Major Protocol Violations

- 42 pts. were considered to have major protocol violations. These 42, together with the 4 patients whose surgery was canceled, were excluded from the Efficacy Evaluable dataset. The proportion of patients with major protocol violations per group, was similar (see computation below).

Frequency (Percent) of Dispositions by Dose

Disposition	PL [n=156]	DOLA©Mesyl Dose (mg)				All Patients [n=793]
		25 [n=159]	50 [n=166]	100 [n=154]	200 [n=158]	
MAJOR VIOLATION	7 (5%)	6 (4%)	9 (5%)	11 (7%)	9 (6%)	42 (5%)
NO SURGERY	0	0	0	0	4 (3%)	4 (1%)
EFFICACY EVALUABLE	149 (96%)	153 (96%)	157 (95%)	143 (93%)	145 (92%)	747 (94%)

- Also similar among the test groups, were the actual major violations, especially the use of concomitant medications proscribed during the trial. This information is summarized below.

	TX GROUP				
	PL	25 mg	50 mg	100 mg	200 mg
Phenothiazines	1				
Benzodiazepines	2	4	1	4	2
Dopamine Antagonist	1	1	3	1	2
Propofol	2		3	1	2
Primary Efficacy Parameters Not Evaluated	1			1	
Failure to Use a Narcotic Intraoperatively		1	1	1	2
Butyrophenones					
Any Surgery other than major gynecological					
Cyclizines					
Study Med: Error					
Study Med: Error					
TOTAL					

NOTE: Patients experiencing more than one protocol violation were counted once.

b. Comparability of Groups/Patient Baseline Characteristics

1) Demographics/Baseline Characteristics (Table 71)

This Table contains the summary statistics by dose and associated p-values. There were no statistically significant differences for demographic and other baseline characteristics. The study population was predominantly Caucasian, 757/793 (95.5%) and of ASA status I, 596/793 (75.2%). The median age was 44y; the median weight was 66.0 Kg; and the median height was 163 cm. History of PONV was reported in 257/793 (32.4%) and history of motion sickness was reported in 146/793 (18.4%) of the patients.

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Demographic and Baseline Characteristics
[ITT Population]

	PL [n=156]	DOLA•Mesyl Dose (mg) 25 [n=159]	50 [n=166]	100 [n=154]	200 [n=158]	All Patients [n=793]	p-value[a]
Race							
Black	0.6%	1.9%	0.0%	2.6%	0.6%	1.1%	
White	94.9%	93.1%	95.8%	97.4%	96.2%	95.5%	N.S.
Other	4.5%	5.0%	4.2%	0.0%	3.2%	3.4%	
Age							
Mean	43.7	43.3	42.4	43.4	42.9	43.2	N.S.
Median	45.0	44.0	43.5	44.0	44.0	44.0	
Height (cm)							
Mean	163.3	162.5	163.7	163.0	163.0	163.0	N.S.
Median	164.8	162.0	164.5	163.0	164.0	163.0	
Weight (Kg)							
Mean	67.9	67.0	68.4	67.2	66.8	67.5	N.S.
Median	67.0	65.0	68.0	65.5	65.0	66.0	
ASA Status							
I	78.2%	73.6%	78.3%	73.4%	72.2%	75.2%	
II	21.2%	25.8%	21.1%	26.6%	27.2%	24.2%	N.S.
III	0.6%	0.6%	0.6%	0.0%	0.6%	0.6%	
History of PONV	32.7%	30.2%	30.7%	29.9%	38.6%	32.4%	N.S.
Hx of Motion Sickness	17.9%	22.0%	14.6%	15.6%	16.5%	18.4%	N.S.
Duration of Anesthesia (h)							
Mean	1.6	1.6	1.6	1.6	1.6	1.6	N.S.
Median	1.4	1.4	1.5	1.5	1.5	1.5	

a) For the continuous variables, p-values are from an analysis of variance for differences among the five dose categories for the continuous variables. p-values are from a χ^2 degrees of freedom likelihood ratio test controlling for investigator.

2) Medical Hx and Physical Examination

There were no marked imbalances among the five test groups in medical history, Pre-Tx and Post-Tx P.E.

3) Concomitant Medications

There were no statistically significant imbalances among Tx groups in doses of medications used for pre-medication, induction, maintenance and reversal of anesthesia (sponsor's Table 10, p. 81).

- The predominant anesthesia premedications utilized were:
  - temazepam (225/790 patients) (mean dose = 18.5 mg)
    and
  - diazepam (191/790 patients) (mean dose = 9.9 mg).
- For induction and maintenance of anesthesia, the predominant agents utilized were:
  - nitrous oxide (787/790 patients) (mean dose = 59.9% for 1.5h)
  - thiopental (774/790 patients) (mean = 325 mg for 1.5h)
  - isoflurane (631/790 patients) (mean = 1.02% for 1.5h)
- The predominant agent utilized in the reversal of anesthesia was neostigmine (546/790 pts.) (mean = 2.4 mg).

4) Previous/Concomitant Other Medications

There were no significant differences among Tx groups with respect to previous medications. The most frequent concomitant medications used Pre-Tx were heparin (147/793 = 19%), enoxaparin (131/793 = 17%) and metronidazole (122/793 = 15%).

There were no statistically significant imbalances among the five test groups in concomitant medications used the 24-h Tx period. The more frequently used concomitant meds. indications taken Post-Tx were:

	PL [n=156]	DOLA®Mesyl Dose (mg)				All Patients [n=793]
		25 [n=159]	50 [n=166]	100 [n=154]	200 [n=158]	
Morphine Sulfate [p=N.S.]	13%	11%	10%	14%	15%	12%
Diclofenac [p=N.S.]	27%	34%	28%	31%	25%	29%
Enoxaparin [p=N.S.]	21%	19%	21%	16%	18%	19%
Heparin [p=N.S.]	16%	18%	16%	19%	15%	17%

5) Escape Medications (Table 72)

There were no statistically significant imbalances among the five test groups in escape medications. As summarized in this Table, the most frequent escape medications were MCP (122/793=15%), prochlorperazine (98/793=12%) and droperidol (66/793=8%).

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Escape Medication

	PL [n=156]	DOLA®Mesyl Dose (mg)				All Patients [n=793]
		25 [n=159]	50 [n=166]	100 [n=154]	200 [n=158]	
MCP [N.S.]a	32 (21%)	29 (18%)	19 (11%)	17 (11%)	25 (16%)	122 (15%)
Prochlorperazine [N.S.]b	26 (17%)	17 (11%)	21 (13%)	19 (12%)	15 (9%)	98 (12%)
Droperidol [N.S.]c	12 (8%)	15 (9%)	9 (5%)	11 (7%)	19 (12%)	66 (8%)
Alizapride	4 (3%)	3 (2%)	3 (2%)	3 (2%)	6 (4%)	19 (2%)
Cyclizine	5 (3%)	6 (4%)	2 (1%)	4 (3%)	2 (1%)	19 (2%)
Ondansetron	3 (2%)	1 (1%)	2 (1%)	2 (1%)	1 (1%)	9 (1%)
a,b,c) P-values were calculated using a 4 degree of freedom Chi-square test.						

c. Clinical Response

1) Analysis of Primary Efficacy Parameters

a) Complete Response (Table 73)

For each of the two population analyses (ITT vs Efficacy Evaluable), results of two types of comparisons are shown: a) comparison of each DOLA•Mesyl dose level against PL and b) comparisons between the DOLA•Mesyl doses.

- In both, the ITT (n=789) and the Evaluable Population (n=747), there was a statistically significant linear trend in the proportion of complete responders across the five dose groups (ITT, p=0.0107; Evaluable Population, p=0.0238).

- The proportion of complete responders in the PL group (ITT=35.3%; Evaluable Population=35.6%) was significantly less than the proportion of complete responders in all DOLA•Mesyl patients combined [ITT, 317/633=50.1% (p=0.0007); Evaluable Population, 300/598=51.4% (p=0.0007)].

- For comparisons to PL, the 50, 100 and 200 mg dose groups were significantly higher than PL [therapeutic gains of 21.9%, 15.3% and 12.1%, respectively, in the ITT population and 22.4%, 14.7% and 11.3%, respectively, in the Evaluable Population]. At only 9.4% (ITT population) and 9.5% (Evaluable Population) the therapeutic gains of 25 mg over PL were not statistically significant.

- In both, the ITT (p=0.0243) and Evaluable Population (p<0.0250), the 50 mg dose group was statistically significantly different from the 25 mg dose groups, with therapeutic gains of 12.5% and 12.9%, respectively. All other DOLA•Mesyl group comparisons, with therapeutic gains ranging from 5.9% to -9.8% in the ITT Population and 5.2 to -11.1% in the Evaluable Populations, were not significant. In the ITT Population, the Mantel-Haenszel test for non-zero correlation was statistically significant (p=0.015).

i) Complete Response Rates by Investigator and Dose (Table 74)

- Overall Complete Response by DOLA•Mesyl groups varied [illegible] among investigators (right hand side column of Table [illegible] = 50%, which is higher than with [illegible]

- Investigator was a statistically significant predictor of complete response (p=0.0366).

- There was no investigator-by-dose interaction [illegible]

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Clinical Response: Analyses of Primary Efficacy Parameters
Complete Response

Response by Dose (mg)/Therapeutic Gain and p-value[a] for PL Comparison					Therapeutic Gain (%) for Comparisons Between DOLA•Mesyl Doses/[p-values[b]]					
I. Intent-To-Treat Analysis (n=789)										
PL [n=135]	25 [n=159]	50 [n=166]	100 [n=154]	200 [n=154]	50 vs 25	100 vs 25	200 vs 25	100 vs 50	200 vs 50	200 vs 100
35 (25.9%)	71 (44.7%)	95 (57.2%)	78 (50.6%)	73 (47.4%)						
	9.4% [N.S.]	22.5% [0.0001]	15.3% [0.0062]	12.1% [0.0181]	12.5% [0.0243]	5.9% [N.S.]	2.7% [N.S.]	-6.6% [N.S.]	-9.8% [N.S.]	-3.2% [N.S.]
II. Efficacy Evaluable Analysis (n=747)										
[n=126]	[n=150]	[n=157]	[n=143]	[n=145]						
33 (26.2%)	68 (45.3%)	91 (58.0%)	72 (50.3%)	68 (46.9%)						
	19.1% [0.0001]	22.4% [<0.001]	14.7% [0.013]	11.3% [N.S.[c]]	12.9% [0.031]	5.2% [N.S.]	1.8% [N.S.]	-7.7 [N.S.]	-11.1 [N.S.[d]]	-3.4 [N.S.]

a) Exact test. Calculated by Dr. M. Fan, FDA Biometrician.
d) Borderline at 0.065.

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135
159
166
154
154
789

TABLE 74
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Complete Response by Investigator and Dose
[ITT Population]

Number of Complete Responders/Number of Patients by Investigator and Dose Cell (%)

Investigator[a]	PL [n=156]	DOLA•Mesyl Dose (mg)[b] 25 [n=159]	50 [n=166]	100 [n=154]	200 [n=154]	Total DOLA•Mesyl [n=633]
7 (n=61)	3/13 (23%)	5/12 (42%)	4/12 (33%)	6/11 (55%)	5/13 (38%)	20/48 (42%)
8 (n=73)	7/15 (47%)	6/15 (40%)	7/15 (47%)	8/14 (57%)	11/14 (79%)	32/58 (55%)
9 (n=50)	4/10 (40%)	5/12 (42%)	7/10 (70%)	3/9 (33%)	2/9 (22%)	17/40 (43%)
13 (n=37)	0/7 (0%)	4/7 (57%)	8/9 (89%)	6/8 (75%)	4/6 (67%)	22/30 (73%)
18 (n=45)	3/9 (33%)	6/9 (67%)	1/9 (11%)	4/10 (40%)	4/8 (50%)	15/36 (42%)
19 (n=17)	1/3 (33%)	1/3 (33%)	2/4 (50%)	3/3 (100%)	1/4 (25%)	7/14 (50%)
20 (n=25)	2/5 (40%)	3/4 (75%)	4/5 (80%)	2/5 (40%)	5/6 (83%)	14/20 (70%)
21 (n=22)	1/4 (25%)	2/3 (67%)	3/6 (50%)	4/5 (80%)	2/4 (50%)	11/18 (61%)
23 (n=19)	1/3 (33%)	1/4 (25%)	3/4 (75%)	0/4 (0%)	2/4 (50%)	6/16 (38%)
25 (n=26)	0/4 (0%)	1/6 (17%)	3/6 (50%)	0/5 (0%)	2/5 (40%)	6/22 (27%)
27 (n=50)	6/10 (60%)	5/10 (50%)	7/10 (70%)	7/10 (70%)	4/10 (40%)	23/40 (58%)
28 (n=24)	3/5 (60%)	2/5 (40%)	3/5 (60%)	1/5 (20%)	1/4 (25%)	7/19 (37%)
30 (n=64)	6/10 (60%)	6/13 (46%)	11/15 (73%)	7/14 (50%)	3/12 (25%)	27/54 (50%)
31 (n=54)	3/13 (23%)	6/10 (60%)	9/10 (90%)	5/11 (45%)	7/10 (70%)	27/41 (66%)
32 (n=16)	0/3 (0%)	3/4 (75%)	3/3 (100%)	3/3 (100%)	2/3 (67%)	11/13 (85%)
33 (n=35)	3/7 (43%)	2/7 (29%)	5/9 (56%)	2/5 (40%)	3/7 (43%)	12/28 (43%)
36 (n=33)	3/6 (50%)	4/7 (57%)	4/8 (50%)	4/7 (57%)	4/5 (80%)	16/27 (59%)
37 (n=13)	1/4 (25%)	0/2 (0%)	2/3 [illegible]	1/2 [illegible]	[illegible]	5/9 (56%)
41 (n=19)	3/5 (60%)	1/5 (20%)	2/3 (67%)	2/4 [illegible]	[illegible]	6/14 (43%)
48 (n=40)	3/8 (38%)	5/8 (63%)	2/8 [illegible]	[illegible]	[illegible]	16/32 (50%)
51,52,54,56, 57,58[c] (n=19)	0/2 (0%)	3/5 (60%)	1/3 [illegible]	[illegible]	[illegible]	7/17 (41%)
24,34,59[d] (n=19)	0/2 (0%)	0/4 (0%)	1/4 [illegible]	[illegible]	[illegible]	[illegible] (29%)
35,47,50[e] (n=28)	2/8 (25%)	0/4 (0%)	2/8 [illegible]	[illegible]	[illegible]	[illegible] (25%)
TOTAL (n=789)	55/156 (35%)	71/159 (45%)	95/166 [illegible]	[illegible]	[illegible]	[illegible] (50%)

a) Investigator p=0.038 from a 12 degree of freedom [illegible]
[illegible] complete response with dose and [illegible]
b) [illegible]
[illegible] from a logistic regression model [illegible]
explanatory variables.
c,d,e) Investigators were pooled in order to estimate parameters [illegible]

ii) Complete Response by Hour and Dose (mg) and by Dose in mg/Kg (Table 75)

- By 2h, all four DOLA•Mesyl dose groups appeared to be equally effective, to and not different from PL.
- Some minor differences between the DOLA•Mesyl dose groups (except 200 mg) and PL are seen by 6h.
- At hour 8, the response with 50 mg DOLA•Mesyl was higher than with PL, statistically significant p- value (0.0116) and a therapeutic gain of 11.1%.
- From 12h onwards, the response with all of the four DOLA•Mesyl was higher than with PL. The p-values (Hazard Ratios) demonstrated a statistically significant difference for the 50 (p=0.002) and 100 mg (p=0.0070) dose levels and the total DOLA•Mesyl (p=0.0010) but not for either 25 (p=N.S.) or 200 mg (p=N.S.) of test med.
- The results of analyses on the bases of mg/Kg (lower panel of Table 75) were similar to those for the primary efficacy analysis for complete response. In this study, dose measured in mg/Kg was not a statistically significant predictor of complete response (p=0.0949).

2) Analyses of Secondary Efficacy Parameters

a) Total Response (Table 76)

- Comparisons of each DOLA•Mesyl dose group to PL of the proportion of Complete Responders with no nausea showed therapeutic gains of 17%, 13% and 11% with the 50, 100 and 200 mg dose group. The p-values for these differences were 0.0007, 0.0055 and 0.0150, respectively. The 25 mg dose level showed a therapeutic gain of only 9% (p=N.S.).
- The proportion of complete responders with no nausea in the combined DOLA•Mesyl group was also significantly greater than PL (therapeutic gain 13%; p=0.0018).
- The results of the Total Response analysis were consistent with those of Complete Response.

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

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

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

Hour	PL [n=156]	DOLA®Mesyl Dose (mg)				Total DOLA®Mesyl [n=633]
		25 [n=159]	50 [n=166]	100 [n=154]	200 [n=154]	
2	154 (98.7%)	153 (96.2%)	159 (95.8%)	148 (96.1%)	149 (96.8%)	609 (96.2%)
6	112 (71.8%)	120 (75.5%)	134 (80.7%)	115 (74.7%)	108 (70.1%)	477 (75.4%)
8	103 (66.0%)	114 (71.7%)	128 (77.1%)	105 (68.2%)	99 (64.3%)	446 (70.5%)
p values for PL Comparison (8 h)		N.S.	0.0116	N.S.	N.S.	N.S.
12	77 (49.4%)	94 (59.1%)	116 (69.9%)	96 (62.3%)	88 (57.1%)	394 (62.2%)
18	67 (42.9%)	73 (52.2%)	105 (63.3%)	89 (57.8%)	82 (53.2%)	359 (56.7%)
24	55 (35.3%)	71 (44.7%)	95 (57.2%)	78 (50.6%)	73 (47.4%)	317 (50.1%)
p values[b] for PL Comparison (Hazard Ratios)		N.S.	0.0002	0.0070	N.S.	0.0010

II. Complete Responders by Dose (mg/Kg)

Number of Complete Responders by Dose Category (%)

	PL [n=156]	DOLA®Mesyl Dose (mg/Kg)[c]				
		≤0.56 [n=168]	>0.56 to 1.11 [n=164]	>1.11 to 2.22 [n=152]	>2.22 [n=149]	
	55 (35.3%)	76 (45.2%)	96 (58.3%)	76 (50%)	71 (47.7%)	

a) p values are calculated from a logistic regression model using pairwise comparisons of each dose to PL controlling for investigator.
b) p values are calculated from tests of the hazard ratios of [illegible] Cox's Proportional Hazards Model of time to first [illegible] for investigator.
c) Dose (mg/Kg) p=0.0949 from a one [illegible] model predicting complete response with [illegible]

TABLE 76
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Clinical Response: Total Response[a] by Dose
[ITT Population]

PL [n=159]	DOLA®Mesyl Dose (mg)				Therapeutic Gain/p-value[b]				Total DOLA®Mesyl[c] vs PL
	25 [n=159]	50 [n=166]	100 [n=154]	200 [n=154]	25 vs PL	50 vs PL	100 vs PL	200 vs PL	
32% [21.2%]	48 (30.2%)	63 (38%)	53 (34.4%)	50 (32.5%)	9% [N.S.]	16.8% [0.0007]	13.2% [0.0088]	11.3% [0.0150]	12.6% [0.0018]

a) Complete Response with no nausea. No nausea is defined as the maximum postdose VAS score <5 mm.
b) p-Value was calculated from a logistic regression model predicting complete response with dose and investigator as explanatory variables.
c) 21.0% - 33.6%

b) Major Response/Escape Medication (Table 77)

- Listed in this Table are the proportions of patients experiencing Complete Response, Major Response, Complete + Major Response, those experiencing 2 to 5 emetic episodes or >5 emetic episodes and those who received escape medication.

- The Complete + Major Responders (0 or 1 emetic episodes) showed a pattern of efficacy similar to that described for Complete Responders.

- The proportion of patients experiencing 2 to 5 emetic episodes was greatest in the PL group 43/156 (27.6%) and lowest in the 100 mg dose group 26/154 (16.9%). The proportion of all patients receiving DOLA•Mesyl that experienced 2 to 5 emetic episodes was 128/633 (20.2%).

- The proportion of patients requiring escape medication was greatest in the PL group 75/156 (48.1%) and lowest in the 50 mg dose group 52/166 (31.3%). The proportion of all patients receiving DOLA•Mesyl that required escape medication was 221/633 (34.9%).

TABLE 77
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Clinical Response: Frequency of Patients by Number of Emetic Episodes and Dose (mg)

Number of Emetic Episodes	PL [n=156]	DOLA•Mesyl Dose (mg)				Total DOLA•Mesyl [n=633]
		25 [n=159]	50 [n=166]	100 [n=154]	200 [n=154]	
0 Complete Responders	55 (35.3%)	71 (44.7%)	95 (57.2%)	78 (50.6%)	73 (47.4%)	317 (50.1%)
1 Major Responders	11 (7.1%)	12 (7.5%)	6 (3.6%)	11 (7.1%)	12 (7.8%)	41 (6.5%)
0 or 1 Complete and Major Responders	66 (42.3%)	83 (52.2%)	101 (60.8%)	89 (57.8%)	85 (55.2%)	358 (56.6%)
p-values[a] for PL Comparison		N.S.	0.0007	0.0078	0.0110	0.0009
2 to 5	43 (27.6%)	40 (25.2%)	28 (16.9%)	26 (16.9%)	34 (22.1%)	128 (20.2%)
>5	7 (4.5%)	4 (2.5%)	2 (1.2%)	4 (2.6%)	4 (2.6%)	14 (2.2%)
Received Escape Medication	75 (48.1%)	39 (24.5%)	52 (31.3%)	71 (46.1%)	69 (44.8%)	221 (34.9%)

a) p-values are calculated from a contrast of the [illegible] logistic regression model predicting complete [illegible] as explanatory variables.

c) Nausea (Table 78)

- Using the mean of all Post-dose scores, [illegible]
The therapeutic gains (test med-PL) for [illegible] groups were 11.8%, 16.9%, 15% and 9.7% for the [illegible]

level, respectively. Statistically significant differences were found between the 25, 50 and 100 mg dose groups and PL. The difference between the 200 mg dose group and PL was not statistically significant. The difference between the combined DOLA•Mesyl dose group and PL (therapeutic gain = 13.4%) was statistically significant.

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Nausea VAS Summary

Scores Range 0 mm="None to 100 mm="Nausea as bad as it can be"							
	Statistic	PL [n=156]	DOLA•Mesyl Dose (mg)				Total DOLA•Mesyl [n=633]
			25 [n=159]	50 [n=166]	100 [n=154]	200 [n=154]	
Hour 2 After Recovery	n	152	154	163	148	151	616
	Median	3.5	1	1	1	0	1
	% NO Nausea[a]	52.6	64.2	64.5	64.3	66.2	64.8
Hour 4 After Recovery	n	153	156	165	149	152	622
	Median	1	0	0	1	0	0
	% NO Nausea[b]	66.7	67.9	70.5	72.7	67.5	69.7
Hour 6 After Recovery	n	152	158	164	152	150	624
	Median	1	1	0	0.4	1	1
	% NO Nausea[c]	65.2	65.4	72.3	73.4	69.5	70.1
Postdose Mean	n	155	158	166	153	153	630
	Median	6.7	2.7	1.7	2.7	2.3	2.3
	% NO Nausea[d]	44.5	56.3	61.4	59.5	54.2	57.9
	P values[e] for Placebo Comparison		0.0339	0.0016	0.0099	N.S.[f]	0.0021
Postdose Maximum	n	155	158	166	153	153	630
	Median	15	5	4	5	6	5
	% NO Nausea	18.1	[illegible]	[illegible]	[illegible]	[illegible]	49.5
	P values for Placebo Comparison		[illegible]	[illegible]	[illegible]	[illegible]	0.0067

a. through d). No ratings for hour 2, 4 and 6 after recovery [illegible] defined as VAS score <5 mm.
e) p-values are calculated using a logistic regression [illegible] nausea, controlling for investigator.
f) Borderline, at p=0.0581.

- At the worst point postdose, the proportion of PL patients with NO nausea was 38.1%. The therapeutic gains (test med. - PL) for each of the four dose levels plus the combined DOLA•Mesyl group were: 10.6%, 13.1%, 10.9%, 10.9% and 11.4% for the 25, 50, 100, 200 mg and combined DOLA•Mesyl group, respectively. The differences between PL and the test med. groups were all statistically significant.

3) Subgroup Analyses (Table 79)

The effect of each of seven variables (age, weight, race, ASA physical status, previous Hx of PONV, type of surgery and duration of anesthesia) on complete response was investigated. A brief description regarding each variable follows.

- Age (p=0.0653)

  - While not statistically significant (p=0.0653), there was a tendency for age to be a predictor of complete response.

  - With the exception of the 25 mg dose group, patients tended to have higher complete response rates if 40 years of age or younger.

  - There was no interaction of age with a linear dose response.

  - When controlling for age along with dose and investigator, the primary test for linear trend in complete response over dose was statistically significant.

- Weight (N.S.)

  This was not a significant predictor of complete response.

- Race (p=0.0249)

  Race was a statistically significant predictor of complete response. Caucasian patients appeared to have a lower response rate than other races combined. However, interpretation of this result is difficult because the number of patients was skewed toward the white category.

  - When controlling for race along with dose and investigator, the primary test for linear trend in complete response over dose remained statistically significant.

- ASA Physical Status (p=N.S.)

  This was not a significant predictor of complete response.

- Previous Hx of PONV (p=0.0001)

  Patients without a Hx of PONV were more likely to [illegible] than were patients with a Hx of PONV.

- 289 of the 522 patients (55.4%) without a Hx of PONV were complete responders, while 78 of the 256 patients (30.5%) with a Hx of PONV were complete responders.

- There was no interaction of previous Hx of PONV with a linear dose response.

- Although previous Hx of PONV was a statistically significant predictor of complete response, when controlling for previous Hx of PONV along with dose and investigator, the primary test for linear trend in complete response over dose remained statistically significant.

- Type of Surgery (p=0.0359)

  Patients having other gynecological surgery were more likely to be complete responders than were patients having a hysterectomy.

  - 92 of the 165 patients (55.8%) having other gynecological surgery were complete responders while 280 of the 624 patients (44.9%) having a hysterectomy were complete responders.

  - There was no interaction of type of surgery with a linear dose response.

  - Although type of surgery was a statistically significant predictor of complete response, when controlling for type of surgery along with dos d investigator, the primary test for linear trend in complete response over dose remained statistically significant.

- Duration of Anesthesia (p=N.S.)

  This was not a significant predictor of complete response.

- When duration of anesthesia, weight and ASA status were entered along with dose and investigator in the logistic regression model, the primary test of linear trend across doses was statistically significant.

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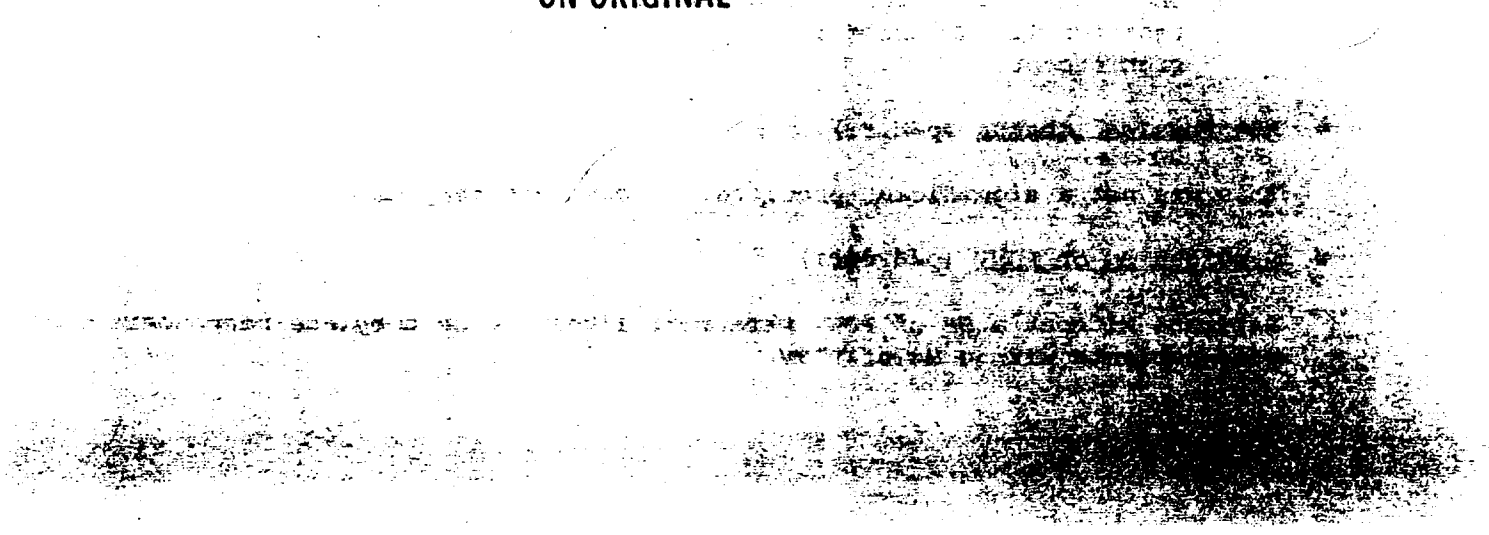

TABLE 79
Study 73147-2-S-095 (Report S-95-0011-C)

Complete Response by Subgroups

Number of Complete Responders/Number of Patients in Dose by Subgroup Category Cell (%)								
Subgroup		PL (n=156)	DOLA•Mesyl Dose (mg)				Total DOLA•Mesyl (n=633)	p values[a]
			25 (n=159)	50 (n=166)	100 (n=154)	200 (n=154)		
Age	≤40 y (n=274)	23/53 (43.4%)	22/55 (40.0%)	39/62 (62.9%)	29/51 (56.9%)	26/53 (49.1%)	116/221 (52.5%)	P(int)=N.S. P(m)=0.0653 p(lin)=0.0125
	>40 y (n=515)	32/103 (31.1%)	49/104 (47.1%)	56/104 (53.8%)	49/103 (47.6%)	47/101 (46.5%)	201/412 (48.8%)	
Weight	≤70 Kg (n=521)	40/102 (39.2%)	46/107 (43.0%)	59/101 (58.4%)	55/104 (52.9%)	49/107 (45.8%)	209/419 (49.9%)	P(int)=N.S. P(m)=N.S. p(lin)=0.0121
	>70 Kg (n=268)	15/54 (27.8%)	25/52 (48.1%)	36/65 (55.4%)	23/50 (46.0%)	24/47 (51.1%)	108/214 (50.5%)	
Race	White (n=753)	52/148 (35.1%)	63/148 (42.6%)	88/159 (55.3%)	75/150 (50.0%)	70/148 (47.3%)	296/605 (48.9%)	P(int)=NA P(m)=0.0249 P(lin)=0.0076
	Other (n=36)	3/8 (37.5%)	8/11 (72.7%)	7/7 (100%)	3/4 (75.0%)	3/6 (50.0%)	21/28 (75.05)	
ASA Physical Status	Excellent(I) (n=593)	46/122 (37.7%)	50/117 (42.7%)	72/130 (55.4%)	53/113 (46.9%)	52/111 (46.8%)	227/471 (48.2%)	P(int)=N.S. P(m)=N.S. P(lin)=0.0113
	Good(II)or (III) (n=196)	9/34 (26.5%)	21/42 (50.0%)	23/36 (63.9%)	25/41 (61.0%)	21/43 (48.8%)	90/162 (55.6%)	
Previous History of PONV	NO (n=522)	46/103 (44.7%)	53/111 (47.7%)	72/112 (64.3%)	68/107 (63.6%)	50/89 (56.2%)	243/419 (58.0%)	P(int)=N.S. P(m)=0.0001 P(lin)=0.0041
	YES (n=256)	9/51 (17.6%)	18/48 (37.5%)	21/51 (41.2%)	10/46 (21.7%)	20/60 (33.3%)	69/205 (33.7%)	
Type of Surgery	Hysterectomy (n=624)	40/123 (32.5%)	54/125 (43.2%)	70/129 (54.3%)	56/118 (47.5%)	60/129 (46.5%)	240/501 (47.9%)	P(int)=N.S. P(m)=0.0359 P(lin)=0.0092
	Other Gynecological (n=165)	15/33 (45.5%)	17/34 (50.0%)	25/37 (67.6%)	23/36 (61.1%)	13/25 (52.0%)	77/132 (58.3%)	
Duration of Anesthesia	≤1 h (n=165)	9/33 (27.3%)	16/33 (48.5%)	13/28 (46.4%)	19/31 (61.3%)	15/30 (50.0%)	64/122 (52.5%)	P(int)=N.S. P(m)=N.S. P(lin)=0.0116
	>1 h (n=624)	46/123 (37.4%)	56/126 (44.4%)	80/138 (58.0%)	60/123 (48.8%)	58/131 (44.3%)	254/518 (49.0%)	

a) All p values were calculated from a logistic regression model with explanatory variables.
- P(int) is the p value for testing for the
- P(m) is the p value for testing the
- P(lin) is the p value for testing
- Continuous measure were entered into the
continuous variables were used for

d. Safety Results

1) Extent of Exposure

In Study 73147-2-S-095, a total of 793 patients received a single dose of test med., with the following distribution:

	DOLA•Mesyl (mg)			
PL	25	50	100	200
[n=156]	[n=159]	[n=166]	[n=154]	[n=158]

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

- One patient in the 100 mg group died from septic shock, which was the result of a perforated GU, resulting in acute hemorrhagic pancreatitis and peritonitis. The investigator assessed the death as unrelated to test med.
- There were no D/Cs from the trial due to AEs.
- A total of 6 patients experienced SAEs, all unrelated to test med.

SERIOUS AEs	
PL	DOLA•Mesyl (50 mg)
1=carcinoma of the appendix, found during scheduled surgery.	1=prolonged hospitalization due to massive hematuria secondary to a perforated bladder, post-operatively.
1=colon cancer with metastatic spread to the ovary, found during scheduled surgery.	1=immediate risk of death and prolonged hospitalization due to hemorrhaging post-operatively.
1=prolonged hospitalization due to possible pulmonary embolus.	1= prolonged hospitalization due to fever.
	DOLA•Mesyl (100 mg)
	1=immediate risk of death and prolonged hospitalization due to post-operative

3) Severe AEs

- The overall incidence of severe-rated AEs was 12/627 (1.9%) in the combined DOLA•Mesyl group and 1/156 (0.6%) in the PL group.

- No event was statistically correlated with dose.
- There was no clear predominance by any system organ class.
- The majority of AEs were considered mild in severity.
- The distribution of severe events was as follows:

	PL	25	50	100	200
Bradycardia	2	1	1	0	0
Headache	0	1	0	1	0
Hemorrhage NOS	0	1	0	1	1
Hypotension	0	1	0	0	0

4) Overall Rate of AE Incidence (Table 80)

- The most frequently occurring AEs (incidence ≥1%) were bradycardia, hypotension and headache.
- No AE showed an increasing linear trend with dose of DOLA•Mesyl.
- AEs occurred with the greatest frequency in the heart rate and rhythm class.
- General cardiovascular AEs occurred with the second greatest frequency in 10/156 (6.4%) of PL and 52/637 (8.2%) of all DOLA•Mesyl patients.
- The most frequently occurring Tx-related AE was headache. Neither headache nor any other Tx-related AE showed an increasing linear trend with dose of DOLA•Mesyl.
- The overall incidence of AEs that were treated with counteracting medications was 22/156 (14.1%) in the PL patients and 72/637 (11.3%) in all DOLA•Mesyl patients combined.
- The system organ class in which [illegible] frequently was the heart rate [illegible] DOLA•Mesyl patients combined [illegible]
- [illegible] AEs that were treated with [illegible] linear relationship to dose of [illegible]
- The percent of patients experiencing mild hypo[illegible]

PL (3.2%)	DOLA•Mesyl Dose (mg) 25 (2.5%)	50 (6.0%)	100 (5.8%)	200 (5.7%)

TABLE 80
Study 73147-2-S-095 (Report S-95-0011-C)

Frequency (%) of AEs and Tx-Related AEs

	PL [n=156]	DOLA•Mesyl Dose (mg) 25 [n=159]	50 [n=166]	100 [n=154]	200 [n=158]	Total [n=637]
Overall Rates (p=N.S.)	30.1%	32.1%	29.5%	29.9%	25.9%	29.4%
Central and Peripheral Nervous System (p=N.S.)	4.5%	6.9%	4.8%	7.8%	7.0%	6.6%
MOST FREQUENTLY OCCURRING AEs						
Bradycardia (p=N.S.)	14/156 (9.0%)	12/159 (7.5%)	13/166 (7.8%)	10/154 (6.5%)	8/158 (5.1%)	43/637 (6.8%)
Hypotension (p=N.S.)	9/156 (5.8%)	6/159 (3.8%)	13/166 (7.8%)	10/154 (6.5%)	10/158 (6.3%)	39/637 (6.1%)
Headache (p=N.S.)	6/156 (3.8%)	9/159 (5.7%)	7/166 (4.2%)	8/154 (5.2%)	8/158 (5.1%)	32/637 (5.0%)
Heart Rate and Rhythm (p=N.S.) - Bradycardia (see above)	17/156 (10.9%)	17/159 (10.7%)	17/166 (10.2%)	13/154 (8.4%)	12/158 (7.6%)	59/637 (9.3%)
Cardiovascular (p=N.S.) - Hypotension (see above) - Hypertension (p=N.S.)	10/156 (6.4%) 2/156 (1.3%)	9/159 (5.7%) 3/159 (1.9%)	15/166 (9.0%) 2/166 (1.2%)	14/154 (9.1%) 4/154 (2.6%)	14/158 (8.9%) 4/158 (2.5%)	52/637 (8.2%) 13/637 (2.0%)
Tx-RELATED AEs						
Overall Rate (p=N.S.)	17/156 (10.9%)	25/159 (15.7%)	11/166 (6.6%)	17/154 (11.0%)	16/158 (10.1%)	69/637 (10.8%)
Central and Peripheral Nervous System (p=N.S.)	5/156 (3.2%)	9/159 (5.7%)	4/166 (2.4%)	7/154 (4.5%)	1/158 (0.6%)	26/637 (4.1%)
Headache (p=N.S.)	5/156 (3.2%)	8/159 (5.0%)	3/166 (1.8%)	5/154 (3.2%)	2/158 (1.3%)	23/637 (3.6%)

5) Clinical Laboratory Evaluation

i) Summary Values

- Of the laboratory chemistries, creatinine and platelet count exhibited a statistically linear relationship across dose in change from baseline. But these changes do not appear to be clinically significant.

Mean Change from Baseline

		DOLA•Mesyl Dose (mg)			
	PL	25	50	100	200
Creatinine (p=0.0182) (μmol/L)	-9.000	8.840	-7.000	-8.840	-8.000
Platelet Count (p=0.0373) (10^9/L)	-30.000	-41.000	-39.000	-38.000	-39.000

ii) Shift Tables

- The following four laboratory tests had 60 or more patients shift from within or above the normal range at Pre-Tx to below the LLNR at Post-Tx: ↓ calcium, ↓ potassium, ↓ sodium and ↓ total protein.

- Two laboratory tests had 60 or more patients shift from within or below the normal range at Pre-Tx to above the ULNR at Post-Tx:

		DOLA•Mesyl Dose (mg)			
	PL	25	50	100	200
↑ Glucose	37/106 (34.9%)	52/110 (47.3%)	39/112 (34.8%)	37/109 (33.9%)	37/108 (34.3%)
↑ Total Bilirubin	16/130 (12.3%)	9/132 (6.8%)	7/139 (5.0%)	12/126 (9.5%)	18/129 (14%)

iii) Significant Changes in Liver Function

iv) Additional Changes in Liver Function

- The number of patients whose GT increased to [illegible] each in the PL and 50 mg group, 2 in the [illegible] group. The corresponding increase in [illegible] and 50 mg groups, and 2 each in the [illegible]

- The reviewer agrees with the sponsor [illegible] at a low incidence level, [illegible] associated with a mild increase in [illegible] trials, the possibility that [illegible] these variables cannot be [illegible]

Pt. #/ Parameter	Pre-Tx Value	ULNR (At Site)	Post-Tx Value	Intensity	Relation to Test Med.
1. 095-0147 (PL)					
OT (U/L)	19	40	69	MOD	POSS
PT (U/L)	27	40	69	MOD	POSS
2. 095-0023 (25 mg)					
OT (U/L)	7	30	82	MILD	POSS
PT (U/L)	13	40	121	MILD	POSS
3. 095-0038 (25 mg)					
OT (U/L)	11	30	67	MOD	POSS
PT (U/L)	23	40	99	MOD	POSS
4. 095-0381 (25 mg)					
PT (U/L)	9	31	93	MOD	PROB
5. 095-0019 (100 mg)					
OT (U/L)	11	30	118	MILD	PROB
PT (U/L)	18	40	212	MILD	PROB

- Twenty-six patients had total BIL levels that increased to >1.5 times the ULN, including 4 PL, 3 in the 25 mg group, 5 in the 50 mg group, 4 in the 100 mg group and 10 in the 200 mg group.

  - There was a tendency for total BIL to rise above BL at 24 h Post-Tx, but the trend was not dose-dependent.

- One patient in the 25 mg group had AP levels that increased to >1.25 times the ULN. Overall, AP levels tended to decline from Pre-Tx values at 24 h Post-Tx; however, the trend was not dose dependent.

6) Descriptive Statistics for EKG Assessments/Graphic Representation of Changes from BL

- From the information provided by the sponsor, the reviewer evaluated data on descriptive statistics for the EKG measures (sponsor's Table 37.1 through 37.6, consisting of EKG summary measures, by dose, on: HR (bpm) and PR, QRS, QT, QTc and JT (
  - The mean changes from BL, at all time points
  - There was no statistically significant
- There was also no dose response across

PONV095

incidence of Tx-related changes for HR, PR, QRS and QTc or when compared to PL [sponsor's Table 38].

- Graphic representation of the changes from BL by Tx (4 and 24 h post-dose) showed little difference in the dose response curves of change from BL to hours 4-5 and h 24 post test med. administration for all six EKG measures.

7) Potentially Clinically Relevant Changes in EKG Intervals

The following is noted:

- Pt. 95-0016 (DOLA•Mesyl 25 mg) had QRS width increase from

- The following four patients had QT_c interval prolongation above 500 msec subsequent to receiving test med.

Dose Group	Pt. ID	QT_c Interval (msec)		Δ
		Pre-Tx	Post-Tx	
25 mg	095-0042[a]	443	565 (4-5h)	122
	095-0280[b]	392	554 (4-5h)	162
	095-0299	436	503 (24h)	67
PL	095-1094	429	527 (4-5h)	98

a) This patient had a QT_c interval above 440 msec Pre-Tx. HR at this time was 104 bpm (site interpretation).
b) HR at this time was 117 bpm (site interpretation).

9. Conclusions (Sponsor)

- "Single oral doses of dolasetron mesylate, administered one to two hours before induction of anesthesia, were effective in decreasing or preventing nausea and/or emetic episodes resulting from 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.

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

10. Reviewer's Comments

Study 095A is one of two pivotal trials the sponsor submitted in support of approval of the marketing of 50 mg dolasetron mesylate given within one hours prior to surgery for the prevention of non-PONV. The reviewer elected to evaluate [illegible] in this study, a larger number of patients [illegible]

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were enrolled. Other things being equal, study -095 is expected to provide very useful information.

Study -095 was a multicenter, double-blind, randomized, parallel, dose-response, 5-arm, set to compare the efficacy and safety of single oral doses of DOLA•Mesyl (25, 50, 100 or 200 mg) with those of PL in the prevention of PONV. The study is therefore testing the effect of the same dose levels of drug used in the prevention of chemotherapy-induced emesis trials. And those doses were chosen on the basis of results of Phase II trials. But whereas in chemo. trials were active-active control in Study -095 the comparator is PL, a negative control. This design, together with the number of patients per arm (ca. 155), also allows comparison of efficacy between DOLA•Mesyl doses. All in all, Study -095 was of adequate design and execution and was conducted in Europe at 32 sites with qualified investigators.

In this and the other pivotal trial, the study population consisted exclusively of females. This brings up the question of whether male patients are expected to respond equally well as females.

In Study -095, 793 females with a mean age of 43 years, scheduled to undergo major gynecological surgery under general anesthesia, and in general, without evidence of major cardiovascular, hepatic or renal dysfunction, were randomized. The patients were required to have an ASA physical status I-III, not to be addicted to alcohol and sign an informed consent before their inclusion into the trial. Excluded were those female patients who were pregnant or lactating, those who were too thin (<45 Kg) or too overweight (>100 Kg), those who were vomiting due to organic condition or were scheduled to receive an intragastric tube post-operatively, and (as in the chemo. trials), those with CHF, second or third degree AV block or those with heart arrhythmia requiring drug treatment.

The randomization schemes and procedures used in this study resulted in five populations of patients that were balanced with respect to variables that may influence outcome. For the five experimental groups, the demographic and other baseline characteristics, including ASA status (the majority were ASA I=75%; ASA II=24% of the patients), Hx of PONV (32%) and Hx of motion sickness (18%) were similar to each other. Other than requiring a major gynecological operation under general anesthesia, the participating females in this trial, were essentially normal.

The experimental groups were balanced with respect to concomitant previous and present medications in general and concomitant medications that may be confounding. There were no statistically significant differences between groups in doses of medications used for pre-medication, induction, maintenance and reversal of anesthesia. Mean duration of anesthesia [illegible] recovery were similar among the test groups. The [illegible] well matched with regards to standardization of the [illegible] appropriate stimuli. In this complex clinical [illegible] factors for emesis, which were well balanced [illegible] abdominal hysterectomy-gynecological laparotomy [illegible] se, together with general anesthesia and the [illegible]

control pain (mainly I.M. or I.V. morphine and NSAIDs). Lack of imbalances among the test groups is important to demonstrate that the differences between PL and the DOLA•Mesyl arms is clearly due to the antiemetic properties of the drug and not to an imbalance in the many prognostic factors that might influence the development of PONV.

The reviewer's comments on efficacy are based on complete and total response in the ITT population, since conclusions based on Efficacy Evaluable analyses are not very different. Two types of comparisons are considered: comparisons of DOLA•Mesyl doses against PL and comparisons of DOLA•Mesyl among themselves. Study -095 demonstrated that DOLA•Mesyl is active because a) there was a statistically significant linear trend in the proportion of complete responders with increasing doses of the drug (ITT, p=0.0107; Evaluable Population, p=0.0238) and b) the proportion of complete responders in the DOLA•Mesyl group combined (ITT=50%; Evaluable Population=51%) was significantly higher (p=0.0007 or less) than the proportion of complete responders in the PL group (ITT=35%; Evaluable Population=36%). This 15% overall therapeutic gain is clinically important.

Individually, the highest therapeutic gain over PL in this trial was 22%, afforded by the 50 mg dose. The effects of the 25 mg dose could not be differentiated from PL and the therapeutic gains over PL with 100 and even 200 mg of DOLA•Mesyl at 15% and 12%, respectively, although statistically significantly different from PL, were lower than those seen with the 50 mg dose. In the main, these results of evaluations in complete responders were consistent with results of evaluations in total responders, although the latter had lower therapeutic gains than the former.

In comparisons against the 25 mg dose, only the 50 mg showed statistically significant differences (p=0.031 or less) with therapeutic gains of 13% (both ITT and evaluable populations). No other significant differences, clinical or otherwise, were demonstrated from comparison among the DOLA•Mesyl groups. Specifically, in this trial, neither the 100 nor the 200 mg DOLA•Mesyl dose could be differentiated from the 25 mg dose.

In Study -095, although investigator was a statistically significant predictor of complete response, there was no investigator-by-dose interaction. Neither weight, ASA physical status nor duration of anesthesia were significant predictors of complete response. The factor [illegible] was a borderline [illegible] (p=0.0653) since, with the exception of the [illegible] tended to have higher complete response rates if [illegible]. Statistically, race was a significant [illegible] those results must be interpreted with caution [illegible] skewed towards the caucasian category. [illegible] 15% more likely to be complete responders [illegible] (p=0.0091) and patients having [illegible] likely to be complete responders [illegible] (p=0.0369). However, when considering [illegible] status, previous hx of PONV and [illegible] investigator, the primary treatment [illegible] statistically significant. In this [illegible]

statistically significant predictor of complete response (p=N.S.). The dose category encompassing the 50 mg dose level, >0.56 to 1.11 mg/Kg (equivalent to 42 to 83 mg single dose in a 75 Kg person) was associated with 22% therapeutic gain over PL.

In an approach similar to that used when commenting on chemo. trials, the reviewer's comments on safety address general safety, cardiovascular AEs and changes in EKG parameters. Serious AEs, including one death (septic shock occurring 15h after the adm. of 100 mg, due to perforated PU, pancreatitis and peritonitis; the patient died 3 days later) and seven additional serious AEs were all unrelated to test med. The majority of AEs were considered mild in severity. The overall incidence of events rated as severe by the investigator was 2% in the combined DOLA•Mesyl group and 3% in the PL group. There was no statistically significant trend with dose in the overall incidence of AEs (PL=30%; total DOLA•Mesyl=29%), most frequently occurring events by system [central and peripheral nervous system (PL=5%; total DOLA•Mesyl=7%)], most frequently occurring AEs [bradycardia, hypotension and headache (DOLA•Mesyl group overall=5%; PL=4%)], treatment with counteractive medications, Tx-related AEs, cardiovascular events, headache or Tx-related EKG changes from BL. The percent of patients in the 50, 100 and 200 mg DOLA•Mesyl groups experiencing mild hypotension were 3% higher than those in the PL group, but these differences were not statistically significant.

In general, changes in clinical laboratory parameters or vital signs showed few alterations of concern. Twenty-six patients (including 4 PL patients) had total BIL that increased to >1.5 times the ULN. There was a tendency for total BIL to rise above BL at 24h Post-Tx but this trend was not dose-dependent. Eight patients, in five of whom the Pre-Tx values were normal, experienced mild to moderate elevations in SGOT and SGPT (but BIL and other enzymes were normal and BIL did not change with Tx). Given the fact that, at a low incidence level, administration of DOLA•Mesyl has been associated with mild increases in transaminases, the possibility that test med. contributed to increases in these variables, cannot be excluded.

In this Study -095, no clinically significant cardiac events occurred. Administration of DOLA•Mesyl resulted in an acute, reversible, dose-related depression in recumbent systolic and diastolic blood pressure. One DOLA•Mesyl patient (25 mg) had severe hypotension. According to a Protocol amendment, additional EKG evaluations were required at 15 [illegible] after test med. administration. From this [illegible] has presented data and graphs at 4 and 24h Post-Tx but not [illegible] of the most interest. Therefore, the [illegible] evaluations are based on [illegible]

The mean EKG changes from BL at 4 and 24 [illegible] dose groups and there [illegible] in change from BL. There was [illegible] groups in the incidence of Tx-[illegible] compared to PL. Mean [illegible] changes in HR were [illegible] from BL by Tx (4 and 24h Post-[illegible]

response curves of changes from BL to hours 4-5 and h24 post test med. administration, for all six EKG measures evaluated. It is to be noted that this trial showed neither increases in QRS nor in QT_c. This is not in keeping with the predictable results based upon the documented relationship between QRS prolongation and plasma levels of MDL 74,156, the active metabolite of DOLA•Mesyl.

In conclusion, orally administered tablets of DOLA•Mesyl are effective in the prevention of post-operative-induced nausea and emesis. Although the response is linearly related to dose, there seemed to be no advantage in increasing the dose to higher than 50 mg per day. But the 100 mg is active in comparison to PL. In this study population and under the experimental conditions and methodology used in Study -095, graded oral doses of DOLA•Mesyl were well-tolerated. Acute effects (1-2h after administration) were not evaluated but at 4 and 24h Post-Tx electrophysiologic effects did not result in the well documented increases in 12-lead PR, QRS and QT_c. Clinically, no significant cardiac events occurred. Specifically, there were no reports of complete BBB, SVT, VT, high degree AV block or torsades de pointes. However, based on observations in chemotherapy-induced N&V studies and in the results of the other PONV pivotal trial, the potential for serious DOLA•Mesyl toxicity on EKG parameters cannot be dismissed.

XII. STUDY AN-PO-0292 (REPORT L-95-0001-CS)

1. Title

"Evaluation of the Efficacy and Safety of Single Oral Doses of Dolasetron Mesylate in Preventing Postoperative Nausea and Vomiting"

NOTE: The summary description that follows includes five general amendments (January 28, 1993, March 4, 1993, March 17, 1993, August 20, 1993 and November 17, 1993) and two specific amendments. The general amendments [for example, switching from morphine to meperidine (pethidine) and allowing certain concomitant medications at doses unlikely to have a significant effect on outcome. Also included in amendment 5 was a redefinition of abnormal EKG intervals to be not only greater but equal to the following figures:

PR ≥220 msec
QRS ≥100 msec
QT_c ≥440 msec

Site Specific Amendments - Site [illegible] was drafted and approved prior to each site's [illegible]

These two sites followed the amendments below [illegible]

- Added two ECGs (end of recovery, week one) and [illegible] monitoring during the recovery room stay.
- Modified exclusion criterion no. 5 to now exclude [illegible] addition to those with second or third AV block as [illegible]

- Modified exclusion criterion no. 16 to now exclude patients taking digitalis or any diuretic, calcium channel blocker, or beta blocker for the treatment of any cardiovascular indication, in addition to those taking bepradil as specified in the original protocol.

Site Specific Amendment - Site #6 (May 10, 1993):

The amendment which is specified below:

- Modified exclusion criterion no. 4 to also exclude any patient with a Hx of arrhythmia investigated and documented by a physician, in addition to excluding patients who required antiarrhythmic medication as specified by the original protocol.

- Modified exclusion criterion no. 5 to also exclude any patient with a conduction abnormality (atrial-ventricular or intraventricular, first degree AV block, intraventricular conduction defect and abnormal QT).

2. Objectives

- To evaluate the dose-response relationship of DOLA•Mesyl 25, 50, 100 and 200 mg compared to PL when administered as a single, oral dose 1 to 2 h preoperatively to prevent N&V in patients undergoing uncomplicated abdominal hysterectomy under general anesthesia.

- To evaluate the efficacy and safety of DOLA•Mesyl.

3. Study Population (Table 81)

The inclusion-exclusion criteria listed in this Table, were adequate for this type of study. The identified risk factors for PONV were: female gender, abdominal hysterectomy, general anesthesia, medications given in relation to anesthesia, pre-, induction and maintenance, narcotic and neuromuscular blocking and analgesics such as morphine. Also adequate were the reasons for excluding patients from the trial, such as those with organic conditions associated with vomiting, those receiving potentially confounding medications and those receiving intragastric tube postoperatively.

It is of interest to note that, from the cardiovascular viewpoint, not included in the trial were patients with cardiomyopathy, CHF or Hx of CHF, arrhythmias requiring antiarrhythmic medication, those with second or third degree AV block, those with pre-existing either L or R BBB (QRS ≥120 msec) and those with significant cardiovascular dysfunction.

4. Concomitant Medications

In their Appendix G, the sponsor listed many classes of prohibited concomitant medications, giving examples of the generic name and the [illegible] depressants (tricyclic antidepressants), [illegible] benzodiazepines, butyrophenones, cannabinoids, [illegible] agents, phenothiazines, sympathomimetics, other [illegible] antagonists. It was clearly stipulated that [illegible] potential antiemetic activity, unless [illegible] considered a protocol violation.

TABLE 81
Study AN-PO-0292 (Report L-95-0001-CS)

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• Females aged 18 and ≤70 y • Scheduled to undergo inpatient uncomplicated abdominal hysterectomy - for dysfunctional or postmenopausal bleeding - with or without salpingo-oophorectomy - due to abdominal endometrial histology - due to abdominal cervical histology • Scheduled to receive balance general anesthesia, with the following general anesthetic regimen: - [illegible]: d-tubocurare - [illegible]: Fentanyl - Induction and intubation (100% O_2 until intubation): - [illegible]: succinylcholine - [illegible]: nitrous oxide/isoflurane - [illegible]: vecuronium - [illegible]: Fentanyl - [illegible]: Glycopyrrolate - [illegible] p.r.n. I.M. or I.V. morphine as a post-operative analgesic - [illegible] Class I or II	• Patient undergoing hysterectomy and: - there was reason to expect that surgery would be more complicated or significantly longer than usual - massive fibroid or extensive pelvic endometriosis was present - surgery involved major extensive dissection extending beyond the uterus • Weight <45 Kg • Cardiomyopathy, CHF or Hx of CHF • Arrhythmias requiring antiarrhythmic medication • Greater than first degree AV block • Pre-existing complete BBB with L or R (QRS ≥120 msec) • Evidence of any other clinically significant respiratory, cardiovascular, metabolic, hepatic or renal dysfunction • Severe disorder requiring anti-convulsant med. • Vomiting from any organic etiology[b] • Vomiting during the week prior to test med. • Scheduled to have nasogastric tube postoperatively • Limited mental capacity • Concomitant medication with potential antiemetic efficacy • Use of an investigational new drug • Receiving chronic treatment with benzodiazepines or a pre-operative tranquilizer[c] • Addiction to alcohol or drugs • Evidence of clinically significant liver disease[d] • Elevated serum creatinine (>180 μmol/L) • Clinically significant abnormality in serum K^+ or Ca^{++} • Allergy to the scheduled, standardized preoperative tranquilizer, operative anesthetic or postoperative analgesia • Hx of allergy to 5-HT$_3$ antagonists[e] • Previous Tx with DOLA®Mesyl

[illegible] bleeding agent; b) Such as gastric outlet obstruction, or small bowel obstruction or active symptomatic [illegible] patients were allowed benzodiazepines intermittently during the 7 d prior to admission and as ordered for bed-[illegible] the night prior to surgery; d) ALT and AST ≥3 times ULN or BIL >34 μmol/L; e) ondansetron (Zofran®), granisetron [illegible], etc.