e. Safety Results

1) Extent of Exposure

In study 73147-2-S-084, 337 patients received single i.v. doses of test medication with the following distribution:

	DOLA•Mesyl (mg)				Total
PL	12.5	25	50	100	DOLA•Mesyl
[n=71]	[n=66]	[n=65]	[n=67]	[n=68]	[n=266]

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

- No deaths were associated with this trial.
- No patients dropped from the trial due to an AE.
- Pt. 084-143 a 23-y old in the 12.5 mg DOLA•Mesyl group was undergoing chromolaparoscopy plus laser surgery. The patient required prolonged hospitalization due to severe pneumoperitonitis. This was not related to test drug administration but rather to the surgical procedure.

3) Overall Rate of AE Incidence, Most Frequently Reported AEs, Incidence by System Organ Class and Treatment-related AEs (Table 11)

- The overall rate of AEs was higher with the 50 (=30%) and 100 mg (=29%) DOLA•Mesyl dose levels than with either PL (=18%) or the lower doses of drug (12.5 mg =18%; 25 mg=15%). Note the statistically significant dose-related incidence of AEs [p=0.0384; Table 11].
- With regards to individual AEs, the most frequently reported were: headache, injection site pain, EKG abnormal nonspecific, hypertension and hypotension (Table 11).
- Regarding system organ class, the most frequent AEs noted were related to the central and peripheral nervous system (Table 11) but there was no statistically significant dose-related trend for the incidence of AEs in this organ system.

TABLE 11
Study 73147-2-S-084

Frequency of AEs, Most Frequently Reported AEs and Treatment-related AEs

System Organ Class and Included Term	PL [n=71]	DOLA•Mesyl Dose (mg)				MDL 73,147EF [n=266]
		12.5 [n=66]	25 [n=65]	50 [n=67]	100 [n=68]	
I. Overall Rate						
Overall Rate (p=0.0384)	18.3%	18.2%	15.4%	29.9%	29.4%	23.3%
II. Most Frequently Reported AEs						
Headache (p=N.S.)	5.6%	10.6%	6.2%	10.4%	14.7%	10.5%
Injection Site Pain	1.4%	0	1.5%	4.5%	1.5%	1.9%
EKG Abnormal - Nonspecific	0	1.5%	0	3%	1.5%	1.5%
Hypertension	1.4%	1.5%	0	3%	0	1.1%
Hypotension	0	9	0	1.5%	2.9%	1.1%
QT Interval Prolongation	0	0	1.5%	1.5%	0	0.8%
III. AEs by System Organ Class						
Central & Periph. Nervous System (p=N.S.)	8.5%	10.6%	10.8%	10.4%	16.2%	12%
Cardiovascular, General (p=N.S.)	1.4%	3%	1.5%	9%	4.4%	4.5%
Application Site	1.4%	0	1.5%	4.5%	1.5%	1.9%
G.I. System	0	3%	0	3%	0	1.5%
Resistance Mechanism	0	1.5%	0	3%	1.5%	1.5%
IV. Treatment Related AEs of Interest						
Overall Rate (p=N.S.)	15.5%	15.2%	15.4%	23.9%	23.5%	19.5%
Headache (p=N.S.)	4.2%	10.6%	4.6%	9%	13.2%	9.4%
EKG Abnormal						
- Nonspecific	0	1.5%	0	1.5%	1.5%	1.1%
- Hypotension	0	0	0	1.5%	2.9%	1.1%
- Hypertension	0	1.5%	0	1.5%	0	0.8%
- QT Interval Prolongation	0	0	1.5%	1.5%	0	0.8%

- For treatment-related AEs, there was no statistically significant dose-related trend for their overall incidence.

- Of the 32 patients reporting a headache, 28 were considered by the investigator to be treatment-related.

- The incidence of treatment-related headache was 2 to 3 times higher with the higher doses of drug 50 and 100 mg (9% and 13.2%) than with PL (4.2%).

- The frequency of headache by Maximum Severity and Dose was:

	Maximum Severity[a]	PL [n=71]	DOLA•Mesyl Dose (mg)			
			12.5 [n=66]	25 [n=65]	50 [n=67]	100 [n=68]
HEADACHE [n=32]	No Information	0	0	0	0	0
	Mild	1	3	2	6	4
	Moderate	2	3	1	1	6
	Severe	1	1	1	0	0

a) For patients experiencing the event more than once, the maximum severity over all occurrences is used.

4) AEs of Potential Concern

- Laryngeal edema was reported in one patient in the 100 mg dose group. This event occurred at the time of dosing, was considered to be moderate in intensity, and was assessed by the investigator to be the result of an "unknown" cause.

- 1 patient in the 50 mg dose group and 2 patients in the 100 mg dose group experienced hypotension.

  - Hypertension was reported in 1 patient each from the PL and 12.5 mg dose groups, as well as two patients in the 50 mg dose group.

- 1 patient from the 50 mg dose group experienced an anaphylactoid reaction which was moderate in intensity and was assessed to be possibly related to administration of study drug.

5) Clinical Laboratory Evaluations

Five clinical chemistry parameters exhibited a significant linear relationship to dose of test drug. The following five parameters exhibited a statistically significant negative (as dose increased, the magnitude of decline in the parameter increased): SGPT (p=0.0053), lymphocytes (p=0.0098), hematocrit (p=0.0161) AND rbc COUNT (P=0.0341). Neutrophils counts exhibited a

statistically significant positive linear relationship to dose with regard to change from baseline (as dose increased, the magnitude of increase in neutrophil counts increased) (p=0.0032). All in all, these changes, although statistically significant did not seem clinically significant since clinidal AEs related to hematology were not recorded.

Two patients experienced abnormal hepatic function as an AE. One of these (Pt. No. MCST084394) was given PL. The other (Pt. No. MCST084-676) entered the study with OT and PT values of 18 and 16 U/L, respectively. The upper limit of normal for this patient was 34 and 33 U/L, respectively. The patient received DOLA•Mesyl at the i.v. dose of 100 mg. Posttreatment values for this patient increased to 65 U/L OT and 74 U/L PT. The investigator made no assessment of severity or causality for these enzyme elevations.

6) Vital Signs

In this study, administration of DOLA•Mesyl resulted in an acute, reversible, dose related decrease in recumbent pulse rate. This change resolved within 24h. Patients also experienced acute, reversible, dose-related depression in recumbent systolic and diastolic blooc pressure. Statistical computations are summarized in Table 12; 3 patients were considered to be clinically hypotensive and none was W/D from the trial due to hypotension. Hypertension was recorded as an AE for 3 patients receiving DOLA•Mesyl but none of these events was rated as serious or definitely related to test drug administration.

7) Changes in EKG Parameters

In study 73147-2-S-084, the data on changes in EKG parameters were of little value because a 12-lead EKG was recorded and evaluated prior to entrance into the trial and 24h post-dose. EKG 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. No wonder that, contrary to findings reported in study -044, changes in these EKG parameters were similar across all dose groups. Nonetheless, among all patients receiving DOLA•Mesyl 5 experienced increases in QRS interval to ≥100 msec and 20 experienced increases in QT_c interval to ≥440 msec.

TABLE 12

Summary of Vital Sign Changes

I. p-values[a] for Statistically Significant Linear Trend With Dose in Change From Baseline (Recumbent)

Time of Evaluation		Pulse Rate	Systolic BP	Diastolic BP
Minuite	1	0.0127	0.0238	0.0060
	5	N.S.	0.0044	0.0035
	10	N.S.	0.0002	0.0006
	15	N.S.	0.0001	0.0005
Hour	1	N.S.	0.0021	0.0019
	2	N.S.	0.0090	0.0826
	3	N.S.	N.S.	N.S.
	4 → 24	N.S.	N.S.	N.S.

II. % of Treatment-Emergent Vital Signs (Recumbent)

		Treatment Emergent Signs			
		BP (mmHg)		Pulse Rate (bpm)	
Dose (mg)	n	Pre SBP≤165 and DBP≤90, Post SBP>165 or DBP>90	Pre SBP≥100 and DBP≥50, Post SBP<100 or DBP<50	Pre≤100 and Post >100	Pre≥60 and Post <60
PL	71	10%	25%	13%	17%
12.5	66	17%	27%	12%	15%
25.	65	15%	26%	8%	12%
50	67	10%	34%	6%	16%
100	68	12%	29%	7%	15%

a) All p-values originate from a two-way rank AOV with a test for linear trend with dose in change from baseline, controlling for investigator.

10. Conclusions (Sponsor)

"Single intravenous doses of dolasetron mesylate were effective in decreasing or preventing nausea and/or emetic episodes resulting from general anesthesia. The effects of dolasetron mesylate on relief from nausea and vomiting appeared to be dose-related, with a maximal response seen in the 50 mg dose group.

"The antiemetic properties of dolasetron mesylate may be reduced by concomitant use of narcotic analgesics, extended periods of anesthesia, older age, and pretreatment emetic episodes.

"Dolasetron mesylate, at the doses tested in this study, was well-tolerated in the tested patient population."

11. Reviewer's Comments

Study 73147-2-S-084 (-2-S-084) is the second of the two 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 treatment of postoperative nausea and/or vomiting.

Study -2-S-084, carried out at 23 centers in Europe, was very similar in design and execution to study -044. Enrolled in study -2-S-084 were 319F and 18M patients (total n=337) with a mean age of 40y, ASA physical status (mean=88%), and mean weight 64 Kg. The patients were essentially normal and exclusions pertaining to the cardiovascular system were as in study -044. The methodology for randomization used in study -2-S-084 resulted in five patient populations that were well balanced with respect to variables that may influence either efficacy or safety results. Each of the dose levels of i.v. DOLA•Mesyl (12.5, 25, 50 or 100 mg) or PL was diluted in a total of 50 ml with a sterile saline injection and administered via intravenous cannula over 5 min.

Study -2-S-084 showed that DOLA•Mesyl is active because 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=0.0114, ITT, n=337).

The CR rate with PL was 11% (both study populations). With a therapeutic gain of 13% in the ITT and 12% in the Evaluable population analyses, respectively, the 12.5 mg DOLA•Mesyl dose could not be differentiated from PL. Each of the three additional dose levels of DOLA•Mesyl (CR rate in the ITT and in the Evaluable Population analyses) was shown to be superior to PL, with clinically important therapeutic gains of in the ITT and in the Evaluable population analyses. Individually, the DOLA•Mesyl dose with the largest therapeutic gain over PL (26% in the ITT and 24% in the Evaluable population analysis) was 50 mg. Thus study -2-S-084 did not replicate the efficacy findings in study -044 because the latter showed that the DOLA•Mesyl dose with the largest therapeutic gain over PL was 12.5 mg (the dose proposed by the sponsor). These findings represent significant constraints when choosing the recommended dose for the Treatment of PONV indication; but this dose is not 12.5 mg, as recommended by the sponsor.

In this study population and under the experimental conditions and methodology used in study -2-S-084, graded intravenous doses of DOLA•Mesyl were - all in all - well tolerated. No deaths were associated with this study. No significant cardiovascular events (complete BBB, high-degree AV block, *Torsades de pointes*, nor other serious ventricular arrhythmias) occurred. No patients dropped from the trial due to an AE.

The overall AE rates were higher with the 50 (=30%) and 100 mg (=29%) DOLA•Mesyl dose levels than with either PL (=18%) or the lower doses (12.5 mg=18%, 25 mg=15%) (p=0.0384). The most frequently occurring AEs were headache, injection site pain, EKG abnormal nonspecific hypertension and hypertension but there was no linear trend across dose in the occurrence of any of these events. Of the 32 patients reporting a headache, 28 were considered by the investigator to be treatment-related. The incidence of treatment-related headache was 2 to 3 times higher with the higher doses of DOLA•Mesyl 50 and 100 mg (9% and 13%) than with PL (4%). Most headaches were mild to moderate in intensity.

The data on EKG interval changes gathered in study -2-S-084 were of little value because the post-Tx evaluations were done at 24h after test drug administration and not at 1½ to 2h when the C_{max} for the DOLA•Mesyl metabolite correlates with PR, QRS and QT_C prolongations. Nevertheless, among all patients receiving DOLA•Mesyl, five experienced increases in QRS interval to ≥100 msec and 20 experienced increases in QT_C interval to ≥440 msec.

III. INDICATION PREVENTION OF PONV

A. Adequacy of Submitted Trials

In support of the prevention of PONV indication, the sponsor submitted results of three adequate and well-controlled studies identified as -045 and -084 (both conducted in the U.S.) and -080 (carried out in Europe). As noted in Table 13, the three studies were randomized, double-blind, multicenter, comparisons of graded doses of DOLA•Mesyl to PL. The study population (predominantly female in the first trial and exclusively female in the other two) consisted of patients scheduled to undergo outpatient surgery under general anesthesia. On account of the number of patients studied, the main studies were the two domestic trials -045 (n=1010) and -084 (n=635), which also allowed dose-response comparisons. In one of these trials, patients were stratified on the basis of gender; in the other, patients were stratified on the basis of whether they had a history of previous PONV. Both stratifications are important because female patients are mor susceptible to emetic symptoms following surgery and previous Hx of PONV is thought to predispose patients to PONV. With significantly less patients studied per group, the European trial (-080, total n=281) may be considered supportive. This study was apparently designed to detect a linear trend in CR with dose but it was not sized to demonstrate differences among the DOLA•Mesyl doses. Of interest, however, stratification of patients on the basis of whether they were undergoing laparoscopic procedures or not allows exploration of the possibility of analysis of response on the basis of this factor (type of surgery). As stated above, for these prevention of PONV trials, the main focus of the MOR is on safety.

TABLE 13
nda 20-624

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

Study Identification	Study Population	Main Design/Execution	Groups Being Compared	Remarks
MCPRO- (-045) (U.S.) [n=1030] F=722 M=308 17 sites	F or M patients scheduled for out-patient surgery under general anesthesia. The type of surgery was primarily gynecologic for females and orthopedic for males. Patients were stratified by gender within each study site. Fewer patients in the PL dose group for both M and F patients had a history of PONV when compared to the DOLA• Mesyl dose groups.	• Randomized, double-blind, parallel group, stratified by gender at each study site, placebo-controlled, dose-response, 5-arm study. • Definitions of emetic episodes and evaluation period (24h observations after test med.) were as in previous protocols. • Test med. was adm. as a 30-sec to 5-min infusion shortly before cessation of (near the end of) anesthesia.	DOLA•Mesyl at single i.v. doses of (mg): 12.5 [n=206] 25 [n=203] 50 [n=206] 100 [n=208] vs PL [n=208]	• Useful design • The study's main objective was to detect a difference between the dose of DOLA•Mesyl with the highest complete response (CR) rate and PL, while controlling for multiple comparisons. • Effectiveness is shown by demo-strating superiority of the identified DOLA•Mesyl dose over PL. • The design allows dose-response comparisons of efficacy. • Stratification of patients on the basis of gender is of interest because this approach allows an independent analysis of efficacy results by gender (females are more susceptible to emetic symptoms following surgery).

TABLE 13 (Con't.)

MCPR0- (-084) (U.S.) [n=635] F=635 M=0 25 sites	F patients scheduled to undergo outpatient laparoscopic gynecologic surgery under general anesthesia. Pts. were stratified by previous history of PONV within each study site.	• Randomized, double-blind, parallel group, stratified by previous Hx of PONV, placebo-controlled, dose-response, 4-arm study. • Definitions of emetic episodes and evaluation period (24h observations after test med.) were as in previous protocols. • Test med. was administered 30-sec to 5-min near the end of anesthesia (ca. 15 min. before the cessation of nitrous oxide.	DOLA•Mesyl at single i.v. doses of (mg): 12.5 [n=159] 25 [n=157] 50 [n=162] vs PL [n=157]	• Useful design but not strictly replicative of the main trial (-045). • The study's main objective was to detect a difference between the dose of DOLA•Mesyl with the highest CR rate and PL while controlling for multiple comparisons. • Effectiveness is shown by demonstrating superiority of the identified DOLA•Mesyl dose over PL. • The design allows dose-response comparisons of efficacy. • Stratification of patients on the basis of whether they had a previous Hx of PONV is of interest to compare effectiveness in both patients since previous Hx of PONV is thought to predispose patients to PONV.
73147-2-S- (-080) (Europe) [n=281] F=281 M=0 11 sites	F patients scheduled to undergo gynecologic surgery (laparoscopic and non-laparoscopid procedures) under general anesthesia, stratified by the type of surgery (laparoscopic vs non-laparoscopic procedures)	• Randomized, double-blind, parallel group, stratified by type of surgery (laparoscopic vs non-laparoscopic procedures), placebo-controlled, 5-arm study. • Definitions of emetic episodes and evaluation period (24h observations after test med. were as in previous protocols. • Test med. consisted of a 5-min. infusion at the cessation of nitrous oxide.	DOLA•Mesyl at single i.v. doses of (mg): 12.5 [n=54] 25 [n=60] 50 [n=54] 100 [n=59] vs PL [n=54]	• Useful design but not strictly replicative of the main trial (-045). • The study's main objective was to assess the efficacy of a range of DOLA•Mesyl doses in preventing N&V in patients undergoing outpatient gynecologic surgery under general anesthesia. The study was designed to detect a linear trend in CR with dose but comparisons of the effect of individual doses to PL are also possible. • The study was apparently not sized to demonstrate a difference among the DOLA•Mesyl doses. • Stratification of patients on the basis of whether they were undergoing laparoscopic procedures or not is of interest to explore the possibility of analysis of response on the basis of type of surgery.

B. Study MCPR-045

"A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Trial to Assess Single Dose Dolasetron Mesylate in Preventing Postoperative Nausea and Vomiting."

1. Objectives

a) Assess the efficacy of a range of doses of i.v. DOLA•Mesyl in preventing N&V in outpatient surgery under general anesthesia.

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

c) Determine the degree of patient satisfaction among the antiemetic dose levels.

2. Study Population/Design/Assessments

- Inclusion-exclusion criteria were as per treatment of PONV protocols. Regarding the cardiovascular system, not included in the trial were patients with complete BBB, either R or L, cardiomyopathy, CHF or Hx of CHF, those with arrhythmias currently requiring antiarrhythmic medication and those with second or third degree heart block.

- This was a randomized, double-blind, placebo-controlled, dose-response, parallel, 5-arm study, stratified by gender within each study site. The study was designed for 1,000 patients with a minimum of 200 patients in each dose group, DOLA•Mesyl (12.5, 25, 50 or 100 mg) or PL. Test medication was administered i.v. over 30 seconds to min. approximately 15 min. before cessation of nitrous oxide.

- Efficacy and safety assessment were as per treatment of PONV protocols. Safety and efficacy were monitored for 24 h.

3. Primary Statistical Analysis

The primary test for efficacy was one pairwise comparison, comparing the dose with the maximum response rate to PL, in the logistic response scale. As in previous trials, the primary analysis was an ITT analysis of CR.

4. Results

a. Patient Accounting/Participating Investigators

- A total of 1030 were enrolled at 17 investigative sites in this study. The following six centers enrolled 70 or more patients each:

	Total Number of Patients Enrolled
Michael H. Pearman/S.G. Graczyk (Columbia, SC)	109
Anthony L. Kovac (Kansas City, MO)	89
Jacques E. Chelly, (Houston, TX)	86
Bernard V. Wetchler (Peoria, IL)	79
H. Ronald Vinik (Birmingham, AL)	70
Jared C. Barlow (Williamsville, NY)	70

- 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 unevaluable for efficacy.

b. Data Showing Comparability of Groups at Baseline

- The study population was predominantly female and white (73.5%). There were no statistically significant imbalances among the groups with respect to age, ASA status (ASA 1 = 52.3%; ASA 2 = 45.1%), smoking status, race, duration of anesthesia (mean = 1.1h) or time to last free fluids (mean = 13.9h). Imbalances were noted in mean height, weight and history of PONV. Of these data on history of PONV and history of motion sickness, which may possibly impact efficacy results, are summarized below.

	PL [n=208]	DOLA•Mesyl Dose (mg) 12.5 [n=206]	25 [n=203]	50 [n=205]	100 [n=208]	p-value[a]
History of PONV	15.4%	21.8%	27.6%	24.9%	23.1%	0.0063
History of Motion Sickness	22.1%	19.9%	25.6	22.9%	18.8%	0.0645

a) For continuous variables p-values are calculated from a three-way analysis of variance F test for mean differences in among the five doses controlling for investigator and gender. For discrete variables p-values are from a 4 degree of freedom Chi-square test calculated from a logistic regression model with treatment, investigator and gender as explanatory variables.

- Fewer patients in the PL dose groups for both M and F patients had a Hx of PONV when compared to the DOLA•Mesyl dose groups.

- More patients in the 25 mg DOLA•Mesyl group had a Hx of motion sickness when compared to the PL group.

- Both imbalances, if anything, may bias the study against the 25 mg DOLA•Mesyl dose.

- There were differences (although not statistically significant) in the proportion of patients undergoing certain types of surgery, based on gender. These data are summarized in Table 14.

- Except as noted, there were no statistically significant differences among the groups in the frequency and percent of patients using various concomitant medications pre- or post-treatment. The pre-treatment use of ketorolac in males yielded statistically significant difference (p=0.031). Use ranged from

  This difference would not be expected to impact the efficacy or safety results of the study.

TABLE 14
Study -045

Type of Surgery According to Dose and Gender

	PL	12.5	25	50	100	p-value
I. Number of Patients						
Female	145	146	144	141	146	
Male	63	60	59	64	62	
Total n (=1030)	208	206	203	205	208	
II. Type of Surgery (Females)						
Breast Surgery	6.2%	4.1%	4.2%	5.0%	4.8%	
ENT	4.1%	6.8%	2.1%	2.8%	4.8%	
Gynecological surgery	68.3%	68.5%	73.6%	68.8%	70.5%	
Opthamologic	4.8%	1.4%	2.8%	3.5%	2.1%	N.S.
Orthopedic	13.1%	12.3%	11.1%	11.3%	9.6%	
Urologic	0.7%	2.1%	1.4%	2.1%	2.7%	
Other	2.8%	4.8%	4.9%	6.4%	5.5%	
III. Type of Surgery (Males)						
ENT	11.1%	11.7%	5.1%	4.7%	4.8%	
Opthamologic	7.9%	10.0%	8.5%	6.3%	8.1%	
Orthopedic	47.6%	38.3%	49.2%	45.3%	50.0%	N.S.
Urologic	7.9%	20.0%	10.2%	14.1%	14.5%	
Other	23.8%	18.3%	27.1%	29.7%	22.6%	

- As shown below, there was not statistically significant difference among the test groups in the proportion of patients receiving escape medication.

Escape Medication	PL [n=208]	DOLA•Mesyl Dose (mg)				Total [n=1030]
		12.5 [n=206]	25 [n=203]	50 [n=205]	100 [n=208]	
DROPERIDOL (p=N.S.)[a]	15%	12%	12%	9%	10%	12%
MCP (p=N.S.)	11%	7%	9%	10%	8%	9%
ONDANSETRON	3%	1%	2%	2%	2%	2%
PCPZ (p=N.S.)	4%	3%	4%	3%	3%	3%
PROMETHAZINE (p=N.S.)	4%	4%	3%	5%	2%	4%
a) p-values are calculated using a 4 degree of freedom Chi-square test.						

c. Clinical Response (Tables 15 and 16)

- In the ITT analysis of all patients (Table 15, upper panel), the therapeutic gains (DOLA•Mesyl > PL) for Complete Response (CR) were modest and varied between According to the sponsor calculations, none of the DOLA•Mesyl group was statistically superior to PL. The efficacy evaluable analyses (Table 15, lower panel) confirmed those of the ITT analysis. The lack of statistically significant differences in CR rates between any of the DOLA•Mesyl treated groups and the PL group for both the ITT and the efficacy evaluable populations was shown after controlling for investigative site and the gender-by-treatment interaction.

- Gender was a significant predictor of outcome ($p<0.0001$). It is to be noted that the PL response was significantly different among females (=40%) than males (=70%). As shown in Table 16 (upper panel), analysis of CR rate in females indicated a statistically significant difference from PL for the 12.5 mg and 100 mg dose groups, with a therapeutic gain of 18% over PL (both groups). Female patients in the DOLA•Mesyl 25 and 50 mg dose groups had CR rates with therapeutic gains over PL of 11% and 10%, respectively. These were not statistically significantly different from PL.

- As shown in Table 16 (lower panel), analysis of CR in males showed therapeutic gains of -7%, -7%, 5% and -10%, for the 12.5, 25, 50 and 100 mg DOLA•Mesyl groups, respectively, over PL. The high PL response among males (70%) made it impossible to differentiate the DOLA•Mesyl groups from PL.

- Investigator was a statistically significant predictor of CR ($p=0.0003$) and was included as a main effect in all statistical analyses where possible. The investigator-by-treatment interaction was not statistically significant ($p=0.4598$) and was not included as a factor for any statistical analysis.

TABLE 15
Study -045

Clinical Response: Analysis 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=1030]									
PL [n=208]	12.5 [n=206]	25 [n=205]	50 [n=205]	100 [n=208]	12.5 vs PL	25 vs PL	50 vs PL	100 vs PL	All DOLA•Mesyl vs PL
102 (49%)	123 (59.7%)	111 (54.7%)	119 (58%)	121 (58.2%)	(10.7%) [N.S.][b]	(5.7%) [N.S.]	(9%) [N.S.]	(9.2%) [N.S.]	8.0% [0.0254][a]
II. Efficacy Evaluable Analysis [n=964][c]									
[n=200]	[n=191]	[n=196]	[n=189]	[n=198]					
97 (49%)	112 (59%)	108 (55%)	110 (58%)	116 (59%)	(10%) [N.S.]	(6%) [N.S.]	(9%) [N.S.]	(10%) [N.S.][d]	8.8% [<0.05]

a) Sponsor's calculated p-values, from a weighted contrast of the parameter estimates for treatment 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.

b) Primary Test: DOLA•Mesyl (12.5 mg) vs PL, p=N.S. [ITT, n=1030]
- Not significant at the 0.05 level after controlling for 4 comparisons to PL using Dunnett's t (sponsor's calculations).
- Significant at the 0.030 level when calculated by the Fisher's exact test (Dr. M.C. Fan).
- Mantel-Haenszel Row Mean Scores Test: DOLA•Mesyl (12.5 mg) vs PL, p=N.S.= (>0.05) [ITT, n=1030].
- Linear Trend, p=N.S. (>0.05) [ITT, n=1030]
- Mantel-Haenszel Test for non-zero correlation, p=N.S. (>0.05) [ITT, n=1030].

c) Efficacy Evaluable (n=974): DOLA•Mesyl (12.5 mg) vs PL, p=N.S. [>0.05].

d) Significant at the 0.045 level when calculated by the Fisher's exact test (Dr. M.C. Fan).

TABLE 16
Study -045

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

[Intent-To-Treat Analysis]

Response by Dose (mg)					Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses and PL/[p-values][a]				
Response in Females [n=722]									
PL [n=145]	12.5 [n=146]	25 [n=144]	50 [n=141]	100 [n=146]	12.5 vs PL	25 vs PL	50 vs PL	100 vs PL	All DOLA•Mesyl[b] vs PL
58 (40%)	85 (58%)	74 (51%)	71 (50%)	84 (58%)	18% [<0.05][c]	11% [N.S.]	10% [N.S.]	18% [<0.05][d]	14.2%
Response in Males [n=308]									
[n=63]	[n=60]	[n=59]	[n=64]	[n=62]					
44 (70%)	38 (63%)	37 (63%)	48 (75%)	37 (60%)	(-7%) [N.S.]	(-7%) [N.S.]	(5%) [N.S.]	-10% [N.S.]	-5%

a) Gender p<0.0001 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 Treatment Interaction p=0.0168 from a 4 degree of freedom Chi-square test using Rao scores from a logistic regression model predicting complete response with dose, investigator and gender as explanatory variables.
b) Actual mean CR=54.2% and 65%, respectively.
c,d) Statistically significant after adjusting for the 5 comparisons to PL using Dunnett's procedure (sponsor).

- The only factor which had a statistically significant interaction with the treatment effect in CR and had a statistically significant DOLA•Mesyl vs PL comparison was age in males.

  - The PL rate in males over 40 y of age was 81%; while in males less than 41 y of age it was only 59%.

  - When age, and the age-by-treatment interaction were controlled for as explanatory variables of CR, the DOLA•Mesyl vs. PL comparison became statistically significant in males (p=0.0491). This comparison was not statistically significant when age was not in the model (p=0.5151). Thus, age for the male population appeared to be a significant confounder of the treatment effect.

  - One other subpopulation, ASA physical status in males, had a statistically significant interaction with the treatment effect (p=0.0176), however, did not have a statistically significant DOLA•Mesyl vs PL comparison (p=0.3817).

d. Safety Results

1) Extent of Exposure

In study -045, 1030 patients received a single dose of test medication intravenously, with the following distribution.

	DOLA•Mesyl (mg)				Total
PL	12.5	25	50	100	DOLA•Mesyl
[n=208]	[n=206]	[n=203]	[n=205]	[n=208]	[n=822]

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

- There were no deaths reported during this trial.

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

- Two of the serious AEs were assessed by the investigator as possibly related to test medication:

  - Patient 0293-0041 (DOLA•Mesyl 25 mg) was hospitalized as a result of excessive drowsiness.

  - Patient 0306-0003 (PL) was hospitalized as a result of a hysterical episode. This began with crying and was followed by difficulty breathing and general muscle weakness.

- Other serious events included hemorrhage, pain, nausea, vomiting, urinary retention, drowsiness, synovitis, sedation and respiratory depression (sponsor's Appendix J2). These were assessed by the corresponding investigators as not related to test medication and were generally attributable to the operative procedure or PO pain relief.

- The following is to be noted.

A 28-y-old F patient (0305-0022) had no history of epilepsy, neurologic disorders, meningitis, encephalitis, or head trauma. In the 24 h before surgery, the patient received Chromagen, Lo/Ovral 28, Alka Seltzer Gold, midazolam, glycopyrrolate, ampicillin, and gentamicin. The general anesthesia administered during surgery consisted of nitrous oxide, alfentanil, thiopental, and isoflurane. She underwent outpatient dilatation and curettage and experienced three episodes of apparent shaking or tonic-clonic movements of the arms, legs and neck. These episodes occurred approximately 65 min. following a single dose of DOLA•Mesyl 50 mg and lasted 1 minute, 45 sec. and 35 sec., respectively, over a total of 10 min. A neurology consult concluded that the patient had questionable tonic/clonic activity upon recovery from anesthesia. The patient was initially treated with two doses of diazepam 2.5 mg intravenous and then a final dose of diazepam 5 mg intravenous and recovered completely about 65 min. after the last episode. After surgery the patient received hydrocodone, ranitidine, acetaminophen, and cephalexin. Vital signs and oxygen saturation were normal before the shaking episodes occurred; blood gases and serum chemistries were WNL shortly after the episodes.

These shaking episodes were assessed by the investigator as moderate and possibly related to DOLA•Mesyl.

3) AEs (Tables 17 and 18)

- There was no statistically significant difference among the test groups regarding the overall rate or the rate in specific organ class (HR & Rhythm, central and peripheral nervous system, body as a whole, etc.).

TABLE 17
Study -045

Overall Rate and Most Frequently Occurring AEs,
Frequency of All and Most Frequent Tx-Emergent EKG Interval Changes

System Open Class and Included Term (p-value)*	PL [n=208]	DOLA•Mesyl Dose (mg) 12.5 [n=206]	25 [n=203]	50 [n=205]	100 [n=208]	MDL 73,147EF [n=822]
I. Frequency (Percent) of All AEs						
Overall Rate (p=N.S.)	54.3%	44.2%	56.2%	54.1%	50.5%	51.2%
Heart Rate & Rhythm (p=N.S.)	33.7%	25.7%	35.5%	32.2%	25.0%	29.8%
Central & Peripheral Nervous System (p=N.S.)	13.0%	15.0%	17.2%	19.5%	16.8%	17.2%
Body as a Whole (p=N.S.)	9.1%	7.3%	7.9%	11.7%	9.6%	9.1%
II. Most Frequent (≥1% of the Study Population) AEs						
Sinus Bradycardia (p=N.S.)	33 (15.9)	33 (16.0)	46 (22.7)	35 (17.1)	26 (12.5)	140 (17.0)
Headache (p=N.S.)	17 (8.2)	20 (9.7)	17 (8.4)	24 (11.7)	23 (11.1)	54 (10.2)
T Wave Change or Abnormality (p=N.S.)	15 (7.2)	12 (5.8)	18 (8.9)	21 (10.2)	19 (9.1)	70 (8.5)
Dizziness (p=N.S.)	9 (4.3)	9 (4.4)	11 (5.4)	8 (3.9)	11 (5.3)	39 (4.7)
Drowsiness (p=0.0293)	3 (1.4)	6 (2.9)	7 (3.4)	9 (4.4)	11 (5.3)	33 (4.0)
Sinus Arrhythmia (p=N.S.)	11 (5.3)	9 (4.4)	7 (3.4)	10 (4.9)	5 (2.4)	31 (3.8)
Pain (p=N.S.)	5 (2.4)	7 (3.4)	7 (3.4)	8 (3.9)	4 (1.9)	26 (3.2)
Light-Headed Feeling (p=N.S.)	4 (1.9)	7 (3.4)	6 (3.0)	6 (2.9)	2 (1.0)	21 (2.6)
III. Frequency (%) of All Tx-Emergent EKG Interval Changes						
Overall Rate (p=0.0001)	36 (17.3)	45 (21.8)	34 (16.7)	55 (26.8)	71 (34.1)	205 (24.9)
Heart Rate & Rhythm (p=0.0001)	36 (17.5)	45 (21.8)	34 (16.7)	55 (26.8)	71 (34.1)	205 (24.9)

QT Interval Prolongation (QTc≥440) (p=0.0001)	28 (13.5)	32 (15.5)	25 (12.3)	43 (21.0)	58 (27.9)	159 (19.2)
EKG Abnormal Specific (QRS≥100) (p=0.0012)	7 (3.4)	13 (6.3)	9 (4.4)	14 (6.8)	28 (13.5)	64 (7.8)
AV Block First Degree (PR≥220)	3 (1.4)	1 (0.5)	3 (1.5)	3 (1.5)	0	7 (0.9)

IV. Frequency (%) of Most Frequent Tx-Emergent EKG Interval Changes

QT Interval Prolongation (QTc≥440) (p=0.0001)	28 (13.5)	32 (15.5)	25 (12.3)	43 (21.0)	58 (27.9)	158 (19.2)
EKG Abnormal Specific (QRS≥100) (p=0.0012)	7 (3.4)	13 (6.3)	9 (4.4)	14 (6.8)	28 (13.5)	64 (7.8)
AV Block First Degree (PR≥220) (p=N.S.)	3 (1.4)	1 (0.5)	3 (1.5)	3 (1.5)	0	7 (0.9)

a) p-value for a linear trend with dose in the occurrence of that event using a logistic regression model with dose as an explanatory value.

- The most frequently occurring AEs were bradycardia, headache, T-wave change or abnormality, dizziness, drowsiness, sinus arrhythmia, pain and light-headed feeling. Of these, the incidence of drowsiness was lowest in the PL group (1.4%) and increased as the dose of DOLA•Mesyl increased (29% → 5.3%); this increase was statistically significant (p=0.0293) (Table 17).

- Similarly, the frequency (%) of all Tx-emergent EKG interval changes (QT interval prolongation >440 and EKG abnormal specific, QRS≥100) increased in a statistically significant fashion [p=0.0001 and 0.0012, respectively] with the increase in the DOLA•Mesyl dose (Table 17). The frequency (%) of the most frequent Tx-emergent EKG interval changes (QT interval prolongation >440 and EKG abnormal specific, QRS ≥100) increased in a statistically significant fashion [p=0.0001 and 0.0012, respectively] with the increase in the DOLA•Mesyl dose (Table 17.)

- As shown in Table 18 (upper panel), there was no statistically significant difference in the frequency of all Tx-related AEs either by organ class or specific terms. As seen in the lower panel of Table 18, there was a statistically significant linear trend across dose in the overall rate (p=0.0001), those related to the HR & rhythm (p=0.0001) and QT interval prolongation (QTc≥440; p=0.0002) and EKG abnormal specific (QRS≥100, p=0.0017) EKG interval changes emerging during the treatment with test medication (Table 18).

- A graphic representation of the change from BL by dose for the six EKG parameters evaluated, is given in Fig. 4. In general, the administration of higher doses, especially 100 mg, was accompanied by larger changes than either PL or the lower DOLA•Mesyl doses.

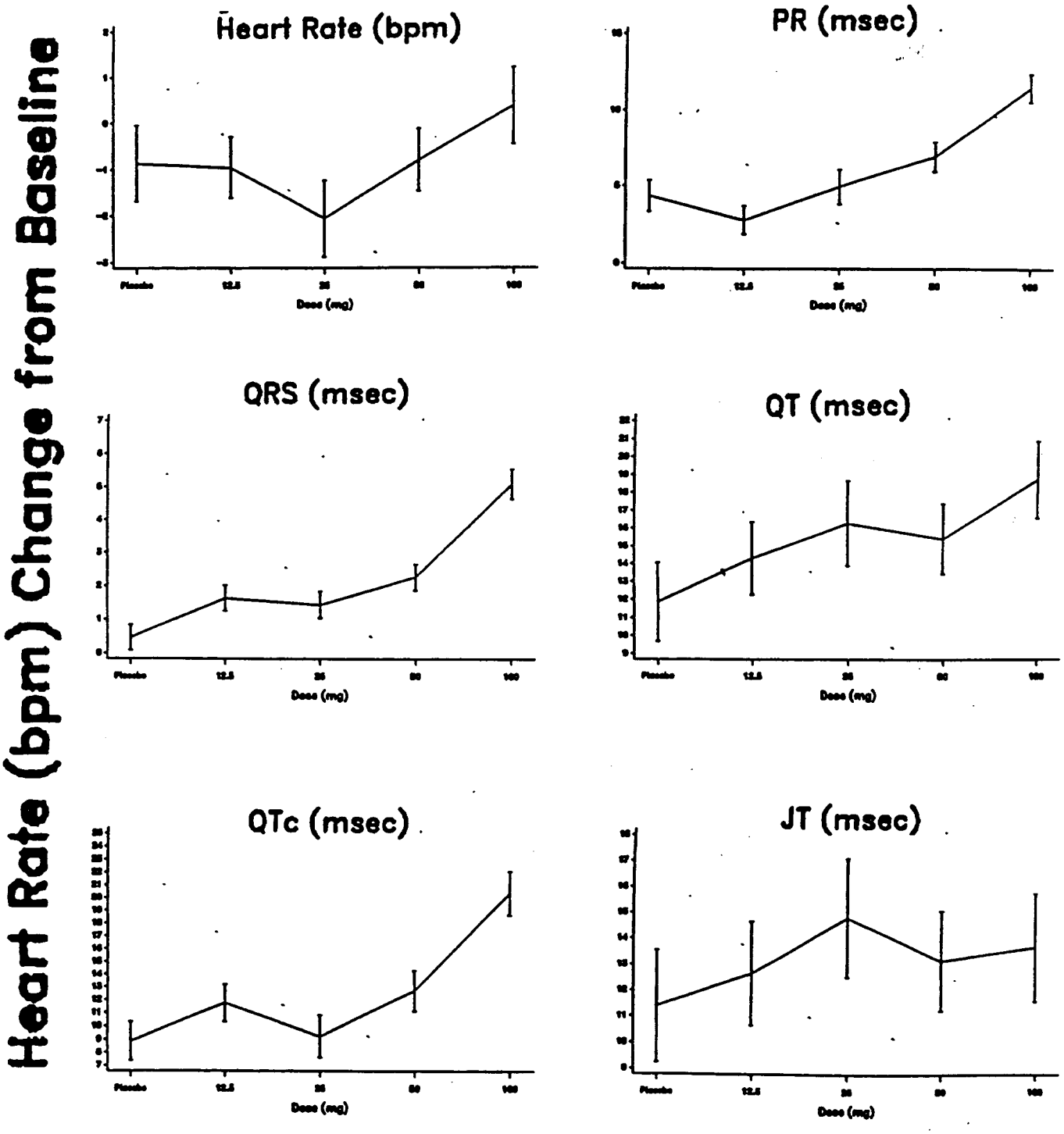

Fig. 4 - *Study -045: Change at 1 to 2 hours from Baseline for EKG Parameters HR, PR, QRS, QT, QTc and JT per Dose Level.*

TABLE 18
Study -045

Frequency of All Treatment-Related AEs and All Tx-Related EKG Interval Changes

System Organ Class and Included Term (p-value)*	PL [n=208]	DOLA®Mesyl Dose (mg) 12.5 [n=206]	25 [n=203]	50 [n=205]	100 [n=208]	MDL 73,147EF [n=822]
I. Frequency (Percent) of All Tx-Related AEs						
Overall Rate (p=N.S.)	51 (24.5)	48 (23.3)	59 (29.1)	57 (27.8)	53 (25.5)	217 (26.4)
Heart Rate & Rhythm (p=N.S.)	23 (15.9)	25 (12.1)	37 (18.2)	33 (16.1)	23 (11.1)	118 (14.4)
Sinus Bradycardia (p=N.S.)	16 (7.7)	11 (5.3)	22 (10.8)	15 (7.3)	9 (4.3)	57 (6.9)
T Wave Change or Abnormality (p=N.S.)	5 (2.4)	10 (4.9	11 (5.4)	12 (5.9)	13 (6.3)	46 (5.6)
Sinus Arrhythmia (p=0.1306)	5 (2.4)	5 (2.4)	3 (1.5)	4 (2.0)	1 (0.5)	13 (1.6)
Central & Peripheral Nervous System (p=N.S.)	20 (9.6)	25 (12.1)	24 (11.8)	27 (13.2)	23 (11.1)	99 (12.0)
Headache (p=N.S.)	14 (6.7)	18 (8.7)	9 (4.4)	20 (9.8)	13 (6.3)	60 (7.3)
Dizziness (p=N.S.)	7 (3.4)	5 (2.4)	10 (4.9)	6 (2.9)	10 (4.8)	31 (3.8)
Light-Headed Feeling (p=N.S.)	3 (1.4)	6 (2.9)	6 (3.0)	4 (2.0)	2 (1.0)	18 (2.2)
Dizziness Postural	0	0	0	0	1 (0.5)	1 (0.1)
Body as a Whole (p=N.S.)	3 (1.4)	5 (2.4)	1 (0.5)	6 (2.9)	6 (2.9)	18 (2.2)
Drowsiness	0	3 (1.5)	1 (0.5)	5 (2.4)	6 (2.9)	15 (1.8)
General Cardiovascular	2 (1.0)	0	1 (0.5)	1 (0.5)	5 (2.4)	7 (0.9)
Hypotension	2 (1.0)	0	1 (0.5)	1 (0.5)	4 (1.9)	6 (0.7)
Hypotension Orthostatic	0	0	0	0	1 (0.5)	1 (0.1)
II. AEs Treated With Counteractive Medication						
Headache (p=0.0232)	7 (3.4)	8 (3.9)	10 (4.9)	11 (5.4)	18 (8.7)	47 (5.7)

III. Frequency (Percent) of All Tx-Related Tx-Emergent EKG Interval Changes						
Overall Rate (p=0.0001)	32 (15.4)	40 (19.4)	32 (15.8)	51 (24.9)	64 (30.8)	187 (22.7)
Heart Rate & Rhythm (p=0.0001)	32 (15.4)	40 (19.4)	32 (15.8)	51 (24.9)	64 (30.8)	187 (22.7)
QT Interval Prolongation (QTc≥440) (p=0.0002)	26 (12.5)	29 (14.1)	24 (11.8)	40 (19.5)	54 (26.0)	147 (17.9)
EKG Abnormal Specific (QRS≥100) (p=0.0017)	5 (2.4)	11 (5.3)	7 (3.4)	13 (6.3)	23 (11.1)	54 (6.6)
AV Block First Degree (PR≥220)	3 (1.4)	1 (0.5)	3 (1.5)	3 (1.5)	0	7 (0.9)
a) p-value for a linear contrast across dose in the occurrence of that event using a logistic regression model with dose as an explanatory variable.						

- The frequency of AEs by maximum severity is summarized in Table 19. The AEs of interest were primarily of mild severity.

4) Clinical Laboratory Evaluation

- Of the laboratory chemistries, phosphate showed a decreasing linear trend across doses in change from pre-treatment; urine pH showed an increasing linear trend across doses in change from pre-treatment. None of these changes was clinically significant.

- The summaries of laboratory shifts did not show clinically significant alterations in liver or renal function, hematology, electrolytes or miscellaneous chemistry.

5) Summary of Changes in Vital Signs

- There were no statistically significant trends in pulse rate changes from baseline at any of the time points evaluated (BL, 0, 15, 30, 60, 90 and 120 min. post-treatment and at post-treatment). There was a decreasing linear trend with dose from change from BL in mean values for systolic BP at all time points. The decreases in mean values for the DOLA•Mesyl groups were 3 to 10 mmHg greater than those in the PL group. There were no statistically significant trends in diastolic BP changes from BL.

TABLE 19
Study -045

Frequency of AEs by Maximum Severity[a]

Incidence >1% in Study Population						
			DOLA•Mesyl Dose (mg)			
Included Term	Maximum Severity	PL [n=208]	12.5 [n=206]	25 [n=203]	50 [n=205]	100 [n=208]
Sinus Bradycardia [n=173]	MILD	32	33	42	35	24
	MOD	1	0	4	0	2
T Wave Change or Abnormality [n=85]	MILD	15	12	18	21	19
Headache [n=101]	MILD	12	15	14	17	15
	MOD	5	4	2	5	8
	SEV	0	1	1	2	0
Drowsiness [n=36]	MILD	0	4	3	5	9
	MOD	3	2	4	4	2
Sinus Arrhythmia [n=42]	MILD	11	9	7	10	5
EKG Abnormal Specific (QRS≥100) [n=71]	MILD	7	13	8	13	28
	MOD	0	0	1	1	0
QT Interval Prolongation (QTc≥440) [n=186]	MILD	28	32	25	41	57
	MOD	0	0	0	2	1

a) For patients experiencing the event more than once, the maximum severity over all occurrences is used.

- Although treatment-emergent decreases in BP appeared to occur more frequently for DOLA•Mesyl-treated patients, there was no indication of a dose response relationship.

6) EKG Interval Changes

- Not unexpectedly, small but consistent increases from baseline were observed in the mean values for PR interval and QRS width.

  - These changes revealed an increasing linear trend with dose.

- The mean change from baseline to 120 min. for PR interval was 4.3 msec in the PL group, 2.8 msec in the 12.5 mg DOLA•Mesyl group, 4.9 msec in the 25 mg DOLA•Mesyl group, 6.9 msec in the 50 mg DOLA•Mesyl group, and 11.5 msec in the 100 mg DOLA•Mesyl group ($p<0.0001$).

- The mean change from baseline in QRS for PL patients was 0.5 msec while it was 1.6 msec for 12.5 mg, 1.4 msec for 25 mg, 2.3 msec for 50 mg, and 5.1 msec for patients who had received 100 mg DOLA•Mesyl ($p<0.0001$).

- The increases in PR interval and QRS width were accompanied by a slight change in heart rate (-2.1 bpm to 0.4 bpm) and increase in JT interval (11 msec to 15 msec) that were of a similar magnitude for all dose groups.

- There was an increasing linear trend with dose in QT ($p=0.0091$) and QT_c ($p<0.0001$) intervals in change from baseline across doses.

  - The mean change from baseline in QT interval for the PL group was 11.9 msec, 14.3 msec, 16.2 msec, and 15.4 msec for the 12.5 mg, 25 mg and 50 mg dose groups, respectively, and 18.7 msec for the 100 mg DOLA•Mesyl group.

  - The mean change from baseline in QT_c interval was 8.8 msec in the PL group, 11.8 msec for 12.5 mg, 9.2 msec for 25 mg, 12.7 msec for 50 mg and 20.3 msec in the 100 mg dose group.

- Sponsor's *Listing 8* provided a listing of the patients in whom EKG treatment-emergent changes at 120 min. after adm. of test medication occurred. The patients entire EKG data was collected over the course of this study.

  - The incidence of treatment-emergent changes for heart rate and PR interval revealed no dose response across DOLA•Mesyl dose groups or when compared to PL.

  - The incidence of treatment-emergent changes for QRS width and QT_c interval suggested a dose response trend.

  - The frequency of reported QRS changes above 100 msec after dosing was comparable across dose groups, except at the 100 mg dose level. QRS prolongation occurred in 3% of the PL group, 6% of the 12.5 DOLA•Mesyl group, 4% of the 25 mg DOLA•Mesyl group, 7% in the 50 mg DOLA•Mesyl group, and increased to 13% in the 100 mg DOLA•Mesyl-treated group.

- QT_c interval treatment-emergent changes in the PL group were 14%, 16% for the 12.5 mg group, 12% for the 25 mg group, 20% in the 50 mg group and 28% for the 100 mg group.

i) Potentially Clinically Relevant Changes in EKG Intervals

- No patients had QRS interval prolongation that went from <100 msec pre-Tx to ≥120 msec post-Tx.

- The following 8 patients had QT_c interval prolongation above 500 msec subsequent to receiving DOLA•Mesyl:

Patient 0299-0034 (100 mg) HR was unchanged.
Other EKG intervals increased as follows: PR from
QRS from , QT from c, and JT from

The patient had the following adverse events: dizziness and hypotension that began ca. 2h after test medication and were possibly related to test medication; and shortness of breath that onset at 5h after administration of test medication, lasted 15 min. and was deemed by the investigator as unlikely related to test medication.

Patient 0293-0066 (25 mg) The patient was taking enalipril and indapamide for hypertension. HR was slightly decreased. Other EKG intervals increased as follows: PR from . QRS from QT from and JT from
The patient had a serious adverse event of respiratory depression that the investigator deemed unrelated to study medication.

There were no AEs that may have been related to the QT_c interval prolongation.

Patient 0293-0058 (100 mg) HR increased from Other EKG intervals increased as follows: PR from QRS from QT from , and JT from

The prolonged QT_c interval did not cause any clinically significant sequelae.

Patient 0301-0018 (25 mg) . HR increased from . Other EKG intervals were essentially unchanged.

There were no AEs attributable to the QT_c prolongation.

Patient 0303-0041 (50 mg) . HR and PR interval were essentially unchanged. Other EKG intervals were increased as follows: QRS from , QT from , and JT from

There were no AEs attributable to the QT_c prolongation.

Patient 0294-0001 (50 mg) . HR increased from . Other EKG intervals increased as follows: PR from QRS from , QT from and JT from

The patient did not have any adverse events that were attributable to the QT_c interval prolongation.

Patient 0293-0027 (50 mg) HR increased from There were no clinically significant changes in other EKG measurements. The patient had serious AEs (required hospitalization) of anxiety and dyspnea that the investigator determined were unrelated to test medication.

There were no apparent clinically significant ramifications of the QT_c interval prolongation.

Patient 0305-0010 (100 mg) . HR increased from Other EKG intervals increased as follows: PR from c, QRS from , QT from :, and JT from

There were no AEs that could be attributed to the QT_c prolongation.

5. Conclusions (Sponsor)

"Dolasetron is safe in the population examined. Dolasetron is effective in the prevention of PONV in females undergoing a variety of surgical procedures.

"Gender was a significant predictor of outcome for the primary efficacy variable of complete response. Efficacy results were analyzed by gender.

"For female patients, analysis of the complete response rate indicated that 12.5 mg and 100 mg dolasetron were statistically superior to placebo by a margin of 18% while 25 mg and 50 mg were superior to placebo by a margin of 11% and 10%, respectively. The results for the incidence of no nausea over the 24-hour study period followed a similar pattern. The margin of difference between placebo and each dolasetron dose group may have been muted since the placebo dose group had fewer female patients with a previous history of postoperative nausea and vomiting compared to the dolasetron dose groups.

"For male patients, analysis of complete response rate and the incidence of no nausea over the 24-hour study period revealed no differences from placebo in any of the dolasetron dose groups. However, complete response is statistically significant when the active versus placebo comparison in males is adjusted for age.

"The most frequently occurring adverse events were sinus bradycardia, headache, T-wave change or abnormality, dizziness,

drowsiness, and sinus arrhythmia. Drowsiness was the only event that increased with dose with incidence rates of 1.4% for placebo to 5.3% for the 100 mg dolasetron dose group.

"There were no clinically significant changes in any clinical laboratory measurement or vital sign measurement.

"There is no evidence from this study that prolongation of ECG intervals occurs for 12.5 mg or 25 mg of dolasetron. Analysis of individual outlier ECG intervals reveals no evidence for increased safety risk for any dose of dolasetron."

6. Reviewer's Comments

Study MCPR0045 (-045) is one of three main trials the sponsor of NDA 20-624 submitted in support of the approval of the marketing of intravenously administered ANZEMET (DOLA•Mesyl) for the prevention of postoperative nausea and/or vomiting. According to the proposed text of the labeling the recommended intravenous dosage is 12.5 mg given as a single dose at the cessation of anesthesia.

Study -045 is an important trial in a large number of patients (total n=1030) carried out at 17 centers throughout the U.S. The study was randomized, double-blind with five parallel arms. The trial's main objective was to detect a difference between the dose of DOLA•Mesyl (either 12.5, 25, 50 or 100 mg) with the highest complete response and a negative control (PL) while controlling for multiple comparisons. This design was expected to allow dose-response comparisons of efficacy. It is important to note that study -045 was well designed and apparently well executed. The inclusion-exclusion criteria used in study -045 especially the exclusions pertaining to the cardiovascular system were the same or similar to those used in the Tx of PONV protocols.

In study -045, 722 female and 308 male patients scheduled for outpatient surgery were stratified by gender and randomized to one of the five test groups. Test med. was administered i.v. approximately 15 min. before the cessation of nitrous oxide. The methodology for randomization/stratification used in study -045 resulted in five patient populations that - in the main - were balanced with respect to variables that may influence outcome. But since the results of this large trial were null, it seems of interest to point out some observed imbalances among the test groups. The study population was predominately female and white (74%). There were no statistically significant imbalances among the groups with respect to ASA physical status and the majority of patients were ASA physical status 1 or 2 (ASA 1=52%; ASA 2=45%), smoking status, race, duration of anesthesia (mean=1h) or time to last free fluids (mean=14h).

Imbalances were noted in mean height, weight, history of PONV and history of motion sickness. Patient baseline characteristics indicated that there were no statistically significant differences among dose groups in the male

population. In the female population, a statistically significant difference for weight was detected among the dose groups. But the difference in the mean values across dose groups of only 2.6 Kg would not be expected to contribute to or enhance the susceptibility for postoperative emetic symptoms in any of the dose groups in the female population. While not statistically significant, fewer patients in PL dose groups for both male patients and for female patients had a history of PONV when compared to the DOLA•Mesyl dose groups. Also, more patients in the 25 mg DOLA•Mesyl group had a Hx of motion sickness when compared to the PL groups. A history of PONV may render a patient more susceptible to emetic symptoms at subsequent surgery. Thus the sponsor speculates that the lower incidence of a history of PONV among patients in the PL dose groups may have decreased the magnitude of difference in the efficacy parameters of CR or nausea when compared to the DOLA•Mesyl groups. The Hx of motion sickness imbalance, although not statistically significant, may have biased somewhat the study against the 25 mg DOLA•Mesyl dose. Except for Pre-Tx use of Ketorolac in males, which yielded statistically significant difference ($p=0.031$) and which would not be expected to impact the efficacy or safety results, the five test groups were balanced in the frequency and percent of patients using various concomitant medication pre- or post-treatment.

Study -045 did not demonstrate that DOLA•Mesyl was active since - for the entire population - neither the ITT nor the Evaluable population analyses demonstrated a statistically significant linear trend in the proportion of complete responders across the five dose groups [$p>0.05$, ITT, $n=1030$; Evaluable, $n=974$].

For CR rate, the PL response was 49% (both study populations) and for the four DOLA•Mesyl groups varied between 55% and 60% for the ITT and between 55% and 59% for the Evaluable population. These CR rates among the DOLA•Mesyl dose levels represented no statistically significant therapeutic gain over PL (6% to 11% in the ITT and 6% and 10% in the Evaluable population).

Since this trial was stratified by gender and the stratification/randomization process yielded a similar group of patients per test group, a brief comment on analysis on CR in males and females is included here. In males, the CR rate with PL (70%) was higher than the DOLA•Mesyl doses except 25 mg. Consequently, the therapeutic gains among males were all N.S. and varied between -10% and 5%. In females, the CR rate with PL (40%) was lower than in male patients; the CR rates among DOLA•Mesyl doses varied between 50% for the two middle doses (25 and 50 mg) and 58% for the two extreme doses [highest (100 mg) and lowest (12.5 mg)]. As a consequence, the therapeutic gains among females (18%) was statistically significant for the comparisons 12.5 vs PL and 100 mg vs PL. But the therapeutic gains with the intermediate doses of DOLA•Mesyl (25 mg=11% and 50 mg=10%) were not statistically significant. There are no explanations, only speculations, for these findings. There seems to be some activity for some doses but again, for the overall study population none of the doses of DOLA•Mesyl tested were efficacious.

In this study population and under the experimental conditions and methodology used in this large trial, 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 de pointes*, nor other serious ventricular arrhythmias) occurred. Two of the serious AEs reported, excessive drowsiness in a DOLA•Mesyl 25 mg treated patient and hysterical episode in a PL-treated patient resulted in hospitalization and were assessed by the investigator as possibly related to test medication. Other serious AEs were generally attributable to the operative procedure or PO pain relief.

The overall AE rates were 54% for PL and varied between among the DOLA•Mesyl groups. The most frequently occurring AEs were sinus bradycardia, headache, T-wave change or abnormality, dizziness, drowsiness, sinus arrhythmia, pain and light-headed feeling. But except for drowsiness (PL=1.4%, total DOLA•Mesyl=4%; p=0.0293) there were no linear trend across dose in the occurrence of any of these events.

On the other hand, for all Tx-emergent EKG interval changes, there was a statistically significant linear trend across dose in the occurrence of the overall rate (p=0.0001), heart rate and rhythm (p=0.0001), QT interval prolongation (p=0.0001) and EKG abnormal specific (p=0.0012). Similarly, for the frequency (%) of the most frequent Tx-emergent EKG interval changes, there was a statistically significant linear trend across dose in the occurrence of QT interval prolongation (p=0.0001) and EKG abnormal specific (p=0.0012).

The changes from Pre-Tx to 120 min. Post-Tx in EKG parameters observed in study -045 are best illustrated in Fig. 4. There were little if any changes in HR and JT. For the other EKG parameters, in general, the higher doses (especially 100 mg, sometimes the 50 mg dose as well) were associated with EKG changes that were larger than those associated with PL or the lower doses of DOLA•Mesyl. A 3-way rank ANOVA with a test for linear trend with dose in change from BL, controlling for investigator and gender yielded statistically significant differences for PR (p<0.0001), QRS (p<0.0001), QT (p=0.0091) and QT_C (P<0.0001) but neither for HR (p=0.6976) nor JT (p=0.2525).

From Fig. 4 it is also evident that the changes in EKG intervals induced by the 12.5 mg DOLA•Mesyl dose were similar to those induced by PL.

This large study also afforded the opportunity to look into potentially clinically relevant changes in EKG intervals. No patients had QRS interval changes that went from <100 msec pre-Tx to ≥120 msec post-Tx. Within the text of the review of study -045 the MO provided succinct narratives for the 8 patients that had QT_C interval prolongation above 500 msec subsequent to receiving DOLA•Mesyl. Note that no increases of this magnitude occurred among the patients treated with either PL or the 12.5 mg DOLA•Mesyl dose. The highest QT_C interval increase in this small series (154 msec) was seen in association with the 100 mg DOLA•Mesyl dose.

Study -045

Distribution of the Eight Patients That Had QT_c Interval Prolongation Above 500 msec Subsequent to Being Treated With DOLA•Mesyl

PL 12.5 [NONE]		(msec) DOLA•Mesyl Dose (mg)		
		25 [n=2]	50 [n=3]	100 [n=3]
		0301-0018 428 → 525 97	0293-0027 437 → 511 74	0305-0010 427 → 500 73
		0293-0066 418 → 544 126	0294-0001 433 → 508 75	0293-0058 387 → 500 113
			0303-0041 424 → 501 77	0299-0034 399 → 553 154

As pointed out above, review of the AE data for all patients in study -045 did not reveal any events that could have been related to QT_c interval prolongation above 500 msec.

C. Study MCPR0084 (-084)

"A Randomized, Double-Blind, Placebo-Controlled, Dose-Response Trial to Assess Single Dose Intravenous Dolasetron Mesylate in Preventing Postoperative Nausea and Vomiting in Outpatient Laparoscopic Gynecologic Surgery."

1. Objectives

a) Assess the efficacy of intravenous DOLA•Mesyl in preventing nausea and vomiting in patients undergoing outpatient gynecologic surgery by laparoscopy under general anesthesia.

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

c) Determine the degree of patient satisfaction.

2. Study Population/Design/Assessments

- Inclusion-exclusion criteria were as in study -045 and prevention of PONV protocols. Regarding the cardiovascular system, not included in the trial were patients with complete BBB, either L or R (QRS >120 msec) and those with Hx of arrhythmias requiring antiarrhythmic medication, those with second or third degree block. The sponsor stated that any waiver of inclusion/exclusion had to be approved by the investigator and the sponsor on a case-by-case basis. In addition, it was recognized that all concomitant medical conditions and nonstudy medications could not be listed in a single protocol; therefore, the advisability of entering or maintaining patients with unusual conditions or conditions not listed in this protocol was discussed on a case-by-case basis. A decision was reached between a representative of the sponsor's monitoring team and investigator prior to patient entry or participation.

- This was a randomized, double-blind, placebo-controlled, dose response, multicenter study with four parallel groups. Patients were stratified by previous history of postoperative nausea and vomiting and randomized within each investigative site. Female patients with ASA physical status Class 1 or 2 undergoing outpatient (scheduled for discharge to home the same day) gynecologic surgery by laparoscopy under general anesthesia were eligible. Male patients were not included in this trial.

- Efficacy and safety assessments were as per treatment of PONV and study -045 protocols. Treatment consisting of a single intravenous dose of DOLA•Mesyl or PL was administered ca. 15 min. before the cessation of nitrous oxide. The 10 ml volume of test medication was administered by syringe over a 30 sec. to 5 min. period. If the patient experienced ≥15 min. of persistent nausea or more than one emetic episode during the study period, or requested alternative antiemetic therapy, or the investigator determined that alternate therapy was needed, the investigator could initiate escape medication according to institutional practice. The antiemetic activity, safety, tolerance, and patient satisfaction were monitored for 24h. QOL measurements were also performed.

3. Primary Statistical Analysis

The primary analysis was an intent-to-treat analysis of CR over 24h using logistic regression with terms for dose, investigator, and stratum. The primary test for efficacy was one pairwise comparison of PL to the DOLA•Mesyl dose with the maximum response rate. A stepwise Dunnett's procedure of comparing DOLA•Mesyl doses to PL was followed until a comparison was not significant.

4. Results

a. Patient Accounting/Participating Investigators

- A total of 635 female patients were enrolled at 25 investigative sites, in the following centers enrolling 30 or more patients each.

	Total Number of Patients Enrolled
Sarena G. Graczyk (Columbia, SC)	79
Ray McKenzie (Pittsburgh, PA)	58
Surindar Kallar (Richmond, VA)	42
Charles B. Hickok (Washington, D.C.)	40
Timothy Melson (Muscle Shoals, AL)	40
Leonard Lind (Cincinnati, OH)	34
Donald Marin (Hershey, PA)	33
Gwendolyn Boyd (Birmingham, AL)	32
Daneshvan R. Solanki (Galveston, TX)	32
Charles H. McLeskey (Temple, TX)	30
Phillip Scuderi (Winston-Salem, NC)	30
Mary Whitley (Washington, D.C.)	30

- There was no statistically significant difference among the four experimental groups in the number and percent (4%) of patients randomized to each dose with major protocol violations that rendered patients unevaluable for efficacy.

b. Data Showing Comparability of Groups at Baseline

- The study population was exclusively females, predominately white (70%), with a mean age of 32 years; 60% of the patients were ASA physical status Class 1, the remainder were Class 2. Ca. 24% of the patients had 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. There were neither gross imbalances nor statistically significant differences among experimental groups for any demographic or baseline characteristic. The groups were also similar in regards to duration of anesthesia (mean=1.1h) and time from last free fluids (mean=13.6h). The groups were also balanced with regards to medical Hx, pre-Tx medical examination, anesthesia procedures for maintenance and reversal.

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

Distribution of Patients by Dose and Stratum

History of PONV	PL	DOLA•Mesyl Dose (mg)			
		12.5	25	50	Total
YES	40	33	38	39	150
NO	117	126	119	123	485
Total	157	159	157	152	635

- Except as noted, there were no statistically significant differences among the groups in the frequency and percent of patients using various concomitant medications pre- or post-treatment. The pre-Tx use of bupivacaine yielded statistically significant difference (p=0.024). Use was 4% in the PL group and ranged from in the DOLA•Mesyl group. This difference would not be expected to impact the efficacy or safety results of the trial.

- As shown below, two escape medications showed statistically significant imbalances: droperidol and promethazine. The first, was taken by 19% of the PL group and by 11%, 8% and 10% of the three DOLA•Mesyl groups. Promethazine was taken by 15% of the PL group and by 8%, 8% and 6% of the three DOLA•Mesyl groups. There were no statistically significant differences among dose groups for other concomitant medications.

ESCAPE MEDICATION

Escape Medication	PL [n=157]	DOLA•Mesyl Dose (mg)			Total [n=635]
		12.5 [n=159]	25 [n=157]	50 [n=162]	
Droperidol (p=0.018)[a]	30 (19%)	17 (11%)	13 (8%)	17 (10%)	77 (12%)
Ephedrine	6 (4%)	4 (3%)	2 (1%)	5 (3%)	17 (3%)
MCP (p=N.S.)	19 (12%)	14 (9%)	14 (9%)	7 (4%)	54 (8%)
Ondansetron (p=N.S.)	16 (10%)	6 (4%)	15 (10%)	11 (7%)	48 (8%)
Prochlorperazine	4 (3%)	5 (3%)	4 (3%)	6 (4%)	19 (3%)
Promethazine (p=0.025)	24 (15%)	12 (8%)	13 (8%)	10 (6%)	59 (9%)
a) p-values are calculated using a 3 degree of freedom Chi-square test.					

c. Clinical Response (Tables 20 and 21)

One evaluation of CR included all patients. Another analysis was done of the number of complete responders per total number of patients in the history of PONV stratum (YES/NO) per dose cell.

- There was not a significant interaction between dose and either stratum or investigator.

- In the ITT analysis (all patients regardless of stratum; see Table 20, upper panel) the CR rate for PL patients was 30.6%, while the response rate for DOLA•Mesyl was 50.3%, 51.6% and 55.6%, respectively, for doses 12.5, 25 and 50 mg.

  - The therapeutic gains (DOLA•Mesyl > PL) ranged from

  - Each DOLA•Mesyl dose showed a statistically higher CR rate than PL ($p<0.0003$).

  - The test for a linear dose trend was statistically significant ($p<0.0001$), as was the comparison of all DOLA•Mesyl dose groups to PL ($p<0.0001$).

  - A confirmatory analysis comparing the row mean scores using the Mantel-Haenszel test also showed that each DOLA•Mesyl dose had a statistically higher CR rate than PL ($p<0.001$).

TABLE 20
Study -084

Clinical Response: Analyses of Primary Efficacy Parameters:
Complete Response

Response by Dose (mg)				Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Dose and PL/[p-value]a			
I. Intent-To-Treat Analysis [n=635]							
PL [n=157]	12.5 [n=159]	25 [n=157]	50 [n=162]	12.5 vs PL	25 vs PL	50 vs PL	All DOLA•Mesyl vs PL
48 (30.6%)	80 (50.3%)	81 (51.6%)	90 (55.6%)	(19.7%) [0.0003]	(21%) [0.0001]	(25%) [<0.0001]	(21.9%) [<0.0001]
II. Efficacy Evaluable Analysis [n=612]							
[n=149]	[n=155]	[n=152]	[n=156]				
44 (30%)	76 (49%)	78 (51%)	86 (55%)	(19%) [0.0007]	(21%) [0.0002]	(25%) [<0.0001]	(21.7%) [<0.0001]

a) p-values are calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting CR with dose, stratum, and investigator as explanatory variables. The significance levels of the comparisons to PL are adjusted for the 3 possible comparisons to PL using Dunnett's procedure.

- Primary Test: ITT (n=635), DOLA•Mesyl (12.5, 25 or 50 mg) vs PL, all statistically significant at the p-value of <0.0003.
  - Haenszel Row Mean Scores Test (ITT, n=635), DOLA•Mesyl (12.5, 25 or 50 mg) vs PL, p-value, p-values are calculated from a Mantel-Haenszel Test for Row Mean Scores Different for dose, controlling for investigator and stratum=0.001 or less.
- Linear Trend (ITT, n=635), p<0.0001.

- As shown in Table 20, lower panel, the primary test for efficacy was repeated for the 612 efficacy evaluable patients. The therapeutic gains ranged from Each DOLA•Mesyl dose showed a statistically higher CR rate than PL ($p<0.0007$).
- The CR rate is listed for each stratum by dose group in Table 21.
    - The dose by stratum interaction was not significant ($p=0.7552$), thus was excluded from all further statistical analyses.
    - The difference between strata was statistically significant ($p=0.0220$), thus was included in all further statistical analyses.
    - Patients with no previous history of PONV showed a higher CR rate, ranging from (PL=32%) than those with previous history of PONV. The latter ranged from Among those with no Hx of PONV, this represented a gain of 3%, 12% and 11% for the 12.5, 25 and 50 mg DOLA•Mesyl doses, respectively [see bottom of Table 21].
- The CR rate was listed for each investigator by dose group in sponsor's Table 15 of the Clinical Report.
    - The dose-by-investigator interaction was not significant ($p=0.6060$), thus was excluded from all further statistical analyses.
    - The difference between investigators was statistically significant ($p=0.0005$), thus was included, when possible, in all further statistical analyses.
    - The CR rate was listed for each investigator by stratum and dose group in sponsor's Table 16 of the Clinical Report.

TABLE 21
Study -084

Clinical Response: Analysis of Primary Efficacy Parameters
Number of Complete Responders/Number of Patients in Stratum by Dose Cell (%)

(History of PONV)[a]

Response by Dose (mg)					Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Dose[b] and PL/[p-value]			
History of PONV	PL [n=157]	12.5 [n=159]	25 [n=157]	50 [n=162]	12.5 vs PL	25 vs PL	50 vs PL	All DOLA•Mesyl vs PL
YES [n=150]	11/40 (28%)	15/33 (45%)	15/38 (39%)	17/39 (44%)	(17%)	(11%)	(16%)	(15%)
NO [n=485]	37/117 (32%)	65/126 (52%)	66/119 (55%)	73/123 (59%)	(20%)	(23%)	(27%)	(23%)
Percent Gain NO > YES					3%	12%	11%	8%

a) Stratum p=0.0220 from a 1 degree of freedom Chi-square test using a logistic regression model predicting CR with dose, stratum and investigator as explanatory variables.
b) Treatment - by - stratum interaction p=0.7552 from a 3 degree of freedom Chi-square test using Rao scores from a logistic regression model predicting CR with dose, stratum and investigator as explanatory variables.

i) Subgroup Analyses
(Data not shown)

- The patient population was broken into various subgroups and the effect of the subgroups on CR was analyzed. The results of these analyses were reported in sponsor's Table 26. The results for continuous subgroups such as age and weight were reported in two groups divided by the median, for convenience, to demonstrate more clearly any effect of the subgroup.

    - There were no statistically significant interactions between any of the subgroups and dose, while the difference in CR between DOLA•Mesyl doses and PL was highly significant for each subgroup ($p<0.0001$); in other words, in this study, the DOLA•Mesyl dosed patients had a significantly higher CR rate than PL patients in each subgroup examined.

- 4 of the subgroup effects examined did not evidence statistically significant differences ($p>0.10$); age, previous Hx of motion sickness, type of surgery, and time from last free fluids to study drug administration.

- The remaining subgroup effects all showed significant effects on CR response.

    - Weight was a significant predictor of CR ($p=0.0208$); heavier patients were more likely to have CR.

    - Race was significant ($p=0.0296$), with white patients less likely to have CR.

    - ASA physical status Class 2 patients had a significantly higher CR rate than Class 1 patients ($p=0.0346$).

    - Smokers had a significantly higher CR rate than non-smokers ($p<0.0001$), ranging from higher across dose groups.

    - Patients with a shorter duration of anesthesia were more likely to have CR ($p=0.0106$).

d. Safety Results

1) Extent of Exposure

In study -084, 635 patients received a single dose of test medication administered intravenously, with the following distribution:

PL [n=157]	12.5 [n=159]	25 [n=157]	50 [n=162]	Total DOLA•Mesyl [n=478]

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

- There were no deaths reported during the trial.
- No patients D/C from the study due to AEs.
- One of the serious AEs was assessed as possibly related to test medication.
  - Pt. 0370-0029 (DOLA•Mesyl 50 mg) was hospitalized as a result of excessive drowsiness and tiredness.
- Other serious events included pulmonary edema, pain, nausea, vomiting, urinary retention, drowsiness, sedation, anxiety, dyspnea, ascites, pelvic pain, hemoptysis, apprehension and retching. These were assessed by the corresponding investigators as not related to test medication and were generally attributable to the operative procedure or PO pain relief.
- Other notable events occurring among patients DOLA•Mesyl are briefly summarized below.

Patient 0363-0027 (51-y-old F) (25 mg)

She underwent outpatient gynecologic surgery, experienced an episode of stridor than began 46 min. after receiving test med. and lasted for 25 min., resolving without sequelae. This patient had no other AEs.

The investigator assessed the event as moderate and possibly related to test medication.

Patient 0364-0029 (25-y-old F) (50 mg)

She underwent outpatient laparoscopy for tubal sterilization, experienced breathing difficulty than began 1h after receiving test med. and lasted for 30 min.

The investigator assessed the event as mild and unlikely related to test medication but possibly due to the patient's history of heavy smoking and bronchitis.

Patient 0367-0010 (35-y-old F) (12.5 mg)

She underwent outpatient laparoscopy for tubal sterilization, experienced chest pain that began 3h after receiving test me. and lasted for 21h, resolving without sequelae. The patient indicated that the pain varied in intensity and occurred on different sides of the chest. The patient had sinus bradycardia at the EKG taken 120 min. after administration of test medication. One possible explanation of this pain was insufflation into the chest cavity of carbon dioxide used to expand the abdominal cavity for the surgical procedure.

The investigator assessed the event as moderate and possibly related to test medication.

Patient 0367-0023 (20y-old F) (25 mg)

She underwent outpatient laparoscopy for tubal sterilization, experienced bronchospasm that began 20 min. after receiving test med. and lasted for 6 min., resolving without sequelae. This patient has a history of asthma with the last attack occurring four years ago.

The investigator assessed the event as mild and possibly related to test medication.

Patient 0378-0025 (37-y-old F) (25 mg)

She underwent outpatient diagnostic laparoscopy, experienced breathing difficulty than began 20 min. after receiving test med. and lasted for 20 min., resolving without sequelae.

The investigator assessed the event as mild and unlikely due to test medication but rather probably caused by airway irritation by endotracheal intubation.

Patient 0378-0074 (23-y-old F) (50 mg)

She underwent outpatient diagnostic laparoscopy, experienced breathing difficulty than began 40 min. after receiving test med. and lasted for 15 min., resolving without sequelae.

The investigator assessed the event as mild and unlikely due to study medication but rather probably caused by sleepiness from the general anesthesia.

There does not appear to be a relationship between increasing dose of DOLA•Mesyl and the events described above.

3) AEs (Tables 22 and 23)

- There was no statistically significant difference among the test groups regarding the overall rate or the rate of specific organ class (HR & rhythm, central and peripheral nervous system, body as a whole, etc.) (Table 22).

- As listed in Table 22, the most frequently occurring AEs were sinus bradycardia, headache, T-wave change or abnormality, sinus arrhythmia, urinary retention, pain, dizziness and drowsiness. But there was no statistically significance among the groups for any of these AEs.

- There were no increases with DOLA•Mesyl (dose in the frequency (%) of all Tx-emergent or of the most frequent Tx-emergent EKG interval changes (Table 22).

- As shown in Table 23 (upper panel), there was no statistically significant difference in the frequency of all Tx-related AEs either by organ class or specific terms, or in those AEs treated with counteractive medication (headache, Table 23, middle panel) or the frequency (%) of all Tx-related Tx-emergent EKG interval changes.

TABLE 22
Study -084

Overall Rate and Most Frequently Occurring AEs, Frequency of All and Most Frequent Tx-Emergent EKG Interval Changes

System Organ Class and Included Term p-value	PL [n=157]	DOLA•Mesyl Dose (mg) 12.5 [n=159]	25 [n=157]	50 [n=162]	MDL 73,147EF [n=478]
I. Frequency (Percent) of All AEs					
Overall Rate (p=N.S.)	49.0%	49.7%	49.0%	45.7%	48.1%
Heart Rate & Rhythm (p=N.S.)	30.6%	31.4%	31.8%	25.3%	29.5%
Centr and Periph Nervous System (p=N.S.)	8.3%	13.8%	7.0%	13.0%	11.3%
Body as a Whole (p=N.S.)	12.1%	9.4%	10.2%	5.6%	8.4%
II. Most Frequent (≥1% of the Study Population)					
Sinus Bradycardia (p=N.S.)	19 (12.1%)	25 (15.7%)	29 (18.5%)	22 (13.6%)	76 (15.9%)
Headache (p=N.S.)	9 (5.7%)	14 (8.8%)	8 (5.1%)	15 (9.3%)	37 (7.7%)
T-Wave Change or Abnormality (p=N.S.)	13 (8.3%)	15 (9.4%)	9 (5.7%)	10 (6.2%)	34 (7.1%)
Sinus Arrhythmia (p=N.S.)	6 (3.8%)	6 (3.85)	9 (5.7%)	7 (4.3%)	22 (4.6%)
Urinary Retention (p=N.S.)	7 (4.5%)	7 (4.4%)	7 (4.5%)	5 (3.1%)	19 (4.05)
Pain (p=N.S.)	7 (4.5%)	6 (3.8%)	6 (3.8%)	3 (1.9%)	15 (3.1%)
Dizziness (p=N.S.)	3 (1.9%)	6 (3.8%)	2 (1.3%)	4 (2.5%)	12 (2.5%)
Drowsiness (p=N.S.)	4 (2.5%)	3 (1.9%)	5 (3.2%)	3 (1.9%)	11 (2.3%)
III. Frequency (%) of All Tx-Emergent EKG Internal Changes					
Overall Rate (p=N.S.)	35 (22.3%)	28 (17.6%)	24 (15.3%)	39 (24.1%)	91 (19.0%)
Heart Rate & Rhythm (p=0.8776)	35 (22.3%)	28 (17.6%)	24 (15.3%)	39 (24.1%)	91 (19.0%)
QT Interval Prolongation (QTc≥440) (p=N.S.)	30 (19.1%)	19 (11.9%)	21 (13.4%)	31 (19.1%)	71 (14.9%)
EKG Abnormal Specific (QRS≥100) (p=N.S.)	6 (3.8%)	11 (6.9%)	4 (2.5%)	12 (7.4%)	27 (5.6%)
AV Block First Degree (PR≥220)	3 (1.9%)	2 (1.3%)	0	3 (1.9%)	5 (1.0%)

IV. Frequency (%) of Most Frequent Tx-Emergent EKG Interval Changes					
QT Interval Prolongation (QTc≥440) (p=N.S.)	30 (19.1%)	19 (11.9%)	21 (13.4%)	31 (19.1%)	71 (14.9%)
EKG Abnormal Specific (QRS≥100) (p=N.S.)	6 (3.8%)	11 (6.9%)	4 (2.5%)	12 (7.4%)	27 (5.6%)
AV Block First Degree (PR≥220)	3 (1.9%)	2 (1.3%)	0	3 (1.9%)	5 (1.0%)

- The AEs listed in Table 22 and 23 including T-wave changes or abnormality and tachycardia were primarily of mild severity.

TABLE 23
Study -084

Frequency of All Tx-Related AEs and All Tx-Related Tx-Emergent EKG Interval Changes

I. Frequency (%) of All Tx-Related AEs					
System Organ Class and Included Term p-value*	PL [n=157]	DOLA•Mesyl Dose (mg) 12.5 [n=159]	25 [n=157]	50 [n=162]	MDL 73,147EF [n=478]
Overall Rate (p=N.S.)	58 (36.9%)	59 (37.1%)	59 (37.6%)	49 (30.2%)	167 (34.9%)
HEART RATE & RHYTHM (p=N.S.)	43 (27.4%)	41 (25.8%)	43 (27.4%)	33 (20.4%)	117 (24.5%)
Sinus Bradycardia (p=N.S.)	18 (11.5%)	21 (13.2%)	24 (15.3%)	15 (9.3%)	60 (12.6%)
T-Wave Change or Abnormality (p=N.S.)	13 (8.3%)	14 (8.8%)	9 (5.7%)	10 (6.2%)	33 (6.9%)
Sinus Arrhythmia (p=N.S.)	5 (3.2%)	5 (3.1%)	9 (5.7%)	7 (4.3%)	21 (4.4%)
CENTR & PERIPH NERVOUS SYSTEM (p=N.S.)	10 (6.4%)	20 (12.6%)	10 (6.4%)	17 (10.5%)	47 (9.8%)

Headache (p=N.S.)	8 (5.1%)	13 (8.2%)	8 (5.1%)	12 (7.4%)	33 (6.9%)
Dizziness (p=N.S.)	3 (1.9%)	4 (2.5%)	2 (1.3%)	3 (1.9%)	9 (1.9%)
Light-Headed Feeling	2 (1.3%)	5 (3.1%)	0	2 (1.2%)	7 (1.5%)
Dizziness Postural	0	1 (0.6%)	0	2 (1.2%)	3 (0.6%)
GENERAL CARDIOVASCULAR (p=N.S.)	3 (1.9%)	2 (1.3%)	5 (3.2%)	1 (0.6%)	8 (1.7%)
Hypotension	2 (1.3%)	1 (0.6%)	5 (3.2%)	0	6 (1.3%)
BODY AS A WHOLE (p=N.S.)	3 (1.9%)	3 (1.9%)	1 (0.6%)	2 (1.2%)	6 (1.3%)
Drowsiness (p=N.S.)	1 (0.6%)	1 (0.6%)	1 (0.6%)	1 (0.6%)	3 (0.6%)
II. AEs Treated With Counteractive Medications					
Headache (p=N.S.)	2 (1.3%)	6 (3.8%)	4 (2.5%)	6 (3.7%)	16 (3.3%)
III. Frequency (%) of All Tx-Related Tx-Emergent EKG Interval Changes					
Overall Rate (p=N.S.)	33 (21.0%)	27 (17.0%)	23 (14.6%)	39 (24.1%)	89 (18.6%)
HEART RATE & RHYTHM (p=0.6846)	33 (21.0%)	27 (17.0%)	23 (14.6%)	39 (24.1%)	89 (18.6%)
QT Interval Prolongation (QTc≥440) (p=N.S.)	29 (18.5%)	19 (11.9%)	21 (13.4%)	31 (19.1%)	71 (14.9%)
EKG Abnormal Specific (QRS≥100) (p=N.S.)	5 (3.2%)	10 (6.3%)	3 (1.9%)	12 (7.4%)	25 (5.2%)
AV Block First Degree (PR≥220)	3 (1.9%)	2 (1.3%)	0	3 (1.9%)	5 (1.0%)

a) p-value for a linear contrast across dose in the occurrence of that event using a logistic regression model with dose and stratum as explanatory variables.

4) Clinical Laboratory Evaluation

- Of the laboratory chemistries BUN and creatinine showed a significant trend across doses in change from Pre-Tx.

  - BUN showed a smaller decrease from Pre-Tx with increasing dose.

- Creatinine showed a greater decrease with increasing dose; however, there were no patients with outlier creatinine values.

- There were no significant trends across doses for laboratory hematology measurements.

- Two urinalysis measurements showed a significant trend across doses:

  - Specific gravity showed larger increases with dose, and

  - Urine pH showed smaller increases with dose.

  None of these trends appeared to be clinically significant when the values for the DOLA•Mesyl-treated patients were compared to the values for PL-treated patients.

- The summaries of laboratory shifts did not show clinically significant alterations in liver or renal function, hematology, electrolytes or miscellaneous chemistry.

5) Summary of Changes in Vital Signs

- Analysis of mean change at 0, 1, 5, 15, 30, 60, 90 and 120 min. post-Tx and at discharge from baseline for vital signs revealed no substantial or sustained effect on BP when compared to the PL.

  - The pulse rate showed a significant trend across doses in change from baseline at 5 min. posttreatment: there was a smaller decrease from baseline with increasing dose.

  - The systolic BP showed a significant trend across doses at 30, 60 and 120 min. post-Tx: in each case, there was a decreasing linear trend with dose.

  - The diastolic BP showed a significant trend across doses at 1, 5 and 90 min. post-Tx and at discharge in each case, there was a decreasing trend with dose.

- Review of AE data reveals that hypotension occurred in 1.9% of the PL patients and 1.7% of the patients that received DOLA•Mesyl and that there were no episodes of severe hypotension in any dose group.

  - One episode of orthostatic hypotension was observed for the PL dose group and the DOLA•Mesyl 50 mg dose group.

  - The incidence of hypertension was identical for all dose groups.

- Additionally, similar numbers of patients in the PL group and the DOLA•Mesyl treated groups were treated with a counteractive medication for either hypotension or hypertension.

- No patient required hospitalization because of a hypotensive or a hypertensive episode.

6) EKG Changes

- Summary statistics for HR, PR, QRS, QT, QT_c and JT interval measurements at baseline and 120 min. post-Tx and the change from baseline to post-Tx were provided by dose group in sponsor's Table 39.

  - The mean values QRS ($p=0.0001$) and QT ($p=0.0496$) intervals each showed a significant increasing trend across doses in change from baseline.

  - The mean QRS interval increased 1.1 msec on PL and 1.2, 1.5 and 3.7 msec respectively, on DOLA•Mesyl doses 12.5, 25 and 50 mg.

  - The mean QT interval increased 15.9 msec on PL and 15.9, 19.4 and 19.2 msec, respective, on DOLA•Mesyl doses 12.5, 25, and 50 mg.

- None of the other EKG intervals showed significant trends.

- The frequencies of Tx-emergent changes were listed by dose group in sponsor's Table 40.

  - 3 patients met the post-Tx HR >100 bpm criteria, 2 on PL and one on DOLA•Mesyl 25 mg.

  - The rate of occurrence of the post-Tx HR <60 criteria was 10% on PL and 15%, 17% and 13%, respectively, on DOLA•Mesyl doses 12.5, 25 and 50 mg.

  - 3 patients each on PL and DOLA•Mesyl 50 mg and two patients on DOLA•Mesyl 12.5 mg met the post-Tx PR interval ≥220 msec criteria.

  - The rate of occurrence of the post-Tx QRS Interval ≥100 msec criteria was 4% on PL and 6%, 3% and 7%, respectively, on DOLA•Mesyl doses 12.5, 25 and 50 mg.

  - The rate of occurrence of the post-Tx QT_c Interval ≥440 msec criteria was 19% on PL and 12%, 14% and 19%, respectively, on DOLA•Mesyl doses 12.5, 25 and 50 mg.

- The change at minute 120 from baseline of QRS and QT_c, by dose, is illustrated 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 than those seen with PL.

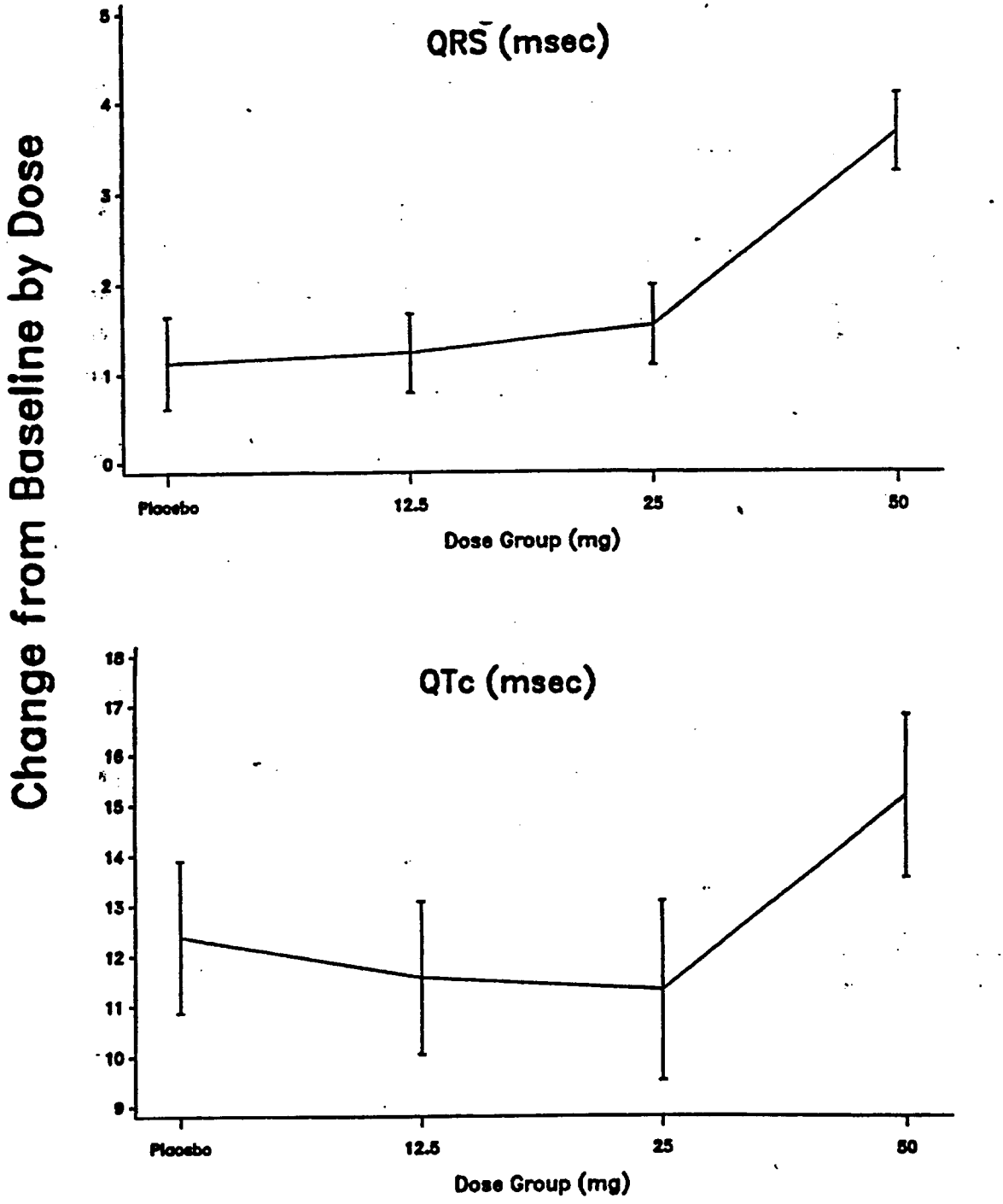

Fig. 5. - Study -084: Change at minute 120 from baseline for QRS (upper graph) and QT_c (lower graph) as a Function of Dose.