LIVER

fixed dose
? dose/kg in the diff grps

TABLE 7
Study Protocol 73147-2-S-085 (Report W-95-0002-D)

Mean MDL 74,156 Plasma PK Parameters in Patients With Liver Impairment in Comparison to Healthy Subjects

Parameter:		GROUP I (n=6)	GROUP II (n=7)	GROUP III (n=4)[a]
C_{max} (ng/mL)	Oral	347	387	410
	Intravenous	424	473	396
t_{max} (h)	Oral	0.51[b]	1.02[c]	0.75[d]
	Intravenous	0.75[e]	0.50[f]	0.50[g]
$AUC_{0-\infty}$ (ng/mL•h)	Oral	1870	2267	3108
	Intravenous	2525	2604	2844
$t_{\frac{1}{2}}$ (h)	Oral	6.95	10.84	11.01
	Intravenous	6.87	8.96	11.69
CL_{app} (ml/min/Kg)	Oral	15.25	13.47	8.83
	Intravenous	10.77	11.26	9.62
Vdß (L/Kg)	Intravenous	6.12	8.60	9.75

This Table corresponds to sponsor's Table 2-42 (vol. 1.2, p. 204) with substantial modifications. Data on % CV and Range were deleted. To facilitate presentation, the mean data were rearranged.

a) Group III excludes #14 after oral dosing and #13 after i.v. dosing
b through g) = median, not mean.

I. PKs in Subjects With Renal Impairment

Study Protocol MCPR0033 (Report K-94-0790-D)

- This open-label, randomized, stratified, two-way complete crossover design study was set to evaluate the impact of renal impairment on the absorption and disposition of DOLA•Mesyl as well as on the formation and disposition of MDL 74,156 following single oral and intravenous dose administration of DOLA•Mesyl. The study was carried out at two U.S. sites

- The two treatments[4] were administered to 36 subjects (M and F, age 19 to 75y) assigned to one of three renal function groups. Renal function was

[4]The Txs consisted of a 10 mg/mL injectable solution (Lot No. 49127) used both for the oral doses and i.v. infusion.

assessed from each subject's 24-h creatinine clearance. Each group contained 12 subjects with renal function classified as:

Group I — Subjects with mild-to-moderate renal impairment: creatinine clearance between 41 to 80 mL/min.

Group II — Subjects with moderate-to-severe renal impairment: creatinine clearance between 11 to 40 mL/min.

Group III — Subjects with end-stage disease: creatinine clearance ≤10 mL/min.

- Each subject randomly received a single dose of the following Txs on two different days:

  Treatment A: 200 mg single i.v. dose of DOLA•Mesyl monohydrate administered by constant-rate infusion over 10 min.

  Treatment B: 200 mg single oral dose of dolasetron mesylate monohydrate solution.

- Serial blood samples were obtained for 60 h after the drug administration. Urine samples were obtained over three consecutive 24-h collection intervals for a total of 72 h after the drug administration. The data from 24 NHVs (age 23.8±5.5y B_{wt} 79.6±9.1 Kg) obtained from Study Protocol MCPR0080 (Report K-94-0734-CDS, S6, vol. 1.68, p. 1) was used as the control group.

  NOTE: Except when noted, only the results after oral administration are presented.

- After oral administration, DOLA•Mesyl plasma levels were sporadic and low. PK parameters were not calculated.

- The mean plasma concentration-time plots for MDL 74,156 after oral administration of DOLA•Mesyl for all three renal impairment groups as well as the control group are shown in Fig. 8.

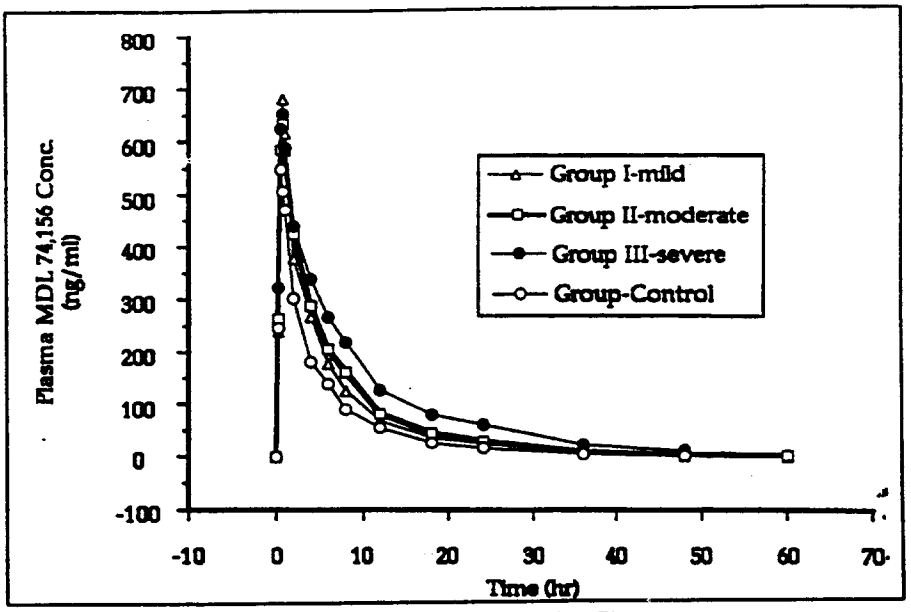

Fig. 8. - *Study Protocol MCPR0033 (Report K-94-0790-D): Mean plasma MDL 74,156 concentration-time plot after oral administration of a 200 mg dose of DOLA•Mesyl in renally impaired and healthy (control) subjects.*

- The Pk parameters for MDL 74,156 after oral administration of DOLA•Mesyl are summarized in Table 8.

200mg dose Renal

? mg/kg dose n=12 each grp

TABLE 8
Study Protocol MCPR0033 (Report K-94-0790-D)

Mean (%CV) Plasma PKs of MDL 74,156 After Oral Administration to Patients With Renal Impairment in Comparison to Controls

Parameter	*Control*	*I-Mild*	*II-Moderate*	*III-Severe*
C_{max} (ng/mL)	601.21 (34.62)	742.7 (40.38)	680.9 (26.97)	700.8 (20.96)
t_{max} (h)	0.74 (43.99)	0.81 (23.57)	0.79 (29.60)	0.72 (25.69)
AUC(0_∞) (h•ng/mL)	2680.28 (30.27)	3596.69 (27.42)	4130.9 (32.16)	5653.22 (30.84)
$CL_{app.po}$ (mL/min/Kg)	12.88 (33.70)	10.24 (34.55)	8.79 (37.02)	7.80 (40.44)
$t_{\frac{1}{2}}$ (h)	8.84 (22.71)	10.34 (36.88)	13.35 (35.77)	18.79 (49.82)
CL_r (mL/min/Kg)	2.61 (28.09)	1.67 (60.39)	0.41 (99.36)	[illegible]
F	0.76 (28.30)	0.77 (25.86)	0.73 (27.77)	[illegible]

This Table corresponds to sponsor's Table 2-45 (S2, vol. 1.2, p. 2-[illegible])
CV = Coefficient of Variation
F = Oral bioavailability

- Urinary excretion of the metabolite results are presented in Table 9.

TABLE 9
Study Protocol MCPR0033 (Report K-94-0790-D)

Mean (%CV) Percentage of Dose Excreted in Urine
Over 72h After Dosing of DOLA•Mesyl

METABOLITE OF MDL 74156

Group	(Total)	R(+)	S(-)	5OH	6OH
200 mg po					
Control	21.62 (30.48)	18.71 (33.40)	2.91 (23.37)	2.60 (30.77)	6.57 (29.07)
I-Mild	16.76 (49.15)	14.76 (51.54)	2.00 (39.26)	1.71 (27.52)	4.88 (26.06)
II-Moderate	4.82 (53.43)	4.11 (57.09)	0.71 (50.38)	0.80 (57.55)	2.09 (55.27)
III-Severe	0.26 (108.15)	0.24 (106.42)	0.02 (133.60)	0.02 (134.58)	0.07 (119.37)

This Table corresponds to sponsor's Table 2-46 (S2, vol. 1.2, p. 271) with some modifications. The results with i.v. administered DOLA•Mesyl have been omitted from this Table.

CV = Coefficient of Variation

Noted below are safety results.

- The most frequently observed AE was headache (6/36=16.8%, patients oral).

- In 2 patients with moderate-to-severe renal impairment, a brief episode of lightheadedness in one, and a episode of orthostasis in another, were considered possibly related to DOLA•Mesyl.

- EKG changes were asymptomatic and reflected the known activity of DOLA•Mesyl in prolonging ventricular depolarization of cardiac muscle, i.e., prolongation of PR interval, QRS width, QT interval and QT_c interval.

    - These effects were greater after i.v. administration than after oral administration, and only slightly more evident in the end stage disease group than in patients with less severe disease.

From these study results the sponsor arrived at the following conclusions.

- The apparent clearance of MDL 74,156 ara oral (and i.v.) doses decreased as renal function decreases.

    - The systemic exposure increased ca. two-fold in patients with severe renal impairment following both oral and i.v. administration.

- DOLA•Mesyl disappeared rapidly from plasma in renally [illegible] and normal healthy volunteers, consistent with [illegible]

- Renal elimination of metabolic products of MDL 74,156 also decreased with an increase in the degree of renal impairment.

- The overall incidence of AEs was higher than in previous phase I studies; but that appeared to be due to occurrences of events known to be associated with renal impairment.

- The safety and PK results suggest that no dose adjustment is necessary for renally impaired cancer or surgery patients.

J. Effect of Cimetidine (CIM) and Rifampin on DOLA•Mesyl Bioavailability

Study Protocol MCPR0083 (Report K-95-0604-CDS)

- The objectives of this open-label, one-center , randomized, three-way crossover trial were two-fold:

  1) To determine if a PK interaction exists after 1 week of oral co-administration of DOLA•Mesyl with CIM and rifampin.

  2) To determine whether DOLA•Mesyl given alone or in combination with CIM or rifampin produce changes in PR, QRS, and QT_c interval duration, BP or HR.

- Subjects were 18 healthy males between the ages of 19 and 45y.

  - 17 subjects completed all study procedures.
  - 1 subject was D/C after 2 periods for a non-drug related reason.

- The 3 Txs[5] consisted of the following:

  Treatment A: 200 mg DOLA•Mesyl oral solution given at 8 AM on days 1 through 7.

  Treatment B: 200 mg DOLA•Mesyl oral solution given at 8 AM on days 1 through 7 and one 300 mg CIM tablet given at 2 AM, 8 AM, 2 PM, and 8 PM starting at 8 AM on day 1 through 2 AM on day 8.

  Treatment C: 200 mg DOLA•Mesyl oral solution and two 300 mg rifampin capsules given at 8 AM on days 1 through 7.

[5] The 10 mg/mL injectable solution of DOLA•Mesyl (Lot No. [illegible]) and was manufactured by Taylor Pharmacol Co. for Marion Merrell [illegible] SmithKline Beecham) and Rifampin capsules (300 mg, Rifadin®, Marion Merrell [illegible] combination treatments.

- Serial blood and urine samples were collected to 48 h after the 8 AM dose on day 7. Also, trough blood samples were collected on days 6 and 7.

- 24-h baseline BP, HR and 12-lead EKG measurements were obtained prior to dosing and postdose on days 3, 5, 6 and 7 of each treatment.

- The data analysis includes results from 18 subjects for Txs A and B and 17 subjects for Tx C. Plasma MDL 74,147 (free base) concentrations were BLLQ[6] of the assay in all samples collected.

- The mean plasma concentration-time plots for MDL 74,156 for the three Txs are presented in Fig. 9.

- Mean plasma PK parameters with statistical analysis results for MDL 74,156 are presented in Table 10.

- Table 11 lists the urinary excretion results of DOLA•Mesyl and metabolites over the 48h urine collection period. Also shown in this Table is the percent of dose excreted in urine as MDL 74,156 (both enantiomers) and 5' and 6' OH MDL 74,156 excreted at steady state over the dose interval.

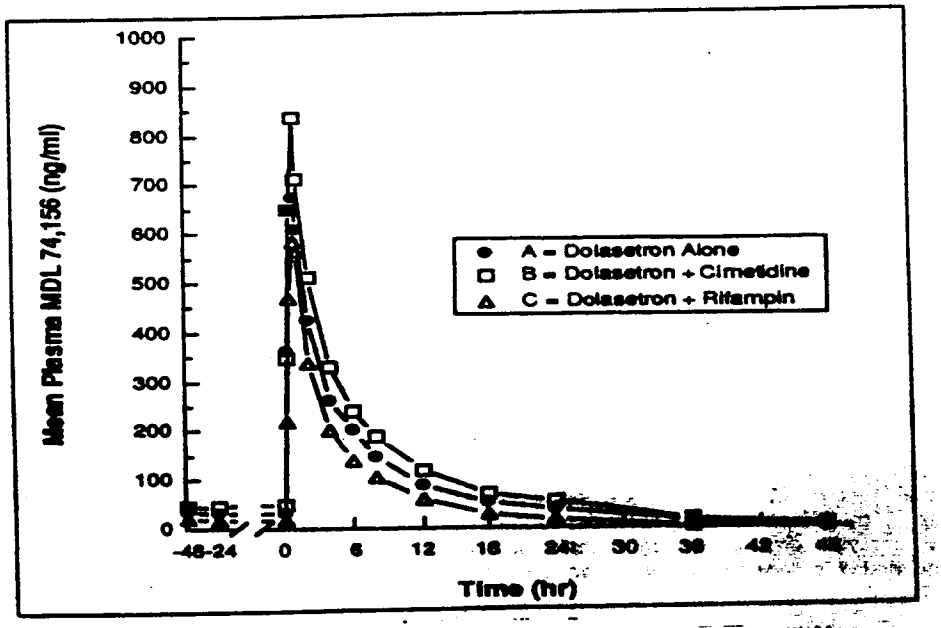

Fig. 9. - Study Protocol MCPR0083 (Report K-94-0604-CDG): Mean Plasma Concentration vs Time Plots for MDL 74,156 (n=18 for Txs A and B and n=17 for Tx C).

[6]Below the lower limit of quantitation.

TABLE 10
Study Protocol MCPR0083 (Report K-94-0664-CDS)

Mean Pharmacokinetic Parameters and Statistical Comparisons for MDL 74,156
Tx A: 200 mg Dolasetron Mesylate Alone, B: 200 mg Dolasetron
Mesylate With CIM, C: 200 mg Dolasetron Mesylate With Rifampin

Variable	*Tx*	*Mean (%CV)[a]*	*Pairwise Difference (%)*	*p value for Pairwise Difference[b]*	*90% CI for Pairwise Difference (%)[c]*
AUC_{ss} (0-24 h)[d] (ng•h/mL)	A	3654 (31)			
	B	4551 (33)	B-A, 23.8	<0.01	17.3, 30.7
	C	2682 (31)	C-A, -27.8	<0.01	-31.7, -23.7
C_{max} (ng/mL)	A	732.7 (24)			
	B	842.2 (31)	B-A, 14.9	0.02	4.9, 25.0
	C	614.3 (23)	C-A, -16.9	<0.01	-27.2, -6.7
t_{max} (h)	A	0.67 (29)			
	B	0.78 (10)	B-A, 16.7	0.01	6.5, 26.9
	C	0.82 (18)	C-A, 23.6	<0.01	13.1, 34.0
$CL_{app.po}$[d] (mL/min/Kg)	A	10.5 (29)			
	B	8.4 (28)	B-A, -19.2	<0.01	-23.5, -14.8
	C	14.4 (30)	C-A, 38.5	<0.01	31.0, 46.4
$t_{\frac{1}{2}}$ (h)[e]	A	8.8 (19)			
	B	8.4 (18)	B-A, -4.2	0.28	-12.6, 4.1
	C	7.4 (20)	C-A, -15.3	<0.01	-21.5, -9.5
CL_r (mL/min/Kg)	A	2.15 (48)			
	B	2.00 (33)	B-A, -6.9	.57	-27.2, 13.4
	C	2.58 (38)	C-A, 21.6	.09	0.8, 42.3

This Table corresponds to sponsor's Table 2-49 (S2, vol. 1.2, p. 283) with minor modifications.

a) Coefficient of variation
b,c) Pairwise difference (%), p value and 90% confidence interval (CI) for the pairwise difference (%) were done using adjusted means from the ANOVA.
d) Statistical analysis done using log transformed data.
e) Statistical analysis done using rank transformed data.

TABLE 11
Study Protocol MCPR0083 (Report K-94-0664-CDS)

Mean Percent of Dose Excreted in Urine for 0-24 h on Day 7 as Total, R(+), and S(-) MDL 74,156 and 5'-OH and 6'-OH MDL 74,156 and Statistical Comparisons. Tx A: 200 mg Dolasetron Mesylate Alone, B: 200 mg Dolasetron Mesylate with Cimetidine, C: 200 mg Dolasetron Mesylate With Rifampin

Variable	Tx	*Mean (%CV)[a]*	*Pairwise Difference (%)*	*p value for Pairwise Difference[b]*	*90% CI for Pairwise Difference (%)[c]*
Amount Excreted for 0-24 h					
R(+)-MDL 74,156	A	19.33 (49)			
	B	22.59 (39)	B-A, 16.9	0.11	-0.4, 34.2
	C	17.58 (52)	C-A, 9.1	0.39	-26.8, 8.5
S(-)-MDL 74,156	A	2.35 (43)			
	B	2.55 (95)	B-A, -11.1	0.50	-27.9, 10.7
	C	2.21 (62)	C-A, -12.0	0.31	-33.0, 10.2
Total MDL 74,156[d] [R(+) + S(-)]	A	21.68 (47)			
	B	25.15 (37)	B-A, 17.3	0.17	0.0, 32.9
	C	19.79 (52)	C-A, -11.6	0.24	-35.4, 10.0
5'-OH MDL 74,156[e]	A	1.38 (61)			
	B	1.22 (54)	B-A, -18.4	0.22	-45.6, 6.9
	C	1.32 (60)	C-A, -2.8	0.61	-24.1, 22.1
6'-OH MDL 74,156[f]	A	4.21 (59)			
	B	4.55 (61)	B-A, -5.9	0.85	-28.6, 24.6
	C	4.99 (51)	C-A, 27.4	<0.01	3.2, 45.0

This Table corresponds to sponsor's Table 2-50 (S2, vol. 1.2, p. 284) with minor modifications.

a) Coefficient of variation
b,c) Pairwise difference (%), p value and 90% confidence interval (CI) for the pairwise difference (%) were done using adjusted means from ANOVA.
d,e,f) Statistical analysis using rank transformed data

- DOLAsetron Mesyl was well tolerated during all Txs administered in this trial.

The sponsor listed the following conclusions:

- AUC_{ss} (0-24 h) of MDL 74,156 increased by 21% when DOLAsetron Mesyl was co-administered with a hepatic Cytochrome P450 inhibitor, CIM and $CL_{ss/F}$ decreased by 19%. $C_{max,ss}$ increased by 15% when these two drugs were given together.

- AUC_{ss} (0-24h) of MDL 74,156 decreased by 28% when DOLA•Mesyl was co-administered with a hepatic Cytochrome P450 inducer, rifampin and $CL_{app,po}$ increased by 39%. Mean $C_{max,ss}$ decreased by 17% when DOLA•Mesyl was administered with rifampin.

- Similar MDL 74,156 renal clearances were observed for all three Txs with mean values ranged from 2.0 to 2.6 mL/min/Kg for MDL 74,156. Co-administration of DOLA•Mesyl with CIM and rifampin did not affect renal clearance of MDL 74,156.

K. Reviewer's Summary/Conclusions on PKs and Bioavailability in Humans

Because there is presently no FDA Biopharm. review available, the clinical reviewer used the information summarized in sponsor's Section IV to get data on PK/Bioavailability after oral administration. The sponsor's section also had PK information after i.v. dosage with the drug but, with a couple of exceptions, these data were not included here. Those data will be summarized in the PK/PD section of the Clinical Review of the Injectable Form. Most PK evaluations used an oral solution prepared from the injectable dosage form, assessing customary PK parameters and, in some instances, linear PD model used a non linear mixed effect modeling (NONMEM). Although, for the most part, the data presented by the Clinical Reviewer were those presented by the sponsor in Table form, in some instances this presentation was substantially modified. The summary that follows is based on all the information reviewed in Section IV. The conclusions are checked against those in sponsor's section on PK in Humans (po) included in their proposed labeling.

In this and other sections of the review, the reviewer identifies dolasetron mesylate as DOLA•Mesyl; the MDL 74,147 is the free base and MDL 74,156 is the most clinically relevant species.

One important realization is that DOLA•Mesyl is extensively metabolized in humans so that parent drug is rarely detected in the plasma or the urine. The orally administered DOLA•Mesyl is well absorbed. MDL 74,156 appears rapidly in plasma, with a maximum concentration occurring ca. 1h after dosing. MDL 74,156 is eliminated with a mean half-life of 7 to 9h. The apparent absolute bioavailability of orally administered DOLA•Mesyl, determined by the major active metabolite MDL 74,156, is ca. 74%. This metabolite is eliminated by multiple routes, including renal and biliary excretion. In addition to reduction of the ketone group in DOLA•Mesyl to form MDL 74,156, metabolism includes glucuronidation, hydroxylation and N-oxidation. Based on the ^{14}C-labeled studies, ca. 2/3 of the administered dose is recovered in the urine and 1/3 in the feces. It is not known if there is [redacted] MDL 74,156 is widely distributed in the body with a mean apparent volume of distribution of 5.0 to 6.1 L/Kg. All in all, the [redacted] PK parameters obtained at steady state are similar to those [redacted] single dose.

One study showed that the apparent absolute bioavailability of the 200 mg prototype table, determined by comparing plasma $AUC_{(0-\infty)}$ of the major metabolite was similar to the 200 mg orally administered solution (and 200 mg administered by intravenous infusion).

The sponsor evaluated the effect of a number of factors in the absorption/bioavailability of MDL 74,156. The conclusions arrived at were as follows. The presence of food in the g.i. tract produced a slight delay in absorption. This was seen when the proposed final marketed DOLA•Mesyl tablet was given with a high fat meal. But the apparent extent of absorption/ bioavailability was not affected by food. The absolute apparent bioavailability as measured by MDL 74,156 of oral DOLA•Mesyl solution was 80% in women and this is similar to findings in men. The PKs of MDL 74,156 in especial and targeted patient populations following oral administration of DOLA•Mesyl are summarized in Table 12. These data show that the PKs of MDL 74,156 are similar between young adult healthy volunteers and adult cancer patients receiving chemotherapeutic agents of moderate emetic potential. One interesting finding is that the apparent oral clearance of MDL 74,156 is ca. 1.6 to 3.4-fold higher in children and adolescents than in adults.

Other conclusions from summary data in Table 12 are that the apparent oral clearance of MDL 74,156 is not affected by age in adult cancer patients. The PKs in pediatric surgery patients are not very dissimilar to those in adolescents with cancer. In patients with severe liver or renal impairment, DOLA•Mesyl is cleared somewhat differently than in young healthy volunteers. The apparent oral clearance of MDL 74,156 decreased 34% in patients with severe hepatic impairment and 46% in those with severe renal impairment. In spite of these changes, DOLA•Mesyl was well tolerated in these patients (see below).

TABLE 12
Summary Table on PK Parameters

Mean Apparent Systemic Clearance/Bioavailability and Terminal Elimination Half-life of MDL 74,156 Following Oral Administration of DOLA•Mesyl

Study Population	Age (y)	CLapp/F mL/min/Kg)	$t_{½}$ (h)
Young Healthy Volunteers	19-45	13.4	8.1
Elderly Healthy Volunteers	65-75	9.5	7.2
Cancer Patients			
Adults	24-84	[illegible]	[illegible]
Adolescents	12-17	26.5	[illegible]
Children	3-11	44.2	[illegible]
Pediatric Surgery Patients	2-12	[illegible]	[illegible]
Severe Renal Impairment Patients	28-74	7.2	[illegible]
Severe Hepatic Impairment Patients	42-52	[illegible]	[illegible]

This Table corresponds to sponsor's Table 1 (84, vol. 1.21, p. [illegible]) [illegible]

CLapp/F: apparent oral clearance (i.e., apparent systemic [illegible]
$t_{½}$: terminal elimination half-life

There have been no definite drug-drug interaction studies to examine PK or PD interaction with chemotherapeutic drugs or drugs commonly prescribed with antiemetic treatments (benzodiazepines, neuroleptics, antacids and other anti-ulcer medications or drugs given around surgical interventions). AUC_{ss} (0-24h) of MDL 74,156 was increased by 24% when DOLA•Mesyl was co-administered with CIM a hepatic cytochrome P_{450} inhibitor and decreased by 28% when DOLA•Mesyl was co-administered with rifampin, a hepatic cytochrome P_{450} inducer. But all three treatments produced similar MDL 74,156 renal clearances, which ranged from a mean of 2.0 to a mean of 2.6 mL/min/Kg for the main metabolite. It is concluded that co-administration of DOLA•Mesyl with either CIM or rifampin does not affect renal clearance of MDL 74,156.

It was also reported that plasma protein binding of MDL 74,156 is ca. 69% to 77% and the distribution of MDL 74,156 to blood cells is not extensive. The binding of MDL 74,156 to α_1-acid glycoprotein is ca. 51%.

Some EKG changes reported are addressed in the subsection that follows. It is worth mentioning that nearly all studies summarized in Section IV showed that the oral doses of DOLA•Mesyl administered (up to 2.4 mg/Kg or 200 mg per day) were well tolerated.

Except for subjects with renal impairment, in the various patient populations studied, no AEs were reported. In the renally impaired patients (Protocol MCPR0033, Report K-94-0790-D), 16.8% of the patients (6/36) given DOLA•Mesyl experienced headache. This is not unexpected, as headache is a known side effect of 5-HT_3 antagonists. But, in this study, there were also increased incidences of hypotension and orthostatic hypotension in these patients with renal impairment. These were generally considered to be due to dialysis, fasting and/or concomitant medications. There were, however, the following two AEs in patients with moderate to severe renal impairment that were considered to be POSS related to DOLA•Mesyl:

- Lightheadedness (brief episode)
- Orthostasis

The sponsor attributed these events to the underlying renal impairment rather than the drug. On the basis of this conclusion the sponsor suggested that no dose adjustment is necessary for renally impaired cancer (or surgery) patients. But this issue must remain open until safety data from clinical trials are reviewed. The possibility that these AEs were manifestations of EKG changes induced by the drug cannot be presently ruled out.

It is also of interest to mention a report in an study set to evaluate the PKs of DOLA•Mesyl in children (aged 2 to 12y) undergoing elective [illegible] uncomplicated surgery under general anesthesia (Protocol [illegible] Report K-95-0122-CD). DOLA•Mesyl was to be administered at a single [illegible] mg/Kg as DOLA mesylate solution. Instead, one patient received [illegible] was five times (6 mg/Kg) the dose stimulated in the protocol.

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- experienced transient prolongation of the QRS and QT_c intervals [Interval changes were similar in duration, onset and causality to those observed in the other children who received 1.2 mg/Kg]

- did not experience any overt AE or clinically significant changes in laboratory parameters or vital signs.

V. Summary of EKG Changes/LFTs Alterations in Phase I Studies

Single Dose

n = ?

Mean Data

- There were slight not dose-dependent increases in the mean acute post-dose heart rate values up to 4 bpm at >200 mg DOLA•Mesyl.

- As shown below, there were dose-related increases in mean acute post-dose PR and QT_c.

Acute Mean Change from BL in	50	100	150	200	≥200
PR (msec)	-3.3	-1.0	9.6	6.7	15.4
QT_c (msec)	-12.0	-8.8	8.9	7.9	20.4

- Mean acute postdose QRS interval was increased in all DOLA•Mesyl dose groups but with no dose relationship.

- No dose dependency was noted in mean acute postdose QT and JT intervals, which were not affected by single doses of the drug.

Shift Data

PR Interval

- 3/308 (1%) of subjects with a PR interval <220 msec at BL had increases to ≥220 msec acutely postdose (PL=0%).

  - No subject developed second degree or higher AV block after receiving oral DOLA•Mesyl.

QRS Deviation

- There were dose-dependent increases in the frequency of DOLA•Mesyl subjects with a QRS duration <100 msec at baseline that increased to ≥100 msec postdose.

	PL	≤50	100	150	200	≥200	Total DOLA•Mesyl
Frequency of Increase in QRS (msec)	1/7 (14.3%)	4/7 (57.1%)	3/51 (5.9%)	4/29 (13.8%)	35/162 (21.6%)	5/17 (29.4%)	51/266 (19.2%)

- 1 subject had a BL QRS duration of <100 msec which increased to ≥120 msec acutely post-dose.
- 3 additional subjects developed an acute postdose QRS duration ≥120 msec (none were ≥140 msec).
  - One of these three subjects was reported to have **RBBB ca. 2h post-dose.**
- All 4 subjects with a QRS duration ≥120 msec acutely post-dose had returned to near BL values at 24-h post-dose.

QT_c Interval

- 8/306 (2.6%) of subjects with a normal QT_c interval (<440 msec) at BL had increases to ≥440 msec acutely post-dose (PL=0%); the frequency of these increases appeared to be dose dependent.
- All of these increases in DOLA•Mesyl subjects were to values 440-459 msec. No subject developed an acute post-treatment QT_c interval ≥480 msec.

The DOLA•Mesyl effects on PR, QRS or QT_c were not present at 24-h post-dose.

MULTIPLE DOSE, CONSECUTIVE DAYS OF EXPOSURE

Mean Data

- **Although the mean change from BL for HR, PR, QRS, QT, QT_c and JT interval measurements varied markedly, these changes were consistent with those 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.**

Shift Data

- **No subject had an acute PR interval ≥220 msec following 7 to 29 consecutive days of DOLA•Mesyl exposure.**
- **1 subject had an acute postdose QRS interval ≥120 msec following 7 or 29 consecutive days of DOLA•Mesyl exposure.**
- **1 subject developed an acute post dose QT_c interval ≥440 msec.**

- No subject developed a significant increase in PR, QRS or QT_c following 7 or 29 consecutive days of DOLA•Mesyl Tx.

- No subject developed a clinically significant arrhythmia or conduction abnormality following repeat oral DOLA•Mesyl exposure.

Data in Elderly Populations n = ?

Mean Data

- Changes seen in elderly population were consistent with those seen in the younger healthy volunteers. Following oral DOLA•Mesyl, the acute mean changes from BL in PR, QRS, QT, QT_c and JT intervals were 11.6, 7.2, 8.8, 11.2 and 1.6 msec, respectively. These values were consistently lower in the oral dose group in comparison to the i.v. dose groups.

Shift Data

- No elderly volunteer receiving oral DOLA•Mesyl experienced an acute PR interval prolongation ≥220 msec, second degree or higher AV block, nor an acute QRS duration ≥100 msec.

- 1 elderly subject had an acute QT_c prolongation ≥440 msec. This subject did not develop an acute QT_c prolongation ≥480 msec.

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

Renal Impairment n = ?

- Mean changes in heart rate acutely post-dose were small (-1.4 to 5.3 bpm) in all Tx groups.

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

- Greater increases in the mean change from BL for PR, QRS, QT and QT_c interval were noted in renally impaired volunteers receiving oral DOLA•Mesyl when compared to data from healthy volunteers.

Shift Data

- 1 subject had an acute QT_c interval ≥480 msec following both oral and i.v. DOLA•Mesyl. No subject developed a clinically significant arrhythmia or conduction abnormality.

Hepatic Impaired

Mean Data

- Acute mean changes in HR were random and not

- There were no apparent differences in the magnitude of the mean acute increases from BL in PR, QRS, QT, QT_c and JT with respect to hepatic function.

- All EKG parameters had returned to near BL values by 48h post-dose (next closest EKG evaluation after acute).

Shift Data

- 1 subject developed an acute PR interval ≥220 msec; the value had returned to BL at 48h post-dosing.

- No subject developed second degree or higher AV block.

- 2 subjects had acute post dose QT_c interval prolongation ≥480 msec, one in each of the mild and the moderate-to-severe hepatic impairment groups. Both subjects had BL QT intervals between 460 and 469 msec and had a QT_c interval increase of ca. 20 msec from BL.

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

Increases in LFTs

These are briefly summarized here to contrast these findings after oral DOLA•Mesyl with those seen after i.v. administration of the drug (reviewed under NDA 20-024).

- After single oral or multiple dose, mean transaminases varied among groups with no pattern suggesting a treatment relationship.

Outliers

In the oral single dose studies, 1/231 (0.4%) SGOT outliers and 3/231 (1.2%) SGPT outliers were observed in the DOLA•Mesyl Tx groups.

In the oral multiple dose studies, 1/181 (1.2%) SGOT outliers and 2/181 (2.5%) SGPT outliers were observed with DOLA•Mesyl.

No SGOT or SGPT outliers were observed in the PL treatment group.

In summary, the overall incidences of large changes in LFT variables ("outliers") were low. But with i.v. administered drug, the recurrence of SGOT/SGPT elevations in three subjects after rechallenge (Study Protocol 73147-1-C-023) indicates that DOLA•Mesyl has the potential for increasing serum transaminases. These elevations were not associated with clinically symptomatic findings.

VI. STUDIES SUBMITTED IN SUPPORT OF THE INDICATION CHEMOTHERAPY-INDUCED N&V

The sponsor is seeking approval for the marketing of 200 mg ANZEMET® tablets, given 30 min. before the start of chemotherapy, for the prevention of N&V associated with emetogenic cancer chemotherapy, including initial and repeat courses. This is a broad indication where the emetic potential of the chemotherapy and whether this is cisplatin-based or not, is not mentioned. As the pivotal trials of this NDA, the reviewer has identified Studies MCPR0043 and -0048. As summarized in Table 13, both are 4-arm, multicenter, double-blind, one-day, parallel-group studies. Both are dose-response trials and include a low dose of 25 mg and a highest dose of 200 mg per tablet, in addition to two intermediate doses.

Additional evidence of efficacy is presented in Study 73147-2-S-087, a 5-arm, multicenter, double-blind, one-day, parallel group study. This is also a dose-response trial. Patients were stratified on the basis of gender (M vs F) and whether they were receiving chemotherapy for the first time or not (chemotherapy naive vs non-naive). Otherwise, in this study, the same dose levels tested in the two pivotal trials were studied. But, in addition, the fifth arm consisted of orally administered ZOFRAN® tablets (ondansetron). The latter was administered at the oral dose of 8 mg x 4 in 24h. This OND regimen is approved in Europe but not in the U.S. Nonetheless, this trial is useful primarily for comparison of the safety of grading doses of DOLA•Mesyl vs OND.

TABLE 13
NDA 20-623

Study Identification, Main Features of Design, Main Characteristics of the Study Population, Emetogenic Potential and Doses Being Compared in the Two Pivotal and One Supportive Clinical Trial(s) Submitted in Support of the Indication Prevention of N&V Associated With Emetogenic Cancer Chemotherapy Including Initial and Repeat Courses

Protocol No. Report No.	Main Design Features	Study Population	Emetogenic Potential	Groups Being Compared	Remarks
I. P I V O T A L T R I A L S					
MCPR0063 (K-95-0009-CDS) [n=307] M=163 F=142 (USA)	4-arm double-blind randomized multicenter dose-response single oral dose 300 patients 24-36h observation Escape Med. of pt. had 3 emetic episodes in 24h	M or F, median age 64y. Patients with a Hx of histologically confirmed malignant disease, with performance status ≥50% on the Karnofsky scale, without evidence of clinically significant hepatic or cardiovascular disease. The site of primary neoplasm was lung for 54.1%, breast for 1% and other sites for 45% of the pts. Naive. Scheduled to receive carboplatin.	Moderate • Carboplatin at mg/m² adm. over no more than 2h (60% of pts.) • Cisplatin at mg/m² (40% of pts.)	DOLA®Mesyl tablet adm. 30 min. before the start of chemo-therapy 25 mg (n=76) vs 50 mg (n=80) vs 100 mg (n=71) vs 200 mg (n=80)	• Useful design. • per group were randomized to one of four levels of orally administered DOLA®Mesyl tablets. • Chemotherapeutic regimens, including those cisplatin-based were of moderate emetogenic potential. • Efficacy (24h) is demonstrated by showing statistical superiority over the lowest dose.
[illegible] (K-95-0007-CDS) [illegible]	4-arm double-blind randomized [illegible] dose-response single oral dose 300-patient 24-36h observation Escape med. if pt. had 3 emetic episodes in 24h.	M or F, median age 54y. Patients with a Hx of histologically confirmed malignant disease with performance status ≥50% on the Karnofsky scale, without evidence of clinically significant hepatic or cardiovascular disease. The site of primary neoplasm was breast for 69.1%, lymphoma for 18.4%, lung for 4.1% and other sites for 8.4% of the pts.	Moderate • Cyclophosphamide at mg/m² and/or • Doxorubicin in doses of mg/m² in combination therapy or • ≥40 mg/m² as a single agent.	DOLA®Mesyl (tablet) adm. 30 min. before the start of chemo-therapy 25 mg (n=79) vs 50 mg (n=83) vs 100 mg (n=80) vs 200 mg (n=78)	• Useful design. • per group were randomized to one of four levels of orally administered DOLA®Mesyl tablets. • Chemotherapeutic regimens, all non-cisplatin-based, were all of moderate emetogenic potential. • As in the trial above, efficacy (24h) is demonstrated by showing statistical superiority over the lowest dose.

II. SUPPORTIVE TRIAL

73147-2-S-087 (S-95-0009-C) [n=398] M=155 F=244 (Europe)	5-arm double-blind randomized multicenter dose response and comparative single oral dose 375-patient Stratified by - gender (M or F) - prior exposure to chemotherapy (naive vs non-naive) observation Escape med. if pt. had >2 emetic episodes in 24h	M or F, age limits not specified; median age 54y Patients with histologically confirmed malignant Disease. The site of primary neoplasm was breast for 40.1%, lung for 20.6%, lymphoma for 13.3% and other sites for 26.1% of the patients. Pts. had performance status ≥50% on the Karnofsky scale, with normal pre-study EKG, without evidence of clinically significant hepatic or cardiavascular disease; receiving no concomitant medication with drugs having antiarrhythmic activity.	Moderate • Carboplatin ≥300 mg/m² • Doxorubicin ≥40 mg/m² (alone) or ≥25 mg/m² (in combination) • epirubin ≥25 mg/m² (alone) or ≥50 mg/m² (in combination) • dacarbazine ≥350 - <500 mg/m² • mustine (N mustard) ≥6 mg/m² • ifosfamide ≥1.8 mg/m²	DOLA●Mesyl (tablet) adm. one hour before the start of chemotherapy. 25 mg (n=80) vs 50 mg (n=79) vs 100 mg (n=76) vs 200 mg (n=80) vs OND (8 mg x 4) (n=83)	• Less useful design. • The stratifications at the beginning of the study are useful to evaluate effects among female vs male patients and naive vs those that had previously received chemotherapy. • Since some patients were non-naive to chemotherapy, this trial gave information about the efficacy of DOLA●Mesyl under conditions of repeat courses of chemotherapy. • Chemotherapeutic regimens were all of moderate emetogenic potential. • Efficacy (24h) is demonstrated by showing statistical superiority over the lowest dose. • Comparison of the efficacy of ondansetron to DOLA●Mesyl does not seem appropriate in view of the fact that the OND regimen has not been approved in the U.S. • The most important contribution of this trial is an assessment of the safety profile of DOLA●Mesyl vs that of ondansetron in side-by-side comparisons, especially in the cardiovascular and EKG arena. • However, with DOLA●Mesyl, the most important EKG changes from BL occur 1 to 2h after drug administration. Although the observations at 24h (exit) are not without merit this information is incomplete. This is why this trial's design is less useful than that used in -043 and -048, the pivotal trials.

VII. STUDY PROTOCOL MCPR0043 (Report K-95-0009-CDS)

1. Title

"A four-arm, double-blind, randomized, dose-response study of oral dolasetron mesylate in patients receiving moderately emetogenic chemotherapy"[7]

NOTE: The description of the Protocol that follows includes two amendments. The first, approved on October 27, 1992, was to characterize the PKs in patients receiving carboplatin-containing chemotherapy. The second, approved September 23, 1993 was to reflect the type of chemotherapy that was to be used in the trial (=moderately emetogenic). Accordingly, several sections in the protocol were modified, including objectives, design, inclusion/exclusion criteria, evaluations, safety, scheduling, treatment periods, chemotherapy, type of resulting information, statistical methods, AEs, EKG abnormalities and the study schema.

2. Objectives

1) Evaluate efficacy by showing that there was a trend toward decreasing acute emesis following carboplatin mg/m²) - or cisplatin mg/m²) -containing chemotherapy regimens with increasing oral doses of DOLA•Mesyl.

2) Evaluate the dose-response relationship across 25, 50, 100 and 200 mg single oral doses of DOLA•Mesyl in preventing acute emesis due to carboplatin- or cisplatin-containing chemotherapy.

3) Evaluate the safety and tolerability of a single oral dose of DOLA•Mesyl in patients undergoing carboplatin- or cisplatin-containing chemotherapy.

4) Compare the degree of patient satisfaction among the antiemetic dose levels.

5. To characterize the PKs of single oral doses of DOLA•Mesyl in patients receiving carboplatin- or cisplatin-containing chemotherapy.

NOTE: Data related to objective #5) were reviewed in Section IV, above.

3. Study Population (Table 14)

This Table lists the inclusion/exclusion criteria. These criteria were adequate for the proposed objectives.

[7]Title reflects amendment of November 23, 1993.

TABLE 14
Study MCPR0043 (Report 95-0009-CDS)

Characteristics of the Study Population

INCLUSION CRITERIA	REASONS FOR EXCLUSION
• M or F patients ≥18y of age • Hx of histologically confirmed malignant disease[a] • Platinum-naive[b] • Karnofsky scale ≥50%[c] • Carboplatin mg/mor cisplatin mg/m² given as the first agent and over no more than 2h - 5-FU or VP16 could be given prior to carboplatin or cisplatin if no nausea and/or vomiting were experienced • Clinical and laboratory criteria required for the administration of carboplatin or cisplatin • Written IC • F patients of childbearing potential must have been using reliable contraceptive measures and have had a negative pregnancy test at the Pre-Tx visit	• Significant neurologic or psychiatric illness (alcoholism was not reason for exclusion) • Investigational drugs within 30 days • Any drug with potential antiemetic efficacy within 24h of the start of DOLA®Mesyl • Corticosteroids • Previous Tx with DOLA®Mesyl • Seizure disorder requiring current anticonvulsant med. • Any vomiting, retching, or SWOG grade 2 or 3 nausea in the 24h preceding chemotherapy • Vomiting from any organic etiology • Nausea or vomiting following any previous nonplatinum-containing chemotherapy • Evidence of clinically significant liver disease • Scheduled to receive cyclophosphamide (≥1 g/m²), nitrogen mustard(s), DTIC, ifosfamide doses ≥1.5 g/m², CCNU (>60 mg/m²), or BCNU (>200 mg/m²) during the 24h following carboplatin or cisplatin chemotherapy infusion • Cardiomyopathy, CHF or Hx of CHF • Arrhythmias requiring antiarrhythmic medication • Greater than first degree heart block • Preexisting complete BBB, either L or R • Abnormal Pre-Tx potassium or calcium results which could not be corrected prior to receiving chemotherapy

IC=Informed Consent; F=female; DOLA®Mesyl=dolasetron mesylate; SWOG=Southwest Oncology Group Toxicity Criteria for N&V;

heart failure; BBB=bundle branch block; L=left; R=right

[a] [illegible] without histologic diagnosis but were confirmed with malignant disease by the investigator from other sources and [illegible] documentation.

[illegible] assistance and frequent medical care

A number of clarifications are in order. No upper age limit was placed on patient eligibility for this trial. Carboplatin or cisplatin should have been the first chemotherapeutic agent given. According to the Protocol, if investigators wished to administer another chemotherapy agent prior to carboplatin or cisplatin, the sponsor was contacted. Waivers were granted in cases where the chemotherapy in question was considered to be minimally emetogenic. 5-FU or VP-16 prior to carboplatin or cisplatin was allowed without a waiver following the second amendment. The SWOG toxicity criteria for N&V is given below.

Nausea and Vomiting Toxicity Scales

TOXICITY	0	1	2	3	4
Nausea	None	Able to eat, reasonable intake	Intake significantly decreased but can eat	No significant intake	
Vomiting	None	1 Episode in 24h	2-5 Episodes in 24h	6-10 Episodes in 24h	>10 Episodes in 24h or requiring parenteral medication

The sponsor did not list the clinical and laboratory criteria required for the administration of carboplatin or cisplatin. Pt. MCST0179-0001 was allowed to enter the trial after receiving investigational chemotherapy medication 26 days prior to test med. The sponsor provided a list of prohibited medication in their Appendix A1 (Protocol, p. 561). In the Clinical Report the sponsor explains that the exclusion of some of the medications on this list became an issue because they are commonly used by cancer patients undergoing chemotherapy. In particular, benzodiazepines are routinely used as hypnotic and as antianxiety agents, both for sleep induction and for use prior to procedures such as insertion of vascular access devices. Exceptions to this exclusion criterion were initially handled on a case-by-case basis, such as in patients who were receiving midazolam (very short acting) prior to catheter insertions. The sponsor agreed to these waivers because the duration of midazolam is so short it was unlikely to affect emesis. Another waiver category was for chronic benzodiazepine use, where these agents were considered to have almost no potential impact on emesis. After consultation with several investigators, the list of prohibited medications was modified by September 23, 1993, protocol amendment as follows:

- Patients taking chronic benzodiazepines (defined as therapy initiated >48h prior to the 24-h Tx period) could be admitted. But the following was noted:
  - Alprazolam (Xanax®) could be used for the [illegible] if therapy was initiated at least 48h prior to the [illegible]

- Midazolam (Versed®) was allowed in the 24h prior to but not during the 24-h Tx period.

- Temazepam (Restoril®) and triazolam (Halcion®) were allowed 24h prior to and/or during the 24-h Tx period.

- Lorazepam (Ativan®) was not allowed in the 24h prior to or during the 24-h Tx period except when prescribed as an escape medication. If the patient received lorazepam during the 24h prior to or during the 24-h Tx period, it was considered a major violation resulting in exclusion of the patient from the efficacy evaluable population.

- Patients who used benzodiazepines for reasons other than rescue medication were analyzed in this report as an efficacy subgroup.

- Patients taking tricyclic antidepressants or serotonin re-uptake inhibitors (e.g., Prozac®, Zoloft®) were allowed to enter the trial.

  - This is appropriate because tricyclic antidepressants have not been implicated as having antiemetic activity. Serotonin re-uptake inhibitors would be expected, if anything, to increase the probability of nausea and emesis.[8]

- Corticosteroids were not permitted by this criterion.[9]

- Patients with a Hx of seizure disorder who were currently receiving anticonvulsant medications were granted waivers to enter the study provided they were clinically stable and free of seizure activity. These patients were enrolled in the study on a case-by-case basis and were safely treated.

  NOTE: During the review of the results of this trial it will be important to show that the test groups were balanced with respect to the medications for which waivers were granted to enter the trial.

- Evidence of clinically significant liver disease meant SGOT/SGPT ≥3 times the ULN (amended from ≥2 times the ULN) or serum BIL ≥2.0 mg/dl.

  - Patients were permitted to enter if they had documented liver metastasis with an SGOT or SGPT ≥3 times the ULN provided they

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[8] R. Bergeron and P. Biller, Amer. J. Psychiatry 151:[illegible] (1994).

[9] However, significant numbers of patients in this population [illegible] therapy for various medical conditions, which would not [illegible] waived, on a case-by-case basis with approval by sponsor and [illegible] steroid dose was less than the following: 30 mg prednisone, [illegible] mg hydrocortisone, or 24 mg methylprednisolone. Steroids administered [illegible] were permitted regardless of dose.

did not have signs or symptoms of hepatic failure, i.e., BIL of ≥2.0 mg/dl and/or abnormal coagulation tests.

- A small number of patients were entered into the study with clinically significant liver disease as determined by prestudy laboratory evaluations and the presence of liver metastasis. It will be of interest to see if these patients had significant changes in their laboratory hepatic function at the post-study evaluation.

- The inclusion-exclusion criteria pertaining to the cardiovascular/EKG status of the patient and listed in Table 14 were initially adhered to.

  - As safety data and preclinical data accumulated, the sponsor, with the advice of cardiology consultants, made exceptions on a case-by-case basis for several types of patients.

  - Patients with history of CHF-like symptoms were allowed to enroll and were safely treated.

  - Patients with atrial arrhythmias (specifically atrial fibrillation and atrial flutter) with well-controlled ventricular rates were allowed to enroll.

  - In addition, slightly abnormal Pre-Tx calcium or potassium levels were waived as exclusion criteria if they were unaccompanied by evidence of CVD or abnormality.

  - Eventually, the only patients who were routinely excluded on the basis of these criteria were those with severe electrolyte abnormalities, those with poor ejection fractions, and those with complete BBBs.

  - Because excluded patients represented a very small fraction of the total patient population, and because the study was advanced nearly to the point of completion, the sponsor elected not to formally address this issue via protocol amendment.

4. Concomitant Medications

- Patients taking a chronic medication permitted by the exclusion criteria at study admission, continued to take the medication through the study. Other medications necessary for the well-being of the patient were used according to the judgement of the investigator. However, if any drug with prominent antiemetic activity (i.e., phenothiazines, other 5-HT$_3$ antagonists) were administered prior to the end of the treatment period or prior to the administration of rescue medication, the patient was excluded from the efficacy evaluable analysis [illegible] (i.e., diphenhydramine, propofol and low dose [illegible]

which are thought to have antiemetic properties, were allowed during the study for other indications because they are not considered effective for chemotherapy induced emesis.[10]

5. Test Medication

a. Identity of Test Medication

- DOLA•Mesyl was supplied by the sponsor as 25, 50, 100 and 200 mg tablets.[11]
- PL tablets identical in size and appearance to each DOLA•Mesyl dose level were also supplied by the sponsor to maintain the blind for the study.

b. Dosing Schedule

- A single dose of test medication (25, 50, 100 or 200 mg) consisted of one DOLA•Mesyl tablet plus three PL tablets. The patient received a total of four tablets. Test med. was ingested 30 min. prior to the start of carboplatin or cisplatin chemotherapy.
- Patients received chemotherapy beginning at HOUR 0 (see Table 14, inclusion criteria) as the first component of the chemotherapeutic regimen infused over no more than 2h.

c. Blinding, Packaging and Labeling

My review of this subsection (S8, vol. 1.253, p. 48 of the Clinical Report) indicate that these aspects of the protocol were adequate.

d. Method of Tx Assignment

Upon entering the trial, patients enrolled at each site were assigned a patient sequence number beginning with 0001. The patient sequence number became the patient's reference number throughout the study. Patients were

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[10]For example,
- antihistamines such as diphenhydramine, possess antiemetic properties, but this is limited mainly to motion sickness or postoperative emesis [S.G. Allan, Gastroenterol. Clin. North Amer. 21:597-611 (1992)].
- Propofol is thought to have antiemetic properties when dosed at subhypnotic doses and when administered by continuous infusion. One time bolus doses of propofol given prior to invasive procedures were allowed during this study because propofol at this dose and schedule does not have antiemetic properties [A. Borgeat et al., Oncol. 50:456-459 (1993)].
- MCP, a proven antiemetic at higher doses, had not been shown to be effective at standard doses (10-20 mg QID) [S.G. Allan (locus cited) (1992)].

[11]DOLA•Mesyl was identified by lot numbers [illegible], numbers 73147EPEAZ41, 73147EPEBY42, 73147EPEDY43 and 73147EPEE[illegible].

also assigned a sequential TAN (treatment assignment number) which corresponded to the randomized study Tx (sponsor's Appendix D3, page 2169).

e. Compliance

The procedures to evaluate compliance were adequate.[12]

6. Study Evaluations

a. Efficacy Parameters

- These were all adequate for this type of study.
- The effectiveness of test medication was assessed by measuring:
  - Number of emetic episodes (see below)
  - Time to first emetic episode
  - Severity of nausea measured by visual analogue scales (VAS)
  - Patient's satisfaction with antiemetic therapy measured by a VAS
  - Time of administration and need for rescue (escape) therapy

Emetic Episodes and escape requirements: Any patient could request escape therapy at any time without meeting the emetic episode escape requirements.
Retching (Unproductive Emesis): Any number of retches in a unique 5 min. period — 1 Emetic Episode
Vomiting (Productive Emesis): One, or a sequence of vomits in very close succession, not relieved by a period of relaxation — 1 Emetic Episode
Vomiting/Retching: Retching of less than 5 min. duration combined with vomiting not relieved by a period of relaxation — 1 Emetic Episode
Escape Requirements: ESCAPE: >2 Emetic Episodes during the 24-h Tx Period
To qualify for escape medication, patient must have had >2 Emetic Episodes during the 24-h Tx Period, or requested escape medication.

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- When a unit dose bottle of medication was dispensed to a patient, the tear off portion of the label was removed intact and attached to the CRF as a record of the patient's [illegible]
- The CRF with the attached label was returned to the sponsor at the end of the [illegible]
- A drug disposition record was also used to record the patient's initials [illegible] the dates the unit dose bottle was dispensed and returned, and the number of [illegible] ingested.
- All unused test medication bottles as well as empty unit dose bottles were [illegible] at the conclusion of the trial (sponsor's Appendix D2, page 2168).

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- Diaries were used as tools to assess emetic episodes and to record escape medications taken by patients during the 24-h Tx period. The information contained in the diary was used to complete the emetic episode and escape medication pages of the CRF.[13]

- The primary evaluation of efficacy was determined by the patient's emetic episodes and/or need for escape medications. Each patient was classified into one of three response categories:

COMPLETE RESPONSE	MAJOR RESPONSE	TREATMENT FAILURE
No emetic episodes in the 24-h Tx period and Received no escape medication in the 24-h Tx period and Monitored for emetic episodes for at least 23.5h after start of carboplatin or cisplatin	One or 2 emetic episodes in the 24-h Tx period and Received no escape medication in the 24-h Tx period and Monitored for emetic episodes for at least 23.5h after start of carboplatin or cisplatin.	>2 emetic episodes during the 24-h Tx period or Received rescue medication in the 24-h Tx period or Monitored for emetic episodes for less than 23.5h after start of carboplatin or cisplatin.

NOTE: During the review of the evidence emphasis is put on Complete Response and Treatment Failure.

- The secondary evaluations of efficacy were determined by the patient's VAS.

  - Nausea VAS scales were completed 45 min. prior to the start of the carboplatin or cisplatin infusion, just prior to the carboplatin or cisplatin infusion (hour 0), and 24h after the start of the carboplatin or cisplatin infusion. Scoring was based on the extremes for nausea where 0 mm = "No Nausea" and 100 mm = "Nausea as bad as it can be".

  - Patient Satisfaction was measured using a VAS which determined the patient's global satisfaction for the duration of the 24-h Tx period and was completed at the end of the period. Scoring was based on the extremes for patient satisfaction with 0 mm = "Not at all satisfied" and 100 mm = "As satisfied as I could be".

[13] Diaries were completed by a trained observer, the patient and/or family member, trained hospital/clinic staff member and/or study coordinator.

b. Safety Parameters

These were assessed by the reporting of AEs, clinical laboratory tests, EKGs, vital signs and PEs from the time of test medication ingestion through the patient's follow-up procedures.

My review of the procedures to report AEs, definitions, including those of treatment-emergent AEs, assessment of relationship to test medication (not related or unlikely, possibly/probably or definitely related) and the severity of the AE (mild, moderate, severe) and the criteria to classify an AE as serious, indicates that these were all adequate. However, because of their importance when assessing the safety of DOLA•Mesyl, the following clarifications of specific AEs are noted:

Nausea and Vomiting

- In the patient population studied in this trial, N&V were not reported as AEs since nausea and vomiting are expected clinical observations following the administration of carboplatin or cisplatin in the doses being studied. These events were accounted for by efficacy measures and not reported as AEs unless the nausea and/or vomiting:

  - Was experienced after receiving test med. and prior to receiving carboplatin or cisplatin chemotherapy.

  - Caused the patient to be hospitalized or prolonged the patient's hospitalization.

  - Was considered by the investigator to be more frequent or severe than the normal clinical observations expected for this patient population.

  NOTE: In a study like this it is important to evaluate whether the test med. is only modifying the kinetics of appearance of the N&V induced by the chemotherapy and thereby emerging as a side effect on the second 24-h after the start of chemotherapy.

Laboratory:

- **Abnormal posttreatment clinical laboratory tests which were assessed by the investigator to be at least possibly related to test medication were reported as AEs.**

P.E.:

- **Any worsening from Pre-Tx to Post-Tx in the P.E. was evaluated by the investigator to determine whether or not an AE was warranted.**

Treatment-Emergent EKG Changes:

- **AE reports were used for signaling [illegible] mechanism for interval changes noted on the [illegible] EKG). The handling of data on Tx emergent [illegible] below [all other Tx-emergent EKG changes reported] listings].**