i) Potentially Clinically Relevant Changes in EKG Intervals

- $QT_c$ interval prolongation above 500 msec was not observed in this patient population.

- At the 2-h post-dose measurements, the following 8 patients (PL, n=3; DOLA•Mesyl, n=5) had prolonged PR interval ≥220 msec subsequent to receiving test medication.

PL [n=3]

Increase in PR

Patient 0357-004
The QRS interval increased from The heart rate decreased from The $QT_c$ interval decreased slightly.

There were no adverse events attributable to the PR interval prolongation.

Patient 0358-013
HR increased from Other EKG intervals were increased as follows: QRS interval from and $QT_c$ interval from

There were no adverse events attributable to the PR interval prolongation.

Patient 0373-003
The $QT_c$ interval increased from . The HR and QRS interval remained essentially unchanged.

There were no adverse events attributable to the PR interval prolongation.

DOLA•Mesyl [n=5]

Patient 0356-0028 (50 mg)
HR decreased from . QRS and $QT_c$ interval remained essentially unchanged.

The patient had an AE for lightheadedness that the investigator deemed as possibly related to test med.

Patient 0357-012 (12.5 mg)
HR increased from Other EKG intervals were increased as follows: QRS interval from and $QT_c$ interval from

The patient did not have any AEs that were attributable to the PR interval prolongation.

Patient 0360-028 (50 mg)
The $QT_c$ interval increased from . Heart rate decreased from . The QRS interval remained unchanged.

The patient did not have any AEs that were attributable to the PR interval prolongation.

Patient 0278-001 (50 mg)

Other EKG intervals were increased as follows: QRS interval from and $QT_c$ interval from . The heart rate decreased slightly.

The patient has a history of hypertension and takes Cardizem 300 mg po, Tenex 2 mg po and Lozol 2.5 mg po daily.

The patient did not have any AEs that were attributable to the PR interval prolongation.

Patient 0416-015 (12.5 mg)

The HR increased slightly. The QRS interval decreased from and the $QT_c$ interval decreased from

The patient had an AE for dizziness that began ca. 2.5h after receiving test medication that the investigator deemed as possible related to test medication.

5. Conclusions (Sponsor)

"All doses of dolasetron administered in this study were effective in the prevention of PONV in females undergoing gynecologic surgery by laparoscopy. Therefore, 12.5 mg dolasetrol is as efficacious as larger doses of the drug in this patient populations.

"No treatment related, clinically important adverse events occurred. Dolasetrol 12.5 mg and 25 mg have a safety profile that is similar to placebo."

6. Reviewer's Comments

Study -084 is the second of the three main trials submitted by the sponsor of NDA 20-624 in support of approval of the marketing of intravenously administered ANZEMET (DOLA•Mesyl 12.5 mg single dose) for the prevention of postoperative nausea and/or vomiting.

Study -084, carried out at 25 centers in the U.S. was similar in design and execution to study -045. Enrolled in study -084 were 635 female (no males were enrolled), predominantly white (70%), with a mean age of 32y; 60% of the patients were ASA physical status class 1, the remainder were ASA class 2. Ca. 76% of the patients did not have a Hx of PONV, 21% had a Hx of motion sickness, 33% were current smokers, 52% were undergoing a laparoscopic sterilization, 33% were undergoing a diagnostic laparoscopy and 15% were undergoing a laparoscopic laser surgery. The patients were essentially normal and exclusions pertaining to the cardiovascular system were as in other PONV and CCNV trials. The methodology for randomization/stratification (on the basis of previous Hx of PONV) resulted in four patient populations that were well balanced with respect to variables that may influence efficacy or safety

outcome.[5] Each of the three dose levels of intravenous DOLA•Mesyl (12.5, 25 and 50 mg) or PL was administered over 30 seconds to 5 min. approximately 15 min. before the cessation of nitrous oxide.

Study -084 showed that DOLA• Mesyl is active since the ITT as well as the Evaluable population analyses demonstrated a statistically significant linear trend in the proportion of complete responders across the four dose groups [p<0.0001, ITT, n=635].

The CR rate with PL was 31% in the ITT and 30% in the Evaluable populations. Each of the three DOLA•Mesyl dose levels (CR of 50% to 56% in the ITT and 49% to 55% in the Evaluable population) was shown to be clinically and statistically superior to PL, with therapeutic gain ranging from 20% to 25% in the ITT and 19% to 25% in the Evaluable population). Individually, the DOLA•Mesyl dose with the largest therapeutic gain over PL (25% in both study populations) was 50 mg. Thus, study -084 did not replicate the efficacy findings in study -045 because the latter showed a) no activity for any of the DOLA•Mesyl doses in the overall population, b) no activity for any of the DOLA•Mesyl doses in male patients and c) superiority to PL in female patients only for the extreme doses tested (12.5 and 100 mg). Furthermore, in study -045, even in the female only stratum, the CR with 50 mg DOLA•Mesyl dose could not be differentiated from PL (therapeutic gain=10%; p=N.S.). The findings in studies -084 and -045 represent very inconsistent results. An analysis of response based on history of PONV stratification showed higher rates for those patients without a previous Hx of PONV vs those that had a Hx of PONV. The therapeutic gains in the NO stratum were 3% to 12% higher than the therapeutic gains in the YES stratum.

In this study population and under the experimental conditions and methodology used in study -084, graded intravenous doses of DOLA•Mesyl were - all in all - well tolerated. No deaths were associated with this trial. No patients D/C from the trial due to AEs. No significant cardiovascular events (complete BBB, high-degree AV block, Torsades de pointes nor other serious ventricular arrhythmias) occurred. One serious AE, excessive drowsiness and resulting in the patient's hospitalization was assessed as possibly related to DOLA•Mesyl 50 mg. Other serious and other notable AEs occurring among DOLA•Mesyl patients were assessed by the correspondent investigators as not related to test med.

The overall AE rates were similar with the 12.5 to 50 mg DOLA•Mesyl doses and PL (49%). The most frequently occurring AEs were sinus bradycardia, headache, T-wave change or abnormality, sinus arrhythmia, urinary

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[5] • The pre-Tx use of bupivacaine was 4% in the PL group and ranged from 9% to 13% in the DOLA•Mesyl groups. But this imbalance (p=0.024) would not be expected to impact the efficacy or safety results of the trial.

• Two escape medications, droperidol and promethazine were taken by a higher proportion of pts. in the PL group (19% and 15%, respectively) than in the DOLA•Mesyl groups (8% to 11% and 6% to 8%, respectively). These imbalances may be the result of less efficacy in the PL group.

retention, pain, dizziness and drowsiness, but there was no linear trend across dose in the occurrence of any of these events.

The changes from Pre-Tx to 2h Post-Tx in EKG parameters showed, not surprisingly, dose dependent increases in mean values for QRS (p=0.0001) and QT (p=0.0496) intervals. These EKG changes are better appreciated in Fig. 5. This illustration leaves no doubt that on the average, the 50 mg DOLA•Mesyl dose induced QRS and $QT_c$ changes from baseline that were greater (although the difference was modest) than those seen with PL. Once again, all in all, the changes in EKG intervals induced by 12.5 mg DOLA•Mesyl were similar to those observed with PL.

Some potentially clinically relevant changes in EKG interval are briefly summarized next. $QT_c$ interval prolongation above 500 msec was not observed in study -084. Instead, at the 2h Post-dose measurement, 8 patients (PL=3; DOLA•Mesyl=5) had prolonged PR interval ≥220 msec subsequent to receiving test medication. The magnitude of PR interval increase among the three PL-treated patients ranged from 8 to 104 msec, among the DOLA•Mesyl-treated patients this magnitude of increase ranged from . Review of the AE data for all patients in study -084 did not reveal any events that could have been related to PR interval prolongation above 220 msec.

D. Study 73147-2-S-080

In the present review, this study is identified as -080.

"A Double-blind, Placebo-controlled, Randomized (Balanced) Multicenter Study to Assess the Effect of Single Doses of Intravenous Dolasetron Mesylate 12.5, 25, 50, and 100 mg in Preventing Postoperative Nausea and Vomiting."

1. Objectives

a) To assess the effect of a range of doses of intravenous DOLA•Mesyl in preventing nausea and vomiting in patients undergoing surgery under general anesthesia.

b) To evaluate the tolerance and the safety of different dose levels of DOLA•Mesyl when given for this indication.

2. Study Population/Design/Assessments

- Inclusion-exclusion criteria were less specific in this protocol than the others. In regard to the cardiovascular system, enrolled in the trial were patients with "evidence of clinically significant" cardiovascular dysfunction or history of similar disorder and those

treated with antiarrhythmic agents. Administration of potentially confounding antiemetic medications was proscribed in the 24h before the proposed start of surgery.

- This was a double-blind, placebo-controlled, randomized, 5-arm multicenter study with five parallel dose groups. Enrolled were 281 female patients with ASA physical status class 1 or 2 undergoing laparoscopic surgery or other gynecological surgery under standardized general anesthesia. In order to ensure that patient groups received similar emetogenic stimuli and were comparable in terms of type of anesthesia and surgical procedure, patients entering the study were stratified for the type of surgery: laparoscopic surgery and other gynecological surgery (laparotomy and vaginal hysterectomy). Random allocation to DOLA•Mesyl (12.5, 25, 50 or 100 mg) or PL was stratified for the type of surgery to ensure balanced numbers of laparoscopy in each dose group.

- Treatment consisting of a single intravenous dose of DOLA•Mesyl (12.5, 25, 50 or 100 mg) or PL was administered postoperatively at the cessation of administration of nitrous oxide, PL via a 5-min. i.v. infusion. Escape medication was initiated if needed during the study period. The time, name, dose, route of administration and frequency of escape medication were recorded in the patient's CRF.

- Each patient was closely observed for nausea and emetic episodes for 8h after study drug administration. Vital signs were monitored. Follow-up evaluations were obtained 24h postdose. The safety of study medication was monitored by 12-lead EKG, vital signs, AEs and clinical laboratory tests.

- Efficacy and safety assessments were as per PONV protocols already reviewed.

3. <u>Primary Statistical Analysis</u>

- The primary analysis was an intent-to-treat analysis of CR over 24h. As in previous protocols, CR was achieved for a patient when she experienced no emetic episode and no escape medication was given during the entire 24-h study period. Logistic regression with a test for a linear contrast in the proportion of complete responders across the 5 treatment groups controlling for investigator and stratum was the primary test for efficacy.

- Investigator and stratum - by - treatment interactions were checked using logistic regression and the Rao score residual Chi-square test. Additionally, a supplemental Mantel-Haenszel test for nonzero correlation (using modified ridit scores) in CR with the 5 dose levels of DOLA•Mesyl, controlling for investigator and stratum, was done. A contrast among the estimated dose parameters was done secondarily to

compare each dose with PL. These analyses were done as intent-to-treat analyses; meaning that all patients which received study drug were included.

- The above logistic regression analysis of CR was done secondarily using only those patients which were deemed efficacy evaluable.

4. Results

a. Patient Accounting/Participating Investigators

- A total of 281 patients were enrolled at 10 investigative sites [one center (#6) enrolled only one patient). The following 5 centers enrolled 30 or more patients each:

| Center No. | | Total Number of Patients Enrolled |
|---|---|---|
| 01 | Prof. J.P. Dupeyron (Strasbourg, FR) | 50 |
| 05 | Dr. Ch. Payeur-Michel (Mulhouse, FR) | 50 |
| 11 | Prof. P. Wessel (Nantes, FR) | 40 |
| 02 | Prof. P. Schoeffler (Clermon-Ferrand, FR) | 34 |
| 09 | Prof. R.S.J. Clarke (Belfast, IR) | 30 |

- There was no statistically significant difference among the five experimental groups in the number and percent of patients randomized to each dose with major protocol violations that rendered patients unevaluated for efficacy. Only 4 of the 281 patients were not evaluable for efficacy [ITT, n=281; Evaluable Population, n=277].

b. Data Showing Comparability of Groups at Baseline'

- In general, the five experimental groups were balanced in regards to demographic and baseline characteristics.

- The study population consisted exclusively of female patients, predominantly of ASA 1 status. About one-third of the patients had a history of PONV. Roughly half of the patients had laparoscopic surgery, ca. a little more than one-third had laparotomy surgery and the rest (or 10%) had vaginal hysterectomy.

- The test groups were balanced in medical history, pre-Tx physical examination and anesthesia procedures (except for the use of fentanyl, p=0.0253, which is not expected to influence outcome).

- There were no statistically significant differences among the groups in the frequency and percent of patients using various concomitant medications pre- and post-treatment. This included the use of morphine.

- There was no statistically significant difference among the test groups in the proportion of patients receiving escape medication (MCP, n=44; cyclizine, n=6).

- Summarized below is the distribution of patients by stratum and dose.

Distribution of Patients by Dose and Stratum

| Laparoscopic Procedure | PL | DOLA•Mesyl Dose (mg) | | | | Total |
|---|---|---|---|---|---|---|
| | | 12.5 | 25 | 50 | 100 | |
| YES | 30 | 28 | 26 | 26 | 32 | 142 |
| NO | 24 | 26 | 34 | 28 | 27 | 139 |
| Total | 54 | 54 | 60 | 54 | 59 | 281 |

c. Clinical Response (Tables 24 and 25)

One evaluation of CR included all patients (Table 24). In another (Table 25) response was examined on the basis of strata and this was based on the type of surgery.

- As shown in Table 24, this study showed an increase in CR with increasing dose level. The test for linear trend in these response rates with dose was significant at a p of 0.0475.

- The therapeutic gains ranged from but of the four DOLA•Mesyl dose levels only the 25 mg dose group was significantly different from PL.

- There was a significant center (=investigator) main effect (p=0.0411).

- The efficacy evaluable analysis supported that in the ITT (again, the only statistically significantly different dose group from PL was 25 mg).

TABLE 24
Study -080

Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response

| Response by Dose (mg) | | | | | Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses and PL/[p-value] | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **I. Intent-to-Treat Analysis [n=281]** | | | | | | | | | |
| PL [n=54] | 12.5 [n=54] | 25 [n=60] | 50 [n=54] | 100 [n=59] | 12.5 vs PL | 25 vs PL | 50 vs PL | 100 vs PL | All DOLA•Mesyl vs PL |
| 23 (42.6%) | 29 (53.7%) | 40 (66.7%) | 32 (59.3%) | 35 (59.3%) | (11.1%) [N.S.] | (24.1%) [0.0042] | (16.7%) [N.S.] | (16.7%) [N.S.] | (17%) [0.0118] |
| **II. Efficacy Evaluable Analysis [n=277]** | | | | | | | | | |
| [n=54] | [n=52] | [n=60] | [n=53] | [n=58] | | | | | |
| 93 (43%) | 27 (52$) | 40 (67%) | 31 (58%) | 34 (59%) | ( 9%) [N.S.] | (24%) [0.014] | (15%) [N.S.] | (16%) [N.S.] | (16%) |

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TABLE 25
Study -080

Clinical Response: Analyses of Primary Efficacy Parameter
Complete Response by Dose and Strata (Type of Surgical Procedure)[a]

| Response by Dose (mg) | | | | | Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses[b] and PL/[p-values] | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **I. Stratum 1: Laparoscopy [n=142]** | | | | | | | | | |
| PL [n=54] 30 | 12.5 [n=54] 28 | 25 [n=60] 26 | 50 [n=54] 26 | 100 [n=59] 32 | 12.5 vs PL | 25 vs PL | 50 vs PL | 100 vs PL | All DOLA•Mesyl vs PL |
| 14 (47%) | 18 (64%) | 21 (81%) | 16 (61%) | 19 (59%) | (17%) | (34%) | (15%) | (12%) | (20%) |
| **II. Stratum 2: Other Gynecological Surgery [n=139]** | | | | | | | | | |
| 24 | 26 | er | 28 | 27 | | | | | |
| 9 (38%) | 11 (42%) | 19 (56%) | 16 (57%) | 16 (59%) | 4% | 18% | 19% | 21% | (16%) |
| **III. Laparotomy [n=108]** | | | | | | | | | |
| 18 | 29 | 26 | 23 | 21 | | | | | |
| 8 (44%) | 9 (45%) | 15 (58%) | 13 (57%) | 13 (62%) | 5% | 14% | 13% | 18% | (12%) |
| **IV. Vaginal Hysterectomy [n=31]** | | | | | | | | | |
| 6 | 6 | 8 | 5 | 6 | | | | | |
| 1 (17%) | 2 (33%) | 4 (50%) | 3 (60%) | 3 (50%) | (16%) | (33%) | (43%) | (33%) | (31%) |

a) Strata p=0.0549, from a 1 degree of freedom Chi-square test for stratum as a main effect using logistic regression with dose, investigator and stratum in the model.
b) Dose p=0.3975, from a 1 degree of freedom Chi-square test for interaction of stratum with a linear dose response effect using Rao's scores from logistic regression.

- There were no center by dose or strata-by-dose interactions with a linear dose response effect.

- There was a marginally significant stratum effect (p=0.0549). The data depicted in Table 25 are only descriptive. Depending on the type of surgery, the therapeutic gains are very variable and inconsistent, especially in instances where the number of patients per cell was very small. The reviewer is unable to draw a firm conclusion as to the possible effect of type of surgery on CR.

I) Subgroup Analysis



This information is summarized below:

Subgroups
Statistically Significant Predictors of CR

| NO | YES |
|---|---|
| - Duration of Anesthesia (p=0.0521)[a]<br>- ASA status<br>- Total dose of morphine<br>- Weight | - Previous Hx of PONV (0.0004)[b]<br>- Age )p=0.0004) |

a) Marginal effect. There was no interaction with duration of anesthesia with the linear dose response model.
b) Pts. with no history were more likely to be complete responders than patients with a history of PONV. There was no interaction of previous history of PONV with a linear dose response effect in CR (p=N.S.).
c) Older patients were less likely to be complete responders than are younger patients. There was a significant interaction of age with the linear dose response effect (p=0.0475). Younger patients tended respond at a lower doses than did older patients.

- When either previous Hx of PONV or age were controlled for as a main effect along with dose, investigator and stratum in the logistic aggression model, the test for linear trend in CR with dose was not significant (p=0.1012 and 0.1413, respectively). When either duration of anesthesia or weight were entered along with dose, investigator, and stratum in the logistic regression model, the test for linear trend in complete response with dose was marginally significant (p=0.064 and 0.0430, respectively). Controlling for ASA status along with dose, investigator, and stratum in the logistic regression model has a minimal increasing effect on the p-value for the test for linear trend (p=0.0516).

- Controlling for total dose of morphine along with dose, investigator and stratum in the logistic regression model had a decreasing effect on the p-value for the test for linear trend (p=0.0385).

d. Safety Results

1) Extent of Exposure

In study -080, 281 patients received a single dose of test medication intravenously, with the following distribution:

| | DOLA•Mesyl Dose (mg) | | | |
|---|---|---|---|---|
| PL | 12.5 | 25 | 50 | 100 |
| [n=54] | [n=54] | [n=60] | [n=54] | [n=59] |

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

- There were no deaths reported during the trial.
- No patients D/C from the trial due to AEs.
- The following three patients (PL=2; 12.5 mg=1) experienced a serious event that resulted in "immediate risk of death". The PL patients experienced respiratory depression and severe bradycardia with a brief cardiac depression. All three patients recovered without sequelae. These three cases are briefly described below.

Patient 080-018/B (12.5 mg)

She experienced, 20 min. after administration of DOLA•Mesyl 12.5, respiratory depression requiring artificial ventilation.

The event was rated by the investigator as severe, but not related to test medication.

Patient 080-022/B (PL)

She experienced, at recovery from anesthesia, respiratory depression due to administration of morphine derivative and potentialized by thiopental and isoflurane. Treatment consisted of administration of naloxone, 0.2 mg.

The severity of the event was rated by the investigator as moderate and the causal relationship to study drug as possible.

Patient 080-075/A (PL)

She exhibited severe bradycardia with a brief cardiac arrest 5 min. after the administration of study medication. Resuscitation was successful after cardiac massage and administration of cardiac stimulants.

The event was rated as of moderate in severity, but not related to test medication.

3) AEs

- The overall rate of AEs was 23.8% for DOLA•Mesyl treated groups and 29.6% for PL.
- There were no significant linear trends with dose in the incidence of any AE, central and peripheral nervous system AEs, gastrointestinal AEs or headache.
- The most frequently reported specific events were headache (DOLA•Mesyl=7.5%; PL=7.4%), appetite increased (3.1% and 1.9%, respectively), and drowsiness (1.8% and 3.7%, respectively) and abdominal pain (1.8% and 1.9%, respectively).
- Two cases of headache (one in a PL-treated patient and one on a DOLA•Mesyl 12.5 mg) were reported as severe. All the other events were reported as mild or moderate with the exception of those events where no information regarding severity was available.

4) Clinical Laboratory Evaluation

There were no clinically significant changes in clinical laboratory measurements.

5) Vital Signs

There were no clinically significant changes in vital signs. Some quantitative changes observed are summarized as follows.

- The frequency of hypotension observed in the 100 mg treated group (42%) was higher than that observed in PL (33%); other doses had frequencies similar or less than the PL group.
- The frequency of hypertension observed in the 100 mg group (22%) was less than that observed in the PL group (33%).
- The 50 mg group had a higher frequency of hypertension (41%) than all other dose groups.
- There was less bradycardia and tachycardia in the 100 mg dose group than in the PL group.

6) Changes in EKGs

Since, in study -080 EKG evaluations were carried out 24h after the administration of test medication, these observations are not very contributory because the $C_{max}$ of the DOLA•Mesyl metabolite though to be

correlated with EKG changes occurs at 2 to 4 hours after administration of the drug. In the present study, the following was recorded. No patients had a treatment emergent PR interval greater than 220 msec. Three patients had QRS intervals greater than 100 msec, 2 in the 25 mg group and 1 in the 50 mg group. Thirty-one patients had $QT_c$ intervals at 24h which exceeded 440 msec; 1 in the placebo group, 9 in the 12.5 mg group, 7 in the 25 mg group, 8 in the 50 mg group and 6 in the 100 mg group.

7. Conclusions (Sponsor)

"In this pilot trial, dolasetron mesylate was shown to be effective and safe in the prevention of postoperative nausea and vomiting undergoing gynecological surgery in patients.

"Analysis of complete response rates indicated that a linear trend existed of increase in complete response with dose. The 25 mg group was statistically different from placebo while only marginal significance was achieved for the 50 mg and 100 mg dose groups. A similar pattern was obtained for the incidence of nausea, also suggesting that there is no gain in increasing the dose above 25 mg.

"Previous history of postoperative nausea and vomiting, age, and duration of anesthesia were found to be predictors of response rates. These factors may have increased the margin between placebo and dolasetron mesylate. Considering the selected sample sizes, the results of the study have to be interpreted with caution.

"Tolerability of dolasetron mesylate was good. Adverse events were few, were predominantly mild to moderate, and were evenly distributed across dose groups. Laboratory parameters changes were unremarkable and did not shown any change that could be attributed to study medication. Vital signs were not consistently altered."

6. Reviewer's Comments

Study -080 is the third of the three main trials submitted by the sponsor of NDA 20-624 in support of approval of the marketing of intravenously administered ANZEMET (DOLA•Mesyl 12.5 mg single dose) for the prevention of postoperative nausea and/or vomiting.

Considered a pilot study, -080 was set to assess the effect of a range of doses of intravenous DOLA•Mesyl (1.2, 25, 50 or 100 mg vs PL) in preventing N&V in patients undergoing surgery under general anesthesia. The study was carried out at 11 centers in Europe (primarily France and Ireland); center #6 enrolled only one patient. In this protocol, the inclusion-exclusion criteria were less specific than in the other prevention of PONV protocols. Exclusions

pertaining to the cardiovascular system were a) "evidence of clinically significant" cardiovascular dysfunction or history of similar disorder and b) those patients treated with antiarrhythmic agents. Administration of potentially confounding antiemetic medications was proscribed in the 24h before the proposed start of surgery.

Enrolled in study -080 were 281 female patients (no males were enrolled), predominantly of ASA 1 status. Ca. one-third had a Hx of PONV, roughly one-half of the patients had laparoscopic surgery, a little more than one-third had laparotomy surgery and the rest (ca. 10%) had vaginal hysterectomy. Random allocation to test medication was stratified for the type of surgery (laparoscopic vs nonlaparoscopic procedures). The patients received DOLA•Mesyl or PL administered i.v. over 5 min. at the cessation of nitrous oxide. Safety and efficacy were monitored for 24h.

The methodology for randomization/stratification (on the basis of the type of surgery) resulted in five patient populations that were well balanced with respect to demographic, characteristic and baseline and other variables that may influence efficacy or safety outcome. An imbalance was noted: the percentage of patients with a previous Hx of PONV was the smallest in the 50 mg group (15%) and the highest in the PL group (36%), an imbalance that may possibly bias the study in favor of the DOLA•Mesyl dose and against PL, since Hx of PONV predisposes the patient to more PONV. There was no imbalance among the test groups in the duration of anesthesia nor in doses of anesthetics except for the mean dose of fentanyl which was higher in 12.5 DOLA•Mesyl-treated patients when compared to PL. But this imbalance would have no expected impact on results.

In study -080, activity was shown since the ITT analysis (n=281) of the percentage of complete responders revealed a significant linear trend (p=0.0475) with increasing dose levels of DOLA•Mesyl. But of the pairwise comparisons (each dose level of drug vs PL), only the 25 mg was shown to be statistically significantly different from PL.

The CR rate with PL was 43% in both the ITT and Evaluable populations. The CR rate in the ITT population ranged from in the Evaluable population. With therapeutic gains of 11% (ITT) and 9% (Evaluable) the 12.5 mg DOLA•Mesyl dose level could not be differentiated from PL. Similarly, with therapeutic gains of 17% and 17% in the ITT population and 15% and 16% for the 50 and 100 mg dose levels, these higher doses of DOLA•Mesyl were not statistically different from PL. As mentioned above, only the 25 mg DOLA•Mesyl dose level, with the high CR rate (67% in both patient populations) was superior to PL. The efficacy results in pilot study -080 replicated neither those in study -084 where the DOLA•Mesyl dose with the largest therapeutic gain over PL was (25% in both study populations) 50 mg nor those in study -045. In the latter study, superiority to PL in female patients for the two extreme doses (the lowest=12.5 mg and the highest=100 mg).

Specifically, in study -045 the CR rate with the 25 or the 50 mg dose levels was not different from PL. In summary, the efficacy findings in studies -045, -084 and -080 represent efficacy of DOLA•Mesyl at the dose of 25 mg once-a-day in the prevention of PONV indication. But results with the other dose levels of the drug are more inconsistent.

In this study population and under the experimental conditions and methodology used in pilot study -080, graded intravenous doses of DOLA•Mesyl were - all in all - well tolerated. No deaths were associated with this trial. No patients withdrew from the trial due to AEs. No significant cardiovascular events (complete BBB, high-degree AV block, Torsades de pointes nor other serious ventricular arrhythmias) occurred. One 12.5 mg DOLA•Mesyl patient experienced respiratory depression (assessed as severe and not related to test med.). One PL patient experienced respiratory depression (assessed as moderate in intensity and possibly related to test med.). An additional PL patient exhibited severe bradycardia with a brief cardiac arrest 5 min. after the adm. of test med. Resuscitation was successful after cardiac massage + administration of cardiac stimulants. This event was assessed as MOD in severity but not related to test med. All three events were rated as serious and thought to result in "immediate risk of death". All three patients recovered without sequelae.

The overall AE rates were similar between the DOLA•Mesyl doses (24%) and PL (30%). The most frequently reported specific AEs were headache, appetite increase, drowsiness and abdominal pain. The only AE that occurred in >5% of the patients was headache but a dose relationship was not observed.

In study -080, EKG evaluations were not very contributory because the tests were done 24h post-Tx, thereby missing the $C_{max}$ of the metabolite (occurring ca. 2 hours after dose), known to correlate with EKG changes. At 24-h postdosing the concentrations of both DOLA•Mesyl and its metabolite MDL 74,156 are extremely low or nil.

## IV. INDICATION: PREVENTION OF CCNV

### A. Adequacy of Submitted Trials (Table 26)

As summarized in this Table, efficacy against two emetogenic stimuli, cisplatin and non-cisplatin-based regimens has been evaluated. Four studies (-080, -031, -093 and -032) assessed effectiveness in cancer patients receiving cisplatin-based chemotherapy regimens considered of high emetogenic potential (≥80 mg/m²). In the other study (-082) effectiveness of DOLA•Mesyl was assessed in cancer patients receiving cyclophosphamide-based chemotherapy regimens of moderate emetogenic potential. All five trials made use of useful designs, consisting of randomized, double-blind, multicenter, parallel observations. In study -081 (2 dose levels of DOLA•Mesyl vs PL), effectiveness is demonstrated by showing statistically superiority of one or the dose levels of DOLA•Mesyl over MCP. In this study the analysis of the

effect of gender and whether the patient was chemotherapy naive is important to explore the effects of these strata on clinical response. Studies -031 (2 dose levels of DOLA•Mesyl vs OND) and -093 (2 dose levels of DOLA•Mesyl vs GRAN) were set to show bioequivalence of DOLA•Mesyl to ca. 32 mg OND or ca. 40 μg/Kg GRAN. But in both studies, in the absence of an internal negative comparator, against which to show superiority, it is not known if any of the tested regimens is active. In both studies, comparisons to a relevant negative historical control (i.e. PL) are needed (see review of individual trials). The main objective of study -032 (five dose levels of DOLA•Mesyl) was to evaluate the dose response relationship across 0.6, 1.2, 1.8, 2.4 and 3 mg/Kg single intravenous doses of DOLA•Mesyl in preventing emesis associated with cisplatin chemotherapy. If the dose response is flat, to show effectiveness (any dose), superiority to a relevant negative control needs to be demonstrated (see review of this trial). The comparator in study -082 (two dose levels of DOLA•Mesyl vs a non-approved regimen of MCP in cancer patients receiving moderately emetogenic chemotherapy regimens) is a non-approved regimen of MCP. Effectiveness of DOLA•Mesyl is demonstrated by showing superiority of DOLA•Mesyl over MCP. If the three arms of the study were to show that they are "equivalent", then, in order to show effectiveness, superiority to a relevant negative historical control (i.e. in moderately emetogenic cyclophosphamide chemotherapy) needs to be demonstrated.

In the subsequent section of the present review, data from each of these five trials are assessed. Although efficacy is only succinctly reviewed, this assessment incorporates not only information from the original NDA 20-624 (DOLA•Mesyl injection) but also the relevant historical control data assembled by the sponsor in their submission of November 18, 1996. These data were submitted in response to our telephone request of November 7, 1996. The emphasis on these reviews of these individual studies is on safety.

TABLE 26
NDA 20-624

Main Features of Design/Execution of the Five Main Studies Submitted by the Sponsor in Support of the Approval of DOLA•Mesyl for the Prevention of CCNV

| Study Identification | Study Population | Main Design/ Execution | Groups Being Compared | REMARKS |
|---|---|---|---|---|
| **I. CISPLATIN-BASED, HIGH EMETOGENIC STIMULUS** | | | | |
| 73147-3-S-(-081) (Europe) 14 centers in Belgium, Germany, France, The Netherlands, U.K. [n=226] F=65 M=160 | F or M cancer patients scheduled to receive cisplatin ≥80 mg/m² were prospectively stratified on the basis of gender and previous Hx of chemotherapy. | • Stimulus of high emetogenic potential=cisplatin (≥80 mg/m²)-based regimens.<br>• Randomized, double-blind, multicenter, parallel group. Stratified by gender and whether chemotherapy naive or not, 3-arm study.<br>• Test med given as a bolus 30 min. before the start of cisplatin; the comparator was followed by a 4 mg/Kg maintenance dose adm. by continuous infusion over 8h.<br>• Definitions of emetic episodes and evaluation period (24h after the initial bolus of test med.) as in previous protocols. | Two DOLA•Mesyl single doses, given i.v. as bolus containing (mg/Kg):<br>1.2 [n=84]<br>1.8 [n=73]<br><br>vs<br><br>MCP [n=69]<br><br>(3 mg/Kg bolus dose 30 min. before cisplatin followed by a 4 mg/Kg maintenance dose adm. by continuous infusion over 8h) | • Useful design<br>• At the start of the trial the MCP regimen used as comparator was approved for prevention of N&V in patients receiving cisplatin. As the trial progressed, the standard of antiemetic care in Europe changed such that this dose of MCP was no longer used for patients receiving high-dose cisplatin. (This lead to an early cessation of the trial).<br>• Efficacious of DOLA•Mesyl is demonstrated by showing statistical superiority of one of the two dose levels against MCP.<br>• Stratification of patients on the basis of gender and previous Hx of chemotherapy is of interest because gender and whether the patient is chemotherapy-naive or not are factors influencing antiemetic response. |

TABLE 26 (Con't.)

| | | | | |
|---|---|---|---|---|
| MCPRO<br>(-031)<br>(US)<br>[n=609]<br>45 centers<br>F=232 M=377 | F or M cancer patients scheduled to receive cisplatin, either 70-80 mg/m² or 100 mg/m² (pts. were prospectively stratified on the basis of the dose of cisplatin being given). | • Stimulus of high emetogenic potential=cisplatin (70-80 or 100 mg/m²)-based regimens.<br>• Randomized, double-blind, multicenter, parallel-group, stratified by cisplatin dose, 3-arm study.<br>• Test med. given as a 15-min. infusion, 30 min. before cisplatin. Definitions of emetic episodes and evaluation period (24-h after adm of test med.) as in previous protocols. | Two DOLA•Mesyl single doses, given i.v. for 15 min., containing (mg/Kg):<br>1.8 [n=198]<br>2.4 [n=205]<br><br>vs<br><br>OND [n=206]<br><br>(Originally 0.15 mg/Kg x 3 doses; later switched to 32 mg single dose). | • Useful design.<br>• The trial set to show bioequivalence of DOLA•Mesyl to an approved regimen of ondansetron, an approved selective inhibitor of the 5-hydroxytryptamine subtype receptor.<br>• However, in the absence of an internal negative comparator, against which to show superiority, it is not known if any of the tested regimens is active.<br>• To demonstrate activity, comparisons to a relevant negative historical control (i.e. placebo), are needed. |
| 73147-3-S-<br>(-093)<br>30 centers in France, Belgium and Spain<br>[n=474]<br>F=159 M=315 | F or M cancer patients scheduled to receive cisplatin (≥80 mg/m²)-based regimens (pts. were prospectively stratified on the basis of gender and previous history of chemotherapy). | • Stimulus of high emetogenic potential=cisplatin (≥80 m/m²); infusion time=87 minutes.<br>• Randomized, double-blind, multicenter, parallel group, stratified by gender and whether patient was chemotherapy-naive or not. | Two DOLA•Mesyl single doses, given i.v. for 5 min., containing (mg/Kg)<br>1.8 [n=163]<br>2.4 [n=161]<br><br>vs<br><br>GRAN [n=150]<br><br>(3 mg one dose fits all or = 40 mg/Kg for a 75 Kg patient) | • Useful design.<br>• The trial was set to show bioequivalence of DOLA•Mesyl to roughly 40 µg/Kg GRAN. Although this is not the approved dose in the U.S., the 10 µg/Kg (approved) and the 40 µg/Kg doses have been shown to be equally effective.<br>• In the absence of an internal negative comparator, against which to show superiority, it is not known if any of the tested regimens is active.<br>• To demonstrate activity, comparisons to a relevant negative historical control (i.e. placebo) are needed. |

TABLE 26 (Con't.)

| | | | | |
|---|---|---|---|---|
| MCPRO-<br>(-032)<br>(US)<br>[n=299]<br>21 centers<br>F=125 M=174 | F or M cancer patients scheduled to receive cisplatin, either 70-80 or 100 mg/m² (patients prospectively stratified on the basis of cisplatin being given). | • Stimulus of high emetogenic potential=cisplatin (70-80 or 100 mg/m²)-based regimens.<br>• Randomized, double-blind, multicenter, parallel group, stratified by cisplatin dose, 5-arm study.<br>• Total med. given as a 15-min. infusion, 30-min. before cisplatin.<br>Definition of emetic episodes and evaluation period (24-h after the test med.) were as in previous protocols. | Five dose levels of DOLA•Mesyl, single doses, given i.v. as a 15-min. infusion, containing (mg/Kg)<br>0,6 [n=59]<br>1.2 [n=59]<br>1.8 [n=63]<br>2.4 [n=60]<br>or<br>3.0 [n=58] | • Useful design.<br>• The study attempts to establish efficacy by showing a trend toward emesis following high dose cisplatin with increasing doses of the drug.<br>• One objective of the trial was 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 in preventing emesis due to cisplatin chemotherapy.<br>• If the five dose levels cannot be differentiated (from one another) in their ability to prevent cisplatin-induced CCNV, then in order to show effectiveness (any dose) superiority to a relevant negative historical control (i.e. placebo) needs to be demonstrated. |
| **II. NON-CISPLATIN-BASED, MODERATELY EMETOGENIC STIMULUS** | | | | |
| 73147-3-S-<br>(-082)<br>(Europe)<br>U.K., France, Belgium, Germany, The Netherlands<br>[n=309]<br>F=213 M=96 | F or M cancer patients scheduled to receive moderately emetogenic non-cisplatin-based chemotherapy (patients prospectively stratified on the basis of gender and on the basis of previous Hx of chemotherapy, infused for no more than 60 min. | • Stimulus of moderately emetogenic potential, either cyclophosphamide given in combination or others such as doxorubicin, daunorubicin or epirubicin, given either alone or in combination.<br>• Randomized, double-blind, multicenter, 3-arm, parallel group, patients stratified by gender and to chemotherapy or not by previous exposure (naive).<br>• Test med. given as a 15-min. infusion starting 15-min. before chemotherapy.<br>• Standardized definition as in previous protocols. | Two dose levels of DOLA•Mesyl given as single i.v. 15-min. infusions, containing (mg/Kg)<br>1.2 [n=104]<br>1.8 [n=101]<br>vs<br>MCP [n=104]<br>(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 cisplatin infusion). | • Useful design.<br>• Since the MCP dose regimen is not approved, effectiveness of DOLA•Mesyl is demonstrated by showing statistical superiority of one of the two (or both) dose levels against MCP.<br>• If there were no differences among the three arms of the study, then in order to show effectiveness (any of the two dose levels or both), superiority to a relevant negative historical control (i.e. in moderately emetogenic non-cisplatin chemotherapy) needs to be demonstrated. |

B. Study 73147-3-S-081

(Identified here as -081)

"A Three-Arm, Double-Blind, Randomized, Parallel Study of the Antiemetic Efficacy of Intravenous MDL 73,147EF versus Intravenous Metoclopramide in Patients Receiving Cisplatin-Containing Chemotherapy."

1. Main Objective

The main objective of this trial was to determine if one or both of two different intravenous (i.v.) doses of DOLA•Mesyl (1.2 or 1.8 mg/Kg) is/are equal or superior to the approved dose regimen of MCP (3 mg/Kg i.v. loading dose followed by 4 mg/Kg as a continuous 8-h infusion, i.e. 7 mg/Kg in total) in preventing emesis due to the administration of cisplatin ≥80 mg/m².

2. Study Population

This consisted of cancer patients scheduled to receive cisplatin at the dose of ≥80 mg/m² given over no more than 3h as the first component of a chemotherapy regimen. The inclusion-exclusion criteria were adequate for this type of study. It is to be noted that a protocol amendment resulted in the listing of the four exclusion criteria related to "significant cardiac disease".

- Patients with CHF or history 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 anthracendiones able to produce cardiotoxicity be examined with echocardiography prior to study entry. Patients with signs of cardiotoxicity on heart echocardiograph were excluded.

3. Concomitant Medications

The protocol proscribed use of any drug with potential antiemetic efficacy: i.e., ondansetron, granisetron, zacopride, batanopride, MCP, alizapride, thiethylperazine, promethazine, trimethobenzamide, tricyclic antidepressants, droperidol, diphenhydramine and steroids within 24h of study day 1, hour 0. Triazolam or temazepam were allowed only the night prior to chemotherapy. Triazolam and temazepam were not allowed during the 24h study period. Use of other benzodiazepines was not allowed (because of possible antiemetic activity). Other medications necessary for the well-being of the patient could be used according to the judgment of the investigator. Escape medication was given only after more than 2 emetic episodes (at least 3 emetic episodes) in the first 24h or on patient request.

4. Test Medication/Dosing Schedule

- DOLA•Mesyl was supplied by the sponsor as a sterile aqueous isotonic i.v. solution in 10 ml ampules (labeled as ampules I and II) each containing either 200 mg of DOLA•Mesyl (20 mg/ml) or PL. Lot numbers used were WN9111-05, -06, -07 and -08.

- MCP was supplied in 10 ml ampules (labeled as ampules III and IV) each containing either 200 mg of drug (20 mg/ml) or PL. Lot numbers used were WN9111-01, -02, -03, -04 and WN911-041.

- Test medication dosing was based on the patient's body weight. However, for blinding purposes, the ampule(s) content was diluted with sterile NaCl 0.9% so that each patient received 50 ml total volume infused over a 15 min. period prior to cisplatin. The continuous eight hour infusion was prepared using a total volume of 500 ml with the addition of NaCl 0.9% to the test medication and was initiated at the same time as the cisplatin infusion.

- Two groups of 100 patients each were to receive DOLA•Mesyl at 1.2 or 1.8 mg/Kg and one group of 100 patients was to receive metoclopramide 7 mg/Kg (total dose) according to the following dosing schedule:

  a. The first administration of MCP (3 mg/Kg) or DOLA•Mesyl (either 1.2 or 1.8 mg/Kg) started 30 min. before the cisplatin infusion and consisted of a 50 ml i.v. infusion over a period of 15 min. Based on body weight requirements (≤100 Kg), not more than 2 ampules of DOLA•Mesyl or PL (solution of ampules I and II) and not more than 2 ampules of MCP or PL (solution of ampules III) were used for an individual patient.

  b. The second administration of MCP (4 mg/Kg or 0.5 mg/Kg/h) or PL started at the same time as the cisplatin infusion and consisted of a 500 ml i.v. infusion over a period of 8h. Based on body weight requirements (≤100 Kg), not more than 2 ampules of MCP or PL (solution of ampules IV) were used for an individual patient.

- Treatment assignment and stratification was accomplished at each center by assigning a sequential number in each strata with the appropriate letter as follows:

  "A" - M non-naive to chemotherapy patient
  "B" - F non-naive to chemotherapy patient
  "C" - M naive to chemotherapy patient
  "D" - F naive to chemotherapy patient.

5. Blinding, Packaging and Labeling

These aspects of the study were adequate.

6. Study Evaluation

Evaluations were done under double-blind, double-dummy, randomized, multicenter, parallel group conditions. Assessments for efficacy and safety included:

Assessments

| EFFICACY | SAFETY |
|---|---|
| • Number of emetic episodes.<br>• Time to first emetic episode and/or to administration of rescue therapy.<br>• Severity of nausea as determined by a VAS completed by the patient.<br>• Most severe nausea over the 24-h study period as determined by the investigator using a discrete scale (0-3 rating).<br>• Investigator's global assessment of efficacy using a 0-3 rating scale.<br>• Patient satisfaction with the antiemetic therapy as assessed by a VAS. | • AEs<br>• Medical Hx and P.E.<br>• EKG (Pre-study and hour 24)<br>• Vital signs<br>• Clinical Lab. tests |

7. Statistical Methods

a. Justification of Sample Size

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: $\alpha$-0.05, $\beta$=0.20, with a CR rate of 40% for the MCP group and a clinically meaningful difference of 20%, i.e., a 60% CR rate for the DOLA•Mesyl 1.8 mg/Kg group. The sample size per group was estimated at 100 patients.

The study was stopped early with 226/300 patients enrolled. According to the sponsor, the early termination was due to slow recruitment.

There were no interim analyses.

b. Primary Statistical Analysis

The definitions of categorical emetic efficacy endpoints were adequate, as per the DOLA•Mesyl tablet protocols. The primary analysis were an ITT logistic regression analysis of CR, a model that included terms for patient stratification, treatment and investigative site. Using such a model, the primary test of efficacy was a pairwise comparison of DOLA•Mesyl 1.8 mg/Kg vs MCP. Pair tests of DOLA•Mesyl 1.2 mg/Kg vs MCP and 1.2 vs 1.8 mg/Kg were also made. Also carried out were Rao scores residual Chi-square tests of the logistic model for investigative site x Tx and stratum x Tx interactions. Subgroup (age, cisplatin dose etc.) were added one at a time to this model to test for any impact on CR. All tests were two sided, with $\alpha$=0.05. Also, 95% confidence intervals (2-sided) for the odds ratio were computed for each pairwise comparison.

8. Data Documentation

Adequate, according to sponsor's description on vol. 1.302 page 98 of the Clinical Report.

9. Results

a. Participating Investigators/Patient Accounting

- Of 15 participating centers, 2 [#01 (Belgium) and #16 (France)] enrolled no patients. The other centers enrolled a total of 226 of which, 225 were included in the ITT dataset. The following five centers enrolled 20 or more patients each: Dr. Cappelaere/Dr. Degarden (#09, FR, n=46), Dr. Splinter (#13, The Netherlands, n=39, Dr. Fabbro/Dr. Rossi (#12, FR, n=37), Dr. Chevallier (#05, FR, n=23) and Dr. Wendling (#99, FR, n=21).

- One patient [No. 081124/B, from Center #17, Dr. Cals (FR)] dropped out due to a serious AE following test medication but before receiving chemotherapy. This patient, who had no efficacy data, was excluded from all efficacy analyses.

  - 7 patients with other major protocol violations were additionally excluded from the Efficacy Analyzable population analyses.

  - 158 patients had minor and 42 had no protocol violations.

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

| | | DOLA•Mesyl (mg/Kg) | | Total |
|---|---|---|---|---|
| | MCP | 1.2 | 1.8 | DOLA•Mesyl |
| ITT | 69 | 84 | 72 | 156 |
| Evaluable | 65 | 82 | 71 | 153 |

b. Data Showing Comparability of Groups at Baseline

- There were no statistically significant imbalances among the three experimental 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 and Hx of alcohol abuse. The study population was ca. predominantly male (160/226 = 71%), 55y of age, with a mean Karnofsky status of ca. 83% and a negative Hx of alcohol abuse (156/226=69%). Roughly one-half of the patients were naive to chemotherapy.

- There were no important imbalances among Tx groups in site of primary neoplasm. The most frequent sites of primary neoplasm were:

  head/neck=31% digestive system=22% lung=15% gynecological=14%

- The treatment groups were also balanced for medical Hx abnormalities, pre-study physical examination, and (with the exception of genitourinary tract abnormalities, an imbalance that would not be expected to influence efficacy response) organ system abnormalities.

i) Cisplatin and Other Chemotherapy

- As shown in Table 27, most patients received highly emetogenic cisplatin-based regimens and there were no significant imbalances across Tx groups in cisplatin dose, duration of cisplatin infusion and the interval between start of test medication administration and start of cisplatin infusion. Cisplatin dose ranged from with a mean of 93 mg/m². The mean duration of cisplatin infusion was 117 min. ; the mean interval between start of study medication administration and start of cisplatin infusion was 31 min. . Seventy (70) patients had cisplatin dose ≤90 mg/m² and 155 patients had cisplatin dose >90 mg/m² within the 24h study period.

- Most patients (209/225=93%) received chemotherapy in addition to cisplatin (Table 27). The most frequent additional agents were fluorouracil (127/225=56%), etoposide (48/225-21%) and cyclophosphamide (27/225=12%).

  - There was a statistically significant, but clinically unimportant imbalance across Tx groups in the rate of additional chemotherapy use (p=0.025). Additional chemotherapy was less frequent in the 1.2 mg/Kg DOLA•Mesyl group: the percent additional chemotherapy was 96%, 87% and 97%, respectively, in the MCP, 1.2 and 1.8 mg/Kg DOLA•Mesyl groups. There were no imbalances across Tx groups in the use of specific additional chemotherapy.

TABLE 27
Study -081

Current Chemotherapy [n=225]

| Variable | MCP [n=69] | DOLA•Mesyl (mg/Kg) 1.2 [n=84] | DOLA•Mesyl (mg/Kg) 1.8 [n=72] | Total DOLA•Mesyl [n=156] | p-value[b] |
|---|---|---|---|---|---|
| Mean Cisplatin Dose (mg/m²) | 94±11 | 92±11 | 95±10 | 93±11 | N.S. |
| Range | | | | | |
| Mean Duration of Cisplatin Infusion (min) | 11±67 | 122±67 | 117±68 | 120±67 | N.S. |
| Range | | | | | |
| Mean Interval between Test Med and Cisplatin (min) | 32±8 | 31±3 | 30±5 | 30±4 | N.S. |
| Range | | | | | |
| Concomitant Chemotherapy: | | | | | |
| YES | 96% | 87% | 97% | 92% | 0.025 |
| NO | 4% | 13% | 3% | 8% | |
| Concomitant Chemotherapy: | | | | | |
| Fluorouracil | 56% | 51% | 61% | 56% | N.S. |
| Etoposide | 20% | 20% | 24% | 22% | N.S. |
| Cyclophosphamide | 13% | 12% | 11% | 12% | N.S. |
| Doxorubicin | 4% | 7% | 10% | 8% | N.S. |

a) Not included was one patient that withdrew before receiving chemotherapy
b) From Fisher's Exact Test

ii) Other Concomitant Medications

- The most frequently used medications , concomitant medications taken in the 24h period before starting chemotherapy, were magnesium sulfate (17% of the patients), paracetamol (17%), potassium chloride (17%); lactulose (8%) and morphine sulfate (7%). Individual non-escape drugs most commonly used during the study evaluation period were paracetamol (20% of patients), furosemide (14%), heparin (8%), potassium chloride (8%), folic acid (8%), lactulose (8%) and morphine sulfate (7%). There were no statistically significant differences across treatment groups in use of these medications.

- A summary of the use of major concomitant medications (non-escape use) during the study evaluation period with potential to affect emesis revealed that 20% (44/125) of patients received narcotic analgesics. Benzodiazepines (4%) and corticoids (3%) were less frequently used. Corticoid use differed across the treatment groups (p=0.020), with greater use of corticoids in the MCP group compared to the DOLA•Mesyl

groups. Corticoid use was 7%, 0% and 3% in the MCP, 1.2 and 1.8 mg/Kg DOLA•Mesyl groups, respectively. This imbalance may have an effect on response, especially if the difference in response among groups is borderline.

iii) Escape Medications (Table 28)

There were no statistically significant imbalances across the treatments in escape medications.

TABLE 28
Study -081

Escape Medications Taken During Study [n=225]

| Escape Medication | MCP [n=69] | DOLA•Mesyl (mg/Kg) 1.2 [n=84] | DOLA•Mesyl (mg/Kg) 1.8 [n=72] | Total DOLA•Mesyl [n=156] |
|---|---|---|---|---|
| Received Escape (p=N.S.) | | | | |
| YES | 21<br>30% | 27<br>32% | 16<br>22% | 43<br>28% |
| NO | 48<br>70% | 57<br>68% | 56<br>78% | 113<br>72% |
| OND (p=N.S.) | 13% | 12% | 8% | 10% |
| GRAN (p=N.S.) | 7% | 10% | 6% | 8% |
| ALIZA (p=N.S.) | 9% | 7% | 4% | 6% |
| Me-PREDNISONE (p=N.S.) | 9% | 6% | 6% | 6% |
| CIM (p=N.S.) | 6% | 7% | 4% | 6% |
| TROPI (p=N.S.) | 3% | 5% | 3% | 4% |
| MCP (p=N.S.) | 4% | 1% | 3% | 2% |

a) 0-24h after start of chemotherapy.

c. Clinical Response

i) Analysis of Primary Efficacy Endpoint (Complete Response) (Table 29)

- The percent CR for both the ITT (upper panel) and the efficacy analyzable population (lower panel) analyses are summarized in Table 29. The comparisons 1.2 mg/Kg vs MCP and 1.8 mg/Kg vs MCP yielded therapeutic gains of 13% and 22%, respectively; both were statistically significant differences. The 1.8 mg/Kg DOLA•Mesyl did not produce significant further benefit than the 1.2 mg/Kg dose level (therapeutic benefit = 9%, p=N.S.).

- The results of the supportive Mantel-Haenszel type tests (row mean table scores statistic) were consistent with the logistic regression analyses (see footnote to Table 29). Both DOLA•Mesyl groups showed a highly significant difference compared to MCP (1.8 mg/Kg vs MCP, p=0.007; 1.2 mg/Kg vs MCP, (p=0.031); there was no statistical difference between the two DOLA•Mesyl groups (p=0.553).

- Logistic regression analysis of efficacy analyzable patients (table 29, lower panel) was also highly consistent with the primary ITT results.

- The test for inconsistency in Tx effect across investigator was non-significant (Tx-by-investigator interaction test, p=N.S.).

- There were differences in the overall CR rate across investigators (investigator main effect test, p=0.0029). Some investigative sites had consistently high or low response rates, for example four sites had 75-100% complete response for the combined DOLA•Mesyl groups, whereas five sites had below 40% response.

TABLE 29
Study -081

Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response

| Response by Test Group | | | Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses and Against MCP [p-value] | | |
|---|---|---|---|---|---|
| **I. Intent-To-Treat Analysis[a] [n=225]** | | | | | |
| MCP [n=64] | 1.2 mg/Kg [n=84] | 1.8 mg/Kg [n=72] | 1.2 mg/Kg vs MCP | 1.8 mg/Kg vs MCP | 1.8 mg/Kg vs 1.2 mg/Kg |
| 24 (35%) | 40 (48%) | 41 (57%) | (13%) [0.0058] | (22%) [0.0009] | (9%) [N.S.] |
| **II. Efficacy Evaluable Analysis [n=218]** | | | | | |
| [n=65] | [n=82] | [n=71] | | | |
| 23 (35%) | 39 (48%) | 40 (56%) | (13%) [0.0090] | (21%) [0.0016] | (8%) [N.S.] |

a) For the ITT analysis, depicted are the logistic regression statistics. The Mantel-Haenszel statistics (Row Mean Scores) were as follows:

| Comparison | p-value |
|---|---|
| 1.2 mg/Kg DOLA•Mesyl vs MCP | 0.031 |
| 1.8 mg/Kg DOLA•Mesyl vs MCP | 0.007 |
| 1.8 mg/Kg DOLA•Mesyl vs 1.2 mg/Kg DOLA•Mesyl | N.S. |

For the Efficacy Analyzable Population analysis, the statistical method use was logistic regression with Tx, investigator and stratum in the model.

ii) CR by Stratum (Table 30)

- This Table gives CR rates by patient stratification (gender x previous chemotherapy) and separately for each patient stratification factor (gender and previous chemotherapy).

- The test for inconsistency in Tx effect across patient stratification was not statistically significant (treatment x stratum interaction test, p=0.9889). Similarly, the interaction tests for inconsistency in treatment effect between sexes (p=0.9107) and between naive and non-naive patients (p=0.6317) were not statistically significant.

- Patient stratification was highly predictive of overall response rate (stratum main effect test, p=0.0002). The overall CR rates were 58% (51/88, 53% (38/72), 40% (12/30) and 11% (4/35) for male naive, male non-naive, female naive and female non-naive patients, respectively.

    - As indicated by the non-significant treatment by stratum interaction test, the response rates within strata showed a similar trend as the overall results 1.8 mg/Kg DOLA•Mesyl higher than 1.2 mg/Kg DOLA•Mesyl higher than MCP. This is indicated by the N.S. Tx-by-stratum interaction test.

- As shown in Table 30, males responded better than females (gender main effect test, p=0.0001). The overall CR rates were 89/160 (56%) for males vs 16/65 (25%) for females.

- Naive patients also responded better than non-naive patients (previous chemotherapy main effect test, p=0.0448). The overall complete response rates were 63/118 (53%) for naive patients vs 42/107 (39%) for non-naive patients (see footnote to Table 30).

iii) Subgroup Analyses

- None of the subgroup analyses (treatment x subgroup interaction test) indicated differences in Tx effect across the specifically defined subgroups: age (<65 years or ≥65 years), cisplatin dose (≤90 mg/m$^2$ or >90 mg/m$^2$), Karnofsky status (<80 percent or ≥80 percent), history of alcohol abuse (yes/no), concomitant use of narcotic analgesice (yes/no), concomitant use of benzodiazepines (yes/no) and concomitant use of corticoids (yes/no). Use of corticoids and benzodiazepines were inestimable (no valid statistical test) due to their low frequency of occurrence.

    - History of alcohol abuse was, however, associated with a higher overall level of CR (main effect test, p=0.0022). Patients without history had an overall 36% (56/155) CR rate, whereas those with history of alcoholism were 70% (49/70) complete responders. The results of the primary analysis were confirmed when controlling for Hx of alcohol abuse.

TABLE 30
Study -081

Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response by Stratum

[ITT Population] (n=225)

| | | Response by Test Group | | | Therapeutic Gain (%) for Comparisons Between DOLA®Mesyl Doses and Against MCP | | |
|---|---|---|---|---|---|---|---|
| | | MCP [n=89] | 1.2 mg/Kg [n=84] | 1.8 mg/Kg [n=72] | 1.2 mg/Kg vs MCP | 1.8 mg/Kg vs MCP | 1.8 mg/Kg vs 1.2 mg/Kg |
| Patient Stratification | M naive [n=88] | 10/27 (37%) | 19/30 (63%) | 22/31 (71%) | (26%) | (34%) | ( 8%) |
| | F naive [n=30] | 3/10 30% | 5/11 45% | 4/9 (44%) | (15%) | (14%) | (-1%) |
| | M non-naive [n=72] | 11/25 (44%) | 14/26 (54%) | 13/21 (62%) | (10%) | (18%) | 8% |
| | F non-naive [n=35] | 0/7 ( 0%) | 2/17 (12%) | 2/11 (18%) | 12% | (18%) | 6% |
| Gender | MALE [n=160] | 21/52 (40%) | 33/56 (59%) | 35/52 (67%) | 19% | (27%) | 5% |
| | FEMALE [n=65] | 3/17 (18%) | 7/28 (25%) | 6/20 30% | 7% | 12% | 5% |
| Previous Chemotherapy | NAIVE [n=118] | 13/37 (35%) | 24/41 (59%) | 26/40 (65%) | 24% | 30% | 6% |
| | NON-NAIVE [n=107] | 11/32 (34%) | 16/43 (37%) | 15/32 47% | 3% | 13% | 10% |

Statistical Comparisons (p-values):

| | Patient Stratification | Gender | Previous Chemotherapy |
|---|---|---|---|
| p(int)[a] | N.S. | N.S. | N.S. |
| p(m)[b] | 0.0002 | 0.0001 | 0.0448 |

a) p(int)=p value from Interaction Test:
Test for inconsistency in treatment effect across levels of factor (such as across strata). Tested using Rao scores residual Chi-square by specifying appropriate design variables in logistic regression with factor, treatment and investigator in the model.

b) p(m)=p value from Main Effect Test:
Test for differences in overall response rate across levels of factor (such as across strata). Factor affect tested in logistic regression with factor, treatment and investigator in the model.

iv) Total Response (Table 31)

The rates of TR [CR + "No Nausea" (not even mild nausea) over 24h period] were 22%, 32% and 44% for the MCP, 1.2 and 1.8 mg/Kg DOLA•Mesyl groups, respectively. The 1.8 mg/Kg DOLA•Mesyl group was highly significantly better than MCP (p=0.0010) and 1.2 mg/Kg DOLA•Mesyl was also significantly better than MCP (p-0.0115). There was no significant difference between the 1.8 and 1.2 mg/Kg DOLA•Mesyl groups (p=0.3778).

TABLE 31
Study -081

Clinical Response: Analyses of Primary Efficacy Parameters
Total Response[a]

[ITT Population, n=225]

| Response by Test Group | | | Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses and Against MCP [p-values][b] | | |
|---|---|---|---|---|---|
| MCP [n=69] | 1.2 mg/Kg [n=84] | 1.8 mg/Kg [n=72] | 1.2 mg/Kg vs MCP | 1.8 mg/Kg vs MCP | 1.8 mg/Kg vs 1.2 mg/Kg |
| 15 (22%) | 27 (32%) | 32 (44%) | 10% [0.0115] | 22% [0.0010] | 12% [N.S.] |

a) Complete Response + "NO NAUSEA" over 24h study period.
b) From logistic regression statistics.

v) Time to First Emetic Episode or Administration of Anti-Emetic Escape Therapy (Table 32)

- Tabulated in this Table are the estimated proportions of Complete Responders at 4h intervals taken from a Kaplan Meier (sponsor's Fig. 3) survival curve of the estimated probability of no emetic episodes or escape medication over the 24-h treatment period for each Tx.

- The Cox regression analysis of time to first emetic episode or escape strongly confirmed the primary analysis of CR (Table 32, lower panel). The time to emesis or escape for 1.8 mg/Kg DOLA•Mesyl was highly significantly lower vs MCP (p=0.0001) as was 1.2 mg/Kg DOLA• Mesyl vs MCP (p=0.0003). There was no difference between the DOLA•Mesyl groups (p=0.3999).

- The median times to first emesis or escape were 5.5, 22.5 and >24h for the MCP, 1.2 mg/Kg and 1.8 mg/Kg DOLA•Mesyl groups. No patients were censored before 24h, i.e., all patients without emesis or escape were monitored for the full 24h.

TABLE 32
Study -081

Time to First Emetic Episode or Escape, for Intent-to-Treat Population [n=225]

**Frequency and Estimated Percent Complete Responders Through a Given Hour by Treatment**

| Hour | Treatment | | |
|---|---|---|---|
| | | DOLA•Mesyl (mg/Kg) | |
| | MCP [n=69] | 1.2 [n=84] | 1.8 [n=72] |
| 4 | 45<br>65% | 78<br>93% | 68<br>94% |
| 8 | 29<br>42% | 63<br>75% | 56<br>78% |
| 12 | 29<br>42% | 58<br>69% | 52<br>72% |
| 18 | 25<br>36% | 50<br>60% | 49<br>68% |
| 24 | 24<br>35% | 40<br>48% | 41<br>57% |

Statistical Methods:

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

Estimated percent complete response at 4 hour intervals computed by Kaplan-Maier method. Note: in this study no patients were censored. Thus all Kaplan-Maier estimates are actual study complete response rates.

Cox Regression Studies:

| Comparison | 95% Confidence Intervals for Odds Ratio | p-value |
|---|---|---|
| 1.2 mg/Kg DOLA•Mesyl vs MCP | (0.3, 0.7) | 0.0003 |
| 1.8 mg/Kg DOLA•Mesyl vs MCP | (0.2, 0.6) | 0.0001 |
| 1.8 mg/Kg DOLA•Mesyl vs 1.2 mg/Kg DOLA•Mesyl | (0.5, 1.3) | 0.3999 |

d. Safety Results

1) Extent of Exposure

In study -081, 226 patients received a single dose of test medication, with the following distribution:

| MCP[a] | DOLA•Mesyl (mg/Kg) | |
|---|---|---|
| | 1.2 | 1.8 |
| [n=69] | [n=84] | [n=73] |

a) 3 mg/Kg loading dose followed by a 4 mg/Kg 8-h continuous infusion.

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

- Three deaths were reported in this study. All 3 patients received DOLA•Mesyl 1.2 mg/Kg. These three events were part of a total of 6 serious events occurring during the trial. Of the three other serious AEs, one resulted in "immediate risk of death" in one patient, the other led to hospitalization. All of these five events rated by the investigator not to be related to test medication. The sixth event (severe hypotension) was considered probably/possibly related to test med. An overall summary of each of these six cases, including possible relationship to drug is given in Table 33.

TABLE 33
Study -081

Summary Table of Deaths, Dropouts Due to AEs and Other Serious Events

| Patient ID -081 | Event | Succinct Narrative | Relation to Test Med. |
|---|---|---|---|
| I. Deaths, DOLA•Mesyl (1.2 mg/Kg [n=3] | | | |
| 212C 59y-old-M | DEATH | Pt. had velum palati tumor (head and neck cancer) with known metastasis to the lung + Hx of bilateral pleural infusion. He experienced dyspnea leading to respiratory distress 27h after receiving test med. This progressed to increased pleural effusion, acute pulmonary edema and respiratory failure. The event lasted 7h and the pt. died. | Related to cancer and hyperhydration. |
| 186C 67-y-old M | DEATH | Pt. had renal insufficiency provoked by cisplatin chemotherapy. He experienced septic shock 8 days after receiving test med. The event lasted 12h. The patient died subsequently. | Related to infection following insertion of a catheter 3 days after test med. |
| 130C 65-y-old M | DEATH | Pt. had Hx of nephrectomy. He developed progressive renal insufficiency. Acute renal failure occurred 7 days after test med. administration. The pt. died the same day. | Related to cancer progression and cisplatin chemotherapy. |

| II. Dropouts Due to AE, DOLA•Mesyl 1.8 mg/Kg [n=1] | | | |
|---|---|---|---|
| 124B<br>59y-Old F | **SEVERE HYPOTENSION** | Chemotherapy was <u>not</u> administered. The pt. dropped out of the study. The hypotension was severe in intensity. The patient recovered completely two days after the event. The patient was a heavy smoker and at entry, chest x-ray revealed bilateral basal pulmonary | The relationship of the event with test med. was rated as "probable" initially but was changed by the investigator to "possible" after follow-up established on impairment of the patient's cardiac function. |

effusions and respiratory insufficiency. Pulmonary function tests were not reported. Pt. had colloid mucinous breast cancer with gastric metastases. She had multiple problems at study entry,including NYHA class II CHF, LBBB and ventricular ectopic beats. Heart failure was being treated with daily doses of benzepril (ACE inhibitor) 25 mg, furosemide 40 mg and digoxin 0.25 mg. She had received each of these medications ca. 12h before receiving DOLA•Mesyl. Other meds. administered on the study day included nitroxoline and tamoxifen. EKG performed at study entry revealed LBBB, PR interval 180 msec, QRS = 160 msec and QT = 400 msec, with a heart beat of 100 bpm.

The pt. received DOLA•Mesyl over 15 min. Collapse started 30 min. after the end of test med. infusion, with symptoms such as sweating, pale-face, cold extremities and vision disturbances. The pt.s HR was 75 bpm during the episode of hypotension. EKG performed during the hypotensive episode revealed neither VF nor VT. Increases in PR (→280 msec), QRS (→180 msec) and QT (→440-480 msec) were observed but, in the investigator's opinion they were not sufficient to explain the hypotensive episode.

- 7 days after the initial event the pt. received chemotherapy (carboplatin + 5-FU) from days 1 to 5 plus MCP. The patient did not vomit.
- 14 days after the initial event and DOLA•Mesyl administration the patient was discharged from the acute care setting. The following day, the patient developed another episode of hypotension and black feces starting some days prior to event with no other g.i. abnormality. EKGs during this hospitalization revealed cardiomyopathy with LV dilation (+++), impaired LV Function, among other alterations. The pt. was discharged after an 11-day hospitalization and was receiving tamoxifen + oxazepam.

<u>NOTE:</u> Due to the temporal relationship and the fact that at that time the patient did not receive cisplatin, or any other chemotherapy or other medications that may be confounding, the reviewer believes that in this instance the severe hypotension was almost certainly related to DOLA•Mesyl. The presence of CHF, LBBB and poor LV Function probably predisposed the patient to the untoward effects of the drug. This information should be included in the labeling.

| III. Other Serious Events [DOLA•Mesyl 1.8 mg, n=1; MCP, n=1] | | | |
|---|---|---|---|
| 056A<br>62y-old M | **RESPIRATORY DISTRESS/PARTIAL OBSTRUCTION** | The severe treatment, described by the French investigator as laryngeal dyspnea, occurred 12h after the end of MCP adm. An emergency tracheotomy was performed and the dyspnea disappeared. | Not related to test med. Related to local extension of an oropharyngeal carcinoma. |
| 075D<br>61y-old F | **HOSPITALIZATION DUE TO FEBRILE NEUTROPENIA** | The event which was MOD in severity occurred 12 days after adm. of DOLA•Mesyl (1.8 mg/Kg). The event lasted 17 days and abated without sequelae. | Not related to test med. but rather to chemotherapy. |

3) AEs (Tables 34 and 35)

- As seen in Table 34 (upper panel) there were no statistically significant treatment differences in the overall incidence of AEs. The rate of cardiovascular AEs was statistically significantly higher (p=0.0324) in the MCP group 13/69 (19%) vs 17/157 (11%) in the DOLA•Mesyl group. Five percent (4/84) of the patients in the DOLA•Mesyl 1.2 mg/Kg group reported cardiovascular events compared to 13/73 (18%) in the DOLA•Mesyl 1.8 mg/Kg group. The most frequently reported cardiovascular event was hypertension (see below).

- The most frequently reported specific events were headache, diarrhea and hypertension. There were some numerical but not statistically significant differences among the test groups (Table 34, middle panel).

- AEs were primarily mild to MOD in severity. There were some numerical but not statistically significant differences among the test groups (Table 34, lower panel).

  - Not unexpectedly, extrapyramidal effects were reported in association with MCP. These events did not appear in the DOLA•Mesyl-treated patients. Eight patients on MCP (12%) experienced events that could be considered as movement disorders. These were extrapyramidal disorder (1 patient), shaking (1 patient), slurred speech (2 patients), stiff jaw (2 patients), thick tongue (1 patient) and tremor (1 patient).

  - Chest pain was reported as an AE in one patient in the DOLA•Mesyl 1.8 mg/Kg group. This AE was described by the investigator in French as "right thoracic pain" and it occurred in a patient with oropharyngeal epidermoid carcinoma with lymph node metastases. The event, moderate in severity, started ca. 8h after DOLA•Mesyl 1.8 mg/Kg administration and lasted 15h.

    The cause was noted as "unknown", no action was taken and the patient recovered from the event without sequelae.

TABLE 34

Frequency of AEs, Most Frequently Occurring AEs and Severity of AEs by Dose Group

| System Organ Class and Included Term | | MCP [n=69] | DOLA•Mesyl (mg/Kg) 1.2 [n=84] | DOLA•Mesyl (mg/Kg) 1.8 [n=73] | DOLA•Mesyl [n=157] |
|---|---|---|---|---|---|
| **I. AE Overall Rates[a] By Organ Class** | | | | | |
| Overall Rate (p=N.S.)[b] | | 61% | 46% | 53% | 50% |
| Gastrointestinal System (p=0.0864) | | 35% | 23% | 21% | 22% |
| Centr & Periph Nervous System (p=N.S.) | | 16% | 12% | 21% | 16% |
| General Cardiovascular (p=0.0324) | | 19% | 5% | 18% | 11% |
| Heart Rate & Rhythm | | 7% | 2% | 0% | 1% |
| **II. Most Frequent AEs** | | | | | |
| Headache (p=N.S.) | | 6% | 12% | 18% | 15% |
| Diarrhea (p=N.S.) | | 22% | 12% | 15% | 13% |
| Hypotension (p=N.S.) | | 13% | 2% | 11% | 6% |
| **III. AEs By Severity[c]** | | | | | |
| Overall Rate (p=N.S.) | | 10% | 7% | 4% | 6% |
| Diarrhea [n=36] | Mild | 8 | 5 | 4 | |
| | MOD | 5 | 4 | 7 | |
| | SEV | 2 | 1 | 0 | |
| Headache [n=27] | Mild | 2 | 4 | 7 | |
| | MOD | 2 | 5 | 5 | |
| | SEV | 0 | 1 | 1 | |
| Hypertension [n=19] | Mild | 7 | 1 | 7 | |
| | MOD | 2 | 0 | 1 | |
| | SEV | 0 | 1 | 0 | |

a) Displayed Rates refer to number of patients with a given SOC or included term. One patient may have more than one event.
b) The statistical methods consisted of logistic regression tests for differences in AE rate across Tx groups, adjusting for strata. Tests only made for system organ classes and included terms with at least one occurrence within each Tx.
c) For patients experiencing the event more than once, the maximum severity over all occurrences was used. Tabulated numbers refer to number of patients with the given AEs and maximum severity.

- As seen in Table 35, there were some numerical but not statistically significant differences among the groups in causality of AE rates (both diarrhea and headache were primarily related to test medication), Tx-related AEs and AEs treated with counteractive medications (see headache, lower panel of Table 35).

TABLE 35
Study -081

AEs by Causality, Tx-Related and AEs Treated With Counteractive Medications

| I. Causality of AE Rates [≥1%] | | | | |
|---|---|---|---|---|
| | | | DOLA®Mesyl (mg/Kg) | |
| System Organ Class or Included Term | Cause | MCP [n=69] | 1.2 [n=84] | 1.8 [n=73] |
| Diarrhea [n=36] | Not Reported | 0 | 0 | 0 |
| | Unknown | 3 | 0 | 2 |
| | Study Drug Related | 10 | 8 | 8 |
| | Not Study Drug Related | 2 | 2 | 1 |
| Headache [n=27] | Not Reported | 0 | 0 | 0 |
| | Unknown | 1 | 0 | 1 |
| | Study Drug Related | 2 | 9 | 10 |
| | Not Study Drug Related | 1 | 1 | 2 |
| **II. Tx-Related AEs** | | | | |
| **Overall Rate (p=N.S.)** | | **46%** | **43%** | **42%** |
| Diarrhea (p=N.S.) | | 19% | 10% | 14% |
| Headache (p=N.S.) | | 4% | 11% | 15% |
| **Cardiovascular, General (p=0.0726)** | | **13%** | **2%** | **12%** |
| Hepatic Function Abnormal (p=0.0890) | | 1% | 7% | 1% |
| **Heart Rate & Rhythm** | | **7%** | **2%** | **0%** |
| Chest Pain | | 0 | 0 | 1% |
| **III. AE Treated With Counteractive Medications** | | | | |
| **Overall Rate (p=N.S.)** | | **19%** | **18%** | **15%** |
| Headache (p=N.S.) | | 1% | 7% | 3% |

4) Clinical Laboratory Evaluation

Statistically but not clinically significant changes in hematology parameters were observed in this study. These were most likely due to hydration

alterations. Other minor changes in laboratory parameters were of no clinical importance.

5) Vital Signs/EKG Interval Changes

- There was increase in median pulse rate in all Tx groups. There were no statistically significant differences among treatments in change from baseline in the recumbent systolic and diastolic BP or HR, regardless of the comparisons.

- As discussed above, one patient in the 1.8 mg/Kg DOLA•Mesyl group experienced severe hypertension that, from the MO's assessment, was almost certainly related to test medication.

- The incidence of cardiovascular events was low and equally distributed among the three Tx groups.

- In study -081 the data on changes in EKG parameters at 24h post-dose in comparison to baseline are of little value. EKG parameter evaluations were not done at the time of $C_{max}$ for the DOLA•Mesyl metabolite known to correlate with prolongations of PR, QRS and $QT_C$.

10. Conclusions (Sponsor)

"The complete response rates for single iv doses of dolasetron mesylate 1.2 and 1.8 mg/kg were superior to metoclopramide 7 mg/kg (standard iv total dose regimen) in preventing emesis due to the administration of cisplatin ≥80 mg/m².

"Significant predictors of response were gender and history of alcohol abuse. The response rate was also consistently higher in chemotherapy naive patients.

"The clinical response to dolasetron mesylate 1.8 mg/kg was consistently better than metoclopramide in secondary efficacy analyses; the order of efficacy being dolasetron mesylate 1.8 mg/kg > dolasetron mesylate 2.1 mg/kg > metoclopramide.

"For complete-plus-major response, the difference between the two dolasetron mesylate doses was statistically significant in favor of 1.8 mg/kg.

"Dolasetron mesylate differed from metoclopramide with a higher incidence of mild-to-moderate headache and the absence of extrapyramidal signs, observed only in the metoclopramide group.

"Overall safety was similar across treatment groups.

"The clinical impact of the severe hypotension in one patient with 1.8 mg/kg dolasetron mesylate with regards to the dolasetron dosing is addressed in a larger patient dataset."

11. Reviewer's Comments

The sponsor of NDA 20-624 submitted results of five clinical trials in support of approval of the marketing of intravenously administered ANZEMET (DOLA•Mesyl, at the recommended single i.v. dose of 1.8 mg/Kg or 100 mg given ca. 30 min. before chemotherapy) for the prevention of N&V associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin. This broad indication encompasses both cisplatin and non-cisplatin-induced emesis in support of which, results of four trials and one trial, respectively, have been submitted.

Study -081 is one of the four main cisplatin trials. Study -081 employed a useful design and was carried out with appropriate methodology. Contributing factors to the proper methodology used in this European trial are a) the standardization of the study population, b) adequate procedures for double-blind observations to minimize bias, [the double-dummy technique used here was required by the different administration regimens of DOLA•Mesyl and MCP], c) randomization/stratification schemes resulting in comparable test groups, d) standardization of the emetogenic stimulus (a highly emetogenic cisplatin-based regimen was used), e) appropriate clinical procedures to gather data to assess efficacy and safety and f) utilization of appropriate statistical methodology to evaluate results. In concert, all of these specific/general factors allow drawing valid, meaningful conclusions from this main trial. The prospective stratification of patients on the basis of gender and previous Hx of chemotherapy is a sound approach because these factors, which may influence antiemetic response[6], should be balanced among Tx groups.

The doses selected for this trial (1.2 and 1.8 mg/Kg) were determined from the efficacy and safety data of Phase II dose-ranging studies with DOLA•Mesyl. From these studies, the antiemetic effect of the drug tended to plateau at doses above 1.8 mg/Kg for emesis induced by ≥100 mg/m² cisplatin. The study used a "positive" comparator, MCP.[7]



[6] There are published observations suggesting that F patients may be more susceptible to emesis than men and that the effectiveness of preventive antiemetic therapy may be lower in chemotherapy non-naive patients than in naive patients.

[7] In the Clinical Report the sponsor included the following explanation. At the initiation of study -081, the choice of the European approved and labeled dose of MCP as a comparator was accepted since this drug was deemed the most effective as a single agent for the prevention of cisplatin-induced emesis. However, during the course of the trial, other regimens showing higher antiemetic activity than MCP alone became available. Among these, combination therapies using MCP and corticoids and/or other agents showed that the antiemetic activity was increased by about 20%. Also, several 5-HT$_3$ receptor antagonists belonging to the same class as DOLA•Mesyl were approved in Europe. These agents used as single agents showed similar activity as the combination therapies including MCP and were rapidly and widely used in the patient population treated with high-dose cisplatin. In most study centers, these new agents were preferred to MCP and patient enrollment for the study slowed down or even stopped. As a consequence, the planned number of patients (100 per arm), was not reached.

In study -081, the study population (total n=226, enrolled at 14 centers in Europe), consisted of chemotherapy-naive or patients with previous chemotherapy scheduled to receive cisplatin at the dose of ≥80 mg/m$^2$. The emetogenic regimen was given over no more than 3h as the first component of a chemotherapy regimen. The study population was predominantly male (160/226=71%), 55y of age, with a mean Karnofsky status of 83%, a negative Hx of alcohol abuse of 69% and ca. 50% naive to chemotherapy. In general the patients were without evidence of significant cardiovascular or hepatic disease. Exclusions pertaining to the cardiovascular system applied to this protocol were patients having pathological prestudy EKG, PR, QRS or QT interval prolongation (10 centers), Hx of significant cardiac illness and abnormal prestudy serum concentrations of potassium and sodium and patients recovering antiarrhythmic therapy. The most frequent sites of primary neoplasm were head/neck (31%), digestive system (22%), lung (15%), and gynecological (14%).

The randomization procedures used in study -081 resulted in three populations of patients (MCP=69, DOLA•Mesyl 1.2 mg/Kg=84, 1.8 mg/Kg=72) that were balanced with respect to age, weight, height, gender, previous chemotherapy, number of patients per stratum, patient VAS nausea severity at Pre-Tx and hour 0, Karnofsky performance status, Hx of alcohol abuse, site of primary neoplasm, medical Hx abnormalities, pre-study P.E. and, with the exception of genito-urinary tract abnormalities, an imbalance that would not be expected to influence efficacy response, organ system abnormalities. The exception was an imbalance in corticoid use (MCP=7%; DOLA•Mesyl 1.2 mg/Kg=0% and 1.8 mg/Kg=3%) which may influence response. But the proportion of patients with this imbalance was low and the effects of corticoids on 5-HT$_3$ receptor antagonist's performance has not been clearly elucidated.

In summary then, the randomization procedures used in study -081 resulted in three populations of patients that were comparable to each other with respect to demographics, primary disease state, other significant medical conditions, P.E., Karnofsky status, prior medications, concomitant medications that may be confounding such as concomitant other chemotherapy (5-FU, etoposide, cyclophosphamide and doxorubicin) and in general, other variables that may influence outcome.

In study -081 the three Tx groups were well matched with regards to standardization of the emetic stimulus, a regimen best characterized as being of high emetogenic potential: mean cisplatin dose=93 mg/m$^2$, mean duration of cisplatin infusion =117 min., mean interval between test med. and cisplatin= 30 min. On average, 92% of the patients received concomitant cancer chemotherapy.

As in PONV and previous CCNV protocols the primary endpoint was CR. The statistical methods included logistic regression with CI for odds ratios for ITT population controlling for stratum, Tx and investigative site. The primary test of efficacy was a pairwise comparison using Rao scores (residual Chi-square) test of the logistic model for center-by-Tx and stratum-by-Tx

interactions. Subgroups were added one at a time to this model to test for any impact on CR. The trial was terminated earlier, with a total of 226 patients all of whom received test med. (one patient dropped out of the trial before receiving chemotherapy). Interim analyses were neither planned nor performed.

The CR rate with MCP was 35% in both the ITT and Evaluable population. Each of the two DOLA•Mesyl dose levels was shown to be clinically and statistically superior to MCP with therapeutic gains of 13% and 22% in the ITT and 13% and 21% in the ITT and Evaluable population analyses, respectively. The best result was achieved with the 1.8 mg/Kg DOLA•Mesyl therapeutic gain over MCP = 22% in the ITT ($p=0.0009$) and 21% in the Evaluable population analyses ($p=0.0016$). Although the CR with the 1.8 mg DOLA•Mesyl dose level was numerically higher than that seen with the 1.2 mg/Kg dose, this difference (9% in the ITT and 8% in the Evaluable Population analyses) was N.S. The superiority of each DOLA•Mesyl dose over MCP in ITT analysis was confirmed by the Mantel-Haenszel statistics (Row Mean scores) and, as already mentioned, by the analysis in the Efficacy Analyzable Population.

In study -081, a highly significant stratum effect for gender ($p=0.0001$) was noted and this gender difference has been commonly observed with other antiemetic treatments. M patients showed an ca. twofold higher response rate than F patients in the three treatment groups (in both strata) with a similar relative efficacy in the overall results (DOLA•Mesyl 1.8 mg/Kg > DOLA•Mesyl 1.2 mg/Kg > MCP). In addition, chemotherapy naive patients showed a significantly higher CR rate (ca. 30%) than chemotherapy non-naive patients ($p=0.0448$, a difference that also has been previously discussed. The higher rate was observed in all three Tx groups. The difference was particularly marked among F patients 12/30 (40%) overall CR in naive vs 4/35 (11%) in non-naive F patients. The same marked difference appeared in all Tx groups. When combining the gender and previous chemotherapy effect, it appeared there was a decreasing antiemetic efficacy in M naive > M non-naive > F naive > F non-naive. The same marked difference appeared in all Tx groups with the highest antiemetic efficacy obtained in the DOLA•Mesyl 1.8 mg/Kg group. In this group, the highest complete response rate was 71% in the M naive group (37% with MCP) and the lowest activity was obtained in the F non-naive group with 18% CR (0% with MCP).

In study -081, subgroup analyses also demonstrated a highly significant effect in patients with a Hx of alcoholism ($p=0.0022$). The CR rate was ca. twofold higher than in patients with no such Hx. The latter result is not unexpected since a Hx of heavy alcoholism has been correlated with a reduced risk of emesis. On the other hand, no effect of age, performance status, narcotic analgesics or benzodiazepines on Tx efficacy was noted.

In this study population and under the experimental conditions and methodology used in study -081, single i.v. doses of DOLA•Mesyl, 1.2 or 1.8 mg/Kg were - all in all - well tolerated. A total of six serious events were reported during the trial. These included three deaths (all three in the DOLA•Mesyl

1.2 mg/Kg group), all related to cancer or secondary to cancer. Of the three other serious AEs one (respiratory distress/partial obstruction in a patient in the DOLA•Mesyl 1.8 mg/Kg group) was related to local extension of an oropharyngeal carcinoma, the other (hospitalization due to febrile neutropenia in a patient in the MCP group) was related to chemotherapy. The other serious AE was one case of severe hypotension.

The one patient (#124B) who withdrew from the trial experienced **severe hypotension** 15 min. after the end of the infusion of 1.8 mg/Kg DOLA•Mesyl. In this patient, chemotherapy was not administered. The pt. dropped out of the trial and recovered completely 2 days before the serious/severe event. Study medication relationship was deemed **"probable"** initially but later changed to **"possible"** when follow-up established a previously unrecognized severely impaired LV function. Owing to the temporal relationship and the fact that the patient was not receiving potentially confounding medications, at the time of the event, the MO believes that this case of severe hypotension was **almost certainly related to i.v. administered DOLA•Mesyl**. This would not preclude the occurrence of other episodes of hypo- or hypertension (alone or with pulmonary edema) in the absence of test medication. This is precisely one of the important safety questions with this drug for which a satisfactory answer is yet to be provided: in the presence of significant (clinically important as in this patient) cardiovascular risk factors and other impaired physiologies, does DOLA•Mesyl induce serious/severe cardiovascular events? The MO believes that a contribution of DOLA•Mesyl to the serious/severe hypotension reported in patient 124B who had impairment of cardiac function pre-drug cannot be excluded. **This information should be included in the labeling.**

The overall AE rates were similar with the 1.2 and 1.8 mg/Kg DOLA•Mesyl doses (46% and 53%, respectively) and MCP (61%). The most frequently reported AEs were diarrhea (DOLA•Mesyl=13%; MCP-22%) and headache (DOLA•Mesyl=15%; MCP-6%) but for these [and for the expected EPS with MCP (12%)] there was no linear trend across dose. Most cases of diarrhea and headache were mild to moderate in intensity.

Treatment related cardiovascular events (mostly hypotension, sometimes related to hydration) were noted in 13% of the patients in the MCP group and in 7% of the patients in the DOLA•Mesyl groups. Mild-to-moderate cases of hypertension or hypotension were also reported.

In study -081 EKG evaluations 1 to 2h post-Tx were not carried out. The EKG 24-h post-dose data are of little clinical value since the EKG interval abnormalities seen with the drug are better appreciated 1 to 2h after the administration of the drug, when the $C_{max}$ of the metabolite that correlates with the EKG is high. By 24h the blood levels of metabolite are either minimal or non-existing.

C. Study MCPR0031

1. Study Objective, Design, Execution, Statistics

- This study was set to compare the antiemetic effectiveness of two dose levels of DOLA•Mesyl, 2.4 and 1.8 mg/Kg administered intravenously as a single dose to the 32 mg single intravenous dose of ondansetron (=OND; Zofran®, Glaxo).

- The study population consisted of cancer patients scheduled to receive cisplatin-based chemotherapeutic regimens, either or 100 mg/m² given in no more than 3 hours. Patients were prospectively stratified on the basis of the amount of cisplatin given. The inclusion-exclusion criteria were adequate for this type of study and were similar to those described for study -081 above. As in study -081, patients with "significant cardiac disease" as per the list below, were not included in the trial.

  - Cardiomyopathy, CHF or Hx of CHF
  - Arrhythmias, requiring antiarrhythmic medication
  - Greater than first degree block
  - Pre-existing complete BBB, either L or R

- Concomitant medications with potentially confounding antiemetic efficacy were proscribed from the study. But medications necessary for the patient's well-being could be used according to the investigator's judgment. Escape medications were equally allowed and those patients were handled as treatment failures.

- The study design was that of a double-blind, randomized, stratified (on the basis of the dose of cisplatin given), multicenter, 3-arm, parallel trial. Included were patients with confirmed malignant disease who were undergoing their first course of a platinum-containing chemotherapy (cisplatin, carboplatin, etc.).

- Patients were prospectively stratified as to cisplatin doses, 70 to 90 mg/m² vs ≥91 mg/m², and then randomly assigned to one of three treatments: OND 0.15 mg/Kg x 3 DOLA•Mesyl 1.8 mg/Kg x 1, PL x 2; and DOLA•Mesyl 2.4 mg/Kg x 1, PL x 2.

  - Study drug was administered as a 15-min. infusion at 4h intervals, with the first infusion beginning 30 min. prior to the start of the cisplatin infusion.

  - After 41 patients had enrolled, the study design was amended at the request of the FDA at a meeting on November 4, 1992, to treat the OND group with a single 32 mg dose, rather than the divided dose schedule in the original protocol. Under the amended design, it was no longer necessary to administer two PL infusions to patients receiving DOLA•Mesyl.

- The 568 patients who were admitted to the study after this change in dosing schedule all received a single dose of test medication, to be infused over a 15-min. period, ca. 30 min. prior to cisplatin therapy.

- Safety and efficacy were monitored throughout the 24h following the start of cisplatin administration.

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

- The study evaluations (assessment of efficacy and safety) were adequate, as per study -081 and previous prevention of CCNV protocols.

- Sample size determination (200 patients per Tx group) was based on establishing that the difference between DOLA•Mesyl (2.4 mg/Kg and OND in CR rates was no greater than 15%.

  - This can be established by showing that the lower limit of a 95% C.I. for this difference (DOLA•Mesyl 2.4 mg/Kg - OND) is not less than -15. Assuming DOLA•Mesyl 2.4 mg/Kg and OND have equal CR rates of 40%, with 200 patients per Tx group, there was an 86% chance (power) of establishing equivalence.

- The definitions of categorical emetic efficacy endpoints were adequate, as per study -081 and the DOLA•Mesyl tablet protocols. Two important statistical analyses were carried out:

  - Logistic regression with a 95% confidence interval for the odds ratio of DOLA•Mesyl 2.4 mg/Kg vs OND controlling for investigator and stratum was the primary assessment of efficacy. This analysis was conducted using the intent-to-treat dataset. The presence of investigator-by-treatment and stratum-by-treatment interactions were tested using logistic regression and the Rao score (residual Chi-square) tests. Additionally, 95% confidence intervals for odds ratios were determined for DOLA•Mesyl 1.8 mg/Kg vs OND, and DOLA•Mesyl 2.4 mg/Kg vs DOLA•Mesyl 1.8 mg/Kg.

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

  - Further secondary analyses included logistic regression as described for the primary analysis using an efficacy evaluable dataset, subgroup analyses using the logistic regression model, and 95% confidence intervals for odds ratios using Mantel-Haenszel techniques.

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

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

2. Results

a. Participating Investigators/Patient Accounting

- Of 45 participating centers, 3 did not enroll any patients. The rest of centers enrolled a total of 609 patients (F-232; M=377); all 609 were

included in the ITT dataset. The following centers enrolled 20 or more patients each: T.H. Grote (n=50), Q. Navari (n=49), L. Porter (n=44), A. Khojasteh (n=36), L.B. Anthony (n=27), R.J. Gralla (n=27), E. Tapazoglou (n=26), N. Savaraj (n=24), J.D. Hainsworth (n=22) and L. Bertoli (n=21).

- 38 patients (6%), equally distributed among the three test groups, had major protocol violations and were excluded from the efficacy evaluable dataset.

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

| Population Analysis | OND | DOLA•Mesyl (mg/Kg) 1.5 | 2.4 | Total DOLA•Mesyl |
|---|---|---|---|---|
| ITT | 206 | 198 | 205 | 609 |
| Evaluable | 194 | 188 | 189 | 571 |

b. Data Showing Comparability of Groups at Baseline

- There were no statistically significant differences among the three treatment groups with respect to gender, race, age, weight, height, Karnofsky performance status and Hx of heavy alcohol use at pre-treatment and hour 0.

- The study population was predominantly male 377/609 (61.9%) and caucasian 525/609 (86.2%) with a median age of 62y, median weight 72.6 Kg; median height 172 cm and median Karnofsky performance status of 90%. Positive Hx of heavy alcohol use was reported in 99/609 (6.3%) of the patients.

- There were no important imbalances among Tx groups in site of primary neoplasm. The most frequent sites of primary neoplasm were lung 332/609 (54.5%), head/neck 66/609 (10.8%), gastrointestinal 65/609 (10.7%) and gynecologic 62/609 (10.2%).

- There were no imbalances in previous cancer Tx Hx among the three Tx groups.

  - 50 patients (8.2%) had previously received chemotherapy; 129 patients (21.2%) had previously undergone radiotherapy; and 196 patients (32.2%) had previously undergone surgery for cancer.

- There were no marked imbalances among the three Tx groups in medical Hx, Pre-Tx P.E., organ system abnormalities, incidence of medication use prior to test drug for medications that were used in >2% of the study population (except for multivitamin, p=0.019, an imbalance that would not be expected to influence efficacy results).

i) Cisplatin and Other Chemotherapy (Table 36)

- As shown in this Table, there were no significant imbalances among Tx groups in cisplatin dose (overall mean=85 mg/m², in the highly emetogenic category)[8], cisplatin dose category (≥91 mg/m²=40%; <91 mg/m²= 60%), duration of cisplatin infusion (overall mean=107 min.), interval between initial test med. and cisplatin (overall mean=34.5 min.), previous cancer treatment (overall, surgery=32%, radiotherapy=21% and chemotherapy=8%), concomitant use of benzodiazepines (10%) and concomitant use of narcotic analgesics (35%).

- There were no statistically significant imbalances among Tx groups in use of concomitant chemotherapies (see bottom of Table 36).

- With the exception of conjugated estrogens (p=0.049) and multivitamin (p=0.024), imbalances that would not be expected to influence efficacy results, there were no statistically significant imbalances among the three Tx groups in concomitant medications, including benzodiazepines or narcotic analgesics.

TABLE 36
Study -031

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

| I. Current Chemotherapy and Cancer Treatment History | | | | | |
|---|---|---|---|---|---|
| | | DOLA•Mesyl (mg/Kg) | | | |
| Variable | OND [n=206] | 1.8 [n=198] | 2.4 [n=206] | All Patients [n=609] | p-value* |
| Mean Cisplatin Dose (mg/m²) | 85.0 | 84.8 | 85.0 | 85.0 | N.S. |
| Range | | | | | |
| Cisplatin Dose Category: | | | | | |
| ≥91 mg/m²[b] | 41.3% | 38.4% | 39.0% | 39.6% | |
| <91 mg/m²[c] | 58.7% | 61.6% | 61.0% | 60.4% | |
| Mean Duration of Cisplatin Inclusion (min) | 108.7 | 107.1 | 105.3 | 107.0 | N.S. |
| Range | | | | | |



[8] 3 patients were excluded from the efficacy evaluable analysis due to receiving cisplatin in doses less than 63 mg/m². Patient MCST0339-0104 received a cisplatin dose of 61.9 mg/m². Patient MCST0064-0102 had the cisplatin infusion (total dose unknown) terminated after 15 min. due to a serious AE. Patient MCST0339-0113 had the cisplatin infusion terminated, restarted and terminated again over a period of 4h with the dose received being unknown, but less than 63 mg/m².

3 patients received highly emetogenic concomitant chemotherapies that were prohibited by the exclusion criteria. Patient MCST0140-0202 (OND Tx group) received >1.5 g/m² ifosfamide during the 24-h Tx period. Patients MCST0067-0106 (DOLA•Mesyl 2.4 mg/Kg x 1, PL x 2 Tx group) and MCST0138-0102 (DOLA•Mesyl 2.4 mg/Kg Tx group) received **dacarbazine** during the 24-h Tx period. These were considered minor protocol deviations, and these three patients were retained in the efficacy evaluable population. Two of these patients were Tx failures, and one (MCST0067-0106) was a major responder.

| | | | | | |
|---|---|---|---|---|---|
| Mean Interval Between Initial Test Drug and Cisplatin (min)<br>Range | 33.8 | 35.5 | 34.2 | 34.5 | N.S. |
| Previous Cancer Treatment: | | | | | |
| Surgery | 34.5% | 33.8% | 28.3% | 32.2% | N.S. |
| Radiotherapy | 19.4% | 21.7% | 22.5% | 21.2% | N.S. |
| Chemotherapy | 7.8% | 7.6% | 9.3% | 8.2% | N.S. |
| Concomitant Use of Benzodiazepines | 13.6% | 8.1% | 8.3% | 10.0% | N.S. |
| Concomitant Use of Narcotic Analgesics | 36.4% | 32.3% | 36.1% | 35.0% | N.S. |
| II. Current Chemotherapy and Cancer Treatment History | | | | | |
| Etoposide | 32.5% | 40.4% | 36.1% | 36.3% | N.S. |
| 5-FU W/NS | 14.1% | 12.6% | 16.6% | 14.4% | N.S. |
| Vinblastine | 11.7% | 8.1% | 8.8% | 9.5% | N.S. |
| Cyclophosphamide | 6.3% | 3.5% | 6.3% | 5.4% | N.S. |
| Doxorubicin | 6.3% | 2.0% | 2.9% | 3.8% | N.S. |
| Mitomycin | 2.4% | 3.0% | 2.9% | 2.8% | N.S. |

a) For continuous variables such as cisplatin dose, length of cisplatin infusion and interval between test drug and cisplatin, p values are calculated from a three-way analysis of variance F test for mean differences among the three treatments controlling for investigator and stratum. For dichotomous variables such as Hx of previous cancer treatments and concomitant chemotherapy, p-values are from a 2 degree of freedom Chi-square test calculated from a logistic regression model with treatment and stratum as explanatory variables.

ii) Escape Medications (Table 37)

There were no statistically significant imbalances among the three Tx groups in escape medications.

TABLE 37
Study -031

Escape Medications Taken During Study

| RECEIVED IN MORE THAN 2% OF THE STUDY POPULATION | | | | |
|---|---|---|---|---|
| | | DOLA•Mesyl (mg/Kg) | | |
| Non-Study Medication | OND [n=206] | 1.8 [n=198] | 2.4 [n=205] | All Patients [n=609] |
| ESCAPE MEDICATION | | | | |
| Lorazepam (p=N.S.) | 15% | 18% | 17% | 17% |
| Prochlorperazine (p=N.S.) | 14% | 12% | 17% | 14% |
| Dexamethasone (p=N.S.) | 14% | 12% | 15% | 13% |
| Ondansetron (p=N.S.) | 8% | 10% | 11% | 10% |
| Metoclopramide (p=N.S.) | 6% | 5% | 5% | 5% |
| Promethazine (p=N.S.) | 5% | 4% | 6% | 5% |
| Dephenhydramine (p=N.S.) | 5% | 4% | 5% | 5% |
| a) p-values are calculated using a 2 degree of freedom Chi-square test. | | | | |

c. Clinical Response

i) Analysis of Primary Efficacy Endpoint (Complete Response) (table 38)

- This Table displays the actual CR rates as a function of test group, with the corresponding 95% Confidence Intervals for % of CR and two types of therapeutic gains computations. One consists of the comparisons between the two dose levels of DOLA•Mesyl vs OND in an approach to demonstrate equivalency and between the two dose levels of DOLA•Mesyl to determine if one dose is superior to the other. The other consists of comparisons of the CR rates of each of the three experimental groups to the upper endpoint of a 95% CI of a historical PL control, based on results of four published studies (11.1%). The latter approach is an attempt to demonstrate that each one of the three experimental groups is active.

- In the ITT (n=609), CR was 44% with the 1.8 mg/Kg DOLA•Mesyl and 40% with the 2.4 mg/Kg dose. This CR was equivalent to that of OND (there were no statistically significant differences in CR among the 3 Tx groups). As detailed in the footnote to Table 38, the 3 Tx groups met the protocol-specified criteria for equivalence.

- The primary analysis was the comparison of DOLA•Mesyl 2.4 mg/Kg and OND. The 95% CI for the odds ratio was (0.571, 1.295), with the lower bound exceeding 0.5. The ca. 95% confidence interval for the difference in CR rates was (-12.6%, 5.9%).

- The 95% CI for the odds ratio of DOLA•Mesyl 1.8 mg/Kg vs. OND was (0.682, 1.546). The ca. 95% CI for the difference in CR rates was (-9.2%, 9.7%).

- The 95% CI for the odds ratio of DOLA•Mesyl 2.4 mg/Kg to DOLA•Mesyl 1.8 mg/Kg was (0.555, 1.264), and the ca. 95% CI for the difference in CR rates was (-13.0%, 5.7%).

- The similar response rates at the two DOLA•Mesyl doses suggests that antiemetic efficacy does not increase at doses above 1.8 mg/Kg.

- When compared to the historical controls each of the three Tx groups showed an ca. therapeutic gain of 30%. All three achieved statistical significance ($p<0.0001$).

- Based on the results of the efficacy evaluable analysis, based on 571 patients (lower panel of Table 38) all three treatments met the protocol-specified criteria for equivalence and each was shown superior to the historical PL control. These results were consistent with those of The ITT analysis (the upper panel of Table 38).

- In this trial, investigator was not a significant predictor of CR ($p=0.1326$) and there was no investigator-by-Tx interaction ($p=0.3115$). The signs and magnitudes of Tx differences varied among investigators in a manner consistent with equivalence of the three treatments.

ii) <u>CR Rate by Cisplatin Dose Stratum and Treatment (Table 39)</u>

- Analysis within strata are provided in this Table. In study -031 cisplatin dose stratum was a significant predictor of CR ($p<0.0001$) but there was no cisplatin dose stratum-by-Tx interaction ($p=0.8559$).

- As shown in Table 39, lower CR rates were associated with higher doses of cisplatin and the Tx differences were consistent across the two strata (see footnote to Table 39).

TABLE 38
Study -031

Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response

| Response by Test Group | | | | Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses and OND and Between Test Groups and Historical PL Control [p-values] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **I. Intent-To-Treat Analysis [n=609]** | | | | | | | | | |
| Hist-PL | OND [n=206] | 1.8 mg/Kg [n=198] | 2.4 mg/Kg [n=205] | 1.8 mg/Kg vs OND | 2.4 mg/Kg vs OND | 2.4 mg/Kg vs 1.8 mg/Kg | OND vs PL | 1.8 mg/Kg vs PL | 2.4 mg/Kg vs PL |
| (11.1%) | 88 (42.7%) | 88 (44.4%) | 82 (40.0%) | (1.7%) | (-2.7%) | (-4.4%) | (31.6%) | (33.0%) | (28.9%) |
| 95% Confidence Interval for % of CR | (35.8%,50.3%) | (36.2%,51.1%) | (32.3%,46.7%) | [N.S.] | [N.S.] | [N.S.] | [<0.0001][a] | [<0.0001] | [<0.0001] |
| **II. Efficacy Evaluable Analysis [n=571]** | | | | | | | | | |
| | [n=194] | [n=188] | [n=189] | | | | | | |
| (11.1%) | 83 (42.8%) | 83 (44.1%) | 74 (39.2%) | (1.3%) | (-3.6%) | (-4.9%) | (31.7%) | (33.3%) | (28.1%) |
| | | | | [N.S.] | [N.S.] | [N.S.] | [<0.0001][b] | [<0.0001] | [<0.0001] |

95% CI for Odds Ratios and Corresponding p values (ITT, n=609)
1.8 mg/Kg DOLA•Mesyl vs OND (0.682, 1.546) p=0.9000
2.4 mg/Kg DOLA•Mesyl vs OND (0.571, 1.295) p=0.4698
2.4 mg/Kg DOLA•Mesyl vs 1.8 mg/Kg DOLA•Mesyl (0.555, 1.264) p=0.3982

Approximate 95% CI for Tx Differences[c]
1.8 mg/Kg DOLA•Mesyl - OND (-9.2%, 9.7%)
2.4 mg/Kg DOLA•Mesyl - OND (-12.6%, 5.9%)
2.4 mg/Kg DOLA•Mesyl - 1.8 DOLA•Mesyl (-13.0%, 5.7%)

a,b) p values are calculated from a logistic regression model predicting CR with Tx. investigator and stratum included in the model. The historical PL response rate was the upper endpoint of a 95% CI based on the results of four published studies (11.1%)
c) Approximate 95% confidence intervals obtained using stratified random sampling techniques with logistic regression predicted probabilities for estimation of variance.

TABLE 39
Study -031

Clinical Response: Analyses of Primary Efficacy Parameters Complete Response by Cisplatin Dose[a] Category and Treatment[b]

| Response by Test Group | | | | Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses and OND | | |
|---|---|---|---|---|---|---|
| **I. Cisplatin Dose <91 mg/m² [n=368]** | | | | | | |
| No. of Pts. in ITT | OND [n=206] | 1.8 mg/Kg [n=1198] | 2.4 mg/Kg [n=205] | 1.8 vs OND | 2.4 vs OND | 2.4 vs 1.8 |
| | 61/121 (50.4%) | 60/122 (49.2%) | 57/125 (45.6%) | (-1.2%) | (-4.8%) | (-3.6%) |
| **II. Cisplatin Dose ≥91 mg/m² [n=241]** | | | | | | |
| | 27/85 (31.8%) | 28/76 (36.8%) | 25/80 (31.3%) | (-5%) | (-0.5%) | (-5.5%) |

95% CIs for ORs and corresponding p values[c] within low-dose stratum:
- 1.8 mg/Kg DOLA•Mesyl vs OND, (0.564, 1.574) p=N.S.
- 2.4 mg/Kg DOLA•Mesyl vs OND, (0.485, 1.350) p=N.S.
- 2.4 mg/Kg DOLA•Mesyl vs 1.8 mg/Kg DOLA•Mesyl (0.515, 1.431) p=N.S.

95% CIs for ORs and corresponding p-values within high-dose stratum
- 1.8 mg/Kg DOLA•Mesyl vs OND, (0.604, 2.356) p=N.S.
- 2.4 mg/Kg DOLA•Mesyl vs OND, (0.482, 1.894) p=N.S.
- 2.4 mg/Kg DOLA•Mesyl vs 1.8 mg/Kg DOLA•Mesyl (0.401, 1.599) p=N.S.

a) Cisplatin dose category p<0.0001, from a 1 degree of freedom Chi-square test using logistic regression with Tx, site and stratum in the model.
b) Cisplatin dose category by Tx interaction p=0.8559, from a 2 degree of freedom Chi-square test using Rao scores from logistic regression with Tx, investigator and stratum in the model.
c) p values and confidence intervals from a logistic regression model predicting CR with Tx, investigator and stratum included in the model.