4) Overall Rate of AE Incidence (Table 90)

- The most frequently reported AEs with DOLA•Mesyl were pruritus, headache, bradycardia, hypotension and dizziness. Except for hypotension (all DOLA•Mesyl groups = 7.7%; PL = 9%)), for all of these terms, the percentages with DOLA•Mesyl (all groups combined) were higher than with PL. None of these AEs demonstrated a statistically significant linear dose trend.

- Although dizziness occurred more frequently in the DOLA•Mesyl dose groups than in the PL group there was no trend toward increased dizziness with increasing DOLA•Mesyl dose.

- The most frequent EKG interval changes by dose group which occurred in ≥1% of the study population were listed in Table 89.

- By system organ class, the most frequent AEs occurring in the DOLA•Mesyl group as a whole were those related to the heart rate and rhythm, central and peripheral nervous system, skin and appendages, cardiovascular and urinary systems. There was no linear trend across dose groups in any of these systems.

- Also presented in Table 90 are Tx-related events and included term (all DOLA•Mesyl groups=24.4%, PL=20%) and Tx-related EKG interval abnormalities (these were discussed above).

TABLE 90
Study AN-PO-0292 (Report L-95-0001-CS)

Frequency (%) of AEs and Tx-Related AEs

System Organ Class and Included Term p value[a]	Dose (mg)					MDL 73,147EF [n=299]
	PL [n=75]	25 [n=76]	50 [n=74]	100 [n=74]	200 [n=75]	
Overall Rate (p=N.S.)	35 (46.7)	48 (63.2)	44 (59.5)	38 (51.4)	37 (49.3)	167 (55.9)
I. Most Frequently Occurring AEs						
Pruritus (p=N.S.)	6 (8.0)	8 (10.5)	10 (13.5)	[illegible]	[illegible]	36 (12.0)
Headache (p=N.S.)	3 (4.0)	7 (9.2)	9 (12.2)	[illegible]	[illegible]	29 (9.7)
Bradycardia (p=N.S.)	4 (5.3)	11 (14.5)	[illegible]	[illegible]	[illegible]	27 (9.0)
Hypotension (p=N.S.)	6 (8.0)	7 (9.2)	[illegible]	[illegible]	[illegible]	23 (7.7)
Dizziness	0	[illegible]	[illegible]	[illegible]	[illegible]	19 (6.4)

II. AEs Related to HR and Rhythm						
Overall Rate (p=N.S.)	11 (14.7)	18 (23.7)	12 (16.2)	12 (16.2)	10 (13.3)	52 (17.4)
Bradycardia (p=N.S.)	4 (5.3)	11 (14.5)	5 (6.8)	8 (8.1)	5 (6.7)	27 (9.0)
Tachycardia	1 (1.3)	2 (2.6)	4 (5.4)	2 (2.7)	0	8 (2.7)
Sinus Bradycardia (p=N.S.)	4 (5.3)	3 (3.9)	1 (1.4)	1 (1.4)	1 (1.3)	6 (2.0)
Sinus Tachycardia	1 (1.3)	1 (1.3)	1 (1.4)	2 (2.7)	0	4 (1.3)
Arrhythmia Nodal	0	0	1 (1.4)	1 (1.4)	1 (1.3)	3 (1.0)
Junctional Arrhythmia	3 (4.0)	0	1 (1.4)	1 (1.4)	0	2 (0.7)
AV Block Third Degree	0	0	0	0	1 (1.3)	1 (0.3)
III. Tx-Related AEs						
Overall Rate (p=N.S.)	15 (20.0)	25 (32.9)	13 (17.6)	19 (25.7)	16 (21.3)	73 (24.4)
HR & Rhythm (p=N.S.)	6 (8.0)	10 (13.2)	4 (5.4)	9 (12.2)	9 (12.0)	32 (10.7)
Bradycardia (p=N.S.)	3 (4.0)	6 (7.9)	1 (1.4)	5 (6.8)	5 (6.7)	17 (5.7)
Headache (p=N.S.)	3 (4.0)	6 (7.9)	6 (8.1)	6 (8.1)	4 (5.3)	22 (7.4)
Hypotension	3 (4.0)	5 (6.6)	1 (1.4)	0	4 (5.3)	10 (3.3
Pruritus	0	1 (1.3)	0	1 (1.4)	2 (2.7)	4 (1.3
Drowsiness	0	0	0	1 (1.4)	3 (4.0)	4 (1.3)
IV. Tx-Emergent EKG Interval Changes						
Overall Rate (p=N.S.)	37 (49.3)	25 (32.9)	31 (41.9)	33 (44.6)	37 (49.3)	126 (42.1)
HR & Rhythm	37 (49.3)	25 (32.9)	31 (41.9)	33 (44.6)	37 (49.3)	126 (42.1)
QT Interval Prolongation ($QT_c \geq 440$) (p=N.S.)	35 (46.7)	25 (32.9)	30 (40.5)	29 (39.2)	34 (45.3)	118 (39.5)
QRS Prolonged (p=0.0180)	2 (2.7)	1 (1.3)	2 (2.7)	5 (6.8)	8 (10.7)	16 (5.4)
AV Block First Degree (PR≥220)	1 (1.3)	0	0	1 (1.4)	1 (1.3)	2 (0.7)

A) p values were calculated from a test for linear trend across dose in the incidence of that event using a logistic regression model with dose as an explanatory variable.

5) Clinical Laboratory Evaluation:

- There was a statistically significant decreasing linear trend across doses for WBC (p=0.0049), AR (p=0.0242), RBC (p=0.0107), and statistically significant linear increasing trend in [illegible] groups. But these changes were not considered to be clinically significant.

i) Shift Tables

- 6 chemistry laboratory tests had ≥40 patients shift from normal and above the normal range at Pre-Tx to below the NL of the NR at Post-Tx: BUN (182/362), calcium (232/356), magnesium (168/340), phosphorus (164/348), uric acid (40/347), sodium (101/367). There were no differences between any of the DOLA•Mesyl dose groups or PL for any of these parameters.

- 2 chemistry parameters had ≥40 patients shift from normal and below the HR at Pre-Tx to above the NR or above the ULNR at Post-Tx: creatine kinase (127/340), glucose (133/349). There were no differences between any of the DOLA•Mesyl dose groups or PL for either of these parameters.

- All other changes in chemistry parameters were present in <40 patients and no differences between any of the DOLA•Mesyl dose groups or PL were present.

ii) Significant Changes in Liver Function

Pt. #/Parameter	Pre-Tx Value	ULNR (At Site)	Post-Tx Value	Intensity	Relation to Test Med.
1. 0007-0148 (PL) OT (U/L)	28	30	72	MOD	N/A
PT (U/L)	Also ↑ but not as high as the alert value				
2. 0002-0018 (25 mg)* OT (U/L)	8	50	407	SEV	POSS
PT (U/L)	26	40	490	SEV	POSS
3. 0005-0118 (50 mg) OT (U/L)	Also ↑ but not as high as the alert value				
PT (U/L)	14	40	101	MOD	POSS
4. 0005-0112 (PL) BIL µmol/L	20	21	54	SEV	N/A
OT, PT	Normal		Normal		

5. 0001-0402 (50 mg)					
BIL μmol/L	17	20	40	SEV	POSS
OT	Normal		Normal		
PT	Normal		Not Done		

a) The patient was asymptomatic. No other AEs were reported for this patient. The blood tests were repeated 10 days later and they were found to be WNLs.

6) Other Safety Assessments

Descriptive statistics were provided for recumbent pulse rates, systolic BP and diastolic BP, as a function of time.

- All dose groups were associated with small median changes, at some point. As shown below some of these were statistically significant including a linear dose trend in systolic BP from minute 120 through hour 20, but these differences did not represent clinically significant changes.

- Sponsor's Fig. 10 (p. 371) provided plots of mean change from BL to each time point by dose group for pulse rate no marked differences among the test groups, systolic BP (the 100 and 200 mg showed decreases from BL) and diastolic BP (decreases with the 100 and 200 mg dose groups were larger than those with the other three test groups).

7) EKG Measurements (Table 91)

→ - The five EKG measurements in this Table are examined on the basis of change from BL, as a function of time. In the lower panel of this Table, the p-values for linear trend across dose in change from BL, controlling for investigator are provided. The most interesting changes were those in the QT_c interval. There was a statistically significant linear dose trend in QT_c interval across dose groups at 90 min. (p=0.0172), arrival to recovery room (p=0.0031) and at 24h post-dose (p=0.0414). The mean increases from BL as the three time evaluations are shown below, by dose.

p-values test for linear trend across PL and DOLA•Mesyl groups in change from BL

Evaluation Time Point	Recumbent		
	Pulse Rate	Systolic BP	Diastolic BP
Minute 30	N.S.	N.S.	0.0120
Minute 60	N.S.	N.S.	N.S.
Minute 90	N.S.	N.S.	N.S.
Minute 120	N.S.	0.0043	N.S.
Hour 3	N.S.	0.0124	N.S.
Hour 4	N.S.	0.0015	0.0289
Hour 5	N.S.	0.0144	0.0294
Hour 6	N.S.	0.0229	0.0484
Hour 7	N.S.	0.0400	N.S.
Hour 8	N.S.	0.0135	N.S.
Hour 12	N.S.	0.0229	0.0267
Hour 16	N.S.	0.0101	N.S.
Hour 20	N.S.	0.0198	N.S.
Hour 24	N.S.	N.S.	N.S.

Time Post-dose	Mean Increases (msec) PL	25	50	100	200
90 min.	3.4	5.0	7.7	7.2	10.7
Arrival to Recovery Room	22.9	23.8	29.8	25.9	34.3
24h	6.5	6.6	3.9	1.0	1.8

- At 90 min. postdose 5% of the patients in each of the PL, DOLA•Mesyl 25 and 50 mg groups had developed QT, prolongation [illegible] The highest incidence was 10% in the 100 mg dose group which decreased to 3% in the 200 mg group.
- At arrival to recovery room, the highest incidence of [illegible] was in the 200 mg dose group (42%). [illegible] any linear trend. The incidence was 37%, 20%, 31% and 31% in the PL, 25, 50 and 100 dose groups, respectively.

- At 24h postdose, the PL now showed the highest incidence of QT_c prolongation (12%). The incidence across the DOLA•Mesyl groups was 4%, 3%, 3% and 1% in the 25, 50, 100 and 200 mg dose groups, respectively.

- None of the patients in the study who had a QT_c <440 msec at BL had an increase to >500 msec.

  - 20 patients in this study had a QT_c interval ≥440 msec at BL. These were distributed across dose groups as follows: PL: 5 patients 25 mg: 5 patients, 50 mg: 3 patients, 100 mg: 4 patients and 200 mg: 3 patients.

  - In most cases the QT_c interval actually decreased postexposure to test medication and was below BL at 24h postdose; others returned to their BL level after increasing slightly temporarily. These patients were asymptomatic and were not treated for the EKG abnormality.

  - Patient 0001-006 (100 mg) had a QT_c =444 msec at BL which increased to 526 msec in the recovery room. The QT_c interval had decreased to 441 msec at 45 to 90 min. postdose and had returned to BL (448 msec) at 24h postdose. The patient was asymptomatic, was not treated for the EKG abnormality. The only AE reported by this patient was pruritis.

A graphic representation of the 24h change from BL for PR, QRS, QT, QT_c and JT are provided in Fig. 20. The data in this Fig. is self-explanatory. The discontinuous line either at 0 (zero) for PR, QRS and QT_c or -20 msec for QT and JT facilitates comparisons between/among groups. The 24h changes from BL are neither very pronounced nor dose-related. For QT_c, the higher DOLA•Mesyl dose levels (100 and 200 mg) were associated with minor changes in comparison to those seen with PL and the 25 mg dose. These data appear to show that for QT_c, as well as for the other EKG parameters, there was a return to Baseline.

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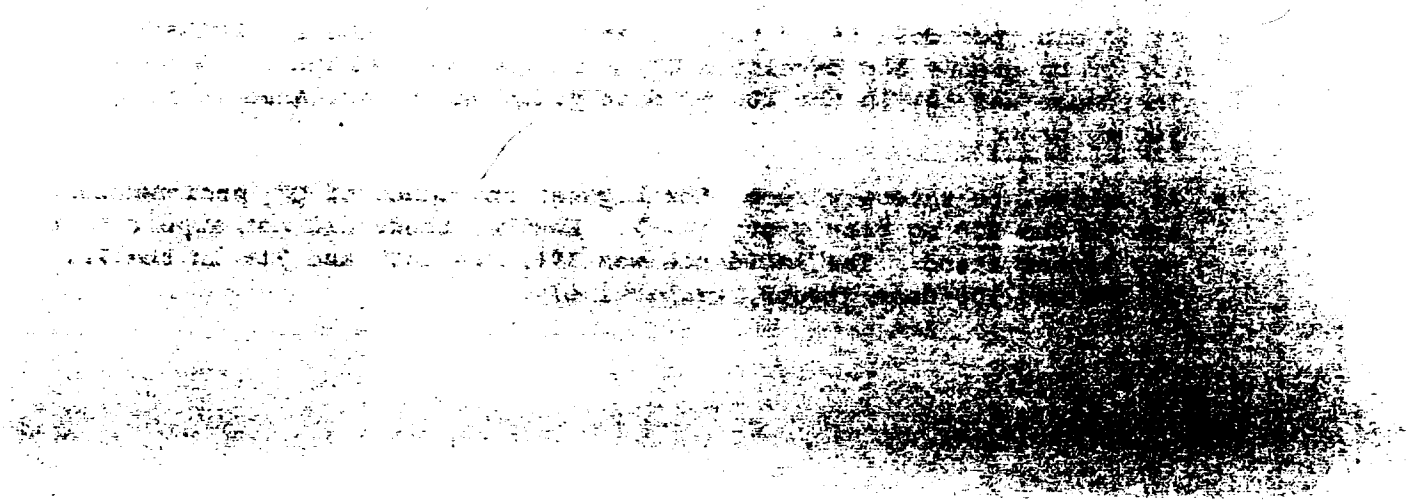
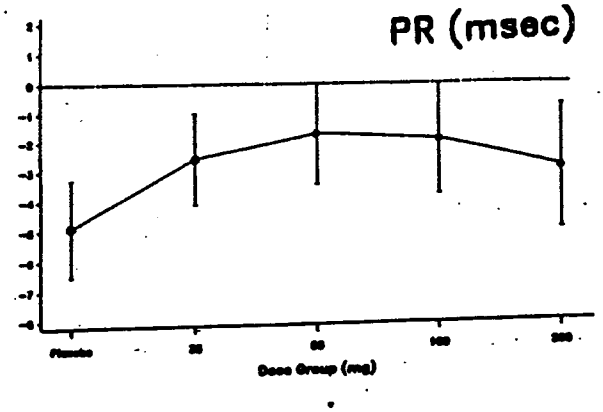
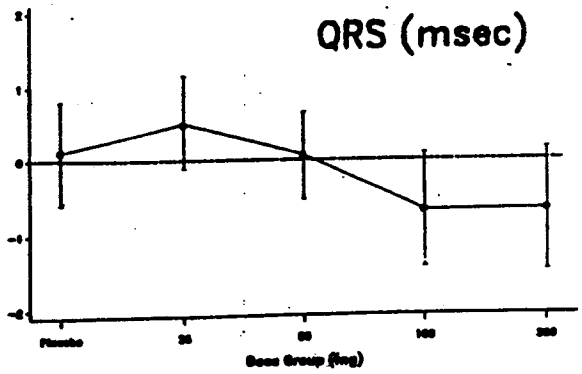
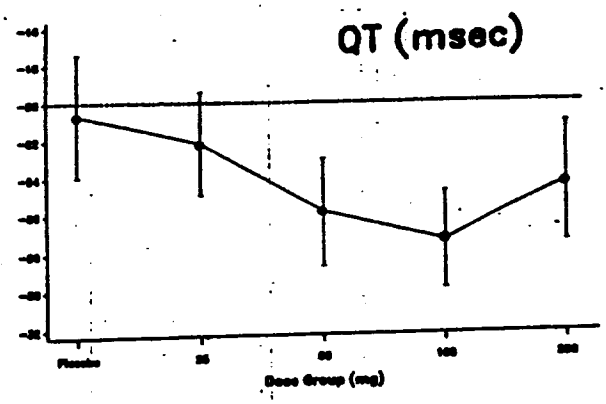


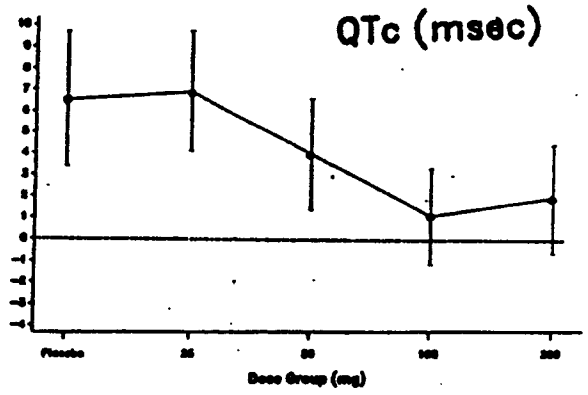
0292

Change from Baseline by Dose









in EKG Parameters as a Function of Dose

TABLE 91
Study AN-PO-0292 (Report L-95-0001-CS)

Changes from BL in EKG Parameters by Time of Evaluation

Dose (mg)	Time of Evaluation	n	PR		QRS		QT		QT_c		JT	
			BL	Change from BL	BL	Change from BL	BL	Change from BL	BL	Change from BL	BL	Change from BL
PL	Baseline	75	153.7		80.8		379.0		408.1		298.2	
	Minute 90	74		0.7		-0.3		-0.3		3.4		-0.1
	Recovery Room, Arr	73		2.5		2.0		27.8		22.9		25.9
	Recovery Room, End	16		-1.4		-0.9		11.3		16.4		12.3
	Hour 8	15		-3.0		-2.1		2.3		8.6		4.4
	Hour 24	75		-4.6		0.1		-20.3		6.5		-20.4
25	[redacted]	76	149.0		81.3		379.1		402.9		297.8	
	Minute 90	76		4.2		1.2		2.3		5.0		1.0
	[redacted]	75		4.3		2.3		35.7		23.8		33.4
	[redacted]	16		-3.4		1.3		21.7		6.3		20.4
	[redacted]	16		-0.6		-0.7		8.3		14.6		8.9
	[redacted]	76		-2.5		0.7		-21.5		6.6		-22.2
	[redacted]	74	148.0		81.8		381.7		402.5		299.9	
	[redacted]	74		2.3		-0.0		-2.7		7.7		-2.7
	[redacted]	72		8.5		3.3		27.8		29.8		24.5
	[redacted]	15		5.4		1.5		4.1		23.5		2.6
	[redacted]	14		2.1		-1.4		-10.6		16.6		-9.1
	[redacted]	74		-1.9		0.1		-26.0		3.9		-26.0

[illegible]	[illegible]oline	74	151.4		83.0		378.5		406.1		295.4	
	[illegible]nute 90	72		4.0		1.3		2.0		7.2		0.7
	Recovery Room, Arr	73		4.1		2.9		36.8		25.9		33.9
	Recovery Room, End	14		5.3		-0.6		-2.6		7.2		-2.1
	Hour 8	14		4.1		0.0		-13.4		23.7		-13.4
	Hour 24	73		-2.1		-0.7		-27.5		1.0		-26.8
200	[illegible]oline	75	154.9		80.0		379.7		404.1		298.9	
	[illegible]nute 90	74		7.5		3.4		3.0		10.7		-0.4
	[illegible]covery Room, Arr	74		9.9		6.6		36.5		34.3		29.9
	[illegible]covery Room, End	15		1.1		4.3		22.9		25.9		18.7
	[illegible] 8	16		-2.3		1.6		12.1		26.3		10.4
	[illegible] 24	75		-3.1		-0.7		-24.5		1.8		-23.8
				0.0005		0.0027		N.S.		0.0172		N.S.
				0.0032		0.0002		N.S.		0.0031		N.S.
				N.S.		0.0187		N.S.		N.S.		N.S.
				N.S.		N.S.		N.S.		N.S.		N.S.
				N.S.		N.S.		N.S.		0.0414		N.S.

It is also important to note Tx-emergent changes in certain EKG parameters in the following individual patients.

- 3 patients experienced a Tx-emergent increase in PR interval ≥220 msec.

	Baseline PR	Post-Tx PR	Δ
1. 0002-0020 (200 mg)	188	205 (90 min)	17
		220 (Arrival to Recovery Rm.)	32
		223 (Hour 24)	35
2. 0003-0072 (PL)	205	194 (90 min)	-11
		265 (Arrival to Recovery Rm.)	60
		183 (Hour 24)	-22
3. 0004-0211 (100 mg)	200	200 (90 min)	0
		232 (End of Recovery Rm.)	32
		244 (Hour 8)	44
		172 (Hour 24)	-28

- 2 patients had a QRS interval <100 msec at BL which was ≥100 msec at 24h.

	Baseline QRS	Post-Tx QRS	Δ
1. 0007-0143 (PL)	95	100 (Hour 24)	5
2. 0001-0050 (100 mg)	99	102 (Hour 24)	3

9. Conclusions (Sponsor)

"Analysis of the complete response rate at 24h postdose indicated that there was an increasing linear dose trend across dolasetron dose groups.

"Dolasetron 100 mg and 200 mg were found to be statistically superior to placebo.

"The 100 mg dose had the maximum complete response [illegible]

10. Reviewer's Comments

Study -0232 is the [illegible] in support of approval of the [illegible] (DOLA-Mesyl) 50 mg tablets, given within [illegible] prevention of PONV. Study -0232 was a multi[illegible]

parallel, dose-response, 5-arm, set to compare the efficacy and safety of single oral doses of DOLA•Mesyl (25, 50, 100 or 200 mg) with those of PL in PONV prevention. Just as in the other pivotal study, in this trial, the comparator was PL, a negative control. In the final analysis, study -0292 was well designed and well executed and was conducted in Canada at 13 sites with qualified investigators.

Enrolled in Study -0292 were 374 female patients with a mean age of 43 years, scheduled to undergo uncomplicated abdominal hysterectomy under general anesthesia and in general, without overt evidence of respiratory, cardiovascular, metabolic, hepatic or renal dysfunction. The patients were required to have an ASA physical status I-II, not be addicted to alcohol or drugs and sign an informed consent before their inclusion into the trial. Excluded were patients <45 Kg in body weight, those who were vomiting due to organic conditions or those who were scheduled to receive an intragastric tube post-operatively. From the cardiovascular viewpoint, not included in the trial were those females with cardiomyopathy, CHF or Hx of CHF, arrhythmias requiring antiarrhythmic medication, those with second or third degree AV block, those with pre-existing either L or R BBB (QRS ≥msec) and those with significant cardiovascular dysfunction.

The methodology for randomization used in this trial resulted in five patient populations that were balanced with respect to variables that may influence outcome. For the five experimental groups, the demographic and other baseline characteristics, were similar to each other. These included, ASA status (as in Study -095, the majority of patients were ASA I=64%; ASA II=36%), Hx of PONV (47%) and Hx of motion sickness (28%). Other than requiring an inpatient, uncomplicated abdominal hysterectomy under general anesthesia, the participating females in this trial were essentially normal.

Except as noted, the experimental groups were balanced with respect to concomitant previous and present medications in general and concomitant medications that may be confounding. There were no statistically significant imbalances among Tx groups in doses of medications used for pre-medication, induction, maintenance and reversal of anesthesia. Mean duration of anesthesia (1.5h), time to recovery and time from last free fluids to test med. administration (8.9h) were similar among the test groups. Of the concomitant medications taken Post-Tx, among those taken as escape medications, a significantly higher proportion of PL patients (51%) took dimenhydrinate (DOLA•Mesyl=39% to 54%) (p=0.01). Numerically, [illegible] patients took prochlorperazine and 0% of all the DOLA•Mesyl [illegible] took this rescue medication. These imbalances were [illegible] efficacy among PL patients.

The five test groups were also well matched [illegible] the emetogenic stimulus (or weather related [illegible] under which these experiments are being [illegible] factors for motion, which were well balanced [illegible]

abdominal hysterectomy, with or without salpingo-oophorectomy, general anesthesia and agents to control pain such as I.M. or I.V. morphine and NSAIDs.

For comments and conclusions on efficacy, two types of comparisons are considered: comparisons of DOLA•Mesyl doses against PL and comparisons of DOLA•Mesyl doses against themselves. Study -0292 showed that DOLA•Mesyl is active since both the ITT and the Evaluable Population analyses demonstrated a statistically significant linear trend in the proportion of complete responders across the five dose groups. Neither the 25 mg nor the 50 mg dose groups could be differentiated from PL and the therapeutic gains with the latter dose over PL were 11% (ITT) and 10% (Evaluable Population). Both the 100 mg and the 200 mg dose groups were clinically and statistically superior to PL, with little differences in responses (therapeutic gains of 25%, and 20% in the ITT and 22% and 21% in the Evaluable Population analyses). Thus, in this study, the highest therapeutic gain over PL was 25% but this was afforded by the 100 mg dose. These findings are to be contrasted with those in Study -095 where the highest therapeutic gain over PL was 22% but this was afforded with the 50 mg dose.

In ITT comparisons against the 25 mg dose, only the 100 mg dose group was shown to be statistically significantly different from (p=0.033), with a therapeutic gain of 18%. In Evaluable Population analyses (sponsor), in spite of a therapeutic gain of 17%, this dose group was not statistically different from PL. Further analyses carried out by the sponsor showed no differences between the 200 mg dose group and the 25 or 50 mg dose groups.

The proportion of patients with a total response was statistically significantly different for those patients given 50, 100 or 200 mg of the drug, with therapeutic gains (over PL) of 14%, 26% and 21%. Although both the 50 and the 100 mg dose groups are shown to be superior to PL, the therapeutic gain with 100 mg is twice as high as with 50 mg. The therapeutic gain with the 25-mg dose (13.3%) was not statistically significant even though this gain was very similar to that with the 50 mg (13.7%) [sponsor's calculations].

Subgroup analyses of complete response examined the effects of a number of variables, of which, only ASA physical status, previous Hx of motion sickness, previous Hx of PONV and total morphine dose were found to be significant predictors of complete response. Thus, patients of ASA physical status II (good) were more likely to be complete responders than were patients of ASA physical status I (healthy). Patients without a Hx of motion sickness were more likely to be complete responders than were patients with a Hx of motion sickness. Patients without a Hx of PONV were more likely to be complete responders than were patients with a Hx of PONV. 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 more.

In study -0292, investigator was not a statistically significant predictor of complete response and there was no dose by investigator interaction. Also, taking sample sizes into consideration, dose groups

investigator. When any of the many variables shown not to be significant predictors of complete response were entered along with dose and investigator in the logistic regression model, the primary test of linear trend across doses remained statistically significant. Similarly, when controlling for each of the factors shown to be significant predictors of complete response, in separate analyses, along with dose and investigator, the primary test in complete response over dose remain statistically significant. In this study, results of analyses on the basis of mg/Kg were similar to those for the primary efficacy analyses for complete response. Dose measured in mg/Kg was a statistically significant predictor of complete response (p=0.0047). The dose category encompassing the 50 mg dose,

was associated with 14% therapeutic gain over PL. This therapeutic gain was lower than the 23% associated with the dose category encompassing the 100 mg dose,

No deaths occurred in this trial. Two serious events occurred: a) complete heart block in a hypertensive and hypothyroided 61y old female patient that had 1° AV block at baseline. She had received 200 mg of the drug 2h and 19 min. prior to event onset. The AE was treated with 0.4 mg glycopyrrolate and it was **definitely related** to DOLA•Mesyl. The attended physician felt that this serious/severe complete heart block, diagnosed from a video monitor, placed the patient at immediate risk of death. b) **Nodal bradycardia** (at 20 bpm) in a 29y old female that received 100 mg DOLA•Mesyl 2h and 55 min. prior to event onset. She had no known medical Hx related to the event, which was also considered **severe and possibly** related to test med. Although not dose related, an additional case of **severe bradycardia** and one of **severe hypotension** were seen in association with the 25 mg dose. On the other hand, the majority of AEs were considered mild in severity.

There was no statistically significant trend with dose in the overall incidence of AEs (PL=47%, total DOLA•Mesyl=56%). The most frequent AEs reported in this study were pruritus, headache, bradycardia, hypotension and dizziness. Except for hypotension (all DOLA•Mesyl=8%; PL=8%), for all of these terms, the percentages with DOLA•Mesyl (all groups combined) were higher than with PL. All of the 19 instances of mild to severe dizziness occurred in the DOLA•Mesyl-treated group (DOLA•Mesyl=5.3 to 6.6%; PL=0%) but there was no difference in the distribution across dose groups.

This trial showed a statistically significant decreasing linear trend across doses for BIL (p=0.0049), AP (0.0249), RBC (

significant linear increasing trend for

in LFTs are not considered to be

not know if they represent early

when one considers that significant

the same patients, have been

findings should be contrasted to

occurring in one and doubling of

patient.

In this trial, observations in EKG changes occurring acutely, that is 1½h and at arrival to the recovery room, were carried out. Results of these observations showed the expected statistically significant increasing linear trends across doses for PR, QRS and QT_c intervals for mean change from BL at 1½h Post-dose and arrival to recovery room. This significant change from BL for QRS persisted at the end of the recovery room interval but not for any other EKG interval at this time, hour 8 and, with the exception of QT_c, hour 24. It is important to note here that, although changes were largest in the 200 mg dose group at arrival to recovery room, changes, in general, were similar across dose groups and PL at 24h postdose. Indeed, at 24h postdose, for QT_c, the higher DOLA•Mesyl dose levels (100 and 200 mg) were associated with minor changes in comparison with those seen with PL and the 25 mg dose. These data appear to suggest that, at least for QT_c, the acute changes are returning to BL by 24h.

The only EKG change worth noting occurred in a patient given 100 mg of the drug and who reported pruritus as an AE. This patient had a QT_c of 444 msec at BL which decreased to 441 msec at 45 to 90 min. postdose. The QT_c interval increased to 526 msec in the recovery room but returned to near BL values (448 msec) at 24h postdose. This patient was asymptomatic and was not treated for this EKG abnormality.

In conclusion, orally administered tablets of DOLA•Mesyl are effective in the prevention of post-operative-induced nausea and vomiting. Although the response was linearly related to dose, there seemed to be no advantage in increasing the dose to higher than 100 mg per day. For the primary parameter of efficacy, complete response, this study did not replicate the findings in Study -095 where there was no advantage in increasing the dose to higher than 50 mg per day. Nevertheless, the 50 mg dose level was shown to be active (although less so than the 100 mg dose) in analysis of total response, a very stringent and rigorous parameter of efficacy. In this study population and under the experimental conditions and methodology used in Study -0292, graded doses of DOLA•Mesyl were - all in all - well-tolerated. Acute effects (defined as those occurring 1½h postdose and at arrival at the recovery room), were as expected from the known pathophysiological effects of the drug. EKG changes from BL for QRS, but not for the other parameters, persisted up to the end of stay in the recovery room but, they all seemed to have returned to BL at 24h postdose observations. Clinically, two significant cardiac events occurred in association with 200 mg and 100 mg dose levels, respectively, of DOLA•Mesyl: progression to 2° AV block and to complete heart block in a patient that had 1° AV at baseline, and nodal bradycardia. An additional case of severe bradycardia and one of [illegible] occurred with the 25 mg DOLA•Mesyl dose. There were no reports of VT or torsades de pointes. As in previous studies, and [illegible] with the reporting of some syncope/near syncope [illegible] patients at immediate risk of death, the [illegible] compound toxicity on AV and cardiovascular [illegible]. Patients receiving MYLERT tablets must be informed [illegible] toxicity, through a box warning (see Recommendations [illegible]

XIII. OVERALL SUMMARY OF EFFICACY

A. Chemotherapy-induced N&V Trials

In NDA 20-623, results from three trials (two of them pivotal) were submitted in support of approval of DOLA•Mesyl, at the oral dose of 200 mg once-a-day, given 30 min. before the start of chemotherapy, for the prevention of N&V associated with emetogenic cancer chemotherapy, including initial and repeat doses. The two pivotal trials -043 and -048 were adequate and well controlled (the control was 25 mg, the lowest dose of compound tested). In the supportive trial, -087, the comparator, ondansetron, was tested at a regimen not approved in the U.S. but marketed in Europe. This trial was reviewed primarily for safety reasons but efficacy data, mainly comparison of the effects of DOLA•Mesyl dose levels between themselves, were also of some utility. Both pivotal trials (-043, n=307 and -048, n=320) were 4-arm, double-blind, randomized, single oral dose, multicenter, dose-response, evaluations in the U.S. Both trials included a low dose of 25 mg and a highest dose of 200 mg per tablet, in addition to two intermediate doses, 50 and 100 mg. Study -087 was a dose-response, 5-arm trial, where the fifth arm consisted of orally administered ondansetron tablets, administered at the dose of 8 mg x 4 in 24h and the patients were stratified on the basis of gender and prior exposure to chemotherapy (naive vs non-naive). In all three trials the study population consisted of patients with histologically confirmed malignant disease who were scheduled to receive chemotherapeutic regimens, mostly non-cisplatin, of moderate emetogenic potential. The trials were apparently well-executed. The randomization procedures resulted in populations of patients that were balanced with regards to demographic and disease baseline characteristics, concomitant medications in general and medications that may be confounding and standardization of the emetic stimulus. The clinical procedures and statistical methodology were adequate to assess efficacy. The primary efficacy parameter was complete response and this is the parameter used by the reviewer to draw conclusions on efficacy.

All three trials showed that DOLA•Mesyl is efficacious for this indication. There was a statistically significant trend in the frequency of complete responders (as well as total responders) with increasing oral doses of the drug. The question is what is the recommended dose? The sponsor's proposed labeling recommends 200 mg. But, as summarized in the next section, this and lower doses of the drug produce electrophysiologic effects that result in increases in EKG parameters. The potential [illegible] dictate the use of doses lower than 200 mg without [illegible] patients. In the efficacy summary in Table [illegible] and the corresponding p-values for [illegible] the 100 mg are compared. For clarity of [illegible] DOLA•Mesyl have been omitted. In one [illegible] trials, this conclusion is reached [illegible] the dose from 100 to 200 mg. The p-[illegible] Study -087. This showed a response [illegible] and a [illegible] with the 200 mg [illegible] Study -043. In Study -087, the [illegible]

Although not statistically significant, the 16% therapeutic gain is clinically important. The main differences between the supportive vs the pivotal trials were that the former a) included a substantial number of patients that were non-naive to chemotherapy (in trial -087, better response was shown in patients who were chemotherapy-naive), b) at entry, stratification of patients on the basis of gender was carried out, c) was a 5-arm rather than a 4-arm study, d) used an active comparator (ondansetron). These discrepancies are mentioned here but they do not seem to be reasons for selective decrease in response with the 100 mg while altering substantially the response with both the 25 and the 200 mg of the drug. Although the use of the data in the supportive trial weakens somewhat the reviewer's recommendation of 100 over the 200 mg dose level, the recommendation to use the lower of these two doses is very well supported by results of the two pivotal trials -043 and -048.

Of the factors that may influence response, only age was a statistically significant predictor of complete response. Age gave consistent results across trials. The complete response rates in older patients were significantly higher than those in younger patients. This information should be included in the labeling.

TABLE 92

Complete Response in Chemotherapy-induced N&V Trials:
Comparison of Therapeutic Gains and
Statistical Significance with
100 vs 200 mg DOLA•Mesyl

Study No.	Complete Response With Comparator (25 mg)	Therapeutic Gain (%)/[p-value] DOLA•Mesyl Dose (mg)	
		100	200
-043 (n=307)	45%	29% [0.0005]	38% [<0.0001]
-048 (n=320)	31%	31% [0.0002]	28% [0.0004]
-087 (n=398)	45%	16% [N.S.]	31% [<0.001]

B. Prevention of PONV Trials

In this submission, results from two adequate and well-controlled studies were provided in support of approval of DOLA•Mesyl at the [illegible] a-day, given within two hours prior to surgery, for the [illegible]. Both of these pivotal trials (-095, n=791 and -028, [illegible] double-blind, randomized, single oral dose, multicenter [illegible] evaluations. Both trials were non-USA. Both trials [illegible] comparator and included the same dose levels as previously [illegible] chemotherapy trials (25, 50, 100 and 200 mg). In [illegible] population consisted exclusively of females, of [illegible]

who were scheduled to undergo major gynecological surgery in one trial, uncomplicated abdominal hysterectomy in the other. Both trials were apparently well-executed. The randomization procedures resulted in populations of patients that were well balanced with regards to demographic and other baseline characteristics, concomitant medications in general and medications that may be confounding. In addition to the already mentioned surgical operation, other risk factors for emesis were well-balanced among the Tx groups and included general anesthesia, agents to control severity of pain such as I.M. or I.V. morphine or NSAIDs. Very detailed review of the evidence demonstrated that the differences in efficacy between PL and the DOLA•Mesyl arms were clearly due to the preventive antiemetic properties of this drug and not to an imbalance in the many prognostic factors that might influence the development of PONV. The clinical procedures and statistical methodology used to assess response (efficacy) were adequate. The primary efficacy parameter was complete response and this is the parameter used by the reviewer to draw the conclusions on efficacy that follow.

Both trials showed that DOLA•Mesyl is efficacious for this indication. There was a statistically significant trend in the frequency of complete responders (as well as total responders) with increasing oral doses of the drug. The question is what dose is to be recommended? The sponsor's proposed labeling recommends 50 mg. The reviewer's evaluations suggest otherwise. In the efficacy summary in Table 93, and in a fashion similar to that under A. above, the therapeutic gains (in %) and the corresponding p-values for statistical significance for the 50 and 100 mg doses are compared. For clarity of presentation, omitted from Table 93, are results with the 25 mg, a dose that could not be differentiated from PL and the 200 mg DOLA•Mesyl dose, a dose that did not seem to afford significantly higher prevention than the 100 mg dose.

TABLE 93

Complete Response in PONV Trials: Comparison of Therapeutic Gains and Statistical Significance with 50 vs 100 mg DOLA•Mesyl

Study	Complete Response With Comparator (PL)	Therapeutic Gain/(p-value) DOLA•Mesyl Dose (mg)	
		50	100
-095	35%	23%	18%
-0292	29%	11%	

It turns out that for the 100 mg dose level [illegible] replicate those in the first. But the efficacy of [illegible] trial is not replicated by the second trial. [illegible] first trial, the 50 mg dose resulted in a 7% [illegible] than the 100 mg dose. But in the second trial, [illegible]

with the latter was 14% higher (a clinically important difference) than the former. It appears that in this clinical setting further benefit is obtained by increasing the dose of DOLA•Mesyl from 50 to 100 mg. The use of 50 mg of the drug may disadvantage patients. Because of this, the reviewer concludes that, for the prevention of PONV indication, the 100 mg is the preferred dose.

Of the factors that may influence response, only Hx of PONV was a significant predictor of complete response. In both trials, patients without a Hx of PONV had significantly higher complete response rates than patients with a previous Hx of PONV. This information should be included in the labeling.

XIV. OVERALL SUMMARY OF SAFETY

Included here is summary of the safety of DOLA•Mesyl tablet formulation for the two indications for which the sponsor is seeking approval: the prevention of cancer chemotherapy-induced N&V and PONV. Information from studies conducted with the I.V. formulation is also briefly summarized. The metabolic profile of the drug is very similar between oral and I.V. formulations. The primary metabolite, R(+)-enantiomer of MDL 74,156, is rapidly formed after either exposure. Thus, upon correction for the 75% bioavailability, similar safety profiles would be expected using oral and i.v. routes of administration. Data from clinical studies completed by 12/31/94 (with all CRFs in-house) and collected in the sponsor's global integrated database (GIDB) served as the basis for calculating AE occurrence rates for this summary.

1. Overall Extent of Exposure

Total Studied	9459[a]
Receiving active control or PL	1839
Receiving DOLA•Mesyl (oral or i.v.)	7620
Of these 7620	
Adults	7512
Pediatric	108[b]
Studies from others, not integrated sources	142
From these 142	
-European compassionate study	24[c]
-Other European studies	4
-Japanese Phase I studies	6[d]
-Smoking-cessation studies	48[d]
	142

a) Total # of patients and subjects in the GIDB. Some patients received more than one exposure. Some were crossed over.
b) Open-labeled studies
c) P.s. received single course of DOLA•Mesyl to coincide with events of cancer chemotherapy.
d) Investigator-sponsor IND

2. Overall Exposure to Orally Administered DOLA•Mesyl

a. Adult Healthy Volunteers in Clinical Pharmacology Studies

Total studied	374 (M=350; F=24) (15 studies)
Of these 374:	
-Received DOLA•Mesyl tablets	216
-Received i.v. formulation	158
	374[a]
In addition	
-Exposed to PL	45
-Pts. with hepatic impairment	11 (oral tablets)
-Pts. with renal impairment	36[b]
-Elderly	17[c]
Total Receiving DOLA•Mesyl	64[d]

a) Most studies used single doses; in 4 multiple dose studies test med. was administered for 7 to 28 consecutive days.
b,c) Received oral solution of i.v. formulation
d) In these special population studies DOLA•Mesyl was administered i.v. and orally in crossover fashion.

b. Cancer Chemotherapy Studies

1) Adult Patients

-Total Exposed to DOLA•Mesyl	943[a]
-Treated with ondansetron	83
Total	1026[b]

a) Exposed to single oral doses of the tablet formulation
b) Studies -043, -048 and -087

2) Pediatric Patients

-Total Exposed (One uncontrolled study)	32[a]

a) Single dose oral DOLA•Mesyl (injection formulation administered orally)

c. PONV Studies

1) Adult Patients

-Total receiving DOLA•Mesyl
-Total receiving PL
Total

a) Studies -095 and -021

2) Pediatric Patients

- Total exposed
(One uncontrolled study)

d. Radiotherapy Studies

-Total Exposed	20[a]

a) Adult cancer patients undergoing consecutive day radiotherapy and chemotherapy prior to BMT in one uncontrolled study were exposed to single dose DOLA•Mesyl for up to 5 consecutive days to coincide with repeat days of radiotherapy and chemotherapy.

3. Safety Results

In a fashion similar to that used in the Comments on the results from the three chemotx. and the two PONV clinical trials reviewed, in the sections that follows, deaths, serious and or severe and D/Cs due to AEs are addressed first, AEs event profile is discussed next, with emphasis on AEs related to the cardiac and hepatic systems. This is followed by a discussion on EKG changes from baseline. Unless specified, the information summarized below pertains to either oral tablets of i.v. solution given orally.

a. AEs in Clinical Pharmacology

- There were no deaths reported in any studies in HVs or special populations.
- Of 5 dropouts, 3 male patients receiving 0.3, 0.45 and 0.3 mg/Kg i.v., respectively, experienced increases in both transaminases (in 2 patients <12h; in one patient <6h) that were considered definitely/probably related to test med. All 3 patients recovered. An elderly subject D/C participation as a result of hypertension (unlikely related to test med.) which resolved. A fifth subject D/C Tx as a result of throat infection.
- 5 HV (all doses) reported 6 AEs rated as severe by the investigator. This included 2 patients who experienced severe headache. These events resolved without sequelae.
- In single dose clinical pharmacology studies, 145/398 (36.4%) of the patients experienced one or more AE regardless of causality (All AEs) compared to 15/30 (50%) of subjects receiving PL.
- Incidences to PL were similar. This is illustrated below:

	DOLA•Mesyl (n=398)	[illegible] (n=30)
	Pts with ≥1% AE	
Headache	15%	[illegible]
Dizziness	5%	[illegible]
Fatigue	6%	[illegible]
↑ Appetite	6%	[illegible]

- There was a higher incidence of bradycardia in subjects receiving DOLA•Mesyl compared to those receiving PL: 5% and 0%, respectively. [It is important to note that in this study, the protocol specified criteria for sinus bradycardia resulted in HR to <60 bpm being recorded as an AE]. All subjects were asymptomatic. These heart measures were considered normal (by the sponsor) for a population of HMs.

- The most frequently reported AEs following multiple oral dosing with oral DOLA•Mesyl were:

  headache 32% constipation 19% dizziness 17%
  abdominal pain 14% bradycardia 20%

  - There were 2/81 (2.5%) pts. for whom "QT increased" was reported as an AE and 4/81 (4.9%) pts. for whom "PT increased" was reported as an AE.

The above-described events were all mild.

- Most frequently reported AEs in Special Populations are summarized below.

	Type of Volunteer		
	Elderly [a,b]	Renal Impairment[c]	Hepatic Impairment[d]
Overall Rate	53%	Mild to MOD 83% MOD to Severe 58% End Stage 67%	MILD 43% MOD to SEV 25% (Healthy = 17%)
Most Frequently Reported	Bradycardia 12% Dizziness 12% Atrial Arrhythmia 12% Drowsiness 12%	Headache T-wave change Hypotension Constipation Diarrhea Taste Perversion	Headache

a) • 1h after receiving oral DOLA•Mesyl Subject AM-EP-0992, 0000-0017 had atrial arrhythmia (atrial premature beats).
• 3h after dosing the subject developed paroxysmal supraventricular tachycardia with a HR of 135 bpm, which lasted for 6 complexes.
• The ECG recorded 60h post-dose was normal.
• The event was assessed as possibly related to test [illegible]
b) 6 additional cases of syncopal episode or dizziness [illegible] to be related to vagal events.
c) The higher incidence of AEs in this study compared to [illegible] appeared to be related to the renal impairment [illegible]
d) The higher overall rate of AEs appeared to be a [illegible]

i) Cardiac Events of Interest (Table 94)

TABLE 94

Heart Rate and Rhythm and General Cardiovascular AEs (%)
Healthy Volunteers Given Single Oral Doses of
DOLA®Mesyl

	PL (n=30)	DOLA®Mesyl (n=398)	DOLA®Mesyl Dose	Severity	Outcome/Remarks
Arrhythmia Sinus[a]	0	4 (1.0%)	200 mg	All mild	No Tx needed
Bradycardia	0	21 (5.3%)	200 mg	All mild All but 1=sinus 1=ectopic atrial bradycardia	In 12 subjects usually 1 day after 200 mg No Tx needed
BBB[b]	0	1 (0.3%)	200 mg	Mild RBBB	QRS changes (msec) Baseline 110 115 min. after drug 122 24h ca. normal
EKG Abnormal-nonspecific	0	1 (0.3%)	200 mg	Mild left axis deviation 4h Post-Tx	No Tx needed
EKG Abnormal-specific	0	1 (0.3%)	200 mg	Mild early repolarization 14 day Post-Tx	No Tx needed
ST-T Wave Change	0	1 (0.3%)	200 mg	Mild, Nonspecific 12h Post-Tx	No. Tx needed
T-Wave Change	0	5 (1.3%)	200 mg	Mild, Nonspecific	No Tx needed
U-Wave Change	0	7 (1.8%)	200 mg	Mild	No Tx needed

a) Among the 5 subjects that were reported to have atrial or ventricular arrhythmia, 2 occurred in elderly subjects and one in a volunteer with renal impairment.
- 1 (elderly; 100 mg): nodal arrhythmia (a single premature junctional complex); mild (POSS)
- 1 (elderly; 100 mg): 1h after dosing: atrial arrhythmia (atrial premature beats)
3h Post-dosing: Paroxysmal Supraventricular Tachycardia with HR of 135 bpm, which lasted six complexes
60h Post-dosing: EKG normal

In this subject, PR, QRS and QT_c intervals remained WNL throughout the study.
- 1 (Hepatic Impairment 200 mg): nodal rhythm 12h Post-Tx; mild (POSS)

b) This event (BBB) was assessed as mild (POSS).

The data summarized in Table 94 must be interpreted [illegible] the number of subjects receiving PL is less than [illegible] receiving test med. Nonetheless, it seems remarkable that of the 21 [illegible] bradycardia occurring in DOLA®Mesyl-treated subjects, none [illegible] receiving 25, 50 or 100 mg of the drug. The [illegible] for the preferred term bradycardia and perhaps for [illegible] 200 mg dose level cannot be ruled out as a causative factor.

[illegible]

It is also of interest to summarize the following cases of hypotension (including preferred terms hypotension/orthostatic hypotension/dizziness/ syncope) that occurred in Clinical Pharmacology studies:

- 1 subject (300 mg)

Pre-study BP	Symptoms/BP Post-Tx: First Event of Hypotension	Symptoms/BP Post-Tx: Second Event of Hypotension
Supine: 108/80 (HR=64)	60 min. after 300 mg DOLA• Mesyl on Day 8	66 min. after 300 mg DOLA• Mesyl on Day 11
Standing: 104/74 (HR=60)	94/70 (HR=76)	98/64
	+	+
	Dizziness	Dizziness
	+	+
	light-headedness	light headedness

No Tx needed. Events resolved. Considered mild (POSS).

- 1 subject (50 mg)

Pre-study BP	Symptoms Post-Tx BP
Supine: 104/60 (HR=48)	100/50 (HR=48)
Standing: 100/68	86/50 (HR=88) Patient fainted 7.9h after receiving test med.

No Tx necessary. Event resolved. Considered mild (Not related); due to a "vasovagal reaction" which was self-limited.

- The following 2 elderly volunteers experienced dizziness that may have been associated with decreased BP.

  - 67y old M (200 mg)

Pre-Study BP	Symptoms/Vital Signs 1 hour/Post-Dose
Supine: 136/68	112/88 (Pulse=68)
Seated Radial Pulse=64	dizziness

There were no accompanying events. Event assessed as MOD in intensity (PROB).

  - 69y old M (200 mg)

Pre-study	1h After Test Med.	2h After Test Med.
No info.	Seated: 132/77 (HR=60) Supine: 120/77 (HR=56) + dizziness and blurred vision + QT_c interval less than BL predose value	QT_c interval=445 msec

Following the event, the subject was immediately placed on the floor with his feet elevated. Event assessed as mild (PROB).

- The following 3 volunteers with renal impairment experienced dizziness.

  - 35y old obese F, with MOD-SEV renal impairment

Previous Hx	Events 6h After 200 mg DOLA•Mesyl
Mitral valve prolapse, chronic interstitial fibrosis and anemia	Orthostatic Hypotension (64/50) upon standing, with N&V Rhythm strip: no change from BL

No Tx required. Event resolved. Concomitant meds. were ranitidine + furosemide. Rated as MOD (POSS).

  - 63y old F, with MOD-SEV renal impairment

Previous Hx	Events 5h and 48 min. after 200 mg DOLA•Mesyl
Mitral valve prolapse, aortic insufficiency, hypertension, PUD, hepatitis, interstitial nephritis, pyelonephritis, anemia and facial palsy	Orthostatic Hypotension= Lightheadedness and an irregular pulse with BP decrease to 86/38.

No Tx required. Event resolved. Rated as MILD (UNLIKELY), thought to be the result of fasting and/or hypertension med. Concomitant meds.: acetylsalicylic acid, aluminum hydroxide, ascorbic acid, enalapril, furosemide, iron, Lipitrol®, multi-vitamin, paracetamol, psyllium and Robitussin DM®.

  - 59y old F with end stage renal disease

Previous Hx
Hypertension and severe kyphosilosis

Events ca. 6h after
200 mg DOLA•Mesyl
Dizziness upon getting out of bed=

	BP
supine:	106/66
Immediate Standing:	104/60

This case reported as dizziness may have been orthostatic hypotension. No Tx necessary. Event resolved. Rated as MILD ("NOT RELATED"). the suspected cause was "slight orthostasis secondary to rising out of bed too quickly". Concomitant meds. were acetate phosphate, clonidine, labetalol and Nephro-Vite®.

ii) EKG Changes

The frequency of Tx-emergent EKG interval changes were presented for all subjects, regardless of whether or not an AE report was completed as a tracking mechanism.

a) Single Dose-Mean Data

- Mean acute post-dose HR values increased by up to 4 bpm at >200 mg DOLA•Mesyl. Increases in HR were not dose dependent. They seemed of apparently little clinical importance.

- As shown below, except for JT, which did not change, the mean acute postdose EKG intervals all eventually increased from BL but were dose dependent for PR and QT_c only.

Acute Mean Changes From BL

	PL	DOLA•Mesyl (mg)				
		50	100	150	200	>200
PR	-0.6	-3.3	-1.0	9.6	6.7	15.4
QRS	-0.6	13.3	1.6	[illegible]	[illegible]	2.5
QT	4.4	16.7	-1.6	[illegible]	[illegible]	[illegible]
QT_c	-0.8	-12.0	-8.8	[illegible]	[illegible]	[illegible]
JT	5.0	3.3	[illegible]	[illegible]	[illegible]	[illegible]

- At 24h postdose, all EKG parameters had returned to near BL values.

b) Shift Data

- No PL, 50 or 100 mg subjects with a PR interval <200 msec at BL had increases to ≥220 msec acutely postdose. Changes of interest were seen with the 200 and especially the >200 mg dose.

  - All in all 3/308 (1%) of subjects with PR interval <200 at BL had increases to ≥220 acutely postdose.

  - 2 subjects (200 mg = 1; >200 mg = 1) experienced an increase from a BL PR interval <200 to ≥220 msec postdose (an increase of >20 msec).

  - 1 subject (300 mg) had an acute postdose PR interval from ≥220 at BL to ≥240 msec postdose (>20 msec increase); which returned to near BL values at 24h postdose.

  - None of these subjects reported a clinically significant arrhythmia or conduction abnormality. The sponsor notes that no subject developed second degree or higher AV block.

- The frequency of DOLA•Mesyl subjects with a QRS duration <100 msec at BL increased to ≥100 msec acutely postdose in a dose-dependent fashion:

Frequency (%) in QRS Increases From BL					
PL	DOLA•Mesyl Dose (mg)				
	≤50	100	150	200	>200
14%	57%	6%	14%	22%	29%

- Overall DOLA•Mesyl: 51/266=19%.
- The majority of these acute increases = 48/51 (94%) were to values in the range of 100 to 109 msec.

  - In one subject an acute increase of 40 msec was seen after 300 mg DOLA•Mesyl (from 80 msec at BL to 120 msec postdose).

  - 3 additional subjects developed an acute postdose QRS duration ≥120 msec but none were ≥140 msec. The following was reported in one of these subjects in whom the QRS increased by 12 msec in 2h:

	QRS (msec)	
	2h after 200 mg DOLA•Mesyl	Relation to
BL		
110	122	
	+	

- All 4 subjects with QRS duration ≥120 msec acutely postdose had returned to nearly BL values at 24h postdose.

- In 8/306 (2.6%) subjects who had a normal QT_c interval (<440 msec) at BL, the interval increased to ≥440 msec acutely postdose.

  - The 8 subjects mentioned above were distributed as follows: 150 mg=4, 200 mg=1, >200 mg=3. The frequency in these increases appeared to be dose dependent. These acute increases were to values in the range No subject developed an acute post-Tx QT_c interval ≥480 msec.

  - It is worth noting that no PL, 50 or 100 mg patients experienced similar changes.

c) Tx-emergent EKG Interval Changes

Although there were numerical differences in the proportion of PL patients experiencing these changes in comparison to the 150 and >200 mg dose groups, the frequency of Tx-emergent interval changes was low and there was no apparent trend with dose in the frequency of PR, QRS or QT_c interval prolongation.

d) Multiple Dose, Consecutive Day Exposure

- Mean change from BL for all EKG parameters was quite variable but consistent with that observed in single dose studies.

  - The magnitude of change for any EKG parameter did not increase with repeat daily exposure to oral DOLA•Mesyl for 7 to 29 days.

- With regard to shift data, no subject had an acute PR interval ≥220 msec following 7 or 29 consecutive days of DOLA•Mesyl exposure.

  - 1 subject had a BL QRS duration of 104 that increased to an acute QRS duration on consecutive day 29 of 120 msec (an acute increase of 16 msec).

  - 1 subject had a BL QT_c of 405 which increased to 445 msec acutely postdose following 7 days of consecutive [illegible] DOLA•Mesyl. (This was a cumulative increase of 40 msec. By [illegible] days of consecutive DOLA•Mesyl therapy, the subject's acute QT interval was 409 msec.

  - No subject reported a [illegible] following 7 or 29 consecutive [illegible]

  - The frequency of [illegible] not seem to increase with [illegible] to 29 days.

- The sponsor notes that no subject reported a clinically significant arrhythmia or conduction abnormality following repeat oral DOLA•Mesyl exposure.

e) Tx-emergent EKG Interval Changes (Multiple Dose)

The number of subjects receiving 29 days of consecutive therapy was ca. one-tenth of that of subjects receiving 7 days of consecutive therapy. No firm conclusions seem possible.

f) Special Populations

- For the elderly population, the acute mean changes from BL in EKG intervals parameters following oral DOLA•Mesyl (msec) were:

  PR=11.6 QRS=7.2 QT=8.8 QT_C=11.2 and JT=1.6

  The sponsor notes that the above were all consistently lower in comparison to the intravenous administration of the compound. This would be consistent with the higher peak plasma levels of MDL 74,156 after i.v. dosage.

  The changes seen in this elderly population were consistent with those seen in the younger HVs.

- The following summaries shift data of interest in the elderly.

  - No elderly volunteer receiving oral DOLA•Mesyl experienced an acute PR interval prolongation ≥220 msec. The elderly subject (AN-EP-0992, 000-0013) with the largest acute shift in PR interval had a baseline PR interval of 197 and shifted to 230 msec acutely postdose [an increase of 33 msec]. This subject's PR interval had returned to BL values by the 60-h postdose EKG.

  - No elderly subject experienced second degree or higher AV block.

  - No elderly subject had an acute QRS duration ≥100 msec.

  - 1 elderly subject (noted above) had an acute QT_C prolongation ≥440 msec following oral DOLA•Mesyl administration. This subject did not develop an acute QT_C prolongation ≥480 msec.

  - 1 subject (AN-EP-0992, 0000-0017) developed atrial [illegible] following 2.4 mg/Kg oral DOLA•Mesyl. At 3 h postdose the subject had paroxysmal atrial tachycardia at a rate of 135 bpm, that lasted 6 [illegible]. All ECG intervals were normal throughout the study period. The [illegible] considered this event as not related to study medication.

  - No elderly subject experienced a clinically significant arrhythmia or conduction abnormality.

- For renally impaired volunteers, mean changes in HR acutely postdose were small (-1.4 to 5.3 bpm) in all Tx groups. Changes in HR were random and not suggestive of drug effect.

  - Acute increases in mean changes from BL in PR, QRS, QT and QT_c interval were noted. The increases seen were less pronounced after oral administration than after the same dose administered i.v. This is consistent with higher peak plasma levels of MDL 74,156 following i.v. administration.

  - Increases in PR interval and QRS duration were somewhat greater in subjects with end stage renal disease than those with less severe renal disease.

  - Greater increases in the mean change from BL for PR, QRS, QT and QT_c interval were noted in renally impaired volunteers receiving oral or i.v. DOLA•Mesyl when compared to data from HVs. This would be predicted based upon increased plasma levels of MDL 74,156 in subjects with renal failure.

- Regarding shift data among renally impaired volunteers, one subject had an acute QT_c interval ≥480 msec following both i.v. and oral DOLA•Mesyl. This subject (MCPR0033, 0191-0019), with endstage renal disease, had the largest acute postdose increase in QT_c interval. This subject had a baseline QT_c interval of 463 msec which increased acutely postdose to 532 msec [an acute increase of 69 msec]. The subject's QT_c interval returned to BL values by 24h postdose. This subject was asymptomatic and reported no clinically important AEs as a result of QT_c prolongation.

  - This patient did have a nodal arrhythmia reported as an AE 12h postdose, which spontaneously resolved.

  - The sponsor notes that all renally impaired subjects were safely treated. Indeed, in no subject a clinically significant arrhythmia or conduction abnormality was reported.

- Mean data in hepatically impaired volunteers showed increases in PR, QRS, QT and QT_c (but not JT) in all Tx groups following oral or i.v. DOLA•Mesyl.

  - There were no apparent differences in the magnitude of acute change from baseline in PR, QRS, QT, QT_c or JT with respect to hepatic function or route of DOLA•Mesyl administration.

  - All EKG parameters had returned to near BL values by 24h postdose (next closest EKG evaluation after acute).

- Regarding shift data in hepatically impaired volunteers:

  - 1 subject developed an acute postdose PR interval [illegible]

[illegible]

- The longest acute postdose PR interval shift was to 228 msec, which represented an increase of 12 msec from BL. This occurred in another subject, a healthy volunteer following oral dosing.

- In both cases, the PR interval had returned to BL values at 48h postdosing.

- In no subject second degree or higher AV block was reported.

- The frequency of QRS duration shifts from a BL <100 BL msec to ≥100 msec acutely postdose was not different between Tx groups. No subject developed an acute postdose QRS duration ≥120 msec.

- 2 subjects had acute postdose QT_c interval prolongations ≥480 msec, one in each the mild and the moderate to severe hepatic impairment group. Both subjects had baseline QT_c intervals between 460 and 469 msec, received oral DOLA•Mesyl, and had a QT_c interval increase of ca. 20 msec from BL.

- The largest postdose increase in QT_c interval occurred in a healthy volunteer (73147-2-S-085, 085-004) who experienced a shift from a baseline of 416 msec to an acute postdose QT_c interval of 455 msec [total QT_c increase of 39 msec].

- The sponsor notes that all hepatically impaired volunteers were safely treated. Indeed, no clinically significant arrhythmias or conduction abnormalities were reported.

iii) Clinical Laboratory Evaluations

- From Clinical Pharmacology studies, DOLA•Mesyl appeared to have little effect on any of the laboratory variables measured with the possible exception of serum transaminases.

- Low incidence of transient increases in SGOT and SGPT were observed in one study where subjects received multiple daily doses of the drug. Similar increases occurred upon rechallenge with the same dose.

- These elevations were clinically asymptomatic and reversible but DOLA•Mesyl was the likely cause of these transaminase elevations.

- DOLA•Mesyl had little or no effect on coagulation [illegible]

- Laboratory changes in elderly subjects [illegible] impairment and subjects with renal impairment [illegible] population and not suggestive of [illegible]

b. Summary of Safety Information for Clinical Studies That Support the Two Indications Using the Tablet Formulation

i) Deaths, Dropouts, Hospitalizations and Other Serious Nonfatal AEs, Severe AEs

- Deaths occurring in chemotherapy (CCNV) or PONV trials are listed below. In CCNV, all 6 deaths were attributed to the underlying malignant disease or concurrent illness. The one death in PONV, was due to an unrecognized GU.

List of Deaths by Indication, Cause of Death and Dose
(Days Following Single Dose)

CCNV [n=6]		PONV [n=1]	
• 83y old M Multi-system Failure (14)	25 mg	• 38y old F Multi-system failure (3) Pt. had perforated PU, pancreatitis, peritonitis and sepsis.	100 mg
• 63y old M MI (34)	25 mg		
• 77y old M Sepsis, Dehydration (59)	100 mg		
• 40y old F Pulmonary Embolism (63)	50 mg		
• 63y old M Carcinoma (90)	100 mg		
• 64y old F Respiratory Insufficiency (4)	CND		

- Dropouts due to AEs

In CCNV studies, one patient experienced fever, rash and chills/shivering 4.5h after receiving DCLA-Mesyl 25 mg. The patient was [illegible] which resolved without sequelae, were classified as serious, [illegible] as possibly related to test med.

There were no patients who D/C from the PONV [illegible]