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USAGE T	00'59
PGS. SENT	4
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 23, 2003

To: Charlene G. Sanders, M.D.	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	**Fax number:** (301) 443-9285
Phone number: (484) 344-2850	**Phone number:** (301) 827-7310

Subject: Comments and Recommendations Regarding the draft Advisory Committee Background Information for NDA 21-549 dated January 15, 2003

Total no. of pages including cover: 2

Comments:

Please note the following comments and recommendations.

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 23, 2003

To: Charlene G. Sanders, M.D.	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	**Fax number:** (301) 443-9285
Phone number: (484) 344-2850	**Phone number:** (301) 827-7310

Subject: Clinical Information Request Regarding NDA 21-549

Total no. of pages including cover: 2

Comments:

Please respond to the attached information request regarding NDA 21-549 ASAP. Thanks

Document to be mailed: ☐ YES ☑ NO

Docetaxel	Aprepitant Regimen	Standard Therapy
≥ 100mg/m^2	n/N	n/N
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
(more)		
≥75mg/m^2 (<100mg/m^2)	n/N	n/N
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
(more)		
<75mg/m^2	n/N	n/N
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
(more)		

1) Create a similar table for each of the concomitant chemotherapeutic agents utilized during the trials. Use dose ranges that reflect High, Moderate, and Low dose administration. Include pre-specified adverse events of interest and serious adverse events.

2) Analyze by treatment group the extent to which randomized patients were exposed to ondansetron for Studies 052 and 054.

The example below does not identify if the use of ondansetron was balanced.

"Adult Patients—Both Treatment Groups The extent to which randomized adult patients (N=526) were exposed to ondansetron is presented in Table 71. The range of days on ondansetron was between 1 to 6 days and the mean number of days on this drug was 2.7 days. Of the 526 randomized adult patients who received ondansetron, 151 patients received this drug for >3 days (Table 71) [4.2]."

3. Account for the differences in Liver Function Studies between the results in the tables submitted on January 8, 2003 and the tables submitted in the original NDA for Studies 052 and 054. (The first two tables below were submitted January 8, 2003 and the third was submitted with the original NDA.)

   Include Bilirubin in this analysis.

TABLE 2: Protocol 054
Number (and Percent) of Patients with
ALT > 2.5 ULN

	Aprepitant	Standard Therapy	Comparison: Aprepitant vs Standard Therapy
Day 6 - 8	14/256 (5.5%)	18/254 (7.1%)	p=0.47
Day 19 - 29	5/245 (2.0%)	9/255 (3.5%)	p=0.42

Number (and Percent) of Patients with
AST > 2.5 ULN

	Aprepitant	Standard Therapy	Comparison: Aprepitant vs Standard Therapy
Day 6 - 8	5/251 (2.0%)	4/251 (1.6%)	p=0.99
Day 19 - 29	1/243 (0.4%)	5/253 (2.0%)	p=0.22

Number (%) of Patients With Specific Laboratory Adverse Experiences (Incidence ≥2% in One or More Treatment Groups) by Laboratory Test Category—Cycle 1

	MK-0869 Regimen (N=283)		Standard Therapy (N=285)†	
	n/m	(%)	n/m	(%)
Patients with one or more adverse experiences	83/281	(29.5)	71/282	(25.2)
Patients with no adverse experience	198/281	(70.5)	211/282	(74.8)
Blood Chemistry	**54/280**	**(19.3)**	**41/282**	**(14.5)**
Alanine aminotransferase increased	27/280	(9.6)	17/281	(6.0)
Alkaline phosphatase increased	10/280	(3.6)	1/281	(0.4)
Aspartate aminotransferase increased	14/279	(5.0)	5/282	(1.8)
Blood urea nitrogen increased	19/280	(6.8)	14/281	(5.0)
Hyponatremia	7/280	(2.5)	3/281	(1.1)
Serum creatinine increased	15/280	(5.4)	17/281	(6.0)
Uric acid increased	1/2	(50.0)	0/2	(0.0)
Hematology	**14/280**	**(5.0)**	**22/280**	**(7.9)**
Leukocytes decreased	3/280	(1.1)	6/280	(2.1)
Neutrophils decreased	3/280	(1.1)	10/280	(3.6)
Platelets decreased	4/271	(1.5)	6/275	(2.2)
Prothrombin time decreased	0/2	(0.0)	1/1	(100.0)
Urinalysis	**36/280**	**(12.9)**	**28/281**	**(10.0)**
Proteinuria	32/280	(11.4)	25/280	(8.9)

4. In a separate table, list patient's ID number and all LFTs for baseline, day 6-8 and 19-29.

5. Generate a table similar to Table 80 in Study 052 that is broken down by chemotherapeutic agent to help assess the safety profile with each chemotherapeutic agent.

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/s/

Brian Strongin
1/23/03 11:43:18 AM
CSO

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PGS. SENT	4
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 23, 2003

To: Charlene G. Sanders, M.D.	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	**Fax number:** (301) 443-9285
Phone number: (484) 344-2850	**Phone number:** (301) 827-7310

Subject: Clinical Information Request Regarding NDA 21-549

Total no. of pages including cover: 2

Comments:

Please respond to the attached information request regarding NDA 21-549 ASAP. Thanks

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: January 3, 2003

To: Charlene G. Sanders, M.D.	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	**Fax number:** (301) 443-9285
Phone number: (484) 344-2850	**Phone number:** (301) 827-7310

Subject: Clinical Information Request for NDA 21-549: Emend

Total no. of pages including cover: 2

Comments:

Please note the following information request and respond ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

Regarding Studies 052 and 054:

For each study, provide a statistical comparison of patients in both treatment groups that developed elevated liver function tests (LFT) after admission to the studies. Please use the protocol-specified Exclusion Criteria to determine LFT elevation (Aspartate transaminase > 2.5 x upper limit of normal and Alanine transaminase > 2.5 x upper limit of normal).

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/s/

Brian Strongin
1/3/03 09:52:00 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: December 3, 2002

To: Charlene G. Sanders, M.D.	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	**Fax number:** (301) 443-9285
Phone number: (484) 344-2850	**Phone number:** (301) 827-7310

Subject: Chemistry, Manufacturing, and Controls Recommendation and Information Request

Total no. of pages including cover: 2

Comments:

Please note the following recommendation and information request and respond ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

• One of the capsule manufacturers, —— is currently not compliant with cGMP requirements. We recommend that this manufacturing site be removed from consideration for the current NDA review cycle or it may impact the Agency's regulatory action.

• All of the drug product manufacturing data submitted with the original NDA derives from Merck R&D in West Point, PA. No data has been submitted for manufacturing at the anticipated commercial site in —— Due to the very low aqueous solubility of aprepitant, the manufacturing formulation steps require careful controls to make sure that the —— drug substance will disperse properly when swallowed. This could adversely affect drug substance bioavailability.

Evidence of successful technology transfer to the new site should be submitted during the current review cycle. This can consist of either of the following:

1. Release testing for three batches made at the new site, or,

2. Three months accelerated stability data on one batch manufactured at the new site.

Adequate time for FDA review of the new data should be allowed, or a due date extension may be imposed.

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/s/

Brian Strongin
12/4/02 08:22:26 AM
CSO

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PGS. SENT	2
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: December 3, 2002

To: Charlene G. Sanders, M.D.	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	**Fax number:** (301) 443-9285
Phone number: (484) 344-2850	**Phone number:** (301) 827-7310

Subject: Chemistry, Manufacturing, and Controls Recommendation and Information Request

Total no. of pages including cover: 2

Comments:

Please note the following recommendation and information request and respond ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: November 8, 2002

To: Charlene G. Sanders, M.D.	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	**Fax number:** (301) 443-9285
Phone number: (484) 344-2850	**Phone number:** (301) 827-7310
Subject: Statistical and pharm/tox information requests	
Total no. of pages including cover: 2	

Comments:

Please respond to the following information requests ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

Statistical

Please provide the following information for both Studies P052 and P054 or provide its location in the submission.

I. Provide the following data (Cycle 1) for both the modified-intent-to-treat and per-protocol populations for Studies P052 and P054. Provide these data in electronic format consistent with the guidance, *Regulatory Submissions in Electronic Format; General Considerations* available on the CDER website. Include the following variables:

Study number;
Investigator or Center code;
Region;
Patient discounted (yes or no);
Patient number/name;
Treatment name;
Population type (modified-intent-to-treat or per-protocol populations);
Use of concomitant chemotherapy (yes or no);
Gender;
Age;
Race;
Weight;
Complete Response in overall phase (success or failure);
Complete Response in acute phase (success or failure);
Complete Response in delayed phase (success or failure);
FLIE total scores;
Impact of CINV on daily life (yes or no);

II. Please perform the statistical efficacy analyses used to generate Table 39 and Table 46 respectively, at pages 157 and 168 of Volume 1.25. In your analysis, please replace region (US or non-US) with investigator.

To the data set described by item I, please add additional variables needed (but not included in the above data set) for the above analyses. Please also modify the programs to be able to input data from the data set described by I.

Pharm/Tox

You conducted three 2-year carcinogenicity studies with aprepitant (2 in rats and 1 in mice) and included the study reports in your application. However, you did not provide any historical control data for tumor incidences in mice and rats from your laboratory. Provide historical control data for tumor incidences in male and female CD-1 mice, and male and female Sprague Dawley rats from carcinogenicity studies conducted in your laboratory during the period of 1995 to 2000.

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/s/

Brian Strongin
11/8/02 01:45:28 PM
CSO

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*** TX REPORT ***
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USAGE T	00'47
PGS. SENT	3
RESULT	OK

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: November 8, 2002

To: Charlene G. Sanders, M.D.	**From:** Brian Strongin, R.Ph., M.B.A.
Company: Merck & Co., Inc.	Division of Division of Gastrointestinal & Coagulation Drug Products
Fax number: (484) 344-2516	**Fax number:** (301) 443-9285
Phone number: (484) 344-2850	**Phone number:** (301) 827-7310

Subject: Statistical and pharm/tox information requests

Total no. of pages including cover: 2

Comments:

Please respond to the following information requests ASAP. Thanks.

Document to be mailed: ☐ YES ☑ NO

MEMORANDUM OF TELECON

DATE: August 23, 2002

APPLICATION NUMBER: IND [redacted] MK-0869

BETWEEN:

Merck Research Laboratories (MRL)	Title
Charlene G. Sanders, M.D.	Director, Regulatory Affairs, Domestic
Dennis Erb, Ph. D.	Executive Director, Regulatory Affairs, Domestic
Susan Mattson	Assistant Council, Trademarks & Copyrights
Tom Hassall	Director, Regulatory Liaison, Global Regulatory Policy
Kevin Horgan, M.D.	Director, Clinical Research
Tom Simon, M.D.	Vice President, Clinical Research
Denise Booker	Sr. Regulatory Coordinator, Worldwide Regulatory Coordination

Phone: (484) 344-7318

AND

The Division of Gastrointestinal and Coagulation Drug Products Attendees (DGICDP)	Title
Joyce Korvick, M.D., M.Ph.	Deputy Director
Hugo Gallo-Torres, M.D., Ph.D., P.N.S.	Medical Team Leader, GI Drugs
Brian Strongin, R.Ph., M.B.A.	Project Manager

The Division of Medication Errors and Technical Support, Office of Drug Safety	Title
Carol Holquist, R.Ph.	Deputy Director
Denise Toyer	Team Leader, Safety Evaluators
Marci Lee, Pharm D.	Safety Evaluator

SUBJECT: MRL's June 25, 2002 Submission to IND [redacted] Requesting Reconsideration of the Proposed Tradename, Emend

Background

MRL is planning to submit an NDA for MK-0869, in September of this year. MK-0869 is an antiemetic for chemotherapy-induced nausea and vomiting and is to be used in conjunction with $5HT_3$ inhibitors (Zofran, Anzemet, or Kytril) and Dexamethasone. MRL claims that MK-0869 increases the complete response rate over dual therapy by approximately 10%. MRL has proposed the tradename, **Emend**. Their proposal was consulted to the Office of Postmarketing Drug Risk Assessment (OPDRA) late in 2000. OPDRA completed their review December 14, 2001.They had concerns about look-alike, sound-alike names for the products **Amen** and **Anu-Med**. DGICDP sent a letter January 29, 2002 conveying these concerns. MRL appealed the decision February 15, 2002. OPDRA completed their review of the appeal March 15, 2002 and reiterated their concerns about **Amen**. They explained that, although **Amen** is no longer marketed, it remains in references and generic versions are on the market. MRL was especially concerned about telephoned prescriptions since the names sound so alike. DGICDP sent a second letter in April 1, 2002. Merck submitted a second appeal on June 25, 2002. DMETS, as OPDRA is now called, completed their review of this appeal July 23, 2002 and provided an item-by-item reply to MRL's arguments in their June 25th submission. DMETS basically reiterated their previous arguments. Today's teleconference concerns this issue.

Today's Call

After introductions, MRL asked the Division and DMETS to elaborate on their concerns regarding the proposed tradename, Emend. DMETS explained that their main concern is the strong sound-alike similarity between Emend and the tradename, Amen (medroxyprogesterone 10 mg) Tablets. They expressed the concern that telephone orders for Emend may be miss-heard as Amen. Although Amen is no longer marketed, generic brands of Medroxyprogesterone 10 mg Tablets are available. Amen also still appears in several reference books commonly used by physicians and pharmacists. DMETS added that a similar situation existed with the tradenames **Evista** and **E-Vista**, where one product was no longer marketed but appeared in reference books. This situation contributed to medication errors.

DMETS explained that MRL proposes to market Emend in unit-of-use packages with complete directions for use on the packages. Although these packages will be helpful for patients, they will increase the likelihood of physicians ordering Emend without specifying the strengths or directions for use. Amen may also be ordered with directions only specifying "Use as directed". A possible scenario for a medication error involves a physician telephoning a prescription for Emend, specifying a number of unit-of-use packages with directions, "Use As Directed". The pharmacist, unfamiliar with the newer product, Emend, hears the more familiar name, Amen and dispenses Medroxyprogesterone 10mg Tablets.

MRL contended that the first dose of Emend will probably be taken in an outpatient chemotherapy clinic setting and that a healthcare professional at the clinic will monitor dosing. They also contended that, in their opinion, enough distinguishing factors exist between Amen

and Emend to make dispensing errors extremely unlikely. These factors include differences in strength, directions for use, indications, and types of physicians prescribing the medications. DMETS acknowledged the differences stated above, but reiterated that a reasonable possibility exists that directions for use and strength will not be included in the telephone prescription and the pharmacist may not be familiar with the prescribers' specialty.

MRL explained that a great deal of research and testing had been performed to choose the tradename, Emend. They added that it is registered in 120 other countries and is acceptable in many languages. They argued that any other tradename proposed must also be reviewed by DMETS and may have a greater chance for medication errors than Emend. MRL explained that Emend would be the subject of an extensive promotional campaign to familiarize healthcare professionals and patients with the product. DGICDP responded that they appreciate MRL's difficulties, but concerns with the proposed tradename still exist. The recommendation to not use the proposed tradename was reiterated. DGICDP added that, although Amen was no longer marketed, the possibility that the product would be reintroduced into the U.S. market does exist. DGICDP added that although the adverse effects of taking a dose of medroxyprogesterone incorrectly may not be great, the effects of missing a dose of an antiemetic before highly emetogenic chemotherapy could be devastating to the patient.

DGICDP acknowledged that the parties were not coming to an agreement on the issue and recommended submitting a formal appeal to the Director of the Office of Drug Evaluation III, Florence Houn, M.D. The Division explained that the appeal could proceed simultaneously with review of the NDA to be submitted in late September, 2002.

The call was then concluded.

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/s/

Brian Strongin
8/29/02 09:38:17 AM
CSO

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 24, 2003
TIME: 11:00AM
LOCATION: Parklawn Building, Potomac Conference Room
APPLICATION: NDA 21-549; Emend (aprepitant) Capsules
TYPE OF MEETING: Type C – Discussion of Merck's Draft Advisory Committee Background Information for the March 6, 2003 Gastrointestinal Drugs Advisory Committee Meeting

MEETING CHAIR: Hugo Gallo-Torres, M.D., Ph.D.

MEETING RECORDER: Brian Strongin, R.Ph., M.B.A.

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Division Name & HFD#
1.Robert Justice, M.D., M.S.	Director	Division of GI and Coagulation Drug Products, HFD-180
2.Joyce Korvick, M.D.	Deputy Director	Division of GI and Coagulation Drug Products, HFD-180
3.Hugo Gallo-Torres, M.D., Ph.D.	Medical Team Leader GI Drugs	Division of GI and Coagulation Drug Products, HFD-180
4. Gary Della'Zanna, D.O.	Medical Officer	Division of GI and Coagulation Drug Products, HFD-180
5. Ryan Barraco	Regulatory Health Project Manager	Division of GI and Coagulation Drug Products, HFD-180
6. Brian Strongin, R.Ph., M.B.A.	Regulatory Health Project Manager	Division of GI and Coagulation Drug Products, HFD-180
7. Tom Permutt, Ph.D.	Team Leader, Biometrics	Division of Biometrics II
8. Wen-Jen Chen, Ph.D.	Mathematical Statistician	Division of Biometrics II
9. Suresh Doddapaneni, Ph.D.	Team Leader, Clinical Pharmacology and Biopharmaceutics	Division of Pharmaceutical Evaluation II
10. Jarugula Venkateswa, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer	Division of Pharmaceutical Evaluation II
11. Myong-Jin Kim, Ph.D.	Clinical Pharmacology and Biopharmaceutics Reviewer	Division of Pharmaceutical Evaluation II

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Dr. Keith Gottesdiener	Clinical Pharmacology	Merck Research Laboratories, Inc.
2. Dr. Kevin Petty	Clinical Pharmacology	Merck Research Laboratories, Inc.
3. Dr. Kevin Horgan	Clinical Research	Merck Research Laboratories, Inc.
4. Dr. Francesca Lawson	Clinical Research	Merck Research Laboratories, Inc.
5. Dr. Scott Reines	Clinical Research	Merck Research Laboratories, Inc.
6. Dr. David C. Evans	Drug Metabolism	Merck Research Laboratories, Inc.
7. Dr. Anup Mauumdar	Drug Metabolism	Merck Research Laboratories, Inc.
8. Dr. Richard Hargreaves	Preclinical Pharmacology	Merck Research Laboratories, Inc.
9. Dr. Dennis Erb	Regulatory Affairs	Merck Research Laboratories, Inc.
10. Dr. Charlene G. Sanders	Regulatory Affairs	Merck Research Laboratories, Inc.
11. Dr. Brian White-Guay	Regulatory Affairs	Merck Research Laboratories, Inc.
12. Mr. Tom Hassall	Regulatory Agency Relations	Merck Research Laboratories, Inc.
13. Ms. Denise Booker	Regulatory Coordination	Merck Research Laboratories, Inc.
14. Dr. Alexandra Carides	Statistics	Merck Research Laboratories, Inc.
15. Dr. Al Getson	Statistics	Merck Research Laboratories, Inc.
16. Dr. Balasamy Thiyagarajan	Statistics	Merck Research Laboratories, Inc.

BACKGROUND:

NDA 21-549 for Emend Capsules was submitted September 27, 2002 for use in combination with other antiemetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin. This application will be the subject of discussion at the March 6, 2003 meeting of the Gastrointestinal Drugs Advisory Committee (GIDAC). In a submission dated January 6, 2003 Merck Research Laboratories, Inc. (MRL) requested a meeting to obtain Agency feedback concerning their GIDAC briefing document. In a submission dated January 15, 2003, MRL submitted their draft Advisory Committee Background Information.

MEETING OBJECTIVES:

To obtain the Agency's comments and recommendations regarding MRL's draft Advisory Committee Background Information dated January 15, 2003

DISCUSSION POINTS:

A. After introductions, discussion turned to MRL's questions. The questions are italicized below followed by the Division's responses in bold. (NOTE: the Division did not receive MRL's questions until January 23 and did not have time to prepare responses in advance.)

1. *As of the date of this correspondence, the Advisory Committee (AC) meeting to discuss NDA 21-549: EMEND has been scheduled for Thursday, March 6, 2003. It is our understanding that EMEND will be reviewed by the Gastrointestinal Advisory Committee.*

   a. *As this drug will be used in the setting of chemotherapy agents, does the Division plan to invite consultants to the Advisory Committee (voting or non-voting) with a background in oncology?*

   Yes.

   b. *Are there plans to include an industry representative on the Advisory Committee?*

   Yes.

   c. *When will the final list of Advisory Committee members and consultants be sent to us?*

   The final list of GIDAC members and consultants will be sent when the conflict of interest screening is finished and the ACS know who may participate in the meeting.

2. *The complete response endpoint was the primary endpoint for the Phase IIb and III*

studies. Complete response was also used as the primary endpoint for two out of four Phase IIa studies. The two remaining studies used a no emesis endpoint. For consistency and to facilitate the comparison between studies, complete response has been highlighted in the background package and in our presentation.

a. *Does the Division concur with this plan for presenting efficacy data with an emphasis on the complete response endpoint throughout both the AC briefing document and our main presentation?*

We have no objection to this plan.

3. *Aprepitant has a unique efficacy profile, which includes distinctive efficacy in the prevention of both acute and delayed symptoms, compared to the 5-HT$_3$ receptor antagonists. Thus, the primary endpoint for the Phase III program evaluates complete response over a 5-day interval (overall). We have also included analyses in the AC briefing document for the acute and delayed phases separately in support of our indication. We are also planning to include these analyses in our main presentation.*

a. *Does the Division concur with this approach to presentation of the efficacy data?*

While we generally agree with this approach, we will request the opinion of the GIDAC on this issue.

b. *What additional information, if any, do you believe would be helpful to the advisory committee regarding the efficacy profile of aprepitant?*

We suggest including a discussion of the nausea component with an analysis of nausea in patients that did not receive rescue therapy.

4. *The development program incorporated cisplatin as the benchmark for highly emetogenic chemotherapy. This benchmark has been used in the development program for other antimetic agents. We believe that data obtained for the program can be generalized to all highly emetogenic chemotherapy.*

a. *Does the Agency concur with this generalization?*

b. *What additional data would be helpful in supporting the generalization of cisplatin to all highly emetogenic chemotherapy?*

These questions will be posed to the GIDAC.

5. *As previously discussed with FDA, we have utilized the safety data from the Safety Update*

Report for the ACM briefing document and presentation. It will be important that we are discussing issues from the same database.

a. *Does the Agency also plan on utilizing the data from the Safety Update Report in its AC briefing document and presentation?*

Yes, we also plan to use these data.

6. *The information contained in the AC briefing document is a synopsis of the relevant information pertaining to the proposed indication and usage.*

   a. *Does the Division have any comments or concerns regarding our briefing document overall and with respect to the discussion of drug interactions and the approach to safety analysis with regards to chemotherapy regimens?*

   b. *Is there information that the Division would consider pertinent to the AC discussions, which is either not included or should be expanded in the briefing document?*

See the comments and recommendations that follow regarding the draft Advisory Committee Background Information.

7. *What does the Agency consider to be the key questions for the Advisory Committee?*

   a. *What will be the Division's position in their briefing document to the Advisory Committee meeting and what will be the timing of the release of the Agency's background material to the ACS?*

The Division's briefing document will be released to the public 14 business days prior to the GIDAC meeting.

   b. *When will the list of questions be shared with us?*

The list of questions will be provided within a few days of the GIDAC meeting.

8. *Our planned presentation will focus on the clinical efficacy, safety and drug interaction profile of aprepitant. We will also briefly discuss the pathophysiology of emesis as well as the non-clinical pharmacology, pharmacokinetics, and safety evaluation of aprepitant.*

   a. *What topics does the Division plan to address in your presentation?*

Our presentation will focus on the areas in which we need GIDAC input, such as drug-drug interactions with chemotherapeutic agents and various clinical issues

including a general discussion of the safety profile and the adequacy of the repeat-cycle efficacy data.

B. Additional Comments Regarding MRL's Draft Advisory Committee Background Information

The following comments and recommendations were provided regarding the draft Advisory Committee Background Information for NDA 21-549 dated January 15, 2003:

1. Regarding Table 37, page 120, we recommend splitting this table into individual tables for each chemotherapeutic agent. Include a list of specific Prespecified Adverse Events with incidences for each event. Also, list Serious Clinical Adverse Experiences separately with incidences for each. A suggested mock-up follows:

Docetaxel	Aprepitant Regimen	Standard Therapy
	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		

(NOTE: MRL promised to expand Table 37 as recommended.)

2. In addition, if the doses of concomitant chemotherapy are known, include tables of adverse events by dose of chemotherapeutic agent. Include Prespecified Adverse Events and Serious Adverse Experiences with incidences greater than 5%. A suggested mock-up follows.

Docetaxel	Aprepitant Regimen	Standard Therapy
≥ 100mg/m^2	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		
≥75mg/m^2 (<100mg/m^2)	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		
<75mg/m^2	n/N (%)	n/N (%)
Anemia		
Febrile Neutropenia		
Neutropenia		
Thrombocytopenia		
Serious Clinical Adverse Experiences (list)		

(NOTE: Although they may not be able to incorporate this change into the Background Document, MRL promised to try to provide this type of table for the Division's review and comment.)

3. Address why granisetron was the 5-HT$_3$ Inhibitor used in earlier Emend clinical trials and ondansetron was used in later clinical trials.

4. Include a discussion of the preclinical and clinical data supporting the statement that Emend has no QT$_c$ effects.

5. Change the phrase, "maximal protection" in the last sentence on page 96 to a protocol defined endpoint.

6. The following sentence appears on page 97: "The efficacy of the aprepitant regimen is unaffected by age, race, or gender." Clarify this statement to reflect that a gender effect was seen when Studies 052 and 054 were analyzed separately.

ACTION ITEMS:

The Agency and MRL will attempt to schedule a meeting in late February, 2003 to preview GIDAC presentations.

Minutes Preparer: *{See attached electronic signature page}*
Brian Strongin, R.Ph., M.B.A.

Chair Concurrence: *{See attached electronic signature page}*
Hugo Gallo-Torres, M.D., Ph.D.

Drafted by: BKS February 12, 2003
R/d init: HGT February 13, 2003
Finalized: BKS February 14, 2003
Emend GIDAC Briefing Document Minutes.doc

MEETING MINUTES

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Hugo Gallo Torres
2/19/03 11:29:46 AM

MEMORANDUM OF MEETING MINUTES

MEETING DATE: January 22, 2002
TIME: 2:30PM
LOCATION: Parklawn Building, Potomac Conference Room
APPLICATION: IND [redacted] MK-0869 Capsules
TYPE OF MEETING: Type B: Pre-NDA Meeting

MEETING CHAIR: Hugo Gallo-Torres, M.D., Ph.D.

MEETING RECORDER: Brian Strongin, R.Ph., M.B.A.

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION

Name of FDA Attendee	Title	Office/Division Name
1. Victor Raczkowski, M.D., M.Sc.	Acting Director	Division of Gastrointestinal and Coagulation Drug Products
2. Joyce Korvick, M.D.	Deputy Director	Division of Gastrointestinal and Coagulation Drug Products
3. Hugo Gallo-Torres M.D., Ph.D.	Medical Team Leader, GI Drugs	Division of Gastrointestinal and Coagulation Drug Products
4. Eric Duffy, Ph.D.	Director	Office of New Drug Chemistry II
5. Liang Zhou, Ph.D.	Team Leader, Chemistry, Manufacturing, and Controls	Division of Gastrointestinal and Coagulation Drug Products
6. Maria Ysern	Review Chemist	Division of Gastrointestinal and Coagulation Drug Products
7. Jasti Choudary, Ph.D., B.V.Sc.	Supervisory Pharmacologist	Division of Gastrointestinal and Coagulation Drug Products
8. Thomas Permutt, Ph.D.	Team Leader, Biometrics	Division of Biometrics II
9. Suliman Al-Fayoumi, Ph.D.	Biopharmaceutics Reviewer	Division of Pharmaceutical Evaluation II
10. Brian Strongin, R.Ph., M.B.A.	Regulatory Health Project Manager	Division of Gastrointestinal and Coagulation Drug Products

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

External Attendee	Title	Sponsor/Firm Name
1. Dr. Charli Sanders	Director, Regulatory Affairs	Merck Research Laboratories
2. Dr. Dennis Erb	Senior Director, Regulatory Affairs	Merck Research Laboratories
3. Mr. Tom Hassall	Director, Regulatory Liaison	Merck Research Laboratories
4. Dr. Scott Reines	VP Clinical Neuroscience & Ophthalmology – Clinical Research	Merck Research Laboratories
5. Dr. Kevin Horgan	Director, Clinical Research Clinical Neuroscience & Ophthalmology	Merck Research Laboratories
6. Dr. Tom Simon	VP Gastroenterology Clinical Research –Clinical Neuroscience & Ophthalmology	Merck Research Laboratories
7. Dr. Lee Chiu	Senior Director, Drug Metabolism	Merck Research Laboratories
8. Dr. Britta Mattson	Director, Compound Management – Safety Assessment	Merck Research Laboratories
9. Dr. Alexandria Carides	Senior Biometrician, Biostatistics & Research Data Systems	Merck Research Laboratories
10. Dr. Balasamy Thiyagarajan	Director, Clinical Biostatistics & Research Data Systems	Merck Research Laboratories
11. Ms. Lori Exley	Regulatory Scientist, Regulatory Analytical Sciences	Merck Research Laboratories
12. Dr. Kevin Petty	Director, Clinical Research – Clinical Pharmacology	Merck Research Laboratories
13. Dr. Anup Majumdar	Senior Research Fellow, Drug Metabolism	Merck Research Laboratories

BACKGROUND: IND [redacted] for MK-0869 was submitted April 9, 1996 by Merck Research Laboratories (MRL) to investigate MK-0869, an NK_1 receptor antagonist, for the prevention of chemotherapy-induced emesis.

An End-of-Phase 2 meeting was held April 14, 1999 and a follow-up meeting to discuss the clinical development program was held September 21, 2001.

MRL submitted a request for a pre-NDA meeting November 28, 2001. The background package was submitted January 4, 2002.

MEETING OBJECTIVES: Obtain agreement with the Agency on the proposed format for the MK-0869 NDA.

DISCUSSION POINTS:

1. After introductions and brief opening comments by Drs. Raczkowski and Gallo-Torres, discussion turned to MRL's questions included in their background package.

2. MRL's questions are italicized below, followed by the Division's responses in bold. Discussion, if any, concerning the response follows in parenthesis.

   Chemistry, Manufacturing, and Controls (CMC) Documentation

   a. *Does the proposed Table of Contents for Item 4 (Tab 4) fulfill the requirements for the Agency Reviewer(s)?*

      Yes, the Table of Contents appears to be acceptable.

   b. *Would the Division like to have a separate Chemistry meeting to review the manufacturing process in greater detail?*

      Yes. Please follow the recommendations in the Guidance for Industry, Formal Meetings with Sponsors and Applicants for PDUFA Products available on the CDER website.

      (NOTE: MRL stated that they would request a separate meeting to review the manufacturing process. In response to MRL's question, the Division stated that the CMC section may be submitted in the Common Technical Document for the Registration of Pharmaceuticals for Human Use format if MRL so desires. The Division added that, although a paper submission of the CMC section is preferred, an electronic submission is acceptable.)

   c. *Does the Agency concur that the inclusion of the tradename on the capsule post approval can be accomplished by a CBE submission?*

      We recommend continuing to seek approval of a tradename prior to NDA submission. If you seek to add a tradename to the drug product post-NDA approval, a prior approval supplement must be submitted if the proposed tradename has not been approved by the Agency. If the proposed tradename has been approved by the Agency, a CBE supplement may be submitted.

      (NOTE: MRL clarified that they will continue to pursue approval of a tradename prior to NDA submission.)

Nonclinical Pharmacology and Toxicology Documentation

Does the proposed Table of Contents for Item 5 (Tab 5) fulfill the requirements of the Agency reviewer(s)?

Yes, the Table of Contents appears to be acceptable. Please identify the 5-week bridging studies in rats and mice intended to link formulations NB (particle size [redacted] and formulation M (particle size [redacted] of MK-0869 in terms of systemic exposure to both parent drug and metabolites. These studies were discussed in your submissions dated August 11, 2000 and March 21 and May 9, 2001. In addition, please identify any preclinical studies submitted to your IND in The Division of Neuropharmacological Drug Products, HFD-120.

(NOTE: MRL identified the 5-week bridging studies as the studies entitled, "Exploratory Five-Week Oral Toxicokinetic Study in Rats" and "Exploratory 5-Week Oral Toxicokinetic Study in Mice" on page 31 of the background package. MRL clarified that all safety and toxicology studies submitted to the IND in HFD-120 were also submitted to IND [redacted] In response to the Division's request, MRL agreed to submit the study reports from the 6-month study in rats and the 9-month study in dogs recently discussed with HFD-120, to IND [redacted] when the studies have been completed.)

Human Pharmacokinetic, Bioavailability Documentation

Does the proposed Table of Contents for Item 6 (Tab 6) fulfill the requirements of Agency reviewer(s)?

Yes, the Table of Contents appears to be acceptable. However, we lack sufficient information (i.e., a description of the study designs and the results) to determine the adequacy of the proposed studies.

(NOTE: The Division clarified that the adequacy of the proposed PK/PD studies is a review issue. In response to the Division's question, MRL explained that a drug-drug interaction study is ongoing and the study report will be submitted after the NDA has been submitted.)

Clinical Documentation

a. *Does the proposed Table of Contents for Item 8 (Tab 6) fulfill the requirements of the Agency reviewer(s)?*

   Yes, the Table of Contents appears to be acceptable. Decisions regarding filability are made upon submission of the application. Please submit separate, complete study reports for all studies, including Studies 52 and 54. Please clarify where the Integrated Summary of Efficacy (ISE) will be located. The Integrated Summary of Safety (ISS) and the ISE must include integrated data from all clinical studies.

(NOTE: MRL stated that they would submit separate study reports for Studies 52 and 54. They identified the ISE as Section D, entitled "Clinical Efficacy" in the Table of Contents on page 56 of the background package and the ISS as Section E entitled, "Clinical Safety" on page 57 of the background package. MRL explained that data from similar studies, i.e., studies in which patients received the same anti-emetic regimen, would be integrated in the ISS and ISE. The Division commented that the plan appears to be acceptable, however, in some cases, it may be useful to include data from all studies when analyzing safety issues.)

b. *Does the Agency agree with the presentation and documentation of efficacy and safety data as displayed in the prototype CSR?*

Yes, the CSR appears to be acceptable.

c. *Does the Agency agree that safety and efficacy data from MK-0869 patients in multiple Cycles 2 and 3, to be included in the NDA filing, will be sufficient to support labeling regarding maintenance of the MK-0869 effect?*

There may be a sufficient number of patients in multiple cycles to support filing the application for the indication proposed. The adequacy of the data to support the proposed indication is a review issue.

(NOTE: MRL explained that 330 patients had received MK-0869 for more than one treatment cycle, representing 870 re-treatment courses. Only data concerning serious adverse events are collected after Cycle 1. MRL stated that, in their opinion, the data from patients in multiple cycles will be adequate to support labeling similar to that given other antiemetic drugs for multiple treatment cycles.)

d. [redacted]

Integrated Safety Summary/Safety Table Format

Does the Agency concur with the approach to the data displays summarized under Tab 7?

This approach appears to be acceptable. Additional analyses or tables may be requested after study reports have been submitted. Please list deaths separately.

(NOTE: The Division explained that a global statement about deaths and other significant adverse events should be included in the ISS with details provided within the document.)

Statistics

a. *Are the planned analyses sufficient to support the proposed indication provided results are consistent with the respective study hypotheses?*

   The planned analyses appear to be acceptable. The plan's adequacy to support the proposed indication is a review issue.

b. *Does the Agency request any additional analyses beyond what are presented in the submitted DAP documents?*

   Please submit analyses of the demographic subgroups age, sex, and race in the ISS and ISE.

   (NOTE: MRL explained that they would present an analysis of data for the primary efficacy endpoint by age, sex, and race. Adverse events will be listed by body system for these subgroups. The emphasis will be on data from the Phase 3 studies.)

Electronic Submission

Does the Agency concur that the proposed electronic submission platforms to be utilized for this submission meet Agency requirements?

Your proposal appears to be acceptable. Please clarify if "Biostatistical review aids" (page 122 of the Background Package) will include safety data files.

(NOTE: MRL explained that SAS datasets and SAS analysis programs for the key efficacy variables will be included in the application. Training will be made available if necessary. The Division requested that safety data also be made available on SAS datasets.)

Miscellaneous

In response to MRL's question, the Division explained that decisions regarding a priority or standard classification are made at filing. MRL may include their arguments for a priority designation in the application if they think it appropriate.

DECISIONS (AGREEMENTS) REACHED:

1. MRL will request a separate meeting to review the manufacturing process for the drug product.

2. The CMC section may be submitted in the Common Technical Document for The Registration of Pharmaceuticals for Human Use format.

3. Although a paper submission of the CMC section is preferred by the Division, an electronic submission is acceptable.

4. MRL will continue to pursue approval of a tradename prior to NDA submission.

5. MRL will submit the study reports from the 6-month study in rats and the 9-month study in dogs recently discussed with HFD-120, to IND [redacted] when the studies have been completed.

6. A drug-drug interaction study is ongoing and the study report will be submitted after the NDA has been submitted.

7. Separate study reports will be submitted for Studies 52 and 54.

8. An analysis of data for the primary efficacy endpoint by age, sex, and race will be included. Adverse events will be listed by body system for these subgroups. The emphasis will be on data from the Phase 3 studies.

9. SAS datasets and SAS analysis programs for the key efficacy variables will be included in the application. Training will be made available if necessary.

10. Decisions regarding a priority or standard classification are made at filing and MRL may include their arguments for a priority designation in the application if they think it appropriate.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Brian Strongin
2/11/02 10:57:20 AM

MEMORANDUM OF MEETING MINUTES

OCT 20 2000

MEETING DATE: September 21, 2000
TIME: 12:00-1:30 P.M.
LOCATION: Conference Room "L" (PKLN)
APPLICATION: IND [redacted] MK-0869 Capsules
TYPE OF MEETING: Follow-Up to April 1999 End of Phase 2 Meeting

MEETING CHAIR: Dr. Lilia Talarico, Division Director

MEETING RECORDER: Ms. Melodi McNeil, Regulatory Health Project Manager

FDA ATTENDEES, TITLES, AND OFFICE/DIVISION:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. Lilia Talarico, Division Director
Dr. Steven Aurecchia, Deputy Division Director
Dr. Hugo Gallo-Torres, Medical Team Leader
Dr. Raymond Joseph, Medical Reviewer
Dr. Jasti Choudary, Pharmacology Team Leader
Ms. Melodi McNeil, Regulatory Health Project Manager

Division of Biometrics (HFD-715)
Dr. Thomas Permutt, Acting Statistical Team Leader

EXTERNAL CONSTITUENT ATTENDEES AND TITLES:

Merck Research Laboratories
Dr. Shuet-Hing Lee Chiu, Senior Director, Drug Metabolism
Ms. Denise Cyle, Senior Regulatory Coordinator, Worldwide Regulatory Coordination
Dr. Dennis Erb, Senior Director, Regulatory Affairs
Dr. Michael Goldberg, Senior Director, Clinical Pharmacology
Dr. Richard Hargreaves, Senior Director, Pharmacology
Mr. Tom Hassall, Director, Regulatory Agency Relations
Dr. Paul J. Hesketh, Chief of Hematology and Oncology Division, St. Elizabeth's Medical Center, Boston, MA
Dr. Kevin Horgan, Director, Clinical Neuroscience & Ophthalmology
Dr. Kaihong Jiang, Senior Biometrician, Clinical Biostatistics and Research Data Systems (CBARDS)
Dr. Anup K. Majumdar, Research Fellow
Ms. Allison Martin, Epidemiologist, Epidemiology
Dr. Britta Mattson, Senior Research Fellow, Safety Assessment
Dr. Scott Reines, Vice President, Clinical Neuroscience & Ophthalmology
Dr. Charlene Sanders, Director, Regulatory Affairs Domestic
Dr. Thomas Simon, Executive Director, GI Research
Dr. Balasamy Thiyagarajan, Director, Clinical Biostatistics and Research Data Systems (CBARDS)

BACKGROUND: IND [redacted] was submitted April 9, 1996 by Merck Research Laboratories to investigate a tablet formulation of L-754,030 (now known as MK-0869), an NK_1 receptor antagonist, for the prevention of chemotherapy-induced emesis. (Subsequently, the firm informed the Division of their intention to investigate a capsule formulation of MK-0869).

An End of Phase 2 meeting (minutes available) was held between the sponsor and the firm in April 1999.

In a July 21, 2000 submission to the IND, the sponsor referenced recent findings and newly available data on the compound. According to the sponsor, these new data necessitated refinements in the clinical development program, therefore, Merck requested an additional meeting with the Division prior to initiation of their Phase 3 studies.

MEETING OBJECTIVE: To discuss and secure FDA concurrence with issues pertaining to the clinical program that will support the submission and claims made in the NDA for MK-0869

DISCUSSION POINTS: The firm's September 5, 2000 pre-meeting submission (and a subsequent September 15, 2000 facsimile) contained a number of specific questions. These questions are reproduced below in regular type. The Division's responses follow in bold type.

Clinical Research

1. Dose Regimen Selection for MK-0869

Following data that became available in November, 1999 in which healthy subjects receiving a 375 / 250 mg MK-0869 regimen displayed plasma levels which were more than two fold greater than predicted as well as significant increases in dexamethasone concentrations associated with the MK-0869 regimen, the program was revised to utilize 125 / 80 mg dosing (Protocol #040[domestic] / #042[international]) which provided 80% of the plasma levels of the 2a regimen but displayed full clinical efficacy. Additionally, a low dose regimen of 40 / 25 mg was evaluated to determine the minimal effective dose. Interim analysis of Protocol #s 040/042showed the 125/80 mg MK-0869 regimen to be fully effective. The 40/25 mg MK-0869 regimen is also efficacious, however it effects are suboptimal in all outcome measures. particularly in regards to control of multiple vomiting episodes and delayed events. Based on these results, the Phase 3 Program will use a MK-0869 regimen of 125 / 80 mg on Day 1 and Days 2 - 4. (Tabs 7 & 8)

a. Does the Agency, concur with the selection of 125 mg on day 1 and 80 mg on days 2 - 4 as the recommended marketed dosing for MK-0869 ?

Agency Response: Based on available data, dose selection appears appropriate.

b. Does the Agency concur with the proposed dosage regimen of 4 days of MK-0869 CINV therapy?

Agency Response: Based on Phase 2 data, the proposed dosage regimen appears appropriate. (Note: At today's meeting the sponsor presented new data to justify a change in the dosage regimen from four days total, as proposed in this question, to three days. In response to the firm's question, Division representatives said [based on the limited data presented today] the three day regimen appeared acceptable.)

Dexamethasone-related Considerations

c. Does the Agency concur with the study provisions for dexamethasone administration?

Agency Response: As we indicated at the April 1999 End of Phase 2 meeting, we remain unsure of the precise dose and regimen of dexamethasone for the prevention of emesis due to HEC or MEC. The role (contribution) of MK-0869 and dexamethasone (alone and in combination) and their two-way interaction must be assessed. In addition, the dose of dexamethasone must be justified, as must the change from i.v. (most regimens recommend 20 mg) to oral (day 1 vs. days 2 to 4).

Please provide scientific support to modify the dose of dexamethasone from 20 to 12 mg PO. We reiterate, as stated in the minutes of the April 14, 1999 End of Phase 2 meeting, that the requirement for ondansetron and dexamethasone as concomitant therapy (per protocol) in the studies may impose substantial limitations. Specifically, the indication which results from the conduct of these studies may state that MK-0869 is intended for use only as an adjunct to these specific background medications. The CLINICAL TRIALS section of the package insert will describe the details of how concomitant medications were used.

(Note: Division representatives added that they do not consider the $5HT_3$ antagonists to be interchangeable, though they invited the firm to provide scientific justification that they are. In the meantime, if the Phase 3 studies use ondansetron as background therapy, any associated labeling may state that MK-0869 is intended for use only as an adjunct to ondansetron [and not to the $5HT_3$'s as a class], as described above.)

2. Program and Protocol Design

A dose of 125 mg, when administered concomitantly with a 5-HT3 antagonist and dexamethasone on day 1 followed by once daily doses of MK-0869 at 80 mg on days 2-5 resulted in superior efficacy compared to standard therapy. (Standard therapy is comprised of a 5-HT3 antagonist and dexamethasone alone.) Additional studies (refer to Tabs 8 & 9) are proposed for Phase 3 to further document the safety and efficacy of MK-0869 in preventing chemotherapy-induced nausea and vomiting. The continuance of Phase 3 is premised on

concurrence with the Agency with regard to the questions articulated in the following pages.

a. Does the Agency concur that the proposed Phase 3 studies in patients; specifically, two in which patients receive highly emetogenic cisplatin and one in which patients receive moderately emetogenic chemotherapy, will meet registration requirements for the proposed indication?

Agency Response: We concur. Note that any regulatory decisions will be dependent on the strength and consistency of the data.

b. Does the Agency concur with the proposed design of the HEC (Highly Emetogenic Chemotherapy) Phase 3 trials as exemplified by the Protocol in Tab 9: *A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of MK-0869 for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated with High-Dose Cisplatin* for documenting safety and efficacy (throughout acute and delayed episodes) of MK-0869?

Agency Response: **We cannot provide concurrence at this time; we advise you to submit the protocols for full review and comment. The protocol design of the HEC Phase 3 clinical trials is subject to the same comments concerning dexamethasone as mentioned in point 1c (above). In addition, we are concerned that, as proposed, the trials do not allow separate assessment of any treatment effect on the acute and delayed phases of CINV. Also, the proposed design does not allow assessment of how the effect of therapy on the acute phase of CINV affects the delayed phase of CINV.** Additional studies (of differing designs) may be needed to answer this question.

(Note: According to the firm, they selected the lowest effective dose of MK-0869 for study to minimize the potential for carryover effects. **Division representatives emphasized that MK-0869 must be shown effective on day 1 to get the proposed indication of "...**

3. **Definitions for Endpoint Evaluation, Duration of Treatment, and Quality of Life Measurements in Supporting Labeling Indications**

In light of these observations and the definitions and descriptive material outlined in the Clinical Development Program for MK-0869 does the Agency concur with the following four study design suppositions?

a. The use of a Complete Response end-point for the HEC studies and a Complete Protection end-point for the MEC study in the Phase 3 program. [A patient has a Complete Response in the HEC

studies if they have no vomiting episodes and do not take rescue therapy. A patient has a Complete Protection Response in the MEC study if they have no vomiting episodes, do not take rescue therapy, and have a maximal nausea VAS (Visual Analog Scale) rating < 25 mm.]

Agency Response: We believe the Complete Response endpoint should be used as the primary endpoint of efficacy for both the acute and delayed phases in both the HEC and MEC studies. The Complete Response should be defined in the same manner as the 5-HT3 antagonist that is used (in this case, ondansetron). All other endpoints or evaluations should be secondary.

b. The use of a zero to 120 hours time framework for the primary hypothesis in all three Phase 3 studies which merges the acute and delayed CINV phases into a continuum of symptomatic responses.

Agency Response: **We do not object to the merged approach you propose, provided that results from the acute and delayed phases are separated first. (Note: FDA agreed that the firm's merged approach can be the primary hypothesis, however, it must be supported by documentation of efficacy in both the acute and delayed phases.)**

c. The outlined definitions (Tab 7 & 8) will be applied to our study designs and subsequently will be suitable for incorporation into labeling indications following Phase 3 completion.

Agency Response: **For standardization purposes and because ondansetron, the 5-HT3 antagonist you propose to use was approved on the basis of Complete Response evaluations, the usual definition of CR should be used. Alternatively, any new definitions must be justified.**

d. The acute and delayed phase efficacy and safety data from Cycle 1 and extension will be acceptable for presentation in the label.

Agency Response: **Please clarify this question further: By "extension" do you mean cycles 2 to 5-6? (Note: In response, the firm said that "extension cycle" refers to any cycle after the first one.) If so, there might be questions about efficacy (for those patients who experienced nausea and vomiting at cycle 1, an anticipatory component may be present at the other cycles). (Note: Regarding data from extension cycles, Division representatives agreed that it is acceptable to include precise response rates in the labeling, however the firm should not us data from the first cycle to extrapolate or predict efficacy in subsequent cycles. The Division also asked the firm to consider describing patients who get MK-0869 in extension cycles.)**

4. <u>Criteria for Adverse Experience (AE) Reporting</u>

[W]ould the Agency be amenable to a waiver agreement that specifies the data collection of only SAE's in the multiple cycle extension portions of the protocols?

Agency Response: We are amenable to a waiver such as the one you propose.

5. **Plans for Enrollment into Multiple Cycle Extension Studies**

Throughout all the Phase 3 studies (HEC and MEC) there will be optional multiple cycle extensions serving to provide treatment for patients and to obtain additional clinical experience with MK-0869. Each study will have an optional multiple cycle extension phase during repeated cycles of chemotherapy. Blinded study therapy will be made available during these subsequent cycles (to a maximum of six cycles) for those patients who received it during Cycle 1, provided continued administration is deemed appropriate by the investigator. We anticipate that > 25% of patients will be treated beyond Cycle 1 during Phase 3, although this is only an estimate based on our recent experience from Phase 2b enrollment patterns.

Does the Agency concur that data on 70+ patients treated through Cycle 3 during Phase 2, plus serious AE data from those who opt to enter Phase 3 extension trials will be sufficient to demonstrate safety during multiple cycles and to meet a threshold for inclusion in the marketed label?

Agency Response: **We are skeptical of extrapolating safety data from this investigator-selected patient population to the target population as a whole. This approach may not be adequate, however, this is a review issue.**

6. [redacted]

PREDECISIONAL

Agency Response:

7. **Compiled Data for Inclusion in NDA**

There will be nine randomized, controlled studies of MK-0869 in the treatment of CINV included in the NDA submission. These studies are detailed in Tab 8. The estimated number of patients exposed to MK-0869 at the time of filing in the CINV program is projected to be approximately 1700. Extension data on multiple cycle use will be available from a proportion of the total patient enrollment as well. There are seven additional studies from non-CINV program studies in which patients were treated over longer durations of time (ranging from two weeks to six months) that offer an additional 757 MK-0869 (treated in dose ranges from 300 mg to 30 mg, Tab 8, Table 3) exposed patients from which safety and tolerability data can be drawn.

a. Does the Agency concur that the projected CINV patient numbers of approximately n = 1700 (treated with MK-0869 in doses ranging from 375 mg to 40 mg, with approximately half treated recurrently [more than one cycle], Tab 8, Table 3) will be sufficient to support the registration submission for MK-0869?

Agency Response: We concur with the overall number of patients, however all regulatory decisions will be data dependent.

b. Will the additional exposure data collected from CINV and non-CINV studies of MK-0869 be acceptable for supporting safety-related labeling claims on recurrent or extended patient exposure?

Agency Response: This is a data dependent review issue.

8. **Assessment of Clinically Relevant Drug Interactions Related to Chemotherapy Use**

Multiple drugs are given concomitantly to patients in the course of chemotherapy treatments. The simultaneous or overlapping use of medications for patients makes the potential for pharmacokinetic interaction among these agents a matter of clinical interest. We have investigated potential drug interactions in detail for MK-0869 (refer to Tab 6). Studies that evaluated diltiazem and ketoconazole interactions have characterized the effects of CYP 3A4 inhibition on MK-0869; and a rifampin interaction study identified the effects of CYP 3A4 induction on MK-0869. Results of interaction studies with dexamethasone, midazolam, and diltiazem defined MK-0869 as a moderate inhibitor of CYP 3A4. A completed digoxin interaction provided negative results for potential drug interaction mediated via P-glycoprotein. We are planning granisetron and docetaxel interaction studies as well. In addition, considerable safety experience with other chemotherapy agents is being collected throughout

Phase 2b/3 studies.

Given the extent of the interaction studies now completed or ongoing, does the Agency concur that the drug interaction profile program for MK-0869 is sufficient for submission in the NDA filing?

Agency Response: In addition, in the Phase 3 clinical trials, please document coadministration of all CYP 3A4 substrates and evaluate these patients separately from a safety perspective. (Note: The Division's biopharmaceutics representative was unable to attend today's meeting. The firm was offered the opportunity to meet with the biopharmaceutics representative by teleconference, to discuss this and/or other biopharmaceutics matters related to their proposed NDA.)

9. <u>MK-0869 Chemotherapy Interaction Data</u>

Does the Agency concur that additional preclinical studies regarding the effects of MK-0869 on chemotherapeutic agents are not required?

Agency Response:

a. **Testing with a moderately emetogenic agent is recommended. (Note: The Division's preclinical representative clarified that this additional testing is recommended, but not required.) Oral dosing with MK-0869 is also recommended.**

b. **Please note, your statement on page 48 of the background package "the Agency agreed that carcinogenicity studies will not be required to support the prevention of CINV indication" is at variance with the minutes of the April 14, 1999 End of Phase 2 meeting. The Agency recommended that reports of such studies be included in your NDA submission, particularly since the studies are already ongoing. The Agency's position continues to be the same. (Note: The firm agreed that they would submit the reports of these studies.)**

Minutes Preparer: /S/ 10/19/00

Chair Concurrence: /S/ 10-19-00

ATTACHMENTS/HANDOUTS: Hard copies of the firm's overheads will be submitted to the IND.

MEMORANDUM OF MEETING MINUTES

Meeting Date: April 14, 1999
Time: 11 AM-1 PM
Location: Room 13-57 (Parklawn Building)

Application: IND [redacted] MK-0869 Capsules

Type of Meeting: End of Phase II

Meeting Chair: Dr. Lilia Talarico, Division Director

Meeting Recorder: Ms. Melodi McNeil, Regulatory Health Project Manager

FDA Attendees, titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Dr. Lilia Talarico, Division Director
Dr. Hugo Gallo-Torres, Medical Team Leader
Dr. Lawrence Goldkind, Medical Officer
Dr. Jasti Choudary, Pharmacology Team Leader
Dr. Tim Robison, Pharmacology Reviewer
Ms. Melodi McNeil, Regulatory Health Project Manager

Division of Biometrics (HFD-715)
Dr. Mohamed Al-Osh, Acting Statistical Team Leader
Dr. Wen-Jen Chen, Statistical Reviewer

Office of Clinical Pharmacology and Biopharmaceutics (HFD-870)
Dr. David Lee, Biopharmaceutics Team Leader

Office of Drug Evaluation III (HFD-103)
Dr. Victor Raczkowski, Acting Office Director

External Constituent Attendees and titles:

Merck Research Laboratories
Dr. Bonnie Goldmann, Regulatory Affairs
Dr. Dennis Erb, Regulatory Affairs
Ms. Marie Dray, Regulatory Agency Relations
Dr. Alexandra Carides, Clinical Biostatistics
Dr. Balasamy Thiyagarajan, Clinical Biostatistics
Dr. Kevin Horgan, Clinical Neurosciences
Dr. Scott Reines, Clinical Neurosciences
Dr. Michael Goldberg, Clinical Pharmacology

Dr. David Tattersall, Preclinical Pharmacology
Dr. Britta Mattson, Safety Assessment
Dr. Lee Chiu, Drug Metabolism
Dr. Anup Majumdar, Drug Metabolism

Background: IND [redacted] **was submitted April 9, 1996 by Merck Research Laboratories to investigate a tablet formulation of L-754,030 (now known as MK-0869) for the prevention of chemotherapy-induced emesis. (Subsequently, the firm informed the Division of their intention to investigate a capsule formulation of MK-0869).**

In a February 22, 1999 amendment, the firm described plans to initiate Phase III studies with MK-0869 and subsequently submit an NDA for the prevention of acute and delayed nausea and vomiting associated with emetogenic cancer chemotherapy. The sponsor's representatives requested an End of Phase II meeting to discuss and secure FDA concurrence with issues pertaining to the clinical program that will support the submission and claims made in the NDA for MK-0869.

In a March 18, 1999 background package, the firm described the following proposed Phase III studies:

1. **Pivotal Phase III Efficacy Study in Highly Emetogenic Chemotherapy with Dose Ranging:**

   This is a double-blind, controlled, dose-ranging, five-day study of MK-0869 in which approximately 760 patients who are to receive highly emetogenic chemotherapy will be randomized to one of the following three treatment groups:

   a. MK-0869 PO (375 mg), ondansetron I.V. (32 mg), and dexamethasone PO (20 mg) on day one, followed by MK-0869 PO (250 mg) and dexamethasone PO (8 mg) on days two through five,

   b. MK-0869 PO (125 mg), ondansetron I.V. (32 mg), and dexamethasone PO (20 mg) on day one, followed by MK-0869 PO (80 mg) and dexamethasone PO (8 mg) on days two through five, or

   c. ondansetron I.V. (32 mg) and dexamethasone PO (20 mg) on day one, followed by dexamethasone PO (8 mg) on days two through five.

   Patients will be administered a course of highly emetogenic chemotherapy (which will include cisplatin, at a dose of $\geq$ 70 mg/m^2), and the co-primary endpoints will be the proportion of patients with no emesis and nausea who also do not receive rescue therapy: 1) on day one (acute phase) as assessed by comparing groups a versus c; and 2) on days two to five (delayed

phase) as assessed by comparing groups a versus c. Nausea will be assessed as a secondary endpoint. The study will include an optional extension protocol to evaluate tolerability during subsequent cycles of chemotherapy.

2. **Pivotal Phase III Efficacy Study in Moderately Emetogenic Chemotherapy with Dose Ranging:**

   This is a double-blind, controlled, dose-ranging, five-day study of MK-0869 in which approximately 830 patients will be randomized to one of the following three treatment groups:

   a. MK-0869 PO (375 mg), ondansetron PO (8 mg BID), and dexamethasone PO (20 mg) on day one, followed by MK-0869 PO (250 mg) and ondansetron PO (8 mg BID) on day two, and MK-0869 PO (250 mg) on days three to five,

   b. MK-0869 PO (125 mg), ondansetron PO (8 mg BID), and dexamethasone PO (20 mg) on day one, followed by MK-0869 PO (80 mg) and ondansetron PO (8 mg BID) on day two, and MK-0869 PO (80 mg) on days three to five. or

   c. ondansetron PO (8 mg BID) and dexamethasone PO (20 mg) on day one, followed by ondansetron PO (8 mg BID) on day two. No active medication is given to this group on days three through five.

   Patients will be administered a course of moderately emetogenic chemotherapy. The primary endpoint will be the proportion of patients with no nausea or vomiting who also do not receive rescue therapy on days two to five (delayed phase) as assessed by comparing groups a versus c. No efficacy assessment is planned for day one (acute phase). Nausea will be assessed as a secondary endpoint. The study will include an optional extension protocol to evaluate tolerability during subsequent cycles of chemotherapy.

Meeting Objective: To discuss and secure FDA concurrence with issues pertaining to the clinical program that will support the submission and claims made in the NDA for MK-0869

Discussion Points (bullet format): In their March 18, 1999 briefing package, the firm requested answers to the following questions:

Non-clinical Toxicology, Pharmacokinetics and Pharmacology

1. MK-0869 was shown to be negative in the standard ICH genotoxicity battery of tests. The proposed dosage regimen for the prevention of acute and delayed chemotherapy-induced emesis indication would allow once daily administration of MK-0869 for a total of 5 days per cycle. The majority of patients would be treated for 3 to 6 cycles. The ICH guidance entitled

"The Need for Long-Term Rodent Carcinogenicity Studies of Pharmaceuticals" suggest that carcinogenicity studies may not be required for drugs like MK-0869 which are dosed infrequently.

Are carcinogenicity studies required for the registration of MK-0869 for the prevention of chemotherapy-induced emesis or similar acute indications (e.g. post bone-marrow transplantation)?

The Agency had the following comment:

Carcinogenicity studies are suggested since 1) this compound is likely to be used in patients receiving several cycles of emetogenic chemotherapy (with a consequent patient exposure of greater than six months), 2) other chronic uses of this compound are planned, and 3) this drug will be used as a palliative (as opposed to an oncolytic) agent.

2. Does the Agency concur that the completed pharmacology and toxicology program is sufficient to support registration of MK-0869 for the prevention of chemotherapy-induced emesis?

The Agency had the following comments:

a. Based on the information currently available, the completed pharmacology and toxicology program is not sufficient to support registration of MK-0869 for the prevention of chemotherapy-induced emesis. This insufficiency is due to the change in formulation ([redacted] particle size), as well as concerns that the drug exposure may not have been optimized in toxicology studies conducted to date. The adequacy of the completed pharmacology/toxicology data can be better assessed once data are available from the proposed 2-week toxicokinetic/toxicology studies in rats and mice. These studies are intended to compare the [redacted] particle sizes and determine the extent of saturation.

b. All future studies, including the proposed 1-year dog toxicology study, should be done using the proposed market image [redacted] capsule formulation).

The sponsor commented that, although they plan to employ the [redacted] particle size in this study, they plan to administer it in a suspension formulation rather than in the

capsule formulation suggested by the Agency. The Division agreed that this approach is acceptable.

c. **If the proposed 2-week toxicokinetic/toxicology studies show that there is no saturation of absorption at tested doses, the reproductive toxicology studies may need to be redone.**

d. **Please consider conducting subacute and subchronic general toxicology studies in sensitive species, such as ferrets and rabbits.**

The sponsor questioned the need for these studies. In response, Division representatives said that the toxicology program for MK-0869 should clearly define the target organs of toxicity, either by using appropriately high doses of the compound or by using sensitive species, such as the ferret and the rabbit.

e. **Please consider conducting combination toxicology studies, since the proposed Phase III studies include coadministration of MK-0869 with a variety of other palliative agents, dexamethasone, serotonin ($5HT_3$) antagonists, etc.**

The sponsor questioned the need for these studies. Division representatives indicated that it is desirable to determine the potential pharmacokinetic and toxicological interaction for coadministered drugs as MK-0869 has manifested effects on hepatic P-450 enzymes in animal species.

Human Pharmacokinetics and Drug Metabolism

1. The proposed Clinical Pharmacology program is outlined in Section 6 [of the sponsor's March 18, 1999 submission]. It consists of a series of studies to document the pharmacokineties of MK-0869 in normal volunteers and special populations and to investigate potential metabolic and drug/drug interactions.

Does the Agency concur that the proposed Clinical Pharmacology program will adequately characterize the pharmacokinetic profile of MK-0869 and the potential for drug/drug interactions?

The Agency had the following comments:

a. **The adequacy of the proposed clinical pharmacology program will be data dependent.**

b. **Previous PK/PD data are acceptable as supporting data.**

c. **All future clinical pharmacology studies should be conducted using the proposed market image — particle size, capsule formulation).**

d. **The proposed studies in special populations appear acceptable.**

e. **More detailed information on exactly which drug-drug interaction studies are planned should be provided. Consideration should be given to conducting drug-drug interaction studies with dexamethasone and the $5HT_3$ antagonists.**

f. **Women seem to handle MK-0869 differently than men. This apparent gender difference in PK parameters should be addressed and explained.**

g. **The dissolution methodology should be provided in the NDA, when submitted.**

h. **Planned pharmacokinetic studies should characterize the food effect seen with the proposed market image. Definitions for "high fat" and "light meal" should be provided.**

i. **Information should be provided in the NDA, when submitted, from the multidose pharmacokinetic study about the linearity (or non-linearity) of the pharmacokinetics of MK-0869.**

j. **Information should be provided in the NDA, when submitted, that describes MK-0869's metabolism in humans. The metabolic profile should be characterized if the metabolites are active.**

2. As described in Section 6, the bioavailability of the tablet formulation used in the Phase 2 program is significantly influenced by food. In parallel to the Phase 2 program a capsule formulation using — particles of MK-0869 was developed resulting in enhanced bioavailability and reduced food effects. The capsule formulation has been selected for market development and will be used in Phase 3. The high dose regimen selected for Phase 3 will approximate the plasma levels obtained in Phase 2 with the tablet formulation.

   Does the Agency concur that the completed and proposed studies with the improved bioavailable capsule formulation are sufficient to support the switch to this formulation for Phase 3 and market use?

   The Agency had the following comments:

   a. **Sufficient pharmacokinetic/pharmacodynamic data on the capsule should be provided.**

In response, the sponsor said that the core pharmacokinetic studies will be performed with the capsule formulation.

b. **Bioequivalence studies, as well as the planned confirmatory studies, will be useful.**

Clinical Research

Note: The March 18, 1999 pre-meeting submission contained only protocol summaries, therefore, the Division's comments are necessarily limited in scope. The firm is expected to submit complete protocols prior to initiation of Phase III trials.

1. The safety and efficacy of MK-0869 in preventing both acute and delayed phase cisplatin-induced emesis has been documented in Phase 2 trials. A dose of MK-0869 400-mg when administered concomitantly with a 5-HT_3 antagonist and dexamethasone on day 1 followed by once daily doses of MK-0869 300-mg on days 2-5 resulted in superior efficacy compared to standard therapy. Two additional studies are proposed for Phase 3 to further document the safety and efficacy of MK-0869 in preventing chemotherapy-induced emesis and establishing dosing recommendations.

   Does the Agency concur with the proposed design of the two Phase 3 trials to document safety and efficacy (acute and delayed) and to establish dosing recommendations for MK-0869?

   No conclusions or agreements were reached on this issue. **Instead, Division representatives expressed the following concerns about the design of the studies as proposed:**

   a. **Based on the available information, it is unclear whether the proposed five-day regimen is necessary for the prevention of chemotherapy-induced emesis.**

   b. **The fact that ondansetron and dexamethasone are required as concomitant therapy (per protocol) in both studies may impose substantial limitations. Specifically, the indication which results from the conduct of these studies may indicate that MK-0869 is intended for use only as an adjunct to these background medications. The CLINICAL TRIALS section of the package insert will describe the details of how concomitant medications were used.**

   c. **Although widely used in clinical practice for the prevention of chemotherapy-induced emesis, dexamethasone is not currently approved for this indication. Further, agreement does not exist within the scientific community with regard to a**

uniform dose, regimen, or route of administration of this compound for this purpose.

Mention of dexamethasone in the package insert (under the circumstances described in point b above) may imply efficacy of the compound in the prevention of chemotherapy-induced nausea and vomiting. However, the studies as proposed are insufficient to characterize the effectiveness of dexamethasone for this indication. The Division strongly encouraged the firm to modify the Phase III studies to include a fourth treatment arm (without dexamethasone) in which patients would receive only MK-0869 (or placebo) and a $5HT_3$ antagonist on day one; and in which patients would not receive dexamethasone on days two thorough five. At the end of the acute phase, patients could be re-randomized. These revisions would allow the effects of dexamethasone, if any, in the acute phase to be assessed, and would allow a comparison of the effects of MK-0869 and dexamethasone in the delayed phase.

d. **As planned, the studies do not allow for characterization of any carryover effect which may occur between the acute and delayed study phases. For this reason the Division advised re-randomization of acute phase patients before they enter the delayed phase.**

Does the Agency concur that the completed Phase 2 studies and a single Phase 3 study in patients receiving highly-emetogenic chemotherapy are sufficient for registration of MK-0869 for the proposed indication.

The Agency agreed that this approach is acceptable, though not optimal, and commented that any regulatory decisions will be dependent on the strength and consistency of the data.

Does the Agency concur that a single study in patients receiving moderately-emetogenic chemotherapy is sufficient to allow description of the study and specific dosing recommendations in the label?

The Agency had the following comment:

In general, the expectation is that at least two adequate and well-controlled studies be submitted in support of each indication. For the moderately-emetogenic indication, the two planned Phase III studies (one with moderately emetogenic chemotherapy and one with highly emetogenic chemotherapy) may be supportive of each other, provided the results are convincingly robust, strong, and consistent. That is, if the data from the trial in patients receiving highly emetogenic therapy are sufficiently strong and consistent, that trial may be adequate to support the moderately

emetogenic indication. However, the converse may not be true. Critical studies should be independently substantiated with other clinical data. See "Guidance for Industry, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products." (May 1998)

2. A highly emetogenic chemotherapy regimen will be defined as patients receiving ≥70 mg/m^2 of cisplatin. Moderately emetogenic chemotherapy will be defined as follows:

Doxorubicin	40-75 mg/m^2
Carboplatin	300-500 mg/m^2
Cyclophosphamide	500-1000 mg/m^2

Does the Agency concur with these definitions for highly and moderately emetogenic chemotherapy?

The Agency had the following comments:

a. **The definition of "highly emetogenic chemotherapy" should also include an infusion time of ≤ 3 hours.**

The sponsor agreed to add the restriction in infusion time to the protocol.

b. **Regarding the definition of "moderately emetogenic chemotherapy," clarification should provided on whether the regimens (shown above) will be used alone or in combination.**

The sponsor said that drugs listed above would be administered either as monotherapy or in combination, but that the emetogenicity would be defined according to the Heskith classification.

c. **Consider subset analyses by chemotherapeutic regimen to allow differences in emetogenicity to be discerned.**

The sponsor commented that both protocols provide for stratification by the number of emetogenic agents.

3. The primary endpoint for efficacy for both delayed and acute phase CIE will be the percent of patients with no vomiting or retching, and no rescue therapy for nausea (NER). Secondary

endpoints include the percentage of patients with nausea and the percentage of patients without emesis regardless of rescue for nausea. In the highly emetogenic study both prevention of acute and delayed phase emesis will be specified as co-primary hypotheses. In the moderately emetogenic study, delayed phase emesis will be the primary endpoint. Efficacy in acute emesis will be specified as a secondary endpoint.

Does the Agency concur with the use of these endpoints to support the proposed indication?

The Agency had the following comments:

a. **The proposed primary endpoints ("complete control") as defined (no nausea and no rescue medications) may be too conservative.**

b. **Prevention of emesis in the acute phase should also be a primary endpoint in the study with moderately emetogenic chemotherapy.**

After additional discussion with the sponsor, it was agreed that control of emesis in the acute phase need not be a co-primary endpoint.

Does the Agency concur that the clinical data including acute and delayed phase nausea and vomiting are appropriate for inclusion into the label?

The Agency agreed that this plan is acceptable.

4. More than 1400 subjects and patients will be administered MK-0869 during the clinical development program for chemotherapy-induced emesis. It is anticipated that approximately 250 patients will complete at least three cycles of therapy with MK-0869. An additional 800 subjects and patients have been administered MK-0869 in the development program for depression.

Does the Agency concur that the safety database is sufficient to support registration of MK-0869?

The Agency had the following comment:

The safety database appears sufficient to support registration of MK-0869. Depending on the types of adverse events that are observed, additional patients may be requested.

Does the Agency concur that the plan to obtain efficacy and safety in multiple cycles is sufficient to support a repeat use indication?

The Agency agreed that this plan is acceptable.

5.

The Agency had the following comments:

a.

b.

c.

Minutes Preparer: /S/ 5/14/99

Concurrence: /S/ 5/14/99

Attachments/Handouts: Hard copies of the sponsor's overheads

cc: Original IND [redacted]
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/CSO
HFD-180/Talarico
HFD-180/Gallo-Torres
HFD-180/Goldkind
HFD-180/Choudary
HFD-715/Al-Osh
HFD-715/Chen
HFD-870/Lee
HFD-103/Raczkowski
Drafted by: mm/April 20, 1999/c:\mydocuments\cso\minutes\[redacted]04-4-14-99-min.doc
Initialed by: JChoudary 4/22/99
DLee 4/26/99
HGallo-Torres 4/27/99
LTalarico 5/7/99
VRaczkowski 5/14/99
final: May 14, 1999
MEETING MINUTES

Redacted 18

pages of trade

secret and/or

confidential

commercial

information

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Santa P. Chawla, M.D.
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2080 Century Park East
Suite 1511
Los Angeles, California 90067

FEB 20 2003

Dear Dr. Chawla:

Between January 13 and 16, 2003, Ms. Yumi Hiramine, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol # 052-01 entitled: "A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions to Examine the Safety, Tolerability, and Efficacy of MK-0869 for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With High Dose Cisplatin") of the investigational drug MK-0869, performed for Merck & Co., Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We are aware that at the conclusion of the inspection, Ms. Hiramine presented and discussed with you the items listed on Form FDA 483, Inspectional Observations. We wish to emphasize the following:

1. You did not conduct your study in accordance with the approved protocol as required by 21 CFR 312.60.

   a. The Electrocardiogram (ECG) for 15 subjects was not performed at the completion of cycles 1-6.

   b. The laboratory tests (blood chemistry, hematology and urinalysis) were not performed for subjects 8004, 9002, and 9074 at day 19-29 visits for certain cycles.

2. You did not maintain documentation of informed consent for subjects 8003, 8007, 8008, 8009, and 8010 as required by 21 CFR 50.27.

Please make appropriate corrections in your procedures to assure that the findings noted above are not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator Hiramine during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact Khin Maung U, M.D., Branch Chief, Good Clinical Practice Branch I, by letter at the address given below.

Sincerely

/S/

Antoine El-Hage, Ph.D.
Associate Director
Good Clinical Practice Branch I & II, HFD-46/47
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, MD 20855

FEI: 3003868371
Field Classification: VAI
Headquarters Classification:
_____1)NAI
_X__2)VAI- no response required
_____3)VAI- response requested
_____4)OAI

Deficiencies noted:
_X _inadequate informed consent form (03)
_X _failure to adhere to protocol (05)
Deficiency Codes: 03, 05

cc:
HFA-224
HFD-180 Doc.Rm
HFD-180 Review Div.Dir . Justice
HFD-180 MO Kaminskas
HFD-180 PM Strongin
HFD-46/47c r/s/ GCP File # 2638
HFD-46 GCP Reviewer Malek
HFR-PA200 DIB Tucker
HFR-PA2565 Bimo Monitor Koller
HFR-PA2585 Field Investigator Hiramine
GCF-1 Seth Ray

r/d: KM: 2/10/03;2/11/03;2/12/03
reviewed:KMU: 2/11/03
reviewed:AEH:
f/t:sg: 2/12/03; ML:2/14/03
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Reviewer Note to Rev. Div. M.O.
The field investigator reviewed 16 case report forms out of 45 enrolled in the study. The inspection revealed some violations mainly:

1. Protocol violations: a) 15 subjects did not have an ECG performed at the end of the study in the multiple cycle phases. b) 3 subjects did not have urine analysis, hematology, and serum chemistry performed at day 19-29 visits in the multiple cycle phases.

2. 5 subjects did not sign the amended informed consent dated 5/29/01.

These violations would not affect the validity of the data. The data from this site can be used in support of the NDA.