3) Severe AEs

In this, as in the other two trials, the majority of AEs were mild to moderate in intensity. Overall, 11 pts. experienced one or more AEs which intensity was rated as severe; 5 of these were considered Tx-related by the investigator. The distribution of these severe AEs was.

	OND (n=83)	DOLA•Mesyl Dose (mg)				Total DOLA•Mesyl (n=316)
		25 (n=80)	50 (n=80)	100 (n=76)	200 (n=80)	
SEVERE AE's (n=11)[a]	2 (2.4%)	2[b] (2.5%)	3 (3.8%)	2 (2.6%)	2 (2.5%)	9 (2.8%)
Tx-related (n=5)			1=weakness	1=drowsiness	1=fatigue + dry throat 1=headache	1=Abd. pain

a) Overall rate, p=N.S.
b) 1 pt. had first degree AV block and prolonged QRS (=120 msec; PR interval=560 msec), unrelated. The pre-study EKG was done 1 week prior to test med. administration.

4) Overall Rate of AE Incidence (Table 64)

- As shown in this Table, the overall rates of AEs were 25%, 37.5%, 39.5% and 33.8% for the 25, 50, 100 and 200 mg DOLA•Mesyl dose groups and 33.9% across all four doses. This was comparable to the overall rate of AEs seen with OND (36.1%).
- As highlighted in Table 64, the most frequently reported individual AE was headache.
- There was no statistically significant trend with DOLA•Mesyl dose in either the overall incidence of AEs or headache.
- The most frequently reported AEs by System Organ Class were those related to the central and peripheral nervous system (no statistically significant trend) and the g.i. system (statistically significant trend, p=0.0442). Of the latter, those occurring in [illegible] of the patients are listed in Table 64.
- As shown in panel II, b[illegible] Table 64, there [illegible] significant trend with dose in the overall [illegible]
- [illegible] instances of headache reported [illegible]
- [illegible] proportion of patients with AEs [illegible] (3/80 = 3.8%), [illegible] (3/83 = 3.6%), [illegible] statistical significance (p=0.0775).

TABLE 64
Study 73147-2-S-087 (Report S-95-0009-C)

List of AEs and Tx-Emergent EKG Changes

I. Frequency (Percent) of Adverse Events						
System Organ Class and Included Term p-value	OND [n=83]	DOLA®Mesyl Dose (mg) 25 [n=80]	50 [n=80]	100 [n=76]	200 [n=80]	Total DOLA®Mesyl [n=316]
Overall Rate (p=N.S.)	30 (36.1)	20 (25.0)	30 (37.5)	30 (39.5)	27 (33.8)	107 (33.9)
CENT & PERISH NERVOUS SYSTEM (p=N.S.)	12 (14.5)	9 (11.3)	10 (12.5)	18 (23.7)	15 (18.8)	52 (16.5)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Gastro-Intestinal System (p=0.0442)	5 (6.0)	4 (5.0)	12 (15.8)	12 (15.8)	9 (11.3)	37 (11.7)
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Obstipation	0	0	1 (1.3)	2 (2.6)	0	3 (0.9)
Abdominal Pain	2 (2.4)	0	0	2 (2.6)	0	2 (0.6)
Body as a Whole (p=N.S.)	8 (9.6)	2 (2.5)	7 (8.8)	6 (7.9)	8 (10.0)	23 (7.3)
Heart Rate & Rhythm (p=N.S.)	2 (2.4)	3 (3.8)	4 (5.0)	4 (5.3)	6 (7.5)	17 (5.4)
Arrhythmia Ventricular	0	0	0	1 (1.3)	2 (2.5)	3 (0.9)
AV Block First Degree	0	1 (1.3)	2 (2.5)	0	0	3 (0.9)
Sinus Tachycardia	0	0	2 (2.5)	0	0	2 (0.6)
Tachycardia	2 (2.4)	0	0	0	2 (2.5)	2 (0.6)
Cardiovascular General (p=N.S.)	1 (1.2)	1 (1.3)	1 (1.3)	2 (2.6)	4 (5.0)	8 (2.5)
Psychiatric	0	1 (1.3)	2 (2.5)	0	0	3 (0.9)
II. Frequency (Percent) of Treatment Related Adverse Events						
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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III. Frequency (Percent) of Adverse Events Treated With Counteractive Medications						
Overall Rate (p=0.0772)	3 (3.6)	3 (3.8)	2 (2.5)	4 (5.3)	9 (11.3)	18 (5.7)
CENTR & PERIPH NERVOUS SYSTEM	0	1 (1.3)	0	4 (5.3)	5 (6.3)	10 (3.2)
Headache	0	1 (1.3)	0	3 (3.9)	5 (6.3)	9 (2.8)

5) AEs of Potential Concern

In this trial, there were no reported chest pain, or chest tightness events or abnormal LFTs in association with DOLA•Mesyl treatment. There were 4 cases of edema (either edema of the legs, edema, or generalized edema) in 3 patients: 1 patient in the DOLA•Mesyl 100 mg dose group, and 2 patients in the DOLA•Mesyl 200 mg dose group. Two of the events were rated as mild and one as moderate in intensity; one case of mild edema was rated as possibly related to study drug, and the other cases were unrelated. Data on alterations of blood pressure or EKG changes are summarized in Table 65.

TABLE 65
Study 73147-2-S-087

List of AEs of Potential Concern

HYPO (↓) or HYPER (↑) TENSION [n=6]	VENTRICULAR ARRHYTHMIA [n=3]
• 087-470/D (↓) (25 mg) - NOD - Not Related • 087-359/D (↓) (50 mg) - NOD - Unknown Cause • 087-246/D (↓) (100 mg) - MILD - PROBABLY Related • 087-176/A* (↑) (200 mg) - Had previous Hx of (↑) and was under Tx for (↑) with a concomitant med. - MILD - Not Related • 087-326/C (↑) (200 mg) - NOD - [illegible] • 087-[illegible] (↑) (200 mg) - NOD - [illegible] * [illegible]	• 1 patient (100 mg) - Mild alterations in ventricular repolarization on Post-Tx EKG (PROBABLY Related) - But the EKG was considered normal by the central cardiologist • 1 patient (200 mg) - Ventricular premature beats on Post-Tx EKG (POSSIBLY Related) - MILD • 1 patient (200 mg) - [illegible] - MILD

6) Clinical Laboratory Evaluation

Other than statistically significant but clinically relevant changes in monocytes, there were no statistically significant changes in laboratory values.

7) Descriptive Statistics for EKG Assessments

The reviewer has assembled Table 66. This Table lists the mean (actual reading) and the change from BL (median and mean) to hour 24 POST-Tx for the six EKG summary measures for each of the DOLA•Mesyl groups and the comparator (OND). None of these comparisons (lower panel of Table 66) was statistically significant. But, for some EKG measures (such as HR, QRS and QT_c), the quantitative differences between DOLA•Mesyl and OND are of interest and this is illustrated in Fig. 18. The frequencies of treatment-emergent changes in the individual EKG parameters together with the graphic representation of the mean change from BL by dose at 24-h POSTDOSE are considered in some detail below, making use of the data depicted in Table 66, Fig. 18 and 18a..

NOTE: From what we already know about the EKG changes at 1-2h POSTDOSE, because in this trial such information was not collected, the data are incomplete and less useful since only 24h comparisons are available.

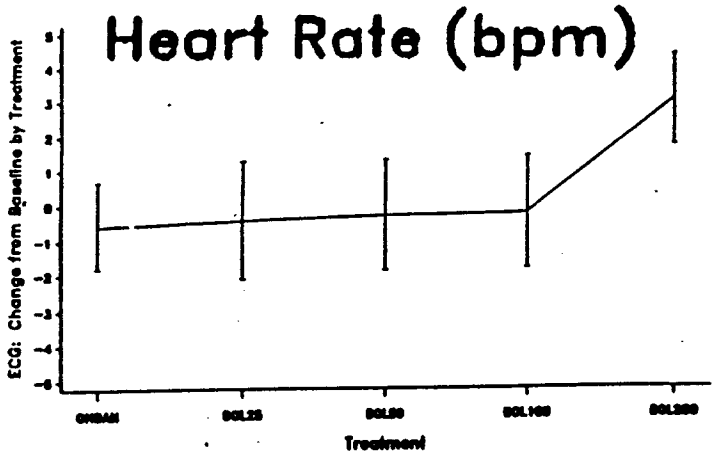
i) Heart Rate (HR) (bpm)

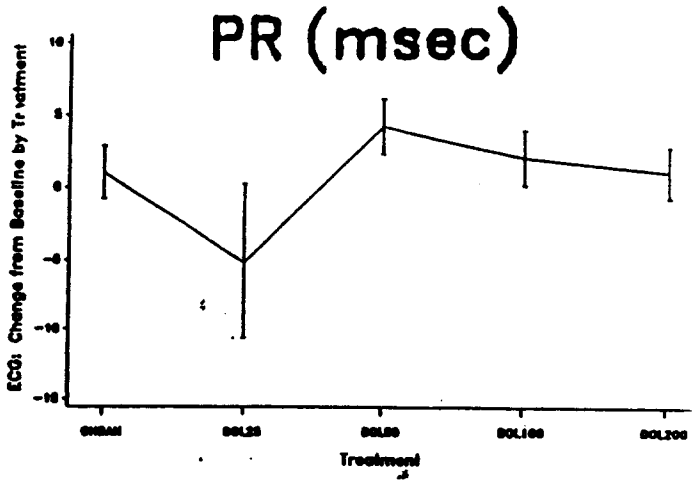
- There was no statistically significant trend with DOLA•Mesyl dose in change from BL at hour 24: mean changes from BL ranged from in the 25 mg group to with the 200 mg group. The mean change from BL for OND was -0.6 bpm (Table 66).
- Fig. 18 shows a clear differentiation between DOLA•Mesyl 200 mg and not only the other three DOLA•Mesyl dose groups but also OND.
- The frequency of treatment-emergent changes for HR was presented in sponsor's Table 38 on page 168.
- 13 patients had exit increases in HR to above 100 bpm: 5/66 patients (8%) in the 25 mg dose group, 1/66 (2%) in the 50 mg dose group, 5/67 (7%) in the 200 mg dose group and 2/75 (3%) in the ondansetron treatment group.
- 10 patients had exit decreases in HR to below 60 bpm: 3/66 patients (5%) in the 25 mg dose group, 1/66 (2%) in the 50 mg dose group, 1/67 (2%) in the 100 mg dose group, 2/67 (3%) in the 200 mg dose group and 3/75 (4%) in the ondansetron treatment group.

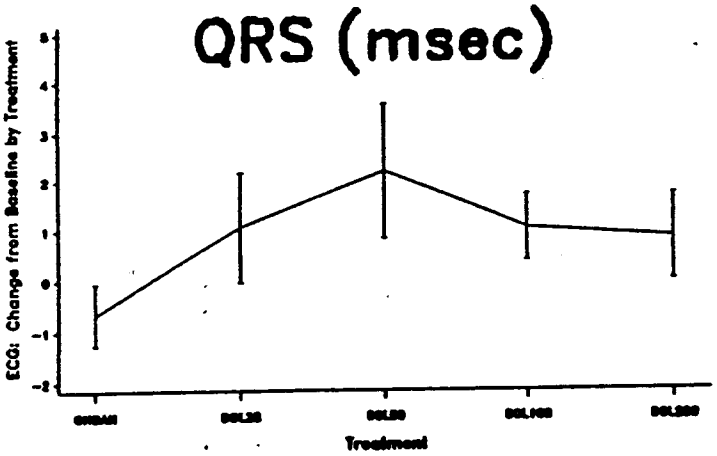
TABLE 66
Study 73147-2-S-087 (Report S-95-0009-C)
EKG Summary Measures (Mean of Actual Reading) Median and Mean Change from BL
at Pre-Tx and 24-h Post-Tx by Treatment Group
[All Patients]

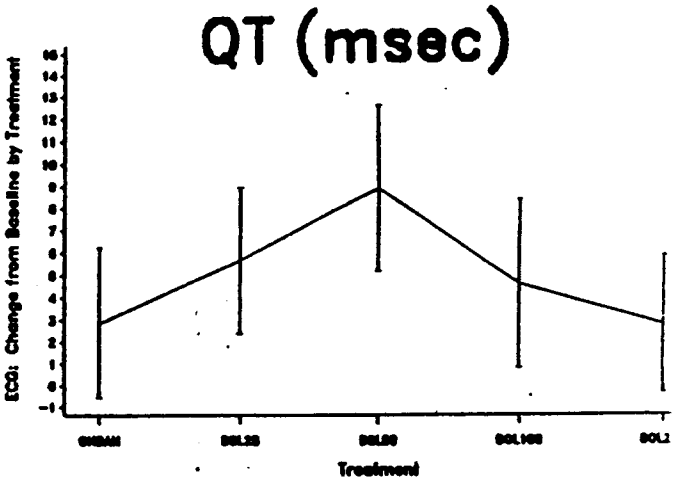
Dose (mg)	Evaluation	HR			PR			QRS			QT			QT_c			JT		
		(bpm)	Change from BL		(msec)	Change from BL		(msec)	Change from BL		(msec)	Change from BL		(msec)	Change from BL		(msec)	Change from BL	
		Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean
[illegible]	PRE-BL	82.2			154.5			84.0			356.7			410.6			271.6		
[illegible]	24-h POST	81.7	0	-0.4	150.8	0	-5.2	85.8	0	1.1	363.5	0	5.7	420.8	9	8.1	277.7	0	4.6
[illegible]	PRE-BL	80.0			150.1			82.3			357.7			409.5			275.4		
[illegible]	24-h POST	78.7	-1	-0.3	153.8	0	4.1	84.7	0	2.2	371.2	0	8.9	421.5	6	9.8	286.5	0	6.8
[illegible]	PRE-BL	76.7			150.6			86.0			376.5			418.6			290.4		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0	2.0	87.1	0	1.0	379.6	0	4.6	427.1	6	7.1	292.5	0	3.6
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	150.7			84.9			362.4			421.2			278.2		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	152.09	0	1.0	84.5	0	0.8	365.7	0	2.8	431.1	12	9.3	281.1	0	2.2
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			83.3			368.2			415.4			285.0		
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	0	1.1	83.1	0	-0.7	370.4	0	2.8	418.8	1	2.1	287.3	0	3.5
					N.S.			N.S.			N.S.			N.S.			N.S.		

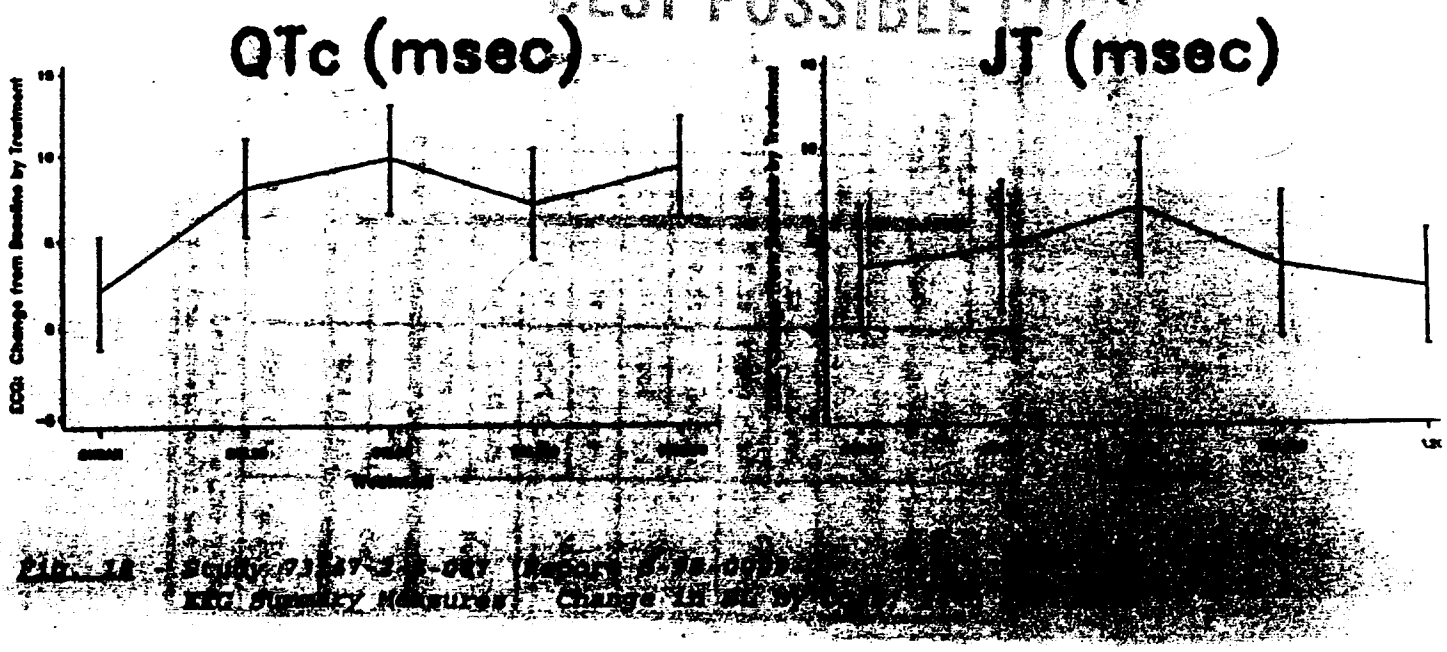
[illegible] analysis of variance F test for linear trend in change from baseline with DOLA•Mesyl dose, controlling

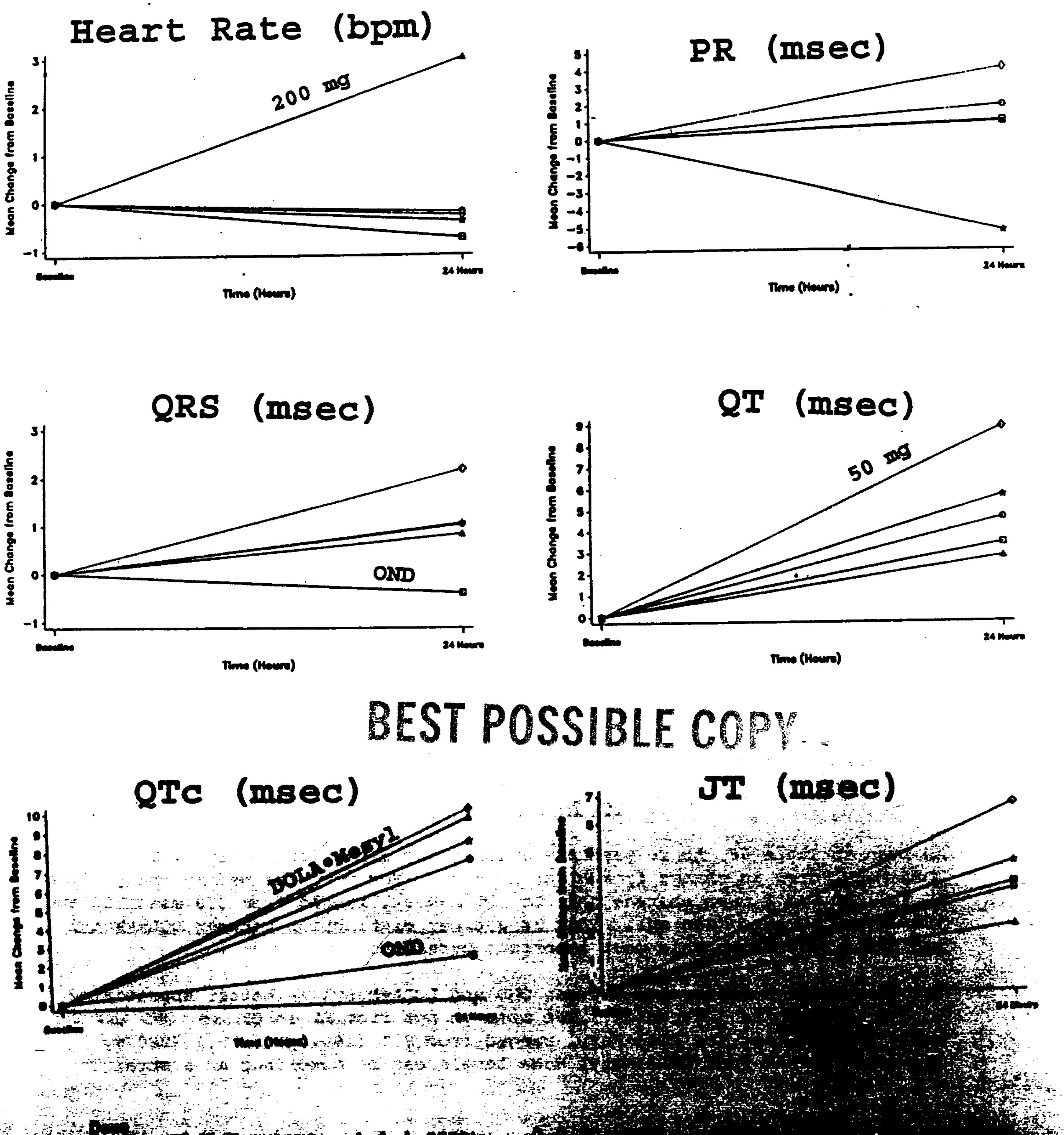












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Dose Group: ONDANS 25DOL

Fig. [illegible] - Study 73147-2-S-087 (Report [illegible]
Change in EKG Measures from BL; Observ[illegible]

ii) PR Interval (msec)

There was no statistically significant trend with DOLA•Mesyl dose in change from BL at hour 24 (Table 66). The mean changes from BL ranged from in the 25 mg dose group to in the 50 mg dose group. The mean change from BL for OND was 1.1 msec.

iii) QRS (msec)

- As shown in Table 66, there was no statistically significant trend with DOLA•Mesyl dose in change from BL at hour 24: mean changes from BL ranged from in the 200 mg dose group to in the 50 mg dose group. The mean change from BL for OND was -0.7 msec.
- The graphical display of these data (Fig. 18) suggests that DOLA•Mesyl differs from OND. Note that the mean change in QRS for OND is below 0 whereas all values for DOLA•Mesyl are 1.0 or more.
- The frequency of treatment-emergent changes for QRS width was presented in sponsor's Table 38 on page 168.
- 15 patients had exit increases in QRS duration to ≥100 msec: 2/66 patients (3%) in the 25 mg dose group, 3/66 (5%) in the 50 mg dose group, 3/64 (5%) in the 100 mg dose group, 5/67 (7%) in the 200 mg dose group and 2/75 (3%) in the OND treatment group.
- 59 patients had BL values ≥100 msec. The sponsor notes that no clinically significant worsening of these abnormalities was reported.

iv) QT Interval (msec)

- There was no statistically significant trend with DOLA•Mesyl dose in change from BL at hour 24: mean changes from BL ranged from in the 200 mg dose group to in the 50 mg dose group. The mean change from BL for OND was 2.8 msec.

v) QTc Interval (msec)

As seen in Table 66, there was no statistically significant trend with DOLA•Mesyl dose in change from BL at hour 24. However, the median change from BL for OND was 1 msec whereas that for DOLA•Mesyl ranged from 0 msec (50 and 100 mg) to 18 msec (200 mg). This is a clear discrimination between DOLA•Mesyl and OND's effects on this most important parameter.

The quantitative difference between OND and DOLA•Mesyl is better illustrated in Fig. 18 and 18a (24h data). The mean change from BL in [illegible] msec, whereas that for DOLA•Mesyl ranged from 7.1 (100 mg) to [illegible] The mean for all four DOLA•Mesyl dose levels can be [illegible]

line, well above that for OND. In the Fig. 18, one sees no overlapping of means and hardly any overlapping of SDs.

- The frequency of treatment-emergent changes for QT_c interval was presented in sponsor's Table 38 on page 168.

- 44 patients had exit increases in QT_c interval to ≥440 msec: 7/65 patients (11%) in the 25 mg dose group, 12/66 (18%) in the 50 mg dose group, 5/67 (8%) in the 100 mg dose group, 8/65 (12%) in the 200 mg dose group and 12/74 (16%) in the OND Tx group.

- 64 patients had BL values ≥440 msec.

The sponsor notes that no clinically significant worsening of the above-mentioned abnormalities were reported. No patients in this study developed Torsades de Pointes.

vi) JT Interval (msec)

There was no statistically significant trend with DOLA•Mesyl dose in change from BL at hour 24: mean changes from BL ranged from in the 200 mg dose group to in the 50 mg dose group. The mean change from BL for OND was 3.5 msec (Table 66). The comparative change from BL to hour 24 for all five groups, including OND, can be described by the straight line depicted in Fig. 18.

8) Subgroup Analysis by Gender and by Chemotherapy (Tables 67 and 68)

Of the six EKG measures, the reviewer has chosen changes in QT_c, an important EKG parameter of evaluation. Descriptive statistics for the mean (msec) measures at Pre-Tx and hour 24 Post-Tx by treatment with the associated changes from BL (median and mean) for males and females and for patients receiving anthracycline vs those not receiving anthracycline chemotherapy are given in Table 67. Also given are the p-values for the tests for interaction of treatment and gender, for a gender main effect, for a linear trend in change from BL with DOLA•Mesyl as well as the p-values for a linear trend in change from BL on the basis of anthracycline chemotherapy.

- As seen in the lower panel of Table 67, there were no statistically significant interactions of gender or chemotherapy with Tx for QT_c at 24h post-dose or in changes from BL to 24h post-dose.

TABLE 67
Study 73147-2-S-087 (Report S-95-0009-C)

Descriptive Statistics for QT_c at Pre-Tx and Hour 24 by Treatment (msec)
and Associated Changes from BL Subgroup Analysis by Gender and by Chemotherapy

Dose (mg)	Evaluations	MALE			FEMALE			Subgroup Receiving Anthracycline* Chemotherapy			Subgroup Not Receiving Anthracycline Chemotherapy		
		(msec)	Change from BL		(msec)	Change from BL		(msec)	Change from BL		(msec)	Change from BL	
		Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean	Mean	MED	Mean
25	PRE-RX	404.9			414.7			414.2			407.6		
	24-H POST	415.1	4	6.6	424.8	12	9.1	427.7	14	10.0	416.4	4	6.9
50	PRE-RX	402.0			414.0			408.1			410.8		
	24-H POST	416.5	8	10.2	424.5	4	9.5	426.8	12	12.5	417.6	3	7.7
100	PRE-RX	400.8			417.0			412.8			425.0		
	24-H POST	416.9	16	7.2	425.9	5	7.1	425.5	7	11.0	428.9	2	3.3
75	PRE-RX	417.1			423.7			421.6			420.7		
	24-H POST	430.8	15	10.7	431.8	11	8.3	433.5	13	12.2	428.9	7	6.6
[illegible]	PRE-RX	[illegible]			417.3			416.8			414.1		
[illegible]	24-H POST	[illegible]	-4	0.1	421.1	5	3.0	426.9	5	6.8	411.3	0	-2.2
		[illegible] interaction p=N.S. [illegible] p=N.S. [illegible]			N.S. N.S. N.S.			24-h N.S.			24-h N.S.		

[illegible], epirubicin, pirarubicin, mitoxantrone)
[illegible] form & three-way rank analysis of variance F test for linear trend in change from BL with DOLA•Mesyl [illegible] for investigator and stratum.

- Nonetheless, the reviewer believes that the QT_c changes from BL to hour 24 Post-dose induced by DOLA•Mesyl are larger (compare medians and means in all four subgroups in Table 67) than those associated with OND. Although, all in all, this evaluation did not show a dose-response with DOLA•Mesyl, the data strongly suggest that the effects of DOLA•Mesyl (regardless of dose) are different from those seen with OND.

Changes in QT_c (msec) From BL to Hour 24

Subgroup		OND	DOLA•Mesyl Range	Δ (msec) 100 mg - OND	Δ (msec) 200 mg - OND
MALE	Median	-4		20	19
	Mean	0.1		7.1	10.6
FEMALE	Median	5		0	6
	Mean	3.0		4.1	5.3
Receiving Anthracycline Chemotherapy	Median	5		2	8
	Mean	6.8		4.2	5.4
NOT Receiving Anthracycline Chemotherapy	Median	0		2	7
	Mean	-2.2		5.5	8.8

- The frequency (%) of exit (hour 24) treatment-emergent EKG changes is provided in Table 68, for all patients and as a function of anthracycline chemotherapy. There is marked overlap between values for OND vs those associated with DOLA•Mesyl. But, as repeatedly mentioned, the most important differentiation of the EKG changes induced by these medications occurs 1 to 2 or at the most 4 hours after administration of the drugs.

9) Vital Signs

Fig. 19 depicts mean change from BL to each time point over the entire study by dose for recumbent HR (bpm), diastolic BP (mmHg) and systolic BP (also mmHg). From sponsors Table 45, p. 199, there were no statistically significant trends with DOLA•Mesyl in recumbent pulse rate or diastolic BP change from BL at any time point (-1 and -0.5h Pre-Dose, 0.5, 1, 2, 4, 8, 12 and Post-Tx).

- With the exception of hour 24, there [illegible] trends with DOLA•Mesyl dose in recumbent systolic [illegible] other time points.
- All Tx groups tended to have mean decreases [illegible] time points.
- At hour 24 there was a statistically [illegible] DOLA•Mesyl dose (p=0.03).

- The mean changes from BL were 1.0 mmHg, 0.3 mmHg - 1.8 mmHg and -3.2 mmHg for 25 mg, 50 mg, 100 mg and 200 mg DOLA•Mesyl dose groups, respectively.

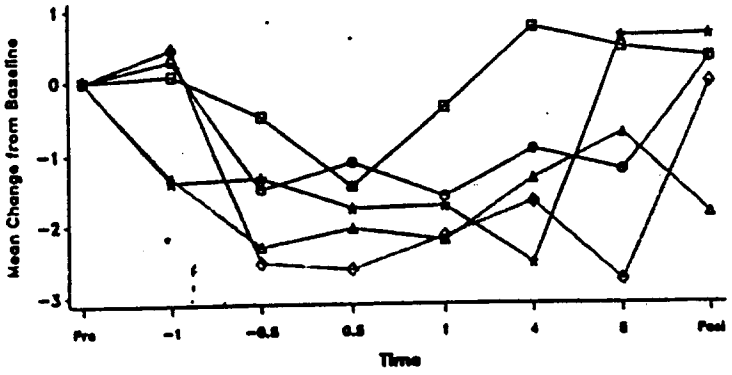
- The mean change from BL at hour 24 was -3.4 mmHg for the OND Tx group.

TABLE 68
Study 73147-2-S-087 (Report S-95-0009-C)

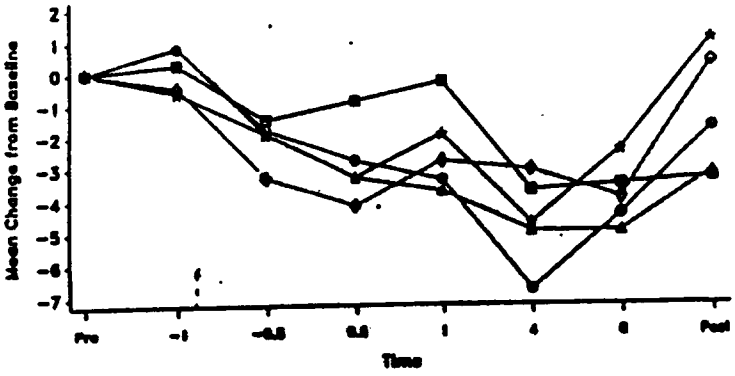
Frequency (Percent) of Exit (Hour 24) Treatment-Emergent EKG Changes

DOLA•Mesyl Dose (mg)	HR Pre ≤100 bpm and Post >100	HR Pre ≥50 bpm and Post <60	PR Pre <220 msec and Post ≥220	QRS Pre <100 msec and Post ≥100	QT_c Pre <440 msec and Post ≥440
I. All Patients					
25	5/66 (8%)	3/66 (5%)	0/55 (0%)	2/66 (3%)	7/65 (11%)
50	1/66 (2%)	1/66 (2%)	2/65 (3%)	3/66 (5%)	12/65 (18%)
100	0/64 (0%)	1/64 (2%)	0.61 (0%)	3/64 (5%)	5/64 (8%)
200	5/67 (7%)	2/67 (3%)	0/65 (0%)	5/67 (7%)	8/65 (12%)
OND	2/75 (3%)	3/75 (4%)	0/74 (0%)	2/75 (3%)	12/74 (16%)
II. Patients Receiving Anthracycline Chemotherapy					
25	3/26 (12%)	0/26 (0%)	0/26 (0%)	2/26 (8%)	4/25 (16%)
50	0/28 (0%)	0/28 (0%)	2/28 (7%)	2/28 (7%)	4/28 (14%)
100	0/32 (0%)	1/32 (3%)	0/30 (0%)	1/32 (3%)	2/32 (6%)
200	2/31 (6%)	1/31 (3%)	0/30 (0%)	3/31 (10%)	3/31 (10%)
OND	1/35 (3%)	1/35 (3%)	0/35 (0%)	1/35 (3%)	7/35 (20%)
III. Patients NOT Receiving Anthracycline Chemotherapy					
25	2/40 (5%)	3/40 (8%)	0/39 (0%)	0/40 (0%)	3/40 (8%)
50	1/38 (3%)	1/38 (3%)	0/37 (0%)	1/38 (3%)	8/38 (21%)
100	0/32 (0%)	0/32 (0%)	0/31 (0%)	2/32 (6%)	3/32 (9%)
200	3/36 (8%)	1/36 (3%)	0/35 (0%)	2/36 (6%)	5/34 (15%)
OND	1/40 (3%)	2/40 (5%)	0/39 (0%)	1/40 (3%)	5/39 (13%)

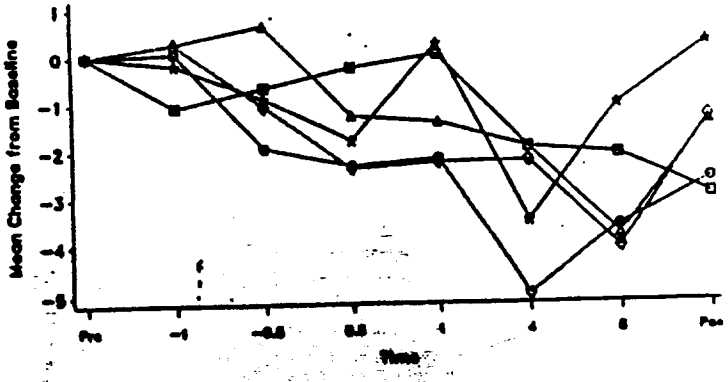
Recumbent Heart Rate (bpm)



Recumbent Systolic Blood Pressure (mm Hg)



Recumbent Diastolic Blood Pressure (mm Hg)



ONDAN DOL15 DOL200

Fig. 12 - Study 73147-2-S-087 (Report S-95-D008-C)
Recumbent Vital Signs by Time

- In their Table 46 on page 206 the sponsor presented the frequency of patients with Tx-emergent changes in recumbent BP or HR that met sponsor-defined alert criteria.

- 54 patients had recumbent BP increases[25].

  - 10/80 (13%) in the 25 mg dose group, 14/79 (18%) in the 50 mg dose group, 8/75 (11%) in the 100 mg dose group, 10/80 (13%) in the 200 mg dose group and 12/83 (14%) in the OND Tx group.

- 40 patients had recumbent BP decreases[26].

  - 10/80 (13%) in the 25 mg dose group, 9/79 (11%) in the 50 mg dose group, 10/75 (13%) in the 100 mg dose group, 6/80 (8%) in the 200 mg dose group and 5/83 (6%) in the OND Tx group.

- 31 patients experienced increased recumbent pulse rates[27].

  - 6/80 (8%) in the 25 mg dose group, 3/79 (4%) in the 50 mg dose group, 9/75 (12%) in the 100 mg dose group, 6/80 (8%) in the 200 mg dose group and 7/83 (9%) in the OND Tx group.

- 6 patients had decreased recumbent pulse rates[28].

  - 2/80 (3%) in the 25 mg dose group, 3/79 (4%) in the 50 mg dose group and 1/75 (1%) in the 100 mg dose group.

9. Sponsor's Conclusions

"Oral dolasetron mesylate and ondansetron were effective in preventing nausea and vomiting induced by moderately emetogenic chemotherapy agents.

"Antiemetic response to dolasetron mesylate increased in a dose dependent manner. Nausea was also controlled in a dose dependant manner. Dolasetron mesylate administered as a single dose of 200 mg was at least equivalent to ondansetron 8 mg X 3 or 4 doses in antiemetic efficacy.

[25] Systolic pressure shift from below 100 mmHg Pre-Tx to above 160 mmHg Post-Tx
or
Diastolic pressure shift from below 90 mmHg Pre-Tx to above 90 mmHg Post-Tx

[26] Systolic pressure shift from above 100 mmHg Pre-Tx to below 90 mmHg Post-Tx
or
Diastolic pressure shift from above 50 mmHg Pre-Tx to below 50 mmHg Post-Tx

[27] Shift from below 100 bpm Pre-Tx to above 100 bpm Post-Tx

[28] Shift from above 60 bpm Pre-Tx to below 60 bpm Post-Tx

"Antiemetic response was better in patients who were older, patients who were male, patients who had no previous history of chemotherapy, and in patients who did not receive a multiple agent chemotherapy regimen.

"No trends in clinical laboratory test results indicated a clinically important effect of study medication. Measured changes in vital signs with dolasetron mesylate and ondansetron were small and indicated no increased patient risk.

"Oral dolasetron mesylate was well tolerated at the doses used in this study and was as safe as ondansetron."

10. Reviewer's Comments

As previously mentioned, Study -087, is not pivotal but some interesting information on efficacy and safety can be gathered from this trial. All in all, the methodology used in this trial was appropriate. Both the study population and the emetogenic potential (different from -043) were standardized, double-blind observations add quality to the trial because this approach minimizes bias. The randomization scheme was apparently properly executed because this resulted in five test groups (the same four used in the pivotal trials vs ondansetron) that were similar to each other. The statistical methodology to evaluate results was appropriate to draw valid, meaningful conclusions.

The dose and dose regimen of ondansetron used in this trial has not been approved in the U.S. but is approved in Europe. Although no firm conclusions on efficacy may be drawn, after all, we already know that DOLA•Mesyl is effective for the indication sought (whether the dose should be 200 mg, as proposed by the sponsor or 100 mg as suggested by the reviewer is another issue discussed under Summary of Efficacy). The ideal comparisons for safety should have taken place from data gathered at 1 to 2 hours after test med. administration. But, as already mentioned, the comparisons at exit obtained in this trial are not without merit. As shown below, these data strongly argues against a class effect with the 5-HT_3 receptor antagonist, especially on prolongation of the most important parameter of EKG evaluation, QT_c interval.

In this trial, patients needed not be naive to chemotherapy to be randomized. The study population consisted of patients with histologically confirmed malignant disease, who were scheduled to receive emetogenic chemotherapy regimens. Indeed, [illegible] had previously received chemotherapy. "Because [illegible] chemotherapy was useful to get information about the [illegible] under conditions of repeat courses of chemotherapy." [illegible] stratification by gender because, according to [illegible] N&V and the response to antiemetics, is gender [illegible] stratification into many cells eventually results [illegible] patients per cell and this complicates comparisons.

The study population consisted of 61% F and 39% M patients, with a median age of 54 years, in general without evidence of significant cardiovascular or hepatic disease. The site for primary neoplasm was breast (40% of the patients), lung (21%) and lymphoma (13%). As in the two pivotal studies, the initial approach was to demonstrate - with regards to cardiovascular status - a dose of DOLA•Mesyl <3 mg/Kg (ca. 200 mg) was safe, with appropriate exclusions (Table 54). But eventually, according to the Clinical Report, the only patients that were routinely excluded were those with severe abnormalities, those with poor ejection fractions and those with complete BBBs. This approach is similar to that used in the pivotal trials.

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 test groups, the demographics, primary cancers, other significant medical conditions, physical examination and prior medications were similar to each other. It is to be noted that, in these patients, the median Karnofsky status score was 100%, which means that, except for having cancer and needing chemotherapy of moderate emetogenicity, the patients participating in this and the pivotal trials, were essentially normal. The five test groups were also balanced with respect to concomitant medications in general and concomitant medications that may be confounding, such as concomitant chemotherapy (FU=35% of the patients, vincristine=23%, etoposide=21% and MTX=19%), benzodiazepines (only 1.5% of the patients), narcotics (6.5%) and steroids (only 1% of the patients).

The experimental groups were also well matched with regards to standardization of the emetic stimulus which consisted of cyclophosphamide (given to 28% of the patients at a mean dose of 637 mg/m^2), doxorubicin (23% at a mean dose of 47 mg/m^2) and carboplatin (21%, at a mean dose of 321 mg/m^2). This regimen is best characterized as being of moderate emetogenic potential.

Based on evaluations of complete and total response, the reviewer's conclusions on efficacy are as follows. Two types of comparisons are considered: comparisons among DOLA•Mesyl doses and comparisons of the effect of DOLA•Mesyl doses vs ondansetron. Study -087 demonstrated that DOLA•Mesyl is active because there was a statistically significant linear trend in the frequency of complete responders with increasing oral doses of the drug for both the ITT ($p<0.0001$) and the Evaluable Efficacy population ($p<0.001$). In comparison to the 25 mg dose, the highest therapeutic gains were seen with the 200 mg dose (ITT=31%, Evaluable Population=35%) which was also statistically superior to the 50 mg dose (therapeutic gain=23% in the ITT and 27% in the Evaluable Population) and even the 100 mg dose (therapeutic gain=19% in the ITT population analyses). In this trial, in spite of the fact that the 100 mg dose had a therapeutic gain of 15%, the 100 mg dose was not statistically different from the 25 mg in the ITT analysis. But the Evaluable Population analysis did show the 100 mg dose to be superior to the 25 mg dose (therapeutic gain=19%, $p=0.0212$).

In both population analyses, ondansetron was shown to be superior to both the 25 and the 50 mg DOLA•Mesyl level, with therapeutic gains ranging from 22% to 29% and p-values 0.0019 or smaller. The complete response with ondansetron could not be differentiated from that with the 200 or the 100 mg DOLA•Mesyl dose. Analyses of total response gave results consistent with those seen in evaluations of complete response.

In Study -087, age, gender, previous Hx of chemotherapy and chemotherapy regimen, were statistically significant predictors of complete antiemetic response. Better antiemetic response was shown in patients that were older, those who were male, those who were chemotherapy-naive and in those who did not receive a multiple agent chemotherapy regimen. These responses by subgroups do not always confirm results of evaluations in Studies -043 and -048. These inconsistencies are probably due to the small number of patients per stratum per treatment cell.

The reviewer's summary/conclusions on safety, using an approach and emphasis similar to those used in studies -043 and -048 are as follows.

Serious AEs (n=5), including 3 deaths (one each in the 50, 100 mg of DOLA•Mesyl and ondansetron), were related to progression of the underlying condition. The majority of AEs were mild in intensity and of the 11 patients experiencing severe AEs, five, roughly evenly distributed among the 50, 100 and 200 mg dose levels, were considered Tx-related by the investigator.

In this study, the most frequently reported individual AE was headache and there was no statistically significant trend with DOLA•Mesyl dose in the overall incidence of AEs or headache. The overall rate of AEs and headache with DOLA•Mesyl (34% and 15%, respectively) was very similar to that seen with dolasetron (36% and 15%, respectively). Comparison of Tx-related AEs allowed the same conclusions. There was, however, a significant linear trend with increasing dose of DOLA•Mesyl for AEs related to the g.i. tract (p=0.0442) and the total incidence of these with the drug (=12%) was higher than with ondansetron (=6%) and these quantitative differences were due to a higher incidence of diarrhea and constipation in all DOLA•Mesyl groups in comparison to ondansetron. Of the individual AEs, those related to the heart rate and rhythm occurred in 2.4% of the dolasetron-treated and in 7.5% of those treated with 200 mg of DOLA•Mesyl. But none of these comparisons, as well as comparisons of individual included terms for heart rate and rhythm AEs were statistically significantly different.

Of the 9 AEs of potential concern reported, one [illegible]
(100 mg) and one case of moderate hypertension [illegible]
related to test medication. In three instances [illegible]
ventricular arrhythmias of mild intensity. [illegible]
ventricular repolarization was considered [illegible]
(although the ECG was considered normal by the [illegible]
of ventricular premature beats [illegible]
additional case of ventricular premature beats [illegible]
the 200 mg [illegible]

There were no significant changes in laboratory parameters or vital signs.

As expected from observations 24h after administration of DOLA•Mesyl when the blood level of the active metabolite, MDL 74,156, are low, there were no statistically significant linear trends with dose toward increases in any of the six EKG variables evaluated (HR, PR, QRS, QT, QT_c and JT). But the material reviewed in detail in the text of this review strongly suggests that, even at 24h observations, for QT_c, the most important parameter of EKG evaluation, DOLA•Mesyl's effects are different from those seen with ondansetron. There was no overlapping whatsoever in the changes in QT_c (msec) from baseline between ondansetron and any (or all) dose of DOLA•Mesyl. With ondansetron, the changes from BL were much smaller than with DOLA•Mesyl and this was seen whether one examined data from males, females, patients receiving anthracyclines or those not receiving anthracyclines. The reader's attention is also directed to Fig. 18a where, for QT_c changes from BL, a clear cut difference between ondansetron and DOLA•Mesyl (any dose) is evident. Although it would be of interest to examine changes from BL at 1-2h Post-Tx (as in trials -043 and -048) the findings in Study -087 strongly argue against a class effect on QT_c changes from BL with 5-HT_3 receptor antagonists.

It is to be noted that, in this study, 15 patients had exit increases in QRS duration to ≥100 msec and 44 patients had exit increases in QT_c interval to ≥440 msec. But the proportions of patients in the five test groups were comparable to each other.

It should also be noted that, in Study -087, 59 patients had QRS baseline values ≥100 msec and 64 patients had QT_c baseline values of ≥440 msec. In this trial, there were no significant cardiac event reported; specifically, there were no reports of torsades de pointes, BBBs or high degree of AV block (the ventricular arrhythmias described in Table 65 were mild and, although they occurred with the 100/200 mg dose, there is no certainty that these were associated with the drug). Therefore, the sponsor's conclusion is valid: under the experimental conditions used in trial -087, patients with prolonged QRS or QT_c at baseline, were safely treated.

In conclusion, the supportive trial -087 showed that orally administered tablets of DOLA•Mesyl are effective in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapeutic regimens, [illegible] linear to dose. Although this trial showed the effect of the 200 mg dose to be superior to the 100 mg dose, both dose levels of DOLA•Mesyl [illegible] efficacy to a dose regimen of ondansetron [illegible] Europe for the sought indication. The effect [illegible] resulting in 12-lead EKG intervals in [illegible] 200 mg of the drug, were seen even after [illegible] compound. For QT_c, these EKG changes from [illegible] DOLA•Mesyl than with ondansetron. These [illegible] EKG changes do not represent a class effect [illegible] effect, DOLA•Mesyl results in much longer [illegible] ondansetron. Once again, although in neither [illegible] nor the supportive trial (-087) evidence of [illegible] presented, the potential for seriousness of this [illegible] cannot be dismissed.

X. STUDIES SUBMITTED IN SUPPORT OF THE INDICATION PREVENTION OF POST-OPERATIVE NAUSEA AND VOMITING (PONV)

The sponsor is seeking approval for the marketing of 50 mg ANZEMET (dolasetron mesylate=DOLA•Mesyl) tablets, given within two hours prior to surgery, for the prevention of PONV. The critical trials for this indication are AN-PO-0292 (Report L-95-0001-CS) and 73147-2-S-095 (Report S-95-0011-C). As summarized in Table 69, both were well designed trials. The effects of graded single doses of DOLA•Mesyl (25 to 200 mg) were compared to a negative control (PL). The patients were female undergoing abdominal hysterectomy under general anesthesia and receiving opiates and other potentially emetogenic analgesics. The results in Study 095 (n=793) are expected to be replicated in Study 0292 (n=374).

Because the experimental subjects in both critical trials were exclusively women, consideration should be given to the question of whether male patients are expected to respond equally well as females.

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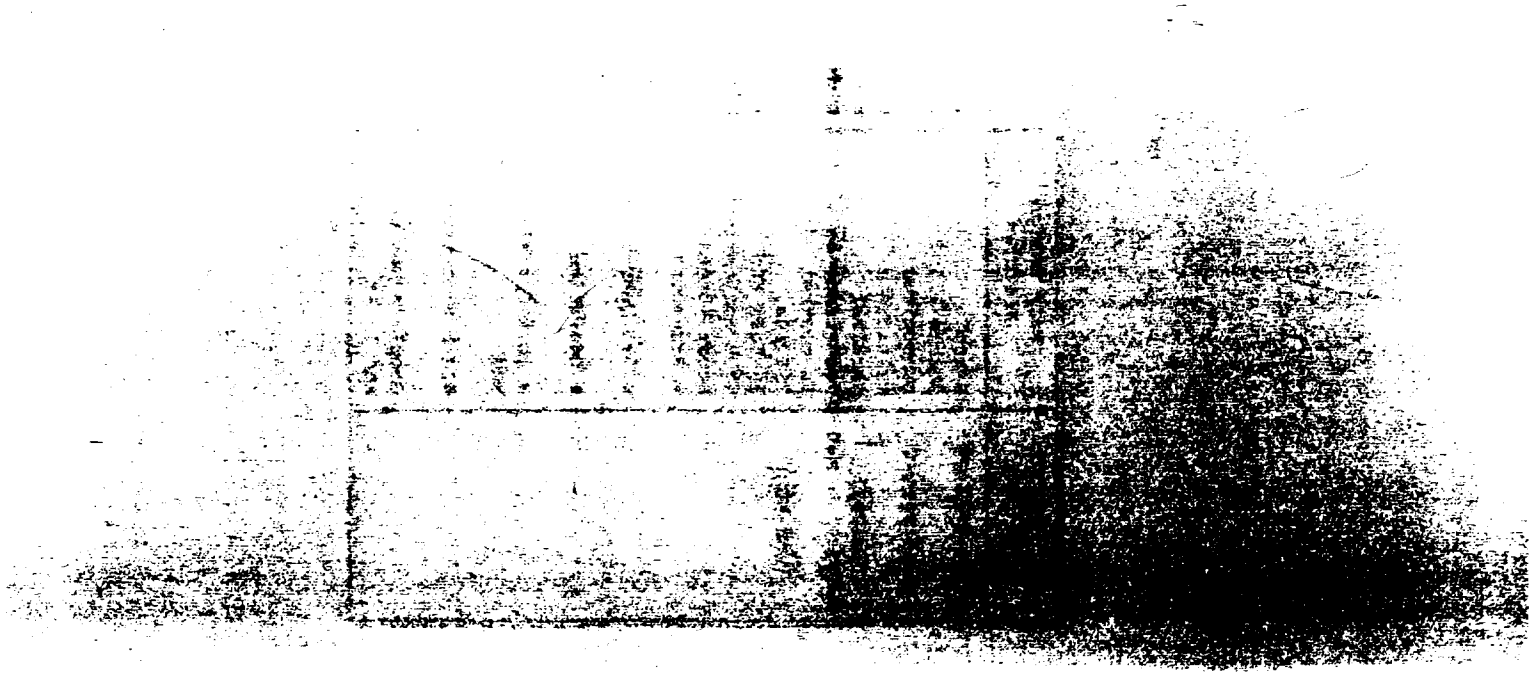

TABLE 69
NDA 20-623

Main Features of Design, Study Population, Dose Levels Being Compared in the Two Pivotal Clinical Trials Submitted in Support of the Indication Prevention of Post-Operative Nausea and Vomiting

Protocol No. Report No.	Main Design Features	Study Population	Risk Factors for Emesis	Groups Being Compared	Remarks
72147-2-8-095 8-95-0011-C [n=793] n=793 N=0 (non-USA)	5-arm double-blind randomized multicenter parallel dose-response PL-controlled 750 pts. 12-lead ECG 24 h monitoring Study Phases: • Screening • Pre-Operative • Operative • Post-Operative and 48-h Post-recovery Complete Response [illegible]	Exclusively female 18 to 60 y of age, with ASA physical status I-III, scheduled to undergo major gynecological surgery, with no evidence of hepatic, renal, endocrine or cardiovascular dysfunction, without 2nd and 3rd degree AV block, arrhythmia requiring anti-arrhythmic medication	Abdominal hysterectomy, gynecological laparotomy or vaginal-hysterectomy, general anesthesia. Agents to control severity of pain: I.M. or I.V. morphine for post-OP analgesia or patient controlled analgesia and/or NSAIDs	DOLA•Mesyl tablets adm. orally 1-2h before induction of anesthesia 25 mg (n=159) vs 50 mg (n=166) vs 100 mg (n=154) vs 200 mg (n=158) vs PL (n=156)	• Useful design. • Ca. 155 pts. were randomized to one of four levels of orally adm. DOLA•Mesyl tablets or PL. • The selected study population, females + general anesthesia + narcotic and other analgesics, including opioid analgesia is highly susceptible to emesis. • Efficacy (24-h) is demonstrated by showing statistical superiority over a negative control (PL). The design also allows comparison of efficacy between DOLA•Mesyl doses.

7[illegible]-PO-0292 [illegible]-95-0001-CS (n=374) [illegible]-374 N=0 (non-USA)	5-arm double-blind randomized multicenter dose-response PL-controlled parallel 350 patients 12-lead ECG 24-h monitoring Complete Response [illegible]	Exclusively female, 18 to 70y of age, with ASA physical status class I and II, scheduled to undergo uncomplicated abdominal hysterectomy, with no evidence of respiratory, cardiovascular, metabolic, hepatic or renal dysfunction, without cardiomyopathy, CHF or Hx of CHF, complete [illegible], greater than 1st degree AV block or arrhythmias requiring antiarrhythmic Tx.	Abdominal hysterectomy, general anesthesia. Agents to control severity of pain: I.M. or I.V. morphine for post-operative analgesia	25 mg (n=76) vs 50 mg (n=74) vs 100 mg (n=74) vs 200 mg (n=75) vs PL (n=75) DOLA•Mesyl tablets adm. orally 1 to 2 h before induction of anesthesia	• Useful design for replicative purposes. • Ca. 75 pts. were randomized to one of four levels of orally adm. DOLA•Mesyl tablets or PL. • The selected study population, females + general anesthesia + narcotic and other analgesics, including opioid analgesia is susceptible to emesis. • Efficacy (24h) is demonstrated by showing statistical superiority over a negative control (PL). The design also allows comparison of efficacy between DOLA•Mesyl doses. NOTE: Since the experimental subjects in both trials were exclusively females it will be important to consider if male patients are expected to respond equally well as females.

[illegible]-treatment failure; ASA=American Soc. of Anesthesiologists; PL=placebo; CHF=congestive heart failure;

XI. STUDY 73147-2-S-095 (REPORT S-95-0011-C)

1. Title

"Evaluation of Oral Dolasetron Mesylate (MDL 73,147EF) as a Prophylactic Treatment of Postoperative Nausea and Vomiting. A Double-Blind, Multicentric, Randomized, Placebo-Controlled, Parallel Study"

NOTE: The description that follows includes the amendments to the original protocol. These dealt with a requirement to have a negative pregnancy test before entering the trial the morning of surgery, for women of childbearing potential, and also to exclude patients who were lactating. The wording for the amendment for each center was somewhat different. In addition, an amendment was written requiring EKGs to be done at 15 centers at

-1 to 2h
or 4 to 5h
or 24h

Again, administratively, these amendments were handled differently at each site. The sponsor presented a long table outlining the amendments written at each study center. For example, at Center 16 (Dr. J. Leeser, Amsterdam, The Netherlands) the rationale given for the amendment read:

"Administration of dolasetron at doses ≥3.0 mg/kg may be associated in some patients with cardiac conduction delays (i.e. increase in PR, QRS, Qtc intervals). However, none of the treatment emergent changes observed with doses ≥3 mg/kg were of clinical significance.

"Taking into account the potential for dolasetron to increase intraventricular or auriculo-ventricular conduction, the scientific committee of this hospital (OLVG, Amsterdam, N.L.) requested that patients entered in this trial be free of any cardiac conduction disturbances.

"In addition, patients under treatment with beta-blockers will not be enrolled in this centre, some of these agents having the potential to delay the auriculo-ventricular conduction."

But, as already noted, this was not uniformly done across centers. Based on the information in the Protocol amendments, β-blockers were not proscribed at all centers.

2. Objectives

- To evaluate the effect of single doses of oral [illegible] in preventing postoperative nausea and vomiting in patients undergoing major gynecologic surgery.
- To evaluate the tolerability and safety of [illegible] in patients receiving general anesthesia.

3. Study Population (Table 70)

The inclusion-exclusion criteria listed in the [illegible]

type of study. The identified risk factors for PONV were: major gynecological surgery, general anesthesia, medications received in relation to anesthesia: pre-, induction and maintenance narcotic and neuromuscular blocking and analgesics, including morphine and NSAIDs. The reasons for exclusion from the trial were also sound. Patients with organic conditions associated with vomiting, those receiving potentially confounding antiemetic medications and those receiving intragastric tube postoperatively were excluded. It is of interest to note that, from the cardiovascular viewpoint, not enrolled into this trial were patients with CHF, those with second or third degree AV block or those with arrhythmia requiring drug treatment. These exclusions were an acknowledgment that i.v. DOLA•Mesyl at doses ≥3.0 mg/Kg may be associated in some patients with cardiac conduction delays (i.e. increase in PR, QRS, QT_c intervals).

4. Concomitant Medications

Although the use of benzodiazepines for pre-medication was allowed, the following medications, with potentially antiemetic properties were excluded during the course of the trial:

- phenothiazines
- butyrophenones
- antihistamines
- systemic corticosteroids
- tricyclic antidepressants
- cannabinoids
- phenols
- dopamine antagonists
- ephedrine
- fluroxamine
- paroxetine
- scopolamine

The use of any medication with potential antiemetic activity unless administered to control emesis, was considered a protccol violation.

5. Test Medication

a. Identity of Test Medication

DOLA•Mesyl was supplied by the sponsor as coated tablets of 4 sizes: 25, 50, 100 or 200 mg. PL consisted of coated tablets, identical to the four doses of DOLA•Mesyl tablets in size and appearance and containing only inert ingredients. The Lot numbers were as follows:

DOLA•Mesyl tablet (mg)	Lot Number	PL	Lot Number
25	WN930117	for 25 mg tbl	/ WN220827
50	WN910116	for 50 mg tbl	[illegible]
100	WN930114	for 100 mg tbl	[illegible]
200	WN921008	for 200 mg tbl	[illegible]

TABLE 70
Study 73147-2-S-095 (Report S-95-0011-C)

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• Aged ≥18 AND ≤60 y • Scheduled to undergo major gynecologic surgery including: abdominal hysterectomy, gynecological laparotomy or vaginal hysterectomy • Scheduled to receive the following general anesthetic regimen: - Premedication with benzodiazepine or nil - Induction: thiopentone; narcotic: fentanyl or sufentanyl; neuromuscular blocking: vecuronium, pancuronium, or atracurium - Maintenance: nitrous oxide in oxygen with a volatile anesthetic - Maintenance narcotic: fentanyl or sufentanyl - Maintenance neuromuscular blocking: vecuronium, pancuronium, atracurium - Reversal agents if needed • Scheduled to receive IM or i.v. morphine for postoperative analgesia via patient controlled analgesia and/or NSAIDs • ASA physical status I-III • Not addicted to alcohol and • Signed an informed consent	• Pregnancy or breast-feeding (patients of child-bearing potential who would remain of child-bearing potential after surgery were required to have a negative pregnancy test prior to entering the study the morning of surgery. The requirement for patients to be using a contraceptive regimen was removed by the protocol amendment. • Body weight less than 45 Kg or more than 100 Kg • Evidence of clinically significant hepatic, renal, endocrine or cardiovascular dysfunction, and CHF • Pre-study abnormal serum potassium concentrations that could not be corrected prior to administration of test medication • Evidence of clinically significant liver disease discovered through medical history review or by P.E. • Clinically significant abnormalities in other laboratory prestudy tests • Second or third degree AV block • An arrhythmia requiring drug treatment • Vomiting due to organic etiologies such as outlet obstruction or small bowel obstruction • Having received any other investigational drug within the last 30 days prior to surgery • Previous treatment with DOLA•Mesyl • Having received any other antiemetic drug within 24h before surgery • Scheduled to receive an intragastric tube postoperatively • Allergy to or intolerance to any of the scheduled, prescribed anesthetic agents

of Anesthesiologists Classification:
systemic physiologic, biochemical or psychiatric disturbance. The pathological process for which the is localized and does not entail a systemic disturbance.
systemic disturbance caused by either the condition to be surgically treated or the pathophysiologic extremes of age are included here, either the neonate or the octogenarian, even though no discernible is present. Extreme obesity and chronic bronchitis are also included in this category.
disturbance or disease from whatever cause, even though it may not be possible to define firmly the degree

b. Dosing Schedule

All patients received 4 tablets, ca. 1 to 2h prior to induction of anesthesia, according to the following dosing schedule:

STUDY GROUP	-2 HOURS to -1 HOUR BEFORE INDUCTION OF ANESTHESIA				
	Test Med. Dose				
	1 tablet	1 tablet	1 tablet	1 tablet	
PL	PL	+ PL	+ PL	+ PL	= 4 tablets
DOLA•Mesyl 25 mg	25 mg	+ PL	+ PL	+ PL	= 4 tablets
DOLA•Mesyl 50 mg	PL	+ 50 mg	+ PL	+ PL	= 4 tablets
DOLA•Mesyl 100 mg	PL	+ PL	+ 100 mg	+ PL	= 4 tablets
DOLA•Mesyl 200 mg	PL	+ PL	+ PL	+ 200 mg	= 4 tablets

c. Blinding, Packaging and Labeling

My review of this subsection indicate that these aspects of the protocol were adequate. Labels were designed to meet national requirements. It was the responsibility of the pharmacist at each center to maintain the blind of the protocol. The Strasbourg statistician was responsible for generating and maintaining the randomization code during the trial. For emergency purposes, individual sealed envelopes were available in the Trial Master File.

d. Method of Assignment

Patients were assigned a dose group via a random code list provided by MMD, Strasbourg, biostatistical group to the investigator at each site. Patients were recruited chronologically and in numerical order according to the random code.

e. Compliance

Adequate procedures to assess compliance were used.

6. Study Evaluations

a. Efficacy Parameters

- The primary evaluation of efficacy of [redacted] during the 24-h study period by the number of [redacted] as per chemotherapy induced [redacted] following four periods post-recovery:

0-2h 2-4h [redacted]

Patients were classified as Complete Responders, Major Responders or Treatment Failures using the same definitions as per chemotherapy-induced N&V studies.

- Secondary assessments of efficacy included both patient and investigator assessments of N&V.

  - Patients assessed the level of nausea experienced using a VAS. The extremes of nausea experienced were scored as 0 mm ("no nausea") to 100 mm ("nausea as bad as it can be"). The VAS assessments were completed by the patient at 2, 4 and 6h after recovery (defined as the first response to the spoken command, "open your eyes") if the patient was awake. Assessment of nausea began when the patient was fully oriented.

  - The investigator assessed the patient's level of nausea using a discrete scale. The severity of nausea was ranked using the following scores: 0=no nausea; 1=mild nausea; 2=moderate nausea; 3=severe nausea. Assessments were made by the investigator during the following time periods: 0-2h, 2-4h, 4-6h and 6-24h after recovery.

  - Time to first emetic episode and onset of nausea and the time to escape medication were recorded.

  - At 24h post study medication administration, the patients rated their overall satisfaction with therapy received using the VAS. The extremes of the scale were 0 mm ("completely satisfied") to 100 mm ("not at all satisfied").

  - The patients assessed the severity of pain during the 24h study period using VAS scores. The scoring ranged from 0 mm ("no pain") to 100 mm ("pain as bad as it can be"). Patients completed VAS assessments for pain at 2, 4 and 6h after recovery.

- The investigator could initiate escape medication therapy if one or more of the following events occurred:

  - the patient experienced 15 min. or more of persistent nausea
  - the patient experienced more than one emetic episode
  - the patient requested alternative antiemetic medication
  - the investigator determined that an alternative antiemetic was necessary

- The time, name, dose, route of administration and [illegible] medication were recorded in the patient's case [illegible]

- All patients receiving escape medication were [illegible] failures.

b. Safety Parameters

My review of the procedures to report AEs, definitions, including those of treatment-emergent AEs, assessment of relationship to test med. and the severity of the AE indicates that these were all adequate.

It is worth noting that BP and HR were recorded just before 1h after adm. of test med., at induction of anesthesia, every 30 min. after induction until recovery and at 2, 4 and 6h after recovery. EKGs were recorded at screening, at one, each, or all of the following time periods: 1-2, 4-5 or 24h after adm. of test med.

7. Statistical Methodology

a. Sample Size Justification

- Sample size determination was based on comparing the most effective dose (i.e., the dose with the maximum response rate) to PL in the logit of the proportion of complete responders.
- A stepwise Dumnett's procedure was used to account for a total of 4 possible comparisons. The calculation postulated that the complete response rates in PL and the most effective dose were 45% and 65%, respectively (20% therapeutic gain).
- Assuming 150 patients in each dose group, for a total of 750 patients, the power of a 2-tailed pairwise comparison with an overall 0.05 significance level of the most effective dose to PL is 93%. Additional patients were studied for a total of 793 patients, 154 to 166 in each dose group.

b. Statistical Methods

1) Primary Analysis

- The primary analysis was an intent-to-treat analysis of complete response (no emetic episodes, no escape medication administered, and patient monitored for at least 23.5h after study drug administration) over 24h using logistic regression with a test for dose trend in the proportion of complete responders with dose, controlling for investigator.
- As documented in the statistical analysis plan dated [illegible] prior to unblinding, patients not monitored for [illegible] were categorized as treatment failures.

2) Secondary Analyses

Examination of the impact of various covariates on complete response was conducted using the logistic regression model with investigator as explanatory variables.

Total Response

Complete response with no nausea (not even mild nausea) was analyzed with a test for linear trend in the proportion of complete responders with dose, controlling for investigator.

Other Parameters

The specific statistical analysis used is listed below.

Secondary Parameters of Efficacy	Statistical Method
Complete plus Major Response (<2 emetic episodes)	Similar logistic regression methods as used for the primary analysis
Complete Responders at 8h after test med. administration	Ibid
Time to first emetic episode or escape medication	Survival techniques
Test hazard ratios that compare each dose to PL and also all DOLA•Mesyl doses to PL	Cox regression model
Nausea VAS score	Mean and maximum overall scores were calculated for each patient
Proportion of Pts. who reported NO Nausea (VAS score <5 mm)	Logistic regression model controlling for dose and investigator to compare each DOLA•Mesyl dose to PL
Pt. satisfaction VAS scores	Nonparametric ANOVA

3) Pooling of Sites

- 32 sites were grouped into 23 pooled sites to satisfy asymptotic considerations for main effects logistic regression.
  - The following pooled sites were created: 51, 52, 54, 56, 57 and 58; 24, 34 and 55; and 35, 47 and 50.
  - All analyses were performed using these pooled sites together with the other twenty sites.
  - The exact method for pooling was described in Sponsor's Appendix X2: Additional Statistical Discussion, page 1405.

4) Safety Analyses

The methodology for safety data was adequate. The following is worth noting.

- Changes in vital signs (recumbent pulse rates, systolic blood pressures and diastolic blood pressures) from Pre-Tx to Post-Tx time points were analyzed using a two-way rank ANOVA controlling for investigator. A test for linear trend with dose in the mean rank change of each vital sign was performed. The frequency of patients who had Tx-emergent vital sign changes was summarized by dose. A line plot of mean change from BL (T0) representing each dose for each vital sign variable was constructed to compare doses and changes in vitals over the 24-h Tx period.

- Changes from baseline to 1-2, 4-5 and 24h poststudy in EKG measurements (12-lead), QT, QT_c, PR, QRS and JT, were also analyzed using a two-way rank ANOVA controlling for investigator. A test for linear trend with dose in the mean rank change of each measurement was performed. EKG changes were summarized by dose.

- EKG were centrally used by a cardiologist as well as being read at the investigative site. Data for EKGs read centrally did not have scheduled time on the paper copy. For these cases, the scheduled time was calculated from the actual data and time recorded on the EKG. The times were re-coded according to the scheduled times from the site read EKGs on the CRF (0, 1 to 2, 4 to 5 and 24h post T0). Where there were two EKGs measured close to a scheduled postdose time, the worst case approach was taken with respect to QT and PR interval. For BL readings the time nearest T0 was used. Visits were defined as follows:

Baseline:	EKG time ≤0.0 h
Hour 1-2:	0.0h < EKG time <3.0 h
Hour 4-5:	3.0h ≤ EKG time <10 h
Hour 24:	12h ≤ EKG time

- Statistical analyses and summaries of EKG readings used the central cardiologist determinations in preference to site readings. Thus, if an EKG for a particular visit was read by the central cardiologist, then the central cardiologist's reading was used instead of the site reading for that visit. In particular, measurements or assessments that were determined by the central cardiologist to be unevaluable, and therefore missing, were assumed to be the corresponding value for that measurement or assessment for that EKG. If an EKG was not read by the central cardiologist, then the site reading was used to determine all changes from BL. The JT interval was calculated as JT = QT - QRS.

8. Results

a. Participating Investigators/Patient Accounting

Of the 38 sites that agreed to do the study,

- 6 (Site #11, 18, 29, 31, 34 and 35) dropped from the trial. Test med. was not shipped to these centers.

- 5 (Site #24, 19, 32, 38 and 14) randomized 4 patients or less (each site).

- 12 (Site #08, 15, 23, 13, 14, 06, 21, 22, 25, 37, 36, 30) randomized between 5 and 19 patients (each site).

- The following 15 sites randomized 20 patients or more (each).

Site		Total # of Pts. Randomized
#03	(Cooper, Birmingham, U.K.)	75
#10	(Helmers, Amersfoort, NL)	64
#01	(Park, Lancaster, UK)	61
#16	(Leeser, Amsterdam, NL)	54
#12	(Wilkey, Cambridge, UK)	50
#27	(Korttila, Helsinki, FIN)	50
#02	(Hopkins, Leeds, UK)	46
#28	(Van Aken, Leuven, BEL)	40
#17	(Diemunsch/Dupeyron, Strasbourg FR)	37
#26	(Radke, Halle, GER)	35
#20	(Gilbert, Karlsruhe, GER)	36
#07	(Aitkenhead, Nottingham, UK)	26
#09	(Onsrud, Trondheim, NOR)	25
#33	(Perrouin, St. Sebastien/Loire, FR)	24
#05	(Pollard, Manchester, UK)	22

- A total of 793 patients were randomized to Tx and received test med. at 32 investigative sites.
  - 789 completed the trial.
  - In four patients surgery was canceled after they had received test med. (200 mg DOLASetron Mesylate). These patients were considered not to have completed the study.[25]

[25] The surgeries were canceled for incidental reasons, such as [illegible] suite time. None of these cancellations involved AEs.