iii) Time to First Emetic Episode or Escape Medication (Table 40)

- Tabulated in this Table are the estimated proportions of Complete Responders at 4h intervals, taken from a Kaplan-Meier survival curves of the estimated probability of no emetic episodes or escape medication over the 24-h Tx period for each Tx.

- The median times to first emetic episode or escape medication, whichever occurred first, were 21.2, 21.5 and 19.8h for the OND, 1.8 and 2.4 mg/Kg DOLA•Mesyl, respectively. There were no statistically significant differences among the three Txs, and the 95% confidence intervals for hazard ratios estimated from Cox's proportional hazards model of time to first emetic episode or escape medication (see Footnote to Table 40) were consistent with equivalence.

TABLE 40
Study -031

Complete Response by Hour and Treatment

Hour	OND [n=206]	DOLA•Mesyl Dose (mg/Kg) 1.8 [n=198]	DOLA•Mesyl Dose (mg/Kg) 2.4 [n=205]	Total DOLA•Mesyl [n=403]
4	93.7%	92.9%	94.1%	93.5%
8	78.2%	77.8%	79.0%	78.4%
12	73.8%	72.2%	71.7%	72.0%
18	61.2%	60.1%	55.6%	57.8%
24	42.7%	44.4%	40.0%	42.2%

Depicted is the Proportion (%) of Complete Responders Through a Given Hour by Treatment Group.

95% CIs for Risk Ratios and Corresponding p values[a]:

1.8 mg/Kg DOLA•Mesyl vs OND (0.801, 1.374) p=N.S.

2.4 mg/Kg DOLA•Mesyl vs OND (0.873, 1.474) p=N.S.

2.4 mg/Kg DOLA•Mesyl vs 1.8 mg/Kg DOLA•Mesyl (0.830, 1.409) p=N.S.

a) Confidence Intervals and p values are calculated from Cox's Proportional Hazards Model stratified by investigator and cisplatin dose category.

iv) Subgroup Analysis (Table 41)

- Results of the subgroup analyses of CR are displayed in this Table and are further summarized below.

Statistically Significant Predictor of CR

NO	YES
- Age[a]	- Non-use of narcotic analgesics (p-0.0051)[b]
- Previous Hx of Chemotherapy	- Male gender (p<0.0001)[c]
- Use of Benzodiazepines	- Heavy alcohol use (p=0.0009)[d]
- Test drug dosing[e]	

a) Although age was not a statistically significant predictor of CR (p=0.0755), older patients showed more of a tendency to be complete responders than younger patients (see Table 41).
b) Patients receiving narcotic analgesics were less likely to be complete responders (Table 41).
c) Male patients had a higher incidence of CR than did female patients (Table 41).
d) Hx of heavy alcohol use was associated with a higher CR (Table 41).
e) As only 41 of 609 patients in this study received test med. as a multiple dose regimen, there is little power for detecting main effects or interactions.

- In adjusting for all significant predictors of CR, history of heavy alcohol use was not included in the model, due to the potential confounding with gender. When adjusting for gender, use of narcotic analgesics, treatment, investigator and stratum in the primary logistic regression model, the three Tx groups were still equivalent.

  - The 95% confidence interval for the odds ratio of DOLA•Mesyl 2.4 mg/Kg vs OND is (0.515, 1.223); for the odds ratio of DOLA•Mesyl 1.8 mg/Kg vs OND the 95% CI is (0.597, 1.428); and the 95% CI for the odds ratio of DOLA•Mesyl 2.4 mg/Kg vs DOLA•Mesyl 1.8 mg/Kg is (0.558, 1.325).

TABLE 41
Study -031

Complete Response by Subgroups

Subgroup		OND [n=206]	DOLA•Mesyl Dose (mg/Kg) 1.8 [n=198]	DOLA•Mesyl Dose (mg/Kg) 2.4 [n=205]	p values[a]
Age	<65 y (n=369)	51/124 (41.1%)	52/117 (44.4%)	47/128 (36.7%)	p(int)=N.S. p(m)=N.S.
	≥65 y (n=240)	37/82 (45.1%)	36/81 (44.4%)	35/77 (45.5%)	
Previous History of Chemotherapy	No (n=559)	80/190 (42.1%)	84/183 (45.9%)	73/186 (39.2%)	p(int)=N.S. p(m)=N.S.
	Yes (n=50)	8/16 (50.0%)	4/15 (26.7%)	9/19 (47.4%)	
Use of Benzodiazepines	No (n=548)	76/178 (42.7%)	80/182 (44.0%)	79/188 (42.0%)	p(int)=N.S. p(m)=N.S.
	Yes (n=61)	12/28 (42.9%)	8/16 (50.0%)	3/17 (17.6%)	
Use of Narcotic Analgesics	No (n=396)	60/131 (45.8%)	64/134 (47.8%)	57/131 (43.5%)	p(int)=N.S. p(m)=N.S.
	Yes (n=213)	28/75 (37.3%)	24/64 (37.5%)	25/74 (33.8%)	
Gender	Male (n=377)	65/121 (53.7%)	73/127 (57.5%)	63/129 (48.8%)	p(int)=N.S. p(m)=<0.0001
	Female (n=232)	23/85 (27.1%)	15/71 (21.1%)	19/78 (25.0%)	
History of Heavy Alcohol Use	No (n=510)	66/167 (39.5%)	65/163 (39.9%)	67/180 (37.2%)	p(int)=N.S. p(m)=0.0009
	Yes (n=99)	22/39 (56.4%)	23/35 (65.7%)	15/25 (60.0%)	
Test Drug Dosing	Multiple (n=41)	5/12 (41.7%)	7/12 (58.3%)	7/17 (41.2%)	p(int)=N.S. p(m)=N.S.
	Single (n=568)	83/194 (42.8%)	81/186 (43.5%)	75/188 (39.9%)	

Depicted is the Number of Complete Responders/Number of Patients in Treatment by Subgroup Category Cell (Percent)

95% Confidence Intervals for Odds Ratios and corresponding p values[b] adjusted for Gender and Use of Narcotic Analgesics Main Effects:

1.8 mg/Kg DOLA•Mesyl vs OND, (0.597, 1.428) p=N.S.

2.4 mg/Kg DOLA•Mesyl vs OND, (0.515, 1.223) p=N.S.

2.4 mg/Kg DOLA•Mesyl vs 1.8 mg/Kg DOLA•Mesyl, (0.558, 1.325) p=N.S.

a) p-values are calculated from a logistic regression model with treatment, investigator and stratum as explanatory variables in the model. p(int) is the p value for testing the subgroup by treatment interaction; p(m) is the p value for testing the subgroup as a main effect.

b) p values and confidence intervals from a logistic regression model predicting complete response with treatment, investigator, stratum and subgroup main effect included in the model.

d. Safety Results

1) Extent of Exposure

In study -031, 609 patients were treated with single i.v. doses of test med., with the following distribution:

OND	DOLA•Mesyl (mg/Kg)	
	1.8	2.4
[n=206]	[n=198]	[n=205]

2) Deaths, Dropouts Due to AEs and Other Serious AEs (Tables 42 and 43)

- In these Tables succinct information is given on the six deaths (DOLA•Mesyl, 2.4 mg/Kg n=4; 1.8 mg/Kg n=1 and OND 32 mg, n=1) and the serious AEs (2.4 mg/Kg, n-4; 1.8 mg/Kg, n=2; OND 32 mg, n=2) reported in this study.

- As shown in Table 42, all 6 deaths - which occurred at least 4 days after test drug administration - were attributed to the patients' cancer by the investigator. The reviewer agrees with this assessment.

TABLE 42
Study -031

Deaths: Succinct Clinical Narratives and Relation to Test Medication

DOLA•Mesyl 2.4 mg/Kg, n=4		
0064-0110 43y-old F SEPSIS/DEATH	Had adenocarcinoma of the L lung, pleural effusion. Died as a result of a septic episode 8 days following i.v. adm. of test drug	Not related
0081-0203 66y-old M MI/DEATH	Had Hx of MI with VF in 1988, left lower lobe pneumonia, cardiomegaly documented a week prior to his death, occurring 21 days following i.v. adm. of test drug.	Not related
0130-0102 66y-old M PULMONARY CARCINOMA/DEATH	Had small cell carcinoma of the lung + extensive metastases to the brain and liver. Died 17 days following i.v. adm. of test drug.	Not related
0145-0202 55y-old F PULMONARY CARCINOMA/DEATH	Had small cell carcinoma of the lung with metastasis to lymph nodes + adrenals. Died 19 days following i.v. adm. of test drug.	Not Related
DOLA•Mesyl 1.8 mg/Kg, n=1		
0150-0202 57y-old M CARDIAC ARREST/ DEATH	Had metastatic lung adenocarcinoma with pericardial infusion. Death occurred 4 days following adm. of a single i.v. dose of test med. At the completion of the 24-h study period, the patient's vital signs were stable and the post-Tx P.E. was unchanged from BL. Occaspremature ventricular complexes were documented on the 24-h post-Tx EKG, not seen on the patient's baseline EKG.	Not related

OND 32 mg, n=1		
0142-0107 63y-old M LUNG CANCER/ DEATH	Had bronchogenic lung cancer + COPD + multiple metastasis including liver + adrenals. Death occurred 12 days following adm. of single i.v. dose of OND 32 mg.	Not related

- The reviewer also agrees with the investigator's assessment of causality for the eight serious AEs reported in this trial (Table 43). These serious events were due to either the underlying clinical condition or the chemotherapeutic regimen being administered.

TABLE 43
Study -031

Serious AEs: Succinct Clinical Narratives and Relation to Test Medication

DOLA®Mesyl 24 mg/Kg, n=4		
079-0205 74y-old M BRONCHOSPASM	Had squamous cell carcinoma of the lung and was at immediate risk of death as a result of a type 1 hypersensitivity Rx manifested by difficulty in breathing, leading to bronchospasm and most likely related to the patient's VP-16 infusion.	Unrelated
147-0204 62y-old M SUPRAVENTRICULAR TACHYCARDIA	Pt. with non-small cell lung cancer and Hx of prior chemo-therapy, superior vena cava syndrome with tumor compressing the superior vena cava. SVT with a rapid ventricular response, + respiratory failure occurred 54.5h following adm. of test med. The event most likely due to his superior vena cava syndrome and 5-FU, lasted 3.5h and the patient returned to pre-event status.	Unlikely related
079-0202 68y-old M SYNCOPE	Had small cell lung cancer and Hx of MI, hypertension, CVA with R-sided weakness, bilateral femoral and carotid bruritsIII/IV, etc. Experienced a syncope episode (passed out for 2-3 seconds) 3 days after receiving test med. Required hospitalization, her condition improved and was eventually discharged to home. Events were assessed as related to patient's cancer and recent chemotherapy Tx.	Not related
064-0101 64y-old F MENTAL STATUS CHANGES AND HALLUCINATIONS	Had malignant pancreatic gastroinoma with metastasis to the liver. Five days following adm. of a single 1.0 dose of test med. The patient was rehospitalized as a result of confabulation, agitation and hallucinations. MRI was consistent with metabolic encephalopathy which lasted 4 days when she returned to the pre-event mental status and was discharged from the hospital. Events were assessed as due to questionable ethanol abuse and/or metabolic encephalopathy.	Not related

DOLA•Mesyl 1.8 mg/Kg, n=2		
081-0205 71y-old M **PNEUMONIA**	Had small cell lung cancer + Hx of pneumonia.	Unlikely related
062-0105 77y-old F **RESPIRATORY DISTRESS**	Had poorly differentiated adenocarcinoma of the R lung + metastasis. Had Hx of radiation Tx to the sternum dyspnea and chest pain. She experienced R hemothorax, difficulty breathing and R-sided chest pain + PVCs, all occurring ca. 24h following adm. of a single i.v. dose of test med. Event was attributed to the pt's lung cancer + collapsed R lung.	Not related
OND, 32 mg, n=2		
064-0102 65y-old M **BRONCHOSPASM**	Pt. with adenocarcinoma of the lung with bilateral pulmonary metastasis + asthma x 20 years. He was at immediate risk of death and had his hospitalization prolonged as a result of acute bronchospasm which quickly progressed to cyanosis and marked hypoxia, etc. The event, which occurred 55 min. following a single i.v. dose of OND and 15 min. following the initiation of chemotherapy was thought due to the pt's. bilateral lung cancer.	
070-021 54y-old F **DEHYDRATION**	Pt. with small cell lung cancer had her hospitalization prolonged 1 day as a result of dehydration thought to be due to vomiting induced by cisplatin adm.	

3) AEs

- There were no statistically significant treatment differences in the overall incidence of AEs and of the specific terms one diarrhea showed statistically significant difference among the Tx groups. There were statistically significant Tx differences in the overall incidence of Tx-emergent EKG interval changes ($p=0.0001$). The most frequently reported individual change in this category was QT interval prolonged but there was no statistically significant difference among the treatment groups for this category. Both dose levels of DOLA•Mesyl had x 4 times incidence of EKG abnormalities ($p<0.001$).

I. Frequency of All AEs				
		DOLA•Mesyl (mg/Kg)		
	OND [n=206]	1.8 [n=198]	2.4 [n=205]	Total DOLA•Mesyl
Overall Rate (p=N.S.)[a]	63.6%	67.7%	73.2%	70.5%
Diarrhea (p=0.0197)	5.8%	13.6%	13.2%	13.4%
II. Treatment-Emergent EKG Interval Changes				
Overall Rate (p=0.0001)	27 2%	42.4%	46.8%	44.7%
Heart Rate & Rhythm (p=0.0001)	27.2%	42.4%	46.8%	44.7%
QT Interval Prolongation QTc≥440) (p=N.S.)	22.3%	28.3%	30.2%	29.3%
EKG Abnormal Specific(QRS≥100) (p<0.0001)	4.4%	19.7%	21.0%	20.3%
AV Block First Degree(PR≥220) (p=N.S.)	1.9%	2.5%	1.5%	2.0%

a) p values for Tx differences are calculated from a logistic regression model with Tx and stratum as explanatory variables.

- As seen in Table 44, the most frequently occurring AEs were headache, diarrhea, sinus tachycardia, fever, ST-T change or abnormality and premature ventricular contraction. There were statistically significant treatment differences in the incidence of diarrhea (p=0.0197).

TABLE 44
Study -031

Frequency (Percent) of Most (Incidences ≥5% in Study (Population) Frequent AEs

Included Term[a] (p value)	OND [n=206]	DOLA•Mesyl (mg/Kg) 1.8 [n=198]	DOLA•Mesyl (mg/Kg) 2.4 [n=205]	Total DOLA•Mesyl [n=403]
Headache (p=N.S.)	18.4%	22.2%	21.5%	21.8%
Diarrhea (p=0.0197)	5.8%	13.6%	13.2%	13.4%
Sinus Tachycardia (p=N.S.)	6.3%	8.1%	10.2%	9.2%
Fever (p=N.S.)	6.8%	7.1%	6.3%	6.7%
ST-T Change or Abnormality (p=N.S.)	4.4%	4.5%	6.8%	5.7%
Premature Ventricular Contraction (p=N.S.)	3.9%	6.1%	5.4%	5.7%

- The frequency (%) of all Tx-related AEs and all Tx-related Tx emergent EKG interval changes is summarized in Table 45. Data on the intensity (severity) of EKG interval changes are also included in this Table.

  - There were statistically significant Tx differences in the overall incidence of Tx-related adverse events (p=0.0060). These differences appear to be due to higher incidences of Tx-related diarrhea, headache, and sinus tachycardia in the DOLA•Mesyl Tx groups. However, only for diarrhea were there statistically significant Tx differences (p=0.0363). Of the 126 instances of headache, 118 were considered Tx-related by the investigator. Of the 66 instances of diarrhea, 38 were considered Tx-related by the investigator. Of the 50 instances of sinus tachycardia, 32 were considered Tx-related by the investigator.

  - There were statistically significant differences in the overall rate (p=0.0001), heart rate & rhythm (p=0.0001) and EKG abnormal specific (p<0.0001) among the Tx groups (lower panel of Table 45). Of the 164 instances of QT interval prolongation, 163 were deemed Tx-related by the investigator. Of the 91 instances of EKG abnormal specific, 89 were deemed Tx-related by the investigator. All 12 instances of AV block first degree were assessed as Tx-related by the investigator.

  - The vast majority of Tx-emergent EKG interval changes were mild in intensity (see lower panel of Table 45). Overall, no patients experienced a Tx-emergent EKG interval change rated as severe in intensity, and only 6 experienced Tx-emergent EKG interval changes rated as MOD in intensity.

TABLE 45
Study -031

Tx-Related AEs, Tx-Related Tx-Emergent and Intensity of EKG Interval Changes

I. Frequency (%) of All Treatment-Related AEs				
System Organ Class and Included Term p-value	OND [n=206]	DOLA•Mesyl (mg/Kg) 1.8 [n=198]	DOLA•Mesyl (mg/Kg) 2.4 [n=205]	Total DOLA•Mesyl [n=403]
Overall Rate (p=0.0060)	38.8%	49.5%	54.1%	51.9%
Heart Rate & Rhythm (p=N.S.)	21.4%	25.8%	27.3%	26.6%
Sinus Tachycardia (p=N.S.)	3.4%	4.5%	7.8%	6.2%
ST-T Change or Abnormality (p=N.S.)	4.4%	4.5%	6.8%	5.7%
Premature Ventricular Contraction (p=N.S.)	2.9%	4.5%	4.4%	4.5%
Sinus Bradycardia (p=N.S.)	3.9%	4.5%	3.4%	4.0%
T Wave Change or Abnormality (p=N.S.)	1.0%	4.5%	3.4%	4.0%
Central & Peripheral Nervous System (p=N.S.)	18.0%	23.2%	21.0%	22.1%

Headache (p=N.S.)		16.0%	21.7%	20.5%	21.1%
Gastro-Intestinal System (p=0.0236)		4.9%	9.1%	12.7%	10.9%
Diarrhea (p=0.0363)		2.9%	6.6%	9.3%	7.9%
II. % of All Tx-Related Tx-Emergent EKG Interval Changes					
Overall Rate (p=0.0001)		26.7%	41.9%	46.3%	44.2%
Heart Rate & Rhythm (p=0.0001)		26.7%	41.9%	46.3%	44.2%
QT Interval Prolongation (QTc≥440) (p=N.W.)		21.8%	28.3%	30.2%	29.3%
EKG Abnormal Specific (QRS≥100) (p=<0.0001)		4.4%	19.2%	20.5%	19.9%
AV Block First Degree (PR≥220) (p=N.S.)		1.9%	2.5%	1.5%	2.0%
III. Intensity of EKG Interval Changes					
Any Treatment-Emergent EKG Interval Change	Mild	26.2%	41.4%	45.9%	
	MOD	1.0%	1.0%	1.0%	
QT Interval Prolongation (QT_c≥440 msec)	Mild	21.8%	27.8%	29.3%	
	MOD	0.5%	0.5%	1%0%	
EKG Abnormal Specific (QRS≥100 msec)	Mild	4.4%	18.7%	21.0%	
	MOD	0	1.0%	0	
AV Block First Degree (PR≥220 msec)	Mild	1.5%	2.5%	1.5%	
	MOD	0.5%	0	0	

4) AEs of Potential Concern

Chest Pain

There were 9 instances of chest pain or chest tightness in 7 patients during the 24-h Tx period. The events were evenly distributed among treatments (3 patients receiving DOLA•Mesyl 1.8 mg/Kg, 1 patient receiving DOLA•Mesyl 2.4 mg/Kg and 3 patients receiving OND 32 mg), and occurred from 1 to 30h after receiving study medication.

- In patient MCST0143-0206 receiving DOLA•Mesyl 2.4 mg/Kg, the event was assessed to be of cardiac origin, "angina", mild in intensity, and having unlikely relationship to test medication as the patient had a positive history of angina.

- In the remaining six patients, chest pain events were attributed to esophagitis, chemotherapy or the patient's cancer.

NOTE: The fact that the pt. had positive Hx of angina pre-drug does not seem reason enough to rule out DOLA•Mesyl as being related to this AE.

Edema

There were 12 instances of edema (either edema, peripheral edema, ankle edema, race edema, feet edema, or laryngeal edema) in 10 DOLA•Mesyl and none of the OND-Tx patients. These events occurred from patients receiving DOLA•Mesyl from 14 to 24h after receiving test medication.

- In patient MCST0143-0102 receiving DOLA•Mesyl 1.8 mg/Kg the edema was considered MOD in intensity, and assessed as possibly related to study drug.

- In patient MCST0339-0203, receiving DOLA•Mesyl 2.4 mg/Kg who experienced face and laryngeal edema, the events were considered MOD in intensity, and having unlikely relationship to study drug.

- In the remaining 8 patients, edema events were mild in intensity and attributed to i.v. hydration, hypertension, superior vena cava syndrome or the patient's cancer.

- There were 11 patients who experienced fluid overload (2 patients receiving DOLA•Mesyl 1.8 mg/Kg, 3 patients receiving DOLA•Mesyl 2.4 mg/Kg and 6 patients receiving OND); all events were attributed to i.v. hydration or the patient's cancer. Four of these events were considered MOD in intensity (2 patients receiving DOLA•Mesyl 2.4 mg/Kg and 2 patients receiving OND); the remaining seven events were mild in intensity.

Hypo- or hypertension

- 1 patient receiving DOLA•Mesyl 2.4 mg/Kg experienced hypotension.

- 12 patients experienced hypertension; 4 patients receiving DOLA•Mesyl 1.8 mg/Kg, 5 patients receiving DOLA•Mesyl 2.4 mg/Kg, and 3 patients receiving OND.

- In addition, one patient receiving OND experienced orthostatic hypotension.

- None of these events were severe in intensity, and only one (hypertension in a patient receiving DOLA•Mesyl 1.8 mg/Kg) was considered possible related to test drug.

5) Summary Results of Clinical Laboratory Evaluations

- There were no statistically significant differences in change from baseline among the 3 Tx groups for any of the clinical laboratory variables.

- 2 DOLA•Mesyl patients were reported as having hepatic function abnormal. Both events were considered possibly related to test drug.

- The number of patients whose SGOT increased from within or below the NR to ≥2 times the ULN was 6 in the DOLA•Mesyl 1.8 mg/Kg group, 2 in the DOLA•Mesyl 2.4 mg/Kg group and 12 in the OND group.

- The corresponding increase in SGPT was observed in 5 patients in the DOLA•Mesyl 1.8 mg/Kg group, 2 in the DOLA•Mesyl 2.4 mg/Kg group and 6 in the OND group.

- The highest SGOT and SGPT values recorded in this study were for patient MCST0073-0203 (OND 0.15 mg/Kg x 3), whose values exceeded 10 times the ULN on a follow-up measurement taken ca. 48h post-Tx, then returned to within the normal range over the ensuing two weeks:

Analyte (U/L)	Normal	Pre-treatment	Day 1	Day 2	Day 3	Day 4	Day 6	Day 14
SGOT	5-40	32	298	450	286	176	ND	22
SGPT	5-40	21	202	403	347	272	148	63

- Patient MCST0083-0204 (DOLA•Mesyl 2.4 mg/Kg) entered the study with liver metastases and
  Post-Tx values for this patient had declined to
  respectively.

- 2 patients had serum total BIL levels that increased from normal to ≥1.5 times the ULN, 1 in the DOLA•Mesyl 2.4 mg/Kg group and 1 in the OND group.

- In addition, there was a trend for AP to decrease at post-Tx, a change which has been associated with malnutrition also present in this patient population.

- Patient MCST0143-0207 (OND) diagnosed with lung cancer with liver metastases had abnormal SGOT and SGPT laboratory values which were assessed as related to test medication. The physician, however, did not complete an AE report for these abnormal laboratory values which were above the NR but below the alert range.

- Patient MCST0075-0211 (DOLA•Mesyl 2.4 mg/Kg) diagnosed with lung cancer had an AE report submitted for abnormal laboratory values of SGOT and SGPT prior to receiving all test results. When all test results were returned, the investigator did not assess the abnormal laboratory values as related to test medication, because he suspected liver metastases.

6) Vital Signs

- In this study, there were no statistically significant Tx differences in recumbent PR at any time point, recumbent diastolic BP or recumbent systolic BP at hours 0.5, 4 and 8. Statistically significant Tx differences were observed at hour 24 (p=0.0231). At this time, the median change from baseline in recumbent systolic BP was 6, 1, and 0 mmHg, for the DOLA•Mesyl 1.8 mg/Kg, DOLA•Mesyl 2.4 mg/Kg and OND Tx groups, respectively.

- 12 pts. (DOLA•Mesyl 1.8 mg/Kg, n=4; 2.4 mg/Kg, n=5; OND 32 mg, n=3) experienced mild to moderate non-serious hypertension. Of these, events in Pt. MCST0083-0103 (DOLA•Mesyl 1.8 mg/Kg) were considered by the investigator to be possibly related to test med.

- Pt. MCST0079-0207 (DOLA•Mesyl 2.4 mg/Kg) experienced hypotension, recorded as an AE unlikely related to test med.

	mmHg	
	30 min.	8h
Pre-Tx	Post-Tx	Post-Tx
126/57	86/47	121/61

- Pt. MCST0133-0107 (OND 32 mg) experienced orthostatic hypotension, which was not considered related to test med.

- The frequency of patients with Tx-emergent changes in recumbent BP or HR that met sponsor-defined alert criteria was similar among the three test groups.

7) EKG Interval Changes

- The sponsor provided descriptive statistics for the EKG measures at Pre-Tx, hour 1 to 2 and hour 24[9] by Tx, along with the associated changes from BL. Also provided were the p-values for the test for Tx differences in change from BL. The reviewer's emphasis is on the 1 to 2h data in comparison to BL. This evaluation was added by protocol amendment, and, therefore, only 545 patients (instead of 609) had hour 1 to 2 EKG measures. These data affords the opportunity of side-by-side comparisons between the effects of two dose levels of DOLA•Mesyl and the recommended dose of OND (32 mg).

- As shown in Fig. 6, at hour 1 to 2, except for JT which did not change much, for all the other EKG parameters treatment-induced mean changes from baseline were greater (usually 2.4 mg/Kg > 1.8 mg/Kg) with DOLA•Mesyl than with OND. But the test for Tx difference was statistically significant only for PR ($p<0.0001$), QRS ($p<0.0001$) and QT_c ($p<0.0001$). This means that the DOLA•Mesyl Tx groups experienced larger mean change in PR, QRS and QT_c from baseline than OND 32 mg. Although the mean changes in these three EKG parameters are reproduced below, these differences between the effects of DOLA•Mesyl and OND can be better appreciated in Fig. 6.

[9] There were no statistically significant Tx differences at hour 24 for any of the six EKG parameters evaluated: HR, PR, QRS, WT, QT_c and JT.

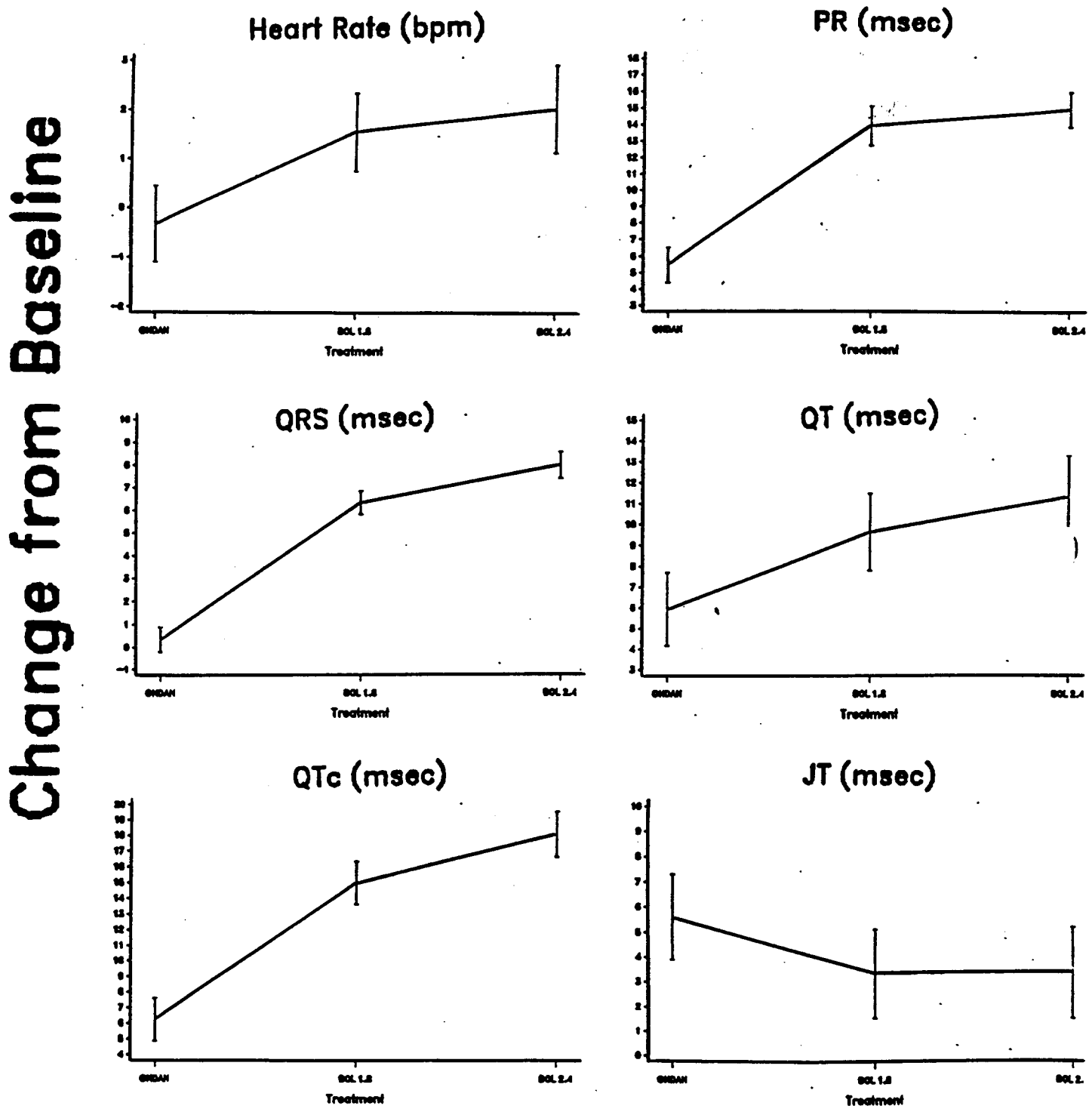

Fig. 6 - *Study -031: Change to 1 to 2 hours from Baseling for the following EKG parameters: HR, -4, QRS, QT, QTc and JT.*

Comparisons between ONDANSETRON (32 mg) and two dose levels of DOLA•Mesyl (1.8 and 2.4 mg/Kg).

APPEARS THIS WAY
ON ORIGINAL

MEAN CHANGE FROM BASELINE TO HOUR 1 TO 2

EKG Parameter	OND 32 mg	DOLA•Mesyl (mg/Kg) 1.8	2.4	p-value
HR (bpm)	-0.3	1.5	2.0	0.0929
PR (msec)	5.4	13.9	15.0	<0.0001
QRS (msec)	0.3	6.3	8.0	<0.0001
QT (msec)	5.9	9.6	11.4	<0.1185
QT_c (msec)	6.3	15.0	18.2[a]	<0.0001
JT (msec)	5.6	3.3	3.4	<0.4530

a) None of the QTc increases progressed to a ventricular arrhythmia.

- Although the EKG interval changes at hour 1 to 2 were clear cut, clinically significant cardiac events were rare. These were limited to 3 reports of complete BBB (OND 32 mg, n=2; DOLA•Mesyl 2.4 mg/Kg). Reports of low BP and DBP <50 mmHg were distributed as follows:

		DOLA•Mesyl (mg/Kg)	
	OND [n=206]	1.8 [n=198]	2.4 [n=205]
Low BP[a]	24 (12%)	14 (7%)	24 (12%)

a) Defined as SBP <100 mmHg and DBP <50 mmHg.

- There were no reports of critical rhythm disturbances, such as VT, high-degree AV block or Torsades de pointes.

- The largest QT_c increase was observed in Pt. MCST0146-022 treated after being admitted to the study with QT_c intervals ≥500 msec.

	Pt. 146-0202			
	Pre-Tx	Hour 1 to 2	Hour 24	Max Δ
QT_c Interval (msec)	404	501	468	97 msec

- The largest changes from baseline were observed in DOLA•Mesyl 1.8 mg/Kg patient MCST0061-0103 whose PR interval increased from 149 msec to 223 msec at 1-2 post-Tx and OND patient MCST0066-0101 whose PR interval increased from 164 msec pre-Tx to 232 msec at 1-2h post-Tx.

  - 2 patients developed second degree AV block. For one of these patients in the 1.8 mg/Kg dose group, MCST0142-0101, the second degree AV block was Mobitz type II, and was assessed by the investigator as **Tx-related**. The event resolved by the end of the 24-h Tx period.

  - In the other patient, MCST0068-0102 (2.4 mg/Kg dose group), second degree AV block Mobitz type I was observed only in the 24-h post-Tx EKG (not in the 1-2h post-Tx EKG), and was considered to be due to a pre-existing condition rather than test medication.

- Ondansetron patient MCST0062-0131 had the largest Tx-emergent QRS increase recorded for any patient in this trial. This patient received a second dose of OND as rescue medication approximately 5h before the 24h post-Tx EKG was recorded. [Hence the QRS increase was not unexpected.]

- In this trial, there was no evidence of adverse clinical consequences resulting from QRS prolongation.

  - 14 pts. were admitted with a QRS≥120 msec: 7 received DOLA•Mesyl 1.8 mg/Kg, 4 received DOLA•Mesyl 2.4 mg/Kg and 3 received OND. For these patients, post-Tx changes were not large. The largest increase was 16 msec (128 msec to 144 msec for DOLA•Mesyl 2.4 mg/Kg patient MCST0339-0117); QRS duration decreased or remained the same for 3 of the 11 DOLA•Mesyl pts. with a Pre-Tx QRS ≥120 msec.

3. Conclusions (Sponsor)

"The primary and secondary study objectives to demonstrate equivalent efficacy to ondansetron were met. This was true for both protocol-defined strata, which included patients who received ≥100 mg/m² cisplatin.

"Antiemetic efficacy of both dolasetron mesylate and ondansetron was negatively affected by concomitant narcotic analgesic use, female gender, and the absence of a history of heavy alcohol use, but not by prior courses of chemotherapy (provided the patients did not vomit during these courses) or by concomitant benzodiazepine use.

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

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

"The active comparator was associated with treatment-emergent changes in these same intervals which, while reported previously, had not been documented in a large randomized trial.

"Based on careful review of both safety and effectiveness data, there is little reason to select the 2.4 mg/kg dolasetron mesylate dose.

"The 1.8 mg/kg dose of dolasetron mesylate dose is safe and effective for the intended indication."

4. Reviewer's Comments

Study -031 is the second of the four main cisplatin trials in NDA 20-624. Study -031, just as study -081 (reviewed above), employed a useful design and was apparently well executed. The prospective stratification of these chemotherapy-naive patients as to cisplatin doses (70 to 90 mg/m² vs ≥91 mg/m²) is a sound approach because patients in the higher cisplatin dose stratum are expected to have lower CR rates.

The doses selected for this trial (1.8 and 2.4 mg/Kg DOLA•Mesyl) are not expected to be differentiated from one another in their efficacy because of Phase II dose-ranging studies showing that the antiemetic effect of the drug tended to plateau at doses above 1.8 mg/Kg for emesis induced by ≥100 mg/m² cisplatin. The study used a positive comparator, OND and was set to show bioequivalence of DOLA•Mesyl to an approved regimen of OND. OND was originally approved as an infusion of 0.15 mg/Kg every 4h for three doses. This dose regimen resulted in a 54/136 (40%) CR rate (65% complete-plus-major response rate) in patients receiving ≥100 mg/m² cisplatin). Later studies indicated that a single 32 mg infusion of OND resulted in a 48/100 (48%) CR and a 73% complete-plus-major response rate in patients receiving ≥100 mg/m² cisplatin). The single 32 mg dose of OND infused over 15 min. is now approved in the US and is an accepted dosing regimen for this agent. Study -031 was initially designed with the t.i.d. infusion of 0.15 mg/Kg OND regimen as the DOLA•Mesyl comparator. However, on November 4, 1992, the FDA requested a revision of the protocol to replace that regimen with a single 32 mg i.v. dose of OND, and the protocol was amended accordingly.

Using the experimental design in study -031 is not enough to demonstrate bioequivalence because in the absence of an internal negative control, against which to show superiority, it is not known if any of the tested regimens is active. To demonstrate activity, comparisons to a relevant negative historical control (i.e. placebo) are needed. The relevance of the historical PL control data is discussed below.

The historical PL control proposed by the sponsor is relevant. This information originates from four literature publications[10] in which the dose of cisplatin was in the range of ≥50 mg/m² and the number of patients who received PL, and the number of those which did not vomit during the 24h period after cisplatin, were reported. The details of these evaluations have been published [M.G. Kris et al: Are more Antiemetic Trials with a Placebo Necessary?, Report of Patient Data from Randomized Trials of Placebo Antiemetics with Cisplatin, Cancer, 78:2193-2198 (1996)]. Two of these trials compared the effects of MCP and PL, the third compared the effectiveness of OND to Pl and the fourth, GRAN to PL. The following Table was taken from the 1996 Kris et al. publication.

Vomiting After Cisplatin: Summary Results

	Cisplatin Dose (mg/m²)		
	47-120	≥100	50-80[A]
No. of Patients	48	28	20
No. With Zero Emetic Episodes	1	1	0
Median No. of Emetic Episodes/ (range)	6	7	5

A) Although technically this is not a "high dose" cisplatin, it is nevertheless considered as highly emetogenic based on the new thinking and the data assessed by Kris et al.

In these four trials, 48 cancer patients received PL prior to ≥50 mg/m² cisplatin. As shown above, of the 48, 47 vomited at least once during the 24h post-chemotherapy. From these data a "CR" rate of 1/48 (2.1%) was calculated. The upper limit of an exact binomial 95% CI for these data is 11%. Results from intravenous DOLA•Mesyl trials in which the cisplatin stimulus was highly emetogenic will be compared to this relevant historical negative PLC control. Studies included the present trial, -031, study -093, consisting of a comparison of DOLA•Mesyl to GRAN and study -032 where the efficacy and safety of graded doses of DOLA•Mesyl were assessed without neither a positive nor a negative internal control.

The inclusion-exclusion criteria were as per other CCNV or PONV protocols. The usual exclusions pertaining to the cardiovascular system also apply here.

The randomization/stratification procedures used in study -031 were apparently well executed since it resulted in three populations of patients that were comparable to each other in any variable that may influence outcome. The data showing comparability of groups at baseline showed that the three experimental groups were well balanced with respect to demographics (gender, M=62%, F=38% median age 62y), primary cancer (the predominant site of primary neoplasm was

[10] 1. [L.X. Cubeddu et al., NEJM 322:810-816 (1990)]
2. [D.R. Cupissol et al., Eur. J. Cancer 26(Suppl):S23-S27 (1990)]
3. [R.J. Gralla et al., NEJM 305:905-909 (1981)]
4. [H.D. Homesley et al., NEJM 307:250 (1982)]

lung=55%), other significant medical conditions, P.E., Karnofsky performance status (median-90%), prior medications, and concomitant medications that may be confounding, such as concomitant other chemotherapy (etoposide, 5-FU, vinblastine, cyclophosphamide, doxorubicin and mitomycin).

In study -031, the three Tx groups were well matched with regards to standardization of the emetic stimulus, a regimen that can be best characterized as being of high emetogenic potential: mean cisplatin dose = 85 mg/m^2, mean duration of cisplatin infusion = 107 min., mean interval between test med. and cisplatin = 35 min. On the average, 60% of the patients received <91 mg/m^2 cisplatin and 40% received ≥91 mg/m^2 cisplatin during the 24-h study period.

The CR rate with OND was 43% in both the ITT and Evaluable populations. None of the two DOLA•Mesyl dose levels (CR rate=44% and 40%, respectively) was shown to be clinically or statistically different from OND (both study populations). Thus the CRs were equivalent among the three Tx groups and the three Txs met the protocol-specified criteria for equivalence. In addition, all three treatments were significantly superior to the above-described historical placebo control ($p<0.0001$), with clinically meaningful therapeutic gains of around 30% over PL. The results of study -031 strongly suggest that doses of DOLA•Mesyl higher than 1.8 mg/m^2 do not provide additional antiemetic efficacy. The MO agrees with the sponsor that the clinically appropriate comparison is DOLA•Mesyl 1.8 mg/Kg vs OND and not the protocol-specified comparison of DOLA•Mesyl 2.4 mg/m^2 vs OND. But in reality both dose levels of DOLA•Mesyl appear to be a) active and b) equivalent to OND in the prevention of high-dose cisplatin-induced N&V in cancer patients. Not unexpectedly, CR rates for patients in the higher cisplatin dose stratum were lower (31% to 37%) than in the stratum given cisplatin at the dose of <91 mg/m^2 (46% to 50%) but again, within each stratum, the three Tx groups were equivalent. The equivalence of the three Tx regimens was confirmed by extensive subgroup analysis. No statistically significant differences among the three Tx groups were detected for any patient subgroup (age, gender, Hx of heavy alcohol use, previous Hx of chemotherapy, use of concomitant benzodiazepines, study drug regimen, i.e., original 3-dose regimen vs postamendment single dose regimen). However, there were statistically significant overall differences indicating higher CR rates in patients who were male ($p=0.0001$), patients who had a history of heavy alcohol use ($p=0.0009$), and patients who did not receive narcotic analgesics during the 24-h Tx period ($p=0.0051$). The response rates changed based upon these factors, but there was no evidence to suggest the dose of DOLA•Mesyl should be adjusted for any subgroup. There were no significant effects on Tx outcome related to patient age, previous Hx of chemotherapy with no emesis, use of concomitant benzodiazepines or test drug regimen.

In this study population and under the experimental conditions and methodology used in study -031, single intravenous doses of DOLA•Mesyl 1.8 or 2.4 mg/Kg were - all in all - well tolerated. Six deaths (DOLA•Mesyl 2.4 mg/Kg=4, 1.8 mg/Kg=1 and OND 32 mg=1), were reported in this trial. The MO agrees with the investigators assessment that the deaths were due to the patients' cancer and the eight additional serious AEs were related either to the underlying clinical condition or the chemotherapeutic regimens being administered.

The overall AE rates were similar with the 1.8 and 2.4 mg/Kg DOLA•Mesyl doses (68% and 73%, respectively) and OND (64%). The most frequently occurring AEs were headache, diarrhea, sinus tachycardia, fever, ST-T change or abnormality and premature ventricular contraction. But, for these, there was statistically significant Tx difference only in the incidence of diarrhea [OND = 6%; DOLA•Mesyl 1.8 mg = 14%' 2/4 ,g = 13%' p=0.0197]. The overall rate, AEs related to the HR & Rhythm and EKG abnormal specific (QRS≥100) of Tx-emergent EKG interval changes were all higher in the DOLA•Mesyl groups in comparison to OND (45% vs 27%; 45% vs 27% and 20% vs 4%, respectively). The comparisons between DOLA•Mesyl and OND were all statistically significant at the p=0.0001 level. Similar conclusions (DOLA•Mesyl significantly higher than OND) were drawn from comparisons of all Tx-related Tx-emergent EKG interval changes. Most EKG interval changes were categorized as mild or intensity.

Among the AEs of potential concern, there were 9 instances of chest pain or chest tightness in 7 patients during the 24-h Tx period. These AEs were, roughly, evenly distributed among the 3 Tx groups. In one patient in the DOLA•Mesyl 2.4 mg/Kg group, the event was assessed by the investigator as being of cardiac origin, "angina", mild in intensity and having unlikely relationship to test medication as the patient had a positive Hx of angina. But the MO does not agree with this assessment of causality. The fact that the patient had a positive Hx of angina does not seem reason enough to rule out the temporal relationship. It seems that DOLA•Mesyl cannot be ruled out with certainty as being the culprit in this case of angina. In the remaining 6 patients, chest pain events were attributed to esophagitis, chemotherapy or the patient's cancer.

Study -031 was important as it afforded the opportunity of side-by-side comparisons between the effects of tx dose levels of DOLA•Mesyl and the recommended dose of OND (32 mg) on EKG parameters taken 1 to 2 hours post-Tx. These comparisons are best appreciated by the graphs in Fig. 6. JT did not change much. But for <u>all</u> the other EKG parameters Tx-induced mean changes from BL were greater (not much difference between the 2.4 and the 1.8 mg/Kg DOLA•Mesyl doses) than with OND. Nonetheless, the test for Tx difference was statistically significant only for PR ($p<0.0001$), QRS ($p<0.0001$) and QT_c ($p<0.0001$). This means that - as evidenced in the Fig. 6 the DOLA•Mesyl groups produced a larger mean change in these three EKG parameters from BL than OND 32 mg. Of the 164 instances of QT interval prolongation, 163 were deemed Tx-related by the investigator. Of the 91 instances of EKG abnormal specific, 89 were deemed Tx-related by the investigator. All 12 instances of AV block first degree were rated as Tx-related by the investigator.

Clinically significant cardiac events were limited to 3 reports of complete BBB (OND 32 mg=2; DOLA•Mesyl 2.4 mg/Kg=1) and the already mentioned episode of hypertension within the DOLA•Mesyl 2.4 mg/Kg test group. But it seems that - all in all - the patients in study -031 were safely treated as there were no reports of critical rhythm disturbances such as VT, high-degree AV block or Torsades de pointes.

D. Study 73147-3-S-093

1. Study Objective, Design, Execution, Statistics

- The main objective of this study was to compare the antiemetic effectiveness of two dose levels of DOLA•Mesyl, 1.8 and 2.4 mg/Kg administered intravenously as a single dose to a single intravenous dose of granisetron (GRAN), given as a 3 mg one dose fits all or 40 μg/Kg for a 75 Kg patient.

- The design, execution and other aspects of this European trial were similar to those in the preceding U.S. study -031.

- The study population consisted of patients with confirmed malignancy scheduled to receive cisplatin base chemotherapeutic regimens, at the dose of ≥80 mg/m² given over no more than 3h as the first component of the anti-cancer regimen. The patients were prospectively stratified on the basis of gender and previous Hx of chemotherapy. The inclusion-exclusion criteria were adequate for this type of study and were similar to those summarized for studies -031 and -081 above. Exclusions pertaining to the cardiovascular system, listed in the protocol, were:

  - CHF or Hx of CHF.
  - Greater than first degree heart block.
  - Abnormal prestudy serum concentrations of potassium and calcium.
  - Arrhythmias requiring antiarrhythmic therapy.
  - It was recommended patients with total cumulative doses of anthracyclines or anthracenediones able to produce cardiotoxicity be examined with echocardiography prior to study entry. Patients with signs of cardiotoxicity on echocardiography were to be excluded.

- Proscribed from the trial were concomitant medications with potentially confounding antiemetic efficacy, but medications necessary for the patient's well-being could be used according to the judgment of the investigator. Also allowed were escape medications and those patients were handled as Tx failures.

- The trial was designed as a double-blind, multicenter, double-dummy, randomized, 3-arm parallel evaluation of 474 cancer patients with Karnofsky status ≥50%.

- Random allocation of the three Tx regimens were stratified by gender and on the basis of naive or non-naive to chemotherapy within each center. Test medication was randomly assigned using a blinded random code provided to the investigator by the sponsor. A randomization schedule was provided including the four strata male naive, male non-naive, female naive and female non-naive. Two groups received DOLA•Mesyl at 1.8 or 2.4 mg/Kg and one group received GRAN 3 mg. Administration of the test medication started 30 min. before the cisplatin infusion and was infused intravenously over a period of 5 min. The double-blind was maintained using corresponding dummy vials.

- The blinding, packaging and labeling of test materials were all adequate.

- The study evaluations (assessment of efficacy and safety) were adequate, as per studies -081 and -031. A 12-lead EKG was obtained within three days prior to study entry for all patients. In designated centers, additional EKGs were done 1.5h and 24h after chemotherapy. A preliminary reading of the EKG was completed at the study site to assure adherence to the inclusion/exclusion criteria (pre-Tx) and to monitor patient safety.

- The total number of patients to be enrolled (n=450) was estimated using the following parameters: α=0.10, β=0.20, with a CR rate of 70% for the GRAN and DOLA•Mesyl groups. It was assumed that a difference of no more than 15% in CR rate (based on use of confidence intervals) was consistent with equivalence in efficacy. Based on these parameters a sample size of 100 patients per group was estimated. In order to compensate for potential dropouts and to allow for addition estimation precision, 150 patients per group were specified in the protocol. This study was not terminated early and there were no interim analyses.

- Randomization was stratified by gender (M or F) and previous chemotherapy Tx (naive or non naive), therefore producing four strata. Within each investigative site and stratum, patients were randomized to receive one of the three antiemetic treatments, using a blocking factor of six.

- The definitions of categorical emetic efficacy endpoints were adequate, as per study -091, -031 and the DOLA•Mesyl tablet protocols. Two types of main statistical analyses were carried out:

  a) <u>Included in the original NDA</u>

  - For all analyses, 3 Tx groups were formed: DOLA•Mesyl 1.8 mg/Kg, DOLA•Mesyl 2.4 mg/Kg and GRAN 3 mg. In addition, for the primary assessment of efficacy, the pooled 1.8 plus 2.4 mg/Kg DOLA•Mesyl group was compared to the GRAN group.

- The primary endpoint was CR (0 emetic episodes and no rescue medication). The primary assessment of efficacy compared the pooled 1.8 and 2.4 mg/Kg DOLA•Mesyl group vs GRAN. Logistic regression with a 95% confidence interval for the odds ratio, together with an appropriate 95% CI for the difference in CR rate was used. This analysis was conducted using the intent-to-treat dataset. The presence of investigator-by-Tx and stratum-by-Tx interactions were tested using logistic regression and the Rao score (residual Chi-square) tests. Additionally, 95% confidence intervals for odds ratios were determined for 2.4 mg/Kg DOLA•Mesyl vs GRAN, 1.8 mg/Kg DOLA•Mesyl vs GRAN, and 1.8 mg/Kg vs 2.4 mg/Kg DOLA•Mesyl.

b) Included in sponsor's submission of November 18, 1996

Comparison to historical contents was not done for Protocol -093 in the original NDA but was included in sponsor's submission of November 18, 1996 in response to our request of November 7, 1996.

- Secondary analyses included logistic regression as described for the primary analysis using an efficacy evaluable dataset, subgroup analyses using the logistic regression model, and 95% CI for odds ratios using Mantel-Haenszel's techniques. Changes from BL in clinical laboratory measurements, vital signs, and EKG parameters were analyzed for Tx differences using a rank analysis of variance. All analyses and summaries of the safety data used the ITT dataset.

2. Results

a. Participating Investigators/Patient Accounting

- Of the 30 participating investigators, one (site #37) recruited no patients; 29 centers enrolled 476 patients (F=159; M=315). Of these 474[11] were included in the ITT dataset. The following 5 centers enrolled 30 or more patients each: Dr. Cappelaere (#06, n=48), Des. Riviere/Heron (#03, n=38, Dr. Fabbro (#23, n=38), Dr. Audhuy (#02, n-31) and Dr. Bleiberg (#21, n=30).

[11] 2 patients (09301 1/d and 093055/B) were randomized but did not receive test medication having withdrawn their consent prior to test drug administration. Neither patient had any safety or efficacy data and both were excluded from all analyses.

- 451[12] patients were included in the efficacy analyzable dataset.
- The number of patients analyzed per study population per group was:

Population Analysis	GRAN	DOLA•Mesyl (mg/m²)		Total DOLA•Mesyl
	3 mg	1.8	2.4	
ITT	150	163	163	326
Evaluable	140	154	157[11]	311

b. Data Showing Comparability of Groups at Baseline

- There were no statistically significant differences among the three treatment groups with respect to gender, previous chemotherapy (naive=60%; non-naive=40%), four strata (M naive, F naive, M non-naive and F non-naive), age, weight, height, mean Karnofsky status (=85%, range 60 to 100), history of alcohol abuse (YES=35%, NO=65%) and Nausea VAS (mm) either 45 min. or just prior to chemotherapy at Pre-Tx and h 0.
- The study population was predominantly male (315/474=66%) with a mean age of 55y, mean weight of 62 Kg, mean height of 167 cm and mean Karnofsky performance status of 85%. Positive Hx of alcohol abuse was reported in 158/474=33% of the patients; 60% of the patients were naive to chemotherapy.
- There were no important imbalances across Tx groups in site of primary neoplasm. The most frequent sites of primary neoplasm were head/neck 172/474 (36%), lung 70/474 (15%), digestive system 68/474 (14%) and gynecologic 68/474 (14%).
- With the two exceptions noted below, there were no marked imbalances among the three Tx groups in medical Hx abnormalities, P.E. and organ system abnormalities Pre-Tx.
  - The GRAN group had a higher percentage of history of cardiovascular abnormality compared to the DOLA•Mesyl groups: 27%, 15% and 19%, respectively, for the GRAN, 1.8 and 2.4 mg/Kg DOLA•Mesyl groups (p=0.018).
  - There were fewer "other" abnormalities in the 2.4 mg/Kg DOLA•Mesyl group compared to the other two groups: 21%, 22% and 12%, respectively for the GRAN, 1.8 and 2.4 mg/Kg DOLA•Mesyl group (p=0.047).

[12] 23 patients with major protocol violations and distributed as shown below, were excluded from the efficacy evaluable dataset.

GRAN	DOLA•Mesyl (mg/Kg)		All
3 mg	1.8	2.4	DOLA•Mesyl
10	9	4	13

i) Cisplatin and Other Chemotherapy (Table 46)

- As summarized in Table 46, there was a statistically significant imbalance in cisplatin dose (p=0.0389): the mean cisplatin dose was 98, 96 and 96 mg/m² for the GRAN, 1.8 and 2.4 mg/Kg DOLA•Mesyl groups, respectively. All of these dose levels of cisplatin are considered highly emetogenic. The three groups were balanced in duration of cisplatin infusion and the interval between start of test med. administration and start of cisplatin infusion.

- In this study, cisplatin dose ranged from with a mean of 97 mg/m². The mean duration of cisplatin infusion was 87 min. the mean interval between start of test med. administration and start of cisplatin infusion was 31 min. . One hundred twelve patients had cisplatin dose ≤90 mg/m² and 362 patients had cisplatin dose >90 mg/m² within the 24-h study period.

- Most patients 400/474 (84%) received chemotherapy in addition to cisplatin (Table 46). The most frequent additional agents were fluorouracil (49%), etoposide (11%) and cyclophosphamide (10%). Additional chemotherapy was well balanced across Tx groups (p=N.S.): the percent additional chemotherapy was 83%, 86% and 84% respectively, in the GRAN, 1.8 and 2.4 mg/Kg DOLA•Mesyl groups. There was balance across Tx groups in use of specific additional chemotherapy.

TABLE 46
Study -093

Summary Information on Cisplatin and Concomitant Cancer Chemotherapy

I. Current Chemotherapy: Cisplatin [n=474]					
		DOLA•Mesyl (mg/Kg)		Total	
Variable	GRAN [n=150]	1.8 [n=163]	2.4 [n=161]	DOLA•Mesyl [n=324]	p-value*
Mean Cisplatin Dose (mg/m²)	98±11	96±12	96±11	96±12	0.0389
Range					
Mean Duration of Cisplatin Infusion (min)	92±121	84±49	83±47	84±40	N.S.
Range					
Mean Interval Between Study Drug and Cisplatin (min)	32±20	31±5	31±5	31±5	N.S.
Range					

II. Concomitant Chemotherapy					
Fluorouracil	54%	46%	48%	47%	N.S.
Etoposide	12%	11%	11%	11%	N.S.
Cyclophosphamide	9%	10%	11%	11%	N.S.
Ifosfamide	5%	9%	7%	8%	N.S.
Vinorelbine	5%	7%	7%	7%	N.S.
Doxorubicin	5%	7%	7%	7%	N.S.
Mitomycin	5%	7%	3%	5%	N.S.
Epirubicin	3%	4%	3%	4%	N.S.
Vindesine	1%	3%	1%	2%	N.S.
Concomitant Chemotherapy					
YES	125 (83%)	140 (86%)	135 (84%)	275 (85%)	N.S.
NO	25 (17%)	23 (14%)	26 (16%)	49 (15%)	N.S.

a) Statistical Methods: From Fisher's Exact test.

Test (and p-value) for imbalance of factor across treatment groups:
- Kruskal-Wallis test for quantitative factors - cisplatin dose, duration of cisplatin infusion and interval between test drug and cisplatin.
- Chi-square test for categorical factors (concomitant chemotherapy agents). If assumptions for validity of Chi-square test (80% of cells with expected frequency ≥5) not met, then Fisher's Exact test used.

- The most frequently used medications were paracetamol (23% of the patients), codeine (13%), lactulose (8%), morphine sulfate (8%) and ranitidine (7%). Morphine sulfate and amoxicillin use differed across the treatment groups (p=0.024 and 0.040, respectively) with greater use of morphine sulfate in the 1.8 mg/Kg DOLA•Mesyl group and greater use of amoxicillin in the 1.8 mg/Kg DOLA•Mesyl group. There were no other significant differences across Tx groups in the use of these medications.

- Data pertaining to the use of major concomitant medications with potential to affect emesis (showed non-escape use), 26% of patients received narcotic analgesics. Benzodiazepines (2%) and corticoids (2%) were less frequently used. Corticoid use differed across the Tx groups (p=0.001), with greater use of corticoids in the 1.8 mg/Kg DOLA•Mesyl group. Corticoid use was 1%, 6% and 0% in the GRAN, 1.8 and 2.4 mg/Kg DOLA•Mesyl groups, respectively.

- Concomitant medication (non-escape) use for individual drugs during the study evaluation period was paracetamol (27%), codeine (12%), furosemide (9%), lactulose (8%), morphine sulfate (8%), allopurinol (7%) and ranitidine (7%). There were no statistically significant differences across Tx groups in use of these medications with the exception of morphine sulfate (p=0.030) and amoxicillin (p=0.043). There was greater use of morphine sulfate in the 1.8 mg/Kg DOLA•Mesyl group and greater use of amoxicillin in the GRAN group.

- The reviewer believes that all the above described statistically significant imbalances among the Tx groups are not expected to have a strong effect on efficacy results.

- The most common escape medication were methylprednisolone (12%), MCP (8%), dexamethasone (8%), alizapride (7%) and granisetron (6%). There were no statistically significant imbalances across the treatments in escape medications.

c. Clinical Response (Table 47)

- The ITT analyses of the CR rates in 474 patients showed therapeutic gains between -7 and + 6% and no statistically significant differences among the three Tx groups. The CR with both and each of the DOLA•Mesyl doses was equivalent to GRAN.

- When compared to the historical PL control rate (11.1%) each of the 3 Tx groups showed therapeutic gains 36% or higher over PL (all statistically, highly significant, p<0.0001).

- The results of the efficacy evaluable analyses (lower panel of Table 47), based on 451 patients, were consistent with those of the ITT analyses.

- The Tx-by-investigator interaction test was N.S. There were differences in the overall CR rate across investigators (investigator main effect test, p=0.0001). Some investigative sites had consistently high or low response rates. For example five sites had complete response for the combined DOLA•Mesyl groups, whereas five other sites had 35% or below response.

- An analysis was carried out of the CR rates by patient stratification (gender x previous chemotherapy) and separately for each patient stratification factor (gender and previous chemotherapy). The test for inconsistency in Tx effect across patient stratification was not statistically significant (Tx x stratum interaction test, p=0.4184). Similarly, the interaction tests for inconsistency in Tx effect between gender (p=0.9322) and between naive and non naive patients (p=0.4500) were not statistically significant. Patient stratification was, however, highly predictive of overall response rate (stratum main effect

test, p=0.0001). The overall CR rates were 63%, 57%, 30% and 23% for male naive, male non naive, female naive and female non naive patients, respectively. As indicated by the non significant treatment by stratum interaction test, the response rates within strata showed a similar trend as the overall results, with the 1.8 mg/Kg DOLA•Mesyl CR rates generally higher than the GRAN and 2.4 mg/Kg DOLA•Mesyl rates.

- In study -093, male patients responded better than females (gender main effect test, p=0.0001). The overall CR rates were 61% for males vs 26% for females. [These difference in response as a function of gender are not unexpected in N&V trials.]

- Naive patients also responded better than non naive patients (previous chemotherapy main effect test, p=0.0008). The overall CR rates were 55% for naive patients vs 42% for non naive patients. [Again, not an unexpected difference in response.]

i) Subgroup Analyses

- Subgroup analyses were conducted to assess inconsistency in Tx differences across specific dichotomous population subgroups. None of the analyses (Tx x subgroup interaction test) indicated differences in Tx effect across the specifically defined subgroups: age (<65 years or ≥65y), cisplatin dose (≤90 mg/m² or >90 mg/m²), Karnofsky status (<80 percent or ≥80 percent), history of alcohol abuse (yes/no), concomitant use of narcotic analgesics (yes/no), concomitant use of benzodiazepines (yes/no) and concomitant use of corticoids (yes/no). Use of corticoids and benzodiazepines were inestimable (no valid statistical test) due to their low frequency of occurrence.

    - As in other studies, Hx of alcohol abuse was associated with a higher overall level of CR (main effect test, p=0.0317). Patients without Hx had an overall 42% CR rate, whereas those with Hx of alcoholism were 65% complete responders.

    - The results of the primary analysis were confirmed when controlling for alcoholism.

TABLE 47
Study -093

Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response

Response by Test Group					Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses and OND and Between Test Groups and Historical PL Control [p-values]					
I. Intent-To-Treat Analysis [n=474]										
Hist. PL		GRAN [n=150]	1.8 mg/Kg [n=163]	2.4 mg/Kg [n=161]	1.8 mg/Kg vs GRAN	2.4 mg/Kg vs GRAN	2.4 mg/Kg vs 1.8 mg/Kg	GRAN vs PL	1.8 mg/Kg vs PL	2.4 mg/Kg vs PL
(11.1%)		72 (48%)	88 (54%)	75 (47%)	6.0% [N.S.]	-1.0% [N.S.]	(-7.0%) [N.S.]	(36.9%) [<0.0001]	(42.9%) [<0.0001]	(35.9%) [<0.0001]
95% Confidence Interval for the % of CR		40%, 50%	46%, 62%	39%, 54%						
II. Efficacy Evaluable Analysis [n=451]										
		[n=140]	[n=154]	[n=157]						
(11.1%)		69 (49%)	81 (53%)	74 (47%)	(4.0%) [N.S.]	-2.0% [N.S.]	-6.0% [N.S.]	(37.9%) [<0.0001]	(41.9%) [<0.0001]	(35.9%) [0.0001]
95% Confidence Interval for the % of CR		45%, 53%	45%, 61%	39%, 55%						

LOGISTIC REGRESSION STATISTICS:

ITT [n=474]

Comparison	95% CI for Odds Ratio	p-value
1.8 mg/Kg DOLA•Mesyl vs GRAN	(0.9,2.5)	N.S.
2.4 mg/Kg DOLA•Mesyl vs GRAN	(0.6,1.6)	N.S.
2.4 mg/Kg vs 1.8 mg/Kg DOLA•Mesyl	(0.4,1.0)	N.S.

Mantel-Haenszel Statistics (Row Mean Score):
All Comparisons: N.S.

Evaluable [n=451]

Comparison	Odds Ratio	p-value
1.8 mg/Kg DOLA•Mesyl vs GRAN	(0.8,2.3)	N.S.
2.4 mg/Kg DOLA•Mesyl vs GRAN	(0.6,1.6)	N.S.
2.4 mg/Kg vs 1.8 mg/Kg DOLA•Mesyl	(0.4,1.2)	N.S.

STATISTICAL METHODS:

- Primary tests and confidence intervals: logistic regression with treatment, investigator and stratum in the model.
- Supportive tests: Mantel-Haenszel type test (row mean scores) of treatment differences, stratifying by investigator.

- Logistic regression with treatment, investigator and stratum in the model.

ii) Time to First Emetic Episode or Escape Medication (Table 48)

- As shown in this Table, the Cox regression analysis of time to first emetic episode or escape strongly confirmed the primary analysis of CR. There were no statistically significant differences in the pairwise tests. The median times to first emesis or escape were 23.2, >24 and 22.2h for the GRAN, 1.8 and 2.4 mg/Kg DOLA•Mesyl groups.

TABLE 48
Study -093

Time to First Emetic Episode or Escape
(CR by Hour and Tx)

		DOLA•Mesyl (mg/Kg)	
Hour	GRAN [n=150]	1.8 [n=163]	2.4 [n=161]
4	97%	93%	91%
8	82%	76%	74%
12	72%	71%	70%
18	61%	58%	60%
24	49%	54%	47%

Depicted is the Estimated % Complete Responders Through a Given Hour.

Cox Regression Statistics:

Comparison	95% CI for Hazard Ratio	p-value
1.8 mg/Kg DOLA•Mesyl vs GRAN	(0.6,1.3)	N.S.
2.4 mg/Kg DOLA•Mesyl vs GRAN	(0.8,1.6)	N.S.
2.4 mg/Kg DOLA•Mesyl vs 1.8 mg/Kg DOLA•Mesyl	(0.9,1.8)	N.S.

Statistical Methods:

Hypothesis tests and confidence intervals for risk ratios computed using Cox regression with Tx investigator and stratum in the model.

Estimated percent CR at 4h intervals computed by Kaplan-Meier method. Note: in this study no patients were censored. Thus all Kaplan-Maier estimates are actual study CR ratios.

d. Safety Results

1) Extent of Exposure

In study -093, a total of 474 patients were treated with single i.v. doses of test med. with the following distribution:

GRAN	DOLA•Mesyl (mg/Kg)	
3 mg	1.8	2.4
[n=150]	[n=163]	[n=161]

2) Deaths, Dropouts Due to AEs and Other Serious AEs (Tables 49 and 50)

- Succinct narratives of the four deaths reported in this study are given in Table 49. None of these events were related to test med. but rather to the patient's progression of cancer or underlying condition.

TABLE 49
Study -093

DEATHS: Succinct Clinical Narratives and Relation to Test Medication

DOLA•Mesyl 2.4 mg/Kg, n=2		
93110A 73y-old M **PULMONARY EMBOLISM/ DEATH**	Pt. had malignant melanoma with metastases to the lung, brain, skin. Had Hx of "arrhythmia" and hypertension. Tx with flecainide. Pulmonary embolism, severe in intensity, most likely caused by prolonged dicubitus and associated thrombosis in the legs. Began 17h after test drug adm. EKG reading proximal to the patient's demisal (21h and 15 min after adm. of test med.) showed signs consistent with pulmonary embolism and no arrhythmia.	None
93316C 65y-old M **CEREBELLUM COMPRESSION/SUDDEN DEATH**	This pt. had head and neck tumor (laryngeal). He died suddenly 4 days after test drug administration. The event was assessed by the investigators as severe and not related to test med. Post-mortem exam. revealed presence of cerebral fluid containing RBCs and cerebellum compression.	None
DOLA•Mesyl 1.8 mg/Kg, n=1		
93434C 53y-old M **HEMORRHAGE OF THE THALAMUS/DEATH**	Pt. had lung cancer. He was re-hospitalized 5 days after test drug adm. with coma. Two days later, a CT scan revealed hemorrhage of the thalamus (9 days after test drug adm.). The investigator assessed the events as severe and related to endocarditis + cerebral infarction. Autopsy revealed endocarditis + possible cerebral infarction.	Unlikely
GRAN 3 mg, n=1		
93026C 70y-old M **DEATH DURING NIGHT**	Pt. had advanced metastatic respiratory cancer. He died during the night 6.5 days after test drug adm. The investigator assessed the death as not related to test med. but rather to Dz progression of his advanced metastatic respiratory cancer.	None

- In Table 50, succinct narratives are given of the serious AEs reported in this study. These events were severe, resulted in prolonged

hospitalization, and in four of the six patients, were due to either the underlying cancer or concurrent chemotherapy. Cardiac ischemia/MI in the fifth patient were thought to be due either to GRAN 3 mg or to the chemotherapeutic agent vinorelbine, which is known to produce pulmonary toxicity (angina + acute pulmonary edema were linked, according to the investigator). Subocclusion in the sixth patient was initially rated as unrelated to test med. This assessment was later changed by the investigator to possibly related to GRAN, who thought that the 5-HT_3 receptor antagonist (GRAN) may potentiate the effect of vinorelbine, a chemotherapeutic agent known to provoke intestinal occlusion. With the exception of the patient experiencing MI whose EKG still showed sequelae of cardiac schema 3 weeks after the event, these patients recovered without sequelae.

TABLE 50
Study -093

Serious AEs: Succinct Clinical Narratives and Relation to Test Medication

DOLA●Mesyl 2.4 mg/Kg, n=2[a]		
93375C VESICAL RETENTION OF URINE/PROLONGED HOSPITALIZATION	Prolonged hospitalization due to vesical retention of urine starting 3 days after test med. and lasting 19 days, due to prostatic cancer. Recovered without sequelae.	None
93377C ORTHOSTATIC HYPOTENSION/ PROLONGED HOSPITALIZATION	Experienced orthostatic hypotension that started 8 days after test drug adm. lasted <4 days was severe, resulted in prolonged hospitalization and was thought due to 5-FU toxicity.	None
DOLA●Mesyl 1.8 mg/Kg, n=2[b]		
93083C ASTHENIA/PROLONGED HOSPITALIZATION	Severe asthenia started 30h after test drug adm., lasted 3 days and resulted in prolonged hospitalization. Pt. recovered without sequelae. Serious AE was due to chemotherapy.	None
93259A DECREASED LEVEL OF ATTENTION AND CONSCIOUSNESS	The event started 72h after test drug adm., was considered severe, lasted 72h and was thought due to concurrent chemotherapy (ifosfamide).	None

GRAN 3 mg, n=3[c]		
90013C **LARYNGEAL DYSPNEA**	Pt. experienced severe laryngeal dyspnea 18h 30 min. after test drug adm. The event lasted 2h and 30 min., put the patient to immediate risk of death and was thought to be due to locally extended pharyngeal tumor provoking obstruction of the upper respiratory splem. The pt. recovered without sequelae.	None
93021C **FEVER AND ABDOMINAL PAIN (SUBOCCLUSION)/IMMEDIATE RISK OF DEATH**	Pt. had Hx of arteritis and stroke. He was diagnosed with lung epidermoid carcinoma; 3h after test drug adm. he developed fever + abdominal pain, considered severe and diagnosed as intestinal subocclusion resulting in prolonged hospitalization. The event lasted 3 weeks, were treated with amoxicillin, clavulanic acid and propacetamol. He recovered without sequelae. The events were assessed by the investigator as severe and unlikely related to test drug adm. but primarily due to the chemotherapeutic agent vinorelbine which is known to provoke intestinal occlusion. He also thought that the 5-HT, receptor antagonist may have potentiated the effect of vinorelbine and in the F/U report, he changed relationship to study drug from unlikely to possible.	Unlikely/(→ Possible
93019C CARDIAC ISCHEMIA/MI	Pt. diagnosed with bronchial cancer had Hx of arteritis, nicotinism, GU and hypercholesterolemia. He was at immediate risk of death as he developed angina, MI and acute pulmonary edema, which started 3h 15 min. after test drug adm. and lasted 4-5h. An EKG Pre-Tx was read as normal by the investigator and as revealing silent ischemia by the central cardiologist. Post-event EKGs revealed clear signs of infarction. Another cause of the severe event was the adm. of the vinorelbine which is known to produce pulmonary toxicity. Three weeks after the event, the pt. had recovered from the events but EKG still showed sequelae of cardiac ischemia.	Possible

a) 2 serious AEs resulting in death (patients 93110A and 93316C) were described in Table 49
b) 1 serious AE resulting in death (pt. 93434C) was described in Table 49.
c) 1 serious AE resulting in death (pt. 93026C) was described in Table 49.

3) AEs

- There were no statistically significant Tx differences in the overall incidence of AEs. By organ system class the most frequent events were those related to central and peripheral nervous system, the g.i. system, cardiovascular in general, liver and biliary system, HR & rhythm and body as a whole. For these, the frequency of g.i. system AEs was significantly higher in the DOLA•Mesyl 1.8 mg/Kg compared to the other two groups.

Overall Frequency of AEs

	GRAN	DOLA•Mesyl (mg/Kg)		
	3 mg [n=150]	1.8 [n=163]	2.4 [n=161]	Total DOLA•Mesyl [n=324]
Overall Rate (p=N.S.)	45%	58%	55%	56%
G.I. System (p=0.0249)	13%	25%	16%	20%
Diarrhea (p=N.S.)	6%	13%	11%	12%
Cardiovascular, General (p=N.S.)	8%	7%	10%	8%
H.R. & Rhythm (p=N.S.)	2%	5%	4%	5%

- The most frequently reported individual AEs were headache, diarrhea and hepatic function abnormal. There was no statistically significant difference in the incidence of any of the three AEs:

Most Frequently Occurring AEs

Included Term	GRAN	DOLA•Mesyl mg/Kg		Total DOLA•Mesyl [n=324]
	3 mg [n=150]	1.8 [n=163]	2.4 [n=161]	
Headache (p=N.S.)	23%	28%	22%	25%
Diarrhea (p=N.S.)	6%	13%	11%	12%
Hepatic Function Abnormal (p=N.S.)	3%	9%	6%	7%

- Although there were no statistically significant differences among the groups in the individual Tx-related AEs there were statistically significant Tx differences in the overall incidence of Tx-related AEs (p=0.0268) (GRAN = 38%, DOLA•Mesyl 1.8 mg/Kg = 53%, 2.4 mg/Kg = 43%).

- The frequency of AEs treated with counteractive medication was similar in the three Tx groups.

- There were no statistically significant Tx differences in the incidence of pts. presenting with severe AEs. The large majority of pts. had mild to MOD AEs.

4) AEs of Potential Concern

Respiratory System

Patient 93100A (DOLA•Mesyl 2.4 mg/Kg)

Pt. experienced "breathing difficulties" 1.5h after test medication administration. This event was MOD in severity and **possibly** related to test medication by the investigator.

The following 2 patients experienced "dyspnea".

> Patient 93013C treated with GRAN 3 mg experienced severe dyspnea at 18.5h after test medication administration. The event was assessed by the investigator as being not related to test medication.
>
> Patient 93011C treated with DOLA•Mesyl 2.4 mg/Kg experienced severe dyspnea at 29.5h after test medication administration. The event was assessed by the investigator as being not related to test medication.

Patient 93086B (DOLA•Mesyl 1.8 mg/Kg)

This pt. experienced "pleural effusion". The event was rated as mild in severity and was assessed by the investigator as being **not related** to test med.

Cardiovascular

Patient 93318C (DOLA•Mesyl 2.4 mg/Kg)

This pt. experienced "mild chest tightness" at 2.5h after test med. administration. The causality was assessed by the investigator as being **unknown**. The patient fully recovered from the event.

Patient 93342C (GRAN 3 mg)

This pt. experienced "mild chest pain" of unknown causality 20h after test med. administration. No action was required as the patient recovered from the event.

Bleeding

Bleeding events were reported in the following 2 patients.

> Patient 93028A (DOLA•Mesyl 2.4 mg/Kg)
>
> Pt. experienced mild nose bleeding (epistaxis). The causality of the event was assessed by the investigator as **unknown**. In this patient a decrease in platelet count from 150 to 127 x 10^3 was noted.

Patient 93432D (DOLA•Mesyl 1.8 mg/Kg)

Pt. experienced vaginal hemorrhage associated with back pain. The event was rated as unknown in causality and MOD in severity by the investigator. This patient had a normal pre-Tx platelet value (319 x 10^9/l) but no follow-up platelet count was available.

5) Tx-Emergent EKG Changes

- In study -093, there were no statistically significant Tx differences in the EKG changes noted as AEs (p=0.3103) and the frequency of pts. presenting with each particular listed EKG change noted as AE ranged from 0 to 3%:

	GRAN	DOLA•Mesyl mg/Kg		
	3 mg [n=150]	1.8 [n=163]	2.4 [n=161]	Total DOLA•Mesyl [n=324]
p=0.3103	5 (3%)	12 (7%)	10 (6%)	22 (7%)
Arrhythmia, sinus	1 (1%)	0 (0%)	0 (0%)	0 (0%)
AV block first degree[a]	0 (0%)	2 (1%)	3 (2%)	5 (2%)
Bradycardia	1 (1%)	1 (1%)	1 (1%)[b]	2 (1%)
Bundle branch block	0 (0%)	0 (0%)	1 (1%)[c]	1 (0%)
EKG abnormal non-specific	1 (1%)	1 (0%)	1 (1%)	2 (1%)
EKG abnormal specific	1 (1%)	1 (1%)	0 (0%)	1 (0%)
Extrasystoles	1 (1%)	5 (3%)	2 (1%)	7 (2%)
QT interval prolongation[d]	0 (0%)	2 (1%)	1 (1%)	3 (1%)
ST-T change/abnormality	0 (0%)	0 (0%)	1 (1%)	1 (0%)

a) Of these 5 events, the central cardiologist confirmed first degree AV block in 2 patients treated with 2.4 mg/Kg DOLA•Mesyl.
b) Bradycardia in one patient treated with DOLA•Mesyl 2.4 mg/Kg was assessed as severe by the investigator. In this patient sinus bradycardia with no sign of ischemia appeared on EKGs performed at hour 1-2 and at hour 24. The HR on entry EKG was 60 bpm and dropped to 48 and 47 bpm at hour 1-2 and 24, respectively. Bradycardia was confirmed by vital signs measurements: supine HR (bpm) was 60, 62, 54, 57, 48 at 45 min. before start of chemotherapy (15 min. before 2.4 mg/Kg DOLA•Mesyl, 30 min. 4 hour, 8 hour and 24 hour after start of chemotherapy, respectively). This event was deemed treatment-related by the investigator.
c) This episode of L posterior BBB in the 2.4 mg/Kg DOLA•Mesyl-treated group was not confirmed by the central cardiologist; sinus tachycardia was recorded.
d) QT prolongation as reported in these 3 DOLA•Mesyl patients was not confirmed by the central cardiologist.

- In 15/27 patients presenting with EKG changes noted as AEs, the relationship to the treatment was deemed "unknown" by the investigator, 11/27 were deemed "possibly or probably" Tx-related and one was deemed not Tx-related.

6) Summary Results of Clinical Laboratory Examinations

- Most laboratory parameters did not change significantly with Tx. There were statistically significant differences in change from baseline among the 3 Tx groups for a) creatinine (p=0.0294, decreased by 0.547 µmol/l in the 1.8 and 2.4 mg/Kg DOLA•Mesyl respectively; b) potassium (decreases in all 3 groups, (p=0.0261) and c) WBC count (increase in the GRAN group vs decreases in the DOLA•Mesyl groups, p=0.0015). These decreases or increases in laboratory tests are expected in the cancer population treated with cisplatin-based chemotherapy regimens.

- Shifts toward increases in glucose and transaminases were higher in the DOLA•Mesyl groups, but not significantly so.

  - For glucose, the shift toward increase in the DOLA•Mesyl 1.8 mg/Kg and 2.4 mg/Kg was 27.2% and 46.8%, respectively, vs 35.5% in the GRAN group.

  - For SGPT, the shift toward increase in the DOLA•Mesyl 1.8 mg/Kg and 2.4 mg/Kg group was 18.4% and 15%, respectively, vs 8.5% in the GRAN group.

  - For SGOT, the shift toward increase in the DOLA•Mesyl 1.8 mg/Kg and 2.4 mg/Kg group was 21.7% and 18.5%, respectively, vs 16.4% in the GRAN group.

7) Vital Signs

Vital signs were assessed at 0.5, 4, 8 and 24h Post-Tx, in comparison to Pre-Tx. Except for recumbent systolic BP (p=0.0402; mean decreases: -1.8, -4.3 and -5.8 mmHg in the GRAN, 1.8 and 2.4 mg/Kg DOLA•Mesyl, respectively), there were no statistically significant differences across treatments at all other time points.

8) EKG Interval Changes

- A Pre-Tx (baseline) EKG was part of the entry screening tests for all pts. but the hour 1-2 and the hour 24 EKGs were performed at selected centers only. Of the 474 patients entered in the trial, 442 had baseline EKG measures, 249 had hour 1-2 and 301 had hour 24 EKG measures, respectively.

- The reviewer's emphasis is in hour 1 to 2 EKG data. Of the hour 24 data, only the change in QT_c showed statistically significant differences (p=0.0194) among the Tx groups:

QT_c: Mean Change from BL (msec) at Hour 24

GRAN	DOLA•Mesyl (mg/Kg)	
3mg	1.8	2.4
-1.0	7.0	9.1

- As shown in the Table below, at hour 1 to 2, except for QRS (which did not change much) and HR (which showed inconsistent results with increase dose), for all the other EKG parameters Tx-induced mean changes from BL were greater with DOLA•Mesyl than with GRAN. But the test-for-Tx difference was statistically significant only for PR (p=0.0002) and QT_c (p=0.0016). This means that the DOLA•Mesyl Tx groups had a larger mean change in PR and QT_c from baseline than did GRAN. The mean changes in EKG parameters at hour 1 to 2 is reproduced below.

MEAN CHANGE FROM BASELINE TO HOUR 1 TO 2

	GRAN	DOLA•Mesyl (mg/Kg)		
EKG Parameter	3 mg	1.8	2.4	p-value
HR (bpm)	-1.0	-2.0	0.2	N.S.
PR (msec)[a]	0.1	7.0	11.9	0.0002
QRS (msec)	2.1	2.2	2.6	N.S.
QT (msec)	3.1	12.8	12.5	N.S.
QT_c (msec)[b]	0.1	9.1	15.2	0.0016
JT (msec)	1.0	10.6	9.8	N.S.

a) None of the patients with PR interval change above 220 msec including those who had BL values ≥220 msec developed second degree or higher heart block.

b) No patient developed Torsades de pointes or ventricular arrhythmia. Overall, 63 patients experienced Tx-related changes in QT_c interval and 45 had BL values ≥440 msec:

Baseline QT_c (msec)	Postbaseline QT_c (msec)	GRAN 3 mg [n=89]	DOLA•Mesyl (mg/Kg) 1.8 [n=99]	2.4 [n=98]
<440	>440	13	23	27
	440-449	5	13	12
	450-459	7	6	8
	460-469	0	3	3
	470-479	1	0	0
	480-489	0	0	1
	490-499	0	0	1
	≥500	0	1	2
440-499	<500	5	18	13
	≥500	4	2	0
≥500	Any	0	2	1

3. Conclusions (Sponsor)

"The primary and secondary study objectives to demonstrate equivalent efficacy to granisetron were met. The efficacy of the three treatments was similar in each of the four strata.

"Antiemetic efficacy of both dolasetron mesylate and granisetron was negatively affected by female gender, previous chemotherapy, and the absence of a history of alcohol use.

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

"Both dolasetron and granisetron elicited effects that resulted in increases in measured 12-lead ECG intervals. There was no evidence of increased patient risk from these effects.

"Based on careful review of both safety and effectiveness data, there is little reason to select the 2.4 mg/kg dolasetron mesylate dose.

"The 1.8 mg/kg dose of dolasetron mesylate dose is safe and effective in the indication studied.

"Patients were equally satisfied with the three treatments."

4. Reviewer's Comments

Study -093 is the third of the four main cisplatin trials in NDA 20-624. Just as the two above-reviewed studies (-081 and -031), study -093 employed a useful design and was apparently well executed. The prospective stratification of these cancer patients into the three Tx regimens by gender and on the basis of naive vs non-naive to chemotherapy within each center is a sound approach as gender and previous exposure to chemotherapy are recognized factors that influence emetic (or antiemetic) response. Male patients and those that are chemotherapy-naive are expected to show higher CR rates than female patients or those who are chemotherapy non-naive.

The doses selected for this trial (1.8 and 2.4 mg/Kg DOLA•Mesyl) are not expected to be differentiated from one another in their efficacy. This is because Phase II trials have shown that the antiemetic effect of the drug tends to plateau at doses above 1.8 mg/Kg for emesis induced by ≥100 mg/m² cisplatin. The study used a positive comparator, Kytril (granisetron=GRAN) at a single 3 mg one dose fits all. This is the dosage approved in Europe. In the U.S., the recommended dosage is 10 μg/Kg infused within 30 min. before initiation of chemotherapy [and only on the day(s) chemotherapy is given]. The dose of GRAN used in study -093 is much higher than needed since it is equivalent to administering 40 μg/Kg to a 75 Kg patient or 60 μg/Kg to a 50 Kg person. Since, for GRAN, doses of up to 160 μg/Kg do not seem to improve efficacy over the recommended 10 μg/Kg dosage, the 3 mg GRAN can be categorized as an active comparator. Hence the main objective of study -093 which was to show equivalence between DOLA•Mesyl 1.8 or 2.4 mg/Kg and the 3 mg GRAN. But, as per study -031, in addition to showing equivalence, in the

absence of an internal negative control, to show activity, statistical comparisons are needed to a relevant negative historical control. This was described in detail in the Reviewer's Comments section of study -031.

The inclusion-exclusion criteria were as per previously described CCNV protocols, with the same exclusions pertaining to the cardiovascular system.

The randomization/stratification procedures used in study -093 were apparently well executed. This approach resulted in three populations of patients that were comparable to each other in important variables that may influence outcome. Comparability of the groups at baseline was demonstrated, except as noted. The three experimental groups were well balanced with respect to demographic (gender, M=77%; F=34%; mean age=55y; mean weight=62 Kg; mean height=167cm), four strata (M naive, F naive; M non-naive, F non-naive), primary cancer (the predominant sites of primary neoplasm were: head/neck=36%, lung=15%, digestive system/gynecological=14% each), P.E., other significant medical conditions, Karnofsky performance status (mean=85%, range 60 to 100%), history of alcohol abuse (YES=35%, NO=65%), nausea, VAS either 45 min or just prior to chemotherapy at Pre-Tx and hour 0, prior medications, and concomitant medications that may be confounding, such as concomitant other chemotherapies (5-FU, etoposide, cyclophosphamide, etc.). The exceptions were the following imbalances: a) a higher percentage of Hx of cardiovascular abnormalities in the GRAN group compared to the two DOLA•Mesyl groups ($p=0.018$); b) fewer "other" abnormalities in the 2.4 mg/Kg DOLA•Mesyl group compared to the other two groups; c) greater use of morphine sulfate or amoxicillin use in the 1.8 mg/Kg DOLA•Mesyl group compared to the other two. Although statistically significant, the MO concludes that these imbalances did not represent variations in large numbers of patients. But, in reality, their impact on the efficacy/safety of the Tx groups is not known.

In study -093, the three Tx groups were well matched with regards to standardization of the emetic stimulus, a regimen that can be best characterized as being of high emetogenic potential. Although the mean cisplatin dose was 97 mg/m^2, there was a statistically significant imbalance in cisplatin dose ($p=0.0389$): the mean cisplatin dose was 98, 96 and 96 mg/m^2, respectively, for the GRAN, 1.8 and 2.4 mg/Kg DOLA•Mesyl groups. In spite of these small differences, the MO still calls the three groups well matched because all of these dose levels of cisplatin (>90 mg/Kg) are considered highly emetogenic. The three groups were balanced in the duration of cisplatin infusion (mean=87 min.) and the interval between start of test med. administration and start of cisplatin infusion (mean=31 min.). On the average, >76% of the patients received >90 mg/m^2 cisplatin; and ca. 24% received cisplatin <90 mg/m^2 within the 24-h study period.

The CR rate with GRAN was 48% in the ITT and 49% in the Evaluable population. None of the two DOLA•Mesyl regimens (CR rate=54% and 47%, respectively) was shown to be clinically or statistically different from GRAN (both study populations). Thus the CRs were equivalent among the three groups and the three Txs appear to meet the protocol-specified criteria for equivalence. In

addition, all three treatments were significantly superior to the above-described historical placebo control ($p<0.0001$), with clinically meaningful therapeutic gains of 36% to 43% in the ITT and 36% to 42% in the Evaluable population. Just as in study -031, the results of study -093 strongly suggest that doses of DOLA•Mesyl higher than 1.8 mg/m² do not provide additional antiemetic efficacy. Thus, the clinically appropriate comparison is DOLA•Mesyl 1.8 mg/Kg vs GRAN. But both dose levels of DOLA•Mesyl appear to be a) active; b) equivalent to GRAN in the prevention of high-dose cisplatin-induced N&V in cancer patients.

In study -093 the analyses of results based on stratification yielded the expected efficacy results. Patients were stratified by gender and on the basis of being naive or non-naive to chemotherapy. A highly significant stratum effect was noted ($p=0.0001$). M patients showed an ca. two fold higher response rate compared to F (61% vs 26%; $p=0.0001$) and this difference was observed in all 3 Tx groups. Chemotherapy naive patients showed a significantly higher CR than chemotherapy non-naive patients (55% vs 42%; $p=0.0008$). In this study, the highest CR rate was 71% in the M naive treated with DOLA•Mesyl 1.8 mg/Kg. The lowest CR rate was 17% in F naive to chemotherapy treated with GRAN 3 mg. It is worth noting that with high dose cisplatin >90 mg/m², the efficacy of DOLA•Mesyl 1.8 mg/Kg was 59% vs 49% in GRAN and 44% in DOLA•Mesyl 2.4 mg/Kg, a numerical difference that may be the result of the statistically significant cisplatin imbalance noted above.

Analyses of subgroups indicated no significant differences among the 3 Tx groups. However, significantly greater antiemetic efficacy was achieved in patients who had a Hx of alcoholism ($p=0.0317$). In other trials, this factor has been shown to influence the outcome of antiemetic therapy. A greater antiemetic efficacy was achieved in patients who received no concomitant narcotic analgesics and this effect was close to statistical significance ($p=0.0565$).

In this study population and under the experimental conditions and methodology used in study -093, single intravenous doses of DOLA•Mesyl 1.8 or 2.4 mg/Kg were - all in all - well tolerated. There were eleven serious AEs. The four deaths reported in the trial were related to the patients progression of cancer or concurrent illness. Two patients did not complete all study measures due to AEs. One patient received DOLA•Mesyl 2.4 mg/Kg and died as a consequence of pulmonary embolism 2h 15 min. after test med. This event was not Tx-related. The other patient in the GRAN 3 mg group developed angina/MI/acute pulmonary edema. This event was possibly related to test med. or the chemotherapeutic agent vinorelbine which is known to produce pulmonary toxicity (angina + MI + acute pulmonary edema were linked, according to the investigator). Except for subocclusion, the six serious AEs occurring in this trial were due to either the underlying cancer or concurrent chemotherapy. Subocclusion in one patient in the GRAN 3 mg group was assessed as possibly related to test med. because the investigator thought that the 5-HT_3 receptor antagonist may potentiate the effect of vinorelbine. The latter is known to provoke intestinal occlusion. With the exception of the patient experiencing

MI whose EKG still showed sequelae of cardiac ischemia 3 weeks after the event, the six patients experiencing these SAEs recovered without sequelae.

The overall AE rates were similar with the 1.8 and 2.4 mg/Kg (58% and 55%, respectively) and GRAN (45%). There was statistically significant Tx difference in the overall incidence AEs related to the g.i. system (GRAN=13%; total DOLA•Mesyl=20%, p=0.0249). The most frequently reported AEs in the overall population were headache, diarrhea and abnormal hepatic function but, for these, there were no Tx-related statistical differences. Also, there were statistically significant Tx differences in the overall incidence of Tx-related AEs (GRAN=38%, DOLA•Mesyl 1.8 mg/Kg=53%, 2.4 mg/Kg=43%). The large majority of patients had AEs that were mild to MOD in severity. Of the AEs of potential concern (respiratory system=3, cardiovascular system=2 and bleeding=2) only moderate "breathing difficulties" occurring 1.5h after administration of test med. was assessed as possibly related to DOLA•Mesyl 2.4 mg/Kg.

In study -093 there were no statistically significant Tx differences in the EKG changes noted as AEs and the frequency of pts. presenting with each particular listed EKG change noted as AE ranged from 0 to 3%.

Study -093 was important as it afforded the opportunity of side-by-side comparisons between the effects of two dose levels of DOLA•Mesyl and GRAN 3 mg on EKG parameters taken 1 to 2h post-Tx. This facilitates evaluations of Tx-related effects at a time when the blood concentration of the active DOLA•Mesyl metabolite is highest. The results were not presented in graphic form and this is unfortunate because in study -031, Fig. 6 provided a quick eyeball difference between DOLA•Mesyl and OND. Similarily, the data in study -093 demonstrated that the EKG interval changes induced by DOLA•Mesyl (both dose levels but the difference between 2.4 mg/Kg and GRAN were larger than those between 1.8 mg/Kg and GRAN) are different from those induced by GRAN. It is to be noted, however, that for the mean changes from baseline, statistically significant Tx-difference was shown only for PR (p=0.0002) and QT_c (p=0.0016). But the changes (rather no changes from baseline) in QRS were different in study -093 to those seen in most other DOLA•Mesyl trials. Another discrepancy was that, contrary to findings in most studies, in study -093 the JT interval was increased by DOLA•Mesyl. In the absence of a graph, these findings are summarized below.

> The mean PR interval was increased by DOLA•Mesyl (7.0 msec in the 1.8 mg/Kg group and 11.9 msec in the 2.4 mg/Kg group) versus 0.1 msec for GRAN. A Tx-emergent PR interval ≥220 msec was classified as first degree AV block. Six patients in the DOLA•Mesyl 1.8 mg/Kg group, seven patients in the DOLA•Mesyl 2.4 mg/Kg group, and one patient in the GRAN group, had reports of first degree AV block. Although the mean QRS width was equally increased in the three Tx groups (about 2.5 msec), the number of patients with post-Tx QRS •100 msec was higher in the DOLA•Mesyl groups: 16 patients in the DOLA•Mesyl 1.8 mg/Kg group, 11 patients in the DOLA•Mesyl 2.4 mg/Kg group and 4 patients in the GRAN group had Tx emergent increases in QRS duration ≥100 msec. Three patients in the DOLA•Mesyl 1.8 mg/Kg group and one patient in the GRAN group, had post-Tx QRS duration ≥120 msec. The mean QT_c was increased by DOLA•Mesyl 1.8 mg/Kg (9.1 msec) and 2.4 mg/Kg (15.2 msec) versus 0.1 msec in the GRAN group. This increase of QT_c in DOLA•Mesyl patients appeared not

to be clearly related to an increase of QRS width. The JT interval was increased by 10.6 msec and 9.8 msec in the DOLA•Mesyl 1.8 mg/Kg and 2.4 mg/Kg groups, respectively, versus 1.0 msec in the GRAN group. The Tx differences were not statistically significant.

The results of study -093 for both QRS (no change) and JT interval (increase) are at variance with EKG data from most other DOLA•Mesyl trials. Although there is no plausible explanation for these discrepancies, Dr. A. Karkewky (HFD-110) has recently shown that most DOLA•Mesyl studies showed an increase in JTc.

It would seem that - all in all - the patients in study -093 were safely treated as there were no reports of critical rhythm disturbances such as VT, high-degree AV block or Torsades de pointes.

E. Study MCPR0032

1. Study Objective, Design, Execution, Statistics

- This study, the fourth in which the emetogenic stimulus consisted of high dose cisplatin was set to evaluate the dose response relationship of increasing single intravenous doses of DOLA•Mesyl, across 0.6, 1.2, 1.8, 2.4 and 3 mg/Kg in preventing emesis due to cisplatin-based regimens.

- The design, execution and other aspects of this U.S. trial were similar to those used in the other prevention of CCNV trials.

- The patients were prospectively stratified on the basis of amount of cisplatin given. The inclusion-exclusion criteria were adequate for this type of trial. Exclusions pertaining to the cardiovascular system, as listed in the protocol, were:

  - Cardiomyopathy or Hx of CHF
  - Arrhythmias, requiring antiarrhythmic medication
  - Abnormal pre-Tx serum potassium or calcium results which could not be corrected prior to receiving chemotherapy
  - Greater than first degree heart block
  - Preexisting complete BBB, either L or R.

- This trial made use of a 5-arm, double-blind, randomized, stratified, parallel, dose-response design in platinum naive cancer patients undergoing their first course of ≥70 mg/m² cisplatin containing chemotherapy. An anticipated 300 patients were prospectively stratified as to cisplatin dose, 150 to receive 70 to 90 mg/m² vs 150 to receive ≥91 mg/m² and then randomized by strata to receive either 0.6, 1.2, 1.8, 2.4 or 3.0 mg/Kg of i.v. DOLA•Mesyl. Cisplatin was administered over no more than 3h. No additional antiemetic medications were permitted during the 24h prior to or after cisplatin. Safety and efficacy were monitored throughout the 24-h Tx period. If the patient experienced at

least three emetic episodes during the 24-h Tx period beginning with the start of chemotherapy, or requested alternative antiemetic therapy, the investigator initiated escape medication according to institutional practice.

- Patients were randomly assigned to one of the five dose regimens (0.6, 1.2, 1.8, 2.4 or 3.0 mg/Kg DOLA•Mesyl), using a random code provided by the sponsor. A separate random code was issued for each cisplatin stratum at each investigational site. DOLA•Mesyl was infused over 15 min., 30 min. prior to cisplatin chemotherapy.

- The blinding, packaging and labeling of test materials were all adequate.

- The study evaluations (assessment of efficacy and safety) were adequate, as per previous prevention of CCNV trials. A 12-lead EKG was obtained Pre-Tx and at 1 to 2 and 24h Post-Tx.

- The sample size determination was based on a linear trend test in the logistic scale, across the five equally spaced DOLA•Mesyl doses, while adjusting for the design factors of investigative site and cisplatin dose stratum. With this assumption, the postulated CR rates were: 25%, 31%, 37%, 43% and 50% for patients in the DOLA•Mesyl doses of 0.6, 1.2, 1.8, 2.4 and 3.0 mg/Kg, respectively, with cisplatin doses ≥91 mg/m^2; and CR rates of 40%, 47%, 54%, 60% and 67% of patients in the DOLA•Mesyl doses of 0.6, 1.2, 1.8, 2.4 and 3.0 mg/Kg, respectively, with cisplatin doses <91 mg/m^2 Assuming 30 patients in each DOLA•Mesyl-cisplatin dose combination for a total of 300 patients, the power for a 2-tailed 0.05 significance linear trend test is 89%. The study was not terminated early and there were no interim analyses.

- The primary assessment of efficacy was CR (defined as 0 emetic episodes, no rescue med., and monitored for emesis at least 23.5h).

  - Logistic regression with a test for linear trend over dose in the proportion of complete responders, controlling for investigator and cisplatin dose stratum was the primary assessment of efficacy. This analysis was conducted using the intent-to-treat dataset.

  - The presence of investigator by dose and stratum by dose interactions were tested using logistic regression and the Rao scores (residual Chi-square) test.

  - As a secondary analysis, CR rates for each dose group were compared to a historical placebo control response rate (11.1%, the upper endpoint of an exact 95% binomial confidence interval based on the results of four published studies) using parameters estimated from the primary logistic regression model.

  - Further secondary analyses included logistic regression as described for the primary analysis using an efficacy evaluable dataset, subgroup analyses using the logistic regression model, and a Mantel-Haenszel test for non-zero correlation.

- AEs were analyzed for a linear dose response using logistic regression. Changes from baseline in clinical laboratory measurements, vital signs, and EKG parameters were analyzed for a linear dose response using a rank analysis of variance.

- All analyses and summaries of the safety data used the intent-to-treat dataset.

2. Results

a. Participating Investigators/Patient Accounting

- Of the 21 participating investigators, two sites (#0093 and 0097) recruited no patients; 19 centers enrolled 299 patients (F=126; M=174); all 299 patients completed the trial and were included in the ITT dataset. The following seven investigators enrolled 20 or more patients each: K.B. Pendergrass, Kansas City, MO (#0094, n=30), M. Thant, Baltimore, MD (#0104, n=30), M.R. Modiano, Tucson, AZ (#0108, n=39), H. Sher, Jacksonville, FL (#0102, n=23), K.S. Sridhan, Miami, FL (#0107, n=23), G. Harman, Lackland AFB, TX (#0072, n=20) and W. Nahhas, Dayton, OH (#0101, n-20).

- 13 pts. with major protocol violations were not included in the ITT analysis.

- The number or patients analyzed per study population per group was:

Population Analysis	DOLA•Mesyl Dose (mg/Kg) 0.6	1.2	1.8	2.4	3.0	Total DOLA•Mesyl
ITT	59	59	63	60	58	299
Evaluable	54	56	62	59	55	286

b. Data Showing Comparability of Groups at Baseline

- There were no statistically significant imbalances among the five dose groups with respect to gender, race, age, weight, height, Karnofsky performance status and history of heavy alcohol use.

- The study population was predominantly caucasian (83.3%) and male (58.2%). The median age was 63.0y; the median weight was 70.8 Kg; the median height was 170 cm; and the median Karnofsky performance status was 90%. A history of heavy alcohol use was reported in 22.1% of the patients.

- There were no important imbalances across the Tx groups in the site of primary neoplasm. The most frequent sites of primary neoplasm were lung (46.8%), head/neck (14.4%) and gynecologic (11.7%).

- There were no marked imbalances in organ system abnormalities and medical histories among the five dose groups. There were no imbalances in previous chemotherapy or previous radiotherapy among the five dose groups. There was a statistically significant imbalance in previous surgery among the five dose groups. Of the 299 patients (32.8%) had previously undergone surgery for cancer. The 1.8 mg/Kg dose group had a smaller proportion of patients with previous surgery (17.5%) than the other dose groups (27.1%, 39.0%, 40.0% and 41.4%, respectively, for the 0.6 1.2, 2.4 and 3.0 mg/Kg dose groups).

- There were no statistically significant imbalances in previous medications among the five dose groups. The most frequent concomitant medications used pre-Tx were sodium chloride (36%), mannitol (31%), potassium (17%), furosemide (14%), magnesium sulfate (13%), Tylox® (oxycodone and acetaminophen (13%) and paracetamol acetaminophen (11%).

i) Cisplatin and Other Chemotherapy (Table 51)

- As shown in this Table, there were no statistically significant imbalances among the dose groups in cisplatin dose, duration of cisplatin infusion and interval between test drug administration and cisplatin infusion.

- The range of cisplatin doses received in this study population was 35 to 106 mg/m², with a mean of 89 mg/m².

  - 55.9% of patients were in the high dose (≥91 mg/m²) cisplatin stratum. Within the high dose stratum, the mean cisplatin dose was 100 mg/m², the mean cisplatin dose within the low dose stratum was 75.5 mg/m².

  - The mean duration of cisplatin infusion was 138.2 min. (range: 40 to 305 min.). The mean interval between test drug administration and cisplatin infusion was 34.7 min. (range: 14 to 255 min.).

- There were no statistically significant imbalances in a) use of concomitant chemotherapies, b) concomitant medications, c) use of benzodiazepines or narcotic analgesic or d) use of escape medications among the five dose groups.

TABLE 51
Study -032

Summary Information on Cisplatin, Previous Cancer Treatment and Concomitant Cancer Chemotherapy

Variable	DOLA®Mesyl Dose (mg/Kg) 0.6 [n=59]	1.2 [n=59	1.8 [n=63]	2.4 [n=60]	3.0 [n=58]	Total DOLA®Mesyl [n=299]	p-value
I. CURRENT CHEMOTHERAPY: CISPLATIN [n=299]							
Mean Cisplatin Dose (mg/m^2) Range	88.2	89.2	90.5	88.8	89.0	89.2	N.S.
Cisplatin Dose Category							
≥91 mg/m^2	52.5%	55.9%	58.7%	55.0%	56.9%	55.9%	N.S.
<91 mg/m^2	47.5%	44.1%	41.3%	45.0%	43.1%	44.1%	
Mean Duration of Cisplatin Infusion (min) Range	137.9	140.4	133.0	140.7	139.4	138.2	N.S.
Mean Interval Between Initial Study Drug and Cisplatin (min) Range	35.0	34.0	32.3	33.4	39.2	34.7	N.S.
II. PREVIOUS CANCER TREATMENT							
Chemotherapy	6.8%	3.4%	6.3%	--	1.7%	3.7%	
Radiotherapy	23.7%	16.9%	14.3%	26.7%	20.7%	20.4%	N.S.
Surgery	27.1%	39.0%	17.5%	40.0%	41.4%	32.8%	
Concomitant use of Benzodiazepines	11.9%	5.1%	11.1%	8.9%	8.6%	9.0%	N.S.
Concomitant Use of Narcotic Analgesics	32.2%	39.0%	30.2%	35.0%	36.2%	34.4%	N.S.
III. CONCOMITANT CANCER CHEMOTHERAPY							
5-FU W/NS	13.6%	16.9%	27.0%	23.3%	19.0%	20.1%	N.S.
Cyclophosphamide	5.1%	5.1%	3.2%	10.0%	5.2%	5.7%	N.S.
Doxorubicin	6.1%	5.1%	7.9%	6.7%	13.8%	7.7%	N.S.
Etoposid	40.7%	37.3%	34.9%	28.3%	22.4%	32.8%	N.S.
Vinblastin	6.8%	11.9%	4.8%	13.3%	20.7%	11.4%	N.S.

TABLE 52
Study -032

Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response

Response by Dose (mg/Kg)						Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses and Historical PL Control/[p-values]					
I. Intent-To-Treat Analysis [n=299][a]											
Hist-PL	0.6 [n=59]	1.2 [n=59]	1.8 [n=63]	2.4 [n=60]	3.0 [n=58]	0.6 vs PL	1.2 vs PL	1.8 vs PL	2.4 vs PL	3.0 vs PL	Total DOLA•Mesyl vs PL
11.1%	24 (41%)	26 (44%)	32 (51%)	26 (43%)	27 (47%)	30% [<0.0001]	33% [<0.0001]	40% [<0.0001]	32% [<0.0001]	36% [<0.0001]	34% [<0.0001]
95% CI for the % of CR	88%,54%	32%,58%	40%,65%	31%,57%	35%,61%						
II. Efficacy Evaluable Analysis [n=286][c]											
	[n=54]	[n=56]	[n=62]	[n=59]	[n=55]						
11.1%	23 (43%)	25 (45%)	31 (50%)	26 (44%)	26 (47%)	32% [<0.0001]	34% [<0.0001]	39% [<0.0001]	33% [<0.0001]	36% [<0.0001]	35% [0.0001]

a) Primary Test: Linear Trend, ITT [n=299], p=N.S.[d]
Mantel-Haenszel Test for Non-Zero Correlation: ITT [n=299], p=N.S.[e]
b) The historical PL control response rate was the upper endpoint of an exact 95% binomial confidence interval based on the results of four published studies (11.1%)
c) Secondary Test: Linear Trend, Efficacy Evaluable [n=286], p=N.S.
d,e) p-value is calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting CR with dose, investigator, and stratum included in the model.