

## Study 052

Aprepitant

**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**

### Clinical Phase III

#### Study Period:

Start: November 20, 2000

End: December 31, 2001

#### Overall Study Design:

Multicenter, randomized, double-blind, parallel-group, controlled trial with in-house blinding to assess the safety and efficacy of MK-0869 in the prevention of Chemotherapy Induced Nausea and Vomiting (CINV) in patients with confirmed solid malignancies who were treated with a chemotherapy regimen that included cisplatin  $\geq 70$  mg/m<sup>2</sup>.

Eligible patients were randomly allocated to one of two treatment groups using a computer generated random allocation schedule. Patients were stratified (at randomization) according to gender and then were further stratified according to the administration of emetogenic chemotherapy in addition to cisplatin.

#### *Medical Officer Comment:*

*The study design appears appropriate and well controlled. Stratification of patients according to concomitant chemotherapy was not routinely done for the approval of other drugs for the prevention of CINV.*

#### Treatments Administered

Each randomized patient received either a triple therapy regimen of MK-0869, dexamethasone, and ondansetron, or Standard Therapy of dexamethasone and ondansetron for 4 days. All treatment medications were administered in a blinded fashion.

During the multiple cycle extension, patients received the same blinded therapy they had been administered during Cycle 1.

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Table 1  
Treatment Regimens

MK-0869	MK-0869 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg IV or 3 doses of 0.15 mg/kg IV †	MK-0869 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning) Dexamethasone Placebo PO Daily (evening)
Standard Therapy	MK-0869 Placebo PO Dexamethasone 20 mg PO Ondansetron 32 mg IV or 3 doses of 0.15 mg/kg IV †	MK-0869 Placebo PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning) Dexamethasone 8 mg PO Daily (evening)

Ref Adapted from (P052.pdf Pg. 46)

### Medical Officer Comment:

*On days 2 through 4, patients in the MK-0869 group received a placebo for the evening dose of dexamethasone because a drug-drug interaction was identified during earlier studies that resulted in plasma levels for dexamethasone that was twofold greater. Ondansetron 32mg IV was administered only on Day 1 of the cycle in both groups.*

Adolescent patients were enrolled at one site in the U.S. under a site-specific amendment. Adolescent patients >12 and <18 years of age, weighing  $\geq 40$  kg, were administered the recommended dose of Ondansetron (0.15 mg/kg IV) for prevention of CINV in adolescent patients according to the U.S. ondansetron label.

### Sample Size:

The original protocol proposed 500 patients (~250 patients per treatment group) be enrolled in order to yield a total of 470 evaluable patients (i.e., about 235 patients per treatment group).

### Ethics:

#### Medical Officer Comment:

*The sponsor states the study was conducted in conformance with applicable country and/or local requirements, however does not specifically state that the study was in accordance with the Declaration of Helsinki or in accordance with Good Clinical Practice.*

### Investigators:

Fifty-eight centers participated in the study. Study sites were located in the United States, Australia, Belgium, Canada, Denmark, France, Germany, Greece, Hungary, Italy, Russia, South Africa, Spain, Sweden, Switzerland, and Taiwan.

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#### *Medical Officer Comment:*

*This was a multicenter, multinational study that included 51 centers.*

#### **Objectives:**

##### Primary Objectives: Cycle 1

- 1) Demonstrate that MK-0869 regimen is superior to Standard Therapy in the control of CINV, as measured by the proportion of patients with complete response in the 120 hours following the initiation of high-dose cisplatin chemotherapy.
- 2) Evaluate the safety and tolerability of the MK-0869 regimen.

##### Secondary Objectives: Cycle 1

- 1) Compare MK-0869 regimen with Standard Therapy in the proportion of patients with:
  - Complete Response—0 to 24 and 25 to 120 hours
  - No Vomiting—0 to 24, 25 to 120, and 0 to 120 hours
  - No Significant Nausea—0 to 120 hours
  - No Nausea—0 to 120 hours
  - No Impact on Daily Life—0 to 120 hours
- 2) To compare MK-0869 regimen with Standard Therapy in terms of the time to first vomiting episode in the 0 to 120 hours time frame.

##### Exploratory Objectives: Cycle 1

To compare MK-0869 regimen with Standard Therapy in the proportion of patients with:

- Complete Protection—0 to 24, 25 to 120, and 0 to 120 hours
- Total Control—0 to 24, 25 to 120, and 0 to 120 hours
- No Significant Nausea—25 to 120 hours
- No Nausea—25 to 120 hours

##### Optional Multiple-Cycle Extension Phase (Maximum of 5 Additional Cycles)

Describe the serious adverse experience profile of MK-0869 Triple Therapy and Standard Therapy when administered to patients receiving multiple cycles of chemotherapy with high-dose cisplatin.

##### Ancillary Objectives: Cycle 1

To collect health care resource utilization data to aid in economic analysis of MK-0869 in Cycle 1.

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**Medical Officer Comment:**

*Treatment cost analysis is not evaluated by the Agency during the review process.*

**Definitions:**

<u>Complete Response:</u>	No Emesis, No Rescue therapy
<u>No Emesis:</u>	No vomiting or retching or dry heaves (includes patients who received rescue therapy).
<u>No Nausea:</u>	Maximum nausea VAS <5 mm.
<u>No Significant Nausea:</u>	Maximum nausea VAS <25 mm.
<u>Complete Protection:</u>	No emesis, no rescue therapy, no significant nausea (maximum nausea <25 mm on VAS).
<u>Total Control:</u>	No emesis, no rescue therapy, and no nausea (maximum nausea <5 mm on VAS).

**Medical Officer Comment:**

*Nausea was self-assessed using a 100-mm horizontal visual analogue scale (VAS) in the patient diary. The left-hand edge of the scale (0 mm) was labeled "no nausea," and the right-hand edge of the scale (100 mm) was labeled "nausea as bad as it could be." Patients recorded their assessment of the degree of nausea during the preceding 24 hours by placing a vertical mark on the scale.*

**Primary Endpoint Analysis:**

Complete Response: Overall phase (0 to 120 hours post cisplatin)

**Medical Officer Comment:**

*Complete response (no emesis and no rescue therapy) was the primary efficacy endpoint for studies that led to the approval of ondansetron. For this study the primary endpoint was Complete Response for the overall phase. The acute and delayed phases were secondary endpoints.*

**Secondary Endpoint Analyses:**

Complete Response: Acute phase (0 to 24 hours post cisplatin)  
Delayed phase (25 to 120 hours post cisplatin)

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<u>Complete Response:</u>	(Per-protocol analysis)—overall, acute, and delayed phases
<u>No Emesis:</u>	Overall, acute, and delayed phases
<u>No Nausea:</u>	(VAS <5) Overall phase and delayed phase (exploratory analysis)
<u>No Significant Nausea:</u>	(VAS <25) Overall phase and delayed phase (exploratory analysis)
<u>Time to First Emesis:</u>	Overall phase
<u>Patient-Reported Impact of CINV on Daily Life:</u>	Overall phase

#### *Medical Officer Comment:*

*The primary and secondary endpoints should be adequate to evaluate the efficacy of MK-0869 regimen. The Sponsor had pre-specified exploratory endpoint analysis for: Complete Protection, Total Control and Severity of Nausea (overall, acute and delayed). Patient-Reported Impact of CINV on Daily Life was measured using Functional Living Index-Emesis (FLIE). The FLIE questionnaire was a VAS-based, validated patient-reported measure of the impact of CINV on daily life.*

#### **Rescue Therapy**

Rescue therapy was defined as any medication administered to treat established nausea or emesis. During Cycle 1, Patients recorded the drug, dosage, and time of rescue medication in their patient diary. Patients who had emesis or required rescue therapy were considered treatment failures for the primary efficacy analyses.

Diary data was initially reviewed prior to unblinding in order to identify protocol violations. Patients who received rescue therapy inappropriately (as defined by the patient and confirmed by the study coordinator) to prevent nausea or vomiting were considered protocol violators.

#### **Inclusion Criteria (Cycle 1)**

Patient  $\geq$  18 years of age.

Scheduled to receive first course of cisplatin chemotherapy ( $\geq 70$  mg/m<sup>2</sup>) over  $\leq 3$  hours for a documented solid tumor malignancy.

Negative serum or urine pregnancy test

Females of childbearing potential agreed to use appropriate contraception

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Karnofsky score  $\geq 60$

Predicted life expectancy of  $\geq 3$  months

Able to read, understand, and complete study questionnaires and diary.

Written informed consent.

#### **Inclusion Criteria (Multiple-Cycle Extension)**

Participation in the study during the next cycle of chemotherapy was considered appropriate by the investigator and did not pose unwarranted risk to the patient. Satisfactory completion of the preceding cycle of chemotherapy and related study procedures.

Scheduled to receive the same chemotherapy regimen as in Cycle 1.

#### **Exclusion Criteria (Cycle 1)**

Mentally incapacitated or a psychiatric disorder that, in the opinion of the investigator, precluded study entry.

Current use of illicit drugs or had current evidence of alcohol abuse.

Scheduled to receive stem cell rescue therapy.

Received investigational drug within 4 weeks prior to study treatment.

Abnormal laboratory values:

- Absolute neutrophil count  $< 1500/\text{mm}^3$  and white blood cell (WBC) count  $< 3000/\text{mm}^3$
- Platelet count  $< 100,000/\text{mm}^3$
- Aspartate transaminase (AST)  $> 2.5$  x upper limit of normal
- Alanine transaminase (ALT)  $> 2.5$  x upper limit of normal
- Bilirubin  $> 1.5$  x upper limit of normal
- Creatinine  $> 1.5$  x upper limit of normal

Treated with the following antiemetic agents within 48 hours prior to Day 1:

- 5-HT<sub>3</sub> antagonists (ondansetron, granisetron, dolasetron, or tropisetron)
- phenothiazines (e.g., prochlorperazine, fluphenazine, perphenazine, thiethylperazine, or chlorpromazine)
- butyrophenones (e.g., haloperidol or droperidol)
- benzamides (e.g., metoclopramide or alizapride)
- domperidone
- cannabinoids

Benzodiazepine or opiate therapy initiated within 48 hours prior to Day 1 except single daily doses of triazolam, temazepam, or midazolam.

- Continuation of chronic benzodiazepine or opiate therapy was permitted provided it was initiated at least 48 hours prior to Day 1.

Systemic corticosteroid therapy initiated within 72 hours prior to Day 1 except as outlined in the protocol or as premedication for patients receiving paclitaxel or docetaxel. Patients who were receiving chronic ( $> 72$  hours) daily corticosteroid

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therapy could have been enrolled provided the corticosteroid dose was not >10 mg of prednisone daily or equivalent.

History of any illness that, in the opinion of the investigator, would have confounded the results of the study or posed unwarranted risk in administering study drug to the patient.

Active infection (e.g., pneumonia) or any uncontrolled disease (e.g., diabetic ketoacidosis, or gastrointestinal obstruction) except for malignancy that, in the opinion of the investigator, might have confounded the results of the study or posed unwarranted risk in administering study drug to the patient.

Scheduled to receive multiple-day chemotherapy with cisplatin in a single cycle. (Rationale: Single-day cisplatin chemotherapy is the standard emetogen for antiemetic studies.)

Scheduled to receive chemotherapy of moderate or high emetogenicity (Hesketh Level 3 or above) on the 6 days prior to the cisplatin infusion and/or during the 6 days following the cisplatin infusion.

There was no restriction on the timing of administration of chemotherapeutic agents of low emetogenicity (Hesketh Level 1 or 2 except: Paclitaxel and docetaxel had to be given on the same day as cisplatin and prior to cisplatin.

Vomiting and/or had dry heaves/retching within 24 hours prior to the start of the cisplatin infusion on Day 1 in Cycle 1.

Received or was scheduled to receive radiation therapy to the abdomen or pelvis within 1 week prior to Day 1, or between Days 1 to 6 in Cycle 1.

Symptomatic primary or metastatic CNS malignancy.

Chronic use, or had taken within 7 days prior to Day 1:

- Terfenadine
- Cisapride
- Astemizole
- Clarithromycin (azithromycin, erythromycin, and roxithromycin were permitted)
- Ketoconazole or itraconazole (fluconazole permitted)
- Amifostine

(Rationale: Agents that are CYP3A4 substrates or inhibitors may interact with MK-0869. Amifostine [not a CYP3A4 inhibitor] causes nausea and vomiting, which might have confounded assessment of efficacy.)

Chronic use, or had taken within 30 days prior to Day

- Barbiturates
- Rifampicin or rifabutin
- Phenytoin or carbamazepine

(Rationale: All are inducers of CYP3A4 that can reduce plasma levels of MK-0869, thereby potentially reducing efficacy.)

Concurrent medical condition that would preclude administration of dexamethasone for 4 days such as a systemic fungal infection or uncontrolled diabetes.

History of hypersensitivity to ondansetron or dexamethasone

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#### *Medical Officer Comment:*

*Amifostine was specifically part of the Exclusion Criteria. Since it is used to decrease the toxicity of chemotherapeutic agents, including cisplatin, the sponsor should evaluate the safety of the co-administration of MK-0869 with Amifostine. There is a high potential for these drugs to be utilized together. Amifostine is not a CYP3A4 substrate or inducer, however the safety of co-administration with aprepitant has not been evaluated and should be considered.*

#### **Exclusion Criteria (Multiple-Cycle Extension)**

Positive pregnancy test.

Active infection (e.g., pneumonia) or any uncontrolled disease (e.g., diabetic ketoacidosis) except for malignancy.

Started any restricted medications

(Azithromycin, erythromycin, roxithromycin, and fluconazole were permitted)

Abnormal laboratory values:

- Absolute neutrophil count  $<1500 \text{ mm}^3$  and WBC count  $<3000/\text{mm}^3$
- Platelet count  $<100,000/\text{mm}^3$
- AST  $>2.5 \times$  upper limit of normal
- ALT  $>2.5 \times$  upper limit of normal
- Bilirubin  $>1.5 \times$  upper limit of normal
- Creatinine  $>1.5 \times$  upper limit of normal

#### *Medical Officer Comment:*

*A single site protocol amendment was made on November 1, 2001 to allow enrollment of pediatric patients at least 12 years of age, weighing at least 40 kg. The Inclusion and Exclusion criteria are acceptable.*

#### **Discontinuation of Patients**

Protocol-defined reasons for discontinuation included:

The patient wished to withdraw.

The patient had an adverse experience and did not want to continue or was advised by the investigator not to continue.

The patient failed to comply with the study requirements and/or the investigator's instructions.

The patient required medication not permitted by the protocol.

Any other reason, in the opinion of the investigator that precluded further participation by the patient.

#### *Medical Officer Comment:*

*The protocol-defined reasons for discontinuation were done in a blinded fashion and should not result in any bias.*

**Definition of Compliance**

A patient was considered to be compliant with therapy if he/she took all the prescribed medication on 4 study treatment days.

**Definition of Study Completion**

A patient was considered to have completed the study if he/she completed the Days 19 to 29 visit of Cycle 1 or if he/she completed the Days 19 to 29 visit of Cycle 6. A patient status of “completed, not continuing” was assigned to any patient who completed the Days 19 to 29 visit of Cycles 1 to 5, but did not participate in a subsequent cycle of treatment. Cessation of the study at any other point was defined as a discontinuation.

**Handling of Dropouts or Missing Data**

For the efficacy analyses of the MITT population, missing data were imputed by carrying forward the preceding data that were not missing in the same phase (acute or delayed).

Acute phase represented only one efficacy measurement, so no carrying forward was possible. Within the delayed phase (25 to 120 hours post cisplatin), carrying forward was done from the preceding non-missing data. If efficacy data were missing on Day 2, no carrying forward was done.

Within the overall phase (0 to 120 hours post cisplatin), if data were missing for Day 1, no data were carried forward for Days 2 through 5, as no data were carried forward between the acute and delayed phases. However, if a patient failed for an efficacy endpoint on Day 1 and the rest of the data were missing, the patient was considered a “failure” in all analyses for that endpoint. If the patient was a “success” for an efficacy endpoint on Day 1 and the rest of the data were missing, the patient was excluded from the delayed and overall phase analyses for that endpoint.

In the per-protocol analysis no imputation for missing data was made.

When there were missing FLIE data, the domain score was calculated by multiplying the average item score for the items present by 9. At least 12 of the 18 FLIE items and both the vomiting and nausea domain had to be present to calculate a FLIE total score.

*Medical Officer Comment:*

*The sponsor submitted analyses on two populations, the MITT, in which missing data were imputed by carrying forward and the per-protocol population where no imputation*

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*for missing data was made. In the per-protocol analysis, patients with missing efficacy data were excluded. The results of this will be discussed in the efficacy section. The defined population is acceptable for efficacy analysis. The primary analysis was performed on the MITT population.*

#### **Efficacy and Safety Monitoring**

During Cycle 1 of chemotherapy, patients reported episodes of nausea and vomiting and use of rescue therapy in a diary. The diary was maintained daily from initiation of cisplatin infusion (0 hours) until the morning of Day 6 (~120 hours). In Cycle 1, telephone contact was made each morning on Days 2 to 6 to assess the patient's status and to ensure that emetic episodes, use of rescue medication, and severity of nausea were recorded appropriately in the diary.

When the patient returned for the Days 6 to 8 Visit, study site personnel reviewed the diary with the patient to ensure that it had been completed appropriately, the patient then corrected errors, omissions, or ambiguities.

After completion of Cycle 1, patients had the option to participate in a multiple-cycle extension. A patient could participate in a maximum of 5 subsequent cycles if they fulfilled the multiple-cycle enrollment criteria.

The diary was maintained only during Cycle 1. For the multiple-cycle phase, the diary was replaced by a Emetic Episodes and Nausea Assessment worksheet. This two-question questionnaire assessed nausea and vomiting during the 120-hour post cisplatin infusion period for each subsequent cycle. This was completed at the Days 6 to 8 visit of each cycle.

#### **Safety Parameters**

All patients who received cisplatin and at least one dose of study drug were included in the safety analysis. During the diary data collection period nausea and vomiting were not considered adverse experiences unless they resulted in hospitalization. After the morning of Day 6, nausea and vomiting were recorded as adverse experiences.

All patients were required to undergo baseline physical examinations, laboratory studies, and an electrocardiogram. These were repeated at the study completion or patient discontinuation. Patients were required to maintain the diary card to record efficacy measurements and to attend office visits according to the protocol schedule. Each visit included the collection of vital signs. Laboratory evaluations were done routinely throughout the study. Each subsequent chemotherapy cycle required blood sampling for laboratory tests.

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During the multiple cycle extension (Cycles 2 to 6) only serious adverse experiences and non-serious adverse experiences that led to discontinuation from study drug, or were considered drug-related by the investigator, were collected.

Table 2  
Schedule of Clinical Observations and Laboratory Measurements—Cycle 1

Procedure	Prestudy <sup>1</sup>	Postinitiation of Cisplatin Infusion																
		Day 1: Hours										Days				Day		
		-2.5	-2	-1.0	-0.5	0	1	2	3	3.5	4	2 & 3	4	5 & 6 <sup>2</sup>	6 to 8 <sup>2</sup>	19 to 29 <sup>2</sup>		
Medical history	X																	
Informed consent form	X																	
Physical examination and 12-lead ECG <sup>3</sup>	X																X <sup>1</sup>	
Vital signs and weight <sup>4</sup>	X	X															X	
Laboratory safety tests <sup>5</sup>	X																X	
Review of laboratory test results		X															X	
Prehydration			X	X	X												X	
MK-0869 or placebo dosing				X														
Ondansetron and dexamethasone dosing <sup>6</sup>				X														
Cisplatin infusion over ≤3 hours					X	X	X	X										
Additional chemotherapeutic agents if indicated							X	X										
MK-0869 or placebo dosing												X						
Dexamethasone or placebo dosing												X	X					
Rescue therapy if required						X											X	
Daily telephone contact												X	X	X				
Diary recording of ematic events		X										X	X	X				
Diary recording of nausea using VAS		X										X	X	X				
Diary recording of use of rescue therapy												X	X	X				
FLIE questionnaire <sup>7</sup>		X												X				
Capsule/tablet count for MK-0869 and dexamethasone																	X	
HEA case report form																	X	
Adverse experience monitoring	X																X	

(Ref. Table 3 P052.pdf)

Table 3  
Schedule of Clinical Observations and Laboratory Measurements—  
Cycles 2 Through 6

Procedure	Baseline <sup>1</sup>	Postinitiation of Cisplatin Infusion																
		Day 1: Hours										Days				Day		
		-2.5	-2	-1.0	-0.5	0	1	2	3	3.5	4	2 & 3	4	5	6 to 8 <sup>2</sup>	19 to 29 <sup>2</sup>		
Physical examination and 12-lead ECG <sup>3</sup>																	X	
Laboratory safety tests	X																X	
Review of laboratory test results	X	X															X	
Vital signs	X	X															X	
Prehydration			X	X	X												X	
MK-0869 or placebo dosing				X														
Ondansetron and dexamethasone dosing <sup>6</sup>				X														
Cisplatin infusion over ≤3 hours					X	X	X	X										
Additional chemotherapeutic agents if indicated							X	X										
MK-0869 or placebo												X						
Dexamethasone or placebo dosing												X	X					
Rescue therapy if required						X											X	
Assessment of nausea and vomiting												X	X	X			X	
Capsule/tablet count for MK-0869 and dexamethasone																	X	
Serious adverse experience monitoring <sup>8</sup>	X																X	

(Ref. Table 4 P052.pdf)

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Table 4

#### Protocol-Specified Laboratory Tests

Hematology	Chemistry	Urinalysis
Hemoglobin	Bicarbonate	pH
Hematocrit	Creatinine	Protein
Total WBC	Total bilirubin	Glucose
Neutrophils	AST (SGOT)	Microscopy: <sup>†</sup> WBCs RBCs Epithelial cells Casts (specify)
Lymphocytes	ALT (SGPT)	
Monocytes	Alkaline phosphatase	
Eosinophils	Glucose (random)	
Basophils	Albumin	
Platelet count	Sodium	
	Potassium	
	Chloride	
	Urea	
	β-hCG <sup>‡</sup>	

<sup>†</sup> To have been performed only if preceding urinalysis values were abnormal.  
<sup>‡</sup> Females of childbearing potential.  
WBC = White blood cell count.  
AST = Aspartate transaminase.  
ALT = Alanine transaminase.  
RBC = Red blood cell count.  
β-hCG = Beta human chorionic gonadotropin.

(Ref. Table 8 P052.pdf)

#### *Medical Officer Comment:*

*The efficacy and safety monitoring was adequate. Since nausea and vomiting are known side effects of highly emetogenic chemotherapy, excluding them as adverse experiences unless they resulted in hospitalization is acceptable.*

#### **Adverse Experiences**

The investigator graded adverse experiences according to the National Cancer Institute (NCI) Common Toxicity Criteria.

#### **Laboratory Adverse Experiences**

Laboratory findings that were determined by the investigator to be inconsistent with the predictable effects of the patient's chemotherapy and that were considered to be clinically significant as adverse experiences were recorded as an adverse experience.

Serious laboratory adverse experiences were categorized by the NCI Common Toxicity Grade and summarized by treatment group and cycle.

Only serious adverse experiences and non-serious adverse experiences that led to discontinuation or were considered drug related by the investigator were reported for Cycles 2 to 6.

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*Medical Officer Comment:*

*The sponsor allowed patients with baseline liver functions that were 1.5-2.5 times the upper normal limit to be included in the study, which is acceptable considering the population studied.*

**Study Population:**

Two patient populations were evaluated for the efficacy analysis: modified-intention-to-treat population (MITT) and the per-protocol population. The MITT population was the primary population used to assess efficacy. This included all patients who received cisplatin, took a dose of study drug, and had at least one post-treatment assessment during Cycle 1. The per-protocol population was the MITT population excluding patients who were identified as protocol violators prior to unblinding.

A total of 534 patients (including 4 adolescents) were enrolled in the study. Patients were randomized into 1 of 2 treatment groups:

266 patients (including 2 adolescents) were in the MK-0869 group  
268 patients (including 2 adolescents) were in the Standard Therapy group

Of the 530 adult patients, 9 patients were excluded from the MITT analyses.

Four patients did not receive study drug or cisplatin  
One patient received study drug but no cisplatin  
Four patients received study drug and cisplatin but did not provide any post-treatment evaluations in the diary.

Breakdown of patients included in the MITT analyses:

262 patients (including 2 adolescents) received the MK-0869 regimen  
263 patients (including 2 adolescents) received the Standard Therapy

*Medical Officer Comment:*

*The defined modified-intention-to-treat (MITT) population and the per-protocol population are acceptable.*

*The number of patients who were randomized and did not meet laboratory inclusion criteria, or who took a prohibited medication(s) or failed for other inclusion/exclusion criteria were well balanced. The sponsor included these patients in the MITT analysis.*

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#### Cisplatin Deviations

Five patients (ANs 8054, 8118, 8206, 8373, and 9049) were discontinued after randomization and did not receive cisplatin. These patients were excluded from the MITT analyses.

One hundred eight randomized patients received less than the protocol defined 70-mg/m<sup>2</sup> dose of cisplatin.

102 patients received >65 mg/m<sup>2</sup> cisplatin

6 patients received <64 mg/m<sup>2</sup> cisplatin with 1 patient receiving 50 mg/m<sup>2</sup>

The sponsor states all patients received a highly emetogenic dose of cisplatin (>50 mg/m<sup>2</sup>); therefore, were included in the safety and efficacy analyses.

#### *Medical Officer Comment:*

*The number of patients who received less than the protocol defined 70-mg/m<sup>2</sup> dose of cisplatin was balanced between treatment groups and would not result in an un-fair bias. (see demographic table). The Agency performed analysis excluding patients who received less than 70 mg/m<sup>2</sup> and the efficacy was maintained for the primary endpoint complete response in the overall phase, as well as the secondary endpoints of complete response in the acute and delayed phases.*

*A literature search confirms that the Hesketh Classification describes a Cisplatin dose of  $\geq 50$  mg/m<sup>2</sup> as a "Level 5" chemotherapeutic agent, the highest level in the classification. This dose is associated with > 90% of the patients developing emesis. The agency accepts the inclusion of patients in the analysis who received a cisplatin dose of  $\geq 50$  mg/m<sup>2</sup>.*

#### **Per-Protocol Analysis Population**

Protocol violators were identified prior to unblinding. Violations that were deemed likely to confound the analysis were excluded from the per-protocol population.

After the data file was frozen and unblinded, the therapy violators were re-evaluated to determine if any of the violations related to only placebo doses. One patient in the MK-0869 group (AN 8073) had a violation relating only to a placebo dose and was included in the per-protocol analysis.

#### *Medical Officer Comment:*

*The difference between the MITT population and the per-protocol population was small. The per-protocol population is not the preferred analysis, but will be considered in the overall evaluation of efficacy. The efficacy results of both populations were comparable.*

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There were 514 patients in the acute phase and 504 patients in the delayed and overall phases included in the per-protocol analysis.

### Demographics and Characteristics

Table 5  
Baseline Patient Demographics and Characteristics by Treatment Group—Cycle 1,  
Adult and Adolescent Patients

	MK-0869 Regimen (N=266)		Standard Therapy (N=268)		Total (N=534)	
	n	(%)	n	(%)	n	(%)
<b>Gender</b>						
Male	168	(63.2)	168	(62.7)	336	(62.9)
Female	98	(36.8)	100	(37.3)	198	(37.1)
<b>Age</b>						
17 and under	2	(0.8)	2	(0.7)	4	(0.7)
18 to 24	6	(2.3)	2	(0.7)	8	(1.5)
25 to 34	5	(1.9)	11	(4.1)	16	(3.0)
35 to 44	22	(8.3)	18	(6.7)	40	(7.5)
45 to 54	48	(18.0)	72	(26.9)	120	(22.5)
55 to 64	84	(31.6)	75	(28.0)	159	(29.8)
65 to 74	82	(30.8)	73	(27.2)	155	(29.0)
Over 74	17	(6.4)	15	(5.6)	32	(6.0)
Mean	58.5		57.4		58.0	
SD	12.97		12.44		12.71	
Median	61.0		59.0		60.0	
Range	15 to 84		14 to 83		14 to 84	
Male	15 to 82		14 to 83		14 to 83	
Female	18 to 84		30 to 79		18 to 84	
<b>Race</b>						
Asian	14	(5.3)	8	(3.0)	22	(4.1)
Black	11	(4.1)	5	(1.9)	16	(3.0)
Hispanic American	4	(1.5)	7	(2.6)	11	(2.1)
Multi-Racial	1	(0.4)	2	(0.7)	3	(0.6)
White	236	(88.7)	246	(91.8)	482	(90.3)
<b>Alcohol Intake</b>						
No consumption per week	152	(57.1)	153	(57.1)	305	(57.1)
1 to 4 drinks per week	45	(16.9)	47	(17.5)	92	(17.2)
5 to 7 drinks per week	12	(4.5)	13	(4.9)	25	(4.7)
8 to 10 drinks per week	6	(2.3)	2	(0.7)	8	(1.5)
>10 drinks per week	44	(16.5)	41	(15.3)	85	(15.9)
Null	7	(2.6)	12	(4.5)	19	(3.6)
<b>History of Morning Sickness</b>						
Yes	19	(7.1)	13	(4.9)	32	(6.0)
No	247	(92.9)	254	(94.8)	501	(93.8)
Null	0	(0.0)	1	(0.4)	1	(0.2)

(Ref. Table 23 P052.pdf)

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Table 5 (cont)

Baseline Patient Demographics and Characteristics by Treatment Group—Cycle 1,  
Adult and Adolescent Patients

	MK-0869 Regimen (N=266)		Standard Therapy (N=268)		Total (N=534)	
	n	(%)	n	(%)	n	(%)
<b>History of Motion Sickness</b>						
Yes	20	(7.5)	12	(4.5)	32	(6.0)
No	246	(92.5)	255	(95.1)	501	(93.8)
Null	0	(0.0)	1	(0.4)	1	(0.2)
<b>History of Chemotherapy</b>						
Yes	41	(15.4)	39	(14.6)	80	(15.0)
No	225	(84.6)	229	(85.4)	454	(85.0)
<b>History of Chemotherapy-Induced Vomiting</b>						
Yes	20	(7.5)	15	(5.6)	35	(6.6)
No	246	(92.5)	253	(94.4)	499	(93.4)
<b>Other Concurrent Emetogenic Chemotherapy</b>						
(Hesketh Level $\geq 3$ )						
With <sup>†</sup>	40	(15.0)	44	(16.0)	83	(15.5)
Without <sup>‡</sup>	226	(85.0)	224	(84.0)	451	(84.5)
<b>Cisplatin Dose</b>						
<70 mg/m <sup>2</sup>	52	(19.5)	56	(20.9)	108	(20.2)
$\geq 70$ to 100 mg/m <sup>2</sup>	187 <sup>§</sup>	(70.3)	185	(69.0)	372	(69.7)
>100 mg/m <sup>2</sup>	24	(9.0)	25	(9.3)	49	(9.2)
Mean Dose (mg/m <sup>2</sup> )	80.6		79.8		80.2	
No Cisplatin	3	(1.1)	2	(0.7)	5	(0.9)

<sup>†</sup> Includes patients who received other concurrent emetogenic chemotherapy (Hesketh Level  $\geq 3$ ) excluding cisplatin.  
<sup>‡</sup> Includes patients who received other concurrent emetogenic chemotherapy (Hesketh Level <3) excluding cisplatin, and patients with no other concurrent emetogenic chemotherapy.  
<sup>§</sup> Does not include patients who received no dose of cisplatin (ANs 8054, 8114, 8206, 8373, and 9049). The lowest dose of cisplatin administered was 50 mg/m<sup>2</sup>.  
<sup>¶</sup> Includes one patient (AN 8287), whose baseline body weight was not measured. The cisplatin dose was calculated based the body weight entered at Visit 5.  
 MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone: 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 Note: For adolescents, ondansetron was given as 0.15 mg/kg IV times 3 on Day 1.  
 P.O. = By mouth.  
 IV = Intravenous.  
 AN = Allocation number.

(Ref. Table 23 P052.pdf)

**Medical Officer Comment:**

*The majority of the patients were Caucasian males with an average age of 59. The study groups were balanced for the distribution of risk factors for CINV which include: female gender, history of alcohol use, morning sickness, motion sickness, and prior chemotherapy-induced vomiting.*

*The number of patients who received a concomitant Hesketh level  $\geq 3$  chemotherapy were balanced between treatment groups. The type of cancer was similarly distributed between treatment groups. Non-small cell lung cancer was the most common primary cancer diagnosis.*

#### Concomitant Chemotherapy Other Than Cisplatin

Concomitant chemotherapy was administered to 94.7% the patients. The pattern of use of these therapies was similar between treatment groups. The most common concomitant agents used were gemcitabine (29.3%), fluorouracil (16.8%), etoposide (13.8%), and vinorelbine tartrate (10.0%).

#### Concomitant Medical Therapy

*Medical Officer Comment:*

*Overall, the use of concomitant medical therapy was similar between treatment groups. The use of antiemetic medication, anti-ulcer therapy and corticosteroids was more common in the Standard Therapy group than the MK-0869 group. This difference would not result in a bias in favor of the MK-0869 regimen.*

#### Efficacy Evaluation and Results

During Cycle 1 of chemotherapy, patients reported episodes of nausea and vomiting and use of rescue therapy in a diary. The diary was maintained from initiation of cisplatin infusion (0 hours) until the morning of Day 6 (~120 hours).

After completion of Cycle 1, patients had the option to participate in a multiple-cycle extension. A patient could participate in a maximum of 5 subsequent cycles if they fulfilled the multiple-cycle enrollment criteria.

The diary was maintained only during Cycle 1. For the multiple-cycle phase, the diary was replaced by an Emetic Episodes and Nausea Assessment worksheet. This two-question questionnaire assessed nausea and vomiting during the 120-hour post-cisplatin infusion period for each subsequent cycle.

*Medical Officer Comment:*

*Approximately 95% of patients in each treatment group were compliant with the study regimen. All adolescent patients were fully compliant with study regimen.*

#### Primary Endpoint:

The primary efficacy endpoint of overall complete response is defined as no emetic episodes and no rescue medication during the 5 days following cisplatin chemotherapy (0 to 120 hours post cisplatin).

During the 5 days post-cisplatin administration, 72.7% of patients in the MK-0869 group and 52.3% of the patients in the Standard Therapy group reported complete response. The MK-0869 group had statistically significant higher

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proportion of responders than the Standard Therapy group ( $p < 0.001$ , adjusted for gender, region, and use of concomitant chemotherapy)

#### *Medical Officer Comment:*

*The primary endpoint was overall complete response, which does not specifically include evaluation for nausea. The sponsor requests an indication for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. The nausea indication will need to be supported by the analyses of the secondary endpoints (see below).*

#### **Secondary Endpoints:**

##### Complete Response: acute phase (0 to 24 hours post cisplatin):

In the first 24 hours following administration of cisplatin, 89.2% and 78.1% of the patients in the MK-0869 group and Standard Therapy group, respectively, had a complete response ( $p < 0.001$ ).

##### Complete Response: Delayed phase (25 to 120 hours post cisplatin):

In the delayed phase, the complete response rate for the MK-0869 regimen was significantly higher than that of Standard Therapy with 75.4% in the MK-0869 group and 55.8% for the Standard Therapy group ( $p < 0.001$ ).

##### Complete Response: (Per-Protocol Analysis)

Table 6

Number (%) of Patients With Complete Response<sup>†</sup>  
by Treatment Group and Phase  
(Per-Protocol Analysis)

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Overall Phase	186/250	(74.4)**	131/252	(52.0)
Acute Phase	229/257	(89.1)**	200/255	(78.4)
Delayed Phase	193/250	(77.2)**	139/252	(55.2)

(Ref. Table 41 P052.pdf)

#### *Medical Officer Comment:*

*The primary analysis was based on the MITT population. The results of the per-protocol analysis were similar to those of the MITT analysis. The per-protocol analysis further supports the efficacy of the aprepitant regimen.*

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#### Complete Response: (Prespecified By Day Analysis)

Table 7

Number (%) of Patients With Complete Response<sup>†</sup>  
by Treatment Group and Day (Modified-Intention-to-Treat Analysis)

Phase	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Day 1	231/259	(89.2)	203/260	(78.1)
Day 2	222/260	(85.4)	176/260	(67.7)
Day 3	224/260	(86.2)	179/260	(68.8)
Day 4	227/260	(87.3)	200/260	(76.9)
Day 5	232/260	(89.2)	215/260	(82.7)

(Ref. Table 53 P052.pdf)

#### *Medical Officer Comment:*

*The percentages of patients in the Cycle 1 MITT population reporting complete response were analyzed by day during Cycle 1 (defined as increments of 24 hours from initiation of cisplatin). The difference of complete response by day between the MK-0869 regimen and Standard Therapy was greatest on Day 2 (17.7%) and declined to 6.5% by Day 5. These results are consistent with the biphasic pattern of vomiting seen with cisplatin administration where the second peak of vomiting occurs between Days 2-3.*

#### No Emesis: Overall, Acute, and Delayed Phases

The secondary endpoint no emesis was defined as the absence of vomiting or retching, regardless of rescue medication. Overall, 77.7% of the MK-0869 patients and 55.0% of the patients on Standard Therapy reported having no emesis during the 5 days post-cisplatin administration ( $p < 0.001$ ).

In the first 24 hours following administration of cisplatin (Acute Phase), 90.0% and 79.3% of the patients in the MK-0869 group and Standard Therapy group, respectively, reported having no emesis ( $p = 0.001$ ).

For the delayed phase, 80.8% and 58.8% of the patients in the MK-0869 group and Standard Therapy group, respectively, reported having no emesis ( $p < 0.001$ ).

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Table 8

Number (%) of Patients With Emesis Frequency<sup>†</sup>  
by Treatment Group—Overall Phase (Modified-Intention-to-Treat Analysis)

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
No emesis	202/260	(77.7)	143/260	(55.0)
1 to 2 episodes of emesis	23/260	(8.8)	44/260	(16.9)
3 or more episodes of emesis	35/260	(13.5)	73/260	(28.1)

<sup>†</sup> Emesis Frequency = Emetic episode frequency regardless of rescue therapy.  
 MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 P.O. = By mouth.  
 IV = Intravenous.  
 n/m = Number of patients with desired response/number of patients included in display category.  
 Overall Phase = 0 to 120 hours following initiation of cisplatin infusion.

(Ref. Table 50 P052.pdf)

Table 9

Number (%) of Patients With No Emesis<sup>†</sup>  
by Treatment Group and Day (Modified-Intention-to-Treat Analysis)

Phase	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Day 1	234/260	(90.0)	207/261	(79.3)
Day 2	232/260	(89.2)	181/260	(69.6)
Day 3	233/260	(89.6)	192/260	(73.8)
Day 4	238/260	(91.5)	216/260	(83.1)
Day 5	243/260	(93.5)	232/260	(89.2)

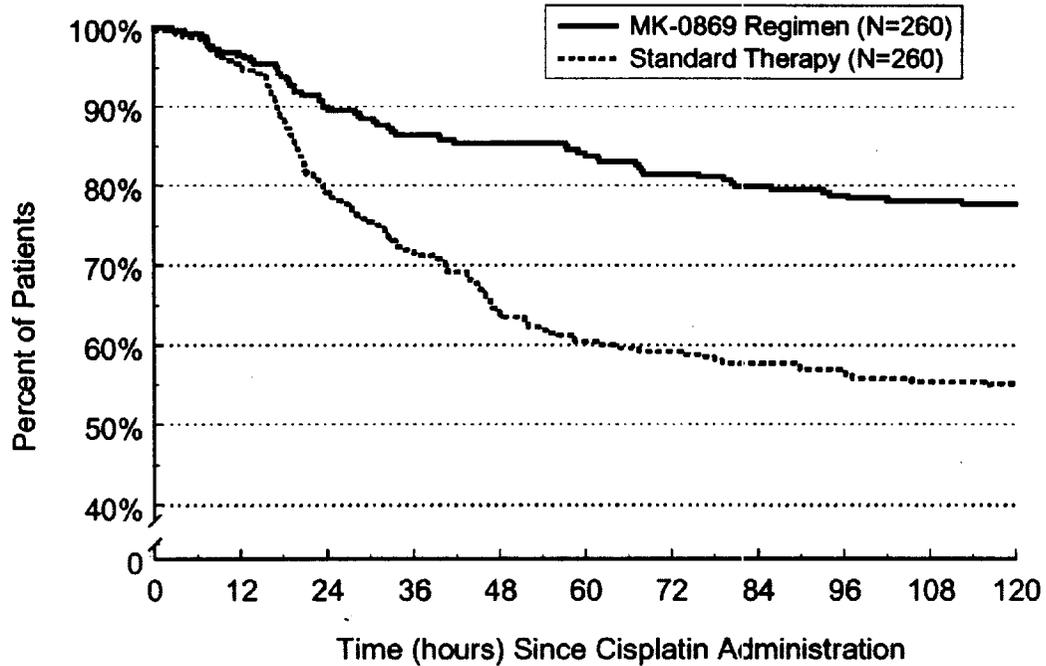
(Ref. Table 54 P052.pdf)

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Table 10

**Kaplan-Meier Curves for Time to First Emesis From Start of Cisplatin Administration in the Overall Phase—Cycle 1 (Modified Intention-to-Treat Analysis)**



(Ref. Figure 5 P052.pdf)

Table 11

**Number (%) of Patients With No Rescue<sup>†</sup> by Treatment Group and Phase (Modified-Intention-to-Treat Analysis)**

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Overall Phase	210/260	(80.8)**	184/260	(70.8)
Acute Phase	244/259	(94.2)*	231/260	(88.8)
Delayed Phase	211/260	(81.2)*	191/260	(73.5)

\* p<0.05 when compared with Standard Therapy.  
 \*\* p<0.01 when compared with Standard Therapy.  
 † No Rescue = No rescue medication.

(Ref. Table 51 P052.pdf)

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#### *Medical Officer Comment:*

*For the secondary endpoint of time to first emesis, the MK-0869 group had more emesis-free time than the Standard Therapy during the overall phase. The Kaplan-Meier curves appear to diverge approximately 12 hours after administration of cisplatin with the MK-0869 group having a longer time to first emesis.*

*The MK-0869 group also had a significantly smaller proportion of patients who required rescue medication than the Standard Therapy for the overall, acute and delayed phases. These results are displayed in Table 51 above. ( $p=0.009$ ,  $p=0.036$ ,  $p=0.039$ ).*

*The difference of no vomiting by day between the MK-0869 regimen and Standard Therapy was greatest on Day 2 (19.4%) and declined to only 4.3% by Day 5. These analyses support the aprepitant regimen is effective in the prevention of CINV in the acute and delayed phase.*

#### Relationship between Acute and Delayed Phase Emesis (Not Prespecified)

Effective control of acute symptoms has been shown to result in a reduced incidence of nausea and vomiting during the delayed phase. This phenomenon is commonly termed “carry-over” effect. To characterize this relationship, the sponsor performed additional analysis on patients stratified according to their emetic response in the acute phase in order to control for the potential influence carry-over effect.

Table 12

Categorization of Delayed Phase Emesis in the  
Subset of Patients With No Acute Phase Emesis by Treatment Group  
Regardless of Rescue Therapy—Delayed Phase (24 to 120 Hours Post Cisplatin)  
(Modified-Intention-to-Treat Analysis)

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
No emesis in delayed phase	202/234	(86.3)	143/206 <sup>†</sup>	(69.4)
≥1 emetic episode in delayed phase	32/234	(13.7)	63/206	(30.6)

<sup>†</sup> One patient was excluded (AN 8517 who had no emesis in the acute phase and no delayed emesis data).

(Ref. Table 57 P052.pdf)

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Table 13

Categorization of Delayed Phase Emesis in the Subset of Patients With Acute Phase Emesis by Treatment Group Regardless of Rescue Therapy—Delayed Phase (24 to 120 Hours Post Cisplatin) (Modified-Intention-to-Treat Analysis)

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
No emesis in delayed phase	8/26	(30.8)	10/54	(18.5)
≥1 emetic episode in delayed phase	18/26	(69.2)	44/54	(81.5)

(Ref. Table 58 P052.pdf)

In the MK-0869 group, 86.3% of patients who did not experience emesis during the acute phase remained emesis free during the delayed phase. In contrast, only 69.4% of the patients in the Standard Therapy group who were emesis-free during the acute phase had no delayed-phase emetic episodes.

There were 26 patients in the MK-0869 group and 54 patients in the Standard Therapy group who experienced at least one emetic episode in the acute phase. In the MK-0869 group, 30.8% of the patients with an acute emetic episode had no delayed emetic episodes. In the Standard Therapy group 18.5% of patients with acute emesis had no delayed emetic episodes. The sponsor proposes this analysis supports that the MK-0869 regimen is effective in controlling delayed emesis regardless of carry-over effect.

*Medical Officer Comment:*

*The Agency conveyed concerns to the sponsor regarding carry-over effect and recommended the protocol have a re-randomization after the acute phase. The sponsor proceeded without re-randomization. Though the analysis was not pre-specified, it does strongly suggest that, regardless of carry-over effect, the MK-0869 regimen was more effective than Standard Therapy in controlling delayed emesis.*

No Nausea/No Significant Nausea: Overall, and Delayed Phases

The secondary endpoint no nausea was self-assessed using a 100-mm horizontal VAS and was defined as a maximum nausea VAS <5 mm.

For both the overall phase and delayed phase, the MK-0869 group had numerically, but *not statistically significant*, higher proportion of patients reporting no nausea than the Standard Therapy group. In regard to severity of nausea, there were small but *not significant* differences between the two treatment groups for both the overall and delayed phases ( $p>0.1$ ) when the severity of nausea was analyzed using a pre-specified exploratory analysis of the VAS score.

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Table 14

Number (%) of Patients With No Nausea<sup>†</sup>  
by Treatment Group and Day (Modified-Intention-to-Treat Analysis)

Phase	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Day 1	185/256	(72.3)	179/259	(69.1)
Day 2	171/259	(66.0)	163/260	(62.7)
Day 3	177/259	(68.3)	157/260	(60.4)
Day 4	166/259	(64.1)	172/260	(66.2)
Day 5	164/259	(63.3)	168/260	(64.6)

(Ref. Table 55 P052.pdf)

Table 15

Number (%) of Patients With No Significant Nausea<sup>†</sup>  
by Treatment Group and Phase  
(Modified-Intention-to-Treat Analysis)

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Overall Phase	188/257	(73.2)	171/259	(66.0)
Delayed Phase	195/259	(75.3)	178/260	(68.5)

<sup>†</sup> No Significant Nausea = Maximum VAS <25 mm.  
 MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 P.O. = By mouth.  
 IV = Intravenous.  
 VAS = Visual analogue scale.  
 n/m = Number of patients with desired response/number of patients included in time point.  
 Overall Phase = 0 to 120 hours following initiation of cisplatin infusion.  
 Delayed Phase = 25 to 120 hours following initiation of cisplatin infusion.

(Ref. Table 45 P052.pdf)

**Medical Officer Comment:**

*In regard to the secondary endpoints of nausea, the MK-0869 regimen failed to demonstrate a statistically significant improvement over Standard Therapy.*

*Chemotherapy induced nausea and vomiting is a clinical syndrome. It is difficult to analyze and separate nausea from vomiting since the progression of nausea leads to vomiting. When taking into consideration that a higher proportion of patients in the Standard Therapy group used rescue therapy, the analyses are supportive for the composite endpoint of nausea and vomiting.*

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#### Patient-Reported Impact of CINV on Daily Life: Overall Phase (Cycle 1)

Patient-Reported Impact of CINV on Daily Life was measured using Functional Living Index-Emesis (FLIE). The FLIE questionnaire was a VAS-based, validated patient-reported measure of the impact of CINV on daily life.

#### *Medical Officer Comment:*

*A higher proportion of MK-0869 patients reported "no impact on daily life" when assessed by the protocol-defined FLIE, a self-administered questionnaire that focused on the effect of nausea and vomiting on the patients' daily life. (74.0% vs. 64.3% p=0.021) When the Agency performed a multiplicity adjustment, this difference no longer remained statistically significant.*

#### Complete Protection: Overall, Acute, and Delayed Phases (Analysis Prespecified)

Complete protection was defined as no emesis, no use of rescue medication, and no significant nausea (maximum nausea VAS<25 mm).

For the overall phase the MK-0869 group had a significantly higher proportion of patients with complete protection than the Standard Therapy group (p=0.001) with 63.4% of the patients in the MK-0869 group and 49.2% in the Standard Therapy reporting complete protection.

In the acute phase, 84.8% and 74.6% of the patients in the MK-0869 group and Standard Therapy group, respectively, reported complete protection (p=0.005).

For the delayed phase, 66.4% and 51.5% of the patients in the MK-0869 group and Standard Therapy group, respectively, reported complete protection. (p<0.001)

#### Total Control: Overall, Acute, and Delayed Phases (Analysis Prespecified)

Total Control was defined as no emesis, no use of rescue medication, and no nausea (maximum nausea VAS<5 mm).

#### *Medical Officer Comment:*

*For the endpoint of complete protection, the MK-0869 regimen was statistically more effective in the overall, acute, and delayed phases than the Standard Therapy.*

*For endpoint of Total Control, the MK-0869 regimen was numerically superior to Standard Therapy for overall, acute, and delayed phases, but the differences were not statistically significant.*

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### Subgroup Analysis: (Pre-specified)

Table 16

Number (%) of Patients With Complete Response<sup>†</sup> by Age Group, Race, and Treatment Group—Overall Phase (Modified-Intention-to-Treat Analysis)

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
<b>Age Group (years)</b>				
Age <65	110/162	(67.9)	86/176	(48.9)
Age ≥65	79/98	(80.6)	50/84	(59.5)
<b>Age &lt;75</b>				
Age <75	173/243	(71.2)	127/247	(51.4)
Age ≥75	16/17	(94.1)	9/13	(69.2)
<b>Race Group</b>				
Asian	9/13	(69.2)	5/8	(62.5)
Black	5/10	(50.0)	3/4	(75.0)
Hispanic American	3/4	(75.0)	1/6	(16.7)
Multi-Racial	0/0	(0.0)	0/2	(0.0)
White	172/233	(73.8)	127/240	(52.9)

<sup>†</sup> Complete Response = No emesis with no rescue therapy.

(Ref. Table 59 P052.pdf)

#### *Medical Officer Comment:*

*For the complete response endpoint in the overall phase, the MK-0869 regimen was more efficacious than the Standard Therapy for all age groups.*

*The number of Asian, Black and Hispanic patients were too small to draw any conclusions. However, the responder rate was lower in the Black population.*

#### Treatment Interactions

For the primary efficacy outcome of overall complete response, the sponsor evaluated treatment interactions with gender, region, and use of concomitant emetogenic chemotherapy. These factors were tested individually at the 10% significance level using logistic models.

The interactions between treatment and region, and treatment and concomitant chemotherapy were not significant ( $p > 0.10$ ). A treatment and gender interaction was identified during this study ( $p < 0.001$ ).

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Table 17

Number (%) of Patients With Complete Response<sup>†</sup> by Stratification Factor  
and Treatment Group—Overall Phase  
(Modified-Intention-to-Treat Analysis)

Stratification Factor	MK-0869 Regimen		Standard Therapy		p-Value <sup>‡</sup>
	n/m	(%)	n/m	(%)	
Female	76/98	(77.6)	38/98	(38.8)	0.001
Male	113/162	(69.8)	98/162	(60.5)	
Concomitant Chemotherapy					0.630
Yes	23/40	(57.5)	19/47	(40.4)	
No	166/220	(75.5)	117/213	(54.9)	
U.S.	42/61	(68.9)	30/60	(50.0)	0.673
Non-U.S.	147/199	(73.9)	106/200	(53.0)	

<sup>†</sup> Complete Response = No emesis with no rescue therapy.  
<sup>‡</sup> p-Value for the treatment-by-factor (gender, concomitant chemotherapy, and region) interaction test in the logistic model adjusting for gender, concomitant chemotherapy, and region.  
 MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 P.O. = By mouth.  
 IV = Intravenous.  
 n/m = Number of patients with desired response/number of patients included for the stratification factor.  
 Overall Phase = 0 to 120 hours following initiation of cisplatin infusion.

(Ref. Table 40 P052.pdf)

**Medical Officer Comment:**

*The interactions between treatment and region, and treatment and concomitant chemotherapy were not significant.*

*There was a treatment by gender interaction. There was difference in efficacy between male and female patients. For the complete response endpoints, the MK-0869 regimen was statistically superior to standard therapy in all three phases for female patients, however was only numerically better in males.*

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### Rescue Medications

Only antiemetic medication that was administered in the context of established nausea or emesis was considered rescue medication.

Table 18

Number (%) of Adult Patients With Specific Rescue Medications  
(Incidence >0% in One or More Treatment Groups) by Drug Category—  
Cycle 1 (Days 2 to 6)

	MK-0869 Regimen (N=264) <sup>†</sup>		Standard Therapy (N=266) <sup>†</sup>		Total (N=530)	
	n	(%)	n	(%)	n	(%)
Patients with one or more rescue medications	50	(18.9)	75	(28.2)	125	(23.6)
Patients with no rescue medication	214	(81.1)	191	(71.8)	405	(76.4)

(Ref. Table 34 P052.pdf)

#### *Medical Officer Comment:*

*The use of rescue medication was more common in the Standard Therapy group than the MK-0869 group. This difference was more pronounced in the delayed phase with 28.2% of the patients in the Standard Therapy requiring rescue therapy compared to 18.9% in the MK-0869 patients. The increased use of rescue therapy in the Standard Therapy group may have affected the efficacy outcome in regard to nausea.*

*Despite the greater uses of rescue medication in the Standard Therapy group, the proportion of patients with no nausea and no significant nausea for the overall and delayed phase was greater with the MK-0869 regimen than with the Standard Therapy; however, this difference did not reach statistical significance.*

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### Summary of Efficacy Results (Cycle 1)

Table 19

Number (%) of Patients With Favorable Response  
by Treatment Group and Phase (Modified-Intention-to-Treat Analysis)

Post-Cisplatin Phase	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
<b>No Emesis (no emetic episodes)</b>				
Overall Phase	202/260	(77.7)**	143/260	(55.0)
Acute Phase	234/260	(90.0)**	207/261	(79.3)
Delayed Phase	210/260	(80.8)**	153/260	(58.8)
<b>Complete Response (no emesis and no rescue therapy)</b>				
Overall Phase (0 to 120 hours)	189/260	(72.7)**	136/260	(52.3)
Acute Phase (0 to 24 hours)	231/259	(89.2)**	203/260	(78.1)
Delayed Phase (25 to 120 hours)	196/260	(75.4)**	145/260	(55.8)
<b>Complete Protection (no emesis, no rescue and maximum nausea VAS &lt;25 mm)</b>				
Overall Phase (0 to 120 hours)	163/257	(63.4)**	128/260	(49.2)
Acute Phase (0 to 24 hours)	217/256	(84.8)**	194/260	(74.6)
Delayed Phase (25 to 120 hours)	172/259	(66.4)**	134/260	(51.5)
<b>Total Control (no emesis, no rescue and maximum nausea VAS &lt;5 mm)</b>				
Overall Phase (0 to 120 hours)	117/257	(45.5)	104/260	(40.0)
Acute Phase (0 to 24 hours)	181/256	(70.7)	167/260	(64.2)
Delayed Phase (25 to 120 hours)	127/259	(49.0)	111/260	(42.7)
<b>No Use of Rescue Medication (for established emesis or nausea)</b>				
Overall Phase (0 to 120 hours)	210/260	(80.8)**	184/260	(70.8)
Acute Phase (0 to 24 hours)	244/259	(94.2)**	231/260	(88.8)
Delayed Phase (25 to 120 hours)	211/260	(81.2)**	191/260	(73.5)
<b>No Significant Nausea † (maximum VAS &lt;25 mm)</b>				
Overall Phase	188/257	(73.2)	171/259	(66.0)
Delayed Phase	195/259	(75.3)	178/260	(68.5)
<b>No Nausea † (maximum VAS &lt;5 mm)</b>				
Overall Phase (0 to 120 hours)	122/257	(47.5)	115/260	(44.2)
Delayed Phase (25 to 120 hours)	132/259	(51.0)	124/260	(47.7)

\* p<0.05 when compared with Standard Therapy.  
\*\* p<0.01 when compared with Standard Therapy.  
MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
P.O. = By mouth.  
IV = Intravenous.  
† Primary endpoint.  
‡ Analysis of acute phase response was not done for no significant nausea and no nausea.  
n/m = Number of patients with desired response/number of patients included in time point.  
VAS = Visual analogue scale.  
Overall Phase = 0 to 120 hours following initiation of cisplatin infusion.  
Acute Phase = 0 to 24 hours following initiation of cisplatin infusion.  
Delayed Phase = 25 to 120 hours following initiation of cisplatin infusion.

(Ref. Table 60 P052.pdf)

#### Medical Officer Comment:

For the endpoints of no emesis, complete response, and complete protection, the MK-0869 regimen demonstrated a statistically significant improvement for the overall, acute and delayed phases compared to Standard Therapy.

## **Safety Evaluation and Results**

### **MK-0869 Exposure (Cycle 1)**

All adult and adolescent patients randomized to the MK-0869 group were to receive MK-0869 125 mg PO on Day 1 and 80 mg PO on Days 2 and 3.

Of the 264 adult randomized patients, 261 patients received study drug with 259 patients completing cycle 1.

Both adolescent patients randomized to the MK-0869 regimen received MK-0869 125 mg on Day 1 and 80 mg on Days 2 and 3.

### **Total Exposure MK-0869 (Cycle 1-6)**

Overall (Cycles 1 to 6), the range of days on study drug was 2 to 18 days, with a mean of 8.3 days. Of the 261 randomized patients who received study drug in the MK-0869 group, 207 patients received study drug for <12 days

### **Dexamethasone (MK-0869 group) Exposure (Cycle 1)**

Day 1:

All adult patients randomized to the MK-0869 group (N=264) were scheduled to receive oral dexamethasone 12 mg on Day 1.

Three patients (ANs 8118, 8206, and 8373) were randomized, but never received study drug or cisplatin.

Twenty-eight patients required dexamethasone premedication for Taxane chemotherapy as defined in the study protocol.

The remaining 233 patients received the protocol dose of dexamethasone (12mg)

Days 2 to 4:

All patients randomized to the MK-0869 group (N=264) were to receive oral dexamethasone 8 mg in the morning and a placebo in the evening on Days 2, 3, and 4.

As described above, three patients (ANs 8118, 8206, and 8373) were randomized, but never received study drug or cisplatin.

One Patient (AN 9198) did not received any dexamethasone in Cycle 1 on Days 2 through 4 (reason unspecified).

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Four patients (ANs 8187, 8193, 8119, and 8336) received 8 mg of dexamethasone for only 2 days.

Two patients (ANs 8069 and 9015) received 8mg of dexamethasone for only 1 day.

Therefore, 254 randomized adult patients received the 8-mg oral dexamethasone dose for 3 days, per protocol. (total 4 days including Day 1)

All adolescent patients randomized to the MK-0869 group (N=2) were to receive 12 mg oral dexamethasone on Day 1 and 8 mg on Days 2, 3, and 4. Both patients followed the treatment regimen per protocol

#### **Dexamethasone (Standard Therapy) Exposure (Cycle 1)**

##### Day 1:

All adult patients randomized to the Standard Therapy group (N=266) were to receive oral dexamethasone 20 mg on Day 1.

One of these patients (AN 8054) was randomized, but never received study drug or cisplatin.

Thirty-one patients required dexamethasone premedication for Taxane chemotherapy as defined in the study protocol.

The remaining 233 patients received 20mg oral dexamethasone on Day 1, per protocol.

##### Days 2 to 4

All adult patients randomized to the Standard Therapy group (N=266) were to receive 8mg oral dexamethasone in the morning and evening daily on Days 2 to 4. (total 16mg)

One patient (AN 8054) was randomized, but never took study drug or cisplatin.

Three patients (ANs 8234, 9049, and 9122) discontinued study drug on Day 2 so they did not receive dexamethasone on Days 2, 3, and 4.

Of the remaining 262 randomized adult patients:

One patient (AN 8008) received dexamethasone for only 1 day.

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Eight patients (ANs 8020, 8077, 8265, 8509, 9004, 9019, 9072, and 9509) received dexamethasone for only 2 days.

Therefore, 253 adult patients received 16mg oral dexamethasone for 3 days, per protocol. (total 4 days including Day 1)

The two adolescent patients randomized to the Standard Therapy received 20mg oral dexamethasone on Day 1 and 16 mg on Days 2, 3, and 4. Both patients received all of the protocol doses of dexamethasone, however one patient (AN 8526) received his doses (16 mg on Days 2, 3, and 4) intravenously while hospitalized.

### **Dexamethasone Overall Exposure (Cycle 1-6)**

The range of days on dexamethasone was between 1 to 24 days with a mean number of days (any dose) of 10.4 days.

The range of days on dexamethasone for the 4 randomized adolescent patients was between 1 to 8 days with a mean number of days (any dose) of 4.2 days.

### **Ondansetron (MK-0869 group) Exposure (Cycle 1)**

Of the 264 adult patients randomized to the MK-0869 group 3 patients (ANs 8118, 8206, and 8373) did not receive study drug therapy.

Therefore, 261 adult patients in the MK-0869 group received 32 mg IV ondansetron on Day 1, per protocol.

Both randomized adolescent patients received three equal doses of ondansetron 0.15 mg/kg IV on Day 1. The average dose was 31.0 mg IV

### **Ondansetron (Standard Therapy) Exposure (Cycle 1)**

Of the 266 adult patients randomized to the Standard Therapy 1 patient (AN 8054) did not receive study drug or cisplatin.

Therefore, 265 patients in the Standard Therapy received 32 mg IV ondansetron.

Both adolescent patients received ondansetron on Day 1. The average dose was 30 mg.

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#### Ondansetron Overall Exposure (Cycle 1-6))

The range of days on ondansetron for the adult patients was between 1 to 6 days with a mean of 2.7 days. Of the 526 randomized adult patients who received ondansetron, 151 patients received it for >3 days.

The range of days on ondansetron for adolescent patients was between 1 to 2 days with a mean of 1.3 days. All 4 of the randomized adolescent patients received ondansetron for <3 days.

#### Adverse Experiences

Of the 530 adult patients randomized, 526 patients (261 patients in the MK-0869 group and 265 patients in the Standard Therapy group) were included in the assessment of safety and tolerability.

Four patients were excluded from the adverse tables:

One Patient (AN 8118) withdrew consent.

Two Patients (AN 8206 and AN 8373) experienced adverse experiences that precluded administration of study drug.

One patient, (AN 8054) randomized to the Standard Therapy group, never received study drug therapy because of ineligibility.

Adverse experiences were reported by 333 of 526 patients. One hundred seventy patients (65.1%) in the MK-0869 group and 163 patients (61.5%) in the Standard Therapy group reported one or more adverse experiences. The most commonly reported adverse experiences included asthenia/fatigue, hiccups, constipation, and nausea.

Drug-related adverse experiences (determined by the investigator to be possibly, probably, or definitely study drug related) occurred in 14.6% and 10.9% of patients in the MK-0869 group and Standard Therapy group, respectively.

#### Serious Adverse Experiences (Cycle 1)

The most commonly reported serious adverse experiences included: dehydration (5 patients [1.9%] and 3 patients [1.1%]), febrile neutropenia (6 patients [2.3%] and 5 patients [1.9%]), neutropenia (7 patients [2.7%] and 0 patients [0%]), and thrombocytopenia (4 patients [1.5%] and 0 patients [0%]) in the MK-0869 group and Standard Therapy group, respectively

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### Adult

Eighty-eight (16.7%) of the 526 randomized adult patients who received study drug had one or more *serious* adverse experiences: 42 (16.1%) and 46 (17.4%) of patients in the MK-0869 group and the Standard Therapy respectively.

Nine patients (5.2%) in the MK-0869 regimen and 10 patients (5.3%) in the Standard Therapy were discontinued from study due to *serious* adverse experiences. Three patients (1 patient in the MK-0869 group and 2 patients in the Standard Therapy group) had a serious adverse experience determined by the investigator to be drug-related.

Table 20

Clinical Adverse Experience Summary—Adult Patients—Cycle 1

	MK-0869 Regimen (N=261) <sup>†</sup>		Standard Therapy (N=265) <sup>‡</sup>	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	170	(65.1)	163	(61.5)
With no adverse experience	91	(34.9)	102	(38.5)
With drug-related <sup>§</sup> adverse experiences	38	(14.6)	29	(10.9)
With serious <sup>¶</sup> adverse experiences	42	(16.1)	46	(17.4)
With serious drug-related adverse experiences	1	(0.4)	2	(0.8)
Who died	7	(2.7)	9	(3.4)
Discontinued <sup>‡</sup> due to adverse experiences	21 <sup>¶</sup>	(8.0)	15	(5.7)
Discontinued <sup>‡</sup> due to drug-related adverse experiences	2	(0.8)	2	(0.8)
Discontinued <sup>‡</sup> due to serious adverse experiences	13	(5.0)	14	(5.3)
Discontinued <sup>‡</sup> due to serious drug-related adverse experiences	0	(0.0)	2	(0.8)

<sup>†</sup> Three (3) additional adult patients (ANs 8118, 8206, and 8373) were randomized to the MK-0869 group but never received study drug therapy and are not included in this summary.

<sup>‡</sup> One (1) additional adult patient (AN 8054) was randomized to the Standard Therapy group but never received study drug therapy and is not included in this summary.

<sup>§</sup> Determined by the investigator to be possibly, probably, or definitely study drug related.

<sup>¶</sup> Determined by the investigator.

<sup>‡</sup> Discontinued from study drug therapy.

<sup>‡</sup> Two (2) additional adult patients (ANs 8206 and 8373) were randomized to the MK-0869 group but never received study drug therapy due to a clinical adverse experience and are therefore not reflected in this summary.

MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.

P.O. = By mouth.

IV = Intravenous.

N=Number of randomized adult patients in Cycle 1 in each treatment group who received study drug.

n= Number of randomized adult patients in Cycle 1 in each treatment group who received study drug in a given category.

AN=Allocation number.

(Ref. Table 73 P052.pdf)

Seventeen patients were reported as having an infection-related serious adverse experience. There were more infection-related serious adverse experiences in the MK-0869 group (10 patients) compared to the Standard Therapy group (6 patients).

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#### Adolescent

One or more adverse experiences were reported by 2 patients (100%) in the MK-0869 group and 1 patient (50%) in the Standard Therapy group.

The most commonly reported adverse experiences in the adolescent patients were fever, heartburn, mucous membrane disorder, and tinnitus (in the MK-0869 group), and nausea, rectal abscess, vomiting, and thrombocytopenia (in the Standard Therapy group). None of these adverse experiences resulted in discontinuation from study drug therapy.

#### *Medical Officer Comment:*

*The percentage of patients with drug related adverse experiences was higher in the MK-0869 group than the Standard therapy group, (14.6%, 10.9% respectively). Drug-related adverse experiences were determined by the investigator to be possibly, probably, or definitely study drug related. It is reassuring that the number of patients with defined drug related serious adverse experiences was smaller in the MK-0869 group than the Standard therapy group.*

*Regardless of investigator attribution to drug, the overall, the proportion of patients with serious adverse experiences, was slightly lower in the MK-0869 group compared to Standard Therapy group (16.1%, 17.4% respectively).*

#### Serious Adverse Experiences (Multiple Cycle)

Only adverse experiences that were considered to be serious or drug-related by the investigator, or resulted in study drug discontinuation, were to be reported in the multiple-cycle extension period.

Of the 526 patients included in the safety analysis, 172 patients (65.9%) in the MK-0869 group and 189 patients (71.3%) in the Standard Therapy group entered Cycle 2.

Adverse experiences were reported by 78 of 361 patients who received study drug therapy during the multi-cycle portion of the study. One or more adverse experiences were reported by 36 patients (20.9%) in the MK-0869 group and 42 patients (22.2%) receiving Standard Therapy.

During this extension period, serious adverse experiences occurred in 30 patients (17.4%) in the MK-0869 group and 38 patients (20.1%) in the Standard Therapy group.

The most commonly reported *serious* adverse experiences included: fever (5 patients [2.9%] and 4 patients [2.1%]), pneumonia (5 patients [2.9%] and 2 patients [1.1%]), anemia (4 patients [2.3%] and 2 patients [1.1%]), and

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dehydration (2 patients [1.2%] and 4 patients [2.1%]) in the MK-0869 group and Standard Therapy group, respectively.

During this period, 12 patients in each group had one or more adverse experiences that resulted in discontinuation of study drug. Of these 24 patients, 9 patients in the MK-0869 group and 10 patients in the Standard Therapy were discontinued due to serious adverse experiences. Only 1 patient (AN 8306, Standard Therapy) was discontinued for an adverse experience that was determined to be possibly drug-related.

Table 21

#### Clinical Adverse Experience Summary Multiple-Cycle Patients (Cycles 2 to 6)

	MK-0869 Regimen (N=172)		Standard Therapy (N=189)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	36	(20.9)	42	(22.2)
With no adverse experience	136	(79.1)	147	(77.8)
With drug-related adverse experiences <sup>†</sup>	4	(2.3)	4	(2.1)
With serious adverse experiences	30	(17.4)	38	(20.1)
With serious drug-related adverse experiences	0	(0.0)	1	(0.5)
Who died	4	(2.3)	9	(4.8)
Discontinued <sup>§</sup> due to adverse experiences	12	(7.0)	12	(6.3)
Discontinued <sup>§</sup> due to drug-related adverse experiences	0	(0.0)	1	(0.5)
Discontinued <sup>§</sup> due to serious adverse experiences	9	(5.2)	10	(5.3)
Discontinued <sup>§</sup> due to serious drug-related adverse experiences	0	(0.0)	1	(0.5)

<sup>†</sup> Determined by the investigator to be possibly, probably, or definitely study drug related.

<sup>‡</sup> Determined by the investigator.

<sup>§</sup> Discontinued from study drug therapy.

Note: Only adverse experiences that were considered to be serious or drug-related by the investigator, or resulted in study drug discontinuation, are presented in this table.

MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.

P.O. = By mouth.

IV = Intravenous.

N = Number of randomized adult patients in multiple cycles in each treatment group who received study drug.

n = Number of randomized adult patients in multiple cycles in each treatment group who received study drug in a given category.

(Ref. Table 75 P052.pdf)

There were no adolescent patients discontinued from study drug due to an adverse experience. One adolescent patient (AN 8530) entered the multiple cycle extension, completed 2 cycles and had no adverse experiences.

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### Summary of Adverse Experience by Body System (Cycle 1)

Table 22

Number (%) of Adult Patients With Specific Clinical Adverse Experiences  
(Incidence  $\geq 2\%$  in One or More Treatment Groups) by Body System—Cycle 1

	MK-0869 Regimen (N=261) <sup>†</sup>		Standard Therapy (N=265) <sup>‡</sup>	
	n	(%)	n	(%)
Patients with one or more adverse experiences	170	(65.1)	163	(61.5)
Patients with no adverse experience	91	(34.9)	102	(38.5)
<b>Body as a Whole/Site Unspecified</b>	<b>88</b>	<b>(33.7)</b>	<b>75</b>	<b>(28.3)</b>
Abdominal Pain	9	(3.4)	3	(1.1)
Asthenia/Fatigue	45	(17.2)	25	(9.4)
Dehydration	11	(4.2)	7	(2.6)
Dizziness	15	(5.7)	12	(4.5)
Fever	13	(5.0)	11	(4.2)
Flushing	6	(2.3)	0	(0.0)
Mucous Membrane Disorder	8	(3.1)	8	(3.0)
<b>Cardiovascular System</b>	<b>25</b>	<b>(9.6)</b>	<b>19</b>	<b>(7.2)</b>
Deep Venous Thrombosis	6	(2.3)	1	(0.4)
<b>Digestive System</b>	<b>94</b>	<b>(36.0)</b>	<b>87</b>	<b>(32.8)</b>
Constipation	21	(8.0)	32	(12.1)
Diarrhea	22	(8.4)	10	(3.8)
Epigastric Discomfort	6	(2.3)	5	(1.9)
Heartburn	17	(6.5)	11	(4.2)
Nausea <sup>§</sup>	28	(10.7)	23	(8.7)
Stomatitis	7	(2.7)	10	(3.8)
Vomiting <sup>¶</sup>	16	(6.1)	6	(2.3)
<b>Eyes, Ears, Nose, and Throat</b>	<b>27</b>	<b>(10.3)</b>	<b>19</b>	<b>(7.2)</b>
Pharyngitis	7	(2.7)	3	(1.1)
Tinnitus	12	(4.6)	7	(2.6)
<b>Hemic and Lymphatic System</b>	<b>28</b>	<b>(10.7)</b>	<b>25</b>	<b>(9.4)</b>
Anemia	10	(3.8)	8	(3.0)
Febrile Neutropenia	8	(3.1)	5	(1.9)
Neutropenia	11	(4.2)	8	(3.0)
Thrombocytopenia	10	(3.8)	4	(1.5)
<b>Metabolism and Nutrition</b>	<b>25</b>	<b>(9.6)</b>	<b>24</b>	<b>(9.1)</b>
Anorexia	12	(4.6)	11	(4.2)
Appetite Decreased	6	(2.3)	2	(0.8)
<b>Musculoskeletal System</b>	<b>23</b>	<b>(8.8)</b>	<b>19</b>	<b>(7.2)</b>
Back Pain	7	(2.7)	2	(0.8)
Myalgia	7	(2.7)	2	(0.8)
<b>Nervous System</b>	<b>35</b>	<b>(13.4)</b>	<b>35</b>	<b>(13.2)</b>
Headache	17	(6.5)	15	(5.7)
Insomnia	12	(4.6)	10	(3.8)
<b>Psychiatric Disorder</b>	<b>9</b>	<b>(3.4)</b>	<b>7</b>	<b>(2.6)</b>

(Ref. Table 76 P052.pdf)

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Table 22 (cont)

Number (%) of Adult Patients With Specific Clinical Adverse Experiences  
(Incidence ≥2% in One or More Treatment Groups) by Body System—Cycle 1

	MK-0869 Regimen (N=261) <sup>1</sup>		Standard Therapy (N=265) <sup>2</sup>	
	n	(%)	n	(%)
<b>Respiratory System</b>	<b>50</b>	<b>(19.2)</b>	<b>31</b>	<b>(11.7)</b>
Dyspnea	6	(2.3)	3	(1.1)
Hiccups	36	(13.8)	18	(6.8)
<b>Skin and Skin Appendages</b>	<b>16</b>	<b>(6.1)</b>	<b>8</b>	<b>(3.0)</b>
Rash	7	(2.7)	2	(0.8)
<b>Urogenital System</b>	<b>17</b>	<b>(6.5)</b>	<b>12</b>	<b>(4.5)</b>

<sup>1</sup> Three (3) additional adult patients (ANs 8118, 8206, and 8373) were randomized to the MK-0869 group, but never received study drug therapy and are not included in this summary.  
<sup>2</sup> One (1) additional adult patient (AN 8054) was randomized to the Standard Therapy group, but never received study drug therapy and is not included in this summary.  
<sup>3</sup> During Cycle 1, nausea or vomiting were to be reported as clinical adverse experiences after the completion of the diary period (Day 6 or greater), unless determined by the investigator to be serious, result in discontinuation, or drug-related, in which case nausea and vomiting were to be considered as clinical adverse experiences and were to be reported at any time.  
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.  
All body systems are listed in which one or more treatment groups had ≥2% incidence.  
MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
P.O. = By mouth.  
IV = Intravenous.  
N = Number of randomized adult patients in each treatment group who received study drug.  
n = Number of randomized adult patients in each treatment group who received study drug, with specific clinical adverse experiences.  
AN=Allocation number.

(Ref. Table 76 P052.pdf)

The 5 most frequent adverse experiences reported during Cycle 1 were asthenia/fatigue (17.2% and 9.4%), hiccups (13.8% and 6.8%), constipation (8.0% and 12.1%), nausea (10.7% and 8.7%), and diarrhea (8.4% and 3.8%) in the MK-0869 group and Standard Therapy group, respectively.

**Medical Officer Comment:**

*Abdominal pain was reported as an adverse experience in 9 patients in the MK-0869 regimen and only 3 in standard therapy. Fatigue and dehydration were reported as adverse experiences in almost twice as many patients in the MK-0869 regimen than the Standard Therapy. Of the five most frequently reported adverse experiences, four occurred more frequently in the MK-0869 group. The clinical significance of these differences is uncertain. The numbers of adolescent patients were too small to have meaningful analysis.*

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*During Cycle 1, Deep Venous Thrombosis occurred in 6 patients in the MK-0869 group compared to only 1 case in the Standard Therapy group. Similarly, Thrombocytopenia occurred in 10 patients in the MK-0869 group compared to only 4 cases in the Standard Therapy group. The incidence of both of these adverse events was smaller in Study 054 and the difference between the treatment groups was also small. The significance of this finding is uncertain.*

### Adverse Experience by Body System (Multiple Cycle)

Table 23

Number (%) of Adult Patients With Specific Serious Clinical Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by Body System—  
Multiple-Cycle Patients (Cycles 2 to 6)

	MK-0869 Regimen (N=172) <sup>†</sup>		Standard Therapy (N=189) <sup>†</sup>	
	n	(%)	n	(%)
Patients with one or more serious <sup>‡</sup> adverse experience	30	(17.4)	38	(20.1)
Patients with no serious adverse experience	142	(82.6)	151	(79.9)
<b>Body as a Whole/Site Unspecified</b>	<b>14</b>	<b>(8.1)</b>	<b>12</b>	<b>(6.3)</b>
Asthenia/fatigue	2	(1.2)	1	(0.5)
Burn	0	(0.0)	1	(0.5)
Cardiopulmonary failure	1	(0.6)	0	(0.0)
Chest pain	0	(0.0)	1	(0.5)
Dehydration	2	(1.2)	4	(2.1)
Fever	5	(2.9)	4	(2.1)
Fistula	0	(0.0)	1	(0.5)
Flank pain	1	(0.6)	0	(0.0)
Infection	1	(0.6)	0	(0.0)
Malignant neoplasm	1	(0.6)	1	(0.5)
Metastatic neoplasm of known primary	1	(0.6)	0	(0.0)
Mucous membrane disorder	2	(1.2)	0	(0.0)
Sepsis	1	(0.6)	0	(0.0)
Tumor lysis syndrome	0	(0.0)	1	(0.5)
<b>Cardiovascular System</b>	<b>7</b>	<b>(4.1)</b>	<b>9</b>	<b>(4.8)</b>
Acute myocardial infarction	0	(0.0)	1	(0.5)
Bradycardia	1	(0.6)	0	(0.0)
Cardiac arrest	0	(0.0)	1	(0.5)
Cardiovascular anomaly	1	(0.6)	0	(0.0)
Cerebrovascular accident	0	(0.0)	2	(1.1)
Deep venous thrombosis	2	(1.2)	1	(0.5)
Hypertension	1	(0.6)	0	(0.0)
Phlebitis	0	(0.0)	1	(0.5)
Pulmonary embolism	1	(0.6)	2	(1.1)
Supraventricular tachycardia	1	(0.6)	0	(0.0)
Venous infusion infection	0	(0.0)	1	(0.5)
Venous thrombosis	1	(0.6)	1	(0.5)
<b>Digestive System</b>	<b>5</b>	<b>(2.9)</b>	<b>6</b>	<b>(3.2)</b>
Constipation	0	(0.0)	1	(0.5)
Diarrhea	2	(1.2)	1	(0.5)
Intestinal obstruction	1	(0.6)	0	(0.0)
Melena	0	(0.0)	1	(0.5)

(Ref. Table 91 P052.pdf)

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Table 23 (cont)

Number (%) of Adult Patients With Specific Serious Clinical Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by Body System—  
Multiple-Cycle Patients (Cycles 2 to 6)

	MK-0869 Regimen (N=172) <sup>1</sup>		Standard Therapy (N=189) <sup>2</sup>	
	n	(%)	n	(%)
Nausea <sup>1</sup>	0	(0.0)	1	(0.5)
Stomatitis	1	(0.6)	1	(0.5)
Tongue malignant neoplasm	1	(0.6)	0	(0.0)
Upper gastrointestinal hemorrhage	0	(0.0)	1	(0.5)
Vomiting <sup>1</sup>	0	(0.0)	1	(0.5)
<b>Hemic and Lymphatic System</b>	<b>10</b>	<b>(5.8)</b>	<b>4</b>	<b>(2.1)</b>
Anemia	4	(2.3)	2	(1.1)
Febrile neutropenia	2	(1.2)	2	(1.1)
Neutropenia	2	(1.2)	1	(0.5)
Pancytopenia	2	(1.2)	0	(0.0)
Thrombocytopenia	3	(1.7)	0	(0.0)
<b>Metabolism and Nutrition</b>	<b>2</b>	<b>(1.2)</b>	<b>1</b>	<b>(0.5)</b>
Anorexia	1	(0.6)	0	(0.0)
Electrolyte imbalance	1	(0.6)	0	(0.0)
Malnutrition	0	(0.0)	1	(0.5)
<b>Musculoskeletal System</b>	<b>0</b>	<b>(0.0)</b>	<b>1</b>	<b>(0.5)</b>
Muscular weakness	0	(0.0)	1	(0.5)
<b>Nervous System</b>	<b>2</b>	<b>(1.2)</b>	<b>0</b>	<b>(0.0)</b>
Seizure	1	(0.6)	0	(0.0)
Seizure disorder	1	(0.6)	0	(0.0)
<b>Psychiatric Disorder</b>	<b>1</b>	<b>(0.6)</b>	<b>0</b>	<b>(0.0)</b>
Confusion	1	(0.6)	0	(0.0)
<b>Respiratory System</b>	<b>9</b>	<b>(5.2)</b>	<b>9</b>	<b>(4.8)</b>
Aspiration pneumonia	0	(0.0)	1	(0.5)
Bronchitis	1	(0.6)	0	(0.0)
Chronic obstructive pulmonary disease	0	(0.0)	1	(0.5)
Dyspnea	0	(0.0)	1	(0.5)
Hemoptysis	0	(0.0)	1	(0.5)
Lung malignant neoplasm	0	(0.0)	1	(0.5)
Non-small cell lung carcinoma	0	(0.0)	1	(0.5)
Pleural effusion	1	(0.6)	1	(0.5)
Pleural malignant neoplasm	1	(0.6)	0	(0.0)
Pneumonia	5	(2.9)	2	(1.1)
Pulmonary aspergillosis	1	(0.6)	0	(0.0)

(Ref. Table 91 P052.pdf)

# Study 052

## Aprepitant

Table 23 (cont)

Number (%) of Adult Patients With Specific Serious Clinical Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by Body System—  
Multiple-Cycle Patients (Cycles 2 to 6)

	MK-0869 Regimen (N=172) <sup>†</sup>		Standard Therapy (N=189) <sup>‡</sup>	
	n	(%)	n	(%)
<b>Skin and Skin Appendages</b>	<b>1</b>	<b>(0.6)</b>	<b>1</b>	<b>(0.5)</b>
Catheter site infection	1	(0.6)	0	(0.0)
Cellulitis	0	(0.0)	1	(0.5)
<b>Urogenital System</b>	<b>0</b>	<b>(0.0)</b>	<b>5</b>	<b>(2.6)</b>
Cystitis	0	(0.0)	1	(0.5)
Epididymitis	0	(0.0)	1	(0.5)
Nephrotoxicity	0	(0.0)	1	(0.5)
Renal failure	0	(0.0)	1	(0.5)
Urinary tract infection	0	(0.0)	1	(0.5)
Urinary tract obstruction	0	(0.0)	1	(0.5)

<sup>†</sup> Three (3) additional adult patients (ANs 8118, 8206, and 8373) were randomized to the MK-0869 group, but never received study drug therapy and are not included in this summary.

<sup>‡</sup> One (1) additional adult patient (AN 8054) was randomized to the Standard Therapy group, but never received study drug therapy and is not included in this summary.

<sup>§</sup> Determined by the investigator.

<sup>¶</sup> During multiple cycles, clinical adverse experiences of nausea or vomiting were to be reported only if determined by the investigator to be serious, result in discontinuation, or study drug related.

Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

All body systems are listed in which at least one patient had a serious clinical adverse experience.

MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.

P.O. = By mouth.

IV = Intravenous.

N = Number of randomized adult, multiple-cycle patients in each treatment group who received study drug.

n = Number of randomized adult, multiple-cycle patients in each treatment group who received study drug, with specific serious clinical adverse experiences.

AN=Allocation number.

(Ref. Table 91 P052.pdf)

**Medical Officer Comment:**

*During the multiple cycle extension, the incidence of most serious adverse experiences was similar between the treatment groups. The only body system that had a notable difference was the hematological system with a 5.8% incidence in the MK-0869 group and 2.1% in the Standard Therapy.*

*Pancytopenia was reported as an adverse event in 2 patients in the MK-0869 group compared to zero in the Standard Therapy. Thrombocytopenia also occurred with a higher incidence in the MK-0869 group during the multiple cycle extension, with 3 cases in the MK-0869 group compared to zero in the Standard Therapy. A causal relationship could not be established by review of the individual case report forms. This will be discussed and analyzed in the executive summary with the combined data from Studies 052 and 054*

# Study 052

## Aprepitant

### Drug-Related Adverse Experiences (Cycle 1)

Drug-related adverse experiences were determined by the investigator to be possibly, probably, or definitely study drug related. 38 patients (14.6%) in the MK-0869 group and 29 patients (10.9%) in the Standard Therapy group had one or more adverse experiences that were reported as *drug-related*. The most frequently reported drug-related adverse experience was hiccups (15 patients [5.7%] and 11 patients [4.2%] in the MK-0869 group and Standard Therapy group, respectively).

No adolescent patients experienced a drug-related adverse experience.

Table 24

Number (%) of Adult Patients With Specific Clinical Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by  
Body System—Cycle 1—Drug Related

	MK-0869 Regimen (N=261) <sup>a</sup>		Standard Therapy (N=265) <sup>b</sup>	
	n	(%)	n	(%)
Patients with one or more drug-related <sup>d</sup> adverse experiences	38	(14.6)	29	(10.9)
Patients with no drug-related adverse experience	223	(85.4)	236	(89.1)
<b>Body as a Whole/Site Unspecified</b>	<b>8</b>	<b>(3.1)</b>	<b>7</b>	<b>(2.6)</b>
Abdominal Pain	1	(0.4)	0	(0.0)
Asthenia/Fatigue	1	(0.4)	0	(0.0)
Chills	0	(0.0)	2	(0.8)
Dizziness	4	(1.5)	4	(1.5)
Edema	1	(0.4)	0	(0.0)
Flushing	1	(0.4)	0	(0.0)
Mucous Membrane Disorder	0	(0.0)	1	(0.4)
<b>Cardiovascular System</b>	<b>1</b>	<b>(0.4)</b>	<b>1</b>	<b>(0.4)</b>
Arrhythmia	0	(0.0)	1	(0.4)
Bradycardia	1	(0.4)	0	(0.0)
<b>Digestive System</b>	<b>19</b>	<b>(7.3)</b>	<b>8</b>	<b>(3.0)</b>
Acid Reflux	2	(0.8)	0	(0.0)
Constipation	5	(1.9)	3	(1.1)
Diarrhea	2	(0.8)	1	(0.4)
Dyspepsia	1	(0.4)	0	(0.0)
Esophagitis	0	(0.0)	1	(0.4)
Gastroesophageal Reflux Disease	2	(0.8)	1	(0.4)
Heartburn	5	(1.9)	3	(1.1)
Nausea <sup>e</sup>	3	(1.1)	0	(0.0)
Perforating Duodenal Ulcer <sup>f</sup>	1	(0.4)	0	(0.0)
Upper Gastrointestinal Hemorrhage	0	(0.0)	1	(0.4)
Vomiting <sup>g</sup>	1	(0.4)	0	(0.0)
<b>Eyes, Ears, Nose, and Throat</b>	<b>2</b>	<b>(0.8)</b>	<b>3</b>	<b>(1.1)</b>
Blurred Vision	0	(0.0)	1	(0.4)
Conjunctivitis	1	(0.4)	0	(0.0)
Tinnitus	1	(0.4)	0	(0.0)
Visual Acuity Decreased	0	(0.0)	1	(0.4)
Vocal Disturbance	0	(0.0)	1	(0.4)
<b>Hemic and Lymphatic System</b>	<b>3</b>	<b>(1.1)</b>	<b>1</b>	<b>(0.4)</b>
Anemia	3	(1.1)	0	(0.0)
Neutropenia	0	(0.0)	1	(0.4)
<b>Metabolism and Nutrition</b>	<b>0</b>	<b>(0.0)</b>	<b>2</b>	<b>(0.8)</b>
Hyperglycemia	0	(0.0)	1	(0.4)
Hyponatremia	0	(0.0)	1	(0.4)
<b>Musculoskeletal System</b>	<b>1</b>	<b>(0.4)</b>	<b>2</b>	<b>(0.8)</b>
Leg Pain	0	(0.0)	1	(0.4)
Myalgia	1	(0.4)	1	(0.4)

(Ref. Table 78 P052.pdf)

# Study 052

## Aprepitant

Table 24 (cont)

Number (%) of Adult Patients With Specific Clinical Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by  
Body System—Cycle 1—Drug Related

	MK-0869 Regimen (N=261) <sup>1</sup>		Standard Therapy (N=265) <sup>2</sup>	
	n	(%)	n	(%)
<b>Nervous System</b>	<b>8</b>	<b>(3.1)</b>	<b>8</b>	<b>(3.0)</b>
Akathisia	0	(0.0)	1	(0.4)
Dream Abnormality	1	(0.4)	0	(0.0)
Headache	6	(2.3)	3	(1.1)
Insomnia	2	(0.8)	2	(0.8)
Peripheral Neuropathy	0	(0.0)	1	(0.4)
Somnolence	0	(0.0)	1	(0.4)
Tremor	0	(0.0)	1	(0.4)
<b>Psychiatric Disorder</b>	<b>1</b>	<b>(0.4)</b>	<b>0</b>	<b>(0.0)</b>
Euphoria	1	(0.4)	0	(0.0)
<b>Respiratory System</b>	<b>15</b>	<b>(5.7)</b>	<b>11</b>	<b>(4.2)</b>
Hiccups	15	(5.7)	11	(4.2)
Sneezing	1	(0.4)	0	(0.0)
<b>Skin and Skin Appendages</b>	<b>2</b>	<b>(0.8)</b>	<b>0</b>	<b>(0.0)</b>
Photosensitivity	1	(0.4)	0	(0.0)
Rash	1	(0.4)	0	(0.0)
<b>Urogenital System</b>	<b>1</b>	<b>(0.4)</b>	<b>0</b>	<b>(0.0)</b>
Polyuria	1	(0.4)	0	(0.0)

<sup>1</sup> Three (3) additional adult patients (ANs 8118, 8206, and 8373) were randomized to the MK-0869 group but never received study drug therapy and are not included in this summary.  
<sup>2</sup> One (1) additional adult patient (AN 8054) was randomized to the Standard Therapy group, but never received study drug therapy and is not included in this summary.  
<sup>3</sup> Determined by the investigator to be possibly, probably, or definitely drug related.  
<sup>4</sup> During Cycle 1, nausea or vomiting were to be reported as clinical adverse experiences after the completion of the diary period (Day 6 or greater), unless determined by the investigator to be serious, result in discontinuation, or drug-related, in which case nausea and vomiting were to be considered as clinical adverse experiences and were to be reported at any time.  
<sup>5</sup> In this instance, for this patient (AN 8477), the test drug relationship refers to a possible relationship to dexamethasone.  
 Although a patient may have had 2 or more drug-related clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.  
 All body systems are listed in which at least 1 patient had a drug-related clinical adverse experience.  
 MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 P.O. = By mouth.  
 IV = Intravenous.  
 AN = Allocation number.  
 N = Number of randomized adult patients in each treatment group who received study drug.  
 n = Number of randomized adult patients in each treatment group who received study drug, with specific drug-related clinical adverse experiences.

(Ref. Table 78 P052.pdf)

**Medical Officer Comment:**

Overall the incidence of drug related adverse experiences was small in both groups. The only body system that had a notable difference in drug-related adverse experiences during Cycle 1 was the digestive system. More than twice as many patients in the MK-0869 group than Standard Therapy reported drug-related adverse experiences (19 patients vs 8 patients, respectively). There were multiple types of events reported in the digestive system. Considering each event independently, there was little difference between treatment groups and these differences do not appear to be clinically significant.

# Study 052

## Aprepitant

### Drug-Related Adverse Experiences (Multiple-Cycle)

Of the 361 patients entering the multiple cycle extension, 4 patients in each group experienced a drug-related adverse experience.

Table 25

Number (%) of Adult Patients With Specific Clinical Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by  
Body System—Multiple-Cycle Patients  
(Cycles 2 to 6)—Drug Related

	MK-0869 Regimen (N=172) <sup>1</sup>		Standard Therapy (N=189) <sup>2</sup>	
	n	(%)	n	(%)
Patients with one or more drug-related <sup>3</sup> adverse experiences	4	(2.3)	4	(2.1)
Patients with no drug-related adverse experience	168	(97.7)	185	(97.9)
<b>Body as a Whole/Site Unspecified</b>	<b>1</b>	<b>(0.6)</b>	<b>0</b>	<b>(0.0)</b>
Dizziness	1	(0.6)	0	(0.0)
<b>Cardiovascular System</b>	<b>1</b>	<b>(0.6)</b>	<b>1</b>	<b>(0.5)</b>
Hypertension	1	(0.6)	1	(0.5)
<b>Digestive System</b>	<b>2</b>	<b>(1.2)</b>	<b>2</b>	<b>(1.1)</b>
Acid Reflux	1	(0.6)	0	(0.0)
Constipation	0	(0.0)	1	(0.5)
Epigastric Discomfort	0	(0.0)	1	(0.5)
Gastroesophageal Reflux Disease	1	(0.6)	0	(0.0)
Upper Gastrointestinal Hemorrhage	0	(0.0)	1	(0.5)
<b>Eyes, Ears, Nose, and Throat</b>	<b>1</b>	<b>(0.6)</b>	<b>0</b>	<b>(0.0)</b>
Blurred Vision	1	(0.6)	0	(0.0)
<b>Metabolism and Nutrition</b>	<b>1</b>	<b>(0.6)</b>	<b>0</b>	<b>(0.0)</b>
Hyperglycemia	1	(0.6)	0	(0.0)
<b>Nervous System</b>	<b>1</b>	<b>(0.6)</b>	<b>0</b>	<b>(0.0)</b>
Tremor	1	(0.6)	0	(0.0)
<b>Respiratory System</b>	<b>1</b>	<b>(0.6)</b>	<b>2</b>	<b>(1.1)</b>
Hiccups	1	(0.6)	2	(1.1)

<sup>1</sup> Three (3) additional adult patients (ANs 8118, 8206, and 8373) were randomized to the MK-0869 group but never received study drug therapy and are not included in this summary.  
<sup>2</sup> One (1) additional adult patient (AN 8054) was randomized to the Standard Therapy group, but never received study drug therapy and is not included in this summary.  
<sup>3</sup> Determined by the investigator to be possibly, probably, or definitely study drug related.  
 Although a patient may have had 2 or more drug-related clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.  
 All body systems are listed in which at least 1 patient had a drug-related clinical adverse experience.  
 MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 N = Number of randomized adult multiple-cycle patients in each treatment group who received study drug.  
 n = Number of randomized adult multiple-cycle patients in each treatment group who received study drug, with specific drug-related clinical adverse experiences.  
 P.O. = By mouth.  
 IV = Intravenous.  
 AN = Allocation number.

(Ref. Table 79 P052.pdf)

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### Aprepitant

#### Discontinued Due to Adverse Experiences

Twenty-one patients (8.0%) in the MK-0869 group and 15 patients (5.7%) receiving Standard Therapy had one or more adverse experiences that resulted in discontinuation from study. Of these 36 patients, only 4 patients (2 patients in each group) discontinued due to an investigator reported drug-related adverse experience.

Of the two MK-0869 patients who discontinued for drug-related adverse experiences, one patient (AN 9015) had a history of gastric carcinoma and experienced moderate abdominal pain on Day 3. The second patient (AN 9441) had a history of tongue pain and tongue carcinoma, and experienced moderate nausea on Day 6.

No adolescent patients experienced an adverse experience that resulted in discontinuation from study drug therapy.

#### Summary of Laboratory Adverse Experiences

##### (Cycle 1)

Laboratory adverse experiences were reported in 36 patients (14.0%) receiving the MK-0869 regimen and 35 patients (13.4%) taking Standard Therapy during Cycle 1. There were no adolescent patients in Cycle 1 who experienced a laboratory adverse experience.

The most common *serious* laboratory adverse experience was hypokalemia, which occurred in 7 patients in each group. Abnormalities in renal function had similar results, with an increased serum creatinine reported in 5 patients [1.9%] in the MK-0869 group and 6 patients [2.3%] in the Standard Therapy group. Blood urea nitrogen was elevated in 6 patients [2.3%] in the MK-0869 group and 5 patients [1.9%] in the Standard therapy group.

Decreased neutrophils occurred in 6 patients in each group and decreased platelets were reported in 8 patients in each group.

# Study 052

## Aprepitant

Table 26

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

	MK-0869 Regimen (N=261)		Standard Therapy (N=265) <sup>1</sup>	
	n/m	(%)	n/m	(%)
Patients with one or more adverse experiences	36/258	(14.0)	35/261	(13.4)
Patients with no adverse experience	222/258	(86.0)	226/261	(86.6)
<b>Blood Chemistry</b>	<b>22/257</b>	<b>(8.6)</b>	<b>23/260</b>	<b>(8.8)</b>
Alanine aminotransferase increased	4/256	(1.6)	6/256	(2.3)
Blood urea nitrogen increased	6/257	(2.3)	5/259	(1.9)
C-reactive protein increased	0 <sup>a</sup>		1/2	(50.0)
Carbon dioxide partial pressure increased	0/2	(0.0)	1/3	(33.3)
Hypocalcemia	0/3	(0.0)	1/6	(16.7)
Hypokalemia	7/256	(2.7)	7/253	(2.8)
Hypomagnesemia	2/4	(50.0)	0/2	(0.0)
Hypophosphatemia	1/1	(100)	0/1	(0.0)
Lactate dehydrogenase increased	0 <sup>a</sup>		1/1	(100)
Serum creatinine increased	5/257	(1.9)	6/259	(2.3)
Total serum protein decreased	0/4	(0.0)	1/2	(50.0)
Troponin I increased	0/1	(0.0)	1/1	(100)
<b>Hematology</b>	<b>15/257</b>	<b>(5.8)</b>	<b>13/258</b>	<b>(5.0)</b>
Granulocytes decreased	1/2	(50.0)	0/5	(0.0)
Neutrophils decreased	6/256	(2.3)	6/254	(2.4)
Platelets decreased	8/252	(3.2)	8/253	(3.2)
<b>Urinalysis</b>	<b>6/248</b>	<b>(2.4)</b>	<b>5/246</b>	<b>(2.0)</b>

<sup>1</sup> Three (3) additional adult patients (ANs 8118, 8206, and 8373) were randomized to the MK-0869 group, but never received study drug therapy and are not included in this summary.

<sup>2</sup> One (1) additional adult patient (AN 8054) was randomized to the Standard Therapy group, but never received study drug therapy and is not included in this summary.

<sup>a</sup> Indicates there was no associated laboratory test or there were no patients for whom the laboratory test was recorded.

Although a patient may have had 2 or more laboratory adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.

P.O. = By mouth.  
IV = Intravenous.  
AN = Allocation number.  
n/m = Number of randomized adult Cycle 1 patients with laboratory adverse experiences/number of randomized adult Cycle 1 patients for whom the laboratory test was recorded.  
N = Number of randomized adult Cycle 1 patients in each treatment group who received study drug.  
n = Number of randomized adult Cycle 1 patients in each treatment group who received study drug, with specific laboratory adverse experiences.

(Ref. Table 98 P052.pdf)

Drug-related laboratory adverse experiences occurred in 6 patients (2.3%) in the MK-0869 group and 3 patients (1.1%) receiving Standard Therapy. Drug-related *serious* laboratory adverse experiences occurred in (0.4%) of the patients (one patient in each group).

There were 4 patients (1 MK-0869 patient [0.4%] and 3 Standard Therapy patients [1.1%]) who were discontinued from study drug therapy due to laboratory adverse experiences; however, these events were not considered by the investigator to be serious or drug-related.

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### Aprepitant

Table 27

**TABLE 1: Protocol 052  
Number (and Percent) of Patients with  
ALT > 2.5 ULN**

	Aprepitant	Standard Therapy	Comparison: Aprepitant vs Standard Therapy
Day 6 - 8	18/236 (7.6%)	16/237 (6.8%)	p=0.72
Day 19 - 29	0/228 (0%)	2/228 (0.9%)	p=0.50

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

	Aprepitant	Standard Therapy	Comparison: Aprepitant vs Standard Therapy
Day 6 - 8	2/233 (0.9%)	2/233(0.9%)	p=0.99
Day 19 - 29	1/224 (0.5%)	0/227 (0%)	p=0.50

(Ref. Table 1 response.pdf date: 01-08-2003)

*Medical Officer Comment:*

*Overall, the incidence of laboratory adverse experiences during Cycle 1 was similar between the two treatment groups.*

*The data presented as laboratory adverse experiences were dependent on the investigator's judgment that the abnormality fulfilled the criteria of an adverse experience. Additional analysis was performed using > 2.5 x upper limit of normal as a criteria for abnormal liver functions. These results were also similar between the two treatment groups.*

**(Multiple Cycle)**

During the multiple-cycle extension only serious, drug-related or adverse events that led to discontinuation were recorded.

Of the 361 randomized adult patients who entered the multiple-cycle extension, four patients (1.1%) experienced a *serious* laboratory adverse experience during the multiple-cycle phase. Three patients (1.7%) in the MK-0869 group and one

## Study 052

### Aprepitant

(0.5%) in and the Standard Therapy group experienced a *serious* laboratory adverse experience during this phase. There were no adolescent patients who experienced a laboratory adverse experience during the multiple-cycle extension.

Table 28

Listing of Adult Patients With Serious Laboratory Adverse Experiences—  
Multiple-Cycle Patients (Cycles 2 to 6)

Study Site Number	AN	Gender	Race	Age (Years)	Phase	Therapy	Total Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Laboratory Value (Unit) and Normal Range (Unit)	Relative Day of Discontinuation	Drug Relationship	Action Taken
<b>Treatment Group: MK-0869 Regimen</b>													
019	8197	Male	White	39	Posttreatment Cycle 6	Off Drug 18 days		139	Neutrophils decreased	0.6 X 10 <sup>9</sup> /L (NR: 1.8 to 8.0 X 10 <sup>9</sup> /L)	121	Probably not	No action with test drug
019	8200	Male	White	23	Posttreatment Cycle 2	Off Drug 9 days		34	Platelets decreased	81 X 10 <sup>9</sup> /L (NR: 130 to 400 X 10 <sup>9</sup> /L)	52	Probably not	No action with test drug
019	8200	Male	White	23	Posttreatment Cycle 2	Off Drug 9 days		34	Hemoglobin decreased	10 gm/dL (NR: 13.5 to 17.5 gm/dL)	52	Probably not	No action with test drug
019	8200	Male	White	23	Posttreatment Cycle 3	Off Drug 9 days		61	Neutrophils decreased	0.2 X 10 <sup>9</sup> /L (NR: 1.8 to 8.0 X 10 <sup>9</sup> /L)	52	Probably not	No action with test drug
032	8464	Male	White	56	Posttreatment Cycle 6	Off Drug 14 days		158	Leukocytes decreased	1.7 X 10 <sup>9</sup> /L (NR: 4.0 to 10.0 X 10 <sup>9</sup> /L)	144	Definitely not	No action with test drug

(Ref. Table 102 P052.pdf)

There were 8 adult patients who were discontinued from the study due to laboratory adverse experiences. Of these eight patients, two were in the MK-0869 group (1.3%) and six were Standard Therapy patients (3.4%).

#### *Medical Officer Comment:*

*The incidence of laboratory adverse experiences during the Multiple Cycle extension was similar between the two treatment groups. Analysis for the effect of treatment on liver functions demonstrated that the MK-0869 regimen added no additional hepatic toxicity to standard therapy for Cycle 1 or during the multiple cycle extension.*

#### **Adverse Experiences by NCI Toxicity Criteria**

Adverse experiences were categorized according to the National Cancer Institute (NCI) Common Toxicity Criteria: Grade 0 being normal, Grade 1 mild, Grade 2 moderate, Grade 3 severe and Grade 4 a life threatening event.

#### **Adult Patients (Cycle 1)**

The most frequent adverse experiences involved the digestive system. There were 69 patients (26.4%) in the MK-0869 group and in 46 patients (17.4%) in the Standard Therapy group who experienced gastrointestinal-related adverse experiences graded by NCI toxicity criteria. Most adverse experiences were NCI toxicity Grade 1 or 2.

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The most commonly reported severe adverse experiences (NCI toxicity Grades 3 to 4) in Cycle 1 for both treatment groups were asthenia/fatigue, hiccups, constipation, nausea, diarrhea, and headache. The incidence of these Grade 3 and/or 4 adverse experiences was small.

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Table 80

Number (%) of Adult Patients With Specific Clinical Adverse Experiences—National Cancer Institute (NCI) Toxicity Grades 1 to 4 (Incidence ≥2% in One or More Treatment Groups) by Body System—Cycle 1

	MK-0869 Regimen (N 261) <sup>1</sup>								Standard Therapy (N 265) <sup>1</sup>								Total (N 526)							
	NCI Toxicity Grade								NCI Toxicity Grade								NCI Toxicity Grade							
	1		2		3		4		1		2		3		4		1		2		3		4	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
<b>Body as a Whole/Site Unspecified</b>	53	(20.3)	39	(14.9)	13	(5.0)	3	(1.1)	40	(15.1)	29	(10.9)	11	(4.2)	3	(1.1)	93	(17.7)	68	(12.9)	24	(4.6)	6	(1.1)
Asthenia/Fatigue	25	(9.6)	16	(6.1)	5	(1.9)	1	(0.4)	20	(7.5)	4	(1.5)	2	(0.8)	0	(0.0)	45	(8.6)	20	(3.8)	7	(1.3)	1	(0.2)
Dizziness	9	(3.4)	6	(2.3)	2	(0.8)	0	(0.0)	8	(3.0)	3	(1.1)	1	(0.4)	0	(0.0)	17	(3.2)	9	(1.7)	3	(0.6)	0	(0.0)
Fever	10	(3.8)	3	(1.1)	0	(0.0)	0	(0.0)	5	(1.9)	5	(1.9)	0	(0.0)	1	(0.4)	15	(2.9)	8	(1.5)	0	(0.0)	1	(0.2)
<b>Cardiovascular System</b>	9	(3.4)	6	(2.3)	6	(2.3)	5	(1.9)	5	(1.9)	8	(3.0)	4	(1.5)	3	(1.1)	14	(2.7)	14	(2.7)	10	(1.9)	8	(1.5)
<b>Digestive System</b>	69	(26.4)	46	(17.6)	8	(3.1)	2	(0.8)	46	(17.4)	46	(17.4)	9	(3.4)	0	(0.0)	115	(21.9)	92	(17.5)	17	(3.2)	2	(0.4)
Constipation	13	(5.0)	8	(3.1)	0	(0.0)	0	(0.0)	11	(4.2)	19	(7.2)	2	(0.8)	0	(0.0)	24	(4.6)	27	(5.1)	2	(0.4)	0	(0.0)
Diarrhea	15	(5.7)	5	(1.9)	2	(0.8)	0	(0.0)	7	(2.6)	5	(1.9)	0	(0.0)	0	(0.0)	22	(4.2)	10	(1.9)	2	(0.4)	0	(0.0)
Heartburn	10	(3.8)	8	(3.1)	0	(0.0)	0	(0.0)	7	(2.6)	4	(1.5)	0	(0.0)	0	(0.0)	17	(3.2)	12	(2.3)	0	(0.0)	0	(0.0)
Nausea	17	(6.5)	6	(2.3)	5	(1.9)	0	(0.0)	11	(4.2)	11	(4.2)	2	(0.8)	0	(0.0)	28	(5.3)	17	(3.2)	7	(1.3)	0	(0.0)
Stomatitis	3	(1.1)	4	(1.5)	0	(0.0)	0	(0.0)	2	(0.8)	6	(2.3)	1	(0.4)	0	(0.0)	5	(1.0)	10	(1.9)	1	(0.2)	0	(0.0)
Vomiting	7	(2.7)	4	(1.5)	4	(1.5)	1	(0.4)	4	(1.5)	1	(0.4)	1	(0.4)	0	(0.0)	11	(2.1)	5	(1.0)	5	(1.0)	1	(0.2)
<b>Endocrine System</b>	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.4)	0	(0.0)	1	(0.2)	0	(0.0)	3	(0.6)	0	(0.0)
<b>Eyes, Ears, Nose, and Throat</b>	14	(5.4)	14	(5.4)	1	(0.4)	0	(0.0)	11	(4.2)	9	(3.4)	1	(0.4)	0	(0.0)	25	(4.8)	23	(4.4)	2	(0.4)	0	(0.0)
Tinnitus	4	(1.5)	7	(2.7)	1	(0.4)	0	(0.0)	3	(1.1)	4	(1.5)	0	(0.0)	0	(0.0)	7	(1.3)	11	(2.1)	1	(0.2)	0	(0.0)
<b>Hemic And Lymphatic System</b>	6	(2.3)	10	(3.8)	9	(3.4)	10	(3.8)	5	(1.9)	9	(3.4)	7	(2.6)	7	(2.6)	11	(2.1)	19	(3.6)	16	(3.0)	17	(3.2)
Anemia	4	(1.5)	6	(2.3)	0	(0.0)	1	(0.4)	3	(1.1)	5	(1.9)	0	(0.0)	0	(0.0)	7	(1.3)	11	(2.1)	0	(0.0)	1	(0.2)
<b>Immune System</b>	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.4)	2	(0.8)	1	(0.4)	0	(0.0)	1	(0.2)	2	(0.4)	1	(0.2)	0	(0.0)

Table 29

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## Aprepitant

Table 29 (cont)

Number (%) of Adult Patients With Specific Clinical Adverse Experiences--National Cancer Institute (NCI) Toxicity Grades 1 to 4 (Incidence ≥2% in One or More Treatment Groups) by Body System--Cycle 1

	MK-0869 Regimen (N=261) <sup>1</sup>								Standard Therapy (N=263) <sup>2</sup>								Total (N=526)							
	NCI Toxicity Grade								NCI Toxicity Grade								NCI Toxicity Grade							
	1		2		3		4		1		2		3		4		1		2		3		4	
n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Metabolism and Nutrition	17	(6.5)	5	(1.9)	4	(1.5)	0	(0.0)	13	(4.9)	4	(1.5)	7	(2.6)	2	(0.8)	30	(5.7)	9	(1.7)	11	(2.1)	2	(0.4)
Anorexia	8	(3.1)	4	(1.5)	1	(0.4)	0	(0.0)	8	(3.0)	2	(0.8)	1	(0.4)	0	(0.0)	16	(3.0)	6	(1.1)	2	(0.4)	0	(0.0)
Musculoskeletal System	14	(5.4)	7	(2.7)	1	(0.4)	0	(0.0)	11	(4.2)	6	(2.3)	1	(0.4)	2	(0.8)	25	(4.8)	13	(2.5)	2	(0.4)	2	(0.4)
Back Pain	6	(2.3)	1	(0.4)	0	(0.0)	0	(0.0)	2	(0.8)	0	(0.0)	0	(0.0)	0	(0.0)	8	(1.5)	1	(0.2)	0	(0.0)	0	(0.0)
Nervous System	21	(8.0)	15	(5.7)	1	(0.4)	0	(0.0)	26	(9.8)	9	(3.4)	4	(1.5)	1	(0.4)	47	(8.9)	24	(4.6)	5	(1.0)	1	(0.2)
Headache	12	(4.6)	5	(1.9)	1	(0.4)	0	(0.0)	11	(4.2)	2	(0.8)	1	(0.4)	1	(0.4)	23	(4.4)	7	(1.3)	2	(0.4)	1	(0.2)
Insomnia	6	(2.3)	6	(2.3)	0	(0.0)	0	(0.0)	8	(3.0)	3	(1.1)	0	(0.0)	0	(0.0)	14	(2.7)	9	(1.7)	0	(0.0)	0	(0.0)
Psychiatric Disorder	5	(1.9)	4	(1.5)	3	(1.1)	0	(0.0)	4	(1.5)	3	(1.1)	0	(0.0)	0	(0.0)	9	(1.7)	7	(1.3)	3	(0.6)	0	(0.0)
Respiratory System	35	(13.4)	12	(4.6)	5	(1.9)	0	(0.0)	20	(7.5)	8	(3.0)	6	(2.3)	0	(0.0)	55	(10.5)	20	(3.8)	11	(2.1)	0	(0.0)
Hiccups	26	(10.0)	9	(3.4)	1	(0.4)	0	(0.0)	15	(5.7)	2	(0.8)	1	(0.4)	0	(0.0)	41	(7.8)	11	(2.1)	2	(0.4)	0	(0.0)

Number (%) of Adult Patients With Specific Clinical Adverse Experiences--National Cancer Institute (NCI) Toxicity Grades 1 to 4 (Incidence ≥2% in One or More Treatment Groups) by Body System--Cycle 1

	MK-0869 Regimen (N=261) <sup>1</sup>								Standard Therapy (N=263) <sup>2</sup>								Total (N=526)							
	NCI Toxicity Grade								NCI Toxicity Grade								NCI Toxicity Grade							
	1		2		3		4		1		2		3		4		1		2		3		4	
n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Skin and Skin Appendages	6	(2.3)	10	(3.8)	1	(0.4)	0	(0.0)	4	(1.5)	3	(1.1)	1	(0.4)	0	(0.0)	10	(1.9)	13	(2.5)	2	(0.4)	0	(0.0)
Rash	1	(0.4)	6	(2.3)	0	(0.0)	0	(0.0)	1	(0.4)	1	(0.4)	0	(0.0)	0	(0.0)	2	(0.4)	7	(1.3)	0	(0.0)	0	(0.0)
Urogenital System	9	(3.4)	6	(2.3)	0	(0.0)	0	(0.0)	6	(2.3)	3	(1.1)	1	(0.4)	2	(0.8)	15	(2.9)	9	(1.7)	1	(0.2)	2	(0.4)

Three (3) additional adult patients (ANs 8118, 8206, and 8373) were randomized to the MK-0869 group, but never received study drug therapy and are not included in this summary.  
 One (1) additional adult patient (AN 8054) was randomized to the Standard Therapy group, but never received study drug therapy and is not included in this summary.  
 Although a patient may have had 2 or more adverse experiences of NCI toxicity Grades 1 to 4, the patient is counted only once within a category. The same patient may appear in different categories.  
 All body systems are listed in which at least 2% of patients in one treatment group had a clinical adverse experience that fell into an NCI toxicity Grade 1 to 4.  
 During Cycle 1, nausea or vomiting were to be reported as clinical adverse experiences after the completion of the diary period (Day 6 or greater), unless determined by the investigator to be serious, result in discontinuation, or drug-related, in which case nausea and vomiting were to be considered as clinical adverse experiences and were to be reported at any time.  
 Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life threatening.  
 MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 P.O. = By mouth.  
 IV = Intravenous.  
 N = Number of randomized adult Cycle 1 patients in each treatment group who received study drug.  
 n = Number of randomized adult Cycle 1 patients in each treatment group who received study drug, with specific clinical adverse experiences that fell into an NCI Toxicity Grade 1 to 4.  
 AN=Allocation number.

(Ref. Table 80 P052.pdf)

## Adolescent

Table 30

Number (%) of Adolescent Patients With Specific Clinical Adverse Experiences--National Cancer Institute (NCI) Toxicity Grades 1 to 4 (Incidence >0% in One or More Treatment Groups) by Body System--Cycle 1

	MK-0869 Regimen (N=2)								Standard Therapy (N=2)								Total (N=4)							
	NCI Toxicity Grade								NCI Toxicity Grade								NCI Toxicity Grade							
	1		2		3		4		1		2		3		4		1		2		3		4	
n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Body as a Whole/Site Unspecified	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)
Fever	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)
Digestive System	0	(0.0)	1	(50.0)	0	(0.0)	0	(0.0)	1	(50.0)	0	(0.0)	1	(50.0)	1	(50.0)	1	(25.0)	1	(25.0)	1	(25.0)	1	(25.0)
Heartburn	0	(0.0)	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)	0	(0.0)	0	(0.0)
Nausea	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)
Rectal abscess	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)	0	(0.0)
Vomiting	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(50.0)	1	(50.0)	0	(0.0)	0	(0.0)	1	(25.0)	1	(25.0)
Eyes, Ears, Nose, and Throat	1	(50.0)	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)	1	(25.0)	0	(0.0)	0	(0.0)
Mucous membrane disorder	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)	0	(0.0)	0	(0.0)	0	(0.0)
Tinnitus	0	(0.0)	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)	0	(0.0)	0	(0.0)
Hemic and Lymphatic System	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)
Thrombocytopenia	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(50.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(25.0)

(Ref. Table 81 P052.pdf)

*Medical Officer Comment:*

*The number of patients with serious and life threatening adverse experiences were small in both groups with slightly more episodes reported with the MK-0869 regimen than Standard Therapy but the significance of this is uncertain. A causal relationship could not be established by review of the individual case report forms. The number of adolescent patients was too small to perform meaningful analysis.*

**Adverse Experiences According Concomitant Administration of CYP3A4 Metabolized Chemotherapy**

MK-0869 is reported to be a *moderate inhibitor* of the CYP3A4 isoenzyme at this dose and regimen. Adverse experiences were tabulated according to the concomitant administration of chemotherapeutic agents metabolized by the CYP3A4 isoenzyme. The Sponsor describes the following chemotherapeutic agents as being metabolized by the CYP3A4 isoenzyme: docetaxel, etoposide, paclitaxel, vinblastine sulfate, and vinorelbine tartrate.

One hundred patients (54.1%) in the MK-0869 group and 85 patients (45.9%) in the Standard Therapy group received chemotherapeutic agents that are metabolized by CYP3A4. The remaining patients were treated with chemotherapeutic agents that are not metabolized by CYP3A4.

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Table 31

**Number (%) of Adult Patients With Specific Serious Clinical Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by Body System—  
Patients Treated With Concomitant Chemotherapy Metabolized  
by CYP3A4<sup>†</sup> (Cycle 1)**

	MK-0869 Regimen (N=100) <sup>‡</sup>		Standard Therapy (N=85) <sup>§</sup>	
	n	(%)	n	(%)
Patients with one or more serious clinical adverse experiences	14	(14.0)	20	(23.5)
Patients with no serious clinical adverse experience	86	(86.0)	65	(76.5)
<b>Body as a Whole/Site Unspecified</b>	<b>3</b>	<b>(3.0)</b>	<b>4</b>	<b>(4.7)</b>
Collapse	0	(0.0)	1	(1.2)
Dehydration	1	(1.0)	0	(0.0)
Dizziness	0	(0.0)	1	(1.2)
Fever	2	(2.0)	1	(1.2)
Sepsis	1	(1.0)	0	(0.0)
Syncope	1	(1.0)	1	(1.2)
<b>Cardiovascular System</b>	<b>2</b>	<b>(2.0)</b>	<b>4</b>	<b>(4.7)</b>
Angina pectoris	0	(0.0)	1	(1.2)
Cardiac arrest	1	(1.0)	1	(1.2)
Hemorrhage	0	(0.0)	1	(1.2)
Myocardial infarction	1	(1.0)	0	(0.0)
Orthostatic hypotension	0	(0.0)	1	(1.2)
Pulmonary edema	1	(1.0)	0	(0.0)
Pulmonary embolism	0	(0.0)	1	(1.2)
<b>Digestive System</b>	<b>2</b>	<b>(2.0)</b>	<b>6</b>	<b>(7.1)</b>
Diarrhea	1	(1.0)	0	(0.0)
Esophageal malignant neoplasm	0	(0.0)	1	(1.2)
Esophagitis	0	(0.0)	1	(1.2)
Necrotizing enterocolitis	1	(1.0)	0	(0.0)
Pancreatitis	0	(0.0)	1	(1.2)
Pseudomembranous enterocolitis	0	(0.0)	1	(1.2)
Stomatitis	0	(0.0)	1	(1.2)
Upper gastrointestinal hemorrhage	0	(0.0)	2	(2.4)
Vomiting <sup>†</sup>	0	(0.0)	1	(1.2)
<b>Endocrine System</b>	<b>1</b>	<b>(1.0)</b>	<b>0</b>	<b>(0.0)</b>
Syndrome of inappropriate antidiuretic hormone	1	(1.0)	0	(0.0)
<b>Hemic and Lymphatic System</b>	<b>8</b>	<b>(8.0)</b>	<b>5</b>	<b>(5.9)</b>
Febrile neutropenia	5	(5.0)	3	(3.5)
Leukopenia	1	(1.0)	2	(2.4)
Neutropenia	3	(3.0)	0	(0.0)
Pancytopenia	0	(0.0)	1	(1.2)
Thrombocytopenia	1	(1.0)	0	(0.0)
<b>Metabolism and Nutrition</b>	<b>1</b>	<b>(1.0)</b>	<b>1</b>	<b>(1.2)</b>
Hyponatremia	1	(1.0)	1	(1.2)
<b>Nervous System</b>	<b>0</b>	<b>(0.0)</b>	<b>1</b>	<b>(1.2)</b>
Spinal cord compression	0	(0.0)	1	(1.2)

(Ref. Table 94 P052.pdf)

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Table 31 (cont)

**Number (%) of Adult Patients With Specific Serious Clinical Adverse Experiences  
(Incidence >0% in One or More Treatment Groups) by Body System—  
Patients Treated With Concomitant Chemotherapy Metabolized  
by CYP3A4<sup>†</sup> (Cycle 1)**

	MK-0869 Regimen (N=100) <sup>‡</sup>		Standard Therapy (N=85) <sup>‡</sup>	
	n	(%)	n	(%)
<b>Respiratory System</b>	<b>1</b>	<b>(1.0)</b>	<b>4</b>	<b>(4.7)</b>
Aspiration pneumonia	1	(1.0)	0	(0.0)
Lung carcinoma	0	(0.0)	1	(1.2)
Non-small cell lung carcinoma	0	(0.0)	1	(1.2)
Pleural effusion	0	(0.0)	1	(1.2)
Pneumonia	0	(0.0)	2	(2.4)
<b>Skin and Skin Appendages</b>	<b>1</b>	<b>(1.0)</b>	<b>0</b>	<b>(0.0)</b>
Catheter-site infection	1	(1.0)	0	(0.0)
<b>Urogenital System</b>	<b>3</b>	<b>(3.0)</b>	<b>3</b>	<b>(3.5)</b>
Acute renal failure	1	(1.0)	0	(0.0)
Nephrotoxicity	1	(1.0)	1	(1.2)
Renal insufficiency	1	(1.0)	0	(0.0)
Urinary tract infection	0	(0.0)	2	(2.4)

<sup>\*</sup> Drugs included in this table are etoposide, vinblastine, vinblastine sulfate, vinorelbine, vinorelbine tartrate, and paclitaxel.  
<sup>‡</sup> Three (3) additional adult patients (ANs 8118, 8206, and 8373) were randomized to the MK-0869 group, but never received study drug therapy and are not included in this summary.  
<sup>‡</sup> One (1) additional adult patient (AN 8054) was randomized to the Standard Therapy group, but never received study drug therapy and is not included in this summary.  
<sup>†</sup> During Cycle 1, nausea or vomiting were to be reported as clinical adverse experiences after the completion of the diary period (Day 6 or greater), unless determined by the investigator to be serious, result in discontinuation, or drug related, in which case nausea and vomiting were to be considered as clinical adverse experiences and were to be reported at any time.  
 MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 and 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 P.O. = By mouth.  
 IV = Intravenous.  
 AN = Allocation number.  
 N=Number of adult randomized patients who received concomitant chemotherapy metabolized by CYP3A4.  
 n= Number of adult randomized patients who received concomitant chemotherapy metabolized by CYP3A4 and who experienced specific, serious clinical adverse experiences.

(Ref. Table 94 P052.pdf)

**Medical Officer Comment:**

*CYP3A4 substrates as well as inhibitors and inducers were part of the exclusion criteria. A large number of patients received a chemotherapeutic agents metabolized by CYP3A4, however, safety information is only available for only some of the concomitant chemotherapeutic agents. This will be discussed in detail in the executive summary.*

*The incidence of neutropenia and febrile neutropenia was higher in the MK-0869 regimen than Standard Therapy, which may suggest an increase in chemotherapy toxicity with the MK-0869 regimen.*

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### Comparisons Analysis of Adverse Experiences (Cycle 1)

#### Pre-specified statistical comparisons Cycle 1

Table 32

Clinical Adverse Experience Risk Difference Assessment—  
Adult Patients—(Cycle 1)

Adverse Experience Category	MK-0869 Regimen (N=261 <sup>1</sup> ) (A) n/m (%)	Standard Therapy (N=264 <sup>1</sup> ) (B) n/m (%)	Risk Difference (A-B) (%)	95% CI	p-Value
With one or more adverse experiences	170/261 (65.1)	162/264 (61.4)	3.8	(-4.5, 12.0)	0.415
With drug-related <sup>2</sup> adverse experiences	38/261 (14.6)	29/264 (11.0)	3.6	(-2.2, 9.4)	0.240
With serious adverse experiences	42/261 (16.1)	45/264 (17.0)	-1.0	(-7.4, 5.5)	0.815
Discontinued <sup>3</sup> due to adverse experiences	21/261 (8.0)	14/264 (5.3)	2.7	(-1.6, 7.3)	0.225

<sup>\*</sup> Three (3) additional adult patients (ANs 8118, 8206, and 8373) were randomized to the MK-0869 group, but never received study drug therapy and are not included in the safety displays and analyses.  
<sup>†</sup> One (1) additional adult patient (AN 8054) was randomized to the Standard Therapy group, but never received study drug therapy and is not included in the safety displays and analyses. One (1) additional patient was excluded (AN 9049 received study drug, but did not receive cisplatin).  
<sup>‡</sup> Determined by the investigator to be possibly, probably, or definitely study drug related.  
<sup>§</sup> Discontinued = Patient discontinued from primary test drug.  
 MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 to 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 P.O. = By mouth.  
 IV = Intravenous.  
 CI = Confidence interval.  
 n/m = Number of randomized adult patients in each treatment group who received study drug and cisplatin and were included in a given category/number of randomized adult patients in each treatment group who received study drug and cisplatin.  
 N = Number of randomized adult Cycle 1 patients in each treatment group who received study drug.  
 AN=Allocation number.

(Ref. Table 82 P052.pdf)

### Risk Difference Assessment for Specific Adverse Experiences

Risk difference was assessed for the specific adverse experiences with incidence of  $\geq 5\%$  in either the MK-0869 or the Standard Therapy group.

#### *Medical Officer Comment:*

*With the exception of constipation, patients receiving the MK-0869 regimen had numerically higher incidents of adverse experiences than those who received Standard Therapy did.*

*The risk difference of nausea as an adverse event was 2% in favor of the Standard Therapy group. Similarly, more patients in the MK-0869 group than the Standard Therapy group reported vomiting as an adverse experience. A total of 16 patients in the MK-0869 regimen compared to 6 patients in the Standard Therapy regimen reported*

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*vomiting as an adverse experience. These differences may have been affected by the more frequent use of rescue therapy in the Standard Therapy group.*

*In all of the patients in the MK-0869 group who reported vomiting as an adverse experience, it occurred on or after Day 6. A rebound effect may have played a role in this adverse experience; however, it is possible that other factors were contributing.*

*Over one third of the 16 patients in the MK-0869 group had a history of gastrointestinal-related carcinomas. These patients had diagnoses that included: gastric carcinoma with gastrectomy (AN 9363); bile duct carcinoma with ascites (AN 9330); esophageal carcinoma (AN 9173); omentum metastasis and omentectomy (AN 9172); metastasis in ileum, liver, and skull base (AN 9305); and esophageal carcinoma, dysphagia (AN 8505).*

*These diagnoses may have increased the patients' susceptibility to vomiting. In contrast, none of the six patients in the Standard Therapy who reported vomiting as an adverse experience had gastrointestinal carcinomas.*

*The sponsor reports that the severity of vomiting was similar between treatment groups. However, five of the 16 patients who reported vomiting as an adverse experience were NCI toxicity Grade 3 to 4; and 1 patient (0.4%) experienced vomiting with NCI toxicity Grade 4. There was only 1 Standard Therapy patients who experienced vomiting with NCI toxicity Grade 3 and there were no Grade 4 reports.*

*Although the incidence was low for both groups, the severity of vomiting was higher in the MK-0869 group. The relevance of this finding is uncertain and again may have been affected by the more frequent use of rescue therapy in the Standard Therapy group.*

### **Vital Signs, Physical Observations**

The sponsor reports that no formal hypothesis testing was performed regarding vital signs or physical exam. The sponsor states that "no notable differences between the treatment groups were evident upon inspection of the data".

Febrile neutropenia was pre-specified before unblinding as an adverse experience of special interest. The sponsor suggested that its frequency might have been increased if MK-0869 enhanced the toxicity of either chemotherapy or dexamethasone.

### *Medical Officer Comment:*

*The incidence of febrile neutropenia was low. A total of 13 patients experienced febrile neutropenia (serious or nonserious). Eight patients (3.1%) in the MK-0869 group and 5 patients (1.9%) receiving Standard Therapy experienced febrile neutropenia. A review of the data sets using JMP did not identify a causal relationship with any specific concomitant therapy.*

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### Deaths

#### Cycle 1

Sixteen deaths occurred during Cycle 1. There were 7 deaths (2.7%) in the MK-0869 regimen and 9 deaths (3.4%) in the Standard Therapy group. The most commonly reported adverse experiences resulting in death during Cycle 1 were in the Cardiovascular System, with 3 patients from each group. None of the fatal adverse experiences were considered drug-related by the investigator.

#### Adolescent Patients

No adolescent patients died in this study

Table 33

Listing of Adult Patients With Clinical Adverse Experiences Resulting in Death—Cycle 1

Study Site No.	Allocation Number	Gender	Race	Age	Therapy	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience (Days)	Intensity	Drug Relationship <sup>1</sup>	Action Taken <sup>2</sup>	Outcome
Treatment Group: MK-0869 Regimen												
002	8045	Male	White	65	Off drug 9 days	13	Cardiac arrest	1.00 day	Severe	Definitely not	Discontinued PRx	Fatal
012	9018	Female	Hispanic	67	Off drug 13 days	17	Myocardial infarction	1.00 day	Severe	Probably not	Discontinued PRx	Fatal
021	8191	Male	White	72	Off drug 11 days	15	Cardiac arrest	1.00 day	Severe	Probably not	Discontinued PRx	Fatal
032	8477	Male	White	60	Off drug 10 days	14	Hypokalemia	2.00 days	Severe	Probably not	Discontinued PRx	Fatal
032	8477	Male	White	60	Off drug 10 days	14	Pancytopenia	2.00 days	Severe	Probably not	No action with test drug	Fatal
032	8479	Male	White	48	Off drug 5 days	10	Aspiration pneumonia	2.00 days	Severe	Probably not	Discontinued PRx	Fatal
032	8479	Male	White	48	Off drug 5 days	10	Febrile neutropenia	2.00 days	Severe	Probably not	No action with test drug	Fatal
032	8479	Male	White	48	Off drug 5 days	10	Necrotizing enterocolitis	2.00 days	Severe	Probably not	No action with test drug	Fatal
032	8479	Male	White	48	Off drug 5 days	10	Thrombocytopenia	2.00 days	Severe	Probably not	No action with test drug	Fatal
032	9469	Female	White	49	Off drug 12 days	16	Cardiopulmonary failure	1.00 day	Severe	Definitely not	Discontinued PRx	Fatal
042	4447	Female	White	71	Off drug 9 days	13	Neutropenia	6.00 days	Severe	Definitely not	No action with test drug	Fatal
042	9447	Female	White	71	Off drug 9 days	13	Sepsis	6.00 days	Severe	Definitely not	Discontinued PRx	Fatal

Listing of Adult Patients With Clinical Adverse Experiences Resulting in Death—Cycle 1

Study Site No.	Allocation Number	Gender	Race	Age	Therapy	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience (Days)	Intensity	Drug Relationship <sup>1</sup>	Action Taken <sup>2</sup>	Outcome
Treatment Group: Standard Therapy												
010	8013	Male	Black	73	Off drug 3 days	7	Cerebrovascular accident	1.00 day	Severe	Definitely not	Discontinued PRx	Fatal
010	8071	Male	Black	83	Off drug 12 days	16	Lung carcinoma	1.00 day	Severe	Definitely not	Discontinued PRx	Fatal
018	8179	Male	White	65	Off drug 3 days	7	Cardiac arrest	1.00 day	Severe	Probably not	Discontinued PRx	Fatal
018	8179	Male	White	65	Off drug 3 days	7	Esophageal malignant neoplasm	1.00 day	Severe	Probably not	Discontinued PRx	Fatal
018	8179	Male	White	65	Off drug 3 days	7	Hemorrhage	1.00 day	Moderate	Probably not	Discontinued PRx	Fatal
018	8179	Male	White	65	Off drug 3 days	7	Upper gastrointestinal hemorrhage	1.00 day	Moderate	Definitely not	Discontinued PRx	Fatal
024	8235	Male	White	71	Off drug 12 days	16	Non-small cell lung carcinoma	1.00 day	Severe	Definitely not	Discontinued PRx	Fatal
032	8476	Male	White	68	Off drug 11 days	15	Cardiopulmonary failure	1.00 day	Severe	Probably not	Discontinued PRx	Fatal
032	8478	Male	White	62	Off drug 2 days	6	Gastritis	15.00 days	Severe	Probably not	Discontinued PRx	Fatal
032	8478	Male	White	62	Off drug 3 days	7	Uremia	17.00 days	Severe	Probably not	No action with test drug	Fatal
032	8478	Male	White	62	Off drug 10 days	23	Cardiopulmonary failure	1.00 day	Severe	Probably not	No action with test drug	Fatal
032	9466	Female	White	50	Off drug 32 days	36	Cardiopulmonary failure	3.00 days	Severe	Probably not	Discontinued PRx	Fatal

(Ref. Table 86 P052.pdf)

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Table 33 (cont)

Study Site No	Allocation Number	Gender	Race	Age	Therapy	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience (Days)	Intensity	Drug Relationship <sup>1</sup>	Action Taken <sup>2</sup>	Outcome
054	9364	Female	White	68	Off drug 10 days	14	Arrhythmia	1.00 day	Severe	Definitely not	Discontinued PRx	Fatal
054	9364	Female	White	68	Off drug 10 days	14	Cardiogenic shock	1.00 day	Severe	Definitely not	Discontinued PRx	Fatal
054	9364	Female	White	68	Off drug 19 days	14	Pulmonary embolism	1.00 day	Severe	Definitely not	Discontinued PRx	Fatal
056	8404	Male	White	45	Off drug 15 days	19	Gastrointestinal perforation	15.00 days	Severe	Definitely not	Discontinued PRx	Fatal

<sup>1</sup> Determined by the investigator to be possibly, probably, definitely, or definitely not drug related.  
<sup>2</sup> With regard to study therapy.  
 MK-0869 Regimen - MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 to 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy - Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 P.O. = By mouth.  
 IV = Intravenous.  
 PRx = Study drug.

(Ref. Table 86 P052.pdf)

### Multiple Cycle

Thirteen deaths occurred during the multiple-cycle extension period. Four patients (2.3%) in the MK-0869 regimen and 9 patients (4.8%) in the Standard Therapy group died during the study. None of these fatal adverse experiences were considered drug-related by the investigator.

Table 34

Listing of Adult Patients With Clinical Adverse Experiences Resulting in Death—  
Multiple-Cycle Patients (Cycles 2 to 6)

Study Site Number	Allocation Number	Gender	Race	Cycle	Age	Therapy	Total Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience (days)	Intensity	Drug Relationship <sup>1</sup>	Action Taken <sup>2</sup>	Outcome
<b>Treatment Group: MK-0869 Regimen</b>														
029	8271	Male	White	4	60	Off drug 13 days		98	Intestinal obstruction	25.00 days	Severe	Probably not	Discontinued PRx	Fatal
032	8473	Male	White	4	50	Off drug 10 days		111	Thrombocytopenia	9.00 days	Severe	Probably not	No action with test drug	Fatal
032	8473	Male	White	4	50	Off drug 37 days		118	Cardiopulmonary failure	2.00 days	Severe	Probably not	Discontinued PRx	Fatal
032	8475	Male	White	4	54	Off drug 15 days		106	Pancytopenia	10.00 days	Severe	Definitely not	No action with test drug	Fatal
032	8475	Male	White	4	54	Off drug 15 days		106	Pneumonia	10.00 days	Severe	Definitely not	Discontinued PRx	Fatal
042	9452	Female	White	3	69	Off drug 1 day		47	Cardiovascular anomaly	1.00 day	Severe	Probably not	Discontinued PRx	Fatal
042	9452	Female	White	3	69	Off drug 1 day		47	Electrolyte imbalance	1.00 day	Severe	Probably not	Discontinued PRx	Fatal
042	9452	Female	White	3	69	Off drug 1 day		47	Malignant neoplasm	1.00 day	Severe	Probably not	Discontinued PRx	Fatal
042	9452	Female	White	3	69	Off drug 1 day		47	Pulmonary embolism	1.00 day	Severe	Probably not	Discontinued PRx	Fatal
<b>Treatment Group: Standard Therapy</b>														
007	8042	Male	White	2	55	Off drug 9 days		35	Lung malignant neoplasm	1.00 day	Severe	Probably not	Discontinued PRx	Fatal
010	8016	Male	Black	4	66	Off drug 16 days		84	Chronic obstructive pulmonary disease	8.00 days	Severe	Definitely not	Discontinued PRx	Fatal

(Ref. Table 88 P052.pdf)

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Table 34 (cont)

Study Site Number	Allocation Number	Gender	Race	Cycle	Age	Therapy	Total Daily Dose (mg)	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience (days)	Intensity	Drug Relationship <sup>1</sup>	Action Taken <sup>1</sup>	Outcome
010	8016	Male	Black	4	66	Off drug 17 days		85	Renal failure	7.00 days	Severe	Probably not	No action with test drug	Fatal
010	9013	Female	White	4	70	Off drug 5 days		98	Aspiration pneumonia	2.00 days	Severe	Probably not	Discontinued PRx	Fatal
020	8181	Male	White	3	53	Off drug 3 days		50	Malignant neoplasm	1.22 mos	Severe	Definitely not	No action with test drug	Fatal
020	8185	Male	White	6	63	Placebo	0 mg	155	Cerebrovascular accident	2.00 days	Severe	Probably not	Discontinued PRx	Fatal
020	8185	Male	White	6	63	Dex	4 mg	155	Cerebrovascular accident	2.00 days	Severe	Probably not	Discontinued PRx	Fatal
032	8470	Male	White	5	67	Off drug 2 days		111	Pulmonary embolism	2.00 days	Severe	Probably not	Discontinued PRx	Fatal
038	8111	Male	White	4	57	Off drug 14 days		87	Hemoptysis	1.00 day	Severe	Definitely not	No action with test drug	Fatal
056	9357	Female	White	2	49	Off drug 15 days		43	Pleural effusion	8.00 days	Severe	Definitely not	Discontinued PRx	Fatal
057	9329	Female	White	3	69	Off drug 8 days		57	Cardiac arrest	1.00 day	Severe	Definitely not	Discontinued PRx	Fatal

<sup>1</sup> Determined by the investigator to be possibly, probably, definitely, or definitely not drug related.  
<sup>2</sup> With regard to study therapy.  
 MK-0869 Regimen = MK-0869 125 mg P.O. on Day 1 and 80 mg P.O. once daily on Days 2 to 3 plus ondansetron 32 mg IV on Day 1 and dexamethasone 12 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.  
 Standard Therapy = Ondansetron 32 mg IV on Day 1 plus dexamethasone 20 mg P.O. on Day 1 and 8 mg P.O. twice daily on Days 2 to 4.  
 P.O. = By mouth.  
 IV = Intravenous.  
 PRx = Study drug.

Data Source: [4.1; 4.2]

(Ref. Table 88 P052.pdf)

### Death and Adverse Experiences of Special Interest

Serious adverse experiences and deaths occurred more frequently at a Hungarian study site where 33 patients were enrolled (Site Number 032).

At this site, there were no serious adverse experiences reported during Cycle 1 in the 17 patients enrolled prior to April 27, 2001. In the 16 patients enrolled after April 27, 2002, 9 had a serious adverse experience during Cycle 1. Of the 9 patients who had a serious adverse experience during Cycle 1, 5 patients (ANs, 9472, 9492, 8477, 8479, and 9469) received the MK-0869 regimen and 4 patients (ANs 8471, 8476, 8478, and 9466) received Standard Therapy. Six of the 9 patients died (3 in each group), (MK-0869 group: ANs 8477, 8479, and 9469; Standard Therapy group: 8476, 8478, and 9466).

During the multiple-cycle extension, 11 patients had a serious adverse experience. Three of these 11 patients died. (MK-0869 regimen: ANs 8473 and 8475; Standard Therapy: ANs 8470).

The Hungarian Regulatory Authorities did not perform an audit of this study site. The sponsor investigated the site. Treatment group assignments of patients who died were unblinded by a Merck statistician not involved with the study. The results were not communicated to the clinical team involved with the study. After a review of the data, no determination could be made as to the cause of the higher frequency of adverse experiences and deaths.

#### *Medical Officer Comment:*

*Fewer deaths occurred in the MK-0869 regimen for both Cycle 1 and Multiple Cycle extension. By analyzing the reported adverse events that contributed to death, it was noted that 9 of the deaths in the MK-0869 group were related to infection or hematologic*

*causes compared to only 1 in the Standard Therapy group. This will be discussed further in the executive summary.*

#### **Medical Officer Conclusions:**

The purpose of this study was to compare the MK-0869 regimen to Standard Therapy for the prevention of acute and delayed chemotherapy induced nausea and vomiting.

The most frequent inclusion criterion not met was that approximately 20% patients received a cisplatin dose below the protocol-required 70 mg/m<sup>2</sup>. This protocol violation was balanced between the treatment groups and should not result in an unfair bias in favor of the MK-0869 regimen. The Sponsor reports all patients received Cisplatin ≥ 50 mg/m<sup>2</sup> and submitted references to justify including these patients in analysis.

A review of medical literature demonstrates that the dose of cisplatin considered highly emetogenic has decreased over the years. When ondansetron was first approved, the highly emetogenic cisplatin regimen was 100 to 120 mg/m<sup>2</sup>. The Anzemet label describes a highly emetogenic cisplatin dose as ≥70 mg/m<sup>2</sup>. Recent literature, as well as the Hesketh Scale used in this study, support that cisplatin ≥ 50 mg/m<sup>2</sup> is a highly emetogenic dose. The Agency performed analysis excluding patients who received less than 70 mg/m<sup>2</sup> and the efficacy was maintained for the primary endpoint complete response in the overall phase, as well as the secondary endpoints of complete response in the acute and delayed phases. The MITT analysis as reported below includes patients who received ≥ 50 mg/m<sup>2</sup> of cisplatin.

#### **Primary Endpoint**

The primary endpoint of this study was complete response (no emesis and no rescue therapy) in the overall phase (0 to 120 hours post-cisplatin initiation). Patients were defined as treatment failures if they had emesis or required rescue medication. The primary endpoint did not include evaluation of nausea. The results of the nausea endpoints independently did not reach statistical significance.

The sponsor was successful in demonstrating that the MK-0869 regimen was more effective than Standard Therapy for the primary endpoint with 72.7% versus 52.3% (p<0.001) of the patients having *overall complete response* in the MITT population analysis. The per-protocol analysis of this endpoint had similar results.

#### **Secondary Endpoints**

The sponsor succeeded in demonstrating that the MK-0869 regimen was superior to Standard Therapy for the secondary endpoints that were related to emesis: complete response, no emesis, and complete protection. The secondary endpoint of complete

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protection included nausea as a variable with a VAS < 25mm and was statistically significant.

The MK-0869 regimen did not reach statistical significance for the secondary endpoints that were specifically related to nausea alone: no significant nausea, no nausea, or for total control endpoint (nausea VAS < 5).

Analyses of the nausea-specific FLIE items in the questionnaire, (no impact of nausea on ability to enjoy meals, daily functioning and personal hardship), demonstrated the MK-0869 regimen was numerically superior to Standard Therapy, however this difference did not reach statistical significance.

The more frequent use of rescue medication in the Standard Therapy group may have resulted in the failure of the MK-0869 regimen to reach statistical significance in regard to the secondary endpoints of nausea. The sponsor suggests that the use of rescue medication is a surrogate measure for nausea control since patients could use this therapy to treat nausea.

#### Acute Phase

The MK-0869 regimen was more efficacious for all endpoints, including the primary endpoint of complete response ( $p < 0.001$ ). With the exception of total control, the differences between MK-0869 regimen and Standard Therapy were statistically significant. Nausea was not independently evaluated as an endpoint during the acute phase (0-24 hours).

#### Delayed Phase

During the delayed phase (25 to 120 hours post-cisplatin) the MK-0869 regimen was more efficacious for endpoints of complete response, no emesis, use of rescue medication, and complete protection, which includes a component of nausea (VAS < 25mm). However, when nausea was evaluated independently it failed to reach statistical significance at a VAS < 25. The study also did not show a statistical significance for the endpoint of total control, which includes a component of nausea (VAS < 5mm).

#### Overall Phase:

The primary MITT analysis showed that the MK-0869 regimen was significantly more effective than the Standard Therapy regimen in the prevention of cisplatin-induced nausea and vomiting in the overall phase (0 to 120 hours post-cisplatin initiation). The per-protocol analysis of this endpoint supported this result. Analyses of several secondary

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endpoints (no emesis, no use of rescue medication) also supported superiority of the MK-0869 regimen. The results of this study were not as robust as Study 054.

#### Carry-Over Effect

The sponsor did not re-randomize after the acute phase of the study. This was recommended by the Agency on several occasions to prevent a possible carry-over effect from efficacy in the acute phase. Although the analysis was not pre-defined, the sponsor has demonstrated that the delayed phase efficacy of the MK-0869 regimen was not a consequence of the prevention of acute emesis.

#### Safety

During Cycle 1, the 5 most frequently reported adverse experiences were asthenia/fatigue (17.2% and 9.4%), hiccups (13.8% and 6.8%), constipation (8.0% and 12.1%), nausea (10.7% and 8.7%), and diarrhea (8.4% and 3.8%) in the MK-0869 group and Standard Therapy group, respectively.

Serious adverse events were reported in 16.1% of the MK-0869 group and 17.4% of the Standard Therapy group. The most commonly reported serious clinical adverse experiences included: dehydration (5 patients [1.9%] and 3 patients [1.1%]), febrile neutropenia (6 patients [2.3%] and 5 patients [1.9%]), neutropenia (7 patients [2.7%] and 0 patients [0.0%]), and thrombocytopenia (4 patients [1.5%] and 0 patients [0.0%]) in the MK-0869 group and Standard Therapy group, respectively.

Overall, there were more serious adverse experiences of hematologic toxicity associated with the MK-0869 regimen than Standard Therapy in Cycle 1. The incidence of hematologic toxicity was small in both groups, but almost twice as many events occurred in the MK-0869 group than the Standard Therapy group (5.7% VS 3.0% respectively).

Only adverse experiences that were considered serious or drug-related or resulted in study drug discontinuation were reported in the multiple-cycle extension period. A similar relationship was seen during the multiple-cycle extension period with 5.8% of the MK-0869 group and 2.1% of the Standard Therapy group reporting a serious hematologic adverse event.

Serious adverse experiences related to infection were also more common in the MK-0869 regimen. Six patients in the MK-0869 regimen reported a pulmonary infection compared to only 2 patients receiving Standard Therapy. Other evaluated infection-related categories were *Sepsis* and *Infection*. The MK-0869 regimen had two patients, one in each of these categories, who reported a serious adverse event. No patients in the Standard therapy group experienced a serious adverse event reported as *Sepsis* or *Infection*.

### Aprepitant

A review of the data sets using JMP and individual case report forms did not identify any causal relationship or specific signal. The small difference in the incidence of hematologic toxicity and adverse experiences related to infection between treatment groups may represent a small signal and should be followed during the post-marketing period.

#### Chemotherapeutic Agents

The chemotherapy regimens were balanced between treatment groups. The incidence of serious adverse experiences was lower in the MK-0869 regimen (14.0%) compared to the Standard Therapy (23.5%) for patients who received concomitant chemotherapeutic agents metabolized by the CYP3A4. The only body system that the MK-0869 group experienced more serious adverse events was in the Hematologic and Lymphatic System (8.0% versus 5.9%)

#### Deaths

The incidence of deaths was low for both groups. There were fewer deaths in the MK-0869 group compared with the Standard Therapy group and none of the deaths were considered drug-related. It is of interest to note that 9 of the deaths in the MK-0869 group were related to infection or hematologic causes compared to only 1 in the Standard Therapy group.

#### Laboratory

Other than the hematologic trends described above, the protocol-specified laboratory data analyses revealed no definitive trends.

#### **Adolescent Patients**

The clinical and laboratory adverse experiences observed in the adolescent patients were similar to those reported in adult patients. The number of adolescent patients evaluated was too small to draw any definite conclusions regarding the safety and efficacy of the MK-0869 regimen in adolescents.

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/s/

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Gary DellaZanna  
3/14/03 08:24:33 AM  
MEDICAL OFFICER

Joyce Korvick  
3/14/03 08:48:43 AM  
MEDICAL OFFICER