5. Test Medication

a. Identity of Test Medication

DOLA•Mesyl was supplied as tablets in blister cards. All tablets, identical in shape and color, were supplied by MMD, Winnersh, England. The corresponding lot numbers were:

DOLA•Mesyl PL (mg)	Lot # (WN-)	DOLA•Mesyl (mg)	Lot # (WN-)
25	920827	25	930117
50	920828	50	930116
100	921012	100	930114
		100	930205

b. Dosing Schedule

- Test med. or PL was given in a double-blind fashion (see below), 1 to 2h pre-operatively, with 50 to 75 ml of water.
- The sponsor noted that the patients were generally not permitted food from midnight the evening prior to surgery. However, the period of time since previous unlimited amount of fluids permitted (free fluids) varied from site to site. This information was collected in the CRF and was examined in sub-group analyses.

c. Blinding, Packaging and Labeling

These aspects of the execution of the trial were adequate.

- Each blister card contained 8 tablets.
- A single dose consisted of 4 tablets. An extra dose (4 tablets), identical to the first one, was supplied in case of inadvertent destruction or loss of the first dose.
- Because three strengths of DOLA•Mesyl tablets were used (25, 50 and 100 mg size), to appropriately blind the study for all [illegible] per group were required:

PL	25	50	100
2 placebo 25 mg	1 active 25 mg	2 placebo	2 placebo 25 mg
1 placebo 50 mg	1 placebo 25 mg	1 active 50 mg	1 placebo 50
1 placebo 100 mg	1 placebo 50 mg	1 placebo 100 mg	1 placebo 100
	1 placebo 100 mg		

d. Method of Assignment

Patients were assigned in a randomized double-blind manner to one of the five dose groups using plan procedure under SAS software version 6.08 (sponsor's Appendix D: Randomization Schedule, page 1038).

e. Compliance

Test med. was administered by the investigator, study coordinator or a delegated registered nurse. Patients were observed during the administration.

6. Study Evaluations

a. Efficacy Parameters

NOTE: Unless clarified, the definitions of primary and secondary efficacy parameters were as per Study -095 and are not repeated here.

- The primary efficacy parameter was determined during the 24h study period by the number of emetic episodes used to classify the patients into complete (0 emetic episodes), major (1 emetic episode) or no responders (Tx Fxs: ≥2 emetic episodes).[30]
- The secondary efficacy parameters (listed in the Protocol) included:
  - Total response (complete response with no nausea).
  - Proportion of Complete Responders after being treated for an 8-h period with different doses of DOLA•Mesyl.
  - Major response (1 emetic episode at 8h and 24h post dose.
  - Time to first emetic episode.
  - Nausea VAS ("0" to "200")
  - Time to onset of nausea.
  - Patient 24-h satisfaction VAS.
  - Time to rescue medication.

[30] The standardized escape antiemetic medication [illegible] 0.5 mg/kg I.V. or I.M. with a maximum of 50 mg. The [illegible] discretion based on the severity of the presenting [illegible] day. If the patient had no vomiting, retching or [illegible] medication (those having met the escape criteria, the [illegible] vomiting, retching or nausea (i.e., 3 emetic episodes [illegible] having met escape criteria, they were considered to be [illegible] rescue therapy were secondary efficacy parameters.

b. Safety Endpoints

- Vital signs
- Resting 12-lead EKG
- Adverse Events
- Physical Exam
- Clinical Laboratory Tests

7. Statistical Methodology

a. Sample Size Justification

- Sample size determination was based on a linear trend test in the logistic scale, across the five doses of DOLA•Mesyl, while adjusting for the design factor of investigative site.
- The calculation postulated complete response rates of 34%, 37%, 41%, 49% and 65% of patients in the DOLA•Mesyl doses of 0, 25, 50, 100 and 200 mg, respectively [31%therapeutic gain with the highest dose over PL].
- Assuming 50 patients in each dose group, for a total of 250 patients, the power for a 2-tailed 0.05 significance linear trend test is 94%.
- In order to increase the safety database, additional patients were studied for a total of 374 patients, in each dose group.

b. Specific Statistical Analyses

The following were the specific statistical methods used to analyze primary and secondary efficacy and safety data.

8. Results

a. Participating Investigators/Patient Accounting

The following 13 investigative sites in Canada enrolled a total of 374 female patients.

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PARAMETER	STATISTICAL METHOD
1. Complete Response	Logistic regression with a test for linear trend in the proportion of complete responders with dose, controlling for investigator as a main effect.
2. Effect of age, race and other factors in the likelihood of complete response	Logistic regression
3. Total response	Logistic regression to test for a linear trend with dose.
4. Proportion of complete responders after being treated for an 8-h period with different doses of test med.	Logistic regression, comparing each DOLA•Mesyl dose to PL
5. Major Response	Logistic regression
6. Major Response at 8h postdose	Analysis not performed*
7. Time to first emetic episode	Cox regression model (SAS PHREG procedure)
8. Nausea VAS (BL, the end of recovery room, hour 8 and hour 24)	Mean change from BL to 24h=AOV, controlling for investigator and BL nausea. Proportion of NO nausea was analyzed by a logistic regression model controlling for dose and investigator.
9. Time to Onset of Nausea	Analysis not performed.*
10. Effect of the phase of the menstrual cycle on complete response	Analysis not performed.
11. Safety/EKG - Change in vital signs from Pre-Tx to Post-Tx - EKG changes from pre-study to 90 min., arrival and end of recovery room stay, 8h, and 24h Post-study in PR, QRS, QT, QT_c and JT	As in Study -095.

* The reasons not to perform these planned analyses, provided by the investigator in the text of the Clinical Report, were sound.

Major Protocol Violations

- 29 pts. (8%) were considered to have major protocol violations. These 29 together with the patient that did not [illegible] were excluded from the efficacy evaluable [illegible] The proportion of patients with major protocol violations was similar.

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Site		Total # of Pts. Randomized
#01	(Warriner; Vancouver, Br. Columbia)	56
#02[a,b]	(Finegan; Edmonton, Alberta)	39
#03	(Knox; Halifax, Nova Scotia)	69
#04	(Belo; Toronto, Ontario)	49
#05	(Perreault; Montreal, Quebec)	38
#06	(Te'trault; Sherbrooke, Quebec)	8
#07	(Cole; Vancouver, Br. Columbia)	23
#08	(Plourde; Montreal, Quebec)	12
#09	(Kronberg; Toronto, Ontario)	26
#10	(Hudson; Winnipeg, Manitoba)	15
#11	(Duval; Edmonton, Alberta)	7
#12	(Cole; Vancouver, Br. Columbia)	23
#14[c]	(Murphy; Vancouver, Br. Columbia)	9
	TOTAL	374

a) Pt. 0002-0016: D/C the study 8h after receiving test med., because of "inadequate pain and nausea relief". Sufficient efficacy and safety information was available, so that the patient was included in the ITT analysis.
b) Pt. 0002-0023: received test med. but surgery was canceled. this pt. was not included in the ITT efficacy analysis.
c) Pt. 0014-0438: a genotypically F patient was undergoing abd. hysterectomy as part of a process to become M. He was legally M at the time of the trial. The pt. was receiving depo-testosterone I.M. every 2 weeks. This pt. was included in the analysis.

FREQUENCY (%) OF DISPOSITIONS BY DOSE

Disposition	Dose (mg)					All
	PL (n=78)	25 (n=76)	50 (n=74)	100 (n=76)	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	0	1 (1%)	0	0	[illegible]	[illegible]
Efficacy Evaluable	68 (87%)	71 (93%)	71 (96%)	[illegible]	[illegible]	[illegible]

- The actual protocol deviations are listed below:

PL [n=7]	25 mg [n=4]	50 mg [n=3]	100 mg [n=8]	200 [n=7]
(1) Benzodiazepines 24h Post (1) <23.5h of evaluation for Complete Responder	(1) Benzodiazepines 24h Post (1) <23.5h of evaluation for Complete Responder	(1) Benzodiazepines 24h Post (1) Rescue inappropriate (1) Surgery not as defined	(3) Benzodiazepines 24h Post (1) Unblinding prior to completion (1) Oral/I.V. steroids 24h prior/post (1) NG tube (1) Surgery not as defined (1) Maxeran/Antiemetic 24h prior/post	(1) Benzodiazepines 24h Post (2) Surgery not as defined (1) Maxeran/Antiemetic 24h prior/post (1) Unblinding prior to completion (1) Vomiting 24h prior (1) Deviations in anesthetic procedure

Listing 1: Dispositions, Section 8, vol. 1.270, p. 380 through 412

b. Comparability of Groups/Patient Baseline Characteristics

1) Demographics/Baseline Characteristics (Table 82)

Summary statistics by dose and associated p-values (all N.S.), show no statistically significant differences among the five test groups for demographic and other characteristics at baseline.

TABLE 82
Study AN-PO-0292 (Report L-95-0001-CS)

Demographic and Baseline Characteristics
[ITT Population]

Variable	Dose (mg)					All Patients [n=374]	p-value[a]
	PL [n=75]	25 [n=76]	50 [n=74]	100 [n=74]	200 [n=75]		
Race							
Black	4.0%	1.3%	4.1%	8.1%	2.7%	4.0%	
White	85.3%	80.3%	85.1%	79.7%	78.7%	81.8%	N.S.
Other	1.3%	5.3%	1.4%	8.1%	2.7%	3.7%	
Oriental	9.3%	13.2%	9.5%	4.1%	16.0%	10.4%	
Age							
Mean	42.49	43.45	44.26	43.74	42.75	43.33	N.S
Median	43.00	43.50	44.00	45.00	42.00	43.00	
Height (cm)							
Mean	162.6	164.5	164.0	163.2	162.7	163.4	N.S.
Median	162.5	164.5	165.3	162.5	162.5	163.5	
Weight (Kg)							
Mean	67.9	69.5	71.0	71.8	71.2	70.3	N.S.
Median	66.0	66.8	71.0	67.7	66.5	67.1	
ASA							
Status I	66.7%	63.2%	67.6%	68.9%	56.0%	64.4%	N.S.
Status II	33.3%	36.8%	32.4%	31.1%	44.0%	35.6%	
History of PONV	53.3%	42.1%	51.4%	43.2%	44.0%	46.8%	N.S.
History of Motion Sickness	22.7%	28.9%	33.8%	24.3%	28.0%	27.5%	N.S.
Duration of Anesthesia (h)							
Mean	1.47	1.49	[illegible]	1.49	[illegible]	1.49	N.S.
Median	1.42	1.42	[illegible]	1.35	[illegible]	1.42	
Time From Last Oral Fluids to Test Med. Administration (h)							
Mean	8.74	8.87	[illegible]	[illegible]	[illegible]	[illegible]	N.S.
Median	8.83	8.92	[illegible]	[illegible]	[illegible]	[illegible]	

a) [illegible] p-values [illegible] controlling for investigator. For [illegible] the [illegible] test calculated from a [illegible]

2) Medical Hx and Physical Examination

The five test groups were similar to each other in medical history, Pre-Tx and Post-Tx P.E.

3) Pre-Tx Concomitant Medications

Listed below are the four most frequent concomitant medications used in >1% of the study population Pre-Tx. No marked imbalances among the five test groups are seen.

Frequency (%) of Concomitant Medications Taken Pre-Tx[a]						
Non-Study Medication p value[b]	Dose (mg)					All Patients [n=374]
	PL [n=75]	25 [n=76]	50 [n=74]	100 [n=74]	200 [n=75]	
Fleet Enema (N.S.)	25 (33%)	31 (41%)	27 (36%)	24 (32%)	28 (37%)	135 (35%)
Lorazepam (N.S.)	22 (29%)	21 (28%)	23 (31%)	23 (31%)	18 (24%)	107 (29%)
Metronidazole (N.S.)	15 (20%)	15 (20%)	13 (18%)	15 (20%)	15 (20%)	73 (20%)
Iron (N.S.)	10 (13%)	10 (13%)	17 (23%)	14 (19%)	12 (16%)	63 (17%)

a) Received in more than 1% of the study population.
b) p values are calculated using a 4 degree of freedom Chi-square test.

4) Anesthesia Medications

There were no statistically significant imbalances among the five test groups in doses of medications used for premedication, induction, maintenance and reversal of anesthesia.

5) Post-Tx Concomitant/Escape Medications

- Listed below are the seven most frequent concomitant medications, used in >1% of the study population Post-Tx. There were no statistically significant imbalances among the five dose groups in concomitant medications taken Post-Tx.

- Also listed are the most frequent escape medications. The most frequent escape medication was dimenhydrinate 178/374 (48%). There was a statistically significant imbalance among the five dose groups in use of dimenhydrinate (p=0.024). More PL patients (43/75, 57%) took dimenhydrinate than patients in the 200 mg group (32/75, 43%), 40/74 (54%), 29/74 (39%) and 10/75 (13%) in the 25, 50, 100 and 200 mg groups, respectively].

Frequency (%) of Concomitant Medications Taken Post-Tx[a]						
Non-Study Medication p value[b]	Dose (mg)					All Patients [n=374]
	PL [n=75]	25 [n=76]	50 [n=74]	100 [n=74]	200 [n=75]	
Morphine (N.S.)	100%	99%	99%	100%	100%	99%
Cefazolin (N.S.)	23%	26%	36%	32%	23%	28%
Ampicillin (N.S.)	20%	16%	15%	18%	13%	16%
Iron (N.S.)	9%	11%	14%	7%	7%	9%
Atropine (N.S.)	5%	11%	9%	7%	5%	7%
Heparin (N.S.)	5%	7%	7%	8%	11%	7%
Diphenhydramine (N.S.)	8%	8%	4%	4%	9%	7%
ESCAPE MEDICATION						
Dimenhydrinate (p=0.024)	61%	43%	54%	39%	40%	48%
Metoclopramide	4%	3%	1%	0	0	2%
Prochlorperazine	5%	0	0	0	0	1%

a) Received in >1% of the study population.
b) p values are calculated using a 4 degree of freedom Chi-square test.

c. Clinical Response

1) Analysis of Primary Efficacy Parameters

a) Complete Response (Table 83)

In this Table, for each of the two population analyses (ITT=upper panel; Efficacy Evaluable=lower panel) results of two types of comparisons are depicted: a) comparison of each of the four DOLA•Mesyl levels to PL and b) comparisons between the DOLA•Mesyl doses.

- For both populations, there was a statistically significant linear trend in the proportion of complete responders across the five dose groups (ITT, n=373, p=0.0015; Efficacy Evaluable, n=344, p=0.0023).
- With low therapeutic gains (ITT=7%, Efficacy Evaluable=8%) effect of the 25 mg dose level could not be differentiated
- Although the 50 mg dose level (ITT) and 9.9% (Efficacy Evaluable) statistically different from PL either
- Both the 100 and the 200 mg dose levels corresponding therapeutic gains of 25% and 21% in the ITT, 22% and 21% in the Efficacy Evaluable population over PL are clinically meaningful.

- The comparisons between DOLA•Mesyl doses yielded a statistically significant difference only for the comparison between the 100 vs the 25 mg dose and only in the ITT population, with a therapeutic gain of 18.1%. The Mantel-Haenszel test for non-zero correlation was statistically significant (p=0.001). No other comparison between DOLA•Mesyl doses was statistically significant.

- The Efficacy Evaluable population analysis did not show any statistically significant difference between any of the DOLA•Mesyl dose levels.

- Thus, in this trial, the results for the primary test for efficacy were not replicated in the efficacy evaluable patients.

i) Complete Response by Investigator and Dose (Table 84)

- Overall Complete Response by DOLA•Mesyl groups ranged from (total average=45%; which is higher than with PL=29%).

- The investigator was not a statistically significant predictor of complete response (p=0.4755).

- There was no dose by investigator interaction (p=0.1692).

- When taking sample sizes into consideration, dose trends were consistent over investigator.

ii) Complete Response by Hour and Dose (mg) and by Dose in mg/Kg (Table 85)

- By 2h, all groups, including PL are highly effective (all 100% complete responders).

- Some differences between the DOLA•Mesyl dose group and PL are seen by 6h. In reality, all groups are falling in efficacy but the PL seems to be going further down than the DOLA•Mesyl groups.

- By 8h, PL is half as effective as it was at 2h. The 25, 50 and 100 mg DOLA•Mesyl groups are ca. 70% effective. All three groups are statistically different from PL. The 200 mg is only 80% effective and could not be differentiated from PL.

- The differences from PL in the hazard ratio in the 50 and 200 mg dose groups and the combined DOLA•Mesyl groups were statistically significant, but neither the 25 mg dose could be differentiated from PL.

- The results of analyses on the basis of [illegible] were similar to those for the primary [illegible] response (Table 85). Complete response [illegible] significant linear fashion from 25 to [illegible] of at 200 mg. Dose emerged as a [illegible] predictor of complete response (p=0.0041).

TABLE 83
Study AN-PO-0292 (Report L-95-0001-CS)

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=373)										
PL (n=75)	25 (n=75)	50 (n=74)	100 (n=74)	200 (n=75)	50 vs 25	100 vs 25	200 vs 25	100 vs 50	200 vs 50	200 vs 100
22 (29.3%)	27 (36%)	30 (40.5%)	40 (54.1%)	37 (49.3%)						
	(6.7%) [N.S.]	(11.2%) [N.S.]	(24.8%) [0.0026]	(20.0%) [0.0139]	(4.5%) [N.S.]	(18.1%) [0.033]	(13.3%) [N.S.]	(13.6%) [N.S.]	(8.8%) [N.S.]	(-4.8%) [N.S.]
II. Efficacy Evaluable Analysis (n=344)										
[n=68]	[n=75]	[n=71]	[n=66]	[n=68]						
22 (32.4%)	27 [illegible]	30 (42.3%)	36 (54.5%)	36 (52.9%)						
	[illegible]	(9.9%) [N.S.]	(22.1%) [0.014]	(20.5%) [0.024]	(4.3%) [N.S.]	(16.5%) [N.S.][c]	(14.9%) [N.S.][d]	(12.2%) [N.S.]	(10.6%) [N.S.]	(-1.6%) [N.S.]

[a] [illegible]'s Exact Test. Calculated by Dr. M. Fan, FDA Biometrician

TABLE 84
Study AN-PO-0292 (Report L-95-0001-CS)

Complete Response by Investigator and Dose
[ITT Population]

Number of Complete Responders/Number of Patients in Investigator by Dose Cell (Percent)

Investigator[a]	Dose (mg)[b]					Total DOLA•Mesyl [n=298]
	PL [n=75]	25 [n=75]	50 [n=74]	100 [n=74]	200 [n=75]	
1 [n=56]	3/11 (27%)	2/11 (18%)	6/11 (55%)	8/11 (73%)	8/12 (67%)	24/45 (53%)
2 [n=38]	2/8 (25%)	1/7 (14%)	3/8 (38%)	5/8 (63%)	2/7 (29%)	11/30 (37%)
3 [n=69]	6/14 (43%)	5/14 (36%)	4/13 (31%)	12/14 (86%)	6/14 (43%)	27/55 (49%)
4 [n=49]	3/10 (30%)	4/9 (44%)	4/10 (40%)	3/10 (30%)	5/10 (50%)	16/39 (41%)
5 [n=38]	1/8 (13%)	1/7 (14%)	1/8 (13%)	5/8 (63%)	4/7 (57%)	11/30 (37%)
7 [n=23]	2/4 (50%)	2/4 (50%)	4/5 (80%)	3/5 (60%)	3/5 (60%)	12/19 (63%)
9 [n=26]	2/5 (40%)	3/6 (50%)	0/5 (0%)	1/5 (20%)	3/5 (60%)	7/21 (33%)
10 [n=15]	2/3 (67%)	2/4 (50%)	1/3 (33%)	0/2 (0%)	0/3 (0%)	3/12 (25%)
12 [n=23]	0/5 (0%)	3/6 (50%)	3/4 (75%)	1/4 (25%)	2/4 (50%)	9/18 (50%)
6, 11[c] [n=15]	0/3 (0%)	1/2 (50%)	2/3 (67%)	0/3 (0%)	2/4 (50%)	5/12 (42%)
8, 14[d] [n=21]	1/4 (25%)	3/5 (60%)	2/4 (50%)	2/4 (50%)	2/4 (50%)	9/17 (53%)
Total [n=373]	22/75 (29%)	27/75 (36%)	30/74 (41%)	40/74 (54%)	37/75 (49%)	136/298 (46%)

a) Investigator p=0.4755 from a 10 degree of freedom Chi-square [illegible] regression model predicting complete response with dose and investigator.

b) Dose by Investigator interaction p=0.1692 from a [illegible] source from a logistic regression model predicting [illegible] as continuous variables.

c,d) [illegible]

TABLE 85
Study AN-PO-0292 (Report L-95-0001-CS)

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	Dose (mg)					Total DOLA®Mesyl [n=298]
	PL [n=75]	25 [n=75]	50 [n=74]	100 [n=74]	200 [n=75]	
2	75 (100%)	75 (100%)	74 (100%)	74 (100%)	75 (100%)	298 (100%)
6	46 (61.3%)	57 (76.0%)	54 (73.0%)	58 (78.4%)	52 (69.3%)	221 (74.2%)
8	38 (50.7%)	51 (68.0%)	53 (71.6%)	52 (70.3%)	45 (60.0%)	201 (67.4%)
p value[a] for PL Comparison (8h)		0.0360	0.0079	0.0140	N.S.	0.0065
12	30 (40.0%)	45 (60.0%)	45 (60.8%)	47 (63.5%)	44 (58.7%)	181 (60.7%)
18	27 (36.0%)	38 (50.7%)	39 (52.7%)	43 (58.1%)	41 (54.7%)	161 (54.0%)
24	22 (29.3%)	27 (36.0%)	30 (40.5%)	40 (54.1%)	37 (49.3%)	134 (45.0%)
p value[b] for PL Comparison (Hazard Ratios)		N.S.	N.S.	0.0039	0.0268	0.0052

II. Complete Responders by Dose (mg/Kg)

Number of Complete Responders by Dose Category (%)

Dose (mg/Kg)[c]				
PL [n=75]	≤0.53 [n=79]	>0.53 to 1.07 [n=74]	>1.07 to 2.13 [n=69]	>2.13 [n=65]
22 (29.3%)	28 (35.4%)	33 (44.6%)	[illegible]	[illegible]

a) p values are calculated from a logistic regression model [illegible] dose to PL controlling for investigator.
b) p values are calculated from tests of the [illegible] for investigator.
c) Dose (mg/Kg) p=0.004[illegible] from a one degree of freedom [illegible] model predicting complete response with dose entered [illegible]

2) Analyses of Secondary Efficacy Parameters

a) Total Response (Table 86)

- The results from this analysis are not entirely consistent with those of complete response (Table 83). Comparison of each dose to PL of the proportion of complete responders with no nausea showed a statistically significant difference not only in the 100 and 200 mg groups (as per complete response) but also in the 50 mg group (therapeutic gain=14%, p=0.0395). At 13.3%, the therapeutic gain with the 25 mg dose over PL was borderline (p=0.0510).

b) Major Response/Escape Medication (Table 87)

- Data in this Table indicate that the major responders and patients experiencing >5 emetic episodes are a relatively small percentage of the patient population. No reasonable conclusions can be drawn from these two subgroups.

- For ITT as well as the Efficacy Evaluable population analyses, the results of complete-plus-major response are consistent with complete response rates (as depicted in Table 83).

- 60% of the PL-treated patients received escape medication compared to 43%, 54%, 39% and 40% of patients who received DOLA•Mesyl at doses of 25, 50, 100 and 200 mg, respectively.

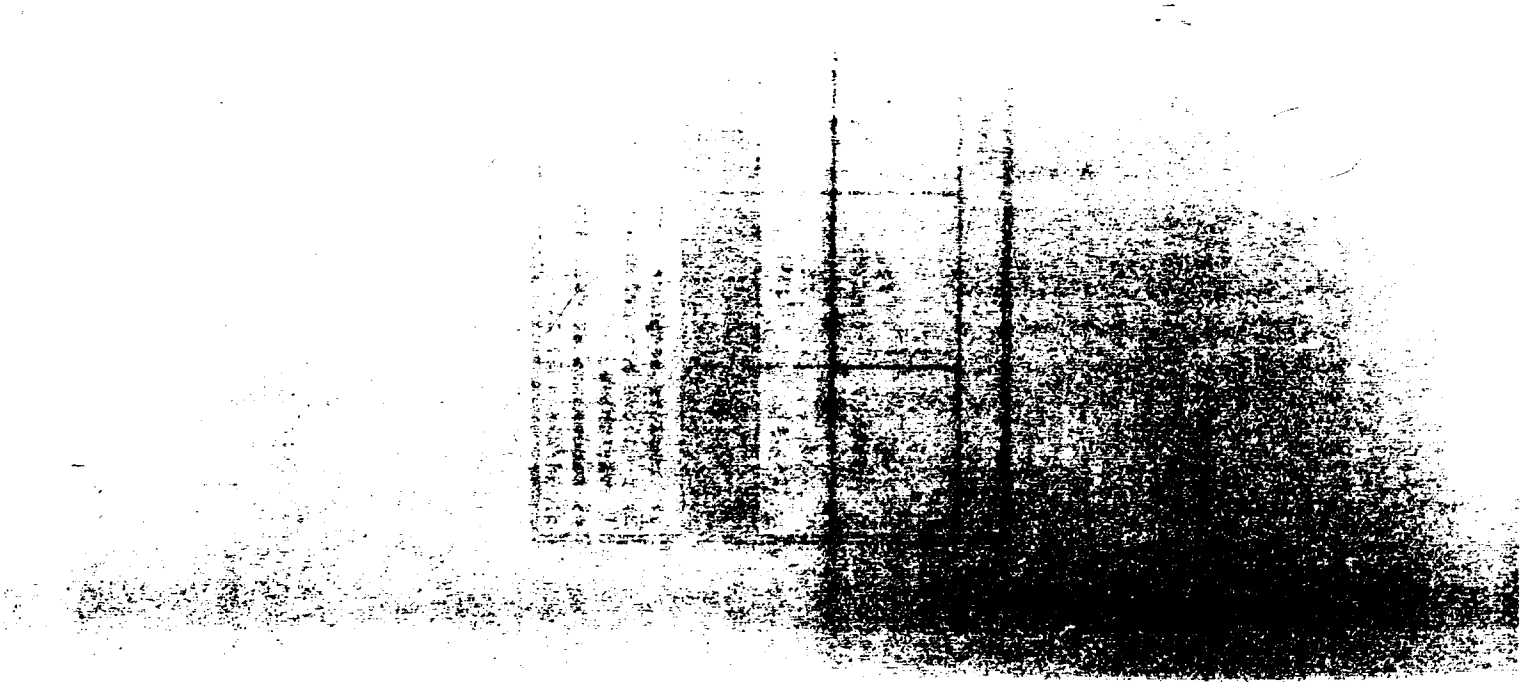

TABLE 86
Study AN-PO-0292 (Report L-95-0001-CS)

Clinical Response: Total Response[a] By Dose
[ITT Population]

Dose (mg)					Therapeutic Gain/p-value[b]				
PL [n=75]	25 [n=75]	50 [n=74]	100 [n=74]	200 [n=75]	25 vs PL	50 vs PL	100 vs PL	200 vs PL	Total DOLA•Mesyl[d] vs PL
11 (14.7%)	21 (28%)	21 (28.4%)	30 (40.5%)	27 (36%)					
					13.3% [N.S.][c]	13.7% [0.0395]	25.8% [0.0005]	21.3% [0.0030]	18.5% [0.0022]

a) Complete response with no nausea; nausea is defined as the maximum postdose VAS score less than 5 mm.
b) p-values are calculated from a logistic regression model predicting complete response with dose and investigator as explanatory
c) Borderline at p=0.0510.
d) 55/298 = 31.2%.

TABLE 87
Study AN-PO-0292 (Report L-95-0001-CS)

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

Number of Emetic Episodes	Dose (mg)					Total DOLA•Mesyl [n=298]
	PL [n=75]	25 [n=75]	50 [n=74]	100 [n=74]	200 [n=75]	
0 Complete Responders	22 (29.3%)	27 (36.0%)	30 (40.5%)	40 (54.1%)	37 (49.3%)	134 (45.0%)
1 Major Responders	4 (5.3%)	10 (13.3%)	2 (2.7%)	3 (4.1%)	4 (5.3%)	19 (6.4%)
0 or 1 Complete and Major Responders	26 (34.7%)	37 (49.3%)	32 (43.2%)	43 (58.1%)	41 (54.7%)	153 (51.3%)
p-value[a] for PL Comparison		N.S.	N.S.	0.0039	0.0133	0.0101
2-5	12 (16.0%)	8 (10.7%)	18 (24.3%)	7 (9.5%)	7 (9.3%)	40 (13.4%)
>5	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	1 (1.3%)	2 (0.7%)
Received Escape Medication	45 (60.0%)	32 (42.7%)	40 (54.1%)	29 (39.2%)	30 (40.0%)	131 (44.0%)

a) p values are calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete-plus-major response with dose and investigator as explanatory variables.

c) Nausea

The sponsor presented summary statistics for nausea VAS values at baseline (BL), recovery room, hour 8, and hour 24 in their Table 20, p. 107. From this information,

- The median VAS change from BL to hour 24 was 17 mm for the PL dose group and 0 mm for each DOLA•Mesyl group. This resulted in a borderline statistically significant linear trend over dose (p=0.0522).

3) Subgroup Analyses

Results of the subgroup analysis of complete response for the following variables were examined:

NSP	SP
- age	- ASA physical status
- body mass index	- previous Hx of motion sickness
- race	- previous Hx of PONV
- duration of anesthesia	- total morphine dose
- time from last free fluids (unlimited fluids) to test drug administration	
- total fentanyl dose	
- use of prophylactic metronidazole (Flagyl) or antibiotics to minimize the risk of postoperative infection	
- method of morphine administration	

Of the above, those listed under NSP were not significant predictors of complete response. Except for the method of morphine administration, those subgroups are not discussed any further. Analyses of the four variables listed under SP showed these three significant predictors of complete response. Results of these analyses are summarized in Table 88 and are briefly described below.

- ASA physical status (p=0.0497)
  - Patients of ASA physical status II (good) were more likely to be complete responders than were patients of ASA physical status I (healthy).
  - 56 of the 107 patients (52%) with a good status were complete responders, while 78 of the 191 patients (41%) with an excellent status were complete responders.
  - There was no interaction of ASA physical status with a linear dose response.
  - When controlling for ASA physical status along with dose and investigator, the primary test for linear trend in complete response over dose remained statistically significant.
- Previous Hx of motion sickness (p=0.0305)
  - Patients without a Hx of motion sickness were more likely to be complete responders than were patients with a Hx of motion sickness.
  - 102 of 212 patients (48%) without a Hx of motion sickness were complete responders, while 31 of the 85 patients (37%) with a Hx of motion sickness were complete responders.
  - There was no interaction of previous Hx of motion sickness with a linear dose response (p=0.5444).

- When controlling for previous Hx of motion sickness along with dose and investigator, the primary test for linear trend in complete response over dose remained statistically significant (p=0.0010).

- Previous Hx of PONV (p=0.0045)

  - Patients without a Hx of PONV were more likely to be complete responders than were patients with a Hx of PONV.

  - 60 of the 135 patients (51%) without a Hx of PONV were complete responders while 48 of the 134 patients (36%) with a Hx of PONV were complete responders.

  - There were no interaction of previous Hx of PONV with a linear dose response (p=0.9536).

  - 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 (p=0.0194).

- Total morphine dose (p=0.0345)

  - Patients with a total morphine dose >55 mg were more likely to be complete responders than were patients with a total morphine dose of 55 mg or less.

  - 69 of the 146 patients (47%) with a total morphine dose >55 mg were complete responders, while 65 of the 152 patients (43%) with a total morphine dose of 55 mg or less were complete responders.

  - There were no interaction of total morphine dose with a linear dose response (p=0.3633).

  - When controlling for total morphine dose along with dose and investigator, the primary test for linear trend in complete response over dose remained statistically significant (p=0.0016).

- Method of morphine administration (p=N.S.)

  - Method of morphine administration was not a statistically significant predictor of complete response.

  - The complete response rate for patients [illegible] of morphine administration was similar to the [illegible] patients with a PCA method of morphine [illegible]

  - There was a method of morphine [illegible] linear dose response (p=0.0433). Non-PCA patients [illegible] than did PCA patients. It is unclear [illegible] lower doses.

- When the method of morphine administration and the method of administration interaction and dose were controlled for along with dose and investigator, the primary test for linear trend in complete response over dose remained statistically significant (p=0.0016).

- When any of the variables listed under NSP above were entered along with dose and investigator in the logistic regression model, the primary test of linear trend across doses remained statistically significant.

TABLE 88
Study AN-PO-0292 (Report L-95-0001-CS)

Complete Response by Subgroups That Were Statistically Significant Predictors of Complete Response
[ITT Population]

Number of Complete Responders/Number of Patients in Dose by Subgroup Category Cell (%)								
		Dose (mg)					Total DOLA®Mesyl [n=298]	
		PL [n=75]	25 [n=75]	50 [n=74]	100 [n=74]	200 [n=75]		
ASA Physical Status	Excellent(I) (n=241)	15/50 (30.0%)	15/48 (31.3%)	19/50 (38.0%)	26/51 (51.0%)	18/42 (42.9%)	78/191 (40.8%)	p(int)=N.S. p(m)=0.0497 p(lin)=0.0019
	Good(II) (n=132)	7/25 (28.0%)	12/27 (44.4%)	11/24 (45.8%)	14/23 (60.9%)	19/33 (57.6%)	56/107 (52.3%)	
Previous History of Motion Sickness	NO (n=270)	18/58 (31.0%)	22/53 (41.5%)	20/49 (40.8%)	34/56 (60.7%)	26/54 (48.1%)	102/212 (48.1%)	p(int)=N.S. p(m)=0.0305 p(lin)=0.0010
	YES (n=102)	4/17 (23.5%)	4/21 (19.0%)	10/25 (40.0%)	6/18 (33.3%)	11/21 (52.4%)	3/185 (35.5%)	
Previous History of PONV	NO (n=163)	9/28 (32.1%)	18/40 (45.0%)	16/27 (59.3%)	16/32 (50.0%)	19/36 (52.8%)	69/135 (51.1%)	p(int)=N.S. p(m)=0.0045 p(lin)=0.0194
	YES (n=174)	12/40 (30.0%)	8/31 (25.8%)	10/38 (26.3%)	17/32 (53.1%)	13/33 (39.4%)	48/134 (35.8%)	
Total Morphine Dose	≤55 mg (n=189)	7/37 (18.9%)	14/37 (37.8%)	19/46 (41.3%)	12/30 (40.0%)	20/39 (51.3%)	65/152 (42.8%)	p(int)=N.S. p(m)=0.0345 p(lin)=0.0016
	>55 mg (n=184)	15/38 (39.5%)	13/38 (34.2%)	11/28 (39.3%)	20/44 (45.5%)	13/36 (36.1%)	69/146 (47.3%)	
Method of Morphine Administr.	Non-PCA (n=189)	13/40 (32.5%)	17/36 (47.2%)	16/39 (41.0%)	28/56 (50.0%)	10/18 (55.6%)	84/149 (56.4%)	p(int)=0.0439 p(m)=N.S. p(lin)=0.0016
	PCA (n=184)	9/35 (25.7%)	10/39 (25.6%)	13/35 (37.1%)	20/46 (43.5%)	16/54 (29.6%)	48/149 (32.2%)	

[1] All p-values were calculated from a logistic regression model [illegible] explanatory variables.
- p(int) is the p value for testing the subgroup by [illegible]
- p(m) is the p value for testing the subgroup as a main effect
- p(lin) is the p value for a linear dose response while controlling for [illegible]

Investigator numbers were entered into the model [illegible]
[illegible] variables were used for presentation purposes.

d. Safety Results

1) Extent of Exposure

In Study AN-PO-0292, a total of 374 patients received a single dose of test med., with the following distribution:

	DOLA•Mesyl Dose (mg)			
PL	25	50	100	200
[n=75]	[n=76]	[n=74]	[n=74]	[n=75]

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

- There were no deaths reported during this trial.
- None of the patients D/C from the trial due to AEs.
- Brief narratives on the two SAEs which occurred in this trial are given below.

Pt. AN-PO-0292, 0010-0290 (61y old F)

- Medical Hx included 1° AV block at BL EKG, hypertension and hypothyroidism. BL (pre-study drug) EKG documented 1° AV block with PR interval of 0.286 seconds.
- Pt. received one oral dose of 200 mg DOLA•Mesyl 2h and 19 min. prior to event onset. Concomitant medications included: verapamil (SR 240 mg, last dose taken morning of surgery), cefazolin, levothyroxine, tubocurarine, fentanyl, thiopental, succinylcholine, nitrous oxide, and isoflurane.
- Pt. experienced complete heart block lasting ca. 15 seconds while under general anesthesia for an uncomplicated abdominal hysterectomy.
- 1 hour post DOLA•Mesyl dose EKG PR interval was 0.259 seconds. Intermittent 2° AV block began 9 min. after initiation of anesthesia and 3 min. prior to the first incision. This lasted 13 min. before progressing to complete heart block.
- The complete heart block occurred during the [illegible] manipulations and was treated with glycopyrrolate.
- The physician investigator [illegible] as definitely related to DOLA•Mesyl. [illegible] placed the patient at immediate risk of

- The diagnosis of complete heart block was made from a video monitor. No EKG confirmation was possible.

Pt. AN-PO-0292, 0001-0403 (29y old F)

- There was no known medical Hx related to the event.

- Pt. received one oral dose of 100 mg DOLA•Mesyl 2h and 55 min. prior to event onset. Concomitant medications included: d-tubocurare, fentanyl, thiopental, succinylcholine and vecuronium.

- Immediately prior to the event the patient had sinus bradycardia ca. 50 beats per min., had just received fentanyl 100 μg and was undergoing surgical traction of the uterus as part of the surgical procedure (abdominal hysterectomy).

- Pt. developed nodal bradycardia at 20 bpm during surgery.

- The patient was treated with atropine 0.6 mg and recovered immediately without sequelae.

- The total duration of the event was <1 min.

- The event was assessed by the investigator (Center #01) to be severe and possibly related to test med. However, the investigator does comment "traction on peritoneum probable cause of increased vagal activity".

3) Severe AEs

As shown below, depending upon test group, different system organ classes were involved. There were no differences in incidence of severe AEs across PL and DOLA•Mesyl dose groups.

	DOLA•Mesyl (mg)			
PL (4%)	25 (5.3%)	50 0	100 (5.4%)	200 (4%)
(1) Hiccup (1) N&V (1) ↓ Hb	(1) Bradycardia (1) ↓ tolerance (1) Hypotension (1) Headache (1) Abnormal liver function[a]		(1) Nodal arrhythmia[c] (1) Pain (1) [illegible] (1) [illegible]	(1) [illegible] (1) [illegible] hypertension (1) [illegible] (1) [illegible]

a) Pt. had highly abnormal AST and ALP but was asymptomatic (discussed under Evaluations).
b) Pt. 0001-0403 (discussed under S.A. Bradycardia).
c) Lasted 10h 5m; had resolved at the start following [illegible].
d) Pt. 0410-0290 (discussed under 3) Serious AEs).

- The frequency of selected AEs and of Tx-emergent EKG interval changes by maximum severity is presented in Table 89.

  - There were more patients experiencing mild bradycardia in the 25, 100 and 200 mg DOLA•Mesyl groups than in the PL or 50 mg groups. But these differences do not appear to be clinically significant.

  - All of the 19 instances of mild or severe dizziness occurred in the DOLA•Mesyl group. There was, however, no difference in the distribution across dose groups.

TABLE 89
Study AN-PO-0292 (Report L-95-0001-CS)

Frequency of AEs and Tx-Emergent EKG Interval Changes by Maximum Severity[a,b]

I. Adverse Events by Maximum Severity

Incidence >1% in Study Population

Included Term	Maximum Severity	Dose (mg)				
		PL [n=75]	25 [n=76]	50 [n=74]	100 [n=74]	200 [n=75]
Bradycardia[c] (n=31)	MILD	2	6	2	5	4
	MOD	2	4	3	1	1
Dizziness (n=19)	MILD	0	3	3	3	3
	MOD	0	2	1	3	1
Headache[d] (n=32)	MILD	3	4	6	3	4
	MOD	0	2	3	4	2
Hypertension (n=12)	MILD	3	0	3	1	0
	MOD	2	1	2	0	0
Hypotension[e] (n=29)	MILD	2	2	1	1	6
	MOD	4	3	0	0	1
Pruritus (n=42)	MILD	4	2	0	1	1
	MOD	0	0	0	0	0
Sinus Bradycardia (n=10)	MILD	1	0	0	0	0
	MOD	0	0	0	0	0
Sinus Tachycardia (n=6)	MILD	2	0	0	0	0
	MOD	0	0	0	0	0

PI 25 50 100 250

II. Treatment-Emergent EKG Interval Changes by Maximum Severity

QRS Prolonged (≥100) (n=18) [p=0.018]	MILD	2	1	2	5	8
	MOD	0	0	0	0	0
QT (QT_c) Interval Prolongation (QT_c ≥440) (N=153)	MILD	35	24	30	28	34
	MOD	0	1	0	1	0

a) This Table lists events of MILD or MOD maximum severity. Severe events were discussed above.
b) For patients experiencing the event more than once, the maximum severity over all occurrences is used.
c) One patient in the 25 mg group experienced SEV bradycardia.
d) One patient in the 25 mg group experienced SEV headache.
e) One patient in the 25 mg group experienced SEV hypotension.

Σn = ? (MP)

- Except for a slight increase in the 50 mg group, there did not appear to be a difference in the occurrence of mild headache across dose groups and PL. No PL patient experienced MOD headache but in each DOLA•Mesyl group, at least two patients developed MOD headache. The one case of SEV headache occurred in the 25 mg dose group.

- Except for a slight increase in mild hypertension in the 200 mg group, hyper- and hypotension and sinus bradycardia were equally distributed across dose groups.

- In comparison to PL, there were slight increases in mild pruritus in the DOLA•Mesyl groups, especially the 200 mg dose group but no differences in the frequency of MOD pruritus.

- 4 pts. were reported as having myocardial ischemia (data not shown in Table 89): PL=1; 25 mg=1; 50 mg=2. These patients all had a normal cardiovascular Hx and their age ranged from 37 to 58y. The occurrence of myocardial ischemia did not demonstrate a trend.

- All of the 18 cases of QRS interval prolongation ≥100 msec were considered to be mild. Both the 100 (n=5) and the 200 mg (n=8) DOLA•Mesyl dose had higher incidences of mild QRS prolongation than PL (n=2). A test for linear trend across dose in the occurrence of QRS prolongation using a logistic regression model with dose as an explanatory variable yielded a p-value of 0.016.

- 151 of the 153 events consisting of (QT) prolongation ≥440 msec were considered mild and there were no [illegible] between each of the DOLA•Mesyl groups and PL. [illegible] events occurred in the 25 and 100 mg dose groups.