IX. STUDY PROTOCOL 73147-2-S-087 (REPORT S-95-0009-C)

INTRODUCTORY NOTE

As pointed out in Table 13, 087 is not a critical trial. For the indication chemotherapy-induced emesis, the question of DOLA•Mesyl efficacy is settled by the assessment of the results in Studies 043 and 048. The efficacy data from Study 087 is not without usefulness. It is of interest to evaluate response in female vs male patients and in naive vs non-naive patients through stratifications at the start of the study on the basis of gender and previous Hx of chemotherapy stratifications. But the most valuable contribution of this non-USA study is an assessment of the safety profile of DOLA•Mesyl, especially in the cardiovascular and EKG arena, in side-by-side comparisons with ondansetron. Consequently, during the review of the evidence, emphasis is put on safety rather than efficacy.

> NOTE: The description of the Protocol that follows includes three amendments to the original Protocol.

1. Title

"European, Double-Blind, Randomized Comparative Study of the Antiemetic Efficacy of Oral MDL 73,147EF (Dolasetron Mesylate) and Ondansetron in Patients Receiving Moderately Emetogenic Chemotherapy."

2. Objectives

● To compare the antiemetic efficacy, safety and tolerance of four single oral doses of MDL 73,147EF (dolasetron mesylate) to the approved dosage regimen of oral ondansetron in patients receiving moderately emetogenic chemotherapy.

● To evaluate patient satisfaction with the study treatments.

3. Study Population (Table 54)

● The protocol stipulated that 375 cancer patients of either sex were to be studied.

● Inpatients were to remain in the hospital for at least 24 after the start of chemotherapy (hour 0).

● Outpatients were to be present in the hospital of chemotherapy for end-of-study assessments to return to the hospital for end of study allowed to receive these assessments at a local

● Initially, 35 centers agreed to participate in the centers dropped out prior to receiving study

- 33 study centers in 5 European countries (Germany, France, Spain, Italy, Belgium) participated in the trial with 26 centers having actually enrolled patients.

- The inclusion criteria and reason for excluding patients from participating in the trial are listed in Table 54.

4. Concomitant Medications

During the conduct of the trial, use of concomitant medications had to conform to the exclusion criteria. Necessary medications could continue throughout the trial.

5. Test Medications

- DOLA•Mesyl was supplied as 4 tablets of different sizes for each dose (25, 50, 100 and 200 mg) with corresponding identical PL tablets.[22]

- Ondansetron was supplied as an 8 mg capsule.[23]

- Blinding was maintained by a double-dummy technique. Each patient received 4 tablets and 4 capsules (3 capsules for Centers 18, 20, 21 and 24, since the fifth dose of test med. was eliminated in these study centers) during the study period.

Dosing Schedule

a. Each patient received one capsule of test medication containing either PL or ondansetron 8 mg 1.5 h before the start of the moderately emetogenic chemotherapy (hour 0).

APPEARS THIS WAY
ON ORIGINAL

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[22] Lot numbers of the 25 mg tablet and identical placebo used were [illegible]

[23] Lot numbers for the 8 mg capsule and identical placebo [illegible]

TABLE 54

Study Protocol 73147-2-S-087 (Report S95-0009-C)

Characteristics of the Study Population

INCLUSION CRITERIA	REASON FOR EXCLUSION

• M or F patients ≥18 y of age
• Histologically confirmed malignant Dz
• Karnofsky scale ≥50%
• Scheduled to receive moderately emetogenic chemotherapy[a] administered over no >3h:
  - carboplatin ≥300 mg/m²
  - cyclophosphamide ≥600 mg/m² when given in combination with other cytostatic agents
  - doxorubicin ≥40 mg/m² as a single agent or ≥25 mg/m² when given in combination with other cytostatic agents
  - epirubicin ≥75 mg/m² as a single agent or ≥50 mg/m² when given in combination with other cytostatic agents
  - dacarbazine   mg/m²
  - mustine (nitrogen mustard) ≥6 mg/m²
  - ifosfamide ≥1.8 g/m²
• Pre-study EKG showing evidence of no greater than first degree of heart block
• Blood and urine tests within normal range or accounted for by the primary disease
• Remained in the hospital for at least 8h after the start of chemotherapy
• Present in the hospital 24-36h after chemotherapy for end-of-study assessments
	• History of CHF, significant neurologic or psychiatric disease (alcoholism was acceptable)
	• Prestudy EKG showing evidence of greater than first degree heart block
	• Evidence of significant liver Dz
	• Serum potassium levels outside the normal range
	• Anticancer drugs in the 72h before chemotherapy
	• Radiotherapy in the 7 days before hour 0
	• Research compound(s) in the 21 days before hour 0
	• Any drug with antiemetic activity in the 24h before hour 0
	• Previous treatment with dolasetron mesylate
	• Arrhythmias requiring antiarrhythmic therapy
	• Vomiting or nausea of SWOG grade 2-4 in the 24h before hour 0
	• Vomiting from any organic etiology
	• Cerebral metastases that impaired communication or induced emesis
	• F patients who were pregnant or of childbearing potential and not using reliable contraceptive measures

a) The moderately emetogenic chemotherapeutic agents allowed as well as the dose of the agents when modified in some centers. The duration of the chemotherapy was <6h at some but not all the centers.
  - Cisplatin ≥20 and ≤40 mg/m² was[||] also added as an agent to Centers 02, 03, 04, 08, 09, 12, 16 and 25. Daunorubicin 40-60 mg/m² was added per amendment to Center 01.
  - In Belgian centers (Centers 29, 30 and 31) pirarubicine 50 mg/m² and mitoxantrone 12 mg/m² were added.
  - French centers (Centers 15, 24, 26, 27, 28, 34 and 36) restricted the doses of carboplatin to ≥300 and ≤400 mg, doxorubicin to ≥40 and ≤50 mg, epirubicin to ≥50 mg/m² as a single agent and ≥50 and ≤90 mg/m² when given in combination, dacarbazine to 350 mg/m², mustine to 6 mg/m², pirarubicine to 50 mg/m², mitoxantrone to 12 mg/m², and ifosfamide to ≥1800 and ≤2500 mg/m².

b. 30 min. later (1 h before hour 0), each patient received 4 tablets containing dolasetron mesylate or the corresponding PL tablet(s) of 25, 50, 100 or 200 mg according to the randomized therapy treatment.

c. Each patient received one capsule of test med. containing either PL or ondansetron 8 mg 6.5 h after the start of the moderately emetogenic chemotherapy (hour 0). In Center 23, an amendment allowed this dose to be given at 5.5 h to accommodate working hours.

d. Each patient received one capsule of test medication containing either PL or ondansetron 8 mg 14.5 h after the start of the moderately emetogenic chemotherapy (hour 0).

e. Each patient received one capsule of test medication containing either PL or ondansetron 8 mg 22.5 h after the start of the moderately emetogenic chemotherapy (hour 0). Note in Centers 18, 20, 21 and 23, the 22.5 hour dose was deleted.

Blinding, Packaging and Labeling

These were all adequate.

Method of Treatment Assignment

The patients were stratified by gender and on the basis of naive or non-naive to chemotherapy and randomly assigned to receive oral dolasetron mesylate (25, 50, 100 or 200 mg) or ondansetron 8 mg for four doses (32 mg total dose) according to a blinded random code list provided by   to the investigator for each study center. A sealed envelope containing the unblinded treatment code was provided for each patient. However, the envelope was to be opened only if a serious adverse event occurred, in which case the investigator was to immediately inform the local   All envelopes were to be returned to   at the end of the study.

- Treatment assignment and stratification[24] was accomplished at each center by assigning a sequential number in each strata with the appropriate letter as follows:

  "A" - male non-naive to chemotherapy patient
  "B" - female non-naive to chemotherapy patient
  "C" - male naive to chemotherapy patient
  "D" - female naive to chemotherapy patient

Compliance

The procedures to assess compliance were adequate.

[24] In their appendix D on page 1575 the sponsor [...] complete listing of these patient numbers assigned/not assigned [...]

6. Study Evaluations

Evaluations that were carried out for efficacy and safety were as described for studies 043 and 048. It is important to note the following.

- Abnormal EKG findings during the 24-h treatment period which were not present at BL were recorded on an AE report only when considered clinically relevant by the investigator. No AE was reported following the independent interpretation by the cardiologist-consultant.

No
EKG
before 24 -36

- A 12-lead EKG was obtained within 3 days prior to study entry for all patients and 24-36 h after the start of the moderately emetogenic chemotherapy in all centers.

- A preliminary reading of the EKG was completed at the study site to assure adherence to the inclusion/exclusion criteria (pretreatment) and to monitor patient safety. In order to standardize the EKG reading performed by the different cardiologists or investigators at the study centers, EKGs were centrally read by an independent cardiologist, Robert Arbogast, M.D., Strasbourg, France. The central reading served as the final interpretation of the EKG and was placed with the patient's CRF.

The following criteria were used in the central reading:

- PR interval ≥220 msec was considered first degree AV block

- QRS width ≥100 msec was considered intraventricular conduction delay (IVCD)

- A corrected QT interval (QT_c) was determined using Bazett's formula (QTc=QT divided by the square root of R-R). A QTc interval of ≥440 msec was considered a prolonged QT interval.

7. Statistical Methodology

- The primary efficacy endpoint was complete response (0 emetic episodes and no rescue medication).

- Patients not monitored for emesis at least 24 h were characterized as treatment failures.

- Logistic regression with a test for linear trend in complete responders with doses was used, with investigator and stratum as the ...

- The presence of interactions between the linear dose response was examined using the residual chi-square test ...

pairwise comparisons among all five treatment groups and to perform subgroup analyses. Descriptive statistics tests were done.

Safety

- Incidence rates for all AEs were given by included term within System Organ Class and dose.

- A test for linear trend with DOLA•Mesyl dose was performed for incidence of any System Organ Classes or included terms with a high frequency of occurrence. This test was from a logistic regression model, including only dose as an explanatory variable. For more commonly occurring AEs, incidence rates were given by severity and dose.

- Changes in recumbent pulse rate, systolic blood pressure and diastolic blood pressure from pretreatment (hour -1.5) to posttreatment time points were analyzed using a three-way rank ANOVA controlling for stratum and investigator. A test for linear trend with DOLA•Mesyl dose in the mean rank change of each vital sign was performed.

  - The frequency of patients who had treatment-emergent vital sign changes were summarized by treatment.

  - A line plot of mean change from baseline representing each dose for each vital sign variable was constructed to compare treatments and changes in vitals over the 24-h treatment period.

- Changes from prestudy to 24 h poststudy in electrocardiogram measurements (heart rate, PR, QRS, QT, QT_c, and JT-QRS) were also analyzed using a three-way rank ANOVA.

  - A test for linear trend with DOLA•Mesyl dose in the mean rank change of each measurement was performed.

  - The frequency of patients who had exit (24 h) EKG changes was summarized by treatment.

  - As a further analysis, the effect of gender was examined by testing for a gender by treatment interaction as well as a gender main effect on change from BL for all six EKG variables at the 24 h evaluation.

- In this study, site and central reader EKG readings and interpretations were obtained. In all instances where a central reader interpretation was available, it was used in place of the site reading and interpretation to promote consistency in evaluation.

8. <u>Results</u>

    a. <u>Participating Investigators/Patient Accounting</u>

A total of 399 patients, 155 M and 244 F, received test medication.

- 14 investigators were grouped into 4 pooled investigators to satisfy asymptotic considerations for main effects logistic regression and minimum information criteria for the secondary Mantel-Haenszel test. The following pooled investigators (by investigator number) were created: 22, 29, 43, 44 and 49; 10, 26, 42 and 46; 5, 39 and 53; 38 and 40. All analyses were performed using these pooled investigators, together with the other 12 investigators.

- With the exception of 3 patients who did not receive chemotherapy (#087-072/B, 087-044/C and 087-116/C on their initial treatments), all pts. completed the trial. Two of these three patients subsequently re-entered the protocol, were assigned a second randomization (patient) number, and received test med and chemotherapy.

- Hence, for all analyses and summaries of efficacy and safety, data for the second Tx of pts. -044/C and -116/C were used in place of the initial Tx.

- The ITT Efficacy analyses included 398 pts. The safety analyses included 399 patients.

- The following 11 sites randomized 16 patients or more (each).

Site	# of Pts. Randomized
Center 15/11 (Prof. Bergrat, Strasbourg, FR)	51
Center 07/3 (Dr. Chemaissani, Kohn, Merheim, GR)	41
Center 21/17 (Prof. Cognetti, Roma, IT)	27
Center 06/1 (Prof. Fauser, Idar-Oberstein, GR)	24
Center 17/45 (Dr. Diaz-Rubio, Madrid, SP)	23
Center 16/14 (Dr. Cortes, Madrid, SP)	21
Center 23/16 (Dr. Conte, Pisa, IT)	21
Center 04/4 (PD Dr. Räth, Wiesbaden, GR)	18
Center 26/38 (Prof. Favre, Marseille, FR)	17
Center 12/15 (Prof. Riess, Berlin, GR)	17
Center 01/2 (Prof. Dr. Kölzar, Frankfurt, GR)	16

Abbreviations used: FR=France, GR=Germany

Major Protocol Violations

- 25 patients (6%) which were considered to have major protocol violations were excluded from the efficacy evaluable dataset. As shown below, the groups were not well-balanced with regards to the occurrence of major protocol violations.

Frequency (Percent) of Dispositions by Dose

| Disposition | OND (n=83) | DOLA•Mesyl Dose (mg) | | | | All Patients (N=399) |
		25 (n=80)	50 (n=80)	100 (n=76)	200 (n=80)	
MAJOR VIOLATION	6 (7%)	9 (11%)	8 (10%)	1 (1%)	1 (1%)	25 (6%)
NO CHEMOTHERAPY	0	0	1 (1%)	0	0	1 (0%)
EFFICACY EVALUABLE	77 (93%)	71 (89%)	71 (89%)	75 (99%)	79 (99%)	373 (94%)

- Whereas one patient in each of the 100 and 200 mg DOLA•Mesyl group had major protocol violations, in the other three groups, the number of patients with protocol violations was 6 to 9. The major protocol violations consisted of the concomitant administration, during the 24-h experimental period, of potentially confounding medications, such as antiemetic, sedatives, antipsychotic, etc.

b. Comparability of Groups/Patient Baseline Characteristics

1) Demographics/Primary Disease (Table 55)

There were no statistically significant differences among the five treatment groups with respect to any of the demographic characteristics. The study population was predominantly female [244/399 = (61.2%)], of median age 54y, median weight 67 Kg and a median Karnofsky performance status of 100% (mean = >91%). This means that the patients participating in this trial appeared normal (they had no overt evidence of Dz) and were able to carry on normal activity or do active work. The most frequent sites of primary neoplasm were: breast (160/399 = 40.1%), lung (20.6%) and lymphoma (13.3%).

TABLE 55
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Demographics and Primary Disease Baseline Characteristics

Variable	OND [n=83]	DOLA●Mesyl Dose (mg)				All Patients [n=399]	p-value
		25 [n=80]	50 [n=80]	100 [n=76]	200 [n=80]		
Gender							
M	32.5%	41.3%	38.8%	43.4%	38.8%	38.8%	N.S.
F	67.5%	58.8%	61.3%	56.6%	61.3%	61.2%	
Age (y)							
Mean	54.3	53.1	50.9	53.2	54.2	53.1	N.S.
Median	55	56	51	57	54	54	
Weight (Kg)							
Mean	68.9	69.6	67.1	68.1	68.6	68.5	N.S.
Median	65	68	65	69	70	67	
Karnofsky Status (%)							
Mean	92.169	89.750	92.375	91.842	90.750	91.378	N.S.
Median	100	90	100	100	90	100	
Site of Primary Neoplasm							
Breast	41.0%	36.3%	40.0%	46.1%	37.5%	40.1%	
Lung	19.3%	20.0%	25.0%	18.4%	20.0%	20.6%	
Lymphoma	8.4%	15.0%	13.8%	11.8%	17.5%	13.3%	N.S.[a]
Other	16.9%	10.0%	12.5%	9.2%	11.3%	12.0%	
Gynecological	7.2%	13.8%	2.5%	5.3%	6.3%	7.0%	

a) Breast vs All Others

2) **Medical Bx and Physical Examination**

There were no marked imbalances among the five treatment groups in the
proportion of patients with a Bx of abnormalities in each body system
pretreatment P.E. or in P.E. results from Prestudy to Poststudy.

3) **Distribution of Previous and Present Chemotherapy Regimens (Table 56)**

● The most frequently administered primary chemotherapeutics were
cyclophosphamide (113/399 = 28% of the patients), doxorubicin
and carboplatin (21%).

- During the 24-h Tx period, 110/399 = (28%) of the patients received a platinum-based agent (carboplatin or cisplatin) alone or in combination with other agents; 148/399 = (37%) received multiple moderately emetogenic, non-platinum agents during the 24-h Tx period and 140/399 = (35%) received a single moderately emetogenic, non-platinum agent during the 24-h Tx period.

TABLE 56
Study 73147-2-S-087 (Report S-95-0009-C)

Distribution of Previous and Present Chemotherapeutic Regimens

| Variables | OND [n=83] | DOLA●Mesyl Dose (mg) | | | | All Patients [n=399] | p-value* |
		25 [n=80]	50 [n=80]	100 [n=76]	200 [n=80]		
Previous Cancer Treatment							
Chemotherapy	55.4%	52.5%	52.5%	48.7%	58.8%	53.6%	N.S.
Radiotherapy	22.9%	17.5%	11.3%	19.7%	26.3%	19.5%	N.S.
Primary Chemotherapy[b]							
Carboplatin	20.5%	26.3%	17.7%	15.8%	22.5%	20.6%	
Cisplatin	6.0%	2.5%	2.5%	6.6%	5.0%	4.5%	
Cyclophosphamide	30.1%	27.5%	31.6%	25.0%	27.5%	28.4%	N.S.
Doxorubicin	24.1%	23.8%	19.0%	22.4%	26.3%	23.1%	
Epirubicin	9.6%	7.5%	11.4%	11.8%	7.5%	9.5%	
Ifosfamide	6.0%	5.0%	7.6%	13.2%	8.8%	8.0%	
Chemotherapy Use: Carboplatin or Cisplatin	28.9%	31.3%	25.3%	23.7%	26.8%	27.6%	
Single Agent[c]	31.3%	35.0%	45.6%	31.6%	32.5%	35.2%	N.S.
Multiple Agents[d]	39.8%	33.8%	29.1%	44.7%	38.8%	37.2%	
Mean Carboplatin Dose (mg/m²)	313.1	323.8	326.7	320.8	322.7	321.4	N.S.
Range							
Mean Cisplatin Dose (mg/m²)	21.7	27.5	26.2	21.7	23.5	25.3	N.S.
Range							
Mean Cyclophosphamide Dose (mg/m²)	607.6	628.8	651.4	659.3	640.9	641.9	N.S.
Range							

Mean Doxorubicin Dose (mg/m²)	48.9	45.4	53.7	43.9	42.9	46.8	
Range							N.S.
Mean Epirubicin Dose (mg/m²)	86.7	74	71.1	77.6	69.5	76.1	
Range							N.S.
Mean Ifosfamide Dose (mg/m²)	1930.2	2466.7	2165	2280.3	2277.1	2197	
Range							N.S.

a) For chemotherapy doses p-values were calculated from a two-way ANOVA F test among the five treatments controlling for stratum. For primary chemotherapy and chemotherapy use, p-values are from a Chi-square test.

b) Although some patients received multiple agents, the first agent given which satisfied the dosage requirement specified in the protocol was considered the primary chemotherapy. The other group includes patients not receiving one of the nine specified primary agents, as well as patients who received one or more of the primary agents, but at doses below those specified in the protocol.

c,d) Patients not receiving carboplatin or cisplatin who received at least one of the other seven primary agents. Patients who did not receive any of the primary agents were considered in the single agent category.

NOTE: Not included in this Table are data on dacarbazine, piranubacin, mitoxantrone and others because only a small number of patients received those medications.

- All the mean doses administered of chemotherapeutic regimens were moderately emetogenic (carboplatin = 321 mg/m²; cisplatin = 25 mg/m²; cyclophosphamide = 637 mg/m²; doxorubicin = 47 mg/m²; epirubicin = 76 mg/m²; and ifosfamide = 2197 mg/m²).

- There were no statistically significant imbalances among Tx groups in primary chemotherapy, chemotherapy regimen, or chemotherapy doses.

- As shown in Table 57, the most frequent concomitant chemotherapy was 5-FU, 139/398 = (35%) of the patients, vincristine (23%), etoposide (21%) and MTX (19%). There were no statistically significant imbalances among the five treatments in use of concomitant chemotherapies or in use of benzodiazepines, narcotic analgesics or steroids.

TABLE 57
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Concomitant Chemotherapy, Benzodiazepines, Narcotic
Analgesics and Steroids

Concomitant Use of	OND [n=83]	DOLA●Mesyl Dose (mg)				All Patients [n=399]	p-value
		25 [n=80]	50 [n=80]	100 [N=76]	200 [N=80]		
Chemotherapy Fluorouracil	36.1%	35.0%	30.4%	39.5%	33.8%	34.9%	N.S.
Vincristine	19.3%	22.5%	26.6%	21.1%	23.8%	22.6%	N.S.
Etoposide	20.5%	22.5%	25.3%	14.5%	20.0%	20.6%	N.S.
Methotrexate	16.9%	22.5%	24.1%	15.8%	16.3%	19.1%	N.S.
Benzodiazepines	3.6%	0	2.5%	0	1.3%	1.5%	N/A
Narcotics	9.6%	3.8%	7.5%	3.9%	7.5%	6.5%	N.S.
Steroids	1.2%	3.8%	0	0	0	1.0%	N/A

4) Previous/Concomitant Other Medications

The most frequently used concomitant medications during the 24-h Tx period
were: allopurinol, 48/399=(12%) of the patients, ranitidine (12%), mesna
(11%), paracetamol (acetaminophen) (8%); and furosemide (6%).

5) Escape Medications (Table 58)

In this study, there were no statistically significant imbalances among the
five Tx groups in escape medication.

TABLE 58
Study 73147-2-S-087 (Report S-95-0009-C)

ESCAPE MEDICATIONS

	OND [n=83]	DOLA●Mesyl Dose (mg)				All Patients [n=399]
		25 [n=80]	50 [n=80]	100 [n=76]	200 [n=80]	
OND (p=0.277)[a]	4 (5%)	7 (9%)	8 (10%)			
MCP	4 (5%)	4 (5%)	6 (8%)			
DEXAMETHASONE	1 (1%)	5 (6%)	3 (4%)			
ALIZAPRIDE	1 (1%)	4 (5%)	2 (3%)			
METHYLPREDNISOLONE	3 (4%)	2 (2%)	3 (4%)			
a) p-values were calculated using a 4 degree of freedom						

c. <u>Clinical Response</u>

1) <u>Analysis of Primary Efficacy Parameters</u>

a) <u>Complete Response (Table 59)</u>

- In both, the ITT (n=398) and the Evaluable Population (n=373), the test for linear trend in the proportion of Complete Responders with DOLA•Mesyl dose was statistically significant (p=0.0001 for both analyses).

- There was a trend toward decreasing acute emesis with increases of DOLA•Mesyl.

    - The response rate with the 200 mg was similar in both populations with therapeutic gains over 25, 50 and 100 mg DOLA•Mesyl of 31% [p<0.0001], 27% [p=0.0002] and 16% [p=0.0184], respectively, in the ITT Population and very similar results in the Evaluable Population analysis.

    - The response rate with DOLA•Mesyl 100 mg showed lower therapeutic gains over the 25 and 50 mg DOLA•Mesyl in both populations. In the ITT population, therapeutic gains of DOLA•Mesyl 100 mg over 25 and 50 mg were 16% and 11%, respectively; both N.S. In the Evaluable Population, the therapeutic gains of DOLA•Mesyl 100 mg over 25 and 50 mg were 19% [p=0.0292] and 12% [N.S.].

    - Neither Population analysis showed 50 mg DOLA•Mesyl to be statistically significantly different from 25 mg.

- In this study, analysis of the ITT population showed OND superior to 25 and 50 mg DOLA•Mesyl, with corresponding therapeutic gains of 27% and 23%. In this population analysis, OND did not differ from either 100 or 200 mg DOLA•Mesyl.

- The results of comparisons of OND to the four groups of DOLA•Mesyl in the Evaluable Population confirmed those seen in the ITT Population.

TABLE 52

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Clinical Response: Analysis of Primary Efficacy Parameter
Complete Response

THERAPEUTIC GAIN (%)/p-value[a]

I. Intent-To-Treat analysis[b] (n=398)

RESPONSE BY DOSE (mg)

OND [n=83]	25 [n=80]	50 [n=79]	100 [n=76]	200 [n=80]
60 (72.3%)	36 (45.0%)	39 (49.4%)	46 (60.5%)	61 (76.3%)

A. Comparisons Among DOLA•Mesyl Doses

	50 vs 25	100 vs 25	200 vs 25	100 vs 50	200 vs 50	200 vs 100
Therapeutic Gain →	4.4%	15.5%	31.3%	11.1%	26.9%	15.8%
p-value →	[N.S.]	[N.S.]	[<0.0001]	[N.S.]	[0.0002]	[0.0184]

B. Comparison of DOLA•Mesyl Doses vs OND

	25 vs OND	50 vs OND	100 vs OND	200 vs OND
Therapeutic Gain →	-27.3%	-22.9%	-11.8%	4.0%
95% Confidence Intervals for Odds Ratios →	0.134, 0.546	0.157, 0.631	0.251, 1.040	0.588, 2.590
p-value →	[0.0003]	[0.0011]	[N.S.]	[N.S.]

II. Efficacy Evaluable Analysis[c] (n=373)

RESPONSE BY DOSE (mg)

OND [n=79]	25 [n=71]	50 [n=75]	100 [n=75]	200 [n=79]
61 (77.2%)	30 (42.3%)	35 (46.7%)	46 (61.3%)	61 (77.2%)

A. Comparisons Among DOLA•Mesyl Doses

	50 vs 25	100 vs 25	200 vs 25	100 vs 50	200 vs 50	200 vs 100
Therapeutic Gain →	7%	19%	34.9%	12%	27.9%	15.9%
p-value →	[N.S.]	[0.0292]	[<0.0001]	[N.S.]	[0.0002]	[0.0217]

B. Comparison of DOLA•Mesyl Doses vs OND

	25 vs OND	50 vs OND	100 vs OND	200 vs OND
Therapeutic Gain →	-29.1%	-22.1%	-10.1%	5.8
95% Confidence Intervals for Odds Ratios →	0.121, 0.532	0.152, 0.653	0.267, 1.144	0.618, 2.823
p-value →	[0.0003]	[0.0019]	[N.S.]	[N.S.]

[a] ... is a contrast of the parameter estimates for Tx obtained from a logistic regression model predicting ... clinic, and investigator as explanatory variables.
[b] ... in DOLA•Mesyl dose, p<0.0001 (ITT), Mantel-Haenszel Test for Non-Zero correlation, p<0.001 (ITT).
[c] ... in DOLA•Mesyl dose, p<0.0001 (Evaluable Efficacy).

i) <u>Complete Response Rates by Investigator and Dose</u>

Data in sponsor's Table 16, p. 106 show that investigator was not a significant predictor of Complete Response (p=0.1882). There was no interaction between investigator and a DOLA•Mesyl linear dose response (p=0.9708). When taking sample sizes into consideration, dose trends were consistent over investigators.

ii) <u>Complete Response by Hour and Dose (mg) and by Dose in mg/Kg</u>

- The response by hour and dose in mg was similar to that seen in studies 043 and 048. The response with OND was similar to that seen with the 100 and the 200 mg DOLA•Mesyl.

- Converting DOLA•Mesyl doses into mg/Kg units, based upon the B_{wt} of each patient, also resulted in a statistically significant increase in Complete Response with increasing DOLA•Mesyl dose in mg/Kg (p=0.0001). As shown below, each dose range included a dose in mg/Kg (0.33, 0.67, 1.33, 2.67) that corresponded to the milligram doses studied (25, 50, 100, 200) for a 75 Kg patient. The reviewer agrees with the sponsor that the overlapping of weights of complete responders for all treatments illustrates that response is not related to weight.

COMPLETE RESPONSE BY DOLA•MESYL DOSE (mg/Kg)			
Number of Complete Responders by DOLA•Mesyl Dose Category (Percent)			
DOLA•MESYL DOSE (mg/Kg) [a]			
≤0.6 (n=89)	>0.6 to ≤1.2 (n=79)	>1.2 to ≤1.8 (n=51)	>1.8 (n=95)
38 (42.7%)	42 (53.2%)	31 (60.8%)	71 (74.7%)

a) DOLA•Mesyl Dose (mg/Kg) p<0.0001 from a one degree of freedom Chi-square test using a logistic regression model predicting complete response with dose entered directly, controlling for investigator and strata.

2) Analysis of Secondary Efficacy Parameters

a) Total Episodes

The results are summarized as follows:

DOLA•Mesyl Dose (mg)	Total Response
25	29/80 (36.3%)
50	26/79 (32.9%)
100	37/76 (48.7%)
200	51/80 (63.8%)
OND	41/83 (49.4%)

- The test for linear trend with DOLA•Mesyl dose in the proportion of complete responders with no nausea was statistically significant ($p < 0.0001$).

- The 200 mg DOLA•Mesyl dose group was significantly different from the 25 mg, 50 mg and 100 mg dose groups.

- The 100 mg DOLA•Mesyl dose group was significantly different from the 50 mg dose group ($p = 0.0426$), but could not be differentiated from the 25 mg DOLA•Mesyl dose [therapeutic gain = 12.4% (p=N.S.)].

- There were no significant differences between the OND group and the DOLA•Mesyl 100 mg group [Therapeutic gain = 0%; both gave identical Total Response (49%), or the OND vs the DOLA•Mesyl 200 mg group [therapeutic gain: 14.4%, p=N.S.].

b) Time to First Emetic Episode or Escape Medication (Table 60)

- The median times to first emetic episode or escape medications, whichever occurred first, were 19.58, 21.75, >24.00 h for the 25 mg, 50 mg, 100 mg and 200 mg DOLA•Mesyl dose groups, respectively, and >24.00 h for the OND Tx group.

- There was a statistically significant linear trend with DOLA•Mesyl dose in time to first emetic episode or escape medication (p=0.0001).

c) Nausea

- There was a tendency toward decreased nausea with increasing dose of DOLA•Mesyl; the test for linear trend in nausea with increasing DOLA•Mesyl dose was statistically significant (p=0.0001).

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- The median VAS change from baseline to hour 24 was 29 mm, 31 mm, 3.5 mm and 0 mm for the 25 mg, 50 mg, 100 mg and 200 mg DOLA•Mesyl dose groups, respectively, and 3 mm for the OND Tx group.

- The 200 mg DOLA•Mesyl dose group was significantly different from the 25 mg, 50 mg and 100 mg DOLA•Mesyl dose groups. In addition, the 200 mg DOLA•Mesyl dose was significantly different from OND in hour 24 change from baseline VAS.

- There were no statistically significant differences among OND and the 25 mg, 50 mg and 100 mg DOLA•Mesyl dose groups.

- The proportions of patients with no nausea for the 25 mg, 50 mg, 100 mg and 200 mg DOLA•Mesyl dose groups were 42.9%, 35.1%, 50.0% and 64.1%, respectively, and 50.6% for the OND Tx group.

- There was a tendency toward decreased nausea with increasing doses of DOLA•Mesyl; the test for linear trend in the proportion of no nausea with DOLA•Mesyl dose was statistically significant (p=0.0007). The 200 mg DOLA•Mesyl dose group was significantly different from the 25 mg, 50 mg and 100 mg dose groups. In addition, the 100 mg DOLA•Mesyl dose group and the OND-Tx group were significantly different from the DOLA•Mesyl 50 mg dose group.

3) Subgroup Analyses

a) Complete Response Rates by Stratum and Treatment (Table 61)

At the time of randomization, the patients were stratified on the basis of gender and whether they were naive or not to chemotherapy. Results of analysis of data in four stratum are presented in Table 61.

- Although dose trends were consistent over strata, the following is to be noted.

- Stratum was a significant predictor of complete response (p=0.0040).

- There was no interaction between stratum and a DOLA•Mesyl linear dose response (p=N.S.).

- Overall complete response rates were highest in the M, naive to chemotherapy stratum and lowest in the F, non-naive to chemotherapy.

- In M naive to chemotherapy 12/12 (100% of patients) DOLA•Mesyl dose group and 9/11 (81.8%) of patients in 39/50 (78%) of patients in this stratum DOLA•Mesyl treated population.

- But in two of the other three strata, complete response rates were statistically higher than with the 200 mg DOLA•Mesyl.

TABLE 60
Study 73147-2-S-087 (Report S-95-0009-C)

Number and Timing of Emetic Episodes
ITT Population

Variable	OND [n=83]	DOLA●Mesyl Dose (mg)				Total DOLA●Mesyl [n=315]
		25 [n=80]	50 [n=79]	100 [n=76]	200 [n=80]	
Number of Emetic Episodes						
0 Complete Response	60 (72.3%)	36 (45.0%)	39 (49.4%)	46 (60.5%)	61 (76.3%)	182 (57.8%)
1	3 (3.6%)	2 (2.5%)	5 (6.3%)	5 (6.6%)	6 (7.5%)	18 (5.7%)
2	2 (2.4%)	8 (10.0%)	3 (3.8%)	4 (5.3%)	1 (1.3%)	16 (5.1%)
1 or 2 Major Response	5 (6.0%)	10 (12.5%)	8 (10.1%)	9 (11.8%)	7 (8.8%)	34 (10.8%)
0-2 Complete-Plus-Major Response[a]	65 (78.3%)	46 (57.5%)	47 (59.5%)	55 (72.4%)	68 (85.0%)	216 (68.6%)
Received Escape Therapy	14 (16.9%)	20 (25.0%)	21 (26.6%)	17 (22.4%)	7 (8.8%)	65 (20.6%)
Total Tx Fx[b]	18 (21.7%)	34 (42.5%)	32 (40.5%)	21 (27.6%)	12 (15.0%)	99 (31.4%)
Median Emetic Episodes Range	0	2	1	0	0	0
Median Time to First Emetic Episode or Escape (h) Range	>24.00	19.58	21.75	>24.00	>24.00	>24.00

a) Complete-Plus-Major Response (p<0.0001) from a test for a linear contrast across DOLA●Mesyl doses
in the parameter estimates obtained from a logistic regression model predicting complete-plus-
major response with treatment, stratum and investigator as explanatory variables. P-values for
pairwise comparisons are as follows:

50 mg vs 25 mg p=N.S;   200 mg vs 25 mg p<0.0001   200 mg vs 50 mg p=0.0002
100 mg vs 25 mg p=0.0454   100 mg vs 50 mg p=N.S   200 mg vs 100 mg p=0.018

p-values for pairwise comparison of OND to each of the four DOLA●Mesyl dose groups:

OND vs 25 mg p=0.0007   OND vs 100 mg p=N.S
OND vs 50 mg p=0.0046   OND vs 200 mg p=N.S

b) >2 emetic episodes and/or received escape therapy and/or monitored off d

● In all strata, Complete Response with OND was
with DOLA●Mesyl 100 mg, with the largest thera

female naive to chemotherapy [OND: 20/26=(76.9%) vs DOLA•Mesyl 100 mg: 13/27 (48.1%)]. This was the stratum with the largest number of patients (n=98). In this stratum, 48/98 (49.0%) of patients were Complete Responders in the total DOLA•Mesyl-treated population.

● It seems fair to summarize these data by stating that the differences highlighted above are likely due to the small number of patients per stratum per treatment cell. In general, dose trends were consistent over strata.

TABLE 61
Study 73147-2-S-087 (Report S-95-0009-C)

Complete Response by Stratum and Treatment

Number of Complete Responders/Number of Patients in Stratum by Treatment Cell (Percent)							
	Stratum[a]	OND [n=83]	DOLA•Mesyl Dose (mg)[b]				Total DOLA•Mesyl
			25 [n=80]	50 [n=79]	100 [n=76]	200 [n=80]	
Naive to Chemotherapy	M (n=61)	9/11 (81.8%)	6/11 (54.5%)	12/15 (80.0%)	*(illegible)*	12/12 (100%)	39/50 (78.0%)
	F (n=124)	20/26 (76.9%)	9/27 (33.3%)	11/23 (47.8%)	*(illegible)*	15/21 (71.4%)	48/98 (40.0)
Non-Naive to Chemotherapy	M (n=94)	12/16 (75.0%)	12/22 (54.5%)	7/16 (43.8%)	*(illegible)*	13/19 (68.4%)	47/78 (60.3%)
	F (n=119)	19/30 (63.3%)	9/20 (45.0%)	9/25 (36.0%)	9/16 *(illegible)*	21/28 (75.0%)	48/89 (53.9%)
TOTAL (n=398)	TOTAL (n=398)	60/83 (72.3%)	36/80 (45.0%)	39/79 (49.4%)	46/76 (60.5%)	61/80 (76.3%)	182/315 (57.8%)

a) Stratum p=0.0040 from a 3 degree of freedom Chi-square test using a logistic regression model predicting complete response with treatment, investigator, and stratum as explanatory variables.
b) DOLA•Mesyl Linear Dose Response by Stratum interaction p=0.8 from a 3 degree of freedom Chi-square test using a logistic regression model predicting complete response with treatment, investigator, and stratum as explanatory variables.

b) Complete Response by Substratum in the 087

The data in this busy Table can be summarized as follows:

● The following four were identified as predictive of Complete Response:

- Age) older patients had a higher complete response than did younger *(illegible)*

- <u>Male Gender</u>: Complete Response was recorded for 107/155 (69%) males, while 135/243 (55.6%) females were complete responders [p(m)=0.0015].

- <u>Previous Hx of Chemotherapy</u>: 126/213 (59%) patients with a previous Hx of chemotherapy were Complete Responders, while 116/185 (63%) patients with no previous Hx were Complete Responders [p(m)=0.0212].

- <u>Patient's Chemotherapy Regimen</u>: 75/110 (68.2%) patients receiving carboplatin or cisplatin were Complete Responders, while 89/140 (63.6%) receiving a single non-cisplatinum, moderately emetogenic agent were Complete Responders and 78/148 (52.7%) receiving multiple non-platinum, moderately emetogenic agents were Complete Responders.

● There was no significant interaction between any of these subgroups and a DOLA•Mesyl linear dose response. When controlling for age, and patient's chemotherapy regimen, together with treatment, stratum, and investigator in the primary logistic regression model, there was still a statistically significant linear trend in complete response with DOLA•Mesyl (p<0.0001).

The study was stratified on the basis of previous Hx of chemotherapy, together with gender and on the basis of gender together with previous Hx of chemotherapy. Hence, the primary logistic regression analysis of complete response did adjust for previous Hx of chemotherapy and for gender.

● As summarized in Table 62, the following were not significant predictors of Complete Response: concomitant use of benzodiazepines (not including those given as part of escape medication), non-use of narcotic analgesics or use of steroids during the 24-h treatment period.

d. Safety Results

1) Extent of Exposure

● In Study 087, 316 patients received single doses of DOLA•Mesyl and 83 received multiple doses of OND, with the following distribution:

DOLA•Mesyl				OND
25 mg (n=80)	50 mg (n=80)	100 mg (n=76)	200 mg (n=80)	83

a) Of these, 21 pts. received OND 8 mg x 3 62 pts. received OND 8 mg x 4

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TABLE 62
Study 73147-2-S-087 (Report S-95-0009-C)

Complete Response by Subgroups

Number of Complete Responders/Number of Patients in Treatment by Subgroup Category Cell (Percent)							
Subgroup		OND [n=83]	DOLA*Mesyl Dose (mg)				p-values*
			25 [n=80]	50 [n=79]	100 [n=76]	200 [n=80]	
Age	<65 y (n=318)	45/64 (70.3%)	29/66 (47.8%)	32/67 (47.8%)	34/61 (55.7%)	42/60 (70.05)	p(int)=N.S. p(m)=0.0078 p(lin)<0.0001
	≥65 y (n=80)	15/19 (78.9%)	7/14 (50.0%)	7/12 (58.3%)	12/15 (80.0%)	19/20 (95.0%)	
Gender	M (n=155)	21/27 (77.8%)	18/33 (54.5%)	19/31 (61.3%)	24/33 (72.75)	25/31 (80.6%)	p(int)=N.S. p(m)=0.0015 p(lin)<0.0001
	F (n=243)	39/56 (69.6%)	18/47 (38.3%)	20/48 (41.7%)	22/43 (51.2%)	36/49 (73.5%)	
Previous Hx of Chemotherapy	NO (n=185)	29/37 (78.4%)	15/38 (39.5%)	23/38 (60.5%)	22/39 (56.4%)	27/33 (81.8%)	p(int)=N. p(m)=0.021. p(lin)<0.0001
	YES (n=213)	31/46 (67.4%)	21/42 (50.0%)	16/41 (39.0%)	24/37 (64.9%)	34/47 (72.3%)	
Use of Benzodiazepines	NO (n=392)	58/80 (72.5%)	36/80 (45.0%)	37/77 (48.1%)	46/76 (60.5%)	60/79 (75.9%)	p(int)=N/A p(m)=N.S. p(lin)<0.0001
	YES (n=6)	2/3 (66.7%)	0/0	2/2 (100%)	0/0	1/1 (100%)	

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Use of Narcotic Analgesics	NO (n=372)	56/75 (74.7%)	34/77 (44.2%)	34/73 (46.6%)	44/73 (60.3%)	56/74 (75.7%)	p(int)=N.S. p(m)=N.S. p(lin)<0.0001
	YES (n=26)	4/8 (50.0%)	2/3 (66.7%)	5/6 (83.3%)	2/3 (66.7%)	5/6 (83.3%)	
Use of Steroids	NO (n=394)	59/82 (72.0%)	34/77 (44.2%)	39/79 (49.4%)	46/76 (60.5%)	61/80 (76.3%)	p(int)=N/A p(m)=N.S. p(lin)<0.0001
	YES (n=4)	1/1 (100%)	2/3 (66.7%)	0/0	0/0	0/0	
Chemotherapy Use	Carboplatin or Cisplatin (n=110)	20/24 (83.3%)	11/25 (44.0%)	11/20 (55.0%)	14/18 (77.8%)	19/23 (82.6%)	p(int)=N.S. p(m)=0.0017 p(lin)<0.0001
	Single Agent[b] (n=140)	23/26 (88.5%)	15/28 (53.6%)	16/36 (44.4%)	16/24 (66.7%)	19/26 (73.1%)	
	Multiple Agents[c] (n=148)	17/33 (51.5%)	10/27 (37.0%)	12/23 (52.2%)	16/34 (47.1%)	23/31 (74.2%)	

Primary Test for Linear Trend adjusted for all significant subgroup main effects p[d]<0.0001 ITT)

a) P values were calculated from a logistic regression model with treatment, stratum, and investigator as explanatory variables. P(int) is the p value for testing the subgroup by linear dose response interaction;
   p(m) is the p value for testing the subgroup as a main effect.
   p(lin) is the p value for a linear dose response while controlling for the subgroup as a main effect.
b,c) Patients not receiving carboplatin or cisplatin who received at least one of the following agents: cyclophosphamide, doxorubicin, epirubicin, pirarubicin, mitoxantrone, ifosfamide or dacarbazine.
d) P value was calculated from a contrast of the parameter estimates for treatment obtained from a logistic regression model predicting complete response with treatment, stratum, investigator, age, and chemotherapy use as explanatory variables.

2) **Deaths, Dropouts Due to AEs, and Other Serious AEs (Table 63)**

Four of these five events, including three deaths, for which details are provided in this Table, were due to worsening and progression of the underlying condition.

The remaining serious AE, consisting of fever, rash and chills occurring in a patient with Hodgkin's Dz with mixed cellularity (pri............left lateral cervical neck) who in addition had a Hx of bron............ reduced lung capacity, was assessed as POSS. related .... investigator. But, in this instance, bleomycin............. out.

TABLE 63
Study 73147-2-S-087 (Report S-95-0009-C)

Serious AEs

Pt. ID/ age gender	Underlying Condition/ Chemotherapy	AE	SEV	Onset (h)	DUR (h)	Outcome/Relation to Test Med.
25 mg (n=1)						
87256/C 49 M	Hodgkin's Dz with mixed cellularity. Hx of bronchial asthma and ↓ lung capacity. Doxorubicin 25 mg/m², Bleomycin 10 mg/m² Vinblastine 6 mg/m² and dacarbazine 375 mg/m²	Fever Rash Chills	MOD	4.5	4.0	● W/D ● Recovered with no clinical sequelae ● POSS. related ● Bleomycin-induced fever cannot be r/o.
50 mg (n=2)						
87249/D 40 F	Anaplastic cancer Ifosfamide 3000 mg/m² + Mitomycin 6.03 mg/m²	Pulmonary Embolus Thrombophlebitis	NO INFO.	63d.	---	● Death due to progression of concurrent illness. ● Not Related
87001/A 31 F	Hodgkin's Dz Normal Pre-study EKG Epirubicin 80 mg Bleomycin 15 mg Vincristine 2 mg Etoposide 200 mg	Dehydration, vomiting (Tx Fx)	SEV	5	9	● W/D (Temporarily) ● EKG Post-study: WNL ● Not related
100 mg (n=1)						
87247/C 63 M	Anaplastic carcinoma Ifosfamide 3000 mg/m² + Mitomycin 6.14 mg/m²	Carcinoma	NO INFO	90d.	---	● Death due to con- current illness and the progression of his cancer. ● Not related
OBD (8 mg x 3) (n=1)						
87447/D 64 F	Small-cell lung cancer + BM metasases Heavy smoker (20 cig/day x 50y. Chronic bronchitis + cough + dyspnea (>20y) Normal study EKG Cyclophosphamide 1000 mg/m², Epirubicin 90 mg/m² Vincristine 1 mg/m²	Respiratory Insufficiency	NO INFO.	96	---	● W/D temporarily ● Death ● EKG Post-Study WNL ● Not related ● Died of sleep. ● Insufficiency due to advanced stage small cell lung