c. Clinical Response (Table 52)

- The results of study -032 revealed all five dose levels of DOLA•Mesyl to be effective at controlling cisplatin-induced N&V.

- Across the five dose groups, there was not a statistically significant linear trend in the proportion of complete responders (0 emetic episodes and no escape medication in the 24-h Tx period).

- Each dose group was significantly superior to a historical (PL) control ($p<0.0001$). The CR rate for the combined DOLA•Mesyl doses was 45.2%.

- Cisplatin dose stratum was a significant predictor of CR ($p=0.0010$), with higher CR rates being associated with the lower doses of cisplatin (<91 mg/m²).

  - Within the low dose cisplatin strata, a trend toward a linear dose response appeared to exist across the first three (low) DOLA•Mesyl doses ($p=0.0533$): 43%, 62% and 69% for the 0.6, 1.2 and 1.8 mg/Kg dose groups, respectively.

- Subgroup analyses of efficacy indicated that there were statistically significant overall differences indicating higher CR rates in patients who were male ($p=0.0016$):

  - The female population, which is generally more susceptible to poor emetic control, appeared to have had the greatest CR rate (12/25=48%) at the 1.8 mg/Kg dose.

  - Patients who received narcotic analgesics during the 24-h Tx period were less likely to have a CR than those patients who did not ($p=0.0882$).

  - Among those patients receiving narcotic analgesics, a linear response was suggested across the first three doses: 21% at 0.6 mg/Kg; 30% at 1.2 mg/Kg; and 42% in the 1.8 mg/Kg DOLA•Mesyl dose group.

Complete Response by Gender

	DOLA•Mesyl (mg/Kg)					
	0.6	1.2	1.8	2.4	3.0	Total DOLA•Mesyl
M [n=174]	42%	51%	53%	47%	62%	51%
F [n=125]	39%	32%	48%	39%	30%	38%
Δ (M>F)	3%	19%	5%	8%	31%	13%

Statistics:

- Testing the subgroup by linear dose response interaction, $p(int)=0.2536$
- Testing the subgroup as the main effect, $p(m)=0.0016$
- Linear dose response while controlling for the subgroup as a main effect, $p(lin)=0.3520$

i) Time to First Emetic Episode or Escape Medication (Table 53)

- The median times to first emetic episode or escape med. whichever occurred first, were: 20.25, 21.33, 23.83, 20.84 and 21.55 for the 0.6, 1.2, 1.8, 2.4 and 3.0 mg/Kg dose groups, respectively.

- Table 53 provides the proportion of complete responders over time (for hours 4, 8, 12, 18 and 24) for each dose group. The hazard ratios estimated from the Cox proportional hazard model of time to first emetic episode or escape medication showed no statistically significant linear trend over dose.

TABLE 53
Study -032

Time to First Emetic Episode or Escape

(CR by Hour and Dose)

Hour	DOLA•Mesyl Dose (mg/Kg)•					Total DOLA•Mesyl [n=299]
	0.6 [n=59]	1.2 [n=59]	1.8 n=63]	2.4 [n=60]	3.0 [n=58]	
4	86.4%	94.9%	100.0%	98.3%	98.3%	95.7%
8	64.4%	79.7%	88.9%	80.0%	77.6%	78.3%
12	61.0%	71.2%	76.2%	73.3%	70.7%	70.6%
18	54.2%	62.7%	61.9%	61.7%	53.4%	58.9%
24	40.7%	44.1%	50.8%	43.3%	46.6%	45.2%

Dose p=0.3819, from a Cox regression model with a test for linear trend in the hazard ratios, controlling for investigator and cisplatin dose stratum.

a) Depicted are the % of Complete Responders through a given hour by dose.

d) Safety Results

1) Extent of Exposure

In study -032, a total of 299 patients were treated with single i.v. doses of test med., with the following distribution:

DOLA•Mesyl (mg/Kg)				
0.6 [n=59]	1.2 [n=59]	1.8 [n=63]	2.4 [n=60]	3.0 [n=58]

2) Deaths, Dropouts Due to AEs and Other Serious AEs

- There were 13 deaths reported in the study. These events occurred from 8 to 147 days after administration of test med. In addition, 6 pts. experienced AEs that resulted in or prolonged hospitalization. As shown below, there was no dose response across the test groups with respect to these events.

	DOLA•Mesyl Dose (mg/Kg)				
	0.6	1.2	1.8	2.4	3.0
Deaths[a]	4	1	1	4	3
SAEs[b]	0	1	1	3	1

a) None of the deaths occurred during the 24-h study period. None was assessed by the investigator as related to test med.
- 5 deaths were related to progression of underlying cancer and occurred 10 or more days following test drug administration.
- 5 deaths followed cardiac arrest. These occurred 8 or more days following test drug administration.
- The remaining 3 deaths occurred at least 10 days after study drug.
  - 1 patient died from cerebral hemorrhage 10 days after test drug (unlikely related).
  - 1 patient had a stroke 6 days after study drug and subsequently died from sepsis 74 days after test drug.
  - 1 patient died from pulmonary embolism 52 days after test drug.

b) 4 of these 6 SAEs were assessed as not related, 1 as unlikely related and 1 as possibly related to DOLA•Mesyl:
  - Pt. MCST0094-0206, a 64y old M experienced pancreatitis 5.75h after receiving 116 mg (1.8 mg/Kg) of DOLA•Mesyl, intravenously. Due to the temporal relationship, this event was assessed as possibly related to DOLA•Mesyl,

3) AEs

- The overall rates of AEs varied between 62% and 81% and there was no statistically significant linear trend over dose in the overall incidence of AEs.

- The most frequently reported AEs by System Organ Class were those related to the HR & rhythm, the central and peripheral nervous system and the g.i. system but there was not statistically significant linear trend over dose in the incidence of AEs for any of these three systems.

- The most frequently reported individual AEs were headache, diarrhea, sinus bradycardia, sinus tachycardia, T wave change or abnormality, ST-T change or abnormality and fever. But there was not statistically significant linear trend over dose in the incidence of any of these AEs.

- The frequency (%) of all Tx-emergent EKG interval changes was as summarized below:

Frequency (%) of All Tx-Emergent EKG Interval Changes

System Organ Class and Included Term p-value[a]	DOLA•Mesyl Dose (mg)					Total DOLA•Mesyl [n=299]
	0.6 [n=59]	1.2 [n=59]	1.8 [n=63]	2.4 [n=60]	3.0 [n=58]	
Overall Rate (p=0.0152)	25.4	39.0	42.9	35.0	51.7	38.8
Heart Rate & Rhythm (p=0.0152)	25.4	39.0	42.9	35.0	51.7	38.8
QT Interval Prolongation (QTc≥440)[b] (p=0.0479)	15.3	30.5	31.7	26.7	34.5	27.8
EKG Abnormal Specific (QRS≥100)[c] (p=0.0820)	13.6	5.1	9.5	16.7	19.0	12.7
AV Block First Degree (PR≥220)	3.4	3.4	6.3	0	3.4	3.3

a) p-values are calculated from a test for linear trend over dose in the occurrence of that event using a logistic regression model controlling for stratum.
b) Of the 83 instances of QT interval prolongation, 82 were assessed as Tx-related by the investigator. Of the 38 instances of EKG abnormal specific, 35 were assessed as Tx-related by the investigator. All 10 instances of AV block first degree were deemed Tx-related by the investigator.
c) The vast majority of Tx-emergent EKG interval changes were mild in intensity, and none were severe; 4 patients experienced Tx-emergent EKG interval changes rated as MOD in intensity.

- There was not a statistically significant linear trend over dose in the overall rates of Tx-related AEs.
- Of the 72 instances of headache, 65 were considered at least possibly Tx-related by the investigator. Of the 39 instances of diarrhea, 26 were considered at least possibly Tx-related by the investigator.
- The majority of AEs were mild to MOD in intensity.
- 22 pts. experienced a severe AE; 3 of these were assessed as Tx-related by the investigator:
  - 2 experienced Tx-related severe headache. Pt. MCST0106-0205 (1.2 mg/Kg) and patient MCST0108-0219 (2.4 mg/Kg). The headaches occurred at ca. 11 and 17h after test drug administration, respectively, and both resolved without sequelae.
  - Patient MCST0100-0203 (1.2 mg/Kg) experienced severe diarrhea assessed as Tx-related. The diarrhea resolved without sequelae after Tx with lomotil.
  - The remaining 19 patients had severe AEs which were not assessed to be study drug related by the investigator.

4) AEs of Potential Concern

Chest Pain

- 2 patients reported non-serious, non-severe chest pain or chest tenderness events during the 24-h Tx period.

  - Patient MCST0094-0201 experienced mild chest pain 8.5h after receiving DOLA•Mesyl 1.8 mg/Kg. The investigator assessed the event as cardiac in origin and possible related to test medication. The patient's history was significant for hypertension and "chest pain" associated with coughing.

  - Patient MCST0107-0104 experienced moderate chest tenderness assessed as being unrelated to DOLA•Mesyl. This AE was attributed to the patient's cancer and obstructive pneumonia with associated rhonchi.

Myocardial Events

- 2 patients reported non-serious, non-severe myocardial ischemia or possible myocardial infraction AEs during the 24-h Tx period.

  - Myocardial ischemia accompanied by T wave changes was noted on the 24-h EKG of patient MCST0099-0101 (DOLA•Mesyl 3.0 mg/Kg). the patient was asymptomatic and had no significant cardiac history. The investigator assessed the event as mild in intensity and having a "possible" relationship to DOLA•Mesyl.

  - The possible MI was identified on the 1-2h and 24-h EKGs of patient MCST0094-0103 (DOLA•Mesyl 2.4 mg/Kg). Though not noted on the pre-Tx EKG, the investigator considered the infarction to have been previously present and unlikely to be related to test medication. Significant medical Hx for this patient included peripheral vascular disease and hypertension.

5) Summary Results of Clinical Laboratory Evaluations

Except for a non-statistically significant trend for SGPT, SGOT and total BIL, which increased from BL to 24h post-Tx in all dose groups, laboratory results were basically unremarkable with no meaningful statistically significant linear trend.

6) Vital Signs

There were no statistically significant linear trends over dose in recumbent pulse rate, systolic or diastolic BP at any time point.

7) EKG Interval Changes

The mean changes in EKG parameters from baseline to hour 1 to 2 post-Tx are summarized below.

Mean Change From BL to Hour 1 to 2

	DOLA•Mesyl Dose (mg/Kg)					
	0.6	1.2	1.8	2.4	3.0	p-value
HR (bpm)	0.6	-2.1	0.9	1.3	-0.4	N.S.
PR (msec)	9.5	10.8	12.4	17.2	15.3	0.0061
QRS (msec)	2.0	3.0	4.1	7.6	7.1	0.0002
QT (msec)	5.3	9.1	8.0	9.0	12.2	N.S.
QT_c (msec)	8.2	7.0	13.0	14.4	14.2	0.0238
JT (msec)	3.3	6.2	3.9	1.5	5.2	N.S.
None of these EKG changes were considered to be of great clinical significance.						

- The most notable increases in EKG parameters occurred with the two larger doses. The linear trend over dose was statistically significant for PR, QRS and QT_c. For these and for QT, **the larger the dose the greater the prolongation.**

- 10 patients experienced a Tx-related first degree AV block (defined as ≥220 msec).

  - 4 patients were in the 1.8 mg/Kg group, none in the 2.4 mg/Kg group and two each were in the remaining dose groups (0.6, 1.2 and 3.0 mg/Kg). There were no first degree AV blocks recorded at the 24-h post-Tx measure.

- The linear trend over dose was also statistically significant for QT (p=0.0085) and JT (p=0.0035) for the changes from BL to 24 hours.

- 2 patients in the 2.4 mg/Kg group developed bundle branch block (BBB) at 1 to 2h post-Tx.

  - 1 patient, with a documented Hx of BBB had a 1 to 2h post-Tx QRS duration of 165 msec which decreased to 91 msec at 24h post-Tx (pre-Tx QRS duration was 82 msec).

  - The second BBB patient experienced a relatively minor increase in QRS from 104 msec at pre-Tx to 122 msec at 1 to 2h post-Tx; at 24h his QRS width had decreased to 110 msec.

- A dose-response relationship did not appear to exist with respect to such events as BBB, AV block, hypotension and low blood pressure. These events appear to occur randomly across the dose groups.

- Overall, 82 patients experienced Tx-emergent changes in QT_c and 55 patients had BL values ≥440 msec. The distribution of patients by post-BL QT_c and dose level was:

		DOLA®Mesyl Dose (mg/Kg)				
Baseline QT_c (msec)	Post-Baseline QT_c (msec)	0.6 [n=59]	1.2 [n=59]	1.8 [n=63]	2.4 [n=60]	3.0 [n=58]
<440	≥440	9	18	20	16	19
	440-449	3	8	7	6	8
	450-459	2	4	4	3	5
	460-469	2	3	7	5	4
	470-479	1	1	1	0	1
	480-489	0	1	0	0	1
	490-499	1	0	0	1	0
	≥500	9	1	1	1	0
440-499	any	12	9	9	16	7
	≥500	1	0	1	0	1
≥600	any	0	1	2	0	0
All patients with baseline QT_c values ≥440 msec were apparently safely treated. No patients in this study developed Torsades de pointes or malignant ventricular arrhythmias.						

3. Conclusions (Sponsor)

"Dolasetron mesylate, in doses of 0.6, 1.2, 1.8, 2.4 and 3.0 mg/kg were safe and effective in preventing cisplatin-induced nausea and vomiting. All doses were significantly superior to a well characterized set of historical controls (placebo).

"In the three doses in which a dose response relationship could be detected (i.e, 0.6, 1.2, and 1.8 mg/kg), such a relationship was observed for primary efficacy (complete response), and combined endpoint (complete response with no nausea). This is also true within the subgroup populations of female gender and concomitant narcotic use.

"Pharmacokinetics of MDL 74,156 in patients was linear and similar to healthy subjects reported in previous studies.

"While dolasetron mesylate elicited electrophysiologic effects that resulted in increases in measured 12-lead ECG intervals, there was no evidence in this study of increased patient risk from this effect. The ECG interval changes were more pronounced in the 2.4 and 3.0 mg/kg dose groups.

"The changes in PR interval and QRS width after administration of dolasetron mesylate can be predicted from plasma concentrations of the active metabolite, MDL 74,156. The magnitude of change in PR interval and QRS width with plasma MDL 74,156 concentration in patients was comparable to healthy subjects reported previously.

"Results of this study suggest 1.8 mg/kg to be the optimal dose of dolasetron mesylate for the prevention of cisplatin-induced nausea and vomiting."

4. Reviewer's Comments

Study -032 is the fourth and last of the main cisplatin trials in NDA 20-624. Just as the three studies reviewed above (-081, -031 and -093), study -032 employed a useful design and was apparently well executed. The prospective stratification of these cancer patients into the three Tx regimens by the dose of cisplatin given is a sound approach because given the same antiemetic dosage, higher doses of cisplatin are expected to be associated with lower CR.

The doses selected for this trial were based on Phase I/Phase II data from several studies. In one study, patients received ≥50 mg/m² cisplatin. The symptoms of N&V were controlled in a dose-dependent manner, with 40 to 50 mg DOLA•Mesyl resulting in a 54% (32/59) CR rate. In another study, the efficacy of single doses of 20, 30, 40 or 60 mg DOLA•Mesyl in preventing emesis in the 24h following administration of a cisplatin dose of ≥80 mg/m², a significant dose-response relationship was shown. The CR was 50% for the 60 mg dose (ca. 0.9 mg/Kg for a 70 Kg patient) vs 20% for the 20 mg dose (ca. 0.3 mg/Kg for a 70 Kg patient). These data suggested that a dose of 0.7 to 0.9 DOLA•Mesyl was effective in controlling emesis following moderately high to high doses of cisplatin. But several other trials indicated that higher doses may be necessary for maximal efficacy. Among these trials was an open label dose escalating study in patients receiving high doses (≥100 mg/m²) of cisplatin. In this 89 patient trial the CR rate was as follows:

Dose (mg/Kg)	0 Emetic Episodes
1.8	24%
2.4	48%
3.0	52%
5.0	50%

Based on the above-summarized information, it seems reasonable to evaluate the dose response relationship across 0.6, 1.2, 1.8, 2.4 and 3.0 mg/Kg single I.V. doses of DOLA•Mesyl, as done in the present study. The main objective of study -032 was to establish efficacy by showing a trend toward decreased emesis following cisplatin with the increasing doses of DOLA•Mesyl. However, in the presence of a flat response, in addition to showing equivalence in the absence of an internal negative control, to demonstrate 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 and found to be relevant.

The randomization/stratification procedures used in study -032 were apparently well executed, resulting in five population of patients that were comparable to each other in important variables that may influence outcome. Comparability of the groups at baseline was demonstrated. The three experimental groups were well balanced with respect to demographics (the study population was predominantly Caucasian=83%, male=58%, median age=63y, median weight=71 Kg, median height=170 cm, 22% reported a Hx of alcohol abuse), primary cancer (lung=47%, head/neck=14%, gynecological=12%), P.E., other significant medical conditions, Karnofsky performance status, prior medications, and concomitant medications that may be confounding (etoposide, vinblastine, doxorubicin, 5-FU, cyclophosphamide).

In study -032, the five 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. the mean cisplatin dose was 89 mg/m^2 ; 56% of the patients were in the ≥91 mg/m^2 cisplatin stratum and within this stratum, the mean cisplatin dose was 100 mg/m^2. The mean cisplatin dose within the lower dose stratum was 76 mg/m^2. The mean duration of cisplatin infusion was 138 min. (range=40 to 305 min.). The mean interval between test drug administration and cisplatin infusion was 35 min.

The CR rate with the 0.6 mg/Kg DOLA•Mesyl dosage was 41% in the ITT and 43% in the evaluable population. The CR with the other DOLA•Mesyl doses ranged between 43% and 51% in the ITT and between 44% and 50% in the evaluable population. Across the five dose groups, there was not a statistically significant linear trend in the proportion of complete responders. Thus, the complete responses were shown to be equivalent across the five groups. In addition, all five treatments were significantly superior to the above-described historical placebo control ($p<0.0001$), with clinically meaningful therapeutic gains of in the ITT and in the Evaluable population. The results of study -032 suggest that in patients receiving high dose cisplatin, doses of DOLA•Mesyl higher than 0.6 mg/Kg afford little additional antiemetic efficacy since all levels of DOLA•Mesyl tested in this trial were active in this patient population.

In study -032 cisplatin dose stratum was a significant predictor of CR. Not unexpectedly doses of cisplatin less than 91 mg/m^2 were associated with higher CR rates. The response rates were 43%, 62%, 69%, 52% and 56% for the five doses. A dose response relationship ($p=0.0533$) appears to exist for the first three doses within the low cisplatin-dose stratum. The subgroup analyses involved age, patients previously exposed to chemotherapy, the use of benzodiazepines, use of narcotics, gender and Hx of heavy alcohol use. Based on previous studies these results are not entirely unexpected. Gender was a statistically significant predictor of CR ($p=0.0016$). More males (51%) were complete responders than females, 38%. A dose response relationship was

demonstrated amongst the male gender for 0.6, 1.2 and 1.8 mg/Kg doses. The response rates were 42%, 51% and 53#. The dose response relationship was not as pronounced in females as the rates were 39%, 32% and 48% for the same doses of the drug. In this study, 50% of patients not receiving narcotics had a CR compared to 36% of patients who did receive narcotics. Again, this is not unexpected because patients receiving narcotic analgesics are generally more resistant to antiemetic therapy than those not receiving narcotics. The dose response relationship was evident in both groups with the 0.6, 1.2 and 1.8 mg/Kg dose groups. Patients not receiving narcotics had a response rate of 50%, 53% and 55% as compared to those receiving narcotics of 21%, 30% and 42% with regards to the 0.6, 1.2 and 1.8 mg/Kg doses. Patients with a Hx of heavy alcohol use have been reported to have a greater antiemetic response to 5-HT_3 antagonists than patients without such a history. This finding was not confirmed in this study. The remaining subgroups (age, chemotherapy Hx and benzodiazepine use) are more difficult to interpret with respect to CR rates. Older patients (>65y) are purportedly more responsive to antiemetic therapy than younger patients. In this study however, there was virtually no difference in the response rate between these two age groups. The chemotherapy Hx and benzodiazepine use group also revealed no differences in response rates.

In this study population and under the experimental conditions and methodology used in study -032, graded single intravenous doses of DOLA•Mesyl were - all in all - well tolerated. Nineteen patients experienced serious AEs; 13 of these were deaths but none of the deaths occurred during the 24h study period and none were assessed by the investigator as being related to DOLA•Mesyl. Of the remaining 6 serious AEs, 4 were assessed as not related, 1 as unlikely related and 1 (acute pancreatitis) was rated as possibly related to DOLA•Mesyl. Acute pancreatitis occurred in a 64y old M patient 5.75h (temporal relationship) after receiving 116 mg (1.8 mg/Kg) of DOLA•Mesyl intravenously.

The overall AE rates varied between 62% and 81% and there was no statistically significant linear trend over dose in the overall incidence of AEs. There was not statistically significant linear trend over dose in the incidence of AEs per organ systems. The most frequently reported individual AEs were headache, diarrhea, sinus bradycardia, sinus tachycardia, T-wave change or abnormality, ST-T change or abnormality and fever, but there was not statistically significant linear trend over dose in the incidence of any of these AEs. There was a statistically significant difference in the overall rate ($p=0.0152$), heart rate & rhythm AEs ($p=0.0152$) and QT interval prolongation ($QT_c \geq 440$, $p=0.0479$) that were Tx-emergent.

There was not a statistically significant linear trend over dose in the overall rates of Tx-related AEs. Of the 72 instances of headache, 65 were considered at least possibly Tx-related by the investigator. Of the 39 instances of diarrhea, 26 were considered at least possibly Tx-related by the investigator. Of the 83 instances of QT interval prolongation, 82 were assessed as Tx-related and of the 38 instances of EKG abnormal specific, 35

were assessed as Tx-related by the investigator. All 10 instances of AV block first degree were deemed Tx-related by the investigator. The majority of AEs were mild to MOD in intensity. The majority of Tx-emergent EKG interval changes were mild in intensity. Two events of potential concern occurred. One was mild chest pain occurring 8.5h after receiving DOLA•Mesyl 1.8 mg/Kg. The other was non-severe myocardial ischemia or possible MI in a patient that was asymptomatic and had no significant cardiac history. The myocardial ischemia was noted on the 24-h EKG after receiving 3 mg of intravenous DOLA•Mesyl. Both events were assessed as being possibly related to DOLA•Mesyl by the respective investigators. This information should be included in the labeling.

Study -032 showed the expected Tx-emergent EKG changes that are associated with DOLA•Mesyl. The most frequent EKG change was "QT interval prolongation", defined as a Tx-emergent QT_c interval ≥440 msec. Mean increases from baseline at 1 to 2h post-Tx were 8.2, 7.0, 13.0, 14.4 and 14.2 msec for doses 0.6, 1.2, 1.8, 2.4 and 3.0 mg/Kg, respectively. The linear trend was statistically significant (p=0.0238) demonstrating the larger the dose the greater the prolongation. Similarly, the mean increase in PR interval at 1 to 2h post-Tx showed a statistically significantly linear trend over dose (p=0.0061). The mean increase from baseline per dose (0.6, 1.2, 1.8, 2.4 and 3.0 mg/Kg) was 9.5, 10.8, 12.4, 17.2 and 15.3 msec, respectively. The most notable increases occurred with the two larger doses (2.4 and 3 mg/Kg) of the drug. Ten patients experienced a Tx-related first degree AV block (defined as ≥220 msec). Four patients were in the 1.8 mg/Kg group, none in the 2.4 mg/Kg group and two each were in the remaining dose groups (0.6, 1.2 and 3.0 mg/Kg). There were no first degree AV block recorded at the 24-h post-Tx measure. The QRS interval was increased across all doses. The mean increases from baseline at 1 to 2h post-Tx relative to the five dose groups were 2.0, 3.0, 4.1, 7.6 and 7.1 msec. Again, the greatest increase occurred with the 2.4 and 3.0 mg/Kg doses. The test for linear trend over dose was statistically significant (p=0.0002).

Two patients in the 2.4 mg/Kg group developed BBB at 1 to 2h post-Tx. One patient, with a documented history of BBB had a 1 to 2h post-Tx QRS duration of 165 msec which decreased to 91 msec at 24h post-Tx (pre-Tx QRS duration = 82 msec). The second BBB patient experienced an increase in QRS from 104 msec at pre-Tx to 122 msec at 1 to 2h post-Tx. At 24h his QRS width had decreased to 110 msec. A dose-response relationship did not appear to exist with respect to such events as BBB, AV block, hypotension and low blood pressure. These events appear to occur randomly across the dose groups and were more related to the patient's condition or an associated event, as in the case of BBB, than test medication. The change in PR interval and QRS width was linearly related to plasma concentrations of the primary metabolite (MDL 74,156). Neither patient demographic variables (age, weight, gender and race) nor concomitant medications (verapamil, atenolol, nifedipine, glibenclamide, furosemide, diltiazem, propranolol, ACE inhibitors and cisplatin) influenced the PR interval or QRS width with MDL 74,156 concentrations was comparable to that reported previously in healthy volunteers.

F. Study 73147-3-S-082

1. Study Objective, Design, Execution, Statistics

- The objective of this double-blind, double dummy, randomized, multicenter, 3-arm study was to evaluate the effectiveness of two dose levels of DOLA•Mesyl (1.2 and 1.8 mg/Kg) administered intravenously in comparison to an approved dose regimen of MCP (2 mg/Kg i.v. loading dose to be followed by 3 mg/Kg i.v. as a continuous 8h infusion, i.e. 5 mg/Kg i.v. in total) in preventing emesis due to moderately emetogenic non-cisplatin chemotherapy.

- All in all, the design, execution and other aspects of this European trial were similar to those used in the cisplatin trials.

- The study population of patients with histologically confirmed malignant disease and Karnofsky status ≥50% who were undergoing chemotherapy with non-cisplatin chemotherapy agents. The inclusion-exclusion criteria were adequate for this type of study. The first chemotherapeutic agent had to be infused over no more than 1h and had to include one of the following:

  - cyclophosphamide ≥600 mg/m² always given in combination with other cytostatic agents.

  - doxorubicin ≥40 mg/m² as a single agent or ≥25 mg/m² when given in combination with other cytostatic agents.

  - epirubicin ≥75 mg/m² as a single agent or ≥50 mg/m² when given in combination with other cytostatic agents.

  NOTE: These regimens are considered to be of low to moderate emetogenic potential.

Additional cytostatic treatment with other agents was allowed after the administration of the above cytostatics. Carboplatin and cisplatin were not allowed during the 24-h study period.

- The following five exclusion criteria related to "significant cardiac disease":

  - Patients with CHF or Hx of CHF.

  - Patients with greater than first degree heart block.

  - Patients with arrhythmias requiring antiarrhythmic therapy.

- It was recommended that 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 heart echocardiography were excluded.

- Patients with abnormal prestudy serum potassium and sodium concentrations and patients receiving antiarrhythmic therapy. Note in Centers 03, 07, 08, 10, 11, 13, 14, 15, 18, 19, 20, 21 and 22, upon request of the French Ethics Committee, this criterion was more specific. The wording in the Protocol read..."and patients having pathological pre-study EKG, PR, QRS or QT interval prolongation".

- Random allocation of the three Tx regimens was stratified by gender (M or F) and previous chemotherapy Tx (naive or non-naive), thereby producing 4 strata. Within each investigative site and stratum, patients were randomized to receive on the three antiemetic regimens, using a blocking factor of six.

- Two groups received DOLA•Mesyl at 1.2 or 1.8 mg/Kg; 15-min. infusion starting 30 min. before chemotherapy. One group received MCP; 15-min. infusion of 2 mg/Kg loading dose starting 30 min. before chemotherapy followed by 3 mg/Kg infused over 8h starting at the same time as the chemotherapy infusion. The double-blind was maintained using corresponding dummy infusions before the moderately emetogenic chemotherapy infusion and during the 8-h continuous infusion.

- 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. Twelve-lead EKGs were performed at pre-study in all centers and at End-study in some centers.

- The study protocol stated that 300 patients meeting the inclusion and exclusion criteria would be entered into the trial. This number was estimated using the following parameters: α=0.05, β=0.20, percent CR rate of MCP group=50%, and clinically meaningful difference in percent complete response=20%. Based on these parameters a sample size of 100 patients per group was estimated.

- The primary assessment was intent-to-treat logistic regression analysis of CR. The model included terms for patient stratification, treatment and investigative site. Using this model, the primary test of efficacy was the pairwise comparison of 1.8 mg/Kg DOLA•Mesyl vs. MCP. Pairwise tests of 1.2 mg/Kg DOLA•Mesyl vs MCP and 1.2 mg/Kg vs 1.8 mg/Kg DOLA•Mesyl were also made. All tests were two-sided, with α=.05. In addition to the hypothesis tests, 95% confidence intervals (2-sided) for the odds ratio were compared for each pairwise comparison.

- Supportive to the primary analysis of efficacy, Mantel-Haenszel tests of pairwise differences were done, stratifying on investigative site.

- Consistency of Tx effect across investigative sites were assessed by testing site-by-Tx interaction in the logistic model. Similarly, Tx effect consistency across strata was assessed by a Tx-by-strata interaction test. The two interaction tests were done using the Rao scores (residual Chi-square) test, by specifying the appropriate design variables in the logistic model.

- An efficacy analyzable analysis of CR was also conducted as supporting evidence of efficacy. Subgroup analyses were conducted to assess inconsistency in Tx effects across specific dichotomous population subgroups.

- Analysis of Secondary Efficacy Endpoints used the ITT population and included time to first emetic episode or use of escape medication.

2. Results

a. Participating Investigators/Patient Accounting

- Of the 21 participating study sites, 8 enrolled no patients; the remaining 13 (U.K., France, Belgium, Germany and the Netherlands) enrolled a total of 309 patients (F=213, M=96) which constituted the ITT population. The following five sites enrolled >30 patients each: Prof. Fauser, Freiburg, GER (#06, n=66), Dr. Bleiberg, Brussel, BEL (#05, n=48), Dr. Chevalier, Rouen, FR (#07, n=40), Prof. Favre, Marseille, FR (#13, n=39) and Drs. Fabbro/Rossi (#15, n=32).

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

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

Population Analysis	MCP	DOLA•Mesyl (mg/Kg) 1.2	1.8	Total DOLA•Mesyl
ITT		104	101	205
Evaluable	98	102	95	197

b. Data Showing Comparability of Groups at Baseline

- There were no statistically significant imbalances across the Tx groups with respect to age, weight, height, gender, previous chemotherapy, patient stratification, patient VAS nausea severity at Pre-Tx and hour 0, Karnofsky performance status or Hx of alcohol abuse.

- Patients were predominantly female (69%) and were 52% naive to chemotherapy. The mean age was 51y; the mean weight was 64 Kg; the mean height was 165 cm; and the mean Karnofsky performance status was 87%. Positive Hx of alcohol abuse was reported in 4% of the patients.

- There were no important imbalances across Tx groups in site of primary neoplasm. The most frequent sites of primary neoplasm were breast (46%), lymphoma (19%), musculoskeletal (13%) and lung (6%).

- Medical Hx abnormalities were balanced across Tx groups with the exception of Hx of genitourinary abnormality (p=0.046) and Hx of neurologic abnormality (p=0.020) which appeared to occur at random and would not be expected to have an impact on response.

- There were no statistically significant differences across Tx groups in P.E. abnormalities.

i) Current Chemotherapy (Table 54)

- There were no significant imbalances across Tx groups in duration of first chemotherapy infusion, interval between start of test medication administration and start of chemotherapy infusion, or use of single or multiple chemotherapy agents.

- The mean duration of first chemotherapeutic agent infusion was 24 min. (range: 1 to 120 min.); the mean interval between start of test med. administration and start of first chemotherapeutic agent infusion was 31 min. (range: -10 to 60 min.). Most patients (87%) received infusion of two or more chemotherapy agents.

- The most frequent chemotherapy agents were cyclophosphamide (69%), doxorubicin (42%), fluorouracil (33%), epirubicin (29%) and vincristine (19%).

- 22% of patients received escape medication. There was greater use of escape medication in the MCP group. This difference across Tx groups was close to statistical significance (p=0.062); the percent escape medication use was 30%, 18% and 18%, respectively, in the MCP, 1.2 and 1.8 mg/Kg DOLA•Mesyl groups.

- There were no statistically significant differences in the use of a) concomitant meds. taken in the 24-h period before starting chemotherapy; b) major concomitant meds. with potential to affect emesis (non-escape use) (narcotic analgesics, benzodiazepines and corticoids) and c) concomitant meds. during the study evaluation period.

TABLE 54
Study -082

Current Chemotherapy and Use of Escape Medications

Variable	MCP [n=104]	DOLA•Mesyl Dose (mg/Kg) 1.2 [n=104]	DOLA•Mesyl Dose (mg/Kg) 1.8 [n=101]	Total DOLA•Mesyl [n=205]	p-value
I. Current Chemotherapy [n=309]					
Mean Interval between Study Drug and first chemotherapy (min.)	31±4	31±3	30±4	30±4	N.S.
Range					
Mean Duration of first chemotherapy agent (min)	24±26	26±29	20±21	23±25	N.S.
Range					
Single Chemotherapy Agent:					N.S.
YES	15%	15%	7%	11%	
NO	85%	85%	93%	89%	
II. Chemotherapy					
Cyclophosphamide	70%	67%	70%	69%	N.S.
Doxorubicin	42%	41%	43%	42%	N.S.
Fluorouracil	35%	26%	38%	32%	N.S.
Epirubicin	28%	27%	33%	30%	N.S.
Vincristine	18%	21%	17%	19%	N.S.
Pirarubicin	16%	18%	12%	15%	N.S.
Dacarbazine	9%	8%	7%	7%	N.S.
Ifosfamide	6%	9%	9%	9%	N.S.
Etoposide	6%	6%	7%	6%	N.S.
Bleomycin	4%	7%	5%	6%	N.S.
III. Use of Escape Medication (p=0.062)					
YES	30%	18%	18%	18%	
NO	70%	82%	82%	82%	
OND (p=N.S.)	13%	5%	9%	7%	
ALIZA (p=N.S.)	7%	6%	5%	5%	
GRAN (p=N.S.)	7%	5%	3%	4%	
MCP (p=N.S.)	6%	3%	4%	3%	
Methylprednisolone (p=N.S.)	4%	4%	4%	4%	

c. Clinical Response (Tables 55 and 56)

- As shown in Table 55, the primary test of efficacy, the intent-to-treat (n=309) logistic regression test of 1.8 mg/Kg DOLA•Mesyl vs MCP was not statistically significant (p=0.1183). The 1.2 mg/Kg DOLA•Mesyl group was also not statistically significantly different vs MCP (therapeutic gain=3%, p=0.7833), as was 1.8 mg/Kg vs 1.2 mg/Kg DOLA•Mesyl (therapeutic gain=8%, p=0.1940).

- The logistic regression analysis of efficacy analyzable patients (n=295) and the supportive Mantel-Haenszel type comparisons (see Footnote to Table 55) were consistent with the primary ITT results.

- The test for inconsistency in Tx effect across investigators was non significant (treatment x investigator interaction test, p=0.4858). The test for differences in the overall CR rate across investigators was also non-significant (investigator main effect test, p=0.0715).

- Table 56 gives CR rates by patient stratification (gender x previous chemotherapy) and separately for each patient stratification factor (gender and previous chemotherapy). The numerical results show some evidence of inconsistency in Tx effect across patient stratification, but the statistical test for Tx inconsistency was not statistically significant (treatment by stratum interaction test, p=0.1755). Also, the interaction tests for inconsistency in Tx effect between male and female patients (p=0.5329) and between naive and non-naive patients (p=0.2372) were not statistically significant.

- As shown in the upper panel of Table 56, patient stratification was, however, predictive of overall response rate (stratum main effect test, p=0.0224). The overall CR rates were 74%, 63%, 57% and 48% for male naive, male non-naive, female naive and female non-naive patients, respectively, with the highest CR rate seen in patients that were male and naive. Males responded better than females (gender main effect test, p=0.0034). The overall CR rates were 68% for males vs 53% for females. Naive patients responded somewhat better than non-naive patients although the difference was not statistically significant (previous chemotherapy main effect test, p=0.3364). The overall CR rates were 61% for naive patients vs 54% for non-naive patients.

TABLE 55
Study -082

Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response

Response Rate by Tx Group					Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses and MCP and Each Tx Group vs Historical PL Control/[p-values]					
I. Intent-To-Treat Analysis [n=309]										
Hist. PL [n=208]		MCP [n=104]	1.2 [n=104]	1.8 [n=101]	1.2 vs MCP	1.8 vs MCP	1.8 vs 1.2	MCP vs PL	1.2 vs PL	1.8 vs PL
23%		56 (53%)	58 (56%)	65 (64%)	(3%)	)11%)	(8%)	(30%)	(33%)	(41%)
					[N.S.]	[N.S.]	[N.S.]	[<0.0001]	[<0.0001]	[<0.0001]
95% CI for the % of CR		43,63	46,65	55,74	(5%)	(11%)	(6%)	(29%)	(34%)	(40%)
II. Efficacy Evaluable Analysis [n=295]										
[n=208]		[n=98]	[n=102]	[n=95]						
23%		51 (52%)	58 (57%)	60 (63%)						
					[N.S.]	[N.S.]	[N.S.]	[<0.0001]	[<0.0001]	[<0.0001]
95% CI for the % of CR		42,62	47,67	53,73						

Logistic Regression Statistics

ITT Population [n=309]

Comparison	95% CI for Odds Ratio	p-value
1.2 mg/Kg DOLA•Mesyl vs MCP	(0.6, 1.9)	N.S.
1.8 mg/Kg DOLA•Mesyl vs MCP	(0.9, 2.9)	N.S.
1.8 mg/Kg vs 1.2 mg/Kg DOLA•Mesyl	(0.8, 2.7)	N.S.

Mantel-Haenszel Statistics (Row Mean Scores)

Comparison	p-value
1.2 mg/Kg DOLA•Mesyl vs MCP	N.S.
1.8 mg/Kg DOLA•Mesyl vs MCP	N.S.
1.8 mg/Kg vs 1.2 mg/Kg DOLA•Mesyl	N.S.

Evaluable Population [n=295]

Comparison	95% CI for Odds Ratio	p-value
1.2 mg/Kg DOLA•Mesyl vs MCP	(0.7, 2.1)	N.S.
1.8 mg/Kg DOLA•Mesyl vs MCP	(0.9, 2.9)	N.S.
1.8 mg/Kg vs 1.2 mg/Kg DOLA•Mesyl		N.S.

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TABLE 56
Study -082

Complete Response by Stratum, Selected Subgroups and Time to First Emetic Episode or Escape

[ITT, n=309]

I. CR by Stratum					
Factor		MCP	DOLA®Mesyl (mg/Kg)		p-values[a,b]
		[n=104]	1.2 [n=104]	1.8 [n=101]	
Patient Stratification	M naive [n=42]	73%	60%	88%	p(int)=N.S. p(m)=0.0224
	F naive [n=118]	56%	51%	63%	
	M non-naive [n=54]	71%	62%	56%	
	F non-naive [n=95]	34%	55%	59%	
Gender	Male [n=96]	71%	61%	72%	p(int)=N.S. p(m)=0.0034
	Female [n=213]	46%	53%	61%	
Previous Chemotherapy	Naive [n=160]	60%	54%	70%	p(int)=N.S. p(m)=N.S.
	Non-naive [n=149]	46%	58%	58%	
II. CR by Selected Subgroups					
Age (years)	< 65 [n=253]	50%	51%	62%	p(int)=N.S. p(m)=0.0399
	≥ 65 [n=56]	65%	86%	73%	
Narcotics	YES [n=35]	62%	69%	89%	p(int)=N.S. p(m)=0.0585
	NO [n=274]	52%	54%	62%	

III. Time to First Emetic Episode or Escape[c]			
4	84%	92%	87%
8	67%	81%	77%
12	63%	71%	71%
18	56%	64%	67%
24	53%	56%	65%

a) p(int)=p value from Interaction Test

Test for inconsistency in treatment effect across levels of factor (stratum, gender or previous chemotherapy). Tested using Rao scores residual Chi-square by specifying appropriate design variables in logistic regression with factor, treatment and investigator in the model (previous chemotherapy is also in the model for the gender interaction test and, similarly, gender is also in the model for the previous chemotherapy interaction test).

b) p(m)=p value from Main Effect Test:

Test for differences in overall response rate across levels of factor (stratum, gender or previous chemotherapy). Factor effect tested in logistic regression with factor, treatment and investigator in the model (previous chemotherapy is also in the model for the gender main effect test and, similarly, gender is also in the model for the previous chemotherapy main effect test).

c) Depicted are the Frequency and Estimated % Complete Responders Through a Given Hour

Cox Regression Statistics:

Comparison	95% CI for Hazard Ratio	p-value
1.2 mg/Kg DOLA•Mesyl vs MCP	(0.6, 1.3)	N.S.
1.8 mg/Kg DOLA•Mesyl vs MCP	(0.5, 1.2)	N.S.
1.8 mg/Kg vs 1.2 mg/Kg DOLA•Mesyl	(0.5, 1.4)	N.S.

- Of the subgroup analyses (Table 56, middle panel) only age indicated differences in Tx effect. Age ≥65y was, however, associated with a higher overall level of CR (main effect test, p=0.0399). Patients <65y old had an overall 54% CR rate, whereas those ≥65y old were 73% complete responders. The results of the primary analysis were confirmed when controlling for age.

- The median times to first emesis or escape were each >24h for the three Tx groups. As shown in Table 56 (lower panel), the Cox regression analysis of time to first emetic episode or escape was consistent with the primary analysis of CR (there were no statistically significant differences in the pairwise tests).

d. Safety Results

1) Extent of Exposure

In study -082, a total of 309 patients were treated with single i.v. doses of test med., with the following distribution:

MCP [n=104]	DOLA•Mesyl (mg/Kg) 1.2 [n=104]	1.8 [n=101]	Total DOLA•Mesyl [n=205]

2) Deaths, Dropouts Due to AEs and Other Serious AEs

There were 3 patients who experienced serious AEs. Of these, one dropped out 6.5h after receiving DOLA•Mesyl 1.8 mg/Kg and 6h after the start of chemotherapy. This pt. died; a detailed narrative of this case is given below. The serious AEs in the two other patients resulted in prolonged hospitalization.

Patient 82110A (43y-old male; DOLA•Mesyl 1.8 mg/Kg)

He experienced febrile neutropenia described as bone marrow aplasia with fever 11 days postdose. The event lasted 4 days, and was severe in intensity. The investigator rated the event as not related to test med. but rather to concomitant chemotherapy. The event abated with no sequelae.

Patient 82227D (81y-old female; MCP)

She experienced diarrhea 3h and 45 min. postdose. The event lasted 1 day and 12h, and was severe in intensity. The investigator rated the event as not related to test medication but rather to concomitant chemotherapy. The event abated with no sequelae.

Patient DER ST-92-00020 Narrative

This was a 66y-old M with recurrent non-Hodgkin's lymphoma (lymphoepithelial tumor grade IV) involving the thorax, abdomen lymph node metastasis, first diagnosed and treated in 1989. Past medical Hx included:

- 4 prior courses (the first in 1989) of combination chemotherapy with doxorubicin, vincristine and cyclophosphamide. The accumulated doses of the chemotherapeutic agents including study day were:
  - doxorubicin: total dose 235 mg/m² or about 406 mg
  - vincristine: total dose 10 mg
  - cyclophosphamide: total dose 6000 mg.
- completion of a 40-gray-course of radiotherapy to the thoracic spine one month prior to entry into the clinical trial.
- mild hypertension) treated with hydrochlorothiazide 25 mg and triamterene 50 mg.
- Goitre

There was no Hx of MI or cardiac arrhythmia. An EKG done seven days prior to the study entry was normal with regular sinus rhythm at A chest X-ray taken the day before study entry revealed no signs of infiltration. Coagulation parameters were normal. Clinical laboratory evaluations showing out-of-range or near out-of-range values the day before the patient's death (11th May, 1992) are listed below:

RBC	3.29
Hemoglobin	95
Hematocrit	0.28
WBC	12.4
Neutrophils	73
Lymphocytes	18
Platelets	469
Total Proteins	59
SGOT	19
Alkaline Phosphatase	229
Calcium	1.95
Sodium	132
Chloride	90
Potassium	3.7

P.E. at study day revealed cachexia. After providing informed consent, the patient was given, per protocol, a 15-min. i.v. infusion of DOLA•Mesyl 30 min. prior to the start of chemotherapy. He also received an i.v. PL infusion (to maintain the study blind) which continued until death. The patient's BP 45 min. before Tx with DOLA•Mesyl was , with a resting tachycardia of 105 beats per min. (bpm). One hour and fifteen minutes later his BP was ; with a pulse rate of 120 bpm. Two hours 15 minutes prior to being found dead (4 hours, 15 minutes after DOLA•Mesyl treatment), he was "well" (investigator comment) with a blood pressure of and a pulse rate of

The patient was found dead in bed 6.5h after receiving 1.8 mg/Kg (119 mg) intravenous dose of DOLA•Mesyl. This was 6.0h after administration of sequential intravenously of doxorubicin 50 mg/m² (approximately 86.5 mg over 15 min); vincristine 1.4 mg/m² (approximately 2.4 mg over 5 min); and cyclophosphamide 750 mg/m² (approximately 1297 mg over 2h). The patient died during the infusion of PL that started 15 min. after the end of DOLA•Mesyl administration. Concomitant medication included omeprazole for ulcer prophylaxis (peptic disease not described) given because of nervousness of the patient before the chemotherapy course as well as during the previous courses.

At the family's request, no autopsy was performed and the exact cause of death remains unknown. The physician-investigator assessed the relationship between DOLA•Mesyl and the patient's death as "unknown". No further information was to be expected for this patient.

The fact that the patient's BP decreased during the study period argues for a cardiovascular etiology, which may have been related to a number of factors alone or in combination. These contributing factors include mild hypertension, moderate hypocalcemia, serum potassium at the low end of the normal range, radiation to the thoracic spine and even goitre. Other possible contributing factors to this patient's death include doxorubicin toxicity and DOLA•Mesyl.

The sponsor provided a detailed description of this event and assessment of EKG changes observed in clinical trials at date of event to investigators worldwide in a letter dated July 10, 1992. In response to the death of this patient, new protocols were written to exclude patients with congestive heart failure, current antiarrhythmic therapy, greater than first degree heart block and electrolyte abnormalities. These exclusions, pertaining to the cardiovascular system, have been listed in all the i.v. protocols reviewed by the MO in NDA 20-624 and the tablet protocols reviewed by the MO in NDA 20-623.

3) AEs

- There were no statistically significant Tx differences in the overall incidence of AEs (MCP=39%; DOLA•Mesyl 1.2 and 1.8 mg/Kg=35% and 33%, respectively).

- By system organ class, the most frequent events were those related to central and peripheral nervous system (p=0.0651 for Tx differences), the g.i. system (p=N.S.), body as a whole (p=N.S.) and cardiovascular in general (p=N.S.).

- As shown below, headache was reported in higher frequency in DOLA•Mesyl groups than in the MCP group and diarrhea in higher frequency in the MCP than in the DOLA•Mesyl groups.

	MCP	DOLA•Mesyl Dose (mg/Kg) 1.2	1/8	p-value
Headache	4%	19%	12%	0.0029
Tx-related	4%	18%	11%	0.0043
Diarrhea	10%	2%	2%	0.0266
Tx-related	9%	2%	2%	0.0479

- There was no statistically significant difference among the Tx groups in the over all rate of AEs assessed as Tx-related by the investigators (MCP=33%; DOLA•Mesyl 1.2 and 1.8 mg/Kg=33% and 24%, respectively).

- There were no statistically significant Tx differences in the frequency of AEs treated with counteractive medication.

- The large majority of patients had mild-to-MOD AEs.

4) AEs of Potential Concern

These are briefly summarized below.

a) Respiratory System

Pt. 82171B (MCP): Pulmonary edema 2h after test med. administration; rated as severe, lasted 24.5h and assessed as of unknown causality. The pt. recovered from the event.

Pt. 82108B (DOLA•Mesyl 1.2 mg/Kg): Dyspnea 10h after test med. administration; rated as MOD in severity and possibly related to test med. administration. The pt. recovered from the event.

b) Cardiovascular

- 9 pts. experienced hypotension; intensity and causality was as follows:

MCP [n=5]			DOLA•Mesyl 1.8 mg/Kg [n=4]		
	Severity	*Causality*		*Severity*	*Causality*
82092A	Mild	Unknown	82091C	Moderate	Possible
82167B	Moderate	Unknown	82092D	Mild	Probable
82205D	Mild	Possible	82164D	Mild	Unknown
82223B	Mild	Not	82225D	Mild	Not
82223D	Mild	Not			

All 9 patients recovered from the event.

c) Heart Rate & Rhythm

Pt. 82175B

Diagnosis: multiple myeloma, primary location, bone marrow sternum and thoracic vertebrae and medical Hx of kyphosis, tachycardia, HF, pneumonia and fractures of femur, thoracic and lumbar vertebrae and pubic bone. The pt. received DOLA•Mesyl 1.8 mg/Kg prior to cyclophosphamide chemotherapy. The day following test med. the patient experienced what was described as arrhythmia (onset time was unknown). The cause of the event was rated as unknown by the investigator. The intensity of the event was MOD and the patient recovered from the event.

The sponsor states that this patient with pre-existing signs of HF and associated pleural and pericardial effusions should probably have been excluded from the protocol. The arrhythmia (in the presence of tachycardia) was probably associated with respiratory acidosis (kyphosis and bilateral pleural effusion) and pre-existing pericardial effusion. Reversion to tachycardia sinus rhythm was observed following reduction of the pericardial effusion.

d) Urinary System

Pt. 82165C (DOLA•Mesyl 1.8 mg/Kg)

This pt. experienced acute renal failure 10.75h after test med. administration. The event lasted 24h, was rated as severe and assessed as of unknown cause by the investigator. But there was evidence of tumor lysis which produced elevation of serum uric acid pre/post-Tx increase from The pt. recovered from the event.

e) Skin

Pt. 82116D developed giant (severe) urticaria 0.42h after test med., probably related to MCP. The pt. recovered from the event.

f) Vision

Pt. 82018B experienced mild blurred vision 0.5h after test med., possibly related to DOLA•Mesyl 1.2 mg/Kg. The event lasted 20h. This patient developed two other AEs: headache 2.5h after test med treated with counteractive medication and nightmare 4.5h after test med. The patient recovered from all events.

5) Summary Results of Clinical Laboratory Evaluations

There were some trends toward post-Tx increases or decreases in some clinical laboratory values but these were of no clinical concern and rather expected of the patient population studied.

6) EKG Interval Changes

These data are not very contributory. This is because the follow-up EKG were taken at 24h (end of study) after the administration of test med. EKGs were not taken 1 to 2h post-Tx.

3. Conclusions (Sponsor)

"The complete response rates for single iv doses of dolasetron mesylate 1.2 and 1.8 mg/kg were numerically superior to metoclopramide 5 mg/kg (standard iv total dose regimen) in preventing emesis due to the administration of moderately emetogenic noncisplatin chemotherapy.

"In secondary efficacy parameters, dolasetron mesylate had higher numerical response rates than metoclopramide for complete-plus-major, total response, patient satisfaction and investigator global assessment of efficacy.

"Significant predictors of response were gender and age. The response rate was higher in males and in patients <65 years old.

"In the most difficult to treat patients (non-naive females) dolasetron appeared to be more effective in controlling emesis.

"There was no significant difference between the two dolasetron mesylate doses for any parameter studied.

"Overall safety was similar across treatment groups."

4. Reviewer's Comments

Study -082's objective was to evaluate the effectiveness of two dose levels of DOLA•Mesyl, administered intravenously in comparison to MCP in preventing emesis due to moderately emetogenic non-cisplatin chemotherapy. The study was well designed and apparently well executed. The random allocation of the three Tx regimens was stratified by gender (M vs F) and previous chemotherapy treatment (naive vs non-naive), thereby producing four strata. The stratification approach is sound because gender and previous exposure to chemotherapy are factors expected to influence efficacy response so it is important to allocate patients in a balanced fashion regarding these potential confounders.

The DOLA•Mesyl doses selected for this trial were based on Phase I/II data from several studies (see comments to study -032): 1.8 mg/Kg DOLA•Mesyl and a lower dose, 1.2 mg/Kg were tested and expected to be effective against the moderately emetogenic chemotherapy used in this trial. The comparator was the approved dose regimen of MCP: 2 mg/Kg loading dose as a 15-min. i.v. infusion followed by 3 mg/Kg as an 8-h i.v. infusion. However, if the CR rates of the

three Tx groups cannot be differentiated from one another then, to demonstrate activity, comparisons to a relevant negative historical control are needed. The relevance of the comparator proposed by the sponsor is discussed below.

From the literature, the sponsor identified five publications[13] which met the following criteria.

- Cyclophosphamide and/or anthracycle chemotherapeutic agents were used at doses comparable to those specified in study -082.
- The number of patients that received PL and the number of these which did not vomit during the 24-h period after chemotherapy, were reported.

In these studies, a total of 208 cancer patients were given PL as their sole antiemetic prophylaxis.

- 173 of these 208 patients vomited at least once during the first 24h post-chemotherapy. From these data a "CR" rate of 35/208 (16.8%) was calculated.
- The upper limit of an exact binomial 95% CI for these data is 22.6%.
- Results from study -082 were compared statistically to historical PL controls using 22.6% as the PL "CR" rate.

The MO agrees with the sponsor that the proposed historical PL control is relevant. The database used for efficacy comparisons in an iv DOLA•Mesyl study in patients receiving cyclophosphamide and/or anthracycles is contemporaneous, identifiable, and all in all applicable for the 24-h study performed.

The randomization/stratification procedures used in study -082 were apparently well executed resulting in three population of patients that were comparable to each other in important variables that may influence outcome. The double-blind was assured by the double-dummy technique required by the different administration regimens of DOLA•Mesyl and MCP. The three experimental groups were well balanced with respect to demographics (F=69%; naive to chemotherapy=52%; mean age=51y), Karnofsky performance status (mean=87%, Hx of alcohol abuse (YES=4%), primary cancer (breast-46%, lymphoma=19%, musculoskeletal=13% and lung=6%), P.E., other significant medical conditions (but Hx of genitourinary abnormality and Hx of neurologic abnormality were statistically significant (p=0.046 and 0.020, respectively; but this imbalance

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1. [T.M. Beck et al., Ann. Intern. Med. 118:407-413 (1993)]
2. [L.X. Cubeddu et al., Clin. Oncol. 8:1721-1727 (1990)]
3. L.X. Cubeddu et al., Amer. J. Clin. Oncol. (CCT) 17:137-146 (1994)]
4. M. David et al., Cancer Treatment Reports, 68:921-922 (1984)]
5. C.F. Pollera et al., Amer. J. Oncol (CCT), 12:524-529 (1989)]

is not expected to have an impact on efficacy response), prior medications and concomitant medications that may be confounding.

In study -082 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 moderate emetogenic potential. The first chemotherapeutic agent (either cyclophosphamide, doxorubicin or epirubicin), used in defined doses, had to be infused over no more than 60 min. There were no significant imbalances across Tx groups in duration of first chemotherapy infusion (mean-24 min.), interval between start of study medication administration and start of chemotherapy infusion (mean=31 min.) or use of single or multiple (87% of the patients) chemotherapy agents.

The CR rate with MCP was 53% in the ITT and 52% in the Evaluable population. The CR with the 1.2 and the 1.8 mg/Kg DOLA•Mesyl doses was (respectively) 56% and 64% in the ITT and 57% and 63% in the Evaluable population. There was no statistically significant difference between each DOLA•Mesyl dose and MCP nor between the two DOLA•Mesyl doses. Each of the two DOLA•Mesyl dosages as well as MCP were significantly more effective than the relevant historical PL comparator.

In study -082, patient stratification was predictive of overall response rate (p=0.0224). A highly significant stratum effect was noted for gender (p=0.0034). Male patients showed, overall, a higher response rate (68%) than female patients (53%). Such a gender difference is commonly observed with other antiemetic treatments.[14] In the present study using moderately emetogenic chemotherapy, the chemotherapy naive patients showed a higher response rate (61%) than chemotherapy non-naive patients (54%) but the difference was not statistically significant. Subgroup analysis, age, performance status, cyclophosphamide dose, narcotic analgesics or benzodiazepines) showed no effect on Tx efficacy except for age. The CR rate was higher in patients ≥65-years-old than in patients <65-years-old (73% vs 54%). The effect of age on control of emesis has been previously observed.

In this study population and under the experimental conditions and methodology used in study -082, single intravenous doses of DOLA•Mesyl (1.2 or 1.8 mg/Kg) and MCP were - all in all - well tolerated. Three patients experienced serious AEs. In one, febrile neutropenia described as bone marrow aplasia with fever 11 days post-dose (DOLA•Mesyl 1.8 mg/Kg) was rated as not related to test med., but rather to concomitant chemotherapy. In the second, severe diarrhea occurring 3h and 45 min. post-dose (MCP) was rated as not related to test med. but rather to concomitant chemotherapy. The MO agrees with these assessments. But events in the third patient are of concern. The third patient was found dead in bed 6.5h after receiving 1.8 mg/Kg (119 mg) intravenous dose of DOLA•Mesyl. This was 6h after administration of

[14] In another study comparing DOLA•Mesyl vs MCP in highly emetogenic chemotherapy treated patients (cisplatin ≥80 mg/m²) the difference of response rate between males and females was about two fold higher in males than in females. In the same study, chemotherapy naive patients showed a significantly higher response rate than chemotherapy non-naive patients.

sequential i.v. of doxorubicin, vincristine and cyclophosphamide. The patient died during the infusion of placebo that started 15 min. after the end of DOLA•Mesyl administration. The MO carried out a very detailed assessment of this case and this information is included in the text of this review. In short, the fact that the patient's BP decreased during the study period argues for a cardiovascular etiology which may have been related to a number of factors alone or in combination. In this particular patient, these contributing factors include mild hypertension, moderate hypocalcemia, serum potassium at the low end of the normal range, radiation to the thoracic spine and even goitre. But other possible contributing factors to this patient's death are doxorubicin toxicity and DOLA•Mesyl (each alone or, more likely, in concert).

Of note, the sponsor provided a detailed description of this event and assessment of EKG changes observed in clinical trials at date of event to investigators world wide in a letter dated July 10, 1992. In response to the death of this patient new protocols were written to exclude patients with CHF, current antiarrhythmia therapy, greater than first degree heart block and electrolyte abnormalities. These exclusions, pertaining to the cardiovascular system, have been listed in all the i.v. protocols reviewed by this MO in NDA 20-624. The MO believes that a brief description of this sudden death, where there is no way to exclude DOLA•Mesyl's contribution, should be included in the labeling.

The overall AE rates were similar for the three Tx groups: 39% for MCP and 35% and 33%, respectively, for the 1.2 and 1.8 mg/Kg DOLA•Mesyl. There was no statistically significant difference among the Tx groups in the overall rate of AEs assessed as Tx-related by the investigator or in the frequency of AEs treated with counteractive medication. Headache (both all and Tx-related) was reported in significantly higher frequency in DOLA•Mesyl groups than in the MCP group and diarrhea (both all and Tx-related) was reported in significantly higher frequency in the MCP group than in the DOLA•Mesyl groups.

In study -082, EKG evaluations were not carried out at 1 to 2h post-Tx. This is the putative time of peak plasma levels of the active metabolite, MDL 74,156. Instead, follow-up EKGs were done at 24h post-Tx at a time when the plasma levels of MDL 74,156 are either very low or non-detectable. This approach would preclude discovering acute, dose-related EKG effects of DOLA•Mesyl amply demonstrated in many other trials.

V. NDA 20-624: OVERALL SUMMARY OF EFFICACY

A. Treatment of PONV Indication

In this NDA, results from two adequate and well controlled studies were submitted by the sponsor in support of approval of ANZEMET (DOLA•Mesyl), at the intravenous dose of 12.5 mg given once-a-day as soon as nausea and

vomiting presents. Within the extent of this review, these trials are identified as -044 (a domestic trial) and -2-S-084 (a study carried out in Europe). Both trials were randomized, double-blind, multicenter, parallel, 5-arm comparisons of four dose levels of DOLA•Mesyl (12.5, 25, 50 and 100 mg) to PL. In both, the study population consisted predominantly of female patients that had undergone surgery under general balanced anesthesia and presented with early PONV requiring antiemetic treatment. Both the design and the execution of the two main trials were adequate to assess efficacy and safety of graded single doses of DOLA•Mesyl (in comparison to a negative control, placebo) in this patient population. In both main trials the methodology for randomization resulted in five patient populations that - in the final analysis - were balanced with respect to variables which may influence outcome.

Both studies showed that DOLA•Mesyl is active. Both ITT and Evaluable population analyses demonstrated a statistically significant linear trend in the proportion of complete responders across the five dose groups, with a p-value of 0.0041 in the ITT (total n=620) in study -044 and 0.0114 in the ITT (total n=337) in study -2-S-084. Having demonstrated activity the important question is what is the recommended dose, 12.5 mg as proposed by the sponsor, or some other dose level?

In an attempt to choose a dose, the reviewer has assembled Summary Table 57. This Table depicts the complete response with the comparator (PL) and the therapeutic gains with each of the four dose levels of DOLA•Mesyl, with the corresponding p-values. Neither of the two extreme doses (12.5 or 100 mg) can be recommended. The effectiveness of the 12.5 mg dose, shown in study -044, is not replicated in study -2-S-084. The effectiveness of the 100 mg dose is not higher than that with the intermediate doses. The options left are the two intermediate doses, 25 and 50 mg. Both are effective. From results in study 2-S-084, a 9% numerical higher response rate with the 50 than with the 25 mg dose. But this difference is not statistically significant. This means that increasing the dose to doses higher than 25 mg (for instance, to 50 mg) does not provide a significant advantage. Therefore, it seems that, based on the point estimate data at hand, the recommended dose is 25 mg (not 12.5 mg as proposed by the sponsor).

TABLE 57
NDA 20-624

Summary of Complete Response (CR) in Treatment of PONV Trials With Intravenous DOLA•Mesyl: Comparison of Therapeutic Gains and Statistical Significance

Study	CR Rate with Comparator (PL)	DOLA•Mesyl Dose (mg)			
		12.5	25[a]	50	100
		Therapeutic Gain/[p-value]			
-044 [n=620]	11%	25% [<0.001]	17% [<0.001]	18.3% [<0.001]	18.7 [<0.001]
2-S-084 [n=337]	11%	13% [N.S.]	17% [0.017]	26% [<0.001]	14% [0.026]

a) This is the MO's recommended dose (see text of review).

B. Prevention of PONV Indication

In this review, results from three adequate and well controlled studies were evaluated. These data were submitted by the sponsor and NDA 20-624 in support of approval of ANZEMET (DOLA•Mesyl), at the intravenous dose of 12.5 mg given once-a-day for the prevention of PONV. These trials are identified as -045 (a U.S. trial), -084 (another domestic trial) and -080 (a European trial). These trials were stratified/randomized, multicenter, double-blind, 4 or 5-arm comparisons of four (or three) dose levels of DOLA•Mesyl (12.5, 25, 50 or 100 in two of the three and 12.5, 25 or 50 in the other study) to placebo. The trials differed substantially with respect to the total number of patients studied, the ratio of female to male patients and the reason for stratification. Study -045 enrolled a total of 1030 patients (of these 722 were female; the remaining 308 were males); these patients were scheduled for outpatient surgery under general anesthesia and they were stratified by gender within each study site. In studies -084 and -080, the number of patients enrolled was 635 and 281, respectively, and in both, the study population consisted exclusively of females. In study -084 the patients were stratified on the basis of previous history of PONV and in study -080, the basis for stratification was the type of surgery (laparoscopic vs non-laparascopic procedures).

Both the design and execution of the three main trials for prevention of PONV were adequate to assess efficacy and safety of graded single doses of DOLA•Mesyl (in comparison to a negative control) in this patient population. In the three main trials the methodology for stratification/randomization resulted in 5 (two trials) or 4 (one trial) patient populations that - in the final analysis - were balanced with respect to variables that may influence outcome.

The question of overall activity was examined first, but the answer to this question is not simple. Study -045 (total population=females + males) was null. This trial did not demonstrate activity: neither the ITT nor the Evaluable population data showed a statistically significant linear trend in the proportion of complete responders across the five dose groups [ITT, n=1030; Evaluable population, n=974; both $p>0.05$]. DOLA•Mesyl is, however, active in this indication. In study -084 both population analyses demonstrated a statistically significant linear trend in the proportion of complete responders across the four dose groups [ITT, n=635 (exclusively females, $p<0.0001$]. Furthermore, in the third trial, -080, activity was also shown since the ITT analysis (n=281, exclusively females) of the percentage of complete responders revealed a linear trend ($p=0.0475$) with increasing dose levels of DOLA•Mesyl.

The therapeutic gains and the corresponding p-values for the pairwise comparisons of DOLA•Mesyl dose vs the negative comparator (PL) in each of the three trials are depicted in Table 58. Note that a large number of female patients were entered in study -045 and this number [n=722] is larger than the total study population of (exclusively) females in the other two trials [study

-084, n=635; study -080, n=281]. This large study population, prompted the MO to include response in the female stratum in study -045 (Table 58). It is seen that, in female patients, there were therapeutic gains of 18% for each of the two extreme doses (lowest=12.5 mg and highest=100 mg). It is also important to note that, as discussed within the text of this review, in the male stratum, the CR with the negative comparator (PL), was very high (70%) and that - for males - there were no therapeutic gains for three of the four dosages (-7%, -7% and -10% for the 12.5, 25 and 100 mg DOLA•Mesyl doses). The fourth DOLA•Mesyl dosage (50 mg) gave a modest 5% therapeutic gain over PL. But none of the pairwise comparison (DOLA•Mesyl vs PL) yielded statistically significant difference. It is also important to note that, for the total study population, the high PL response in study -045 (49%) in comparison to the DOLA•Mesyl groups, results in therapeutic gains (all N.S.) that are generally lower than those realized in the other two trials. Since -045 was a large trial, factors other than power may play a role in the lack of statistically significant differences between DOLA•Mesyl and PL in this trial. Realizing that the tablet formulation of DOLA•Mesyl is effective in the prevention of PONV and that the PK/PDs of the two formulations of the drug are similar, it is not understood why the i.v. formulation is not effective in this indication. Since the results in study -045 are null, the decision to choose a dose for this indication can be based on results of studies -084 and -080.

The sponsor recommends 12.5 mg DOLA•Mesyl as the dose for the prevention of PONV indication. Although this dose of DOLA•Mesyl was statistically significantly superior to PL in study -084 these results are not duplicated in study -080. So 12.5 mg cannot be recommended. Similarly, neither 50 nor 100 mg can be recommended. The efficacy of the former dose shown in study -084 is not replicated in study -080. The 100 mg dose was not studied in Study -084 and this dose of DOLA•Mesyl was not differentiated from placebo in study -080.

From the above considerations, the MO believes that it is reasonable to elect 25 mg as the recommended dose for the prevention of PONV indication. The administration of 25 mg of DOLA•Mesyl intravenously was accompanied by therapeutic gains of 21% and 24% in studies -084 and -080, respectively. Both therapeutic gains were shown to be superior (statistically significantly different) to placebo. It is, however, important to reiterate that since studies -084 and -080 enrolled female patients exclusively and study -045 did not demonstrate effectiveness in males due to a high PL response (i.e. 70%), the labeling should indicate that effectiveness of intravenous DOLA•Mesyl in male patients has not been demonstrated.

TABLE 58
NDA 20-624

Summary of Complete Response (CR) in Prevention of PONV Trials With
Intravenous DOLA•Mesyl: Comparison of Therapeutic Gains and Statistical Significance

Study	CR Rate With Comparator (PL)	DOLA•Mesyl Dose (mg)			
		12.5	25	50	100
		Therapeutic Gain/[p-value]			
-045 [n=1030]	49%	11% [N.S.]	6% [N.S.]	9% [N.S.]	9% [N.S.]
Response Intervals in Females [n=722]	40%	18% [<0.05]	11% [N.S.]	10% [N.S.]	18% [<0.05]
-084 [n=635]	31%	20% [0.0003]	21% [0.0001]	25% [<0.0001]	N/A
-080 [n=281]	43%	11% [N.S.]	24% [0.0042]	17% [N.S.]	17% [N.S.]

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ON ORIGINAL

C. Prevention of CCNV Indication

In NDA 20-624, results from five trials (four in cisplatin and one in non-cisplatin-based regimens) were submitted in support of approval of ANZEMET (DOLA•Mesyl), at the single intravenous dose of 1.8 mg/Kg [or 100 mg], for the prevention of N&V associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin. The requested indication presupposes efficacy against two emetogenic stimuli: high-dose cisplatin and non-cisplatin regimens. Indeed, the sponsor has provided evidence that DOLA•Mesyl is effective in this indication and against the two types of emetogenic stimuli. Studies -081 (European trial, -031 (U.S.), -093 (another European study) and -032 assessed effectiveness of DOLA•Mesyl in cancer patients receiving high-dose cisplatin (≥80 mg/m²) regimens. These regimens are considered to be of high emetogenic potential. Study -082 assessed effectiveness of DOLA•Mesyl in cancer patients receiving cyclophosphamide-based chemotherapy regimens. These regimens are considered to be of moderate emetogenic potential. All five trials utilized useful designs and were apparently well executed.

The four cisplatin trials are of interest because in these studies, high dose cisplatin was given to the patients and it was important to demonstrate that DOLA•Mesyl is both safe and effective in this important target population (that needs to be treated with high dose cisplatin). All five trials were double-blind, multicenter, parallel observations. Three of the four cisplatin trials used an active-active design (MCP or OND or GRAN)! In the fourth trial, the effect of graded doses of the drug, without "positive" or "negative" comparator was tested. Since, not unexpectedly with this class of drugs, the dose response was flat in nearly all trials, in addition to demonstrating equivalence to approved dose regimens, it was necessary to show effectiveness to relevant negative historical controls.

The negative historical controls originated from cisplatin studies for three of the four cisplatin trials and from non-cisplatin trials for the moderately emetogenic setting. As demonstrated within the text of this review the MO evaluated the validity of the proposed historical controls and found them to be contemporaneous, identifiable and applicable (relevant). In the summary that follows emphasis to draw conclusions on efficacy is on the results on Complete Response (CR) in the overall study population; virtually no comments are given on results by stratum.

The efficacy results are summarized in Table 59. All four trials showed that DOLA•Mesyl is efficacious in preventing high-dose cisplatin-induced emesis. In study -081, the prospective stratification of patients based on gender and previous history of chemotherapy was sound because these factors - which were balanced among the treatment groups in this study - may influence antiemetic response. In both the ITT and Evaluable population, the CR with MCP was 35%; each of the two DOLA•Mesyl dosages was clinically and statistically superior to MCP. The best result was achieved with the 1.8 mg/Kg DOLA•Mesyl with which a therapeutic gain of 22% in the ITT (p=0.0009) and 21% in the Evaluable population analyses (p=0.0016) was achieved. Thus, the results in study -081 are important because they settle the question of efficacy in high-dose cisplatin and at 1.8 mg/Kg, the dose proposed by the sponsor.

TABLE 59
NDA 20-624

Summary of Complete Response (CR) in Prevention of CCNV Trials With
Intravenous DOLA•Mesyl: Comparison of Therapeutic Gains and Statistical Significance

Study	CR Rate With Comparator	DOLA•Mesyl Dose (mg/Kg)					
		0.6	1.2	1.8	2.4	3.0	Active Comparator
		Therapeutic Gain/[p-value]					
I. High Dose Cisplatin Trials							
-081 [n=225]	35% (MCP)	---	13% [0.0058]	22% [0.0009]	---	---	---
-031 [n=609]	11.1% (Historical PL)	---	---	33% [<0.0001]	29% [<0.0001]	---	32% [<0.0001] OND (32 mg)
-093 [n=474]	11.1% (Historical PL)	---	---	43% [<0.0001]	36% [<0.0001]	---	37% [<0.0001] GRAN (40 µg/Kg)
-032 [n=299]	11.1% [Historical PL)	30% [<0.0001]	33% [<0.0001]	40% [<0.0001]	32% [<0.0001]	36% [<0.0001]	---
II. Non-cisplatin Trial							
-082 [n=309]	23% (Historical PL)	---	33% [<0.0001]	41% [<0.0001]	---	---	30% [<0.0001] MCP (5 mg)

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ON ORIGINAL

Studies -031 and -093 provide good supporting data. Each tested two dose levels of DOLA•Mesyl (1.8 and 2.4 mg/Kg) in comparison to either 32 mg of OND or 40 μg/Kg GRAN. Both studies showed that both dose levels of DOLA•Mesyl, 1.8 and 2.4 mg/Kg were equivalent to either OND (study -031) or GRAN (study -093). But in addition, each of the three arms of both studies was shown to be superior to a relevant historical negative control. Thus, studies -031 and -093 showed that the 1.8 and 2.4 mg/Kg DOLA•Mesyl were not only active but also equivalent to the active comparators (OND and GRAN). For the 1.8 mg/Kg DOLA•Mesyl dose, the therapeutic gain over the historical PL control was 33% ($p<0.0001$) and 43% ($p<0.0001$) in studies -031 and -093, respectively. In both trials, there was no advantage in increasing the dose to levels higher than 1.8 mg/Kg DOLA•Mesyl.

Results of study -032 do not add much to the overall assessment of efficacy. In this study, comparisons of CR showed some minor numerical but not statistically significant differences among the five DOLA•Mesyl groups. This means a flat response encompassing doses as low as 0.6 and as high as 3 mg/Kg of the intravenously administered DOLA•Mesyl. But all five test groups were shown to be superior to a historical PL control, with therapeutic gains ranging from all at the p level of <0.0001. The flat response observed in this trial has been shown in many other trials with DOLA•Mesyl and other 5-HT_3 receptor inhibitors. In study -032, in particular, there was no further benefit when increasing the dose of DOLA•Mesyl to dosages over 0.6 mg/Kg.

Finally, in study -082, activity in cancer patients receiving non-cisplatin regimens of moderate emetogenic potential was demonstrated. The three arms of the study (DOLA•Mesyl 1.2 and 1.8 mg/Kg as well as MCP, 5 mg/Kg) were all superior to a relevant historical PL control, with corresponding therapeutic gains of 33%, 41% and 30%. The three arms of this trial gave comparable response rates and comparable therapeutic gains when compared to PL. There was no advantage in increasing the dose from

VI. NDA 20-624: OVERALL SUMMARY OF SAFETY

In NDA 20-624, the sponsor submitted and the MO assessed the results of ten controlled studies in support of three indications: treatment of PONV (studies -044 and 2-S-084), prevention of PONV (-045, -084, -080) and prevention of CCNV [(-081, -031, -093 and -032) in high-dose cisplatin and -082 in non-cisplatin-based regimens].

1. Overall Extent of Exposure[a]

Total Studied in Treatment of PONV	957
Received PL	192
Received DOLA•Mesyl i.v.	765
(DOLA•Mesyl, mg: 12.5=196, 25=184, 50=191, 100=194 patients)	
Total Studied in Preventing PONV	2464
Received PL	547
(DOLA•Mesyl, mg: 12.5=419, 25=548, 50=551, 100=267)	
Received OND	132
Adults Receiving DOLA•Mesyl i.v.	1785
Pediatric Patients Receiving DOLA•Mesyl i.v.	18
Total Surgical Patients Receiving DOLA•Mesyl	1803
Total Studied in Prevention of CCNV	2455
Received MCP	193
Received OND/GRAN	356
= Total	1906
(DOLA•Mesyl, mg/Kg ≤0.6=342, 1.2=271, 1.8=731, ≥24=562)	
Of these, in U.S. + Non-U.S. controlled studies	1715 (U.S., n=1029)
(DOLA•Mesyl, mg/Kg ≤0.6=284, 1.2=251, 1.8=695, ≥2.4=485	

a) Computation include both controlled and non-controlled studies and both U.S. and non-U.S. trials.

2. Deaths, Dropouts Due to AEs and Other Serious AEs

- In Tx of PONV trials, -044 and -2-S-084, there were neither deaths nor serious cardiovascular events reported, no patients were W/D due to AEs. None of the SAEs that occurred were assessed as related to test med. but they were attributable to the operative procedure or PO pain relief.

- In the prevention of PONV trials, -045, -084, -080 [and -091][15] no deaths or serious cardiovascular events - that could be attributed to DOLA•Mesyl - were reported and no patients were W/D due to AEs.

  - In study -045, **excessive drowsiness** in a DOLA•Mesyl 25 mg group and historical episode in a PL-treated patient resulted in hospitalization. Both episodes were assessed as **possibly related** to test med.

  - In study -084 **excessive drowsiness** in a DOLA•Mesyl 50 mg group resulting in hospitalization, was assessed as **possibly related** to test med.

[15] A fourth prevention of PONV trial that compared two dose levels of DOLA•Mesyl, 25 and 50 mg to PL and OND. This trial was prematurely terminated after 518 pts. were enrolled in the study when DOLA•Mesyl clinical supplies appeared to contain a degree of particulate contamination in a routine inspection. This study (-091) was briefly reviewed for general safety.

- In study -080, respiratory depression occurred in a 12.5 mg DOLA•Mesyl group patient and in one PL-treated patient. Severe bradycardia was reported in another PL-treated patient. None of these events were related to test med.

- In study -091, one OND patient experienced septicemia, was W/D from the study and eventually died of pre-existing cancer and surgery. Another patient, also in the OND group was W/D from the study due to cholelithiasis. Both serious AEs were unrelated to test med.

- Except as noted, none of the deaths, serious AEs or W/Ds occurring in prevention of CCNV studies was attributable to test med.

  - In study -081, **severe hypotension** occurred in a 1.8 mg/Kg DOLA•Mesyl patient 15 min. after the end of test med. infusion and before chemotherapy was instituded. The pt. was W/D from the trial. As discussed in detail within the text of this review from his assessment, the MO concluded that this case of severe hypotension was **almost certainly** related to DOLA•Mesyl.

  - In study -032, **acute pancreatitis** occurred in a patient 5.75h after receiving 116 mg (1.8 mg/Kg) of DOLA•Mesyl intravenously. Due to the temporal relationship, this event was considered as **possibly related** to test med.

  - The AE of most concern was reported in study -082. A case of sudden death 6h after receiving 119 mg (1.8 mg/Kg) DOLA•Mesyl and 6h after sequential chemotherapy) occurred. The patient's BP decreased during the study period, a sequence of events that appears to argue for a cardiovascular etiology. Contributing factors to the patient's death include mild hypertension, moderate hypocalcemia, serum potassium at the low end of the normal range, radiation to the thoracic spine, goitre and possibly doxorubicin toxicity and/or DOLA•Mesyl. In response to the death of this patient the sponsor provided a detailed description of this events to all investigators and amended clinical protocols to exclude patients with CHF, current antiarrhythmia therapy, greater than first degree heart block and electrolyte abnormalities.

3. Overall Incidence of AEs, Most Frequently Occurring AEs

a. Treatment of PONV Studies

- As shown below, the proportion of patients reporting one or more AEs was similar among all DOLA•Mesyl doses and PL in the US study. In the non-US study, higher AE incidences were seen following the two highest DOLA•Mesyl doses.

Incidence of AEs

Study	PL	DOLA•Mesyl Dose (mg) 12.5	25	50	100
US	66/121 (55%)	67/130 (52%)	52/119 (44%)	55/124 (44%)	61/126 (48%)
non-US	13/71 (18%)	12/66 (18%)	10/65 (15%)	20/67 (30%)	20/67 (30%)

- The most frequently occurring AEs were headache and dizziness. The reported incidence for these AEs was as follows:

AE	PL	DOLA•Mesyl Dose (mg) 12.5	25	50	100	All DOLA•Mesyl
Headache[a]	14/192 (7%)	19/196 (10%)	14/184 (8%)	17/191 (9%)	21/194 (11%)	71/765 (9%)
Dizziness[b]	5/192 (3%)	9/196 (5%)	12/184 (7%)	3/191 (2%)	7/194 (4%)	31/765 (4%)

a,b) These AEs were likely to be due to DOLA•Mesyl but they did not exhibit a dose response relationship.

b) Prevention of PONV Studies

- The proportion of patients reporting one or more AEs in these trials was similar among the DOLA•Mesyl groups and PL. This data are summarized below. No trend for increased AEs with increasing dose is seen.

Incidence of AEs

Studies	PL	DOLA•Mesyl Dose (mg) 12.5	25	50	100
U.S.	190/365 (52%)	170/365 (47%)	191/360 (53%)	185/367 (50%)	105/208 (51%)
Non-U.S.	47/182 (26%)	18/54 (33%)	45/188 (24%)	42/184 (23%)	14/59 (24%)

- The most frequently occurring AEs were headache and dizziness. The reported incidence for these AEs was as follows.

	PL	DOLA•Mesyl Dose (mg) 12.5	25	50	100	All DOLA•Mesyl
Headache[a]	37/547 (7%)	39/419 (9%)	39/548 (7%)	49/551 (9%)	27/267 (10%)	154/1785 (9%)
Dizziness[b]	18/547 (3%)	25/419 (6%)	21/548 (4%)	22/551 (4%)	13/267 (5%)	81/1785 (5%)

a,b) These AEs were likely to be due to DOLA•Mesyl but they did not exhibit a dose response relationship.

c) Prevention of CCNV Studies

- The proportion of patients reporting one or more AEs in these trials is summarized below.

Incidence of AEs

Studies	MCP	OND/ GRAN	DOLA•Mesyl Dose (mg) ≤0.6	1.2	1.8	≥2.4	All DOLA•Mesyl
U.S. (Controlled)	[n=20] (20%)	[n=206] (64%)	[n=284] (61%)	[n=63] (79%)	[n=358] (67%)	[n=324] (74%)	[n=1029] (68%)
Non-U.S. (Controlled)	[n=173] (46%)	[n=150] (45%)	N/A N/A	[n=188] (39%)	[n=337] (49%)	[n=161] (55%)	[n=686] (48%)
Controlled plus Non-Controlled	[n=193] (43%)	[n=356] (56%)	[n=342] (66%)	[n=271] (50%)	[n=731] (60%)	[n=562] (70%)	[n=1906] (62%)

Regardless of the type of study analyzed, there was a higher incidence of AEs with the ≥2.4 mg/Kg DOLA•Mesyl than PL, but there was no dose response relationship. The dose of interest, 1.8 mg/Kg, gave AE rates similar to those with OND/GRAN.

- The incidence of headache and dizziness, two AEs that are likely to be related to DOLA•Mesyl, was:

AE	MCP	GRAN	≤0.6	1.2	1.8	≥2.4
Headache[a]	9/193 (5%)	73/356 (21%)	101/342 (30%)	51/271 (19%)	188/371 (26%)	
Dizziness[b]	1/193 (0.5%)	7/356 (2%)	27/342 (8%)	3/271 (1%)	15/731 (2%)	

a,b) None of these two AEs exhibited a dose response relationship.

d) Severe AEs

In all studies, for all three indications, the observed AEs were mostly of mild to moderate severity. There were only a few severe AEs. None of these exhibited a dose response relationship.

4. AE Profiles in DOLA•Mesyl Patients Who Were Potentially at Greater Cardiac Risk

As per the tablet formulation, clinical experience with DOLA•Mesyl injection in patients that are considered to be at greater cardiac risk is limited. These patients included those with cardiovascular history, baseline arrhythmia, low baseline serum potassium or those that were currently taking cardiovascular medications.

DOLA•Mesyl patients in the treatment of PONV or prevention of PONV trials had comparable AE profiles to those in patients with no cardiac risk and were similar to patients receiving PL who had the same underlying cardiac conditions. Similarly, DOLA•Mesyl patients with greater cardiac risk who were enrolled in the prevention of CCNV studies, had AE profiles that were comparable to those from patients with no cardiac risk and were similar to patients receiving comparator agents (OND, GRAN, MCP) who had the same underlying cardiac conditions.

5. Overall Changes in Vital Signs

Changes in vital signs occurred in almost all studies throughout the study period but there was no consistent pattern with respect to time and onset and the changes did not demonstrate a dose-dependent trend. Overall, the frequency of alert level changes in BP from baseline was similar to the frequency of patients with AEs reported for hypertension or hypotension following i.v. DOLA•Mesyl. Overall, the changes in vital signs induced by DOLA•Mesyl were similar to those seen with PL or active comparators.

6. Electrocardiographic Data

It is worth mentioning that the collection of EKG data and the process for reporting Tx-emergent EKG changes evolved during the clinical development program, which led to differences in reporting practices among the trials. Specifically, the most important EKGs are those carried out at baseline and at 1 to 2h post-dose, thereby approximating the putative time of peak plasma concentrations of MDL 74,156. The reviewer believes that the best way of presenting the median or mean averages is in graphic form. But, as discussed within the text of this review, graphic representation of the EKG changes at 1-2h from baseline were available only for one of the two Tx of PONV studies, two of the four prevention of PONV studies and two of the five prevention of CCNV studies. The reviewer paid little if any attention to EKG changes at 24h post-dose because at this time, MDL 74,156 plasma levels would be low.

From what is known about the pharmacodynamics of the drug, changes in EKG parameters especially PR, QRS and QT_c intervals are no longer unexpected. The reviewer discussed these finding in detail within the text of this review. For simplification of presentation purposes, the MO has elected to summarize data on alert level increase in QT_c interval (defined as QT_c <440 msec pre and ≥480 msec post) in studies for each of the three indications. This information is presented in Table 60.

TABLE 60
NDA 20-624

Proportion of Patients Who Exhibited an Alert Level Increase in QT_c Interval[a]

Studies	Comparator PL		DOLA•Mesyl Dose (mg)			
			12.5	25	50	100
Treatment of PONV[b]	2/104 (1.9%)		1/111 (0.9%)	2/104 (1.9%)	3/101 (3%)	8/108 (7.4%)
Prevention of PONV[c]	8/386 (2.1%)		5/336 (1.5%)	4/381 (1.3%)	16/393 (4.1%)	9/191 (4.7%)
			DOLA•Mesyl Dose (mg/Kg)			
	OND	GRAN	0.6	1.2	1.8	≥2.4
Prevention of CCNV[d]	1/155 (0.6%)	0/62 (0%)	1/72 (1.4%)	1/51 (2%)	1/278 (0.4%)	9/375 (2.4%)

a) QT_c <440 msec pre and ≥480 msec post.
b) Of the 16 patients who exhibited an alert level increase in QT_c interval, 3 patients (1 in the 12.5 mg, 1 in the 50 mg and 1 in the 100 mg dose groups, respectively) developed an acute prolongation ≥500 msec and the patient in the 100 mg group had a post-study QT_c interval ≥550 msec.
c) Of the 43 patients who exhibited an alert level increase in QT_c interval, 14 (3 in the 25 mg, 8 in the 50 mg and 3 in the 100 mg dose groups, respectively) had a post-study interval ≥550 msec.
d) Of the 13 patients who exhibited an alert level increase in QT_c interval, 5 (1 in the 1.8 and 4 in the 2.4 mg/Kg dose groups, respectively) developed an acute QT_c interval prolongation of ≥550 msec.

i) Patients Exhibiting an Alert Level Increase in QT_c Interval

- In Tx of PONV trials, dose-related alert level increases in QT_c interval were seen following the intravenous administration of DOLA•Mesyl. The incidence of these increases in QT_c interval with the 12.5 and 25 mg DOLA•Mesyl doses were similar to the incidence among PL-treated patients. The proportion of patients experiencing these increases in QT_c interval was 3 to 4 times higher with 100 mg DOLA•Mesyl than PL.

- In prevention of PONV trials, the proportion of patients that exhibited an alert increase in QT_c interval was 2 times higher with the 50 and 100 mg DOLA•Mesyl doses, whereas the lower two doses of the drug (12.5 and 25 mg) had incidences similar to those seen with PL.

- In prevention of CCNV trials, the proportion of patients who exhibited an alert level increase in QT_c patients was lowest in the GRAN group (0%). This was followed by the 1.8 mg/Kg DOLA•Mesyl (0.4%) and the OND group (0.6%). Although low (2.4%), the proportion of patients in the ≥2.4 mg/Kg DOLA•Mesyl group was ca. 4 times higher (2.6%) than that seen with the 1.8 mg/Kg DOLA•Mesyl or active comparators.

ii) Clinically Important Arrhythmias

- In Tx of PONV trials, none of the patients with alert level EKG interval increases, nor any other patient enrolled in the two trials, developed Torsades des pointes. Also, there was no correlation between these interval changes and the occurrence of clinically significant arrhythmias.

  - 1 pt. in the 25 mg DOLA•Mesyl dose group developed AF, considered related to mitral valve prolapse by the investigator. This pt. did not exhibit Tx-emergent changes in PR, QRS or QT_c intervals.

  - 1 pt. in the 50 mg dose group who had an alert level increase in QRS duration developed a RBBB.

- In prevention of PONV trials, none of the patients with alert level EKG interval increases, nor any other patient enrolled in the four trials developed Torsades des pointes. Also, there was no correlation between these interval changes and the occurrence of clinically significant arrhythmias.

  - 1 PL-treated patient developed SVT but did not exhibit Tx-emergent increases in PR, QRS and QT_c.

  - 1 OND-treated patient who had an alert level of QRS duration developed a RBBB.

  - 1 PL-treated patient developed severe bradycardia with brief cardiac pause, but EKG tracing was not done at the time of this event.

- In prevention of CCNV trials, none of the patients developed Torsades des pointes. In these studies there was no indication of any relationship between occurrence of alert level EKG interval changes and the development of clinically significant arrhythmias. Although in the following groups of patients clinically significant cardiac arrhythmias were reported, these were not accompanied by alert level EKG changes.

But the overall exposure (denominator) is vastly different since 1906 patients received DOLA•Mesyl whereas only 356 were given OND/GRAN.

	OND	GRAN	DOLA•Mesyl
Atrial Flutter/Fibrillation	1	1	8
SVT	0	0	3
Asymptomatic Ventricular Triplet	0	0	1
Ventricular[a] Fibrillation	0	0	1

a) This VF occurred as a periagonal event 9 days after test medication

iii) Other

- Two cases of excessive drowsiness occurred in the prevention of PONV studies (1 case each in studies -045 and -084, respectively) and were attributed to the 25 mg and 50 mg dose levels, respectively.

- In prevention of CCNV study -081, the case of severe hypotension occurring in Pt. #124B, who had impairment of cardiac function pre-drug, and W/D from the trial was - in the MO's assessment - almost certainly related to the intravenous administration of DOLA•Mesyl. The angina reported in one patient in the 2.4 mg/Kg group was in the MO's assessment - at least possibly related to DOLA•Mesyl.

  - Study -031 allowed side-by-side comparisons between DOLA•Mesyl and OND at the i.v. recommended dose of 32 mg. Except for JT which did not change much, for all the other EKG parameters Tx-induced mean changes from BL were greater with DOLA•Mesyl than OND, although the test for Tx difference was statistically significant for PR ($p<0.0001$), QRS ($p<0.0001$) and QT_c ($p<0.0001$) but not for the other two EKG parameters.

  - Study -093 showed greater and statistically significant changes in patients treated with DOLA•Mesyl (especially the 2.4 mg/Kg) than those treated with GRAN, namely PR ($p=0.0001$) and QT_c ($p=0.0016$). The results of this study for both QRS (no change although QT_c changed) and JT [increase GRAN, 3 mg=1.0 msec, 1.8 mg/Kg=10.6 msec and 2.4 mg/Kg=9.5 msec] were at variance with EKG data from most other DOLA•Mesyl trials.

  - In study -032, one case of acute pancreatitis apparently related to test medication, occurred in a 64y old M patient 6h after receiving 116 mg (1.8 mg/Kg) of DOLA•Mesyl intravenously. In this study one case of mild chest pain occurring 9h after receiving 1.8 mg/Kg DOLA•Mesyl and one case of non-severe myocardial

ischemia or possible MI in a patient with no significant cardiac history were (both events) assessed as possibly related to test med. by the investigator.

- In study -082, the contribution of DOLA•Mesyl (1.8 mg/Kg=119 mg) to the dismissal of a patient that was found dead 6.5h after receiving test med. cannot be excluded with certainty. This case is discussed in detail within the text of this review. Other contributing factors included the sequential intravenous administration of doxorubicin, vincristine and cyclophosphamide starting 0.5h after test med., mild hypertension, moderate hypocalcemia, serum potassium at the low end of the normal range, radiation to the thoracic spine and even goitre.

VII. RECOMMENDATIONS FOR REGULATORY ACTION

EFFICACY

Treatment of PONV indication

In the present submission (NDA 20-624), results of two adequate and well controlled trials (-044 and 2-S-084) submitted by the sponsor in support of the approval of ANZEMET® injection for this indication showed that intravenously administered dolasetron mesylate (ANZEMET® injection) is effective in the treatment of postoperative nausea and vomiting.

Prevention of PONV indication

In support of the approval of ANZEMET® injection for this indication, the sponsor submitted results from three clinical trials (-045, -084 and -080). Results from study -045 were null. Evaluations based on studies -084 and -080 demonstrated that intravenously administered DOLA•Mesyl is effective in the presention of postoperative nausea and vomiting.

Prevention of CCNV indication

In support of the approval of ANZEMET® injection for this indication, the sponsor submitted results of five clinical trials: four from patients being treated with high-dose cisplatin (-081, -031, -093 and -032) and one (-082) in non-cisplatin-base regimens. Results of these five adequate and well controlled trials in chemotherapy-induced emesis showed that intravenously administered dolasetron mesylate (ANZEMET® injection) is effective in the prevention of chemotherapy-induced nausea and vomiting. In four of these trials, the emetogenic stimulus consisted of high dose cisplatin (≥80 mg/m²). The most convincing demonstration of effectiveness emanated from study -081 which showed doses of i.v. DOLA•Mesyl of 1.8 (and 1.2) mg/Kg to be superior to metoclopramide (study -081). Drug effectiveness at 1.8 mg/Kg was replicated

in studies -031 and -093, which showed this dose of DOLA•Mesyl to be superior to a relevant historical placebo control and equivalent in efficacy recommended intravenous doses of either 32 mg of ondansetron (study -031) 40 μg/Kg granisetron (study -093). A fourth study in high cisplatin patients (-032) demonstrated effectiveness of doses as low as 0.6 and as high as 3 mg/Kg when the effects of the drug were compared to those of a relevant historical placebo control. This flat response over the five dose levels of drug tested, further replicated the effectiveness of the 1.8 mg/Kg. Results of the three trials were doses of the drug higher than 1.8 mg/Kg were tested (-031, -093 and -032), clearly demonstrated that there was no advantage in increasing the dose of DOLA•Mesyl to doses higher than 1.8 mg/Kg. In addition, this dose level of i.v. administered DOLA•Mesyl was shown to be superior to a relevant historical placebo control in patients in whom the stimulus consisted of non-cisplatin chemotherapeutic regimens of moderately emetogenic potential (study -082). In this study, a numerical although not statistically significant difference to the comparator MCP was seen.

Safety

In a fashion similar to the data with DOLA•Mesyl tablets, the intravenously administered drug produces acute, usually but not always dose-dependent prolongations of PR and QT_c, widening of the QRS and also prolongation of the JTc. In one study, JT prolongation was parallel to the changes in QTC_c. EKG changes with doses higher than 1.8 mg/Kg occurred more frequently than with the recommended dose of 1.8 mg/Kg. The EKG changes can be categorized as being usually reversible.

In the three types of trials in NDA 20-624, the most frequently occurring AEs were headache and dizziness. Although, regardless of the type of study analyzed, a higher incidence of AEs was seen with the 2.4 mg/Kg i.v. DOLA•Mesyl, there was no dose response relationship. Administration of the dose of interest, 1.8 mg/Kg, was accompanied by AE rates comparable in incidence to those seen with active comparators (ondansetron or granisetron). In controlled studies, the incidence of AEs was invariably higher in US than in non-US controlled studies. In all studies, for all three indications, the observed AEs were primarily of mild to moderate severity and none exhibited a dose response relationship. Overall, changes in vital signs induced by i.v. DOLA•Mesyl were similar to those seen with either placebo or active comparators.

Analysis of the proportion of patients who exhibited an alert level increase in QT_c interval (QTC_c <440 msec pre and ≥480 msec post) in studies for the three indications, showed higher numerical incidences with the two highest dose levels of drug tested (50 mg, but especially with the 100 mg in the PONV trials and with ≥2.4 mg/Kg in the CCNV studies). None of the patients in any of the trials for the three indications developed Torsades de pointes. But some clinically important arrythmias were seen in individual patients. These included one case of RBBB in a patients in the 50 mg group who had an alert level increase in QRS duration in the treatment of PONV trials. Individually,

in CCNV trials, most cases of some clinically important arrythmias, such as atrial fibrillation/flutter, SVT, asymptomatic ventricular triplet and ventricular fibrillation were reported in patients receiving DOLA•Mesyl than in those receiving comparators (ondansetron/granisetron). But because the total number of patients in the DOLA•Mesyl group was considerably larger (n=1906) than in the other group (n=356), no sound conclusions can be drawn from these comparisons. Other instances of AEs in individual patients were the occurrence of two cases of excessive drowsiness in the prevention of PONV trials, one case of severe hypotension in a patient who had impairment of cardiac function pre-drug in the prevention of CCNV studies and one case of angina, assessed as possibly related to the 2.4 mg/Kg DOLA•Mesyl dose. In study -032 (high-dose cisplatin trial), one case of mild chest pain occurred in a patient 9h after receiving the 1.8 mg DOLA•Mesyl dose and one case of non-severe myocardial ischemia or possibly MI in a patient with no significant cardiac history pre-drug occurred. Both events were assessed as possibly related to test medication by the investigator. In study -082 (non-cisplatin chemotherapy regimens), the contribution of DOLA•Mesyl (1.8 mg/Kg=119 mg) to the sudden death of a patient that was found dead 6.5h after receiving test medication cannot be excluded with certainty. All this information should be included in the labeling.

As with the tablet dosage form, the clinical experience with intravenously administered DOLA•Mesyl is limited. More experience is needed on the potential interaction between DOLA•Mesyl and cardiovascular medications in general, those drugs that accumulate in the heart (such as anthracyclines and anthracendiones) and those drugs and conditions that prolong the PR, QRS and the QT_c interval in particular. The list of these drugs is vast but they may be grouped on the basis of class and mentioned in the labeling. Also lacking are data on possible interaction of this drug with clinical conditions involving patients with history of cardiovascular disease. As in the case of tablet formulation, the MO concludes that there is a potential safety hazard that should be acknowledged in the labeling.

The appraisal of the information of NDA 20-624 seems to justify the following recommendations for regulatory action.

1. Approval of ANZEMET® (DOLA•Mesyl) injection for the treatment of PONV.

   Based on results of pivotal trials -044 and 2-S-084, the recommended dose regimen is 25 mg given as a single i.v. dose as soon as nausea or vomiting presents.

2. Approval of ANZEMET® (dolasetron mesylate) injection for the prevention of PONV.

   Based on results of pivotal trials -084 and -080, the recommended dose i.v. regimen is 25 mg given as a single dose at the cessation of anesthesia.

3. Approval of ANZEMET® (dolasetron mesylate) injection for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin.

   Based on results of pivotal studies -081, -031, -093, -032 (high dose cisplatin) and -082 (non-cisplatin-based regimens), the recommended i.v. dosage is 1.8 mg/Kg (or 100 mg). This dose is to be given as a single dose, approximately 30 min. before chemotherapy.

4. The labeling, being considered separately, should include a warning, preferably in a box. Such warning should state that, with dolasetron mesylate injection, there is reasonable evidence for the potential for serious and severe safety hazards - primarily in the cardiovascular/ cardiac electrophysiological area - that may place patients at the risk of death. A brief description of the sudden death occurring 6.5h after the patient received test medication at the intravenously recommended dose (1.8 mg/Kg or 119 mg) should be included in this warning. Note that this report is incomplete and does not constitute conclusive proof that the observed sudden death resulted from ANZEMET®. But it is prudent to include this information in the labeling. Also included in the Precautions section of the labeling should be a statement indicating the need for close patient monitoring during dolasetron mesylate therapy (injection or oral) in patients that have received long-term anthracyclines or anthracendiones (or other drugs that accumulate in the heart that induce cardiac arrythmias).

February 5, 1997

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APPEARS THIS WAY
ON ORIGINAL

Hugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20,624
HFD-180
HFD-180/SFredd
HFD-180/HGallo-Torres
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
r/d 1/29/97 jgw
f/t 2/4/97 jgw
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