55.6%)	18/20 (90.0%)	
Use of Steroids	NO (n=285)	33/72 (45.8%)	55/77 (71.4%)	42/60 (70.0%)	62/76 (81.6%)	p (int) = N.S. p (m) = N.S. p (lin) = <0.0001
	YES (n=22)	1/4 (25.0%)	2/3 (66.7%)	10/11 (90.9%)	4/4 (100%)	
History of Heavy Alcohol Use	NO (n=280)	31/69 (44.9%)	52/72 (72.2%)	46/65 (70.8%)	61/74 (82.4%)	p (int) = N.S. p (m) = N.S. p (lin) = <0.0001
	YES (n=27)	3/7 (42.9%)	5/8 (62.5%)	6/6 (100%)	5/6 (83.3%)	
Primary Chemotherapy	Carboplatin (n=184)	25/49 (51.0%)	36/51 (70.6%)	28/36 (77.8%)	[illegible]	[illegible]
	Cisplatin (n=123)	9/27 (33.3%)	21/29 (72.4%)	24/35 (68.6%)	[illegible]	

Primary Test for Linear Trend adjusted for all significant subgroup main effects, p=0.0001

a) p values were calculated from a logistic regression model with dose and investigator as explanatory variables in the model.
- 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
- For history of heavy alcohol use and use of steroids, the dose by subgroup interactions were not estimable.

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, and age as explanatory variables.

2) Deaths, Dropouts Due to AEs, and Other Serious AEs (Table 28)

- There were 5 SAEs (25 mg=3; 50 mg=1; 100 mg=1), two of which resulted in death and three in hospitalizations. Un 3 of these five patients, the SAEs were also severe.
- All events were due to worsening and progression of the underlying condition.
- Both deaths were assessed as not related to test med.
- Two of the other 3 SAEs were assessed as unlikely related; the other as not related to test med.

3) Severe AEs

- As summarized below, 6 patients (2%) experienced one or more AEs with an intensity rated as severe.

Pt. ID/(DOLA•Mesyl dose)	Severe AE
0173-0002 (25 mg)	M.I.
0176-0007 (25 mg)	DIC, Hepato-renal failure, intestinal perforation, septic shock
0158-0018 (100 mg)	Back pain, flushing, leg pain, ↑ sweating,
0169-0003 (100 mg)	Allergic Reaction
0394-0003 (100 mg)	Respiratory acidosis, pleural effusion, wheezing
0152-0001 (200 mg)	Allergic Reaction

TABLE 28
Study MCPR0043 (Report K-95-0009-CDS)

Serious AEs

Pt. ID/ Age/Gender	Underlying Condition/ Chemotherapy	AE	SEV	Onset (h)	DUR (h)	Outcome/Relationship to Test Med.
			25 mg (n=3)			
0173-002 63 M	Undifferentiated non-small cell lung cancer. CARBOPL 540 mg i.v. Previous MI, left femoro-popliteal arterial by-pass, mild stroke, COPD, obstructive pneumonia, dyspnea.	MI	SEV	792	0.6	• Death (Pt. Hx of coronary artery Dz) • Not Related
0176-0007 83 M	Adenocarcinoma of the colon, with metastasis to the liver and lung CARBOPL 550 mg i.v.	Hepato-renal failure, DIC, shock, sepsis, advanced adenocarcinoma complications, intestinal perforation	All SEV	192		• Death (Progressive malignancy + DIC) • Not Related
0151-0009 64 M	Papillary adenocarcinoma of unknown primary, with metastasis CARBOPL 600 mg ETOP 150 mg	Dehydration, Intractable N&V	MOD	48	96	• Hospitalization (Resolved with no sequelae) • Unlikely
			50 mg (n=1)			
0159-0023 56 F	Mesothelioma of the lung + malignant pleural effusion CISPL 80 mg ETOP 160 mg	Increased drainage (Pleural effusion)	MOD	14	480	• Hospitalization (Resolved with sequelae) • Not Related
			100 mg (n=1)			
[illegible]	Non-small cell lung cancer + metastasis CISPL 40 mg ETOP 240 mg	Respiratory acidosis pleural effusion, wheezing	SEV	9		• Hospitalization (Did not resolve; F/U deemed unnecessary) • Unlikely

[illegible]=Severity (SEVERE); DUR=Duration of AE; RELAT=Relationship; CARBOPL=Carboplatin; ETOP=Etoposide; MOD=Moderate; DIC=Disseminated [illegible] coagulopathy.

- None of these patients experienced severe AEs assessed as Tx-related by the investigator.

- The vast majority of AEs were mild to moderate in intensity.

4) Overall Rate of AE Incidence (Table 29)

In this trial, asymptomatic, treatment-emergent EKG interval changes were coded as AEs for signaling and tracking purposes. In the presentations given in this section, and in all tables and listings, treatment-emergent events are dichotomized into AEs and EKG interval changes.

- As displayed in Table 29, the overall rates of AEs, by dose, were 53.9%, 47.5%, 54.9% and 60%, for the 25, 50, 100 and 200 mg dose groups, respectively. There was no statistically significant trend with dose in the overall incidence of AEs.

- There was no statistically significant trend with dose in the incidence of headache and sinus bradycardia, the most frequently reported individual AEs (identified as shadowed rows in Table 29).

- The most frequently reported AEs by System Organ Class were those related to the heart rate and rhythm, the central and peripheral nervous system, and the gastrointestinal system. There was no statistically significant trend with dose in the incidence of AEs related to any of these three or any other System Organ class.

- By dose, the overall rates of treatment-emergent EKG interval changes were 25/76 (32.9%), 26/80 (32.5%), 17/71 (23.9%) and 41/80 (51.3%) for 25 mg, 50 mg, 100 mg and 200 mg, respectively. There was no statistically significant trend with dose in the overall incidence of treatment-emergent EKG interval changes (p=0.0783), although the incidence with the 200 mg dose was 18.4% higher than that with the 25 mg dose and 27.4% higher than with the 100 mg dose.

?which

?wt

- By dose, the frequency (%) of heart rate and rhythm changes were: 25/76 (32.9%), 26/80 (32.5%), 17/71 (23.9%) and 41/80 (51.3%), for 25, 50, 100 and 200 mg, respectively. There was no statistically significant trend with dose in the frequency of heart rate and rhythm changes (p=0.0783), although the incidence with the 200 mg dose was **18.4%** higher than the 25 mg dose and **27.4%** higher than with the 100 mg dose.

- The frequency (%) of the most frequent treatment-emergent EKG interval changes, per dose, is given in the lower panel of Table 29. These showed a p-value of **0.0029** for a linear trend with dose for **QT interval prolongation** (QT_c ≥440):

see p 65

25 mg	50 mg	100 mg	200 mg	Total
14/76	16/80	14/71	34/80	78/307
(18.4%)	(20.0%)	(19.7%)	(42.5%)	(25.4%)

Note that the 200 mg dose was accompanied by 22.8% higher incidence of QT_c interval prolongation than the 100 mg dose.

but the difference for "EKG abnormal specific" (IVCD)[18] did not show a statistically significant trend (p=N.S.)

25 mg	50 mg	100 mg	200 mg	Total
12/76	14/80	2/71	11/80	39/307
(15.8%)	(17.5%)	(2.8%)	(13.8%)	(12.7%)

1° AV Bl
IVCD
& QT
prolong

APPEARS THIS WAY
ON ORIGINAL

[18] "EKG abnormal specific" is the coded term that includes the number of patients with intraventricular conduction defect [IVCD; treatment-emergent increases in QRS [illegible] diagnosed as complete bundle branch block (complete BBB)].

TABLE 29
Study MCPR0043 (Report K-95-009-CDS)

List of AEs and EKG Interval Changes

System Open Class and Included Term p value[a]	DOLA®Mesyl Dose (mg)				Total (n=307)
	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)	
I. Frequency (Percent) of All Adverse Events					
Overall Rate (p=0.3109)	41 (53.9)	38 (47.5)	39 (54.9)	48 (60.0)	166 (54.1)
Heart Rate & Rhythm (p=0.5039)	21 (27.6)	16 (20.0)	17 (23.9)	25 (31.3)	79 (25.7)
Sinus Bradycardia (p=0.5017)	9 (11.8)	3 (3.8)	4 (5.6)	5 (6.3)	21 (6.8)
Premature Atrial Contractions (p=0.1237)	1 (1.3)	3 (3.8)	4 (5.6)	5 (6.3)	13 (4.2)
Sinus Tachycardia (p=0.5022)	5 (6.6)	2 (2.5)	2 (2.8)	3 (3.8)	12 (3.9)
ST-T Change or Abnormality (p=0.2241)	1 (1.3)	3 (3.8)	3 (4.2)	4 (5.0)	11 (3.6)
T Wave Change or Abnormality	0	1 (1.3)	3 (4.2)	5 (6.3)	9 (2.9)
Premature Ventricular Contraction (p=0.9912)	2 (2.6)	2 (2.5)	2 (2.8)	2 (2.5)	8 (2.6)
Arrhythmia, Sinus (p=0.9938)	1 (1.3)	1 (1.3)	1 (1.4)	1 (1.3)	4 (1.3)
EKG Abnormal Specific	1 (1.3)	1 (1.3)	0	2 (2.5)	4 (1.3)
Pulse Irregularity	1 (1.3)	0	0	0	1 (0.3)
Central and Peripheral Nervous System (p=0.6848)	15 (19.7)	14 (17.5)	15 (21.1)	17 (21.3)	61 (19.9)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Gastro-Intestinal System (p=0.4158)	7 (9.2)	4 (5.0)	5 (7.0)	10 (12.5)	26 (8.5)
Body as a Whole (p=0.9734)	1 (1.3)	6 (7.5)	7 (9.9)	1 (1.3)	15 (4.9)
Chest Pain	0	1 (1.3)	0	0	1 (0.3)
Chest Pressure	0	1 (1.3)	0	0	1 (0.3)
Resistance Mechanism (p=0.3742)	3 (3.9)	4 (5.0)	5 (7.0)	1 (1.3)	13 (4.2)
Respiratory System (p=0.7654)	4 (5.3)	2 (2.5)	1 (1.4)	4 (5.0)	11 (3.6)
Cardiovascular, General (p=0.2755)	1 (1.3)	1 (1.3)	2 (2.8)	3 (3.8)	7 (2.3)
Hypertension	1 (1.3)	0	1 (1.4)	0	2 (0.7)
Ankle Edema	0	0	0	1 (1.3)	1 (0.3)
Feet Edema	0	0	0	1 (1.3)	1 (0.3)
Edema Face	0	0	1 (1.4)	0	1 (0.3)
Hypotension	0	0	1 (1.4)	0	1 (0.3)
Hypotension Orthostatic	0	1 (1.3)	0	0	1 (0.3)

25 50 100 200

Hypotension Orthostatic Symptomatic	0	0	0	1 (1.3)	1 (0.3)
Urinary System (p=0.3663)	3 (3.9)	1 (1.3)	1 (1.4)	1 (1.3)	6 (2.0)
Application Site	2 (2.6)	0	1 (1.4)	2 (2.5)	5 (1.6)
Metabolic and Nutritional	2 (2.6)	2 (2.5)	1 (1.4)	0	5 (1.6)
Musculo-skeletal System	0	1 (1.3)	3 (4.2)	1 (1.3)	5 (1.6)
Psychiatric	0	1 (1.3)	1 (1.4)	3 (3.8)	5 (1.6)
Autonomic Nervous System	0	1 (1.3)	2 (2.8)	0	3 (1.0)
Skin and Appendages	0	2 (2.5)	1 (1.4)	0	3 (1.0)
Hearing and Vestibular	1 (1.3)	1 (1.3)	0	0	2 (0.7)
Liver and Biliary System	1 (1.3)	0	1 (1.4)	0	2 (0.7)
SGOT Increased	1 (1.3)	0	1 (1.4)	0	2 (0.7)
Hepatic Failure	1 (1.3)	0	0	0	1 (0.3)
Myo-, Endo-, Pericardial and Valve	1 (1.3)	0	0	1 (1.3)	2 (0.7)
Myocardial Infarction	1 (1.3)	0	0	0	1 (0.3)
Platelet, Bleeding and Clotting	1 (1.3)	1 (1.3)	0	0	2 (0.7)
II. Frequency (Percent) of All Treatment-Emergent EKG Interval Changes					
Overall Rate (p=0.0783)	25 (32.9)	25 (32.5)	17 (23.9)	41 (51.3)	109 (35.5)
Heart Rate and Rhythm (p=0.0783)	25 (32.9)	26 (32.5)	17 (23.9)	41 (51.3)	109 (35.5)
QT Interval Prolongation ($QT_c \geq 440$) (p=0.0029)	14 (18.4)	16 (20.0)	14 (19.7)	34 (42.5)	78 (25.4)
EKG Abnormal Specific (QRS≥100) (p=0.1128)	12 (15.8)	14 (17.5)	2 (2.8)	11 (13.8)	39 (12.7)
AV Block First Degree (PR≥220) (p=0.1563)	1 (1.3)	2 (2.5)	4 (5.6)	4 (5.0)	11 (3.6)

a) This is the 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.

- "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 1/76 (1.3%) patients in the 25 mg dose group, 2/80 (2.5%) in the 50 mg dose group, 4/80 (5.0%) in the 100 mg dose group, and 4/80 (5.0%) in the 200 mg dose group.
  - There was no statistically significant trend with dose in the incidence of AV block first degree.

- Of the 78 instances of QT interval prolongation, 77 were deemed treatment-related by the investigator.

- Of the 39 instances of IVCD, 38 were assessed as treatment-related by the investigator.

- All instances of AV block first degree were assessed as treatment-related by the investigator.

- 15 of the 21 instances of sinus tachycardia were assessed as treatment-related by the investigator.

5) Treatment Emergent EKG Interval Changes by Severity and Dose (Table 30)

As shown in this Table, none of these EKG changes were assessed as severe. Some (n=5) were assessed as moderate but the majority of treatment-emergent EKG interval changes were mild in intensity.

6) AEs of Potential Concern (Table 31)

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 of the AE, and possible relationship to test medication. All in all, these data 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.

Note that the one case of orthostatic hypotension was considered probably related to the 200 mg DOLA•Mesyl.

Table 30
Study MCPR0043 (Report K-95-0009-CDS)

Classification of Treatment-Emergent EKG Interval Changes
by Severity and Dose

		DOLA•Mesyl DOSE (mg)			
	Severity	25 (n=76)	50 (n=80)	100 (n=71)	200 (n=80)
Any Treatment-Emergent EKG Interval Change	MILD	24 (31.6%)	26 (32.5%)	17 (23.9%)	39 (48.8%)
	MOD	1 (1.3%)	0 (0.0%)	0 (0.0%)	2 (2.5%)
	SEV	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
QT Interval Prolongation (QT_c ≥440 msec)	MILD	13 (17.1%)	16 (20.0%)	14 (19.7%)	39 (42.5%)
	MOD	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	SEV	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
IVCD (QRS ≥100 msec)	MILD	11 (14.5%)	14 (17.5%)	2 (2.8%)	10 (12.5%)
	MOD	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	SEV	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
AV Block First Degree (PR ≥220 msec)	MILD	0 (0.0%)	2 (2.5%)	4 (5.6%)	3 (3.8%)
	MOD	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)
	SEV	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

TABLE 31
Study MCPR0043 (Report K-95-009-CDS)

List of AEs of Potential Concern

Chest Pain [n=2]	Edema [n=3]	HYPO (↓) or HYPER (↑) Tension [n=5]	Abnormal LFTs [n=2]
• MCST0158-0013 (50 mg) - At least 24-h after test drug adm. - MILD - Unlikely Related • MCST0176-0005 (50 mg) - At least 24-h after test drug adm. - MILD - Unlikely related	• MCST0165-009 (100 mg) - MILD - Attributed to hydration • MCST0165-0010 (200 mg) - MILD - Attributed to hydration • MCST0170-0001 (200 mg) - MILD - Attributed to hydration	• MCST0188-0001 (↓) (100 mg) - MILD - Unlikely related • MCST0160-0001 (↓) (50 mg) - MILD - **Possibly related** • MCST0156-0003 (ORTHO ↓) (200 mg) - MILD - **Probably related** • MCST0158-0012 (↑) (25 mg) - MOD - Unlikely related • MCST0165-0009 (↑) (25 mg) - MOD - Unlikely related	• MCST0176-0007 (25 mg) - DIC - Developed multi-system failure, including hepatic failure 8 days following test drug adm. - Death - SERIOUS - MILD → SEVERE - NOT RELATED MCST0394-0003 (100 mg) - Also had respiratory acidosis pleural effusion, wheezing - SERIOUS - MILD → SEVERE - Unlikely Related[a]

a) The elevations in serum enzymes were considered POSS. related to test med.

7) Subgroup Summaries of AEs

- 29 patients received at least one additional full dose of a 5-HT$_3$ receptor antagonist (ondansetron or granisetron) during the 24-h treatment period.

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- For 24 of these patients, ondansetron was administered as rescue medication or early premedication for the next day's chemotherapy.

- For 5 remaining patients, granisetron was administered as rescue medication or early premedication for the next day's chemotherapy.

- Of these 29 patients, the initial dolasetron mesylate antiemetic treatment was 25 mg for 10 patients, 50 mg for 3 patients, 100 mg for 10 patients, and 200 mg for 6 patients.

- In this sub-population, the overall rates of AEs were 4/10 (40%), 1/3 (33.3%), 4/10 (40%) and 4/6 (66.7%) for 25 mg, 50 mg, 100 mg and 200 mg dose groups, respectively.

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

  - The heart rate and rhythm adverse events occurred at a lower rate for this subgroup than for the overall population, but central and peripheral nervous system adverse events occurred at a slightly higher rate in this sub-population. This was primarily due to higher incidences of **headache** in this subgroup population.

- Of these 29 patients, one [MCST0151-0009 (25 mg)] experienced SERIOUS dehydration and intractable N&V (see Table 28) 24-h after receiving the last 3 doses of OND as rescue med. Another pt. [MCST0158-0018 (100 mg)] experienced SEVERE back pain et al., 0.8h prior to rescue with OND.

- Although there were some small numerical 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. For example, the overall incidence of treatment-emergent EKG interval changes were 10/29 (34.5%) in this subgroup. This is comparable to the incidence in all patients 109/307 (35.5%).

8) Clinical Laboratory Evaluation

- **Except for BIL, noted below, there were no laboratory variables for which a significant linear trend was observed.**

- **Total BIL showed a statistically significant negative trend with dose in change from baseline (p=0.0002). Smaller mean decreases from baseline were seen for the higher doses:**

	DOLA•Mesyl (mg)				
	25	50	100	200	p-value
Serum Total BIL in micmol/L (change from baseline)	1.607	1.421	0.066	0.337	0.0002

- One chemistry laboratory test (glucose) had 25 or more patients shift from within or below the normal range at Pre-Tx to above the ULNR at Post-Tex:

	DOLA•Mesyl (mg)			
	25	50	100	200
Serum Glucose	13/46 (28.3%)	9/45 (20.0%)	16/49 (32.7%)	18/51 35.3%)

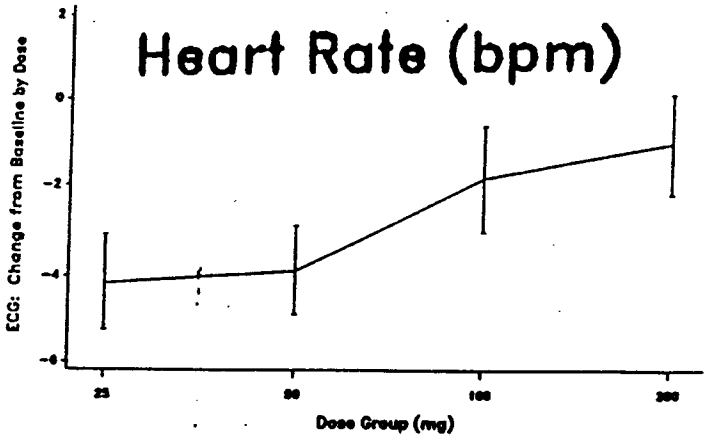
But the shift does not appear to be clinically meaningful.

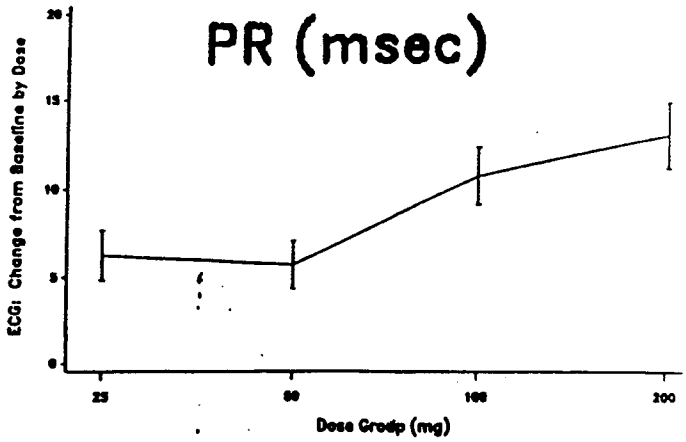
- LFT elevations of concern occurred in 2 patients (Table 31).
- Treatment-related ↑s in SGOT to ≥ the ULN at Post-Tx occurred in 1 pt. in the 25 mg dose group and 1 in the 50 mg dose group.
- A treatment-related ↑ in SGPT to ≥ the ULN was seen in 1 pt. in the 200 mg group.
- Other changes in serum chemistry are not considered clinically important.

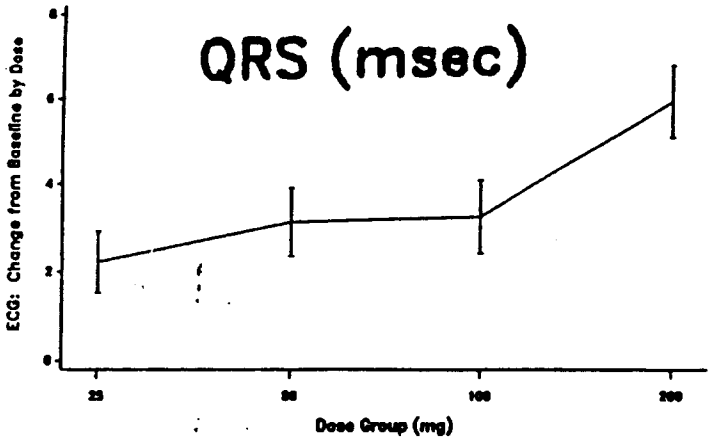
9) Descriptive Statistics for EKG Assessments

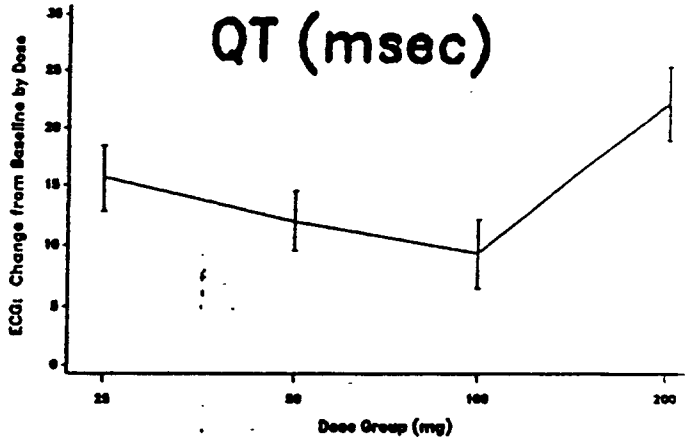
Descriptive statistics for the six EKG measures, at Pre-Tx, hour 1-2 and hour 24-36 by dose, are given in Table 32. The associated changes from BL (median and mean) are also included in this Table. The p-values for the test for linear trend in change from BL with dose are provided in the lower panel of this Table. A graphic representation of the change from BL by dose 1-2h post dose is given in Fig. 10, that for 24-36h post dose is depicted in Fig. 11. The average changes by time for those EKG parameters that showed a statistically significant trend in change from BL (Qr, QRS and QTc) are shown in Fig. 12.

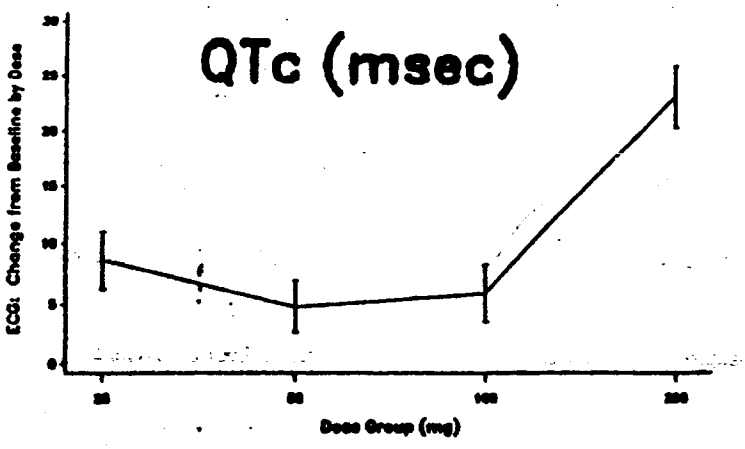
The frequency (%) of Tx-emergent changes at Acute (hour 1-2) and Exit (hour 24-36) are given in Table 33.











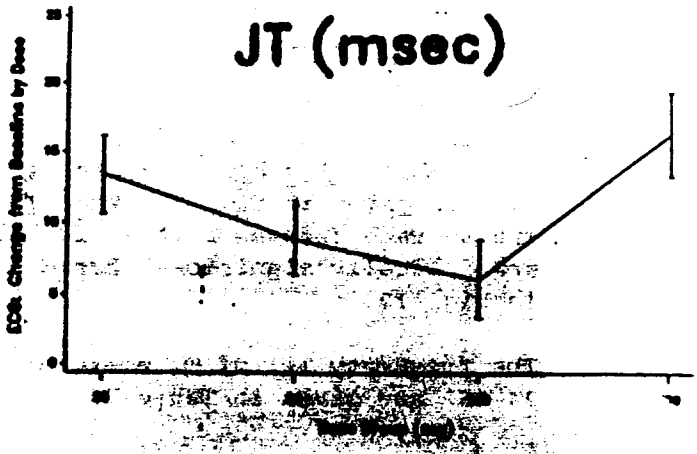
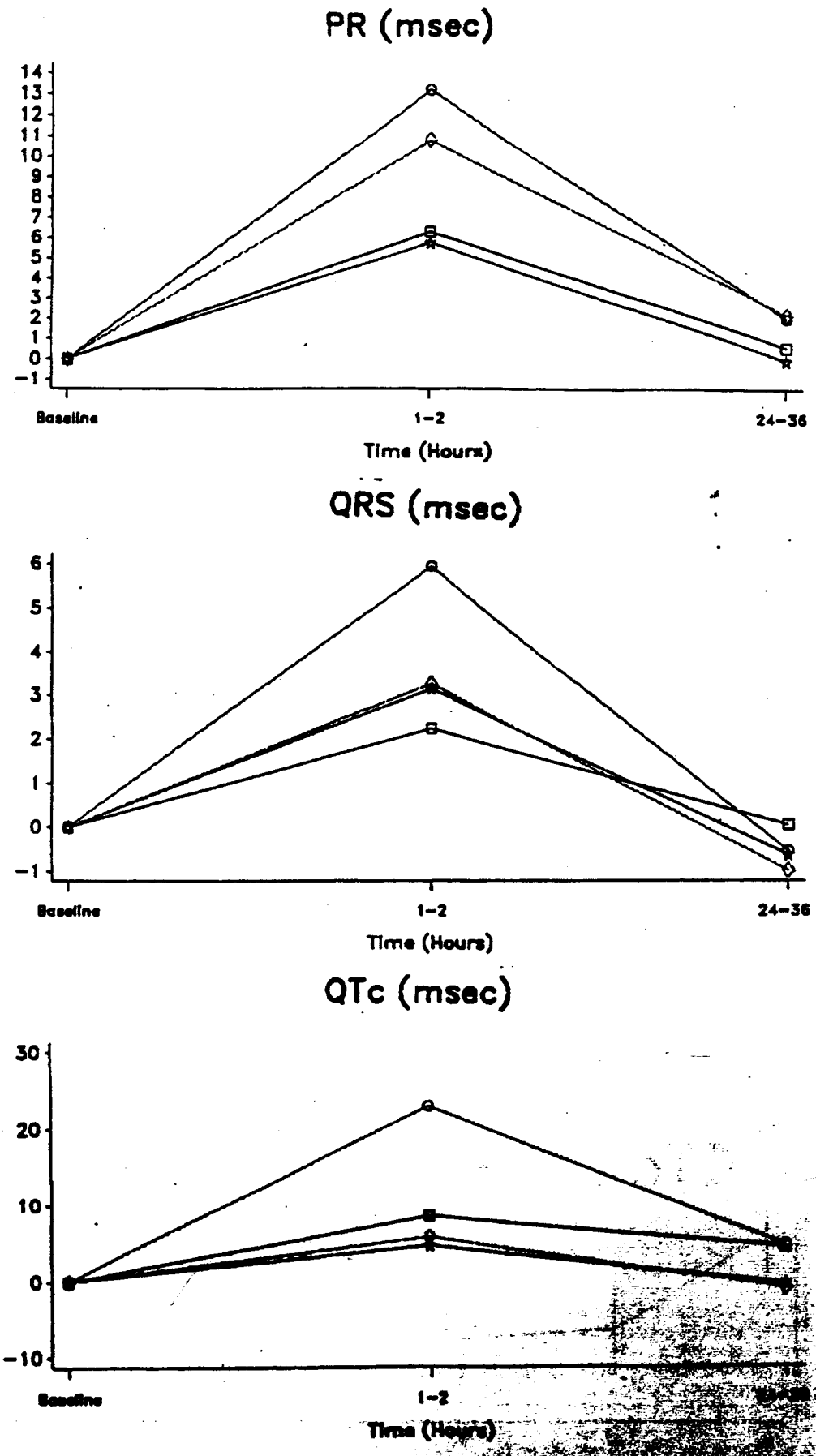
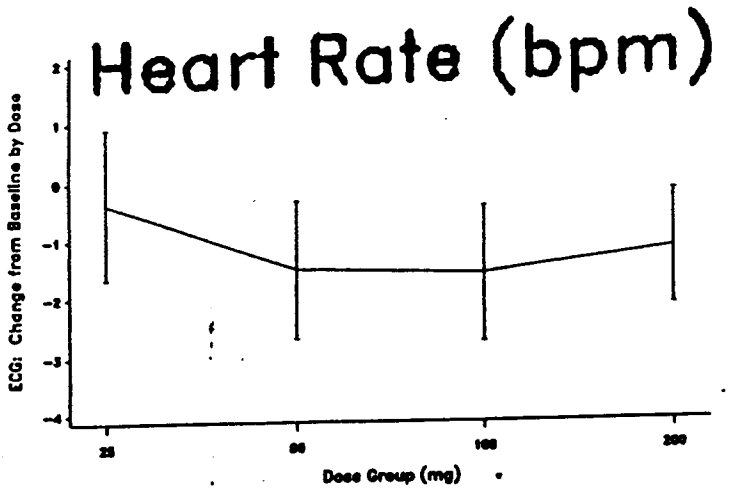


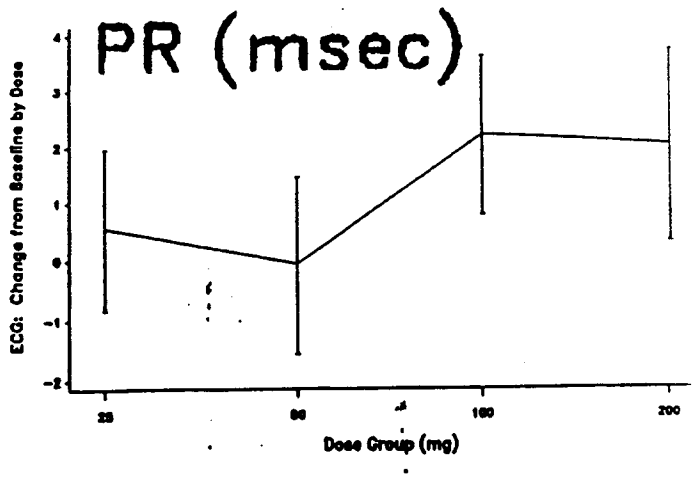
Fig. 10: Study MCPR0043 (Report K-95-009-CDS)
EKG: Change from BL by Dose 1-2h POSTDOSE

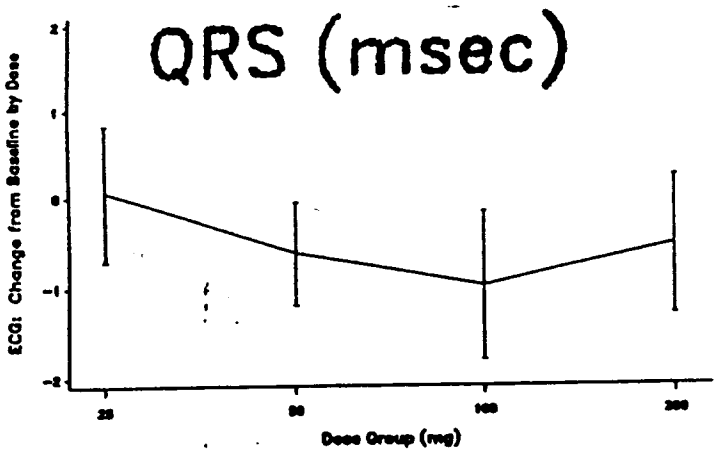


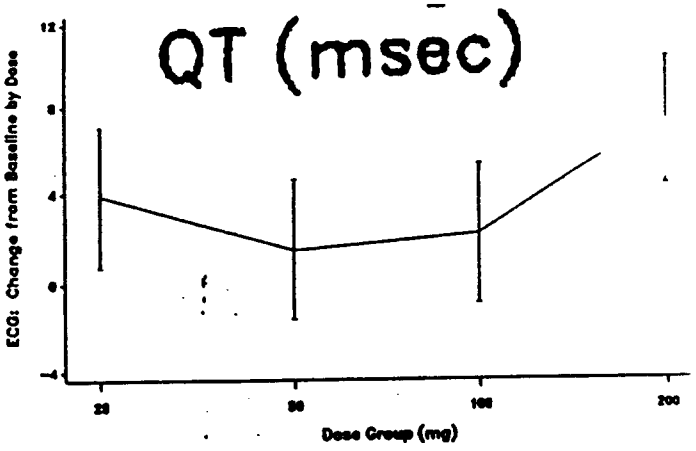
What was BL ?

Fig. 12 - Study MCPR0043: EKG changes from baseline as a function of time (All Patients)









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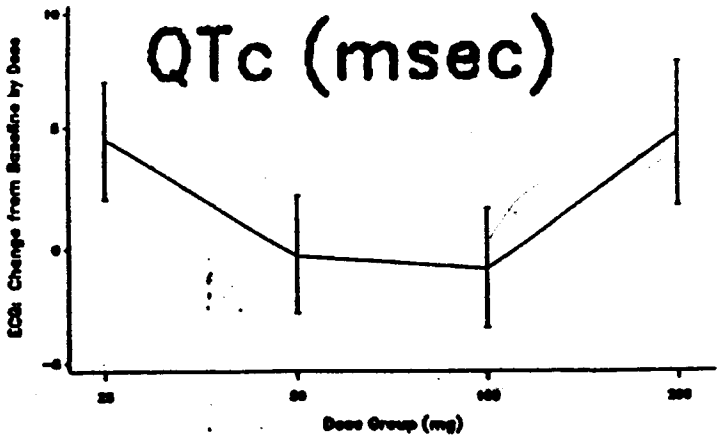

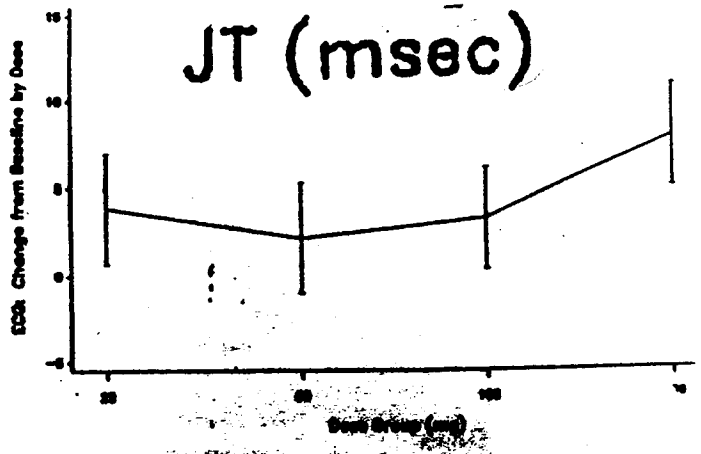

Fig. 11: Study MCPR0043 (Report K-95-009-CDS)
EKG: Change from BL by Dose 24-36h POSTDOSE