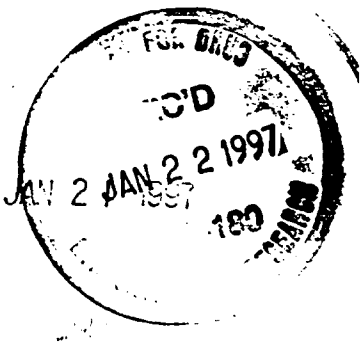
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020624

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION --- NDA



Date:

NDA #: 20-624

Applicant: Hoechst Marion Roussel, Inc.

Name of Drug: Anzemet (dolasetron mesylate) Injection

Indication: The prevention of nausea and vomiting associated with emetogenic cancer chemotherapy, including initial and repeat courses.
(Separate reviews for the prevention of postoperative nausea and vomiting and the treatment of postoperative nausea and vomiting).

Documents Reviewed: NDA vol. 1.1, 1.19, 1.27, 1.45-47 Dated February 19, 1996
NDA vol. 1.302-1.390 Dated September 28, 1995
NDA Supplemental Dated Nov. 18, 1996

Medical Reviewer: This review has been discussed with the medical Officer, Hugo Gallo-Torres, M.D.,Ph.D.

Key Words: Dose response, historical control, equivalent

A. **Background**

In the current NDA, the sponsor seeks approval of dolasetron mesylate intravenous (iv) injection in three primary indications:

1). the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy including initial and repeat courses

2). the prevention of postoperative nausea and vomiting

3). the treatment of postoperative nausea and vomiting

This review addresses only the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy including initial and repeat courses. Separate reviews address the other two indications.

B. Indication of the Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy Including Initial and Repeat Courses

The sponsor has submitted five clinical trials (73147-3-S-081, MCPR0031, 73147-3-S-093, MCPR0032 and 73147-3-S-082) in support of the proposed claim: for prevention of cancer chemotherapy-induced nausea and vomiting (CCNV). Four of these studies (73147-3-S-081, MCPR0031, 73147-3-S-093 and MCPR0032) were cisplatin studies. One study (73147-3-S-082) was a non-cisplatin study.

1. Cisplatin Studies

Two of these trials (MCPR0031 and MCPR0032) were conducted in the United States while the other two trails (73147-3-S-081, 73147-3-S-093, and) were conducted in Europe. In these trial, the emetic stimulus was high-dose cisplatin.

Three of these trials compared single doses of dolasetron mesylate to an active control (ondansetron, granisetron, or metoclopramide). The fourth trial (protocol MCPR0032) was a dose-response trial which evaluated a range of five doses of dolasetron mesylate.

These four studies required patients be administered cisplatin at doses that would be expected to induce emesis in virtually 100% of patients unprotected by effective antiemetic therapy, specifically ≥70 mg/m^2.

2. Non-Cisplatin Study

In the this trial (Protocol 73147-3-S-082), it was moderately emetogenic chemotherapy. This trial compared single doses of dolasetron mesylate to an active control (metoclopramide). This trial required the use of drugs and doses considered "moderately emetogenic".

All five trials (cisplatin and non-cisplatin) were prospectively design as adequate and well-controlled trials and used the same definition for an emetic episode (a single episode of vomiting or any number of retches within 5-minute period), the same evaluation period (24 hours after beginning primary chemotherapy) and the same primary efficacy measure (complete response, defined

as 0 emetic episodes, no rescue medication and monitored for at least 23.5
hour after initial of primary chemotherapy).

C. **Historical Control Data**

1. **Cisplatin Studies (MCPR0031, 73147-3-S-093, and MCPR0032)**

The sponsor conducted a literature search using Medline to collect published data on response to placebo antiemetic in patients receiving cisplatin chemotherapy. From the results of this search, four papers were identified which met the following criteria:

> The dose of cisplatin was in the "highly emetogenic" range, ie ≥50 mg/m^2.
>
> The number of patients who received placebo, and the number of these which did not vomit during the 24 hour period after cisplatin, were reported.

In these studies, 48 cancer patients received placebo prior to ≥50 mg/m^2 cisplatin. Of these, 47 vomited at least once during the first 24 hours post-chemotherapy. From these data, a "complete response" rate of 1/48 (2.1%) was calculated. The upper limit of an exact binomial 95% confidence interval for these data is 11%. Results from studies (MCPR0031, 73147-3-S-093, and MCPR0032) were compared statistically to these historical placebo controls using 11% as the placebo "complete response" rate.

By defining "complete response" for placebo as simply "0 emetic episodes", some bias was introduced. The sponsor defined "complete response" for patient who received dolasetron mesylate as "0 emetic episodes, no rescue medication, and patient monitored for at least 23.5 hours after chemotherapy". Some patients in dolasetron mesylate studies did not vomit, but were classified as "treatment failures" for the intent-to-treat analysis because they received rescue medication or they were monitored for less than 23.5 hours. In the four published reports used as the historical control database, it was not always possible to determine the incidence and timing of rescue medication or the length of time patients were monitored. Therefore, a more broadly defined "complete response", simply 0

emetic episodes, was applied to placebo data and this was compared to dolasetron mesylate data derived using the more restrictive definition. The bias worked in favor of the placebo data, since applying a definition of only "0 emetic episodes" to dolasetron mesylate data would increase the complete response rate.

A second possible source of bias relates to the chemotherapeutic regimens. The placebo database includes patients who received ≥50 mg/m^2 cisplatin while the dolasetron mesylate studies all required that cisplatin dose be at least ≥70 mg/m^2. Since emetogenicity of cisplatin is related to dose, any bias introduced by this difference would also favor the placebo patients.

In summary, the historical control database used for efficacy comparisons in dolasetron mesylate studies in patients receiving cisplatin was contemporaneous, identifiable and applicable to the 24-hour studies performed. Biases inherent in this conservative approach worked against dolasetron mesylate. The highly significant difference in each study will provide compelling evidence of efficacy for the drug.

2. **Non-Cisplatin Study (73147-3-S-082)**

The sponsor conducted a literature search using Medline to collect published data on response to placebo antiemetic in patients receiving cyclophosphamide and/or anthracycline chemotherapy. From the results of this search, five papers were identified which met the following criteria:

> Cyclophosphamide and/or anthracycline chemotherapeutic agents were used at doses comparable to those specified in protocol 73147-3-S-082.
>
> The number of patients who received placebo, and the number of these which did not vomit during the 24 hour period after chemotherapy, were reported.

In these studies, 208 cancer patients received placebo as their sole antiemetic prophylaxis. Of these, 173 vomited at least once during the first 24 hours post-chemotherapy. From these data, a "complete response" rate of 35/208 (16.8%) was calculated. The

upper limit of a an exact binomial 95% confidence interval for these data was 22.6%. Results from protocol 73147-3-S-082 were compared statistically to historical placebo control using 22.6% as the placebo "complete response" rate.

Differences in efficacy measures biased these data in favor of placebo for the reasons described above for cisplatin studies. Since the patient populations and doses of cyclophosphamide and doxorubicin used in the historical control database are comparable to those required in protocol 73147-3-S-082, it is reasonable to conclude that emetogenicity of regimens were also comparable. In protocol 73147-3-S-082, there was an approximate 9/1 ratio of patients receiving both cyclophosphamide and an anthracycline to those receiving single agent (cyclophosphamide or an anthracycline) therapy. In the historical placebo database, this ratio was approximately 3/1. This imbalance again favors the placebo data, since the combination is more emetogenic than either agent given alone.

D. **Study MCPR0031**

1. **Description of Study**

This was a three arm, double-blind, randomized, multicenter trial.

The objectives of this study was

1) to compare 2.4 mg/kg single iv dose of dolasetron mesylate to the 32 mg iv dose of ondansetron;

2) to compare 1.8 mg/kg single iv dose of dolasetron mesylate to the 32 mg iv dose of ondansetron;

3) to compare 1.8 mg/kg and 2.4 mg/kg single iv doses of dolasetron mesylate.

Patients entering this trial were prospectively stratified by cisplatin dose ([redacted] and ≥91 mg/m²) with the intent to clearly delineate cisplatin dose of [redacted] and 100 mg/m².

Cancer patients scheduled to receive cisplatin ≥70 mg/m² were

randomly assigned to dolasetron mesylate (1.8 mg/kg or 2.4 mg/kg, 30 minutes before beginning cisplatin) or ondansetron (0.15 mg/kg x 3 dose). The dosage of ondansetron was changed by protocol amendment early in the study to a 32 mg single dose.

Logistic regression with a 95% confidence interval for the odds ratio of dolasetron mesylate 2.4 mg/kg vs ondansetron, controlling for investigator and stratum was the primary assessment of efficacy.

Sample size determination is based on establishing that the difference between dolasetron mesylate 2.4 mg/kg and ondansetron in complete response rate will be no greater than 15%. This can be established by showing the lower limit of a 95% confidence interval for this difference (dolasetron mesylate 2.5 mg/kg-ondansetron) is not less than -15%. Assuming dolasetron mesylate 2.4 mg/kg and ondansetron have equal complete response rates of 40%, with 200 patients per treatment group, there is an 86% power of establishing equivalence.

For this multicenter, stratified design, equivalence will be established by showing the lower limit of a 95% confidence interval for the odd ratio (OR) exceeds 0.5. The chance of establishing equivalence will still be approximately 86% when design factors are incorporated in the estimation of the OR.

2. **Sponsor's Analysis**

A total of 609 patients, 377 males and 232 females, were enrolled in the study, which was conducted in 41 US investigators. One hundred ninety-eight (198) patients received dolasetron mesylate 1.8 mg/kg, 205 received dolasetron mesylate 2.4 mg/kg, and 206 received ondansetron 32 mg.

The mean cisplatin dose was 85.0 mg/m^2 and mean duration of infusion was 107.0 minutes.

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in Table 1.

As seen from Table 1, there were no statistically significant

differences among the three treatment groups with respect to gender, age, race, weight, height, Karnofsky performance status, history of heavy alcohol use, and site of primary neoplasm.

2.2 Sponsor's Analysis of Primary Efficacy Parameter

The primary efficacy endpoint was "complete response". Complete response was achieved when a patient experienced no emetic episode, received no escape medication, and was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent.

The summary of the sponsor's analysis results for the complete response is given below.

Protocol MCPR0031
Complete Response by Treatment
(Intent-to-Treat Analysis)

Treatment	Rate	vs. Onda P-value	vs. 1.8 P-value	vs. Onda 95% C.I. for O.R.	vs. 1.8 95% C.I. for O.R.
Onda	88/206 (43%)				
1.8 mg/kg Dola	88/198 (44%)	0.9000		(0.682,1.546)	
2.4 mg/kg Dola	82/205 (40%)	0.4698	0.3982	(0.571,1.295)	(0.555,1.264)

From a logistic regression model predicting complete response with treatment, investigator, and stratum included in the model.
Copied from Table 14, S8-V1.313-P159.

As seen from table above, there were no statistically significant differences among the three treatment groups, and the protocol-specified criterion for equivalence was met by all three treatment groups. This criterion was met when the lower bound of a 95% confidence interval for the odds ratio exceeded 0.50; this is equivalent to showing the difference in complete response rates between two treatments is no more than 15% when the assumed common rate is 40%.

Complete response was equivalent among the three treatment groups. There were no statistically significant differences among

the three treatment groups.

This study demonstrated statistical equivalence among the three treatment groups, with the highest complete response rate (44%) observed at the dolasetron mesylate 1.8 mg/kg dose.

2.3 Sponsor's Analysis of Complete Responses by Treatment Versus Historical Placebo Control

The results of sponsor's analysis of complete responses by treatment versus historical placebo control is given below.

Protocol MCPR0031
Complete Response by Treatment vs Historical Control
(Intent-to-Treat Analysis)

	Ondansetron	1.8 mg/kg dolasetron	2.4 mg/kg dolasetron
Rate	88/206 (43%)	88/198 (44%)	82/205 (40%)
P-value for Comparison to Historical Placebo Control	<0.001	<0.001	<0.001

P-values are calculated from a logistic regression model predicting complete response with treatment, investigator, and stratum included in the model. The historical placebo response rate was the upper endpoint of a 95% confidence interval based on the results of four published studies (11.1%).
Copied from Table 14, S8-V1.313-p157.

As seen from table above, statistically significant superiority of each of the three treatment groups over historical placebo was demonstrated.

2.4 Sponsor's Analysis of Secondary Efficacy Parameter

The secondary efficacy parameters are complete-plus-major response, time to first emetic episode or escape medication, and FDA requested complete response with no nausea.

2.4.1 Complete-Plus-Major Response

Major response was achieved for a patient when he or she experienced one or two episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period,

and was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent.

The summary of results of sponsor's analysis of complete-plus major response is given below.

Protocol MCPR0031
Complete-Plus-Major Response by Treatment
(Intent-to-Treat Analysis)

Treatment	Rate	vs. Onda P-value	vs. 1.8 P-value	vs. Onda 95% C.I. for O.R.	vs. 1.8 95% C.I. for O.R.
Onda	122/206 (59%)				
1.8 mg/kg Dola	125/198 (63%)	0.5197		(0.755,1.743)	
2.4 mg/kg Dola	111/205 (54%)	0.1951	0.0546	(0.507,1.149)	(0.439,1.008)

From a logistic regression model predicting complete response with treatment, investigator, and stratum included in the model.
Copied from Table 16, s8-v1.313-p159.

2.4.2 Complete Response with No Nausea

Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period, was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent, and had an hour 24 nausea VSA less than 5mm.

The summary of results of analysis of complete response with no nausea is given below.

Protocol MCPR0031
Complete Response with No Nausea by Treatment
(Intent-to-Treat Analysis)

Treatment	Rate	vs. Onda P-value	vs. 1.8 P-value	vs. Onda 95% C.I. for O.R.	vs. 1.8 95% C.I. for O.R.
Onda	58/206 (28%)				
1.8 mg/kg Dola	65/198 (33%)	0.3872		(0.781,1.889)	
2.4 mg/kg Dola	48/205 (23%)	0.2007	0.0329	(0.467,1.173)	(0.387,0.961)

No nausea was defined as maximum nausea VAS≤5mm.
From a logistic regression model predicting complete response with treatment, investigator, and stratum included in the model.
Copied from Table 23 S8-V1.313-P166

Complete response with no nausea rates were 33% (64/197) and 23% (47/204) in the 1.8 and 2.4 mg/kg dolasetron mesylate treatment groups, respectively, and 28% (58/206) in the ondansetron treatment group.

The results from this study indicate there was no increase in antiemetic activity above the 1.8 mg/kg dolasetron mesylate.

2.5 **Subgroup Analysis**

The sponsor performed a logistic regression model for subgroup analysis. The logistic regression model predicted complete response with treatment, stratum, investigator, and subgroup as explanatory variables. The treatment by subgroup interaction was included in the model as appropriate.

Cisplatin dose category, use of narcotic analgesics, gender, and history of heavy alcohol use were significant predictors of complete response. Patients receiving lower dose of cisplatin (<91 mg/m^2), patients not receiving narcotic analgesics, male patients, and patients with a history of heavy alcohol use were more likely to be complete responders.

Headache, rarely severe, was the most frequently reported adverse event for both drugs: 22% in dolasetron mesylate 1.8 mg/kg

patients and 2.4 mg/kg patients; 18% in ondansetron patients. The incidence of diarrhea was: about 13% in dolasetron mesylate 1.8 mg/kg patients and 2.4 mg/kg patients; and 6% in ondansetron patients.

3. Reviewer's Evaluation and Comments

3.1 Reviewer's Comments on Sponsor's Analysis of Complete Responses by Treatment Versus Historical Placebo Control

For a more conservative approach, instead of using the upper limit of an exact binomial 95% confidence interval for these data as historical placebo control, the reviewer used the upper limit of 99% confidence interval. The historical placebo response rate is 14.5%.

The results from the reviewer's re-analysis of complete response by treatment versus historical placebo control were similar to those given by the sponsor in terms of significance.

Each of the three treatment groups was statistically significantly superior over historical placebo.

3.2 Reviewer's Comments on Equivalence between 1.8 mg/kg Dolasetron and Ondansetron and 2.4 mg/kg Dolasetron and Ondansetron

In the protocol it was stated that equivalence will be established by showing the lower limit of a 95% confidence interval for the odd ratio (OR) exceeds 0.5.

This criterion for equivalence was specified for the primary endpoint: complete response. It could not apply to the other endpoints: complete-plus-major response and complete response with no nausea.

Hence, the 1.8 mg/kg and 2.4 mg/kg dolasetron mesylate and ondansetron have equivalent efficacy only in complete response in this patient population.

E. Study 73147-3-S-081

1. Description of Study

This was a three arm, double-blind, randomized, multicenter trial.

The objective of this study was to determine if one or both of two different iv doses of dolasetron mesylate (1.2 or 1.8 mg/kg) is/are equal or superior to the approved European dose regimen of metoclopramide (3 mg/kg iv loading dose followed by 4 mg/kg as a continuous 8-hour infusion, ie, 7 mg/kg in total) in preventing emesis due to cisplatin ≥80 mg/m^2.

Patients entering this trial were prospectively stratified on the basis of gender and previous history of chemotherapy.

Cancer patients scheduled to receive cisplatin ≥80 mg/m^2 were randomly assigned to dolasetron mesylate (1.2 mg/kg or 1.8 mg/kg, 30 minutes before beginning cisplatin) or metoclopramide (3 mg/kg bolus dose 30 minutes before cisplatin followed by a 4 mg/kg maintenance dose administered by continuous infusion over 8 hours).

As the trial progressed, the standard of antiemetic care in Europe changed such that this dose of metoclopramide was no longer used for patients receiving high dose cisplatin, leading to an early cessation of the trial.

The primary analysis was an intent-to-treat logistic regression analysis of complete response. The model included terms for patient stratification, treatment, and investigative site. The primary test of efficacy was a pairwise comparison of dolasetron 1.8 mg/kg vs. metoclopramide. Pairwise tests of dolasetron 1.2 mg/kg vs. metoclopramide and 1.2 mg/kg vs. 1.8 mg/kg dolasetron were also done.

The sample size was estimated using the following parameters: α=0.05, β=0.20, with a complete response rate of 40% for the metoclopramide group, and a clinically meaningful difference of 20%, i.e., a 60% complete response rate for the dolasetron 1.8 mg/kg group. The sample size per group was estimated as 100 patients.

2. **Sponsor's Analysis**

The study was planned to recruit 300 patients (100 per arm). The

study was stopped early due to slow recruitment, with 226 patients enrolled. This study was conducted at 12 European centers.

A single patient was excluded from all efficacy analyses because the patient had no efficacy data. This patient (081124/B) dropped out due to a serious adverse event following study medication administration, but before receiving chemotherapy.

The number of patients by treatment group for the intent-to-treat (ITT) analyses (n=225) was 69, 84 and 72 for metoclopramide, 1.2 and 1.8 mg/kg dolasetron mesylate, respectively.

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in Table 2.

As seen from Table 2, there were no statistically significant differences among the three treatment groups with respect to gender, age, weight, height, Karnofsky performance status, history of heavy alcohol use, and site of primary neoplasm.

2.2 **Sponsor's Analysis of Primary Efficacy Parameter**

The primary efficacy endpoint was "complete response". Complete response was achieved when a patient experienced no emetic episode, received no escape medication, and was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent.

The summary of the sponsor's analysis results for the complete response is given below.

Protocol 73147-3-S-081
Complete Response by Treatment
(Intent-to-Treat Analysis)

Treatment	Rate	vs. Meto P-value	vs. 1.2 P-value	vs. Meto 95% C.I. for O.R.	vs. 1.2 95% C.I. for O.R.
Meto	24/69(35%)				
1.2 mg/kg Dola	40/84(48%)	0.0058		(1.367,6.311)	
1.8 mg/kg Dola	41/72(57%)	0.0009	0.4733	(1.738,8.519)	(0.626,2.742)

From a logistic regression model predicting complete response with treatment, investigator, and stratum included in the model.
Copied from Table 15, S8-V1.302-P161.

As seen from table above, compared to metoclopramide, the dolasetron mesylate treatment groups had statistically significantly greater complete response rate.

The complete response rates for single iv doses of dolasetron mesylate 1.2 and 1.8 mg/kg were superior to metoclopramide 7 mg/kg in preventing emesis.

2.3 Sponsor's Analysis of Secondary Efficacy Parameter

The secondary efficacy parameters are complete-plus-major response, time to first emetic episode or escape medication, and FDA requested complete response with no nausea.

2.3.1 Complete-Plus-Major Response

Major response was achieved for a patient when he or she experienced one or two episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period, and was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent.

The summary of results of sponsor's analysis of complete-plus major response is given below.

Protocol 73147-3-S-081
Complete-Plus-Major Response by Treatment
(Intent-to-Treat Analysis)

Treatment	Rate	vs. Meto P-value	vs. 1.2 P-value	vs. Meto 95% C.I. for O.R.	vs. 1.2 95% C.I. for O.R.
Meto	43/69(62%)				
1.2 mg/kg Dola	47/84(56%)	0.9693		(0.479,2.030)	
1.8 mg/kg Dola	53/72(74%)	0.0650	0.0467	(0.955,4.667)	(1.011,4.533)

From a logistic regression model predicting complete response with treatment, investigator, and stratum included in the model.
Copied from Table 21, S8-V1.302-P169,S8-V1.305-P140,146.

As seen from table above, for complete-plus-major response, the difference between the two dolasetron mesylate doses was statistically significant in favor of 1.8 mg/kg at 0.05 level.

2.3.2 **Complete Response with No Nausea**

Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period, was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent, and had an hour 24 nausea VSA less than 5mm.

The summary of results of analysis of complete response with no nausea is given below.

Protocol 73147-3-S-081
Complete Response with No Nausea by Treatment
(Intent-to-Treat Analysis)

Treatment	Rate	vs. Meto P-value	vs. 1.2 P-value	vs. Meto 95% C.I. for O.R.	vs. 1.2 95% C.I. for O.R.
Meto	15/69(22%)				
1.2 mg/kg Dola	27/84(32%)	0.0115		(1.271,6.664)	
1.8 mg/kg Dola	32/72(44%)	0.0010	0.3778	(1.769,9.491)	(0.658,3.011)

No nausea was defined as maximum nausea VAS≤5mm.
From a logistic regression model predicting complete response with treatment, investigator, and stratum included in the model.
Copied from Table 22 s8-v1.302-p170, s8-v1.305-p152, 158.

As seen from table above, compared to metoclopramide, the dolasetron mesylate treatment groups had statistically significantly greater complete response with no nausea rate.

2.4 **Subgroup Analysis**

The sponsor performed a logistic regression model for subgroup analysis. The logistic regression model predicted complete response with treatment, stratum, investigator, and subgroup as explanatory variables. The treatment by subgroup interaction was included in the model as appropriate.

Previous history of chemotherapy, gender, and history of heavy alcohol use were significant predictors of complete response. Patients with no previous history of chemotherapy, male patients, and patients with a history of heavy alcohol use were more likely to be complete responders.

The overall rate of adverse events was 61%, 46%, and 53% in the metoclopramide, dolasetron 1.2 mg/kg, and dolasetron 1.8 mg/kg groups, respectively. The most frequently reported adverse events in the overall population were diarrhea (16%) and headache (12%). Headache was more frequent with dolasetron mesylate than metoclopramide (15% vs 6%).

3. Reviewer's Evaluation and Comments

3.1 Sample Size

The study was planned to recruit 300 patients (100 arm). But, the study was stopped early due to slow recruitment, with only 226 patients (75%) enrolled.

The sample size was insufficient to detect the treatment difference.

3.2 Reviewer's Comments on Sponsor's Results for the Primary Efficacy Variable

The sponsor used logistic regression method to perform a pairwise comparison of dolasetron 1.8 mg/kg vs. metoclopramide. The logistic regression method is a model based approach. It has been used mainly in the explorative analysis. For confirmatory analysis, the design based approaches, e.g. Mantel-Haenzel, Fisher's exact test might be more appropriate.

This reviewer performed an alternative analysis of complete response using Fisher's exact test for pairwise comparisons among treatment groups. The results are given below.

Protocol 73147-3-S-081
Complete Response by Treatment
(Intent-to-Treat Analysis)

Treatment	Rate	vs. Meto P-value	vs. 1.2 P-value
Meto	24/69(35%)		
1.2 mg/kg Dola	40/84(48%)	0.138	
1.8 mg/kg Dola	41/72(57%)	0.0011	0.264

P-values are obtained by Fisher's exact test.

contrary to sponsor's finding, in terms of the proportion of complete responders, the 1.2 mg/kg dolasetron was not statistically significantly different from metoclopramide.

The results by Fisher's exact test is similar to that given by

the sponsor using logistic regression method in favor of 1.8 mg/kg dolasetron over metoclopramide.

3.3 Reviewer's Comments on Sponsor's Results for the Secondary Efficacy Variable

This review performed an alternative analysis using Fisher's exact test for pairwise comparisons among treatment groups for complete-plus-major response and complete response with no nausea.

3.3.1 Complete-Plus-Major Response

The results of reviewer's re-analysis of complete-plus-major response is given in Table 3.

As seen from Table 3, the results by Fisher's exact test are similar to those given by the sponsor using logistic regression method in terms of significance.

3.3.2 Complete Response with No Nausea

The results of reviewer's re-analysis of complete response with no nausea is given below.

Protocol 73147-3-S-081
Complete Response with No Nausea by Treatment
(Intent-to-Treat Analysis)

Treatment	Rate	vs. Meto P-value	vs. 1.2 P-value
Meto	15/69(22%)		
1.2 mg/kg Dola	27/84(32%)	0.202	
1.8 mg/kg Dola	32/72(44%)	0.005	0.137

P-values are obtained by Fisher's exact test.

contrary to sponsor's finding, in terms of the complete response with no nausea rate, the 1.2 mg/kg dolasetron was not statistically significantly different from metoclopramide.

The results by Fisher's exact test is similar to that given by

the sponsor using logistic regression method in favor of 1.8 mg/kg dolasetron over metoclopramide.

F. **Study 73147-3-S-093**

1. **Description of Study**

This was a three arm, double-blind, randomized, multicenter trial.

The objective of this study is to determine if dolasetron mesylate given intravenously as a single 1.8 mg/kg or 2.4 mg/kg dose is equal or superior to the single intravenous 3 mg dose of granisetron in preventing emesis due to cisplatin ≥80 mg/m².

Patients entering this trial were prospectively stratified on the basis of gender and previous history of chemotherapy.

Cancer patients scheduled to receive cisplatin ≥80 mg/m² were randomly assigned to dolasetron mesylate (1.8 mg/kg or 2.4 mg/kg, 30 minutes before beginning cisplatin) or European approved granisetron dose of 3 mg (40 μg/kg for a 75 patient).

The primary assessment of efficacy compared the pooled 1.8 and 2.4 mg/kg dolasetron group vs granisetron.

The sample size was estimated using the following parameters: α=0.10, β=0.20, with a complete response rate of 70% for the granisetron and dolasetron groups. It was assumed that a difference of no more than 15% in complete response rate was consistent with equivalence in efficacy. The sample size per group was estimated as 100 patients. In order to compensate for potential dropouts and to allow for additional estimation precision, 150 patients per group were specified in the protocol.

2. **Sponsor's Analysis**

A total of 476 patients were enrolled in the study, which was conducted at 29 European centers.

Two patients (093011/D and 093055/B) were randomized but did not receive study medication. These patients had no efficacy data and

were excluded from all analyses.

Of 474 patients, 150, 163 and 161 patients received granisetron, 1.8 and 2.4 mg/kg dolasetron mesylate, respectively.

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in Table 4.

As seen from Table 4, there were no statistically significant differences among the three treatment groups with respect to gender, age, weight, height, Karnofsky performance status, history of heavy alcohol use, and site of primary neoplasm.

2.2 **Sponsor's Analysis of Primary Efficacy Parameter**

The primary efficacy endpoint was "complete response". Complete response was achieved when a patient experienced no emetic episode, received no escape medication, and was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent.

The summary of the sponsor's analysis results for the complete response is given below.

Protocol 73147-3-S-093
Complete Response by Treatment
(Intent-to-Treat Analysis)

Treatment	Rate	vs. Gran P-value	vs. 1.8 P-value	vs. Gran 95% C.I. for O.R.	vs. 1.8 95% C.I. for O.R.
Gran	72/150(48%)				
1.8 mg/kg Dola	88/163(54%)	0.0893		(0.934,2.596)	
2.4 mg/kg Dola	75/161(47%)	0.8839	0.0602	(0.580,1.599)	(0.374,1.021)

From a logistic regression model predicting complete response with treatment, investigator, and stratum included in the model.
Copied from Table 15, S8-V1.337-P155.

As seen from table above, for complete response, there were no statistically significant differences among the three treatment groups.

This study demonstrated statistical equivalence of both dolasetron mesylate dose groups to an approved dose of granisetron, with the highest complete response rate (54%) achieved in the 1.8 mg/kg dolasetron mesylate group.

2.3 Sponsor's Analysis of Complete Responses by Treatment Versus Historical Placebo Control

The results of sponsor's analysis of complete responses by treatment versus historical placebo control is given below.

Protocol 73147-3-S-093
Complete Response by Treatment vs Historical Control
(Intent-to-Treat Analysis)

	Ondansetron	1.8 mg/kg dolasetron	2.4 mg/kg dolasetron
Rate	72/150 (48%)	88/163 (54%)	75/161 (47%)
P-value for Comparison to Historical Placebo Control	<0.001	<0.001	<0.001

P-values are calculated from a logistic regression model predicting complete response with treatment, investigator, and stratum included in the model. The historical placebo response rate was the upper endpoint of a 95% confidence interval based on the results of four published studies (11.1%).
Copied from Table 1, NDA Supplemental page 5, Nov. 18, 1996.

As seen from table above, statistically significant superiority of each of the three treatment groups over historical placebo was demonstrated.

2.4 Sponsor's Analysis of Secondary Efficacy Parameter

The secondary efficacy parameters are complete-plus-major response, time to first emetic episode or escape medication, and FDA requested complete response with no nausea.

2.4.1 Complete-Plus-Major Response

Major response was achieved for a patient when he or she experienced one or two episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period, and was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent.

The summary of results of sponsor's analysis of complete-plus major response is given below.

Protocol 73147-3-S-093
Complete-Plus-Major Response by Treatment
(Intent-to-Treat Analysis)

Treatment	Rate	vs. Gran P-value	vs. 1.8 P-value	vs. Gran 95% C.I. for O.R.	vs. 1.8 95% C.I. for O.R.
Gran	95/150(63%)				
1.8 mg/kg Dola	101/163(62%)	0.8361		(0.620,1.804)	
2.4 mg/kg Dola	100/161(62%)	0.8760	0.7107	(0.563,1.633)	(0.538,1.527)

From a logistic regression model predicting complete response with treatment, investigator, and stratum included in the model.
Copied from Table 21, S8-V1.337-P165, s8-v1.343-p.249, 257.

As seen from table above, for complete-plus-major response, there were no statistically significant differences among the three treatment groups.

2.4.2 **Complete Response with No Nausea**

Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes in the 24-hour treatment period, received no escape medication in the 24-hour treatment period, was monitored for at least 23.5 hours after initiation of the primary chemotherapy agent, and had an hour 24 nausea VSA less than 5mm.

The summary of results of analysis of complete response with no nausea is given below.

procedure, the significance of dolasetron 12.5 mg and 100 mg dose groups held, but it did not hold for dolasetron 25 mg group.

3.5 Reviewer's Re-analysis of the Primary Efficacy Variable Adjusting for Previous History of Motion Sickness

This reviewer re-analyzed complete response using Cochran-Mantel-Haenszel method for adjusting for previous history of Motion Sickness. The results are given below.

Protocol MCPR0045
P-value after Adjusting for Previous History of Motion Sickness
(Intent-to-Treat Analysis)

Gender	Dose (mg)	P-value vs. Placebo	P-value vs. Dola 12.5	P-value vs. Dola 25	P-value vs. Dola 50
Male	Placebo				
	Dola 12.5	0.416			
	Dola 25	0.461	0.926		
	Dola 50	0.520	0.185	0.113	
	Dola 100	0.169	0.650	0.600	0.069
Female	Placebo				
	Dola 12.5	0.002*			
	Dola 25	0.049	0.253		
	Dola 50	0.066	0.200	0.874	
	Dola 100	0.003*	0.879	0.316	0.259

P-values were obtained by this reviewer using Cochran-Mantel-Haenszel method for adjusting for previous history of motion sickness.
*significant after adjusting 4 comparisons to placebo using Hochberg's procedure.

As seen from table above, after adjusting for previous history of motion sickness, the 12.5 mg and 100 mg groups were statistically significantly better than placebo at 0.05 level. The 25 mg group was marginally statistically significantly better than placebo at 0.05 level. However, when adjusted for multiple comparisons to placebo using Hochberg's procedure, the significance of

dolasetron 12.5 mg and 100 mg dose groups held, but it did not hold for dolasetron 25 mg group.

3.6 Reviewer's Comments on Sponsor's Results for the Secondary Efficacy

For complete-plus-major response and complete response with no nausea, this reviewer performed an alternative analysis by gender using Fisher's exact test for pairwise comparison among dose groups. The results are given in Tables 6 and 7 for complete-plus-major response and complete response with no nausea, respectively.

As seen from Table 6, in female patients, the complete-plus-major response rates for all dolasetron dose groups, except 50 mg, were statistically superior to the placebo group at 0.05 level. The dolasetron 12.5 mg dose group was statistically significantly different from dolasetron 50 mg dose group at 0.05 level. After adjusting for the comparisons to placebo using Hochberg's procedure, the 12.5 mg and 100 mg dose groups were still statistically significantly different from the placebo.

There were no statistically significant differences from placebo in any of the dolasetron-treated groups in proportion of complete-plus-major responders for males. For males the dolasetron 50 mg dose group was statistically significantly different from dolasetron 25 mg and 100 mg dose groups at 0.05 level.

As seen from Table 7, in terms of complete response with no nausea, the results by Fisher's exact test are similar to those given by the sponsor using logistic regression method in terms of significance.

In this study, due to insufficient sample size, there is not enough power to detect the differences among 12.5. 25, 50, and 100 mg groups. However, for female, there was a significant overall effect in complete-plus-major response and complete response with no nausea rates with dolasetron dose.

E. Study 73147-2-S-080

1. Description of Study

This study was a randomized, double-blind, placebo-controlled, multicenter dose ranging trial conducted in Europe. This study was stratified for the type of surgery (laparoscopic and non laparoscopic procedures).

The study objective is to assess the effect of a range of intravenous dolasetron mesylate in preventing nausea and vomiting in patients undergoing surgery under general anesthesia.

Patients received dolasetron mesylate (12.5, 25, 50, or 100 mg) or placebo administered intravenously over 5 minutes at the cessation of nitrous oxide.

Efficacy were monitored for 24 hours.

Female patients with ASA physical status class 1 or 2 who would undergoing laparoscopic surgery or gynecological surgery through laparotomy and vaginal hysterectomy under general anesthesia were eligible.

Each patient was closely observed for nausea and emetic episodes for 8 hours after study drug administration.

This study was designed to treat 250 female patients.

Assuming the global incidence of complete responders is 50% under placebo and 80% under dolasetron and type I and II errors is respectively 0.05 and 0.20, a sample size of 50 patients per group was chosen.

2. **Sponsor's Analysis**

A total of 281 female patients were enrolled in 11 investigators in this study. Fifty-four (54) received placebo, 54 received dolasetron 12.5 mg, 60 received dolasetron 25 mg, 54 received dolasetron 50 mg, and 59 received dolasetron 100 mg.

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in Table 8.

As seen from Table 8, the treatment groups were comparable

regarding age, weight, and height. However, the proportion of patients in each treatment group with a history of PONV did show some imbalance among the dose groups (p=0.0528). The percentage of patients with such a history was the smallest in the 50 mg group (15%) and the highest in the placebo group (36%).

There was no imbalance between treatment groups in the duration of anesthesia nor in doses of anesthetics used except for the mean dose of fentanyl which was higher in 12.5 mg treated patients when compared to placebo.

2.2 **Sponsor's Analysis of Primary Efficacy Parameter**

The primary efficacy endpoint was "complete response." Complete response was achieved when a patient experienced no emetic episode and received no escape medication during the entire 24-hour study period.

The summary of the sponsor's analysis results for the complete response is given below.

Protocol 73147-2-S-080
Complete Response by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. placebo
placebo	23/54 (43%)	
Dolasetron 12.5	29/54 (54%)	0.1849
Dolasetron 25	40/60 (67%)	0.0042*
Dolasetron 50	32/54 (59%)	0.0590
Dolasetron 100	35/59 (59%)	0.0537

p=0.0475 for linear trend.
P-values were calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose, stratum, and investigator as explanatory variable. The significance levels of the comparisons to placebo are adjusted for the 4 possible comparisons to placebo using Dunnett's procedure.
*statistically significant after adjusting for the 4 comparisons to placebo using Dunnett's procedure.
Copied from S8-V1.477-p61.

There was a statistically significant linear trend in the proportion of complete responders across the five dose group. But, if the placebo was excluded, the dose response of dolasetron

became flat.

The 12.5 mg dolasetron treated group with 54% of complete responders was statistically not different from placebo (43%). The 25 mg group with 67% of complete responders was statistically superior to placebo, while the 50 mg (59%) and the 100 mg (59%) dose groups were numerically, but not statistically superior to the placebo group. After adjusting for the comparisons to placebo using Dunnett's procedure, the 25 mg dose group was still statistically significantly different from the placebo group.

2.3 **Sponsor's Analysis of Secondary Efficacy Parameter**

The secondary efficacy parameters are complete-plus-major response, and time to first emetic episode or escape medication, nausea.

2.3.1 **Complete-Plus-Major Response**

Major response was achieved when the patient experienced one episode and received no escape medication during the entire 24-hour study period.

The summary of results of sponsor's analysis of complete-plus-major response is given below.

Protocol 73147-2-S-080
Complete-Plus-Major Response by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. placebo
placebo	33/54 (61%)	
Dolasetron 12.5	34/54 (63%)	0.6286
Dolasetron 25	45/60 (75%)	0.0467
Dolasetron 50	41/54 (76%)	0.0529
Dolasetron 100	43/59 (73%)	0.1360

p=0.0448 for linear trend.
P-values were calculated from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose, stratum, and investigator as explanatory variable. The significance levels of the comparisons to placebo are adjusted for the 4 possible comparisons to placebo using Dunnett's procedure.
Copied from S8-V1.477-p108.

As seen from Table above, the 25 mg group was statistically superior to placebo at 0.05 level. there was numerical difference of in favor of 50 mg and 100 mg dose groups as compared with placebo.

3. **Sponsor's Subgroup Analysis**

Subgroup analysis of complete response revealed that previous history of PONV and age were significant predictors and duration of anesthesia a marginally significant predictor of complete response, patients with a history of PONV, older patients and patients with longer period of anesthesia were less likely to be complete responders.

4. **Reviewer's Evaluation and Comments**

4.1 **Sponsor's Sample Size Determination**

Sponsor's sample size determination is based on establishing a linear trend in complete response with dose using a logistic regression. A sample size of 50 patients per dose group would give 93% power for detecting a linear trend with dose in complete response rates at the 0.05 significance level.

However, if the logit of the complete response rate increases linearly with the logarithm of dose to a complete response rate of only 70% at the highest dose of 100 mg, a sample size of 50 in each dose group gives only 62% power for detecting a linear trend at the 0.05 significance level.

The sample size might be insufficient to detect a low dose effect on differences between the dose groups.

4.2 **Reviewer's Comments on Imbalance of Previous History of PONV**

A slight imbalance of previous history of motion sickness was observed between placebo and dolasetron 25 mg and 50 mg patients and between dolasetron 50 mg dose group and dolasetron 12.5 mg and 100 mg dose groups as seen table below.

Protocol 73147-2-S-080
History of PONV at Baseline
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo	P-value vs. Dola 12.5	P-value vs. Dola 25	P-value vs. Dola 50
Placebo	19/54 (35%)				
Dola 12.5	18/54 (33%)	0.839			
Dola 25	12/60 (20%)	0.069	0.106		
Dola 50	8/54 (15%)	0.015	0.024	0.467	
Dola 100	18/59 (31%)	0.597	0.748	0.187	0.048

P-values were obtained by the reviewer using Chi-square method.

The placebo group had 35% of patients with a previous history of PONV. This percentage of patients with a previous history of PONV was much higher than that for dolasetron-treated patients which ranged from in dolasetron 25 mg and 50 mg dose groups. This difference may have increased the magnitude difference of complete response between the placebo group and the dolasetron 25 mg and 50 mg dose groups. Hence, this imbalance might be in favor of test drug, especially for dolasetron 25 mg and 50 mg dose groups.

4.2 Reviewer's Comments on Sponsor's Analyses

In the original analysis plan, the pairwise comparisons were to be performed as the primary analysis. The sponsor modified the analysis plan so that a test for a linear contrast across the doses would be the primary test. This modification was made for two reasons: (1) the expectation that this would be a more powerful test, and (2) this would be a single test rather than multiple comparisons of dose.

The sponsor's test for a linear contrast across the doses was a post-hoc analysis.

4.3 Reviewer's Comments on Sponsor's Results for the Primary Efficacy Variable

This reviewer performed an alternative analysis using Fisher's exact test for pairwise comparisons among dose groups. The results are given in Table 9.

As seen from Table 9, the results by Fisher's exact test are similar to those given by the sponsor using logistic regression method in terms of significance at 0.05 level. However, when adjusted for multiple comparisons to placebo using the Hochberg's procedure, significance of dolasetron 25 mg dose group did not hold.

4.4 Reviewer's Re-analysis of the Primary Efficacy Variable Adjusting for Previous History of PONV

This reviewer re-analyzed complete response using Cochran-Mantel-Haenszel method for adjusting for previous history of PONV. The results are given below.

Protocol 73147-2-S-080
P-value after Adjusting for Previous History of PONV
(Intent-to-Treat Analysis)

Dose (mg)	P-vale vs. Placebo	P-value vs. Dola 12.5	P-value vs. Dola 25	P-value vs. Dola 50
Placebo				
Dola 12.5	0.307			
Dola 25	0.047	0.323		
Dola 50	0.244	0.821	0.318	
Dola 100	0.113	0.582	0.595	0.830

P-values were obtained by this reviewer using Cochran-Mantel-Haenszel method for adjusting for previous history of PONV.

As seen from table above, the 25 mg group was marginally statistically significantly better than placebo at 0.05 level after adjusting for previous history of PONV. However, when adjusted for multiple comparisons using Hochberg's procedure, the significance of dolasetron 25 mg dose group did not hold.

4.5 Reviewer's Comments on Sponsor's Results for the Secondary Efficacy Variable

For complete-plus-major response, this reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The results are given in Table 10.

As seen from Table 10, contrary to the sponsor's finding, the results by Fisher's exact test showed that all dolasetron dose groups were not statistically significantly different from the placebo.

In this study, due to insufficient sample size, there is not enough power to detect the differences among 12.5 mg. 25 mg, 50 mg, and 100 mg groups.

The sponsor did not analyze a commonly used secondary efficacy variable: complete response with no nausea. Furthermore, the efficacy endpoint of complete response with no nausea is more stringent than complete response.

This reviewer has performed the analysis of this secondary endpoint and the results are given in the next section.

4.5.1 **Complete Response with No Nausea**

Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes, received no escape medication, and had maximum nausea VAS score less 5 mm.

The summary of results of analysis of complete response with no nausea is given below.

Protocol 73147-2-S-080
Complete Response with No Nausea by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. placebo	p-value vs. Dola 12.5	p-value vs. Dola 25	p-value vs. Dola 50
placebo	18/54(33%)				
Dola 12.5	23/54(43%)	0.428			
Dola 25	33/60(55%)	0.024	0.196		
Dola 50	18/54(33%)	1.000	0.428	0.024	
Dola 100	27/58(47%)	0.180	0.707	0.461	0.180

P-values were obtained using Fisher's exact test.

As seen from table above, the dolasetron 25 mg dose group was statistically superior to placebo at 0.05 level. The dolasetron 25 mg dose group was also statistically significantly better than the dolasetron 50 mg dose group at 0.05 level. When adjusted for multiple comparisons to placebo using Hochberg's procedure, the significance of dolasetron 25 mg dose group did not hold.

F. **Overall Summary and Recommendation**

Primary Endpoint: Complete Response

Two studies (MCPR0084 and 73147-2-S-80) showed that there was a significant overall effect for the "complete response" endpoint. For this endpoint, the highest observed complete response rates were achieved for the 50 mg dose in Study MCPR0084 and for the 25 mg dose in study 73147-2-S-80.

Study MCPR0084 showed the 12.5 mg, 25 mg, and 50 mg dose groups were statistically significantly more effective than placebo. Study 73147-2-S-80 showed that only 25 mg dose group was statistically significantly better than the placebo.

Furthermore, study MCPR0045 showed that for females there was statistically significant difference of 18 percent in favor of 12.5 mg dose group as compared with placebo. Study 73147-2-S-80 showed there was numerical difference of 11 to 16 percent in

favor of 12.5 mg, 50 mg and 100 mg dose group as compared with placebo.

The results of studies MCPR0084 and MCPR0045 indicate that complete response does not increase with doses above 12.5 mg.

Secondary Endpoint: Complete Response with No Nausea

For more stringent efficacy measure requested by FDA, study MCPR0084 showed that the 25 mg and 50 mg doses were statistically significantly more effective than placebo. Study 73147-2-S-80 showed that the 25 mg doses were statistically significantly more effective than placebo.

Furthermore, study MCPR0045 showed that for females there was numerical difference of 13 percent in favor of 12.5 mg dose group as compared with placebo. Study 73147-2-S-80 showed there was numerical difference of in favor of 12.5 mg and 100 mg dose groups as compared with placebo.

In these studies, due to insufficient sample size, there is not enough power to detect the differences among 12.5 mg, 25 mg, 50 mg, and 100 mg dose groups.

It is very difficult to choose the appropriate effective dose among 12.5 mg, 25 mg and 50 mg dose groups as seen below.

Study	Endpoint	Dol 12.5	Dol 25	Dol 50	Dol 25 - Dol 12.5	Dol 50 - Dol 25
MCPR0084	Complete response	50%	52%	56%	2%	4%
	Complete plus major response	59%	64%	64%	5%	0%
	Complete response with no nausea	28%	30%	30%	2%	0%
MCPR0045 Female	Complete response	58%	51%	50%	-7%	-1%
	Complete plus major response	72%	62%	60%	-10%	-2%
	Complete response with no nausea	37%	28%	31%	-9%	3%
73147-2-S-080	Complete response	54%	67%	59%	13%	-8%
	Complete plus major response	63%	75%	76%	12%	1%
	Complete response with no nausea	43%	55%	33%	12%	-22%

As seen from table above, there were inconsistent results in favor of 25 mg against low dose (12.5 mg). In the comparison between 12.5 mg and 25 mg dose groups, there was a numerical difference of about 12% in favor of 25 mg dose group in complete response, complete-plus-major, and complete response with no nausea in study 73147-2-S-80. In study MCPR0084, there is a slight difference of about in favor of 25 mg dose group.

However, for the larger study MCPR0045, there was a numerical difference of about in favor of 12.5 mg dose group for females in complete response, complete-plus-major, and complete response with no nausea.

Among these three studies, only study MCPR0045 recruited males with limited males enrolled (30%). No treatment effect for males was observed in this study.

There is a need for another large study to determine whether the low dose 12.5 mg or higher dose 25 mg is the optimal effective dose. However, two studies (MCPR0084 and 73147-2-S-80) show an overall effect of dolasetron mesylate injection for the prevention of postoperative nausea and vomiting with regard to the prespecified defined primary endpoint.

G. **Comments to be conveyed to the Sponsor**

The contents of Section of F may be conveyed to the sponsor.

/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 33 pages of text and 10 pages of tables.

concur: Dr. Huque /S/ 1/14/97
Dr. Smith /S/ 1/17/97

cc:
Archival NDA 20-624
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-344/Dr. Lisook
HFD-720
HFD-720/Chron. copy
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/01/13/97

Table 1 Comparability of Treatment Groups at Baseline --- Protocol MCPR0084

		Intent-to-Treat Population				
Variable	Level	Placebo (n=157)	Dolasetron 12.5 mg (n=159)	Dolasetron 25 mg (n=157)	Dolasetron 50 mg (n=162)	Between treatment p-value
Age (mean)		32.3	32.3	31.4	31.2	0.3374
Height (cm) (mean)		163.5	163.6	163.0	163.4	0.9109
Weight (kg) (mean)		67.2	69.5	67.6	69.2	0.4677
Race	White	120 (76%)	109 (69%)	105 (67%)	113 (70%)	0.556
	Black	32 (20%)	45 (28%)	45 (29%)	41 (25%)	
	Other	5 (3%)	5 (3%)	7 (5%)	8 (5%)	
Smoking Status		49 (31%)	51 (32%)	54 (34%)	53 (33%)	0.9461
ASA	Status 1	90 (57%)	92 (58%)	94 (60%)	102 (63%)	0.7123
	Status 2	57 (43%)	67 (42%)	63 (40%)	60 (37%)	
History of PONV		40 (26%)	33 (21%)	38 (24%)	39 (24%)	0.7683
History of Motion Sickness		42 (27%)	33 (21%)	29 (19%)	30 (19%)	0.2445
Type of Surgery	Gyn. Laparascop-sterilization	76 (48%)	78 (49%)	82 (52%)	92 (57%)	0.131
	Gyn. diagnostic laparascopy	51 (33%)	55 (35%)	48 (31%)	55 (34%)	
	Gyn. Laparascop-laser	30 (19%)	26 (16%)	27 (17%)	15 (9%)	
Duration of Anesthesia (hrs) (mean)		1.145	1.094	1.091	1.056	0.6725
Time from Last Free Fluids to Study Drug Administration (hrs) (mean)		13.849	13.684	13.249	13.468	0.7227

For continuous variables, p-values are calculated from a three-way anova among the five doses controlling for investigator and stratum. For binary variables, p-values are from a 3 degree of freedom chi-square test from a logistic regression model controlling for investigator and stratum. For other categorical variables, p values are from a 3 degree of freedom chi-square test calculated from a Cochran-Mantel-Haenszel Row Mean Scores analysis.
Copied from Table 6, S8-V1.418-p91.

Table 2 Reviewer's Re-analysis of Complete Response --- Protocol MCPR0084

Analysis	Treatment	Rate	vs. placebo p-value	vs. 12.5 mg p-value	vs. 25 mg p-value
ITT	Placebo	48/157 (31%)			
	Dolasetron 12.5 mg	80/159 (50%)	<0.001*		
	Dolasetron 25 mg	81/157 (52%)	<0.001*	0.823	
	Dolasetron 50 mg	90/162 (56%)	<0.001*	0.372	0.502
Evaluable	Placebo	44/149 (30%)			
	Dolasetron 12.5 mg	76/155 (49%)	<0.001*		
	Dolasetron 25 mg	78/152 (51%)	<0.001*	0.732	
	Dolasetron 50 mg	86/156 (55%)	<0.001*	0.308	0.568

P-values are obtained by Fisher's exact test.
* Statistical significant after adjusting for 3 comparisons to placebo using Hochberg's procedure.

Table 3 Reviewer's Re-analysis of the Secondary Efficacy Variables ---- Protocol MCPR0084

(Intent-to-Treat Analysis)

Efficacy Variable	Treatment	Rate	vs. placebo p-value	vs. 12.5 mg p-value	vs. 25 mg p-value
Complete-plus-major response	Placebo	69/157 (44%)			
	Dolasetron 12.5 mg	94/159 (59%)	0.009*		
	Dolasetron 25 mg	100/157 (64%)	<0.001*	0.421	
	Dolasetron 50 mg	104/162 (64%)	<0.001*	0.361	1.000
Complete response with no nausea	Placebo	29/157 (19%)			
	Dolasetron 12.5 mg	44/159 (28%)	0.062		
	Dolasetron 25 mg	47/157 (30%)	0.026	0.710	
	Dolasetron 50 mg	48/162 (30%)	0.026	0.713	1.000

P-values are obtianed from Fisher's exact test.
*Statistical significant after adjusting for 3 comparisons to placebo using Hochberg's procedure.

Table 4 Comparability of Treatment Groups at Baseline --- Protocol MCPR0045

		Intent-to-Treat Population					
Variable	Level	Placebo (n=208)	Dolasetron 12.5 mg (n=206)	Dolasetron 25 mg (n=203)	Dolasetron 50 mg (n=205)	Dolasetron 100 mg (n=208)	Between treatment p-value
Sex	Male	63 (30%)	60 (29%)	59 (29%)	64 (31%)	62 (30%)	
	Female	145 (70%)	146 (71%)	144 (71%)	141 (69%)	146 (70%)	
Age (mean)		37.6	37.0	35.9	35.6	36.9	0.3497
Height (cm) (mean)		168.8	167.9	168.3	169.3	167.0	0.0240
Weight (kg) (mean)		77.1	73.4	74.7	74.2	72.1	0.0238
Race	White	154 (74%)	153 (74%)	151 (74%)	150 (73%)	152 (73%)	0.870
	Black	49 (24%)	44 (21%)	47 (23%)	47 (23%)	49 (24%)	
	Other	5 (2%)	9 (4%)	5 (2%)	8 (4%)	7 (3%)	
Smoking Status		58 (28%)	59 (29%)	52 (26%)	64 (31%)	59 (28%)	0.8046
ASA	Status 1	110 (53%)	113 (54%)	102 (50%)	102 (50%)	112 (54%)	0.910
	Status 2	91 (44%)	87 (42%)	98 (48%)	98 (48%)	91 (44%)	
	Status 3	7 (3%)	6 (3%)	3 (1%)	5 (2%)	5 (2%)	
History of PONV		32 (15%)	45 (22%)	56 (28%)	51 (25%)	48 (23%)	0.0063
History of Motion Sickness		46 (22%)	41 (20%)	52 (26%)	47 (23%)	39 (19%)	0.0645
Type of Surgery	Breast Surgery	9 (4%)	7 (3%)	6 (3%)	7 (3%)	7 (3%)	
	ENT	13 (6%)	17 (8%)	6 (4%)	7 (5%)	10 (5%)	
	Gyn. surgery	100 (48%)	100 (49%)	106 (52%)	97 (47%)	103 (50%)	
	Opthamologic	12 (6%)	8 (4%)	9 (4%)	9 (4%)	8 (4%)	
	Orthopedic	49 (24%)	41 (20%)	45 (22%)	45 (22%)	45 (22%)	
	Urologic	6 (3%)	15 (7%)	8 (4%)	12 (6%)	13 (6%)	
	Other	19 (9%)	18 (9%)	23 (11%)	28 (14%)	22 (11%)	
Duration of Anesthesia (hrs) (mean)		1.102	1.059	1.101	1.124	1.180	0.3746
Time from Last Free Fluids to Study Drug Administration (hrs) (mean)		13.820	14.185	13.844	13.833	13.913	0.9791

For continuous variables, p-values are calculated from a three-way anova among the five doses controlling for investigator and gender. For binary variables, p-values are from a 4 degree of freedom chi-square test from a logistic regression model controlling for investigator and gender. For other categorical variables, p values are from a 4-degree of freedom chi-square test calculated from a Cochran-Mantel-Haenszel Row Mean Scores analysis.

P-values for sex and type of surgery was obtained by the reviewer using Chi-square method.
Copied from Table 6, S8-V1.441-p99.

Table 5 Reviewer's Analysis of Complete Response by Gender --- Protocol MCPR0045

(INTENT-TO-TREAT ANALYSIS)

Gender	Treatment	Rate	vs. placebo p-value	vs. 12.5 mg p-value	vs. 25 mg p-value	vs. 50 mg p-value
Male	Placebo	44/63 (70%)				
	Dolasetron 12.5 mg	38/60 (63%)	0.452			
	Dolasetron 25 mg	37/59 (63%)	0.447	1.000		
	Dolasetron 50 mg	48/64 (75%)	0.556	0.177	0.173	
	Dolasetron 100 mg	37/62 (60%)	0.265	0.713	0.852	0.087
Female	Placebo	58/145 (40%)				
	Dolasetron 12.5 mg	85/146 (58%)	0.002*			
	Dolasetron 25 mg	74/144 (51%)	0.059	0.288		
	Dolasetron 50 mg	71/141 (50%)	0.096	0.196	0.906	
	Dolasetron 100 mg	84/146 (58%)	0.003*	1.000	0.346	0.238

P-values were obtained using Fisher's Exact test.
* statistically significant after adjusting for the 4 comparisons to placebo using Hochberg's procedure

Table 6 Reviewer's Analysis of Complete-plus-major Response by Gender --- Protocol MCPR0045

(INTENT-TO-TREAT ANALYSIS)

Gender	Treatment	Rate	vs. placebo p-value	vs, 12.5 mg p-value	vs. 25 mg p-value	vs. 50 mg p-value
Male	Placebo	49/63 (78%)				
	Dolasetron 12.5 mg	43/60 (72%)	0.534			
	Dolasetron 25 mg	40/59 (68%)	0.229	0.693		
	Dolasetron 50 mg	54/64 (84%)	0.373	0.127	0.035	
	Dolasetron 100 mg	41/62 (66%)	0.167	0.561	1.000	0.023
Female	Placebo	72/145 (50%)				
	Dolasetron 12.5 mg	105/146 (72%)	<0.001*			
	Dolasetron 25 mg	89/144 (62%)	0.044	0.081		
	Dolasetron 50 mg	84/141 (60%)	0.098	0.034	0.717	
	Dolasetron 100 mg	98/146 (67%)	0.003*	0.446	0.391	0.220

P-values were obtained using Fisher's Exact test.
* statistically significant after adjusting for the 4 comparisons to placebo using Hochberg's procedure

Table 7 Reviewer's Analysis of Complete Response with No Nausea by Gender --- Protocol MCPR0045

(INTENT-TO-TREAT ANALYSIS)

Gender	Treatment	Rate	vs. placebo p-value	vs, 12.5 mg p-value	vs. 25 mg p-value	vs. 50 mg p-value
Male	Placebo	30/63 (48%)				
	Dolasetron 12.5 mg	24/60 (40%)	0.468			
	Dolasetron 25 mg	22/59 (37%)	0.276	0.851		
	Dolasetron 50 mg	30/64 (47%)	1.000	0.473	0.361	
	Dolasetron 100 mg	24/62 (39%)	0.368	1.000	1.000	0.374
Female	Placebo	35/145 (24%)				
	Dolasetron 12.5 mg	54/146 (37%)	0.022			
	Dolasetron 25 mg	41/144 (28%)	0.425	0.134		
	Dolasetron 50 mg	44/141 (31%)	0.189	0.321	0.698	
	Dolasetron 100 mg	53/146 (36%)	0.030	1.000	0.169	0.384

P-values were obtained using Fisher's Exact test.
* statistically significant after adjusting for the 4 comparisons to placebo using Hochberg's procedure

Table 8 Comparability of Treatment Groups at Baseline --- Protocol 73147-2-S-080

		Intent-to-Treat Population					
Variable	Level	Placebo (n=54)	Dolasetron 12.5 mg (n=54)	Dolasetron 25 mg (n=60)	Dolasetron 50 mg (n=54)	Dolasetron 100 mg (n=59)	Between treatment p-value
Age (mean)		34.7	37.1	38.2	38.5	38.3	0.1282
Height (cm) (mean)		163.1	161.3	161.6	161.9	163.0	0.3579
Weight (kg) (mean)		59.2	62.1	61.8	63.9	61.4	0.3426
ASA	Status 1 Status 2	53 (98%) 1 (2%)	50 (93%) 4 (7%)	57 (95%) 3 (5%)	46 (85%) 8 (15%)	53 (90%) 6 (10%)	0.115
History of PONV		19 (36%)	18 (33%)	12 (20%)	8 (15%)	18 (31%)	0.0528
Type of Surgery	Laparoscopy Laparotomy Vaginal hysterotomy	30 (56%) 18 (33%) 6 (11%)	28 (52%) 20 (37%) 6 (11%)	26 (43%) 26 (43%) 8 (13%)	26 (48%) 23 (43%) 5 (9%)	32 (54%) 21 (36%) 6 (10%)	0.755

For continuous variables, p-values are calculated from a three-way anova among the five doses controlling for investigator and gender. For binary variables, p-values are from a 4 degree of freedom chi-square test from a logistic regression model controlling for investigator and gender. For other categorical variables, p values are from a 4-degree of freedom chi-square test calculated from a Cochran-Mantel-Haenszel Row Mean Scores analysis.
P-values for sex and type of surgery were obtained by the reviewer using Chi-square method.
Copied from Table 6, S8-V1.441-p99.

Table 9 Reviewer's Re-analysis of Complete Response --- Protocol 73147-2-S-080

Analysis	Treatment	Rate	vs. placebo p-value	vs. 12.5 mg p-value	vs. 25 mg p-value	vs. 50 mg p-value
ITT	Placebo	23/54 (43%)				
	Dolasetron 12.5 mg	29/54 (54%)	0.336			
	Dolasetron 25 mg	40/60 (67%)	0.014	0.182		
	Dolasetron 50 mg	32/54 (59%)	0.123	0.698	0.442	
	Dolasetron 100 mg	35/59 (59%)	0.091	0.574	0.451	1.000
Evaluable	Placebo	23/54 (43%)				
	Dolasetron 12.5 mg	27/52 (52%)	0.437			
	Dolasetron 25 mg	40/60 (67%)	0.014	0.126		
	Dolasetron 50 mg	31/53 (58%)	0.123	0.559	0.437	
	Dolasetron 100 mg	34/58 (59%)	0.130	0.565	0.447	1.000

P-values are obtained by Fisher's exact test.

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Table 10 Reviewer's Re-analysis of Complete-Plus-Major Response --- Protocol 73147-2-S-080

Treatment	Rate	vs. placebo p-value	vs. 12.5 mg p-value	vs. 25 mg p-value	vs. 50 mg p-value
Placebo	33/54 (61%)				
Dolasetron 12.5 mg	34/54 (63%)	1.000			
Dolasetron 25 mg	45/60 (75%)	0.157	0.222		
Dolasetron 50 mg	41/54 (76%)	0.146	0.210	1.000	
Dolasetron 100 mg	43/59 (73%)	0.230	0.314	0.837	0.830

P-values are obtained by Fisher's exact test.

Johnson

STATISTICAL REVIEW AND EVALUATION --- NDA

Date

NDA #: 20-624

Applicant: Hoechst Marion Roussel, Inc.

Name of Drug: Anzemet (dolasetron mesylate) Injection

Indication: Treatment of postoperative nausea and vomiting (Separate reviews for the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy and the prevention of postoperative nausea and vomiting).

Documents Reviewed: NDA vol. 1, 1.49, 500, 501 Dated February 19, 1996

Medical Reviewer: This review has been discussed with the medical Officer, Hugo Gallo-Torres, M.D.,Ph.D.

Key Words: Dose response, multiple comparisons, Dunnett's Procedure, Hochberg's procedure.

A. Background

In the current NDA, the sponsor seeks approval of dolasetron mesylate intravenous (iv) injection in three primary indications:

1). the prevention of nausea and vomiting associated with emetogenic cancer chemotherapy including initial and repeat courses

2). the prevention of postoperative nausea and vomiting

3). the treatment of postoperative nausea and vomiting

This review addresses only the treatment of postoperative nausea and vomiting. Separate reviews address the other two indications.

B. Indication of the Treatment of Postoperative Nausea and Vomiting

The sponsor has submitted two clinical trials (MCPR0044, 73147-3-S-084) in support of the proposed claim: the treatment of postoperative nausea and vomiting (PONV treatment).

Protocol MCPR0044 was conducted in the U.S. and Protocol 73147-2-S-084 was conducted in Europe.

Both trials were randomized, double-blind, placebo-control, multicenter studies in patients who had undergone surgery with general balanced anesthesia, and presented with early postoperative nausea and vomiting requiring antiemetic treatment.

Both protocols utilized the same definition for an emetic episode (a single episode of vomiting or any number of retches within 1 minute period), the same evaluation period (24-hour treatment period) and the same primary efficacy measure (complete response, defined as 0 emetic episodes, no rescue medication and monitored for at least 23.5 hours after study drug).

A global assessment of the degree of nausea each patient experienced was obtained using a visual analog scale (VAS) which consisted of 100 mm line with extremes labeled "no nausea" (0 mm) and "nausea as bad as it can be" (100 mm) with no intermediate markings. Patients were asked to mark the position along the scale that indicated the maximum degree of nausea he/she had experienced over a specified portion of the study period. A VAS score of <5mm was retrospectively established as a definition of "no nausea."

C. **Study MCPR0044**

1. **Description of Design**

This trial was a randomized, double-blind, placebo-controlled, multicenter study conducted in the U.S. This study was stratified by gender within each study site.

The study objective was to assess the efficacy of a range of doses of intravenous dolasetron mesylate in terminating nausea and vomiting in patients who have just undergone outpatient surgery under general anesthesia.

Patients scheduled for outpatient surgery were randomized and

stratified by gender within each study site to study medication after an emetic episode or moderate to severe nausea of at least 5 minutes duration.

Patients having ASA physical status class 1, 2 or 3 and complaining of postoperative nausea (lasting for ≥5 minutes and reported as moderate to severe by the patient) or developing ≥1 emetic episode within 2 hours after arriving in the recover room were eligible.

Patient received dolasetron (12.5 mg, 25 mg, 50 mg, or 100 mg) or placebo, administered intravenously over 30 seconds to 5 minutes.

Postdose nausea VAS scores were collected at hours, 0.5, 1, 1.5, 2, at discharge, upon arrival at home, and hour 24.

This protocol was designed to detect a difference between the dose of dolasetron mesylate with the highest complete response rate and placebo while controlling for multiple comparisons.

2. **Sponsor's Analysis**

A total of 620 patients were enrolled in this study. One hundred twenty-one (121) patients received placebo, 130 patients received 12.5 mg , 119 patients received 25 mg, 124 patients received 50 mg, and 126 patients received 100 mg of dolasetron mesylate.

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in Table 1.

As seen from Table 1, the five treatment groups were comparable with respect to gender, race, height, weight, ASA status, history of PONV, type of surgery, duration of anesthesia, and time between cessation of anesthesia and study drug administration. An imbalance in mean age among the dose groups was detected. The 100 mg group had a slightly older population with a mean age of 36.1 years vs mean ages of 32.2 to 33.5 years in the other dose groups. This imbalance in age is not going to impact the efficacy results.

2.2 Sponsor's Analysis of Primary Efficacy Parameter

The primary efficacy endpoint was "complete response." Complete response was achieved when a patient experienced no emetic episode, received no escape medication, and was monitored for at least 23.5 hours after study drug administration.

There was a statistically significant dose by gender interaction. The complete response rate in the placebo group was 8% (8/102) for females vs 26% (5/19) for males. The 12.5 mg dose group had the highest complete response rate among female (36%, 39/107), while the 100 mg dose group had the highest complete response rate among males (64%, 14/22). The relatively small number of male patients precludes a definitive conclusion for the male subgroup.

The summary of the sponsor's analysis results for the complete response is given below.

Protocol MCPR0044
Complete Response by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo
placebo	13/121(11%)	
Dolasetron 12.5	46/130(35%)	<0.001*
Dolasetron 25	33/119(28%)	0.0007*
Dolasetron 50	36/124(29%)	0.0003*
Dolasetron 100	37/126(29%)	0.0005*

P-values were calculate from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose, gender and investigator as explanatory variables.
* significant at 0.05 level when controlling for 4 multiple comparisons to placebo using Dunnett's procedure.
Copied from Table 8-76, S8-v1.49-p133.

Each dolasetron mesylate dose showed a significantly higher complete response rate than placebo, after controlling for the statistically significant dose by gender interaction. When adjusted for multiple comparisons using Dunnett's procedure, all dolasetron mesylate dose groups were still significantly

different from placebo.

The results from this study indicate that a dose of 12.5 mg dolasetron mesylate was statistically superior to placebo for complete response and that higher doses did not confer any greater efficacy.

2.3 Sponsor's Analysis of Secondary Efficacy Parameter

Secondary efficacy results are derived from patient assessments of nausea severity using a visual analog scale (VAS). An analysis of no nausea in the postdose maximum VAS score was performed, where no nausea was defined retrospectively as a postdose maximum VAS score less than 5 mm.

The summary of the sponsor's analysis results for no nausea is given below.

Protocol MCPR0044
No Nausea by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo
placebo	6/121(5%)	
Dolasetron 12.5	8/130(6%)	0.4635
Dolasetron 25	14/119(12%)	0.0416
Dolasetron 50	14/123(11%)	0.0572
Dolasetron 100	16/125(13%)	0.0261

No nausea was defined as a postdose maximum VAS score less than 5 mm.
P-values were calculate from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose, gender and investigator as explanatory variables.
* significant at 0.05 level when controlling for 4 multiple comparisons to placebo using Dunnett's procedure.
Copied from Table 8-79, S8-v1.49-p137.

As seen from Table above, dolasetron mesylate 25 mg and 100 mg dose groups were statistically significantly different from placebo at 0.05 level. However, when adjusted for multiple comparisons using Dunnett's procedure, dolasetron mesylate 25 mg and 100 mg dose groups were not statistically significantly different from placebo.

The most frequently occurring adverse events were sinus bradycardia, headache, T-wave change or abnormality, and sinus arrhythmia.

3. Reviewer's Evaluation and Comments

3.1 Sponsor's Sample Size Determination

This study was designed to detect a difference between the dose of dolasetron mesylate with the highest complete response rate and placebo while controlling for multiple comparisons.

Due to insufficient sample size, there is not enough power to detect the differences among 12.5 mg, 25 mg, 50 mg and 100 mg dose groups.

3.2 Reviewer's Comments on Sponsor's Results for the Primary Efficacy Variable

This reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The results are given in Table 2.

As seen from Table 2, the results by Fisher's exact test are similar to those given by the sponsor using logistic regression method in terms of significance.

3.3 Reviewer's Comments on Sponsor's Results for the Secondary Efficacy Variable

The sponsor did not analyze two commonly used secondary efficacy variables: complete-or-major response and complete response with no nausea. Furthermore, the efficacy endpoint of complete response with no nausea is more stringent than complete response.

This reviewer has performed the analyses of these two secondary endpoints and the results are given in the next two sections.

3.3.1 Complete-Plus-Major Response

Major response was achieved when the patient experienced one episode, received no escape medication, and was monitored for at least 23.5 hours after study drug administration.

The summary of results of analysis of complete-plus-major response is given below.

Protocol MCPR0044
Complete-Plus-Major Response by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo	p-value vs. 12.5	P-value vs. 25	p-value vs. 50
placebo	22/121(18%)				
Dola 12.5	56/130(43%)	<0.001*			
Dola 25	46/119(39%)	<0.001*	0.520		
Dola 50	51/124(41%)	<0.001*	0.800	0.697	
Dola 100	47/126(37%)	0.001*	0.374	0.895	0.605

P-values were calculate from Fisher's exact test
*statistically significant after adjusting for 4 comparisons to placebo using Hochberg's procedure.

As seen from Table above, all dolasetron mesylate dose groups were significantly different from placebo at 0.05 level. When adjusted for multiple comparisons using Hochberg's procedure, all dolasetron mesylate dose groups were still significantly different from placebo.

3.3.2 Complete Response with No Nausea

Postdose nausea VAS scores were collected at hours 0.5, 1, 1.5, 2, at discharge, upon arrival at home, and hour 24. Nausea VAS scores for the postdose maximum are provided in the submission.

Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes, received no escape medication, was monitored for at least 23.5 hours after initiation of test drug, and had postdose nausea maximum VAS score less than 5 mm.

The summary of results of analysis of complete response with no nausea is given below.

Protocol MCPR0044
Complete Response with No Nausea by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo	p-value vs. 12.5	P-value vs. 25	p-value vs. 50
placebo	3/121(2%)				
Dola 12.5	7/130(5%)	0.337			
Dola 25	12/119(10%)	0.017	0.232		
Dola 50	9/124(7%)	0.136	0.611	0.498	
Dola 100	7/126(6%)	0.335	1.000	0.234	0.615

No nausea was defined as a postdose maximum VAS score less than 5 mm.
P-values were calculate from Fisher's exact test

As seen from Table above, only dolasetron 25 mg dose group was statistically significantly different from placebo at 0.05 level. However, when adjusted for multiple comparisons using Hochberg's procedure, dolasetron mesylate 25 mg dose was not statistically significantly different from placebo.

D. **Study 73147-2-S-084**

1. **Description of Design**

This trial was a randomized, double-blind, placebo-controlled, multicenter (24 sites) study conducted in Europe.

The study objective was to assess the efficacy of a range of doses of intravenous dolasetron mesylate at terminating nausea and vomiting in patients who have just undergone surgery under general anesthesia.

Patients who had undergone surgery under general anesthesia and presented with early postoperative nausea or vomiting requiring antiemetic treatment were randomized to study medication.

Patients having ASA physical status class 1 or 2 and complaining of postoperative nausea (lasting for ≥10 min and reported as moderate to severe by the patient) or developing ≥1 emetic episode within 2 hours after arriving in the recover room were

eligible.

Dolasetron mesylate 12.5 mg , 25 mg , 50 mg, 100 mg, or placebo was administrated iv over 5 minutes.

Postdose nausea visual analog scale (VAS) scores were collected every hour while awake during the first 8 hours after study drug administration.

This protocol was designed to detect a difference between the combined dolasetron mesylate doses and placebo.

Assuming the global incidence of complete responders is 50% under placebo and 80% under dolasetron and type I and II errors is respectively 0.05 and 0.20, a sample size of 50 patients per group was chosen.

2. **Sponsor's Analysis**

A total of 337 patients presented with early postoperative nausea and vomiting were randomized to treatment. Seventy-one (71) patients received placebo, 66 received dolasetron 12.5 mg, 65 received dolasetron 25 mg, 67 received dolasetron 50 mg, and 68 received dolasetron 100 mg.

2.1 **Treatment Group Comparability**

The summary of results of comparability of treatment groups at baseline is given in Table 3.

As seen from Table 3, there were no significant differences among the five dose groups with respect to gender, age, height, weight, ASA status, history of PONV, type of surgery, duration of anesthesia, and time between cessation of anesthesia and study drug administration.

2.2 **Sponsor's Analysis of Primary Efficacy Parameter**

The primary efficacy endpoint was "complete response." Complete response was achieved when a patient experienced no emetic episode, received no escape medication, and was monitored for at least 23.5 hours after study drug administration.

The summary of the sponsor's analysis results for the complete response is given below.

Protocol 73147-2-S-084
Complete Response by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo
placebo	8/71 (11%)	
Dolasetron 12.5	16/66 (24%)	0.0428
Dolasetron 25	18/65 (28%)	0.0094*
Dolasetron 50	25/67 (37%)	0.0005*
Dolasetron 100	17/68 (25%)	0.0388

p=0.0114 for test for linear trend.
P-values were calculate from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.
* significant at 0.05 level when controlling for 4 multiple comparisons to placebo using Dunnett's procedure.
Copied from Table 15, S8-V1.500-p107.

The proportion of complete responders in the placebo group (11%, 8/71) was significantly less than the proportion of complete responders in all dolasetron mesylate dose groups combined (29%, 76/266) (p=0.003).

There was a significant overall linear dose effect including placebo with respect to complete response, but the dose response for dolasetron doses appeared flat.

All dolasetron mesylate dose groups were significantly different from placebo at 0.05 level. However, when adjusted for multiple comparisons using Dunnett's procedure, only the 25 mg and 50 mg dose groups were significantly different from placebo.

2.3 Sponsor's Analysis of Secondary Efficacy Parameter

Secondary efficacy results are derived from patient assessment of nausea severity using a visual analog scale (VAS). An analysis of no nausea in the postdose maximum VAS score was performed, where no nausea was defined retrospectively as a postdose maximum VAS

score less than 5 mm.

The summary of the sponsor's analysis results for no nausea is given below.

Protocol 73147-2-S-084
No Nausea by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo
placebo	8/71 (11%)	
Dolasetron 12.5	19/66 (29%)	0.0125
Dolasetron 25	16/65 (25%)	0.0459
Dolasetron 50	15/67 (22%)	0.0849
Dolasetron 100	17/68 (25%)	0.0393

No nausea was defined as a postdose maximum VAS score less than 5 mm.
P-values were calculate from a contrast of the parameter estimates for dose obtained from a logistic regression model predicting complete response with dose and investigator as explanatory variables.
* significant at 0.05 level when controlling for 4 multiple comparisons to placebo using Dunnett's procedure.
Copied from Table 8-78, S8-V1.49-p136.

As seen from Table above, all dolasetron mesylate dose groups except 50 mg dose group were statistically significantly different from placebo at 0.05 level. However, when adjusted for multiple comparisons using Dunnett's procedure, all dolasetron mesylate dose groups were not statistically significantly different from placebo.

The difference from placebo (11%, 8/71) was statistically significantly different for all dolasetron mesylate groups combined (25%, 67/266) ($p<0.05$).

The most frequently reported adverse event was headache.

3. Reviewer's Evaluation and Comments

3.1 Sponsor's Sample Size Determination

This study was designed to detect a difference between the combined dolasetron mesylate doses and placebo. The sample size

might be insufficient to detect the differences among 12.5 mg, 25 mg, 50 mg and 100 mg dose groups.

3.2 Reviewer's Comments on Sponsor's Results for the Primary Efficacy Variable

This reviewer performed an alternative analysis using Fisher's exact test for pairwise comparison among dose groups. The results are given in Table 4.

As seen from Table 4, the results by Fisher's exact test are similar to those given by the sponsor using logistic regression method in terms of significance at 0.05 level for all dolasetron mesylate dose groups except 12.5 dose group. But, contrary to sponsor's finding, when adjusted for multiple comparisons using Hochberg's procedure, only dolasetron mesylate 50 mg group was statistically significantly different from placebo.

3.3 Reviewer's Comments on Sponsor's Results for the Secondary Efficacy Variable

The sponsor did not analyze two commonly used secondary efficacy variables: complete-or-major response and complete response with no nausea. Furthermore, the efficacy endpoint of complete response with no nausea is more stringent than complete response.

This reviewer has performed the analyses of these two secondary endpoints and the results are given in the next two sections.

3.3.1 Complete-Plus-Major Response

Major response was achieved when the patient experienced one episode, received no escape medication, and was monitored for at least 23.5 hours after study drug administration.

The summary of results of analysis of complete-plus-major response is given below.

Protocol 73147-2-S-084
Complete-Plus-Major Response by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo	p-value vs. 12.5	P-value vs. 25	p-value vs. 50
placebo	17/71 (24%)				
Dola 12.5	25/66 (38%)	0.096			
Dola 25	30/65 (46%)	0.007*	0.379		
Dola 50	36/67 (54%)	<0.001*	0.082	0.486	
Dola 100	28/68 (41%)	0.045	0.727	0.603	0.169

P-values were calculate from Fisher's exact test
*Statistical significance after adjusting for 4 comparisons to placebo using Hochberg's procedure.

As seen from Table above, all dolasetron mesylate dose groups except 12.5 mg dose group were significantly different from placebo at 0.05 level. When adjusted for multiple comparisons using Hochberg's procedure, both dolasetron mesylate 25 mg and 50 mg groups were statistically significantly different from placebo.

The difference from placebo (24%, 17/71) was statistically significantly different for all dolasetron mesylate groups combined (45%, 119/266)(p=0.002).

3.3.1 Complete Response with No Nausea

Nausea VAS scores for the postdose maximum over the 8 hours after study drug administration are provided in the submission.

Complete response with no nausea was achieved for a patient when he or she experienced no emetic episodes, received no escape medication, was monitored for at least 23.5 hours after initiation of test drug, and had postdose nausea maximum VAS score less than 5 mm.

The summary of results of analysis of complete response with no nausea is given below.

Protocol 73147-2-S-084
Complete Response with No Nausea by Treatment
(Intent-to-Treat Analysis)

Dose (mg)	Rate	P-value vs. Placebo	p-value vs. 12.5	P-value vs. 25	p-value vs. 50
placebo	5/71 (7%)				
Dola 12.5	10/66 (15%)	0.173			
Dola 25	8/65 (12%)	0.385	0.800		
Dola 50	10/67 (15%)	0.175	1.000	0.801	
Dola 100	11/68 (16%)	0.114	1.000	o.623	1.000

No nausea was defined as a postdose maximum VAS score less than 5 mm.
P-values were calculate from Fisher's exact test
Compiled by this reviewer from S8-v1.49-p189-197 and p214-222.

As seen from Table above, all dolasetron mesylate dose groups were not statistically significantly different from placebo.

The difference from placebo (7%, 5/71) was not statistically significantly different for all dolasetron mesylate groups combined (15%, 39/266)(p=0.112).

E. **Overall Summary and Recommendation**

Primary Endpoint: Complete Response

Both studies (MCPR0044 and 73147-2-S-084) showed that there was a significant overall treatment effect for the "complete response" endpoint. For this endpoint, the highest observed complete response rates were achieved for the 12.5 mg dose in study MCPR0044 and for the 50 mg dose in study 73147-2-S-084.

Study MCPR0044 showed that all dolasetron mesylate dose groups were statistically significantly better than placebo. Study 73147-2-S-084 showed the 50 mg dose group was statistically significantly more effective than placebo.

Secondary Endpoint: Complete Response with No Nausea

For more stringent efficacy measure suggested by FDA, only study MCPR0044 showed that the 25 mg dose was statistically

significantly more effective than placebo.

The study 73147-2-S-084 showed that the difference from placebo was not statistically significantly different for all dolasetron mesylate groups combined. All dolasetron mesylate dose groups were not statistically significantly different from placebo.

In these studies (MCPR0044, 73137-2-S-084), there is not enough power to detect the differences among 12.5 mg, 25 mg, 50 mg, and 100 mg dose groups due to insufficient sample size.

It is very difficult to choose the appropriate effective dose among 12.5 mg, 25 mg and 50 mg dose groups as seen in the table below. There were inconsistent results to recommend a specific dose.

Study	Endpoint	Dol 12.5	Dol 25	Dol 50	Dol 25 - Dol 12.5	Dol 50 - Dol 25
MCPR0044	Complete response	35%	28%	29%	-7%	1%
	Complete plus major response	43%	39%	41%	-4%	2%
	Complete response with no nausea	5%	10%	7%	5%	-3%
73147-2-S-084	Complete response	24%	28%	37%	4%	9%
	Complete plus major response	38%	46%	54%	8%	8%
	Complete response with no nausea	15%	12%	15%	-3%	3%

In terms of complete response and complete-plus-major response, the 50 mg dose group was shown statistically significantly better

than the placebo by both studies (MCPR0044 and 73147-2-S-084). However, there were inconsistent results in favor of 50 mg against 25 mg in terms of more stringent endpoint: complete response with no nausea.

There were a few male patients who were recruited into these two studies (17%, 106/620 for MCPR0044, and 5%, 18/337 for 73147-2-S-084). The gender issues need to be resolved.

There is a need for a third study to determine whether the lower dose 12.5 mg or higher dose 50 mg is the optimal effective dose. However, two studies (MCPR004 and 73147-2-S-084) show an overall effect of dolasetron mesylate injection for the treatment of postoperative nausea and vomiting with regard to the prespecified defined primary endpoint.

F. Comments to be conveyed to the Sponsor

The contents of Section of E may be conveyed to the sponsor.

/S/

Milton C. Fan, Ph.D.
Mathematical Statistician

This review consists of 16 pages of text and 4 pages of tables.

concur: Dr. Huque /S/ 1/14/97
Dr. Smith /S/ 1/17/97

cc:
Archival NDA 20-624
HFD-180
HFD-180/Dr. Fredd
HFD-180/Dr. Gallo-Torres
HFD-180/Ms. Johnson
HFD-344/Dr. Lisook
HFD-720
HFD-720/Chron. copy
HFD-720/Dr. Smith
HFD-720/Dr. Huque
HFD-720/Dr. Fan
Dr. Fan/x73088/mcf/01/13/97

Table 1 Comparability of Treatment Groups at Baseline — Protocol MCPR0044

		Intent-to-Treat Population					
Variable	Level	Placebo (n=121)	Dolasetron 12.5 mg (n=130)	Dolasetron 25 mg (n=119)	Dolasetron 50 mg (n=124)	Dolasetron 100 mg (n=126)	Between treatment p-value
Sex	Male	19 (16%)	23 (18%)	19 (16%)	23 (19%)	22 (18%)	0.9734
	Female	102 (84%)	107 (82%)	100 (84%)	101 (82%)	104 (83%)	
Age (mean)		32.6	32.8	32.2	33.5	36.1	0.0180
Height (cm) (mean)		166.7	165.7	165.8	166.4	165.9	0.6425
Weight (kg) (mean)		71.3	72.0	74.1	73.9	72.7	0.6665
Race	White	95 (79%)	103 (79%)	88 (74%)	97 (78%)	97 (77%)	0.967
	Black	20 (17%)	19 (15%)	20 (17%)	22 (18%)	21 (17%)	
	Hispanic	6 (5%)	7 (5%)	10 (8%)	4 (3%)	7 (6%)	
	Other	0 (0%)	1 (1%)	1 (1%)	1 (1%)	1 (1%)	
ASA	Status 1	72 (60%)	76 (59%)	76 (64%)	72 (58%)	73 (58%)	0.802
	Status 2	47 (39%)	50 (39%)	41 (35%)	51 (41%)	48 (38%)	
	Status 3	2 (2%)	4 (3%)	2 (2%)	1 (1%)	5 (4%)	
History of PONV		40 (33%)	39 (30%)	43 (36%)	43 (35%)	40 (32%)	0.7925
Type of Surgery	Gyn. surgery	52 (43%)	63 (49%)	61 (51%)	60 (48%)	63 (50%)	0.929
	Orthopedic	29 (24%)	24 (19%)	24 (20%)	24 (19%)	22 (18%)	
	Other	40 (33%)	43 (33%)	34 (29%)	40 (32%)	41 (33%)	
Duration of Anesthesia (hrs) (mean)		1.26	1.32	1.32	1.33	1.30	0.9639
Time between Cessation of Anesthesia and Study Drug Administration (hrs) (mean)		0.89	0.89	0.90	0.88	0.92	0.9901

For continuous variables, p-values are calculated from a three-way anova among the five doses controlling for investigator and gender. For binary variables, p-values are from a 4 degree of freedom chi-square test from a logistic regression model controlling for investigator and gender. For other categorical variables, p values are from a 4-degree of freedom chi-square test calculated from a Cochran-Mantel-Haenszel Row Mean Scores analysis.
Copied from Table 8-71, S8-V1.49-p126.

Table 2 Reviewer's Re-analysis of Complete Response — Protocol MCPR0044

Analysis	Treatment	Rate	vs. placebo p-value	vs. 12.5 mg p-value	vs. 25 mg p-value	vs. 50 mg p-value
ITT	Placebo	13/121 (11%)				
	Dolasetron 12.5 mg	46/130 (35%)	<0.001*			
	Dolasetron 25 mg	33/119 (28%)	<0.001*	0.221		
	Dolasetron 50 mg	36/124 (29%)	<0.001*	0.287	0.887	
	Dolasetron 100 mg	37/126 (29%)	<0.001*	0.350	0.888	1.000
Evaluable	Placebo	13/116 (11%)				
	Dolasetron 12.5 mg	43/121 (36%)	<0.001*			
	Dolasetron 25 mg	29/106 (27%)	0.003*	0.201		
	Dolasetron 50 mg	32/114 (28%)	0.001*	0.263	1.000	
	Dolasetron 100 mg	34/119 (29%)	0.001*	0.270	0.882	1.000

P-values are obtained by Fisher's exact test.
*Statistical significance after adjusting for 4 comparisons to placebo using Hochberg's procedure

Table 4 Reviewer's Re-analysis of Complete Response — Protocol 73147-2-S-084

Analysis	Treatment	Rate	vs. placebo p-value	vs. 12.5 mg p-value	vs. 25 mg p-value	vs. 50 mg p-value
ITT	Placebo	8/71 (11%)				
	Dolasetron 12.5 mg	16/66 (24%)	0.071			
	Dolasetron 25 mg	18/65 (28%)	0.017	0.694		
	Dolasetron 50 mg	25/67 (37%)	<0.001*	0.133	0.269	
	Dolasetron 100 mg	17/68 (25%)	0.026	1.000	0.844	0.140
Evaluable	Placebo	8/70 (11%)				
	Dolasetron 12.5 mg	15/65 (23%)	0.108			
	Dolasetron 25 mg	18/65 (28%)	0.028	0.687		
	Dolasetron 50 mg	23/65 (35%)	0.001*	0.177	0.450	
	Dolasetron 100 mg	17/66 (26%)	0.045	0.839	0.845	0.259

P-values are obtained by Fisher's exact test.
P=0.003 placebo vs. all dosetron mesylate dose groups combined for ITT analysis.
P=0.004 placebo vs. all dosetron mesylate dose groups combined for evaluable analysis.
*Statistical significant after adjusting for 4 comparisons to placebo using Hochberg's procedure.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020624

MICROBIOLOGY REVIEW(S)

Johnson

MAY - 3 1996

REVIEW FOR HFD-180
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF HFD-805

Microbiologist's Review # 1 of NDA 20-624
April 30, 1996

A. 1. APPLICATION NUMBER: 20-624

APPLICANT: Marion Hoechst Roussel, Inc.
10236 Marion Park Drive
Kansas City, Missouri 64134

2. PRODUCT NAMES: Anzemet (dolasetron mesylate) Injection

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 20 mg/ml, sterile drug solution for intravenous use. It is packaged for single-use in ampule or vial containing 12.5, 100, or 200 mg of dolasetron mesylate.

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, and for the prevention and treatment of postoperative nausea and vomiting.

6. DRUG PRIORITY CLASSIFICATION: 1S

B. 1. DATE OF INITIAL SUBMISSION: February 19, 1996

2. AMENDMENT: none

3. RELATED DOCUMENTS: NDA 20-623

4. RECEIVED FOR REVIEW: March 12, 1996

5. DATE OF CONSULT REQUEST: February 27, 1996

C. REMARKS:

Anzemet (dolasetron mesylate) Injection, a single use parenteral formulation, is packaged in vial or ampule in a concentration of 20 mg/ml

The commercial product will be manufactured at Ben Venue Laboratories Inc. in Bedford, Ohio

D. CONCLUSIONS:

The heat sterilization data of the drug product are adequate for sterility assurance. The submission is recommended for approval for issues concerning microbiology.

APPEARS THIS WAY ON ORIGINAL

/S/

4/30/96

Brenda Uratani, Ph.D.

5/3/96

cc:

/S/

NDA 20-624
HFD-180 / Div. File
HFD-805 /Uratani
HFD-150 /CSO/K. Johnson
drafted by: Brenda Uratani, 4/30/96
R/D initialed by P.Cooney, 4/30/96

APPEARS THIS WAY ON ORIGINAL