CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020624

MEDICAL REVIEW(S)

1946

NDA 20-624

ANZEMET® (Dolasetron Mesylate) Injection

a) Prevention of Nausea and Vomiting Associated With Initial and Repeat Courses of Emetogenic Cancer Chemotherapy

b) Prevention of Postoperative Nausea and Vomiting

c) Treatment of Postoperative Nausea and/or Vomiting

Reviewer:
Hugo E. Gallo-Torres, M.D., Ph.D.
HFD-180

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-624
Sponsor:	Hoechst Marion Roussel, Inc. Kansas City, MO
Date Submitted:	February 20, 1996
Draft to Supervisor:	January 29, 1997
Name of Drug:	ANZEMET® (Dolasetron Mesylate) Injection
Pharmacological Category:	Selective Inhibition of the 5-hydroxytryptamine subtype receptor
Formulation:	ANZEMET (dolasetron mesylate) injection is a clear, colorless, nonpyrogenic, sterile solution for intravenous (IV) injection. Each milliliter of ANZEMET injection contains 20 mg of dolasetron mesylate and 38.2 mg mannitol with an acetate buffer in water for injection. The pH of the resulting solution is 3.1 to 4.1.
Route of Administration:	Intravenous
Proposed Clinical Use:	a) Prevention of Nausea and Vomiting Associated With Initial and Repeat Courses of Emetogenic Cancer Chemotherapy (1.8 mg/Kg given as a single dose approximately 30 min. before chemotherapy, or 100 mg given ca. 30 min. before chemotherapy) b) Prevention of Postoperative Nausea and Vomiting (12.5 mg given as a single dose at the cessation of anesthesia) c) Treatment of Postoperative Nausea and/or Vomiting (12.5 mg given as a single dose as soon as nausea or vomiting presents)
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.

MEDICAL OFFICER REVIEW OF

NDA 20-624

ANZEMET® (Dolasetron Mesylate) Injection

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I. INTRODUCTION/RATIONALE

Dolasetron mesylate (DOLA•Mesyl; brand name ANZEMET®) is a selective inhibitor of the 5-hydroxytryptamine subtype receptor. Data on a tablet formulation of this compound (main trials -095 and -0292) reviewed under NDA 20-623 (MOR of May 31, 1996) was considered approvable for the prevention of postoperative nausea and vomiting (PONV), at the recommended dose regimen of one 100 mg tablet within two hours prior to surgery. The sponsor also requested approval of DOLA•Mesyl for the prevention of N&V associated with cancer chemotherapy, including initial and repeat courses. Based on what was submitted by the sponsor as pivotal trials, studies -043 and -048, the MO recommended approval of DOLA•Mesyl for the CCNV indication, at the dose of one 100 mg tablet one hour prior to chemotherapy. Because of well-established EKG changes induced by the drug and the very limited clinical experience with DOLA•Mesyl, in the MO recommendation for approval, a warning, preferably in a box, was to be included in the labeling. Incorporating data from Study -087 (identified by the sponsor and HFD-180 as non-pivotal) the Division Director selected 200 mg as the recommended dose for the prevention of CCNV was 200 mg. But, in order to approve the drug for prevention of CCNV, clinical experience is needed in the potential interaction between DOLA•Mesyl and cardiovascular medications in general and conditions that prolong the PR, QRS and the QT_c interval in particular. Also lacking are data on possible interaction of this drug with clinical conditions involving patients with history of cardiovascular disease. Although this information was most notoriously lacking in clinical settings involving the use of the drug for the PONV indication, it was felt (the MO agrees with this statement) that the PONV patients are being closely supervised and monitored. If and when abnormal EKG changes are detected in these PONV patients, clinical intervention may be quickly instituted. So, the PONV patients would be properly covered while the CCNV patients may be taking the tablets at home and may not be closely monitored initially.

Through the present submission, NDA 20-624, the sponsor expects to obtain approval of an injection formulation of DOLA•Mesyl for the two indications requested for the tablet formulation, in addition to the treatment of PONV.

It is of interest to consider salient points in regards to the PKs of DOLA•Mesyl in humans, with emphasis on correlations between the i.v. and the oral routes of administration. As stated in the proposed labeling, i.v. administered DOLA•Mesyl is rapidly eliminated ($t_{\frac{1}{2}}$ <10 min) and completely metabolized to the most clinically relevant species, MDL 74,156. The latter metabolite appears rapidly in plasma, with a maximum concentration occurring ca. 0.6h after end of i.v. treatment and is eliminated with a mean half-life of 7 to 8h in adult cancer patients. MDL 74,156 is eliminated by multiple routes, including renal excretion and metabolism, mainly glucuronidation and hydroxylation. MDL 74,156 exhibits linear PKs over the i.v. dose range of 50 to 200 mg and, according to the sponsor, PKs are independent of the infusion rate.

It is important to note that the metabolism profile of DOLA•Mesyl is identical for both oral and i.v. routes of administration (see Fig. 1 and 2, taken from Biopharm. review of August 15, 1996). Ca. two-thirds of the administered dose is recovered in the urine and one third in the feces. MDL 74,156 is widely distributed in the body with a mean apparent volume of distribution of 5 to 6.1 L/Kg. Plasma protein binding of MDL 74,156 is < and the distribution of this metabolite to blood cells is not extensive. The binding of MDL 74,156 to α-acid glycoprotein in ca. 51%. The PKs of MDL 74,156 is similar in males and females.

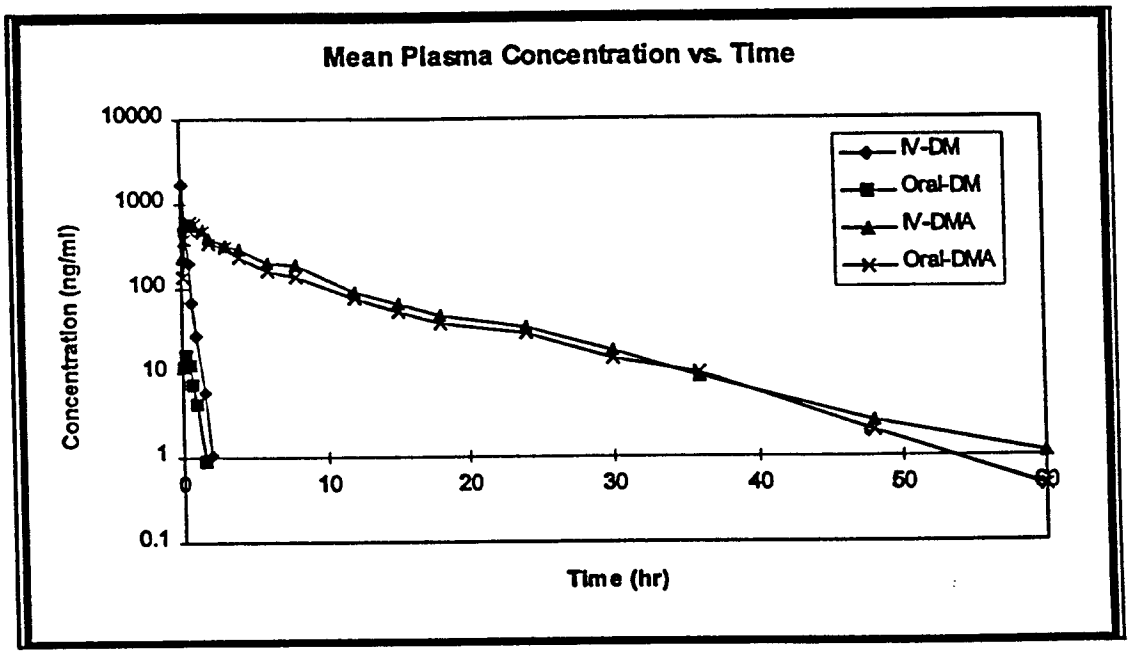

Fig. 1. - Plasma concentration time plots for DOLA•Mesyl (DM) and its main ingredient (DMA) obtained from I.V. and oral administration of 2.4 mg/Kg of DOLA•Mesyl. The mean PK parameters of DOLA•Mesyl following single I.V. and P.O. doses of 2.4 mg/Kg of DOLA•Mesyl were as follows:

Parameters	I.V.	Oral
AUC_{0-last} (ng.h/ml)	395.27 ± 177.33	11.17 ± 5.81
$AUC_{0-\infty}$ (ng.h/ml)	398.19 ± 177.54	18.00 ± 5.73
Kel (h-1)	3.25 ± 0.97	1.76 ± 0.74
t 1/2 (h)	0.24 ± 0.11	0.50 ± 0.27

[This Fig. corresponds to Fig. 1 on page 61 of Biopharm. Review of August 15, 1966 (R.S. Pradhan)]

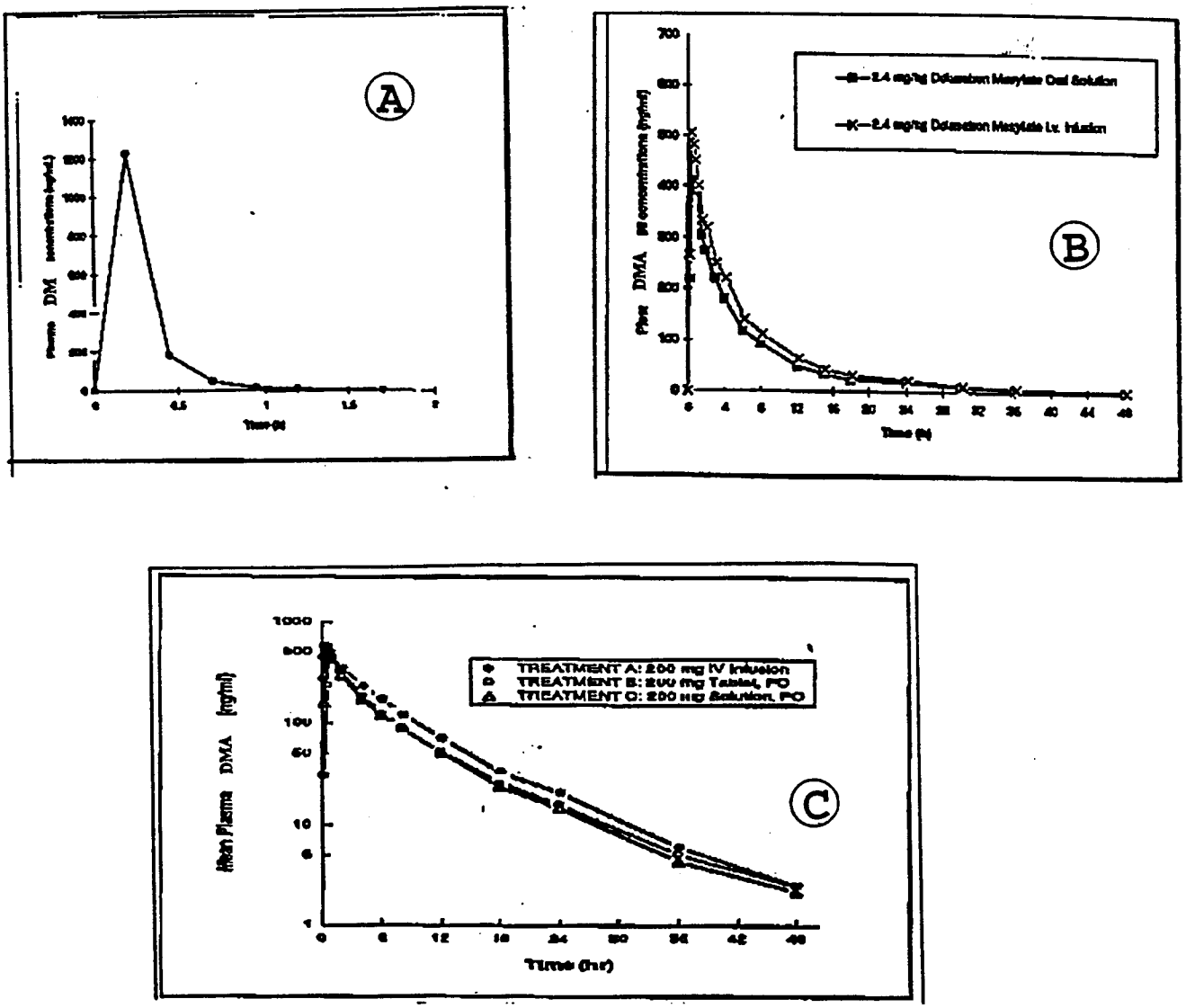

Fig. 2. - *A = Mean Plasma Concentration vs Time Plots for DOLA•Mesyl (DM) following i.v. administrations (n=22)*
B = Mean Plasma Concentration vs Time Plots for DMA following i.v. and oral administration (n=24)
C = Mean Plasma Concentration vs Time Plots for DMA [Treatment A and C, n=31; Treatment B, n=30).
These figures were taken from pages 22 and 59 of Biopharm. Review of August 15, 1996 (R.S. Pradhan).

As summarized in Table 1, the PKs of MDL 74,156 is similar in adult healthy volunteers and adult cancer patients receiving chemotherapeutic agents. The apparent clearance of MDL 74,156 in pediatric and adolescent patients is 1.4 times to twofold higher compared to adults. The apparent clearance of MDL 74,156 is not affected by age in adult cancer patients. Following i.v. administration, the apparent clearance of MDL 74,156 remains unchanged with severe hepatic impairment and decreases 47% with severe renal impairment. According to the sponsor, DOLA•Mesyl is well tolerated in these populations over the therapeutic dose range. No dose adjustment is necessary for elderly and renally or hepatically impaired patients.

TABLE 1
NDA 20-624

Mean PK Parameters of MDL 74,156 Following I.V. Administration of DOLA•Mesyl

	Age (years)	CLapp (mL/min/Kg)	$t_{1/2}$ (h)
Young Healthy Volunteers	19-40	9.4	7.3
Elderly Healthy Volunteers	65-75	8.3	6.9
Cancer Patients Adults Adolescents Children	 19-87 12-17 3-11	 10.2 12.5 19.2	 7.5 5.5 4.4
Pediatric Surgery Patients	2-11	13.1	4.8
Severe Renal Impairment Patients (Creatinine clearance ≤ 10 mL/min)	28-74	5.0	10.9
Severe Hepatic Impairment Patients (Child-Pugh class B or C1)	42-52	9.6	11.7
CLapp: apparent clearance $t_{1/2}$: terminal elimination half-life			

Through the present submission, the sponsor is requesting approval of ANZEMET® injection for the following three indications: a) the prevention of N&V associated with initial and repeat courses of emetogenic cancer chemotherapy; b) prevention of PONV; and c) treatment of PONV.

Of the three indications listed above, a) and b) are the same as those requested in NDA 20-623 reviewed by the MO. Efficacy data for these indications, other than studies in high dose cisplatin-induced emesis, will not be reviewed in detail in the present review. Efficacy data for the treatment of PONV indication will be reviewed in detail. Also reviewed in detail will be the Safety data from all studies. One of the aims of the MOR of the i.v. formulation data is to ascertain if additional data exist that would be helpful in decisions regarding the 100 mg of the oral formulation of

TABLE 2
NDA 20-624

Main Features of Design/Execution of the Two Main Studies Submitted by the Sponsor in Support of the Approval of DOLA•Mesyl for the Treatment of PONV

Study Identification	Study Population	Main Design/ Execution	Groups Being Compared	REMARKS
MCPRO (-044) (US) [n=620] 31 sites F=514 M=106	F or M patients scheduled for outpatient surgery with general balanced anesthesia were randomized and stratified by gender within each study site to test med. after an emetic episode or MOD to SEV nausea of at least 5-min. duration • 33% of the patients reported a history of PONV.	• Randomized, double-blind parallel group, stratified by gender, placebo-controlled, multicenter dose-response, 5-arm study. • Definitions of emetic episodes and evaluation period (24h observations after test med.) were as in previous protocols. • 30 sec. to 5 min. infusion of test med.	DOLA•Mesyl at single i.v. doses of (mg): 12.5 [n=130] 25 [n=119] 50 [n=124] 100 [n=126] vs PL [n=121]	• Adequate design. • Effectiveness is shown by comparing results of each dose of DOLA•Mesyl to PL, a negative control. • The design allows dose-response comparisons of the efficacy of larger (i.e. 100 mg) vs smaller doses of the drug (i.e. 12.5 mg). • Although the PKs of MDL 74,156 is similar in F and M, and no differences in gender response are expected, stratification of the patients on the basis of gender is of interest to ascertain if efficacy is independent of gender (females are more susceptible to emetic symptoms following surgery).
73147 (-2-S-084) (Europe) [n=337] 23 centers in N. Ireland, UK, Belgium, Germany, Switzerland, Netherlands, France F= 319 M=18	Predominantly F, but also some M patients who had just undergone surgery under general anesthesia and who presented with early PONV were randomized to test med. • 46% of the patients reported a history of PONV.	• Randomized, double-blind, parallel group, placebo controlled, multicenter, 5-arm study. • Definitions of emetic episodes and evaluation period (24h observations after test med.) were as in previous protocols. • 5 min. infusion of test med.	DOLA•Mesyl at single i.v. doses of (mg): 12.5 [n=66] 25 [n=65] 50 [n=67] 100 [n=68] vs PL [n=71]	• Useful design but not strictly replicative of the main trial (-044). • The study was designed to assess the efficacy of a range of doses of i.v. DOLA•Mesyl, in combination, against PL. • The study was apparently not sized as a dose-response trial.

DOLA•Mesyl. This is important because, as previously stated, the metabolism profile of DOLA•Mesyl is identical for both oral and i.v. routes of administration.

II. INDICATION: TREATMENT OF PONV

A. Adequacy of Submitted Trials

In support of the treatment of PONV indication, the sponsor has submitted results of two adequate and well-controlled studies, identified as -044 (a domestic study) and 2-S-084 (a study conducted in Europe). As noted in Table 2, both trials were randomized, double-blind, multicenter and placebo-controlled. In both 5-arm trials, the study population consisted of patients who had undergone surgery with general balanced anesthesia, and presented with early PONV requiring antiemetic treatment. Both the design and the execution of both main trials were adequate to assess efficacy and safety of graded, single doses of DOLA•Mesyl (vs placebo) in this patient population.

B. Study MCPRO-044

"A randomized, double-blind, placebo-controlled, dose-response trial to assess single dose intravenous dolasetron mesylate in patients experiencing post-operative nausea and vomiting."

1. Objectives

a) To assess the efficacy of a range of doses of i.v. DOLA•Mesyl in terminating N&V in patients who had just undergone outpatient surgery under general anesthesia.

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

c) To determine the degree of patient satisfaction among the antiemetic doses levels.

2. Study Population

Inclusion-exclusion criteria were as per the studies of prevention of PONV indication with the tablet formulation (Studies -095 and -0292; reviewed on pages 213 through 288 of MOR of May 31, 1996). Regarding the cardiovascular system, the presence of the following required exclusion from the study; complete BBB, either R or L (QRS >120 msec), cardiomyopathy, CHF or Hx of CHF, Hx of arrhythmias requiring antiarrhythmic medication and second or third degree heart blocks.

3. Concomitant Medications

As in previous protocols, medications with potentially antiemetic properties were excluded during the course of the trial. The use of any medication with potential antiemetic activity, unless administered to control emesis, was considered a protocol violation.

4. Test Medication[1] /Dosing Schedule

- DOLA•Mesyl 12.5, 25, 50 or 100 mg and PL were supplied in 10 ml ampules which were identical in appearance. Important information is displayed below.

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[1] The composition of the to-be-marketed formulations is as follows:

Composition of Dolasetron Mesylate Injection 12.5 mg (20 mg/mL, 0.625 mL Ampoules)		
Component		
Dolasetron Mesylate Monohydrate Mannitol Acetate		

Composition of Dolasetron Mesylate Injection 100 mg (20 mg/mL, 5 mL Vials)			
Component	Formula Amount (per vial)	Representative Batch of 215 Liters (218.4 kg)*,‡	Representative Batch of 425 Liters (431.8 kg)†,‡
Dolasetron Mesylate Monohydrate Mannitol Acetate			

Dose of Test Medication[a] (mg)	Finished Product Number	Lot Number
12.5	MC025-01	RC9318
25	MC026-01	RC9319
50	MC027-01	RC9320
100	MC001-01	C-49127-1
PL	MC029-01	RC9317

a) Ampules of PL and DOLA®Mesyl contained mannitol, sodium acetate, and acetic acid to adjust isotonicity and pH, in water for injection.

- Test medication was administered post-operatively if the patient experienced MOD to SEV nausea and/or vomiting, as a single i.v. dose, in a 10 ml volume over a minimum of 30 seconds.

5. Blinding, Packaging and Labeling

These aspects of the study adequate.

6. Study Evaluations

These were done under randomized, double-blind, dose-response, PL-controlled, parallel group, multicenter conditions. M or F patients with ASA physical status, Class 1, 2 or 3, who had just undergone outpatient surgery (scheduled for discharge to home the same day) under general anesthesia were eligible to enter the trial of the developed PO nausea (≥5 min. and reported as MOD to SEV by the patient) or ≥1 emetic episode within 2h of arriving in the recovery room. If after test med. administration the pt. developed persistent nausea for ≥15 min. or ≥1 emetic episode, or he/she requested alternative antiemetic therapy, or the investigator determined that alternative medication was needed, the investigator could initiate escape medication according to institutional practice.

- The activity and duration of test med. action was evaluated for 24h. Safety, tolerance and patient satisfaction was monitored and QOL measurements were performed (as described for previous protocols).

- Patients were stratified by gender and randomized within each investigative site.

- Efficacy Measures

1) Number of emetic episodes prior to Tx and after Tx.
2) Time to first emetic episode after Tx.
3) Nausea (VAS)
4) Patient satisfaction (VAS)
5) Need for and timing of rescue (escape) antiemetic therapy after Tx.

- Safety Measures

1) P.E. and medical Hx
2) AEs
3) Clinical Laboratory Evaluations
4) 12-lead EKGs
5) Vital Signs

7. Statistical Methods

- Sample Size Justification

Sample size determination was based on fitting a logistic response curve across the five dose groups; and then comparing the most effective dose (i.e., the dose with the maximum CR rate) to placebo in the logit of the proportion of complete responders. A stepwise Dunnett's procedure was used to account for a total of four possible comparisons. The sponsor's calculations postulated that the CR rates in PL and the most effective dose were 20% and 40% respectively (expected therapeutic gain = 20%). Assuming 120 patients in each dose group, for a total of 600 patients, the power of a 2-tailed pairwise comparison with an overall 0.05 significance level of the most effective dose to placebo was 81%.

- Primary Statistical Analysis

The primary analysis was an ITT analysis of complete response (CR) (0 emetic episodes, no escape medications, and monitored for emesis at least 23.5h) over 24h using logistic regression with terms for investigator and the dose-by-gender interaction.

- The primary test for efficacy was one pairwise comparison of PL to the DOLA•Mesyl dose with the maximum CR rate. A stepwise Dunnett's procedure of comparing DOLA•Mesyl doses to PL was followed until a comparison was not significant.

8. Data Documentation

The sponsor documented the QC procedures used in the present trial by submitting the following: pre-entry review of data, data entry, exception process (to document computer checks and confirm the accuracy of the data), QC

of the database (verification of CRFs), end study audit of data, database finalization and unblinding of drug code. A list of all CRF data was available in Report K-95-0004-S

9. Results

a. Participating Investigators/Patient Accounting

Thirty-one centers enrolled a total of 620 patients [F=514; M=106]. The following 5 sites enrolled 30 or more patients each.

MCST		Total # of Patients Enrolled
-0412	[T. Melson, Muscle Shoals, AL]	60
-0273	[M. Pearman/S. Graczyk, Columbia, SC]	59
-0263	[A. Kovac, Kansas City, KS	48
-0279	[P. Scuderi, Winston-Salem, NC	40
-0337	[W.D. Walkins/T. Boerner, Pittsburgh, PA]	34

b. Major Protocol Violations

There were no statistically significant differences among the 5 groups in the proportion of patients with major protocol violations (PL=4%; DOLA•Mesyl=6% to 11%). The number of patients analyzed per population by group were:

Population for Analysis	DOLA•Mesyl (mg)				
	PL	12.5	25	50	100
ITT	121	130	119	124	126
Evaluable	116 (96%)	121 (93%)	106 (89%)	114 (92%)	119 (94%)

c. Data Showing Comparability of Groups at Baseline

- The study population was predominantly female (83%) and Caucasian. An imbalance in mean age among the dose groups was detected (p=0.018): the 100 mg group had a slightly older population with a mean age of 36y vs mean ages of 32 to 33y in the other dose groups. Although age is a factor that may influence response, the imbalance in age detected in the

present study (3 to 4 years) is not expected to substantially impact the safety or efficacy results of the trial. Otherwise, there were no statistically significant imbalances among the five dose groups with respect to height, weight, gender, ASA physical status (Class 1=60%, Class 2=38% and Class 3=2%), race, Hx of PONV (33% of the patients had a Hx of PONV), Hx of motion sickness (29% of the patients had a Hx of motion sickness), smoking status (27% of the patients were current smokers), type of surgery (the most frequent types of surgery were gynecological=48% and orthopedic=20%), duration of anesthesia (mean=1.306h), time between cessation of anesthesia and test med. administration (mean=0.899h) and time from last free fluids to test med. administration (mean=14.987h).

- There were no marked imbalances among the 5 dose groups in medical Hx, pre-Tx P.E., underlying medical conditions. Ca. 20% of the patient population reported a previous medical Hx of cardiovascular system.

- There were no statistically significant differences among the dose groups in anesthetic procedures.

- There were also no differences among the five groups in eligibility criteria. This is documented below.

Eligibility Criteria	ELIGIBILITY CRITERIA [No. (%) of patients]						
	PL [n=121]	DOLA•Mesyl (mg)				All Patients [n=620]	p-value
		12.5 [n=130]	25 [n=119]	50 [n=124]	100 [n=126]		
NAUSEA (only)	49 (40.5%)	48 (36.9%)	42 (35.3%)	50 (40.3%)	35 (27.8%)	224 (36.1%)	N.S.
VOMITING (only)	30 (24.8%)	35 (26.9%)	32 (26.9%)	31 (25%)	35 (27.8%)	163 (26.3%)	
N&V	42 (34.7%)	47 (36.2%)	45 (37.8%)	43 (34.7%)	56 (44.4%)	233 (37.6%)	

d. Clinical Response

i) Overall Complete Response

- In the ITT analysis (Table 3, upper panel) for complete response, the therapeutic gains for all the DOLA•Mesyl groups over PL varied between 17% to 25%. Each and all of these therapeutic gains represented a statistically significant difference from PL for the DOLA•Mesyl dose groups. The response with all DOLA•Mesyl groups combined was 20% greater than PL (p=highly significant).

TABLE 3
Study MCPR0044

Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response

Response by Dose (mg)					Therapeutic Gain (%) for Comparisons Betweem DOLA•Mesyl Doses and PL/[p-values][a]				
I. Intent-to-Treat Analysis [n=620][b]									
PL [n=121]	12.5 [n=130]	25 [n=119]	50 [n=124]	100 [n=126]	12.5 vs PL	25 vs PL	50 vs PL	100 vs PL	All DOLA•Mesyl[c] vs PL
13 (10.7%)	46 (35.4%)	33 (27.7%)	36 (29%)	37 (29.4%)	24.7% [<0.001]	17.0% [<0.001]	18.3% [<0.001]	18.7% [<0.001]	19.8% [0.0003]
II. Efficacy Evaluable Analysis [n=576][d]									
[n=116]	[n=121]	[n=106]	[n=114]	[n=119]					
13 (11.2%)	43 (35.5%)	29 (27.4%)	32 (28.1%)	34 (28.6%)	24.3% [<0.001]	16.2% [<0.003]	16.9% [<0.001]	17.4% [<0.001]	18.8% [0.0008]

a) • p-values are calculated from a weighted contrast of the parameter estimates for the dose by gender interaction obtained from a logistic regression model predicting complete response with dose, investigator and gender as explanatory variables.
• The contrast is weighted proportionally to the sample sizes of each gender.
• p-values are adjusted for the 4 comparisons to PL using Dunnett's test.

b) Primary test: DOLA•Mesyl (12.5 mg) vs PL, $p<0.05$ [ITT, n=620]
• Mantel-Haenszel Row Mean Scores Test: DOLA (12.5 mg) vs PL, $p<0.001$ [ITT]
• Linear Trend, $p=0.0041$ [ITT, n=620]
• Mantel-Haenszel Test for Non-Zero Correlation, $p=0.018$ [ITT, n=620]

c) For ITT 152/499 ± 30.5% (Therapeutic Gain over PL=19.8%)
For Efficacy Evaluable 138/460 = 30% (Therapeutic Gain over PL=18.8%)

d) Secondary test: DOLA•Mesyl (12.5 mg) vs PL, $p<0.05$ [Efficacy Evaluable, n=576]

- In the Efficacy Evaluable analysis (Table 3, lower panel), for complete response, the therapeutic gains for all the DOLA•Mesyl groups over PL varied between These data confirmed the results of ITT analysis. The response with all DOLA•Mesyl groups combined was 19% greater than PL (p=highly significant).

ii) Complete Response by Gender per Dose Cell

- As shown in Table 4, gender was statistically significant predictor of CR (p=0.0301).

- There was a statistically significant dose by gender interaction (p=0.0088).

- The CR rate in the PL group was 8/102 (8%) for females and this was substantially lower than in males (5/19=26%).

- In males (upper panel of Table 4), neither the 12.5 nor the 25 or the 50 mg dose level showed statistically significant therapeutic gains (4%, -5% and 9%, respectively) over PL; only the 100 mg dose, with a rate of 64% showed a statistically significant improvement in CR over PL (therapeutic gain=38%).

- In females (lower panel of Table 4), all DOLA•Mesyl dose groups showed a statistically significant therapeutic gain over PL that varied between 14% and 28%. But, oddly enough, the highest therapeutic gain was seen with the 12.5 mg dose (36% -8%=28%), and the lowest, with the 100 mg dose (22% -8%=14%).

iii) Complete Response by Investigator and Dose
(Data not shown)

- Investigator was a statistically significant predictor of CR (p=0.0415) and was included in all statistical analyses where possible.

- The dose by investigator interaction was not statistically significant (p=0.8146) and was excluded from all statistical analyses.

TABLE 4
Study MCPR0044

Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response By Gender[a] Per Dose Cell

Response by Dose (mg)					Therapeutic Gain (%) for Comparisons Between DOLA®Mesyl Doses and PL/(p-values)				
I. CR in Males [n=106]									
PL [n=121]	12.5 [n=130]	25 [n=119]	50 [n=124]	100 [n=126]	12.5 vs PL	25 vs PL	50 vs PL	100 vs PL	All DOLA®Mesyl vs PL
5/19 (26%)	7/23 (30%)	4/19 (21%)	8/23 (35%)	14/22 (64%)	4% [N.S.][b]	-5% [N.S.]	9% [N.S.]	38% [<0.05]	37/87 (38%)
II. CR in Females [n=514]									
8/102 (8%)	39/107 (36%)	29/100 (29%)	28/101 (28%)	23/104 (22%)	28% [<0.05]	21% [<0.05]	20% [<0.05]	14% [<0.05]	119/412 (29%)

a) Gender p=0.0301 from a 1 degree of freedom Chi-square test using a logistic regression model predicting complete response with dose, investigator and gender as explanatory variables.
- Gender by Dose Interaction p=0.0088 from a 4 degree of freedom Chi-square test using Pao scores from a logistic regression model predicting complete response with dose, investigator, and gender as explanatory variables.

b) N.S.=not significant at the 0.05 level after controlling for 4 comparisons to PL using Dunnett's t

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iv) Complete Response by Hour and Dose
(Time to Failure Analysis)

- CR rates at hours 2, 6, 12, 18 and 24 are presented for each dose group in Table 5 (upper panel). An analysis of time to first emetic episode or escape medication is also provided in this table.

- The CR rates at hour 2 were compared, and each DOLA•Mesyl dose group showed a significantly higher CR rate than PL ($p \leq 0.0007$).

- The differences from PL in the hazard ratios for each of the DOLA•Mesyl doses and for the combined DOLA•Mesyl dose were statistically significant ($p=0.0001$).

- The sponsor plotted Kaplan-Meier survival curves of the estimated probability of no emetic episodes or escape medication over the 24-h study period by dose. These curves are not presented in this review.

v) Complete Response by Dose in mg/Kg

Refer to lower panel of Table 5. The dose was converted to units of mg/Kg for each patient and tested directly on its effect on CR. The results of analysis on the basis of mg/Kg were similar to those for the primary efficacy analyses for CR: a statistically significant effect on CR ($p=0.0039$) was shown.

vi) Subgroup Analysis

For this analysis, the patient population was divided into various subgroups and the effects of the subgroups on CR was analyzed. Results of these analyses are not shown, but are briefly summarized below. The results for continuous subgroups such as age and weight were reported in two groups divided by the median. This is done for convenience, to demonstrate more clearly any effect of the subgroup. All of these analyses were conducted with models using the dose by gender interaction.

- Of all the subgroups examined, only time from last free fluids to study drug administration had a statistically significant interaction with dose ($p=0.0032$).

  - The CR rate for the 12.5 mg group was 29/60 (48%) in patients with last free fluids taken ≤14.4 h before test drug administration, while the CR rate was 17/70 (24%) in patients with last free fluids taken >14.4 h before study drug administration.

  - However, time from last free fluids to study drug administration was not a statistically significant predictor of CR.

  - The comparison of the CR rate for 12.5 mg to PL was statistically significant ($p=0.0003$), when controlling for time from last free fluids and its interaction with dose.

TABLE 5
Study MCPR0044

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

[ITT Population]

I. Complete Response by Hour and Dose (Time to Failure Analysis)

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

		DOLA•Mesyl Dose (mg)				
Hour	PL [n=121]	12.5 [n=130]	25 [n=119]	50 [n=124]	100 [n=126]	Total [n=499]
2	33 (27.3%)	72 (55.4%)	59 (49.6%)	60 (48.4%)	64 (50.8%)	255 (51.1%)
p-values[a] for PL Comparison (2 hours)		[<0.0001]	[0.0004]	[0.0007]	[0.0002]	[0.0001]
6	15 (12.4%)	50 (38.5%)	41 (34.5%)	43 (34.7%)	39 (31.0%)	173 (34.7%)
12	13 (10.7%)	49 (37.7%)	35 (29.4%)	39 (31.5%)	37 (29.4%)	160 (32.1%)
18	13 (10.7%)	49 (37.7%)	34 (28.6%)	38 (30.6%)	37 (29.4%)	158 (31.7%)
24	13 (10.7%)	46 (35.4%)	33 (27.7%)	36 (29.0%)	37 (29.4%)	152 (30.5%)
p-values[b] for PL Comparison (Hazard Ratios)		[0.0001]	[0.0001]	[0.0001]	[0.0001]	[0.0001]

II. Complete Responders by Dose (mg/Kg)

Number of Complete Responders by Dose Category (Percent)

	DOLA•Mesyl Dose (mg/Kg)[c]			
Placebo [n=121]	≤0.26 [n=138]	>026 to 0.52 [n=122]	>0.52 to 1.03 [n=123]	>1.03 [n=116]
13 (10.7%)	47 (34.1%)	36 (29.5%)	37 (30.1%)	32 (27.6%)

a) p-values are calculated from a weighted contrast of the parameter estimates for the dose by gender interaction obtained from a logistic regression model using pairwise comparisons of each dose to PL, controlling for intestigator and gender.
b) p-values are calculated from tests of the hazard ratios of each dose to PL, estimated from Cox's Proportional Hazards Model of time to first emetic episode or escape medication, controlling for investigator and gender.
c) Dose (mg/Kg) p=0.0039 from a one degree of freedom Chi-square test using a logistic regression model predicting complete response with dose entered directly, controlling for investigator and gender.

- The 12.5 mg patients had a significantly higher CR rate than PL in each of the subgroups examined [the therapeutic gain in CR between this DOLA•Mesyl dose and PL was significant for each subgroup ($p \leq 0.0051$)].

- Subgroups that were statistically significant predictors of CR and those that were not, are listed below.

Subgroups

Statistically Significant Predictors of CR

NO	YES
- Age - Weight - Race - APA Physical Status - Previous Hx of PONV - Type of Surgery	- Previous Hx of motion sickness ($p=0.0010$)[a] - Eligibility Criteria ($p=0.0171$)[b] - Duration of Anesthesia ($p=0.0385$)[c] - Time between cessation of anesthesia and test med. administration ($p=0.0002$)[d] - Time from last free fluids to test med. administration. ($p<0.05$)

a) Patients without a Hx of motion sickness were more likely to be CRs.
b) Patients who qualified for the study with only nausea were more likely to have CR.
c) Patients with a shorter duration of anesthesia were more likely to be CRs.
d) Patients with a longer time between cessation of anesthesia and test med. administration were more likely to have CR.

e. Safety Results

1) Extent of Exposure

In study -044, 620 patients received a single dose of test medication intravenouxly, with the following distribution:

	DOLA•Mesyl (mg)			
PL	12.5	25	50	100
[n=121]	[n=130]	[n=119]	[n=124]	[n=126]

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

- There were no deaths reported during this trial.

- No patients D/C from the trial due to AEs.

- None of the serious events was deemed to be related to test med. by the investigators.

- The events that were assessed by the investigators as not related to test med. were generally attributable to the operative procedure or PO pain relief. Included among such events were: pain, nausea, vomiting, urinary retention, drowsiness, hyperglycemia, hypertension, dizziness, breast discharge, respiratory depression and headache.

- Brief narratives of two notable events occurring in the trial are given below.

Patient 0272-0019, a 27-year old F

- She underwent outpatient laparoscopy for tubal sterilization, experienced chest pain that began 95 min. after administration of 12.5 mg DOLA•Mesyl and lasted for 25 minutes, resolving without sequelae.

- The investigator assessed the event as mild and as unlikely related to test medication but rather caused by insufflation into the chest cavity of carbon dioxide used to expand the abdominal cavity for the surgical procedure.

Patient 0260-0020, a 37-year old F

- She underwent outpatient orthopedic surgery and received 25 mg DOLA•Mesyl, had atrial fibrillation with unknown onset or duration.

- The investigator assessed the event as mild and probably related to the patient's history of mitral valve prolapse.

3) Overall Rate of AE Incidence (Table 6)

- There were no statistically significant differences between DOLA•Mesyl (any dose or all doses combined) for overall rate of AEs or events related to heart rate and rhythm, central and peripheral NS and cardiovascular system (see upper panel of Table 6).

- The most frequently occurring AEs (incidence ≥5%) were: T-wave change or abnormality, headache, sinus bradycardia, sinus arrhythmia and light-headed feeling. There was no linear trend across dose in the occurrence of any of these events using a logistic regression model with dose and gender as explanatory variables.

- The most frequent treatment-emergent EKG interval changes (Table 6, lower panel) were QT interval prolongation (QT_c ≥440) and EKG abnormal specific (QRS ≥100). For both of these changes, there was a statistically significant (p=0.0091 and 0.0067, respectively) for linear trend across dose in the occurrence of these events, using a logistic regression model with dose and gender as explanatory variables.

TABLE 6
Study MCPRO044

Frequency (%) of AEs, Tx-related AEs and Tx-Emergent EKG Changes

System Organ Class and Included Term p-value[a]	PL [n=121]	DOLA•Mesyl Dose (mg) 12.5 [n=130]	25 [n=119]	50 [n=124]	100 [n=126]	Total DOLA•Mesyl [n=499]
FREQUENCY (PERCENT) OF ALL ADVERSE EVENTS						
Overall Rate (p=N.S.)	54.5%	51.5%	43.7%	44.4%	48.4%	47.1%
Heart Rate & Rhythm (p=N.S.)	34.7%	28.5%	23.5%	25.0%	32.5%	27.5%
Centr & Periph Nervous System (p=N.S.)	11.6%	16.9%	15.1%	9.7%	13.5%	13.8%
Cardiovascular, General (p=N.S.)	0.8%	3.1%	1.7%	1.6%	0.8%	1.8%
MOST FREQUENT (≥5% INCIDENCE IN STUDY POPULATION) AEs						
T Wave Change or Abnormality (p=N.S.)	14 (11.6&)	13 (10.0%)	9 (7.6%)	15 (12.1%)	19 (15.1%)	56 (11.2%)
Headache (p=N.S.)	10 (8.3%)	11 (8.5%)	9 (7.6%)	10 (8.1%)	10 (7.9%)	40 (8.0%)
Sinus Bradycardia (p=N.S.)	15 (12.4%)	13 (10.0%)	7 (5.9%)	9 (7.3%)	10 (7.9%)	39 (7.8%)
Arrhythmia, Sinus (p=N.S.)	8 (6.6%)	6 (4.6%)	8 (6.7%)	2 (1.6%)	7 (5.6%)	23 (4.6%)
Light-Headed Peeling (p=N.S.)	1 (0.8%)	3 (2.3%)	6 (5.0%)	2 (1.6%)	3 (2.4%)	14 (2.8%)
MOST FREQUENT Tx-EMERGENT EKG INTERVAL CHANGES						
QT Interval Prolongation (QT_c≥440) (p=0.0091)	22 (18.2%)	23 (17.7%)	27 (22.7%)	24 (19.4%)	42 (33.3%)	116 (23.2%)
EKG Abnormal Specific (QRS≥100) (p=0.0067)	3 (2.5%)	10 (7.7%)	8 (6.7%)	9 (7.3%)	18 (14.3%)	45 (9.0%)

a) p-values are calculated from a test for linear trend across dose in the occurrence of that event using a logistic regression model with dose and gender as explanatory variables.

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4) Frequency (Percent) of All Treatment-Related Treatment-Emergent EKG Interval Changes (Table 7)

- As shown in the upper panel of Table 7, there was a statistically significant linear trend across dose in overall rate and heart rate and rhythm AEs as well as in individual categories such as QT interval prolongation and EKG abnormal specific. As seen in Table 7, particularly large were the differences between PL and the 100 mg dose.

5) Frequency of Treatment-Emergent EKG Interval Changes by Maximum Severity

As shown in the lower panel of Table 7, the majority of EKG interval changes was considered mild. No events were considered severe.

TABLE 7
Study MCPR0044

Treatment-Related Treatment-Emergent EKG Changes and
Treatment-Emergent EKG Interval Changes
by Maximum Severity

FREQUENCY (PERCENT) OF ALL TX-RELATED TX-EMERGENT EKG INTERVAL CHANGES						
System Organ Class and Included Term p value[a]	DOLA•Mesyl Dose (mg)					Total Dolasetron [n=499]
	PL [n=121]	12.5 [n=130]	25 [n=119]	50 [n=124]	100 [n=126]	
Overall Rate (p=0.0005)	22 (18.2)	31 (23.8)	30 (25.2)	28 (22.6)	53 (42.1)	109 (21.8)
HEART RATE 7 RHYTHM (p=0.0005)	22 (18.2)	31 (23.8)	30 (25.2)	28 (22.6)	53 (42.1)	109 (21.8)
QT INTERVAL PROLONGATION (QTc≥440) (p=0.0098)	20 (16.5)	22 (16.9)	25 (21.0)	22 (17.7)	40 (31.7)	109 (21.8)
EKG ABNORMAL SPECIFIC (QRS≥100) (p=0.0076)	3 (2.5)	9 (6.9)	7 (5.9)	9 (7.3)	17 (13.5)	42 (8.4)
AV BLOCK FIRST DEGREE (PR≥220)	1 (0.8)	0	0	0	1 (0.8)	1 (0.2)

FREQUENCY OF TX-EMERGENT EKG INTERVAL CHANGES BY MAXIMUM SEVERITY[b]							
Incidence >1% in Study Population							
Included Term	Severity						
EKG ABNORMAL SPECIFICATIONS (QRS≤100) (n=48)	MILD	3	10	8	9	18	
	MOD	0	0	0	0	0	
QT INTERVAL PROLONGATION (QTc≤440) (n=138)	MILD	21	23	26	23	39	
	MOD	1	0	1	1	3	

a) p-values are calculated from a test for linear trend across dose in the occurrence of that event using a logistic regression model with dose and gender as explanatory variables.
b) For patients experiencing the event more than once, the maximum severity over all occurrences is used.

6) Clinical Laboratory Evaluation

There were no clinically significant changes in any clinical laboratory measurement.

7) Vital Signs

There are no clinically significant changes in vital signs.

8) Changes in EKG Intervals

Because, by now, EKG changes induced by DOLA•Mesyl are well documented, only certain findings will be emphasized here. From the data in Table 8 and Fig. 3, an attempt is made to answer the following two important questions:

- Does the 12.5 mg dose, which is the sponsor's recommended dose for the treatment of PONV indication, induce EKG changes? (in comparison to PL?).
- What is the magnitude of the changes induced by the 100 mg dose (the dose recommended for the other indications in a tablet formulation).

The sponsor provided summary statistics for HR, PR, QRS, QT, QTc and JT interval measurements at baseline and 2 hours post-treatment and the change from baseline to post-treatment. From these tables, the reviewer has assembled Summary Table 8. From this Table, the following is noted:

TABLE 8
Study MCPR0044

Mean and Mean Changes at 2 Hours From Baseline in EKG Interval Measurements

		DOLA•Mesyl Dose (mg)				Linear Trend Across Dose (p-value)
	PL	12.5	25	50	100	
HR (bpm) Median	1	1	3	0	3	
HR (bpm) Mean	1.8	1.3	3.7	0.9	3	N.S.
PR (msec) Median	2	4	4	8	8	
PR (msec) Mean	3.5	3.3	5.5	7	10.7	<0.0001
QRS (msec) Median	0	0	2	4	4	
QRS (msec) Mean	0.2	1.8	2.4	3	4.6	<0.0001
QT (msec) Median	4	4	3	4	10	
QT (msec) Mean	5.9	8.9	5.1	7	12.7	N.S.
QT_c (msec) Median	10	10	16	7	23	
QT_c (msec) Mean	11.2	12	16.2	10.6	22.8	0.0031
JT (msec) Median	4	0	4	4	6	
JT (msec) Mean	5.7	7.1	2.7	4	8.1	N.S.

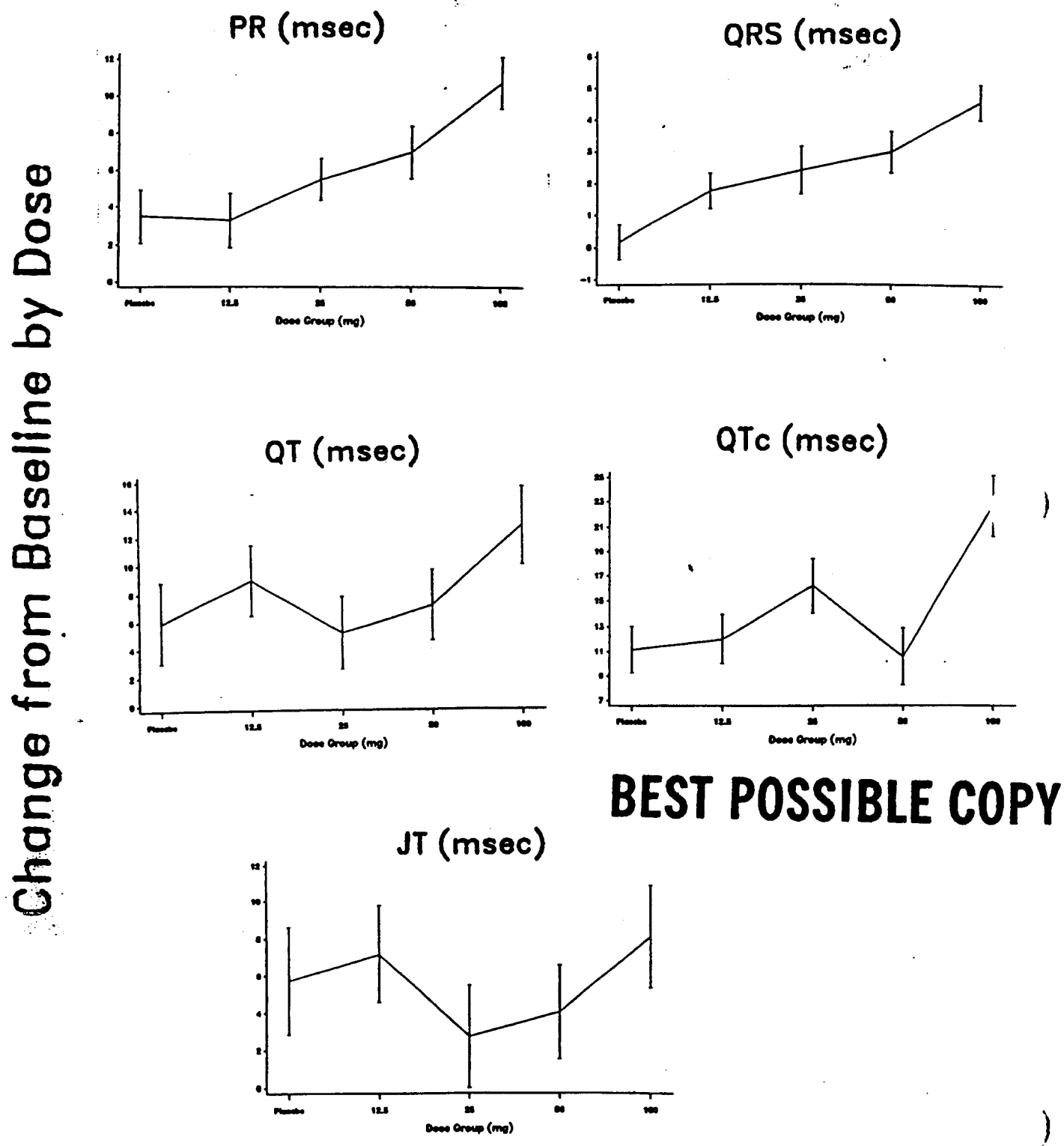

Fig. 3. - *Study MCPR044: Summary Graphic Presentation of Changes in EKG Parameters at 2h from Baseline as a Function of i.v. Administered Dose.*

- The mean values for PR interval ($p<0.0001$), QRS width ($p<0.0001$) and QTc interval ($p=0.0031$), each showed a statistically significant increasing linear trend across dose in change at 2 hours from baseline. These are not unexpected findings.

- Regarding magnitude of changes in EKG parameters, the 12.5 mg DOLA•Mesyl dose could not be differentiated from PL with regards to mean or median changes from BL in PR or QTc or median changes in QRS. But mean changes in QRS were higher with all dose levels of drug, including the 12.5 mg dose level ; than with PL (0.2 msec).

- With the 100 mg DOLA•Mesyl dose level, the mean value changes from BL for PR, QRS and QTc intervals were all higher (10.7, 4.6 and 22.8 msec, respectively) than those seen with PL (3.5, 0.2 and 11.2, respectively).

- Accordingly, the i.v. administered DOLA•Mesyl dose of 100 mg showed the following increase at 2h from baseline for the three EKG parameters of interest.

	Mean Increase (over PL) at 2h from Baseline DOLA•Mesyl 100 mg i.v. (msec)
PR	7.2
QRS	4.4
QT_c	11.6

10. Conclusions (Sponsor)

"All doses of dolasetron mesylate administered in this study were effective in the treatment of postoperative nausea and vomiting. Therefore, 12.5 mg dolasetron mesylate is as efficacious as larger doses of the drug in this patient population.

"No treatment-related, clinically important adverse events occurred. Dolasetron mesylate 12.5 mg, 25 mg, and 50 mg have a safety profile that is similar to placebo."

11. Reviewer's Comments

Study MCPR0044 (-044) is one of two main trials the sponsor of NDA 20-624 submitted in support of approval of the marketing of intravenously administered ANZEMET (DOLA•Mesyl) for the treatment of postoperative nausea and/or vomiting. According to the proposed text of the labeling the sponsors recommended intravenous dosage is 12.5 mg given as a single dose as soon as nausea or vomiting presents.

Study -044 was multicenter, double blind, randomized, parallel, dose-response, 5-arm in design, set to compare the efficacy and safety of single i.v. doses of DOLA•Mesyl (12.5, 25, 50 or 100 mg) with those of a negative control (PL) in the treatment of PONV. All in all, study -044 was well designed and well executed and was conducted in the U.S. at 31 centers with qualified investigators.

Enrolled in study -044 were 514 female and 106 male patients (total n=620), predominantly Caucasian, with mean age of 36y in the 100 mg group and 32 to 33y in the other dose groups (p=0.018; an imbalance that is not expected to influence outcome). Patients scheduled for outpatient surgery were randomized and stratified by gender within each study site to test med. after an emetic episode or moderate to severe nausea of at least 5 min. duration. The patients did not have overt evidence of respiratory, metabolic, hepatic or renal dysfunction. In this and all the other protocols reviewed in NDA 20-624, the following exclusions pertained to the cardiovascular system: complete BBB, either L or R, cardiomyopathy, CHF or Hx of CHF, arrhythmias, current requirement of antiarrhythmic medication, second or third degree heart block and abnormal pre-study serum potassium concentration which could not be corrected prior to surgery.

The methodology for randomization used in this trial resulted in five patient populations that were balanced with respect to variables that may influence outcome which - in addition to demographics - included ASA physical status, previous Hx of PONV, Hx of motion sickness, smoking status, type of surgery, duration of anesthesia, time between cessation of anesthesia and test med. administration, concomitant medications in general and concomitant medications that may be confounding. The five test groups were also well matched with regards to the standardization of the emetogenic stimulus (gynecological/ orthopedic surgery under general anesthesia).

Test medication was administered post-operatively as a single i.v. dose, in a 10 ml volume over a minimum of 30 seconds. The activity and duration of test medication was evaluated for 24h. Efficacy and safety measures were as per previous PONV and CCNV protocols. Complete Response (CR) is defined as the % of the patients within each dose group who did not experience an emetic episode nor receive antiemetic escape medication during the study period of 24h after administration of test medication.

Study -044 showed that DOLA•Mesyl is active since both the ITT and the Evaluable population analyses demonstrated a statistically significant linear trend in the proportion of complete responders across the five dose groups (p=0.0041 for ITT, n=620).

For CR, each of the four dose levels of DOLA•Mesyl was shown to be statistically different from PL (CR rate=11%), with clinically important

therapeutic gains of . Individually, the DOLA•Mesyl dose with the largest therapeutic gain over PL (25%) was 12.5 mg. Thus in this instance, the lowest dose tested appeared to be the most efficacious.

In this study population and under the experimental conditions and methodology used in study -044, graded intravenous doses of DOLA•Mesyl were - all in all - well tolerated. No deaths occurred in this trial. No significant cardiovascular events, complete BBB, high-degree AV block Torsades des pointes or other serious ventricular arrhythmias occurred. None of the serious AEs experienced by 27 patients were considered related to test medication. These events were attributable to the operative procedure or PO pain relief. No patient withdrew from the trial due to an AE.

The overall AE rates were 55% for PL and varied between among the DOLA•Mesyl groups. The most frequently occurring AEs (incidence ≥5%) were T-wave change or abnormality, headache, sinus bradycardia, sinus arrhythmia and light-headed feeling but there was no linear trend across dose in the occurrence of any of these events. For all Tx-related Tx-emergent EKG interval changes, there was a statistically significant linear trend across dose in the occurrence of the overall rate ($p=0.0005$), heart rate and rhythm ($p=0.0005$), QT interval prolongation ($QT_c \geq 440$; $p=0.0098$) and EKG abnormal specific (QRS ≥100, $p=0.0076$).

The changes from Pre-Tx to 2h Post-Tx in EKG parameters observed in study -044 are best illustrated in Fig. 3. Generally the higher doses (especially 100 mg sometimes the 50 mg dose as well) induced EKG changes that were larger than those induced by PL or the lower dose but the linear trend across dose yielded a statistically significant p-value for PR ($p<0.0001$), QRS ($p<0.0001$) and QT_c ($P<0.0001$). All in all, the changes in EKG intervals induced by 12.5 mg DOLA•Mesyl were similar to those observed with PL.

C. Study 73147-2-S-084
(Identified inthe present review as Study -2-S-084).

"A Double-Blind, Placebo-Controlled, Randomized, Multicenter Study to Compare the Effects of Single Dose of Intravenous Dolasetron Mesylate (MDL 73,147EF) 12.5, 25, 50 and 100 mg vs Placebo in Patients Experiencing Early Postoperative Nausea and Vomiting."

1. Objectives

a) to assess the efficacy of a range of single doses of intravenous DOLA•Mesyl at terminating nausea and vomiting in patients who have just undergone surgery under general anesthesia

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

2. Study Population

Inclusion-exclusion criteria were as per the studies of prevention of PONV indication with the tablet formulation (Studies -095 and -0292; reviewed on pages 213 through 288 of MOR of May 31, 1996). The study population consisted predominantly of female patients who had just undergone surgery under general anesthesia and who presented with early PONV. The eligibility and non-eligibility criteria were similar to those used in study -044. The study was designed to screen an estimated 800 patients; 250 completed the study. Regarding the cardiovascular system not included in the trial were patients with evidence of clinically significant cardiovascular disease and those being treated with antiarrhythmic agents.

3. Concomitant Medications

As in previous protocols, medications with potentially antiemetic properties were excluded from the trial. Specifically, administration of the following potential antiemetic treatments in the 24h before administration of DOLA•Mesyl or PL was proscribed: ondansetron, granisetron, metoclopramide, domperidone, thiethylperazine, promethazine, hydroxyzine, trimethobenzamide, prochlorperazine, tricyclic antidepressants, droperidol, diphenhydramine, corticosteroids, fluxetine, scopolamine, and ephedrine; administration of another research drug in the previous 21 days. Previous treatment with DOLA•Mesyl and intragastric tube placement postoperatively were additional reasons for exclusion from the trial.

4. Test Medication/Dosing Schedule

- DOLA•Mesyl 12.5 through 100 mg and PL were supplied as a sterile aqueous solution in 10 ml ampules which were identical in appearance. Lot information was as listed below.

Dose of Test Medication (mg/ml)	Lot Number
2.5	911110
5	911111
10	911112
20	911105, 911106
PL	911107, 911108

- The five experimental groups received a single intravenous dose of DOLA•Mesyl 12.5 mg, 25 mg, 50 mg, 100 mg or placebo. Each dose was diluted in a total of 50 ml with sterile saline injection and administered via an intravenous cannula over 5 minutes. The start of infusion of DOLA•Mesyl or PL marked the start of the study period (time 0).

5. Blinding, Packaging and Labeling

These aspects of the study were all adequate.

6. Study Evaluations/Procedures

These were done under randomized, double-blind, dose-response, PL-controlled, parallel group, multicenter conditions. Predominantly F patients with physical status 1 or 2 who met all the inclusion-exclusion criteria who had just undergone surgery under general anesthesia were entered into the trial.

- The study period (time 0) began at the start of administration of test medication and lasted 24 h after time 0, during which the patient remained in hospital.
- Follow-up evaluations were completed 24h after test drug administration.
- Vital signs were monitored immediately prior to administration of DOLA•Mesyl or PL and at 1, 5, 10 and 15 min., hourly during the first 4 h after dosing, and 6, 8 and 24 h postdose.
- Respiratory rate was monitored only during the first 2 h after dosing.
- The assessment of recovery score was monitored immediately prior to study drug administration and at 5, 10, 15 minutes, 1 and 2 h after dosing.
- The nausea VAS was completed prior to administration of DOLA•Mesyl or PL and every hour for 8h after dosing, if the patient was awake.
- Emetic episodes and AEs were monitored continuously throughout the study period.
- If the patient experienced any emetic episodes beyond the first 30 min. postdose or spontaneously requested rescue (escape) antiemetic medication(s) due to moderate to severe persistent (lasting ≥30 min) nausea after dosing, the investigator initiated standardized antiemetic medication according to institutional practice. The time, name, dose, route of administration and frequency of such escape medication were recorded in the patient's CRF.
- EFFICACY ASSESSMENT INCLUDED:

  1) Number of emetic episodes
  2) Severity of nausea by VAS and discrete scale
  3) Patient satisfaction VAS
  4) Investigator's global assessment of efficacy
  5) Time of rescue therapy

- SAFETY ASSESSMENT INCLUDED:

  1) Medical history and physical examination
  2) 12-lead EKG
  3) Vital signs
  4) AEs
  5) Clinical laboratory tests

7. Statistical Methods

- Sample Size Justification

Assuming the CR rate under PL is 50% and the logit of the rate increases linearly with the logarithm of dose to a CR rate of 80% at the highest dose of 100 mg, a sample size of 50 patients per group will give 93% power for detecting a linear trend with dose in CR rates at the 0.05 significance level.

- This was the assumption at the time the protocol was developed, and thus, 50 patients were planned for each dose group.

- However, if the CR rate under PL is 10% and that for DOLA•Mesyl is 30%, then with 50 PL and 250 DOLA•Mesyl patients, the power is 83% for detecting this difference at the 0.05 significance level.

- This study was not terminated early and there was no interim analyses.

- Primary Statistical Analysis

The primary analysis was an ITT analysis of CR (0 emetic episodes, no escape medication, and monitored for emesis at least 23.5 hours). As documented in the statistical analysis plan finalized prior to unblinding, patients not monitored for emesis at least 23.5 h were categorized as treatment failures (TxFs).

- Logistic regression with a test comparing PL to DOLA•Mesyl (i.e., total active), controlling for investigator, was the primary test for efficacy. This analysis was conducted using the ITT dataset.

- The presence of investigator by treatment interaction was tested using logistic regression and the Rao score residual Chi-square.

- A contrast among the estimated dose parameters was examined secondarily to compare each dose with PL.

- Additionally, a supplemental Mantel-Haenszel row mean scores test comparing PL to DOLA•Mesyl in complete response, controlling for investigator, was performed.

- As a further secondary analysis, the primary logistic regression analysis was conducted using only those patients who were deemed efficacy evaluable.

8. Data Documentation

The sponsor stated that data relevant to the protocol were recorded in the paper CRF provided by the sponsor. Data management was performed in accordance with standard operating procedures, including independent double-data entry, third party resolution of errors, and an independent quality check of the data. Data entry was performed using FOCUS (Information Builders), version 6.1 for VAX/VMS. Statistical analysis was carried out using SAS Version 6.08.

Prior to unblinding, disposition codes were assigned to each patient based on predefined criteria. The sponsor performed a 100% verification of the disposition codes against the database to ensure accuracy of the data entry. The study was unblinded on 20 May 1994.

Complete raw data listings were submitted by the sponsor in the CRF Tabulations, Report S-94-0062-C.

9. Results

a. Participating Investigators/Patient Accounting

Nineteen investigational sites enrolled a total of 337 patients (5 sites did not enroll any patients)[2]; of these, 319 were F; only 18 were M.

One patient (#084-676) discontinued from the study early. This patient withdrew from the trial 1.70 h after receiving 100 mg test medication due to lack of efficacy. After experiencing two emetic episodes, this patient received escape medication 4.87 h after the administration of test medication.

The following six centers enrolled 24 or more patients each.

[2] There was one patient whose CRF was found after the database was closed and the data from that CRF was not entered into the database. This patient was randomized to DOLA•Mesyl 25 mg and had no AEs and no emetic episodes following test medication administration.

Center No.	Investigator	Total # of Patients Enrolled
2	Dr. J. Lerser [Amsterdam, NL]	66
10	Dr. P. Wessel [Nantes, FR]	51
13	Dr. C. Payeur-Michael [Mulhouse, FR]	45
6	Prof. P. Feiss [Limoges, FR]	41
9	Prof. J.P. Dupeyron, Dr. Diemunsch [Strasbourg, FR]	34
20	Dr. B.G. Bradbum [Canterbury, U.K.]	24

b. Major Protocol Violations

A total of six patients (2%) had major protocol violations and were subsequently excluded from the efficacy evaluable dataset. In their Table 5 (page 7 of Clinical Report) the sponsor gave the number of patients with major protocol violations by dose group. All patient disposition codes were presented in Listing 1 on page 305 of the Clinical Report. The number of patients analyzed by group were:

Population for Analysis	PL	DOLA®Mesyl (mg)			
		12.5	25	50	100
ITT	71	66	65	67	68
Evaluable	70 (99%)	65 (99%)	65 (100%)	65 (99%)	66 (97%)

c. Data Showing Comparability of Groups at Baseline

The study population was predominantly female (95%) and ASA Status (average = 87.5%) with a mean age of 40.3 years, a mean weight of 64.2 Kg. There were no statistically significant imbalances among the five dose groups with respect to any of the demographic and baseline cnaracteristics. On the average, 45.8% of the patients had a history of PONV, 62.3% underwent gynecological surgery and 37.7% underwent other type of surgery, the mean time to first emetic episode after the start of anesthesia was 2.6 h, the duration of anesthesia 1.7 h and the mean time between cessation of anesthesia and test drug administration was 1.1 h. The five groups were similar to each other in all of these characteristics.

There were no marked imbalances among the 5 dose groups in medical history and pre-Tx P.E. On the average, 17% of the study population had a history of abnormalities in the cardiovascular system.

The frequency of concomitant medications taken pre-Tx was similar among the five groups. During this period, the most frequently taken medications were heparin (taken by an average of 21% of the patients, propacetamol (21%), morphine (19%), diazepam (17%), amoxicillin (16%), lorazepam (15%) and clavulanic acid (15%).

The frequency of concomitant medications taken post-Tx was also similar among the five groups. During this period the most frequently taken medications were heparin (taken by an average of 49% of the patients), propacetamol (42%), morphine (33%) and paracetamol (14%).

There were no statistically significant differences among the dose groups in anesthetic procedures, including pre-medication, induction or maintenance and reversal.

The five groups were also comparable to each other with regard to eligibility criteria. This is documented below.

Eligibility Criteria [No./(%) patients]

	PL [n=71]	DOLA•Mesyl Dose (mg)				All Patients [n=337]	p-value
		12.5 [n=66]	25 [n=65]	50 [n=67]	100 [n=68]		
NAUSEA (Only)	10 (14.1%)	10 (15.2%)	17 (26.2%)	8 (11.9%)	9 (13.2%)	54 (16%)	N.S.
VOMITING (Only)	17 (23.9%)	22 (33.3%)	16 (24.6%)	24 (35.3%)	24 (35.3%)	103 (30.6%)	
N&V	44 (62%)	34 (51.5%)	32 (49.2%)	35 (52.2%)	35 (51.5%)	180 (53.4%)	

APPEARS THIS WAY
ON ORIGINAL

ESCAPE MEDICATION

The most frequently used (received in >2% of the study population) escape medication is summarized below.

APPEARS THIS WAY
ON ORIGINAL

	PL [n=71]	DOLA•Mesyl (mg) 12.5 [n=66]	25 [n=65]	50 [n=67]	100 [n=68]	Total [n=357]
ALIZAPRIDE	7 (10%)	3 (5%)	2 (3%)	0	2 (3%)	14 (4%)
MCP[a] (p=0.070)[b]	23 (37%)	18 (27%)	14 (22%)	11 (16%)	15 (22%)	84 (25%)
PCPZ[c] (p=0.107)	12 (17%)	10 (15%)	9 (14%)	3 (4%)	5 (7%)	39 (12%)

a) = Metoclopramide
b) p-values were calculated using a 4 degree of freedom Chi-square test.
c) = Prochlorperazine

d. Clinical Response

i) Overall Complete Response (Table 9)

- In the ITT analysis (Table 9, upper panel), for complete response, the therapeutic gains for all DOLA•Mesyl test groups over PL varied between

Comparison of the results with the 12.5 mg dose vs PL gave inconsistent results. These depended on whether one used the calculations presented by the sponsor, or those carried by Dr. M.C. Fan, the FDA Biometrician. According to the sponsor, the 12.5 mg DOLA•Mesyl dose (CR=24%) was superior to PL, with a therapeutic gain of 13% and a p-value of 0.0428. The latter was calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with the dose and investigator as explanatory variables. However, the p-value of this comparison (therapeutic gain = 13%) as calculated by Dr. M.C. Fan (FDA Biometrician) using the Fisher's exact test was 0.071 (N.S.)

Each and all the other DOLA•Mesyl dose levels were superior to PL (p=0.026 or less). The therapeutic gains of the 25, 50 and 100 mg DOLA•Mesyl dose levels over PL were 17%, 26% and 14%, respectively (all statistically significantly different from PL).

The p-value for the test for linear trend was p=0.0114. That for the primary test, PL vs DOLA•Mesyl was highly significant (p=0.0030).

TABLE 9
Study 73147-2-S-084

Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response

Response by Dose (mg)					Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses and PL/[p-values][a]				
I. Intent-To-Treat Analysis [n=337][b]									
PL [n=71]	12.5 [n=66]	25 [n=65]	50 [n=67]	100 [n=68]	12.5 vs PL	25 vs PL	50 vs PL	100 vs OL	All DOLA•Mesyl vs PL
8 (11%)	16 (24%)	18 (28%)	25 (37%)	17 (25%)	13% [N.S.]	17% [0.017]	26% [<0.001]	14% [0.026]	18% [<0.001]
II. Efficacy Evaluable Analysis [n=331][c]									
[n=70]	[n=65]	[n=65]	[n=65]	[n=66]					
8 (11%)	15 (23%)	18 (28%)	23 (35%)	17 (26%)	12% [N.S.]	17% [0.028]	24% [0.001]	15% [0.045]	17% [<0.001]

a) p-values obtained by Fisher's exact test (calculated by Dr. M.C. Fan)
b) Primary Test, PL vs DOLA•Mesyl, p=0.0030 (ITT, n=337)
   - Mantel-Hanszel Test of PL vs DOLA•Mesyl, p=0.0002 (ITT, n=337)
   - Test for Linear Trend, p=0.0114 (ITT, n=337)
c) Efficacy Evaluable, p=0.0049 (n=331)

- In the Efficacy Evaluable analysis (Table 9, lower panel) the therapeutic gains for each of the DOLA•Mesyl over PL were similar to those discussed above for the ITT analysis. In other words, statistical analysis in the Efficacy Evaluable population confirmed those in the ITT population.

ii) CR Rates by Investigator
(Data not shown)

These data were summarized in sponsor's Table 17 (p.84 of Clinical Report). There was a significant difference between investigators in the proportion of complete responses (p=0.0131). CR rates varied from between investigators. There was no investigator by dose interaction (p=0.2776). When sample size was taken into consideration, dose trends were consistent over investigators.

iii) Secondary Analyses of the Primary Endpoint
(Data not shown)

These data were summarized in sponsor's Table 15 (p.82 of Clinical Report). According to the sponsor, the Mantel-Haenszel row mean scores test comparing PL against all DOLA•Mesyl dose groups, controlling for investigator, provided similar results to that of the logic regression (p=0.002). A logistic regression analysis of the efficacy evaluable population resulted in a significant difference between PL and all DOLA•Mesyl dose groups (p=0.0049) (sponsor's calculations).

iv) CR by Hour and Dose

The proportion of complete responders within each dose group over time is depicted in the upper level of Table 10.

- At all time points after administration of test medication, the proportion of complete responders in the PL group was smaller than that in each of the DOLA•Mesyl groups.

- The hazard ratio, estimated from Cox's proportional hazards model of time to first emetic episode or escape medication, was significant (p=0.0056) when the PL group was compared to all DOLA•Mesyl groups.

- When compared individually to PL, the 12.5 mg, 25 mg and 50 mg groups were all significantly different ($p \leq 0.05$); however, there were no significant differences among DOLA•Mesyl groups.[3]

[3] In addition, the sponsor presented Fig. 2 (p.158 of Clinical Report), depicting the Kaplan Meier survival curves of the estimated probability of no emetic episodes or escape medication during the 24 h postdosing for PL vs all DOLA•Mesyl groups, while their Fig. 3 on p.160 of Clinical Report depicted Kaplan Meier survival curves for each dose. From these figures, the probability of experiencing a CR was determined within the first 12 h (i.e., virtually all patients that failed did so within that time period).

TABLE 10
Study 73147-2-S-084

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

I. Complete Response by Hour and Dose

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

Hour	PL [n=71]	DOLA•Mesyl Dose (mg)[a]				Total [n=266]
		12.5 [n=66]	25 [n=65]	50 [n=67]	100 [n=68]	
1	27 (38.0%)	43 (65.2%)	31 (47.7%)	38 (56.7%)	31 (45.6%)	143 (53.8%)
2	22 (31.0%)	42 (63.6%)	30 (46.2%)	33 (49.3%)	29 (42.6%)	134 (50.4%)
4	15 (21.1%)	35 (53.0%)	23 (35.4%)	32 (47.8%)	23 (33.8%)	113 (42.5%)
6	11 (15.5%)	27 (40.9%)	20 (30.8%)	28 (41.8%)	19 (27.9%)	94 (35.3%)
12	8 (11.3%)	21 (31.8%)	18 (27.7%)	26 (38.8%)	17 (25.0%)	82 (30.8%)
24	8 (11.3%)	16 (24.2%)	18 (27.7%)	25 (37.3%)	17 (25.0%)	76 (28.6%)
p-values[b] for Comparison to PL (Hazard Ratio)		0.0254	0.0450	0.0061	0.1754	

II. Complete Response by Dose (mg/Kg)

Number of Complete Responders by Dose Category (Percent)

PL [n=71]	DOLA•Mesyl Dose (mg/Kg)[c]			
	<.3 [n=71]	.3 to <.6 [n=65]	.6 to <1.2 [n=65]	≥1.2 [n=64]
8 (11.3%)	17 (23.9%)	18 (27.7%)	26 (40%)	15 (23.4%)

a) PL vs DOLA•Mesyl p=0.0056.
b) All p-values calculated from the hazard ratios estimated from Cox's Proportional Hazards Model of time to first emetic episode or escape medication, controlling for investigator.
c) Dose (mg/Kg) p=0.1833 from one degree of freedom Chi-square test using a logistic regression model predicting CR with dose entered directly, controlling for investigator.

v) Analysis of CR by Dose in mg/Kg

Refer to the lower panel of Table 10, which summarizes the proportion of complete responders in the PL group and four dose range groups for DOLA•Mesyl. The dose ranges were established based on a 65 Kg patient. When the proportion of patients experiencing complete responses was analyzed on the basis of dose per unit body weight, no clear trends were evident.[4]

vi) Subgroup Analysis

The sponsor presented these data in their Table 25, p.117-118 of the clinical report. As summarized below, age, time between cessation of anesthesia and test drug administration, duration of anesthesia, total morphine dose, total fentanyl dose and eligibility criteria were all significant predictors of CR.

- There was no interaction between any of the predictors of CR and the main test medication effect. Controlling for each of the subgroups predictors of CR along with dose and investigator, the PL-test medication effect remained significant in all instances.

- It is worth noting that although there was no interaction of eligibility status with the main test drug effect, PL patients experienced a greater incidence of CR (40%) than did DOLA•Mesyl patients when entering the trial with nausea alone. In adjusting for all significant predictors of complete response, eligibility status was not included due to its potential confounding effects on other predictors. The sponsor also noted that because duration of anesthesia and fentanyl dose were so highly correlated, only duration of anesthesia was included in the regression model. Therefore when controlling for patient age, time between cessation of anesthesia and study drug administration, duration of anesthesia, total morphine dose, and investigator, the main (study drug) effect remained significant.

[4] In addition, sponsor's Figure 4 (page 162 of Clinical Report) illustrated in scatter-plot form the relationship of complete responders and nonresponders to dose and body weight. From this figure, at each dose level, the body weights of complete responders overlap those of nonresponders; thus, the response to DOLA•Mesyl does not appear to be weight-related.

Subgroups

Statistically Significant Predictors of CR

NO	YES
- Weight	- Age (p=0.0209)[a]
- Previous Hx of PONV	- Time between cessation of anesthesia and test drug administration (p=0.0026)[b]
- Type of Surgery	- Duration of anesthesia (p=0.0026)[c]
- ASA Physical Status	- Total morphine dose (p=0.0183)[d]
- Gender	- Total fentanyl dose (p=0.0001)[e]
	- Eligibility Criteria (p=0.0326)[f]

a) The percentage of patients over 40 y of age experiencing a complete response was consistently lower than in patients 40 y of age and under. Thirty-eight of 170 patients (22.4%) over 40 y of age were complete responders, whereas 46 of 167 patients (27.5%) age 40 or less were complete responders.

b) Thirty-five of 181 (19.3%) patients receiving study drug within one hour of cessation of anesthesia were complete responders, while 49 of 156 patients (31.4%) receiving study drug more than 1 h after cessation of anesthesia were complete responders.

c) Patients which endured longer periods of anesthesia were less likely to be complete responders. Of patients undergoing anesthesia for 1 h or less, 35.2% (25/71) were complete responders, while 22.2% (59/266) of patients under anesthesia for longer than an hour experienced a CR.

d) Those receiving larger doses were less likely to experience a CR as compared to those receiving less or no morphine. Of those receiving more than 10 mg of morphine, 17.5% (11/63) were complete responders, while 26.6% (73/274) of those receiving up to 10 mg of morphine experienced a CR.

e) Those receiving larger doses being less likely to experience a CR as compared to those receiving smaller doses. Of those receiving more than 250 μg of fentanyl, 17.2% (28/163) were complete responders, while 32.2% (56/174) of those receiving up to 250 μg of fentanyl experienced a CR.

f) Patients who experienced nausea alone were more likely to experience a CR as compared to those enterine the study with vomiting or a combination of nausea and vomiting. Of those experiencing nausea alone, 25.2% (19/54) experienced a CR, while 29 of 103 (28.2%) experiencing vomiting alone had complete responses; 36 of 180 (20.0%) of those experiencing both nausea and vomiting experienced a CR.