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: April 10, 2001
End: February 23, 2002

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 naïve to cisplatin chemotherapy, with confirmed solid malignancies who were treated with a chemotherapy regimen that included cisplatin ≥70 mg/m^2. This study was conducted in parallel in the United States, Australia, Belgium, Canada, Denmark, France, Germany, Greece, Hungary, Italy, Russia, South Africa, Spain, Sweden, Switzerland, and Taiwan.

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.

Table 1
Treatment Regimens

MK-0869	MK-0869 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg 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	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 (P054.pdf Pg. 41)

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.

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:

The Sponsor states the study was conducted in conformance with applicable country and/or local requirements.

Medical Officer Comment:
The Sponsor does not specifically state that this study was in accordance with the Declaration of Helsinki or in accordance with Good Clinical Practice.

Investigators:

Eighteen centers participated in the study. Study sites were located in Argentina, Brazil, Chile, Colombia, Guatemala, Mexico, Peru, and Venezuela.

Medical Officer Comment:
This was a multicenter, multinational study that included 18 centers.

Objectives:

Primary Objectives: Cycle 1

1) Demonstrate that MK-0869 Triple Therapy 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. The expected difference between the MK-0869 Triple Therapy regimen and standard therapy is assumed to be ~15 percentage points.

2) Evaluate the safety and tolerability of Triple Therapy with MK-0869.

Secondary Objectives: Cycle 1

1) Compare MK-0869 Triple Therapy 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 Triple Therapy 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 Triple Therapy 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 (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.

Medical Officer Comment:
Treatment cost analysis is not evaluated by the Agency during the review process.

Definitions:

Complete Response:	No emesis, no rescue therapy
No Emesis:	No vomiting or retching or dry heaves (includes patients who received rescue therapy).
No Nausea:	Maximum nausea VAS <5 mm.
No Significant Nausea:	Maximum nausea VAS <25 mm.
Complete Protection:	No emesis, no rescue therapy, no significant nausea (maximum nausea <25 mm on VAS).
Total Control:	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)
Complete Response:	(per-protocol analysis)—overall, acute, and delayed phases
No Emesis:	overall, acute, and delayed phases
No Nausea:	(VAS <5) overall phase and delayed phase (exploratory analysis)
No Significant Nausea:	(VAS <25) overall phase and delayed phase (exploratory analysis)
Time to First Emesis:	Overall phase
Patient-Reported Impact of CINV on Daily Life:	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 ≥ 18 years of age.
Scheduled to receive first course of cisplatin chemotherapy (≥70 mg/m^2) over ≤3 hours for a documented solid tumor malignancy.
Negative serum or urine pregnancy test.
Females of childbearing potential agreed to use appropriate contraception.
Karnofsky score ≥60.
Predicted life expectancy of ≥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/mm^3 and white blood cell (WBC) count<3000/ mm^3
- Platelet count <100,000/ mm^3
- Aspartate transaminase (AST)>2.5x 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-HT3 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 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.)

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.

Chronic use, or had taken within 30 days prior to Day 1:

- 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.

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 mm 3 and WBC count <3000/mm^3
- Platelet count <100,000/ mm^3
- AST >2.5 x upper limit of normal
- ALT >2.5 x upper limit of normal
- Bilirubin >1.5 x upper limit of normal
- Creatinine >1.5 x upper limit of normal

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 and randomized 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. Approximately 96% of the patients were compliant with the protocol for Cycle 1.

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 analysis on two populations, the MITT, in which missing data were imputed by carrying forward and the per-protocol population where no imputation 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.

Protocol Amendment

During the course of the study, the Sponsor reports it determined that the efficacy data from 40 patients randomized at Study Site 001 were unreliable. As a result, the Firm decided that the efficacy data from this study site would not be included in the efficacy analyses. In order to ensure an adequate number of patients to support the primary objectives of the study, enrollment was extended and a total of 569 patients were randomized.

Medical Officer Comment:
The Sponsor did not elaborate on the reasons for excluding study site 001 from efficacy analysis. The data from this study site were included in the safety analysis. An efficacy analysis of the primary endpoint including these 40 patients was performed by the sponsor and reviewed by the Agency. The Complete Response endpoint remained statistically significant with these patients included.

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 a baseline physical examination, 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.

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.

Aprepitant

Table 2

Schedule of Clinical Observations and Laboratory Measurements—Cycle 1

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

[1] Within 1 month of treatment with cisplatin.
[2] Telephone contact was only made on Day 6 if the Days 6 to 8 Visit was not occurring on that day.
[3] One visit occurred during this designated period of study days.
[4] Was done at study completion or discontinuation (including the Days 19 to 29 Visit if the patient was not entering into the Multiple-Cycle extension).
[5] Weight was obtained only at the prestudy visit, study completion, or discontinuation.
[6] See Section II. 5.5.1.2 Safety Measurements. Prestudy laboratory tests were to be done within 7 days of treatment and were to include a pregnancy test in women of childbearing potential.
[7] FLIE questionnaire was completed on Day 6.
VAS = Visual analogue scale.
FLIE = Functional living index-emesis.
HEA = Health economics assessment.
ECG = Electrocardiogram.

Data Source: [3.3]

(Ref. Table 3 Protocol 054)

Table 3

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

Procedure	Baseline[1]	Postinitiation of Cisplatin Infusion: Day 1: Hours -2.5	-2	-1.0	-0.5	0	1	2	3	3.5	4	Days: 2 & 3	4	Day: 5	6 to 8[2]	19 to 29[2]
Physical examination and 12-lead ECG[3]																
Laboratory safety tests[3]	X															X
Review of laboratory test results	X	X														X
Vital signs		X													X	X
Prehydration			X-	-	-	-	X									
MK-0869 or placebo dosing				X												
Ondansetron and dexamethasone dosing					X											
Cisplatin infusion over ≤3 hours						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
Capsule/tablet count for MK-0869 and dexamethasone															X	
Adverse experience monitoring[4]	X-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-X

[1] The evaluations done at the poststudy visit on Days 19 to 29 in Cycle 1 could have served as baseline observations for entry into the Multiple-Cycle extension.
[2] One visit occurred during this designated period of study days.
[3] Physical examination and ECG were done at study completion or discontinuation.
[4] See Section II. 5.5.1.2 Safety Measurements. Laboratory tests were to be done within 7 days of treatment and were to include a pregnancy test in women of childbearing potential.
[5] Adverse experiences were only collected if they were determined by the investigator to be drug related or serious, or caused the patient to discontinue from the study. Concomitant therapies were only collected for those adverse experiences that were reported.
ECG = Electrocardiogram.

Data Source: [3.3]

(Ref. Table 4 Protocol 052)

Table 4

Protocol-Specified Laboratory Tests

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

† To have been performed only if preceding urinalysis values were abnormal.
‡ 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 Protocol 054)

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.

AdverseExperiences

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.

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 569 patients were enrolled in the study and randomized into 1 of 2 treatment groups:

283 patients were in the MK-0869 group
286 patients were in the Standard Therapy group

Of the 569 adult patients, 44 patients were excluded from the MITT analyses.

Forty randomized patients at Study Site 001 were excluded when it was determined efficacy data were unreliable
One patient did not receive study drug or cisplatin
One patient received study drug but no cisplatin
Two patients received study drug and cisplatin but did not provide any post-treatment evaluations in the diary.

As a result, 525 patients were included in the MITT analyses.

Breakdown of patients included in the MITT analyses:

262 patients received the MK-0869 regimen
263 patients 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.

Cisplatin Deviations

Two patients (AN 5012, MK-0869 group, and AN 6027, Standard Therapy group) did not receive cisplatin. These patients were excluded from the MITT analyses.

Seventy-eight randomized patients received less than the protocol defined 70-mg/m^2 dose of cisplatin. The Sponsor states all patients received a highly emetogenic dose of cisplatin (>50 mg/m^2); 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^2 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^2 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 ≥ 50 mg/m^2 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 ≥ 50 mg/m^2.

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.

Twenty-five patients were identified as protocol violators (16 received the MK-0869 regimen and 9 received Standard Therapy).

Inappropriate dose of corticosteroids:
(3 patients MK-0869 group; 4 patients Standard Therapy)

Inappropriate dose of antiemetic:
(7 patients MK-0869 group; 2 patients Standard Therapy)

Emesis within 24 hours of randomization
(3 patients MK-0869 group; 0 patients Standard Therapy)

Radiation to the abdomen or pelvis
(1 patient MK-0869 group; 1 patient Standard Therapy)

No study drug on Day 1 or missed study drug on 2 out of the 3 Days
(2 patient MK-0869 group; 2 patient Standard Therapy)

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. Two patient in the MK-0869 group (ANs 5408 and 6079) who had a violation relating only to a placebo dose were included in the per-protocol analysis.

There were 518 patients in the acute phase and 499 patients in the delayed and overall phases included in the per-protocol analysis. 498 patients were included in the delayed and overall phases of rescue data.

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.

Demographics and Characteristics

Table 5

Baseline Patient Demographics and Characteristics by Treatment Group—Cycle 1

	MK-0869 Regimen (N=283)		Standard Therapy (N=286)		Total (N=569)	
	n	(%)	n	(%)	n	(%)
Gender						
Male	148	(52.3)	146	(51.0)	294	(51.7)
Female	135	(47.7)	140	(49.0)	275	(48.3)
Age						
17 and under	0	(0.0)	0	(0.0)	0	(0.0)
18 to 24	6	(2.1)	6	(2.1)	12	(2.1)
25 to 34	18	(6.4)	26	(9.1)	44	(7.7)
35 to 44	49	(17.3)	46	(16.1)	95	(16.7)
45 to 54	54	(19.1)	72	(25.2)	126	(22.1)
55 to 64	85	(30.0)	70	(24.5)	155	(27.2)
65 to 74	59	(20.8)	55	(19.2)	114	(20.0)
over 74	12	(4.2)	11	(3.8)	23	(4.0)
Mean	54.2		53.1		53.6	
SD	13.45		14.11		13.79	
Median	56.0		54.0		55.0	
Range	18 to 82		18 to 81		18 to 82	
Male	18 to 82		18 to 81		18 to 82	
Female	19 to 80		19 to 81		19 to 81	
Race						
Asian	3	(1.1)	3	(1.0)	6	(1.1)
Black	15	(5.3)	18	(6.3)	33	(5.8)
Hispanic American	61	(21.6)	64	(22.4)	125	(22.0)
Multi-Racial	117	(41.3)	121	(42.3)	238	(41.8)
White	87	(30.7)	80	(28.0)	167	(29.3)
Alcohol Intake						
No consumption per week	237	(83.7)	248	(86.7)	485	(85.2)
1 to 4 drinks per week	27	(9.5)	21	(7.3)	48	(8.4)
5 to 7 drinks per week	8	(2.8)	11	(3.8)	19	(3.3)
8 to 10 drinks per week	6	(2.1)	4	(1.4)	10	(1.8)
>10 drinks per week	5	(1.8)	2	(0.7)	7	(1.2)
History of Morning Sickness						
Yes	29	(10.2)	19	(6.6)	48	(8.4)
No	254	(89.8)	267	(93.4)	521	(91.6)

(Ref. Table 21 Protocol 054)

Table 5 (cont)

Baseline Patient Demographics and Characteristics by Treatment Group—Cycle 1

	MK-0869 Regimen (N=283)		Standard Therapy (N=286)		Total (N=569)	
	n	(%)	n	(%)	n	(%)
History of Motion Sickness						
Yes	11	(3.9)	10	(3.5)	21	(3.7)
No	272	(96.1)	276	(96.5)	548	(96.3)
History of Chemotherapy						
Yes	21	(7.4)	29	(10.1)	50	(8.8)
No	262	(92.6)	257	(89.9)	519	(91.2)
History of Chemotherapy-Induced Vomiting						
Yes	14	(4.9)	17	(5.9)	31	(5.4)
No	268	(94.7)	269	(94.1)	537	(94.4)
Null	1§	(0.4)	0	(0.0)	1	(0.2)
Other Concomitant Emetogenic Chemotherapy						
(Hesketh level ≥3)						
With †	49	(17.3)	48	(16.8)	97	(17.0)
Without ‡	234	(82.7)	238	(83.2)	472	(83.0)
Cisplatin Dose						
<70 mg/m²	40	(14.1)	38	(13.3)	78	(13.7)
≥70 to 100 mg/m²	231	(81.6)	235	(82.2)	466	(81.9)
>100 mg/m²	11	(3.9)	12	(4.2)	23	(4.0)
Mean dose (mg/m²)		80.2		80.2		80.2
Null	1‖	(0.4)	1¶	(0.3)	2	(0.4)

† "With" includes patients who received other concurrent emetogenic chemotherapy (Hesketh level ≥3) excluding cisplatin.

‡ "Without" includes patients who received other concurrent emetogenic chemotherapy (Hesketh level <3) excluding cisplatin, and patients with no other concurrent emetogenic chemotherapy.

§ AN 6212 was chemotherapy naïve.

‖ AN 5012 received study therapy but did not receive cisplatin.

¶ AN 6027 did not receive study therapy or cisplatin.

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.

(Ref. Table 21 Protocol 054)

Medical Officer Comment:
Overall the study groups were well balanced. Relatively equal proportions of patients were male and female. Approximately 30% of the patients were White with 40% described as multi-racial. This is due to the location of the study sites. There were few Blacks (5%) and Asians (1%) evaluated in this study. The mean age of the patients was 54 years.

There was a higher incidence of morning sickness in the MK-0869 group than the Standard Therapy group (10.2% vs 6.6% respectively)

The specific primary cancer diagnoses were similar across treatment groups with non-small cell lung cancer being the most common primary cancer diagnosis. Of all patients entered in the study, 36.5% had a respiratory cancer.

Concomitant Chemotherapy Other Than Cisplatin

Concomitant chemotherapy was administered to 96.5% the patients. The pattern of use of these therapies was similar between treatment groups. The most common (overall incidence >10%) concomitant antineoplastic agents were cyclophosphamide, etoposide, fluorouracil, paclitaxel, and vinorelbine tartrate.

Concomitant Medical Therapy

Medical Officer Comment:
Overall, the use of concomitant medical therapy was similar between treatment groups and should not effect analysis.

Efficacy Evaluation and Results

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, 62.7% of patients in the MK-0869 group and 43.3% of the patients in the Standard Therapy group reported complete response. The MK-0869 group had statistically significant higher 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, 82.8% and 68.4% 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 67.7% in the MK-0869 group and 46.8% for the Standard Therapy group ($p<0.001$).

Complete Response: *(Per-Protocol Analysis)*

Table 6

Number (%) of Patients With Complete Response
by Treatment Group and Phase
(Per-Protocol Analysis)

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
Overall Phase	154/244 (63.1)**	111/255 (43.5)
Acute Phase	212/256 (82.8)**	179/262 (68.3)
Delayed Phase	166/244 (68.0)**	120/255 (47.1)

** $p<0.01$ when compared with Standard Therapy.

(Ref. Table 34 Protocol 054)

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.

Complete Response: (*Prespecified By Day Analysis*)

Table 7
Number (%) of Patients With Complete Response
by Treatment Group and Day
(Modified-Intention-to-Treat Analysis)

	MK-0869 Regimen		Standard Therapy	
Phase	n/m	(%)	n/m	(%)
Day 1	216/261	(82.8)	180/263	(68.4)
Day 2	213/260	(81.9)	160/263	(60.8)
Day 3	210/260	(80.8)	180/263	(68.4)
Day 4	210/260	(80.8)	181/263	(68.8)
Day 5	218/260	(83.8)	207/263	(78.7)

(Ref. Table 45 Protocol 054)

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 (21.1%) and declined to 5.1% 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, 66.2% of the MK-0869 patients and 44.5% 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), 83.5% and 68.8% of the patients in the MK-0869 group and Standard Therapy group, respectively, reported having no emesis ($p=0.001$).

For the delayed phase, 71.5% and 48.3% of the patients in the MK-0869 group and Standard Therapy group, respectively, reported having no emesis ($p<0.001$).

Aprepitant

Table 8

Number (%) of Patients With No Emesis
by Treatment Group and Phase
(Modified-Intention-to-Treat Analysis)

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Overall Phase	172/260	(66.2)**	117/263	(44.5)
Acute Phase	218/261	(83.5)**	181/263	(68.8)
Delayed Phase	186/260	(71.5)**	127/263	(48.3)

** $p<0.01$ when compared with Standard Therapy.

(Ref. Table 35 Protocol 054)

Table 9

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

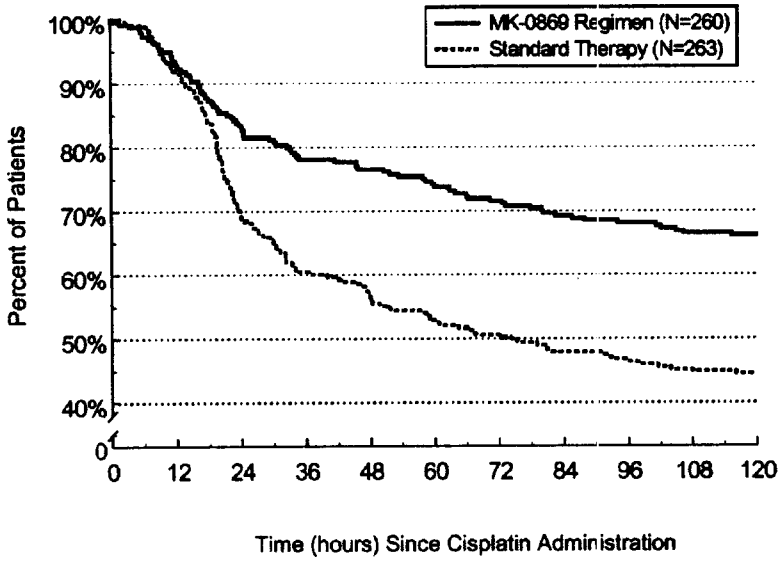
	MK-0869 Regimen		Standard Therapy	
Phase	n/m	(%)	n/m	(%)
Day 1	218/261	(83.5)	181/263	(68.8)
Day 2	222/260	(85.4)	163/263	(62.0)
Day 3	213/260	(81.9)	189/263	(71.9)
Day 4	217/260	(83.5)	191/263	(72.6)
Day 5	223/260	(85.8)	213/263	(81.0)

(Ref. Table 46 Protocol 054)

Medical Officer Comment:
The difference of no vomiting by day between the MK-0869 regimen and Standard Therapy was greatest on Day 2 (23.4%) and declined to only 4.8% by Day 5. These results are consistent with the biphasic pattern of vomiting seen with cisplatin administration.

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 Protocol 054)

Table 11

Number (%) of Patients With No Rescue by Treatment Group and Phase (Modified-Intention-to-Treat Analysis)

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Overall Phase	214/260	(82.3)**	191/263	(72.6)
Acute Phase	251/261	(96.2)**	236/263	(89.7)
Delayed Phase	216/260	(83.1)*	195/263	(74.1)

* p<0.05 when compared with Standard Therapy.
** p<0.01 when compared with Standard Therapy.
No Rescue = No rescue medication.
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 time point.
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 43 Protocol 054)

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 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	172/217[†]	(79.3)	117/181	(64.6)
≥1 emetic episode in delayed phase	45/217	(20.7)	64/181	(35.4)

(Ref. Table 49 Protocol 054)

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	14/43	(32.6)	10/82	(12.2)
≥1 emetic episode in delayed phase	29/43	(67.4)	72/82	(87.8)

(Ref. Table 50 Protocol 054)

In the MK-0869 group, 79.3% of patients without acute phase emesis also had no emesis in the delayed phase. In contrast, only 64.6% of the patients in the Standard Therapy group without acute phase emesis had emetic episodes in the delayed phase.

There were 43 patients in the MK-0869 group and 82 patients in the Standard Therapy group who experienced at least one emetic episode in the acute phase. In the MK-0869 group, 32.6% of the patients with an acute emetic episode had no delayed emetic episodes. In the Standard Therapy group 12.2% 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 with out 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: *Overall, and Delayed Phases*

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

For the overall and delayed phase, the MK-0869 group had a *statistically significant* higher proportion of patients reporting *no nausea* than the Standard Therapy group. For the overall phase, 48.8% of the patients in the MK-0869 group and 38.8% of the patients in the Standard Therapy group had no nausea in the 5 days post-cisplatin administration. This difference in efficacy was even greater for the delayed phase with 52.7% of the patients in the MK-0869 group and 39.9% of the patients in the Standard Therapy group having no nausea.

Table 14

Number (%) of Patients With No Nausea
by Treatment Group and Phase
(Modified-Intention-to-Treat Analysis)

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Overall Phase	127/260	(48.8)*	102/263	(38.8)
Delayed Phase	137/260	(52.7)**	105/263	(39.9)

* p<0.05 when compared with Standard Therapy.
** p<0.01 when compared with Standard Therapy.

(Ref. Table 36 Protocol 054)

Table 15

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

	MK-0869 Regimen		Standard Therapy	
Phase	n/m	(%)	n/m	(%)
Day 1	176/260	(67.7)	174/263	(66.2)
Day 2	174/260	(66.9)	141/263	(53.6)
Day 3	167/260	(64.2)	153/263	(58.2)
Day 4	177/260	(68.1)	155/263	(58.9)
Day 5	169/260	(65.0)	156/263	(59.3)

(Ref. Table 47 Protocol 054)

Medical Officer Comment:
In regard to the secondary endpoint of no nausea, the MK-0869 regimen successfully demonstrated a statistically significant improvement over Standard Therapy in the overall and delayed phase. These results were not replicated in Study 052.

In exploratory analysis of Cycle 1, the difference of no nausea by was greatest on Day 2 with a 13.3% difference in favor of the MK-0869 group. This difference remained in favor of the MK-0869 regimen for Days 3-5 but was not consistent.

No Significant Nausea: *Overall and Delayed Phases*

The secondary endpoint no significant nausea was self-assessed using a 100-mm horizontal VAS and was defined as a maximum nausea VAS <25 mm.

Table 16

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

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Overall Phase	185/260	(71.2)	168/263	(63.9)
Delayed Phase	189/260	(72.7)	172/263	(65.4)

No Significant Nausea = Maximum VAS <25 mm.

(Ref. Table 37 Protocol 054)

Medical Officer Comment:
For both the overall and delayed phases, the MK-0869 group had numerically, but not statistically significant, higher proportion of patients reporting no significant nausea than the Standard Therapy group. 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.

The Sponsor submitted supportive exploratory analysis on the severity of nausea by comparing the distributions of the average VAS scores for the MK-0869 group and the Standard Therapy group using Wilcoxon's rank-sum test. The Sponsor states there were significant differences between the 2 treatment groups for both the overall and delayed phases (p=0.022 and p=0.012, respectively) in favor of the MK-0869 regimen

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 focused on the effect of nausea and vomiting on the patients' daily life. (74.7% vs. 63.5% p=0.007)

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 55.6% of the patients in the MK-0869 group and 40.7% in the Standard Therapy reporting complete protection.

In the acute phase, 80.0% and 64.6% of the patients in the MK-0869 group and Standard Therapy group, respectively, reported complete protection (p=0.001).

For the delayed phase, 60.9% and 44.1% of the patients in the MK-0869 group and Standard Therapy group, respectively, reported complete protection. (p<0.001)

Medical Officer Comment:
For the endpoint of complete protection, the MK-0869 regimen was significantly more effective in the overall, acute, and delayed phases than the Standard Therapy.

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).

For the overall phase the MK-0869 group had a significantly higher proportion of patients with total control than the Standard Therapy group (p=0.001) with 44.4% of the patients in the MK-0869 group and 31.9% in the Standard Therapy reported complete protection.

In the acute phase, 63.6% and 56.7% of the patients in the MK-0869 group and Standard Therapy group, respectively, reported total control (p=0.104).

For the delayed phase, 49.8% and 33.8% of the patients in the MK-0869 group and Standard Therapy group, respectively, reported total control. (p<0.001)

Medical Officer Comment:
For the overall and delayed phases, the MK-0869 regimen was significantly more effective than Standard Therapy with respect to the total control endpoint; for the acute phase, the MK-0869 regimen was numerically superior to Standard Therapy, but the differences were not statistically significant.

Subgroup Analysis: *(Pre-specified)*

Table 17

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

	MK-0869 Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Age Group (Years)				
Age <65	118/195	(60.5)	84/199	(42.2)
Age ≥65	45/65	(69.2)	30/64	(46.9)
Age <75	154/249	(61.8)	109/253	(43.1)
Age ≥75	9/11	(81.8)	5/10	(50.0)
Race Group				
Asian	2/3	(66.7)	2/3	(66.7)
Black	10/15	(66.7)	10/17	(58.8)
Hispanic American	36/60	(60.0)	28/64	(43.8)
Multi-Racial	57/98	(58.2)	41/102	(40.2)
White	58/84	(69.0)	33/77	(42.9)

Complete Response = No emesis with no 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 time point.
Overall Phase = 0 to 120 hours following initiation of cisplatin infusion.

(Ref. Table 51 Protocol 054)

Medical Officer Comment:
Regardless of age category and ethnicity, the MK-0869 regimen was equal to or better than the Standard Therapy with respect to the complete response endpoint.

The number of Asian, Black and Hispanic patients were too small to draw any conclusions, however, the responder rate in the Black and Asian population was similar to the Caucasian 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 gender, and treatment and concomitant emetogenic chemotherapy were not significant (p>0.10).

Table 18

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

Stratification Factor	MK-0869 Regimen n/m	(%)	Standard Therapy n/m	(%)	p-Value†
Female	67/118	(56.8)	51/121	(42.1)	0.294
Male	96/142	(67.6)	63/142	(44.4)	
Concomitant Chemotherapy					
Yes	31/49	(63.3)	16/48	(33.3)	0.257
No	132/211	(62.6)	98/215	(45.6)	

(Ref. Table 33 Protocol 054)

Medical Officer Comment:
The interaction between treatment and gender that was seen in study 052 did not occur in this study. For the complete response endpoints, the MK-0869 regimen was numerically superior to standard therapy in all three phases for both male and female patients.

There were no statistically significant treatment interaction identified during this study.

Rescue Medications

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

Table 19

Number (%) of Patients With No Rescue by Treatment Group and Phase (Modified-Intention-to-Treat Analysis)

	MK-0869 Regimen n/m	(%)	Standard Therapy n/m	(%)
Overall Phase	214/260	(82.3)**	191/263	(72.6)
Acute Phase	251/261	(96.2)**	236/263	(89.7)
Delayed Phase	216/260	(83.1)*	195/263	(74.1)

* p<0.05 when compared with Standard Therapy.
** p<0.01 when compared with Standard Therapy.

(Ref. Table 43 Protocol 054)

Medical Officer Comment:
For the secondary endpoint use of rescue medication, the MK-0869 regimen was significantly more effective than Standard Therapy in acute and overall phase. In the delayed phase, the MK-0869 regimen was numerically superior to Standard Therapy, but the differences were not statistically significant.

Despite the greater uses of rescue medication in the Standard Therapy group, the rates of no nausea and no significant nausea in the overall and delayed phases were greater with the MK-0869 regimen than with the Standard Therapy.

Time to First Rescue—Overall Phase: (Analysis Not Prespecified)

Kaplan-Meier curve for the time to first use of rescue medication in the overall phase for Cycle 1 demonstrated the MK-0869 group had more rescue-free time than the Standard Therapy group. The timing of the use of first rescue medication was similar in the 2 treatment groups for the first 12 hours post-cisplatin administration. Beyond 12 hours, the first use of rescue medication occurred earlier with Standard Therapy than with the MK-0869 regimen. The MK-0869 group had significantly more rescue-free time than the Standard Therapy group.

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

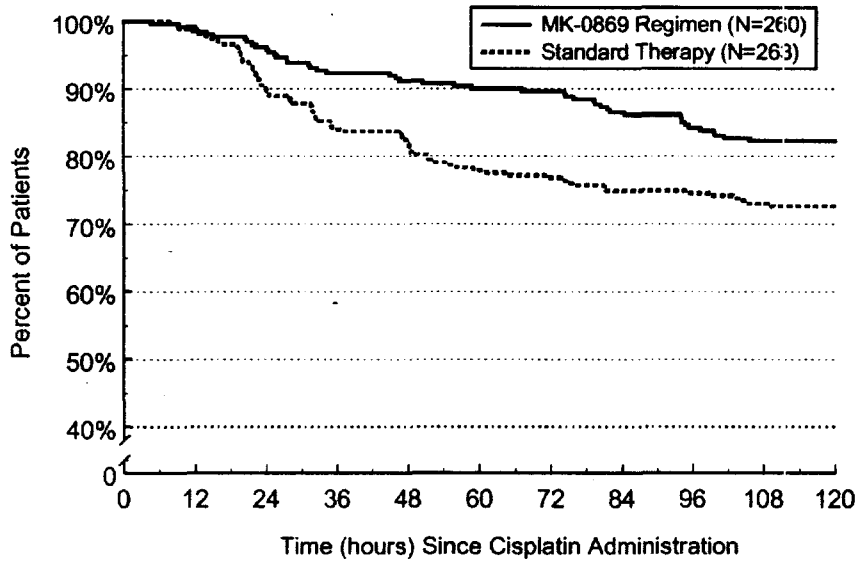


Table 20

(Ref. Figure 7 Protocol 054)

Summary of Efficacy Results (Cycle 1)

Table 21

Number (%) of Patients With Favorable Response by Treatment Group and Phase (Modified-Intention-to-Treat Analysis)—Cycle 1

Post-Cisplatin Phase	MK-0869 Regimen n/m	(%)	Standard Therapy n/m	(%)
No Emesis (No Emetic Episodes)				
Overall Phase (0 to 120 hours)	172/260	(66.2)**	117/263	(44.5)
Acute Phase (0 to 24 hours)	218/261	(83.5)**	181/263	(68.8)
Delayed Phase (25 to 120 hours)	186/260	(71.5)**	127/263	(48.3)
Complete Response (No Emesis and No Rescue Therapy)				
Overall Phase (0 to 120 hours)	163/260	(62.7)**	114/263	(43.3)
Acute Phase (0 to 24 hours)	216/261	(82.8)**	180/263	(68.4)
Delayed Phase (25 to 120 hours)	176/260	(67.7)**	123/263	(46.8)
Complete Protection (No Emesis, No Rescue and Maximum Nausea VAS <25 mm)				
Overall Phase (0 to 120 hours)	145/261	(55.6)**	107/263	(40.7)
Acute Phase (0 to 24 hours)	208/260	(80.0)**	170/263	(64.6)
Delayed Phase (25 to 120 hours)	159/261	(60.9)**	116/263	(44.1)
Total Control (No Emesis, No Rescue and Maximum Nausea VAS <5 mm)				
Overall Phase (0 to 120 hours)	116/261	(44.4)**	84/263	(31.9)
Acute Phase (0 to 24 hours)	166/261	(63.6)	149/263	(56.7)
Delayed Phase (25 to 120 hours)	130/261	(49.8)**	89/263	(33.8)
No Use of Rescue Medication (for Established Emesis or Nausea)				
Overall Phase (0 to 120 hours)	214/260	(82.3)**	191/263	(72.6)
Acute Phase (0 to 24 hours)	251/261	(96.2)**	236/263	(89.7)
Delayed Phase (25 to 120 hours)	216/260	(83.1)*	195/263	(74.1)
No Significant Nausea (Maximum VAS <25 mm)				
Overall Phase (0 to 120 hours)	185/260	(71.2)	168/263	(63.9)
Delayed Phase (25 to 120 hours)	189/260	(72.7)	172/263	(65.4)
No Nausea (Maximum VAS <5 mm)				
Overall Phase (0 to 120 hours)	127/260	(48.8)*	102/263	(38.8)
Delayed Phase (25 to 120 hours)	137/260	(52.7)**	105/263	(39.9)

* $p<0.05$ when compared with Standard Therapy.
** $p<0.01$ when compared with Standard Therapy.

(Ref. Table 52 Protocol 054)

Medical Officer Comment:
The MK-0869 regimen demonstrated a statistically significant improvement for the primary endpoint and many of the secondary endpoints. Study 054 was statistically significant for no nausea and total control, where Study 052 was not.

Safety Evaluation and Results

MK-0869 Exposure (Cycle 1)

All adult 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 283 adult randomized patients, all patients took MK-0869 125 mg on Day 1. Of these 283 patients, 281 patients took MK-0869 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 1 to 18 days, with a mean of 9.8 days. Of the 283 randomized patients who received study drug in the MK-0869 group, 201 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=283) were scheduled to receive oral dexamethasone 12 mg on Day 1.

Thirty-five patients required dexamethasone premedication for Taxane chemotherapy as defined in the study protocol. These patients received two 20-mg doses of dexamethasone. One patient, AN 5354, was inadvertently administered study drug from Bottle B even though he had already received his dexamethasone premedication for Taxane chemotherapy.

Days 2 to 4:

All patients randomized to the MK-0869 group (N=283) were to receive oral dexamethasone 8 mg in the morning and a placebo in the evening on Days 2, 3, and 4.

Two (2) patients did not take oral dexamethasone 8 mg on Days 2 to 4.

One patient, AN 6267, discontinued study drug on Day 2 due to a protocol deviation and one patient, AN 5012, discontinued study drug on Day 1 due to a adverse experience.

Three patients took 8 mg of dexamethasone for only 2 days and 1 patient (AN 6266) took 8 mg of dexamethasone for only 1 day.

Therefore, 277 patients took oral dexamethasone 8 mg for 3 days, per protocol (total 4 days including Day 1).

Dexamethasone (Standard Therapy) Exposure (Cycle 1)

Day 1:

All adult patients randomized to the Standard Therapy group (N=286) were to receive oral dexamethasone *20 mg* on Day 1.

One of these patients (AN 6027) was randomized, but never received study drug or cisplatin due to an adverse experience that precluded study drug initiation.

Forty patients required dexamethasone premedication for Taxane chemotherapy as defined in the study protocol. . These patients received two 20-mg doses of dexamethasone.

One patient, (AN 5077) only took 16 mg of dexamethasone on Day 1.

Therefore, 244 patients took oral dexamethasone 20 mg on Day 1, per protocol

Days 2 to 4:

All adult patients randomized to the Standard Therapy group (N=286) were to receive 16mg oral dexamethasone in the morning and evening daily on Days 2 to 4.

One patient (AN 6027) was randomized, but never took study drug or cisplatin.

One patient (AN 5280) did not meet eligibility criteria causing discontinuation of study drug on Day 1.

Six patients took dexamethasone for only 2 days and 3 patients and took dexamethasone for only 1 day.

One patient, (AN 5077), took 16 mg of dexamethasone on Days 2 to 4 per protocol, but also took 16 mg of dexamethasone on Day 1 when he was required to take 20 mg per protocol.

Therefore, 274 patients took oral dexamethasone 16 mg for 3 days, per protocol (total 4 days including Day 1).

Dexamethasone Overall Exposure (Cycle 1-6)

The range of days on dexamethasone (any dose) was between 1 to 24 days and the mean number of days was 12.9 days

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

All of the 283 patients randomized into the MK-0869 group received ondansetron 32 mg IV on Day 1, per protocol.

Ondansetron (Standard Therapy) Exposure (Cycle 1)

Of the 286 adult patients randomized to the Standard Therapy 1 patient (AN 6027) did not receive study drug or cisplatin.

One patient was treated with locally supplied ondansetron and received the standard dose used by the patient's hospital (24 mg). The investigator intended to discontinue the patient from the study due to high serum creatinine. This patient had received one dose of study drug (placebo for MK-0869) and was included in all safety analyses.

Therefore, 284 patients in the Standard Therapy received 32 mg IV ondansetron.

Ondansetron Overall Exposure (Cycle 1-6)

The range of days on ondansetron was between 1 to 6 days and the mean number of days was 3.4 days

Adverse Experiences

Of the 569 adult patients randomized, 568 patients (283 patients in the MK-0869 group and 285 patients in the Standard Therapy group) were included in the safety analysis.

Four patients were excluded from the adverse tables:

One Patient (AN 6027) experienced adverse events that precluded administration of study drug.

Adverse experiences were reported by 413 of 568 patients. Two hundred six patients (72.8%) in the MK-0869 group and 207 patients (72.6%) in the Standard Therapy group reported one or more adverse experiences.

Table 22

Clinical Adverse Experience Summary—Cycle 1

	MK-0869 Regimen (N=283)		Standard Therapy (N=285)†	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	206	(72.8)	207	(72.6)
With no adverse experience	77	(27.2)	78	(27.4)
With drug-related‡ adverse experiences	55	(19.4)	41	(14.4)
With serious adverse experiences	31	(11.0)	28	(9.8)
With serious drug-related adverse experiences	1§	(0.4)	2	(0.7)
Who died	13	(4.6)	11	(3.9)
Discontinued‖ due to adverse experiences	21	(7.4)	15	(5.3)
Discontinued‖ due to drug-related adverse experiences	1§	(0.4)	0	(0.0)
Discontinued‖ due to serious adverse experiences	18	(6.4)	14	(4.9)
Discontinued‖ due to serious drug-related adverse experiences	1§	(0.4)	0	(0.0)

(Ref. Table 61 Protocol 054)

Drug-related adverse experiences (determined by the investigator to be possibly, probably or definitely study drug related) occurred in 19.4% and 14.4% of patients in the MK-0869 group and Standard Therapy group, respectively. Drug-related adverse experiences were more common in the MK-0869 group compared with the Standard Therapy group.

Medical Officer Comment:
The proportion of patients with one or more adverse experiences was balanced.
The percentage of patients with drug related adverse experiences were higher in the MK-0869 group then the Standard therapy group, (19.4%, 14.4% respectively).

The number of patients with drug-related serious adverse experiences was small in both groups, with one patient in the MK-0869 group and two in the Standard therapy group. 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.

Summary of Adverse Experience by Body System (Cycle 1)

Table 23

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

	MK-0869 Regimen (N=283)		Standard Therapy (N=285)†	
	n	(%)	n	(%)
Patients with one or more adverse experiences	206	(72.8)	207	(72.6)
Patients with no adverse experience	77	(27.2)	78	(27.4)
Body as a Whole/Site Unspecified	**112**	**(39.6)**	**94**	**(33.0)**
Abdominal pain	15	(5.3)	15	(5.3)
Asthenia/fatigue	52	(18.4)	40	(14.0)
Dehydration	21	(7.4)	21	(7.4)
Dizziness	21	(7.4)	12	(4.2)
Fever	3	(1.1)	8	(2.8)
Malaise	12	(4.2)	9	(3.2)
Mucous membrane disorder	6	(2.1)	9	(3.2)
Cardiovascular System	**23**	**(8.1)**	**23**	**(8.1)**
Hypertension	7	(2.5)	4	(1.4)
Phlebitis	7	(2.5)	7	(2.5)
Digestive System	**140**	**(49.5)**	**135**	**(47.4)**
Constipation	35	(12.4)	35	(12.3)
Diarrhea	34	(12.0)	30	(10.5)
Dyspepsia	12	(4.2)	8	(2.8)
Epigastric discomfort	16	(5.7)	12	(4.2)
Gastritis	18	(6.4)	14	(4.9)
Heartburn	12	(4.2)	16	(5.6)

(Ref. Table 63 Protocol 054)

Table 23 (cont)

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

	MK-0869 Regimen (N=283)		Standard Therapy (N=285)†	
	n	(%)	n	(%)
Nausea‡	41	(14.5)	41	(14.4)
Salivation increased	7	(2.5)	2	(0.7)
Vomiting‡	25	(8.8)	36	(12.6)
Eyes, Ears, Nose, and Throat	**25**	**(8.8)**	**27**	**(9.5)**
Pharyngitis	5	(1.8)	7	(2.5)
Tinnitus	8	(2.8)	13	(4.6)
Hemic and Lymphatic System	**10**	**(3.5)**	**11**	**(3.9)**
Neutropenia	6	(2.1)	8	(2.8)
Metabolism and Nutrition	**50**	**(17.7)**	**45**	**(15.8)**
Anorexia	43	(15.2)	40	(14.0)
Musculoskeletal System	**26**	**(9.2)**	**28**	**(9.8)**
Back pain	1	(0.4)	6	(2.1)
Leg pain	6	(2.1)	3	(1.1)
Muscular weakness	11	(3.9)	8	(2.8)
Nervous System	**41**	**(14.5)**	**49**	**(17.2)**
Headache	28	(9.9)	33	(11.6)
Insomnia	4	(1.4)	7	(2.5)
Psychiatric Disorder	**10**	**(3.5)**	**3**	**(1.1)**
Respiratory System	**51**	**(18.0)**	**33**	**(11.6)**
Cough	8	(2.8)	3	(1.1)
Dyspnea	10	(3.5)	4	(1.4)
Hiccups	23	(8.1)	13	(4.6)

(Ref. Table 63 Protocol 054)

Table 23 (cont)

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

	MK-0869 Regimen (N=283)		Standard Therapy (N=285)†	
	n	(%)	n	(%)
Skin and Skin Appendages	**17**	**(6.0)**	**17**	**(6.0)**
Alopecia	7	(2.5)	6	(2.1)
Pruritus	2	(0.7)	6	(2.1)
Urogenital System	**10**	**(3.5)**	**15**	**(5.3)**
Urinary tract infection	2	(0.7)	6	(2.1)

† One (1) patient (AN 6027) in the Standard Therapy group was randomized, but did not receive study drug therapy or cisplatin and is not included in the safety displays and analyses.

‡ 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.

(Ref. Table 63 Protocol 054)

Medical Officer Comment:
The 5 most frequent adverse experiences reported during Cycle 1 were asthenia/fatigue (18.4% and 14.0%), anorexia (15.2% and 14.0%), constipation (12.4% and 12.3%), nausea (14.5% and 14.4%), and diarrhea (12.0% and 10.5%) in the MK-0869 group and Standard Therapy group, respectively. The incidence of hematologic adverse events was balanced between treatment groups.

During Cycle 1, nausea or vomiting were reported as adverse experiences only if they occurred after the completion of the diary period (Day 6 or greater), or were determined to be serious, resulted in discontinuation, or were drug related, in which case they were considered adverse experiences.

Nausea was reported as an adverse experience by 41 patients (14.5%) in the MK-0869 group and 41 patients (14.4%) in the Standard Therapy group in Cycle 1. During this same period vomiting, as an adverse experience, was reported by fewer patients in the MK-0869 group, with 25 patients (8.8%) in the MK-0869 group and 36 patients (12.6%) in the Standard Therapy group in Cycle 1.

Serious Adverse Experiences (Cycle 1)

Fifty-nine (10.4%) of the 568 randomized patients who received study drug had one or more *serious* adverse experiences: 31 (11.0%) and 28 (9.8%) of patients in the MK-0869 group and the Standard Therapy respectively.

The most commonly reported serious adverse experiences in Cycle 1 were neutropenia (5 patients [1.8%] and 6 patients [2.1%]), dehydration (5 patients [1.8%] and 2 patients [0.7%]), respiratory insufficiency (5 patients [1.8%] and 1 patient [0.4%]), septic shock (3 patients [1.1%] and 2 patients [0.7%]), and dyspnea (3 patients [1.1%] and 2 patients [0.7%]) in the MK-0869 group and Standard Therapy group, respectively

Thirty-two of 568 patients (5.6%) discontinued study drug therapy due to a serious adverse experience: 18 (6.4%) and 14 (4.9%) patients in the MK-0869 group and Standard Therapy group, respectively.

Three (3) of the serious adverse experiences (1 [0.4%] in the MK-0869 group and 2 [0.7%] in the Standard Therapy group) were determined to be study drug related.

Twenty-one patients, (7.4%) in the MK-0869 regimen and 15 patients (5.3%) in the Standard Therapy were discontinued from study due to adverse experiences.

There were 24 deaths that occurred in Cycle 1 (13 [4.6%] in the MK-0869 regimen and 11 [3.9%] in the Standard Therapy group). This will be reviewed in the appropriate section.

Prior to unblinding, a review of all serious adverse experiences identified 16 patients (10 patients in the MK-0869 group and 6 patients in the Standard Therapy group) who experienced a serious infection. The Sponsor reports that this difference was not statistically significant (p=0.323).

Table 24

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

	MK-0869 Regimen (N=283)		Standard Therapy (N=285)[‡]	
	n	(%)	n	(%)
Patients with one or more serious[†] adverse experiences	31	(11.0)	28	(9.8)
Patients with no serious adverse experience	252	(89.0)	257	(90.2)
Body as a Whole/Site Unspecified	**15**	**(5.3)**	**8**	**(2.8)**
Abdominal pain	2	(0.7)	0	(0.0)
Abnormal consciousness	0	(0.0)	1	(0.4)
Dehydration	5	(1.8)	2	(0.7)
Fever	1	(0.4)	0	(0.0)
Fistula	1	(0.4)	0	(0.0)
Infection	0	(0.0)	1	(0.4)
Malignant neoplasm	2	(0.7)	0	(0.0)
Metastatic neoplasm of known primary	1	(0.4)	1	(0.4)
Septic shock	3	(1.1)	2	(0.7)
Syncope	0	(0.0)	1	(0.4)
Unknown cause of death	1	(0.4)	1	(0.4)
Upper respiratory infection	1	(0.4)	0	(0.0)
Cardiovascular System	**5**	**(1.8)**	**8**	**(2.8)**
Arrhythmia	1	(0.4)	0	(0.0)
Arterial thrombosis	0	(0.0)	1	(0.4)
Atrial fibrillation	1	(0.4)	1	(0.4)
Cardiac arrest	0	(0.0)	2	(0.7)
Cerebrovascular accident	1	(0.4)	0	(0.0)
Deep venous thrombosis	0	(0.0)	2	(0.7)
Hypovolemic shock	0	(0.0)	1	(0.4)
Pulmonary embolism	2	(0.7)	1	(0.4)
Venous thrombosis	1	(0.4)	1	(0.4)
Digestive System	**4**	**(1.4)**	**5**	**(1.8)**
Diarrhea	2	(0.7)	1	(0.4)
Gastrointestinal perforation	1	(0.4)	1	(0.4)
Nausea[§]	0	(0.0)	1	(0.4)
Oral candidiasis	0	(0.0)	1	(0.4)
Paralytic ileus	1	(0.4)	0	(0.0)
Vomiting[§]	0	(0.0)	2	(0.7)
Endocrine System	**1**	**(0.4)**	**2**	**(0.7)**
Carcinoid syndrome	0	(0.0)	1	(0.4)
Diabetes mellitus	1	(0.4)	1	(0.4)

(Ref. Table 73 Protocol 054)

Table 24 (cont)

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

	MK-0869 Regimen (N=283)		Standard Therapy (N=285)[‡]	
	n	(%)	n	(%)
Hemic and Lymphatic System	**7**	**(2.5)**	**8**	**(2.8)**
Anemia	1	(0.4)	0	(0.0)
Febrile neutropenia	1	(0.4)	2	(0.7)
Leukopenia	0	(0.0)	2	(0.7)
Neutropenia	5	(1.8)	6	(2.1)
Thrombocytopenia	0	(0.0)	1	(0.4)
Metabolism and Nutrition	**1**	**(0.4)**	**3**	**(1.1)**
Hyperglycemia	0	(0.0)	1	(0.4)
Hypoglycemia	0	(0.0)	1	(0.4)
Hypokalemia	1	(0.4)	1	(0.4)
Hyponatremia	0	(0.0)	1	(0.4)
Musculoskeletal System	**1**	**(0.4)**	**1**	**(0.4)**
Bone pain	0	(0.0)	1	(0.4)
Muscular weakness	1	(0.4)	0	(0.0)
Nervous System	**0**	**(0.0)**	**2**	**(0.7)**
Encephalopathy	0	(0.0)	1	(0.4)
Head trauma	0	(0.0)	1	(0.4)
Psychiatric Disorder	**1**	**(0.4)**	**0**	**(0.0)**
Disorientation	1	(0.4)	0	(0.0)
Respiratory System	**12**	**(4.2)**	**7**	**(2.5)**
Airway obstruction	0	(0.0)	1	(0.4)
Bacterial pneumonia	0	(0.0)	1	(0.4)
Chronic obstructive pulmonary disease	1	(0.4)	0	(0.0)
Dyspnea	3	(1.1)	2	(0.7)
Hemoptysis	0	(0.0)	1	(0.4)
Lung malignant neoplasm	2	(0.7)	0	(0.0)
Non-small cell lung carcinoma	2	(0.7)	0	(0.0)
Pneumonia	3	(1.1)	1	(0.4)
Pneumonitis	0	(0.0)	1	(0.4)
Pneumothorax	1	(0.4)	0	(0.0)
Pulmonary hemorrhage	0	(0.0)	1	(0.4)
Respiratory insufficiency	5	(1.8)	1	(0.4)
Skin and Skin Appendages	**1**	**(0.4)**	**0**	**(0.0)**
Herpes Zoster	1	(0.4)	0	(0.0)

(Ref. Table 73 Protocol 054)

Table 24 (cont)

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

	MK-0869 Regimen (N=283)		Standard Therapy (N=285)‡	
	n	(%)	n	(%)
Urogenital System	**4**	**(1.4)**	**1**	**(0.4)**
Breast cellulitis	1	(0.4)	0	(0.0)
Renal failure	1	(0.4)	0	(0.0)
Renal insufficiency	1	(0.4)	0	(0.0)
Testicular malignant neoplasm	0	(0.0)	1	(0.4)
Urinary tract infection	1	(0.4)	0	(0.0)

(Ref. Table 73 Protocol 054)

Medical Officer Comment:
Overall the incidence of infection-related and hematologic serious adverse events were balanced. There was a higher incidence of serious adverse events in the Body as a Whole and Respiratory System. There were multiple types of events reported in each system. Considering each event independently, there was little difference between treatment groups. A causal relationship could not be established by review of the individual case report forms.

Adverse Experience by Body System (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 568 patients included in the safety analysis, 222 patients (78.4%) in the MK-0869 group and 239 patients (83.9%) in the Standard Therapy group entered Cycle 2.

Sixty-six of the 461 randomized patients who entered during the Multiple-Cycle extension period had one or more serious adverse experiences during the Multiple-Cycle extension period: 32 patients (14.4%) in the MK-0869 group and 34 patients (14.2%) in the Standard Therapy group

The number of patients who discontinued study drug therapy due to an adverse experience was balanced between treatment groups: 22 (9.9%) and 23 (9.6%) patients in the MK-0869 group and Standard Therapy group, respectively.

Three of the serious adverse experiences (2 [0.9%] in the MK-0869 group and 1 [0.4%] in the Standard Therapy group) were determined by the investigator to be study drug related.

The most commonly reported serious adverse experiences in Cycles 2 to 6 were neutropenia (6 patients [2.7%] and 4 patients [1.7%]), diarrhea (7 patients [3.2%] and 0 patients [0.0%]), dehydration (3 patients [1.4%] and 2 patients [0.8%]), septic shock (3 patients [1.4%] and 2 patients [0.8%]), pneumonia (3 patients [1.4%] and 2 patients [0.8%]), and respiratory insufficiency (2 patients [0.9%] and 3 patients [1.3%]) in the MK-0869 group and Standard Therapy group, respectively.

Serious adverse experiences of diarrhea were more common in the MK-0869 group compared with the Standard Therapy group. However, this was not the case in Cycle 1.

There were 25 deaths that occurred during Cycles 2 to 6 (14 [6.3%] in the MK-0869 group and 11 [4.6%] in the Standard Therapy group)

Table 25

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

	MK-0869 Regimen (N=222)		Standard Therapy (N=239)	
	n	(%)	n	(%)
Number (%) of patients:				
with drug-related† adverse experiences	18	(8.1)	14	(5.9)
with serious adverse experiences	32	(14.4)	34	(14.2)
with serious drug-related adverse experiences	2	(0.9)	1	(0.4)
who died	14	(6.3)	11	(4.6)
discontinued‡ due to adverse experiences	22	(9.9)	23	(9.6)
discontinued‡ due to drug-related adverse experiences	2	(0.9)	0	(0.0)
discontinued‡ due to serious adverse experiences	11	(5.0)	14	(5.9)
discontinued‡ due to serious drug-related adverse experiences	1	(0.5)	0	(0.0)

(Ref. Table 62 Protocol 054)

Table 26

Number (%) of 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=222)		Standard Therapy (N=239)	
	n	(%)	n	(%)
Patients with one or more serious† adverse experiences	32	(14.4)	34	(14.2)
Patients with no serious adverse experience	190	(85.6)	205	(85.8)
Body as a Whole/Site Unspecified	**11**	**(5.0)**	**11**	**(4.6)**
Abdominal pain	1	(0.5)	1	(0.4)
Asthenia/fatigue	0	(0.0)	1	(0.4)
Bacteremia	1	(0.5)	0	(0.0)
Dehydration	3	(1.4)	2	(0.8)
Infection	1	(0.5)	1	(0.4)
Metastatic neoplasm of unknown primary	1	(0.5)	1	(0.4)
Peritonitis	0	(0.0)	1	(0.4)
Sarcoma	1	(0.5)	0	(0.0)
Sepsis	1	(0.5)	1	(0.4)
Septic shock	3	(1.4)	2	(0.8)
Syncope	0	(0.0)	1	(0.4)
Unknown cause of death	1	(0.5)	1	(0.4)
Cardiovascular System	**1**	**(0.5)**	**6**	**(2.5)**
Congestive heart failure	0	(0.0)	1	(0.4)
Deep venous thrombosis	1	(0.5)	0	(0.0)
Hypotension	0	(0.0)	1	(0.4)
Pericardial effusion	0	(0.0)	2	(0.8)
Pulmonary embolism	1	(0.5)	2	(0.8)
Venous thrombosis	0	(0.0)	1	(0.4)
Digestive System	**10**	**(4.5)**	**4**	**(1.7)**
Anorectal hemorrhage	1	(0.5)	1	(0.4)
Appendicitis	0	(0.0)	1	(0.4)
Diarrhea	7	(3.2)	0	(0.0)
Gastrointestinal bleeding	1	(0.5)	0	(0.0)
Gastrointestinal perforation	0	(0.0)	1	(0.4)
Intestinal amebiasis	0	(0.0)	1	(0.4)
Intestinal obstruction	1	(0.5)	0	(0.0)
Oral cavity malignant neoplasm	1	(0.5)	0	(0.0)
Perforating duodenal ulcer	1	(0.5)	0	(0.0)
Vomiting‡	2	(0.9)	1	(0.4)

(Ref. Table 74 Protocol 054)

Table 26 (cont)

Number (%) of 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=222)		Standard Therapy (N=239)	
	n	(%)	n	(%)
Endocrine System	**0**	**(0.0)**	**2**	**(0.8)**
Diabetes mellitus	0	(0.0)	1	(0.4)
Diabetic ketoacidosis	0	(0.0)	1	(0.4)
Hemic and Lymphatic System	**8**	**(3.6)**	**7**	**(2.9)**
Anemia	1	(0.5)	0	(0.0)
Febrile neutropenia	1	(0.5)	3	(1.3)
Leukopenia	0	(0.0)	1	(0.4)
Neutropenia	6	(2.7)	4	(1.7)
Thrombocytopenia	1	(0.5)	0	(0.0)
Metabolism and Nutrition	**2**	**(0.9)**	**3**	**(1.3)**
Anorexia	0	(0.0)	1	(0.4)
Hypercalcemia	0	(0.0)	1	(0.4)
Hyperglycemia	2	(0.9)	0	(0.0)
Hypoglycemia	0	(0.0)	1	(0.4)
Hypokalemia	1	(0.5)	0	(0.0)
Musculoskeletal System	**2**	**(0.9)**	**0**	**(0.0)**
Back pain	1	(0.5)	0	(0.0)
Bone malignant neoplasm	1	(0.5)	0	(0.0)
Nervous System	**1**	**(0.5)**	**4**	**(1.7)**
Aphasia	0	(0.0)	1	(0.4)
Encephalopathy	0	(0.0)	1	(0.4)
Paresis	0	(0.0)	1	(0.4)
Seizure	1	(0.5)	0	(0.0)
Vertigo	0	(0.0)	1	(0.4)
Respiratory System	**12**	**(5.4)**	**12**	**(5.0)**
Bacterial pneumonia	0	(0.0)	1	(0.4)
Bronchitis	1	(0.5)	0	(0.0)
Dyspnea	1	(0.5)	0	(0.0)
Lower respiratory infection	1	(0.5)	0	(0.0)
Lung carcinoma	0	(0.0)	1	(0.4)
Non-small cell lung carcinoma	2	(0.9)	2	(0.8)
Pleural effusion	2	(0.9)	1	(0.4)
Pneumonia	3	(1.4)	2	(0.8)
Respiratory failure	0	(0.0)	1	(0.4)
Respiratory infection	1	(0.5)	0	(0.0)

(Ref. Table 74 Protocol 054)

Table 26 (cont)

Number (%) of 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=222)		Standard Therapy (N=239)	
	n	(%)	n	(%)
Respiratory insufficiency	2	(0.9)	3	(1.3)
Small cell lung carcinoma	1	(0.5)	1	(0.4)
Thoracic empyema	1	(0.5)	1	(0.4)
Urogenital System	**5**	**(2.3)**	**3**	**(1.3)**
Bladder malignant neoplasm	0	(0.0)	1	(0.4)
Ovarian malignant neoplasm	1	(0.5)	0	(0.0)
Pyelonephritis	1	(0.5)	0	(0.0)
Renal failure	1	(0.5)	1	(0.4)
Urinary tract infection	1	(0.5)	2	(0.8)
Urinary tract obstruction	1	(0.5)	0	(0.0)

† Determined by the investigator.

‡ 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 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 Multiple-Cycle patients in each treatment group who received study drug.

n = Number of randomized Multiple-Cycle patients in each treatment group who received study drug with specific serious clinical adverse experiences.

(Ref. Table 74 Protocol 054)

Medical Officer Comment:

During the multiple cycle extension the incidence of most serious adverse experiences was similar between the treatment groups. The body system that had a notable difference was the digestive system with a 4.5% incidence in the MK-0869 group and 1.7% in the Standard Therapy.

Diarrhea was reported as a serious adverse event in 7 patients in the MK-0869 group compared to zero in the Standard Therapy. A causal relationship could not be established by review of the data.

Drug-Related Adverse Experiences (Cycle 1)

Adverse experiences that were determined by the investigator to be possibly, probably or definitely drug related were reported as drug-related adverse experiences.

Ninety-six of the 568 patients (16.9%) who received study drug had one or more drug-related adverse experiences: 55 patients (19.4%) in the MK-0869 group and 41 patients (14.4%) in the Standard Therapy group.

The most frequently reported adverse experiences determined to be drug-related were asthenia/fatigue (5.3% and 3.2%), constipation (2.5% and 2.8%), anorexia (3.9% and 1.1%), and hiccups (3.5% and 1.8%) in the MK-0869 group and Standard Therapy group, respectively. However, there was no statistically significant risk difference between the MK-0869 group and the Standard Therapy group for drug-related adverse experiences in Cycle 1

Drug related adverse experiences of asthenia/fatigue, anorexia, and hiccups were more common in the MK-0869 group compared with the Standard Therapy group. However, this was not the case in the Multiple-Cycle extension period.

Medical Officer Comment:
Almost four times as many patients in the MK-0869 group than Standard Therapy reported anorexia as a drug-related adverse experience (11 patients vs 3 patients, respectively). Asthenia/fatigue were reported in 15 patients in the MK-0869 group, compared to 9 patients receiving Standard Therapy. Dyspepsia was reported as a drug-related adverse experience in almost twice as many patients receiving the MK-0869 regimen, with 7 patients compared to 4 in the Standard Therapy group.

Drug-Related Adverse Experiences (Multiple-Cycle)

Of the 461 patients entering the multiple cycle extension, 32 patients (6.9%) experienced a drug-related adverse experience: 18 patients (8.1%) in the MK-0869 group and 14 patients (5.9%) in the Standard Therapy group.

The most frequently reported adverse experiences determined by the investigator to be drug related were asthenia/fatigue (7 patients in each group) and diarrhea (9 patients [4.1%] and 5 patients [2.1%] in the MK-0869 group and Standard Therapy group, respectively). Drug-related adverse experiences of diarrhea were more common in the MK-0869 group compared with the Standard Therapy group. However, this was not the case in Cycle 1.

Medical Officer Comment:
Overall the incidence of drug related adverse events was balanced for the multiple cycle extension. The only event that that was markedly different between the groups was diarrhea with 9 patients (4.1%) in the MK-0869 group and 5 patients (2.1%) in the Standard Therapy group.

Discontinued Due to Adverse Experiences

Twenty-one patients (7.4%) in the MK-0869 group and 15 patients (5.3%) receiving Standard Therapy had one or more adverse experiences during Cycle 1 that resulted in discontinuation from study.

The most commonly reported adverse experiences resulting in discontinuation during Cycle 1 were in the Body as a Whole/Site Unspecified Body System (9 patients [3.2%] and 5 patients [1.8%] in the MK-0869 group and Standard Therapy group, respectively). Within this Body System, septic shock (3 patients [1.1%] and 2 patients [0.7%] in the MK-0869 group and Standard Therapy group, respectively) was the most commonly reported adverse experience resulting in discontinuation of study therapy.

Within the Respiratory System, respiratory insufficiency was reported in 5 patients [1.8%] in the MK-0869 group and 1 patient [0.4%] in the Standard Therapy group. Adverse experiences of respiratory insufficiency resulting in discontinuation of therapy were more common in the MK-0869 group compared with the Standard Therapy group. However, this was not the case in the Multiple-Cycle extension period (Cycles 2 to 6).

Summary of Laboratory Adverse Experiences

(Cycle 1)

Laboratory adverse experiences occurred in 83 patients (29.5%) receiving the MK-0869 regimen and 71 patients (25.2%) taking Standard Therapy during Cycle 1.

Laboratory adverse experiences were more common in the MK-0869 group compared with the Standard Therapy group. However, the Sponsor reports there was no statistically significant risk differences between the MK-0869 group and the Standard Therapy group for the incidence of laboratory adverse experiences in Cycle 1.

The 5 most frequently reported laboratory adverse experiences in Cycle 1 were proteinuria (11.4% and 8.9%), alanine aminotransferase increased (9.6% and 6.0%), blood urea nitrogen increased (6.8% and 5.0%), serum creatinine increased

(5.4% and 6.0%), and aspartate aminotransferase increased (5.0% and 1.8%) in the MK-0869 group and Standard Therapy group, respectively.

Medical Officer Comment:
The data presented as laboratory adverse experiences was dependent on the investigator's judgment that the abnormality fulfilled the criteria of an adverse experience.

Abnormal blood chemistry values were more frequent in the MK-0869 group compared with the Standard Therapy group. Alkaline phosphatase was recorded as a laboratory adverse experience in 10 patients in the MK-0869 group compared with only one patient in the Standard Therapy group.

Alanine aminotransferase was reported as a laboratory adverse experience in 9.6% of the patients in the MK-0869 group compared to 6.0% receiving Standard Therapy. It was the most frequently reported laboratory adverse experience determined by the investigator to be drug related.

Aspartate aminotransferase had similar results with 5.0% of the patients in the MK-0869 group compared to 1.8% receiving Standard Therapy.

The majority of these abnormalities were graded NCI Grade 1 (mildly abnormal) or NCI Grade 2 (moderately abnormal). With regard to liver functions, there were fewer patients in the MK-0869 group with NCI Grade 3 laboratory abnormalities and no patients reported a Grade 4.

Table 27

Risk Difference and 95% Confidence Intervals for the Most Common Laboratory Adverse Experiences (Incidence ≥5% in One or More Treatment Groups)—Cycle 1

Laboratory Adverse Experience	MK-0869 Regimen (A) n/m	(%)[1]	Standard Therapy (B) n/m	(%)[2]	Risk Difference (A-B) (%)	95% CI
Alanine aminotransferase increased	27/279	(9.7)	17/281	(6.0)	3.6	(-0.9, 8.3)
Aspartate aminotransferase increased	14/278	(5.0)	5/282	(1.8)	3.3	(0.3, 6.7)
Blood urea nitrogen increased	19/279	(6.8)	14/281	(5.0)	1.8	(-2.2, 6.0)
Proteinuria	32/279	(11.5)	25/280	(8.9)	2.5	(-2.5, 7.7)
Serum creatinine increased	15/279	(5.4)	17/281	(6.0)	-0.7	(-4.7, 3.3)

(Ref. Table 89 Protocol 054)

Table 28

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

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

(Ref. Table 83 Protocol 054)

Medical Officer Comment:
Drug-related laboratory adverse experiences were determined by the investigator to be possibly, probably, or definitely drug related. Drug-related laboratory adverse experiences occurred in 16 patients (5.7%) in the MK-0869 group and 11 patients (3.9%) in the Standard Therapy group for Cycle 1. Drug-related laboratory adverse experiences were more common in the MK-0869 group compared with the Standard Therapy group. No serious laboratory adverse experiences were reported during Cycle1. There was approximately a 3.5% risk difference for AST and ALT in the MK-0869 group.

One patient in each group discontinued study drug therapy due to a laboratory adverse experience. None of these events were determined by the investigator to be serious or drug related.

Table 29

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

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

(Ref. Table 2 response.pdf date: 01-08-2003)

Table 30

AST > 2.5 ULN

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

(Ref. Table 2 response.pdf date: 01-08-2003)

Medical Officer Comment:
Additional analysis was performed for AST and ALT using 2.5x upper normal limit as a criterion. This analysis does not suggest that the aprepitant regimen adversely affected liver functions.

The mean changes in AST, ALT and bilirubin seen on Day 6-8 visit returned near baseline on follow up labs Day 19-29.

(Multiple Cycle)

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

Table 31

Laboratory Adverse Experience Summary—
Multiple-Cycle Patients (Cycles 2 to 6)

	MK-0869 Regimen (N=222)		Standard Therapy (N=239)	
	n	(%)†	n	(%)†
Number (%) of patients:				
With at least one laboratory test postbaseline	216		236	
With drug-related‡ adverse experiences	0	(0.0)	0	(0.0)
With serious adverse experiences	1	(0.5)	1	(0.4)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued§ due to adverse experiences	3	(1.4)	2	(0.8)
Discontinued§ due to drug-related adverse experiences	0	(0.0)	0	(0.0)
Discontinued§ due to serious adverse experiences	1	(0.5)	0	(0.0)
Discontinued§ due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)

(Ref. Table 82 Protocol 054)

Two of the 461 randomized patients, one in each group, experienced one or more serious laboratory adverse experiences during the Multiple-Cycle extension period. None were determined to be drug related. A patient in the MK-0869 group, AN 6025 (a 67-year-old female), experienced leukocytosis on Day 41 that was determined to be not related to study drug.

There were 5 patients who were discontinued from study due to laboratory adverse experiences during the Multiple-Cycle extension period: 3 (1.4%) and 2 (0.8%) patients in the MK-0869 group and Standard Therapy group, respectively.

Medical Officer Comment:
The incidence of serious laboratory adverse experiences during the Multiple Cycle extension was similar between the two treatment groups.

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.

Table 31

Number (%) of 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=283)								Standard Therapy (N=285)†								Total (N=568)							
	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	**70**	**(24.7)**	**44**	**(15.5)**	**20**	**(7.1)**	**3**	**(1.1)**	**54**	**(18.9)**	**40**	**(14.0)**	**17**	**(6.0)**	**1**	**(0.4)**	**124**	**(21.8)**	**84**	**(14.8)**	**37**	**(6.5)**	**4**	**(0.7)**
Abdominal pain	10	(3.5)	3	(1.1)	2	(0.7)	0	(0.0)	9	(3.2)	5	(1.8)	1	(0.4)	0	(0.0)	19	(3.3)	8	(1.4)	3	(0.5)	0	(0.0)
Asthenia/fatigue	26	(9.2)	19	(6.7)	6	(2.1)	1	(0.4)	19	(6.7)	17	(6.0)	4	(1.4)	0	(0.0)	45	(7.9)	36	(6.3)	10	(1.8)	1	(0.2)
Dehydration	3	(1.1)	12	(4.2)	6	(2.1)	0	(0.0)	1	(0.4)	17	(6.0)	2	(0.7)	1	(0.4)	4	(0.7)	29	(5.1)	8	(1.4)	1	(0.2)
Dizziness	17	(6.0)	4	(1.4)	0	(0.0)	0	(0.0)	9	(3.2)	3	(1.1)	0	(0.0)	0	(0.0)	26	(4.6)	7	(1.2)	0	(0.0)	0	(0.0)
Fever	3	(1.1)	0	(0.0)	0	(0.0)	0	(0.0)	6	(2.1)	0	(0.0)	2	(0.7)	0	(0.0)	9	(1.6)	0	(0.0)	2	(0.4)	0	(0.0)
Malaise	5	(1.8)	6	(2.1)	1	(0.4)	0	(0.0)	5	(1.8)	4	(1.4)	0	(0.0)	0	(0.0)	10	(1.8)	10	(1.8)	1	(0.2)	0	(0.0)
Mucous membrane disorder	3	(1.1)	3	(1.1)	0	(0.0)	0	(0.0)	7	(2.5)	2	(0.7)	0	(0.0)	0	(0.0)	10	(1.8)	5	(0.9)	0	(0.0)	0	(0.0)
Cardiovascular System	**10**	**(3.5)**	**7**	**(2.5)**	**6**	**(2.1)**	**1**	**(0.4)**	**9**	**(3.2)**	**6**	**(2.1)**	**6**	**(2.1)**	**1**	**(0.4)**	**19**	**(3.3)**	**13**	**(2.3)**	**12**	**(2.1)**	**2**	**(0.4)**
Digestive System	**86**	**(30.4)**	**71**	**(25.1)**	**14**	**(4.9)**	**3**	**(1.1)**	**90**	**(31.6)**	**65**	**(22.8)**	**8**	**(2.8)**	**1**	**(0.4)**	**176**	**(31.0)**	**136**	**(23.9)**	**22**	**(3.9)**	**4**	**(0.7)**
Constipation	16	(5.7)	16	(5.7)	3	(1.1)	0	(0.0)	20	(7.0)	14	(4.9)	2	(0.7)	0	(0.0)	36	(6.3)	30	(5.3)	5	(0.9)	0	(0.0)
Diarrhea	20	(7.1)	12	(4.2)	4	(1.4)	0	(0.0)	17	(6.0)	11	(3.9)	2	(0.7)	0	(0.0)	37	(6.5)	23	(4.0)	6	(1.1)	0	(0.0)
Dyspepsia	9	(3.2)	3	(1.1)	0	(0.0)	0	(0.0)	6	(2.1)	2	(0.7)	0	(0.0)	0	(0.0)	15	(2.6)	5	(0.9)	0	(0.0)	0	(0.0)
Epigastric discomfort	12	(4.2)	5	(1.8)	0	(0.0)	0	(0.0)	10	(3.5)	2	(0.7)	0	(0.0)	0	(0.0)	22	(3.9)	7	(1.2)	0	(0.0)	0	(0.0)
Gastritis	5	(1.8)	13	(4.6)	1	(0.4)	0	(0.0)	6	(2.1)	8	(2.8)	0	(0.0)	0	(0.0)	11	(1.9)	21	(3.7)	1	(0.2)	0	(0.0)
Heartburn	7	(2.5)	4	(1.4)	1	(0.4)	0	(0.0)	7	(2.5)	9	(3.2)	0	(0.0)	0	(0.0)	14	(2.5)	13	(2.3)	1	(0.2)	0	(0.0)
Nausea‡	30	(10.6)	9	(3.2)	3	(1.1)	0	(0.0)	31	(10.9)	7	(2.5)	3	(1.1)	0	(0.0)	61	(10.7)	16	(2.8)	6	(1.1)	0	(0.0)
Salivation increased	6	(2.1)	1	(0.4)	0	(0.0)	0	(0.0)	2	(0.7)	0	(0.0)	0	(0.0)	0	(0.0)	8	(1.4)	1	(0.2)	0	(0.0)	0	(0.0)
Vomiting‡	9	(3.2)	14	(4.9)	2	(0.7)	0	(0.0)	20	(7.0)	13	(4.6)	3	(1.1)	0	(0.0)	29	(5.1)	27	(4.8)	5	(0.9)	0	(0.0)

(Ref. Table 66 Protocol 054)

Table 31 (cont)

Number (%) of 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=283)								Standard Therapy (N=285)†								Total (N=568)							
	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	(%)
Eyes, Ears, Nose, and Throat	**17**	**(6.0)**	**9**	**(3.2)**	**0**	**(0.0)**	**0**	**(0.0)**	**17**	**(6.0)**	**12**	**(4.2)**	**2**	**(0.7)**	**0**	**(0.0)**	**34**	**(6.0)**	**21**	**(3.7)**	**2**	**(0.4)**	**0**	**(0.0)**
Tinnitus	5	(1.8)	3	(1.1)	0	(0.0)	0	(0.0)	10	(3.5)	3	(1.1)	0	(0.0)	0	(0.0)	15	(2.6)	6	(1.1)	0	(0.0)	0	(0.0)
Metabolism and Nutrition	**26**	**(9.2)**	**19**	**(6.7)**	**5**	**(1.8)**	**0**	**(0.0)**	**20**	**(7.0)**	**21**	**(7.4)**	**6**	**(2.1)**	**0**	**(0.0)**	**46**	**(8.1)**	**40**	**(7.0)**	**11**	**(1.9)**	**0**	**(0.0)**
Anorexia	23	(8.1)	17	(6.0)	3	(1.1)	0	(0.0)	16	(5.6)	20	(7.0)	4	(1.4)	0	(0.0)	39	(6.9)	37	(6.5)	7	(1.2)	0	(0.0)
Musculoskeletal System	**14**	**(4.9)**	**11**	**(3.9)**	**1**	**(0.4)**	**1**	**(0.4)**	**18**	**(6.3)**	**9**	**(3.2)**	**2**	**(0.7)**	**0**	**(0.0)**	**32**	**(5.6)**	**20**	**(3.5)**	**3**	**(0.5)**	**1**	**(0.2)**
Nervous System	**31**	**(11.0)**	**12**	**(4.2)**	**1**	**(0.4)**	**1**	**(0.4)**	**30**	**(10.5)**	**19**	**(6.7)**	**2**	**(0.7)**	**0**	**(0.0)**	**61**	**(10.7)**	**31**	**(5.5)**	**3**	**(0.5)**	**1**	**(0.2)**
Headache	21	(7.4)	8	(2.8)	0	(0.0)	0	(0.0)	19	(6.7)	11	(4.9)	0	(0.0)	0	(0.0)	40	(7.0)	22	(3.9)	0	(0.0)	0	(0.0)

(Ref. Table 66 Protocol 054)

Table 31 (cont)

Number (%) of 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=283)								Standard Therapy (N=285)†								Total (N=568)							
	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	(%)
Respiratory System	**26**	**(9.2)**	**15**	**(5.3)**	**10**	**(3.5)**	**2**	**(0.7)**	**19**	**(6.7)**	**9**	**(3.2)**	**1**	**(0.4)**	**1**	**(0.4)**	**45**	**(7.9)**	**24**	**(4.2)**	**11**	**(1.9)**	**3**	**(0.5)**
Cough	7	(2.5)	1	(0.4)	0	(0.0)	0	(0.0)	2	(0.7)	1	(0.4)	0	(0.0)	0	(0.0)	9	(1.6)	2	(0.4)	0	(0.0)	0	(0.0)
Hiccups	19	(6.7)	3	(1.1)	1	(0.4)	0	(0.0)	12	(4.2)	1	(0.4)	0	(0.0)	0	(0.0)	31	(5.5)	4	(0.7)	1	(0.2)	0	(0.0)
Skin and Skin Appendages	**10**	**(3.5)**	**8**	**(2.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**12**	**(4.2)**	**5**	**(1.8)**	**0**	**(0.0)**	**0**	**(0.0)**	**22**	**(3.9)**	**13**	**(2.3)**	**0**	**(0.0)**	**0**	**(0.0)**
Urogenital System	**5**	**(1.8)**	**4**	**(1.4)**	**2**	**(0.7)**	**0**	**(0.0)**	**9**	**(3.2)**	**4**	**(1.4)**	**1**	**(0.4)**	**0**	**(0.0)**	**14**	**(2.5)**	**8**	**(1.4)**	**3**	**(0.5)**	**0**	**(0.0)**

† One (1) patient (AN 60277) in the Standard Therapy group was randomized, but did not receive study drug therapy or aprepitant and is not included in the safety database and analyses.

(Ref. Table 66 Protocol 054)

Medical Officer Comment:
The majority of the adverse events for both groups were NCI Toxicity Grade 1 or 2. Overall the number of patients with NCI Toxicity Grade 3 or 4 adverse events were small for both groups, but the MK-0869 group had slightly more patients with adverse events for the following systems: Body as a whole, digestive, muscular skeletal, and nervous system. A causal relationship could not be established by review of the individual case report forms. The differences were too small to draw any conclusions.

Adverse Experiences According Concomitant Administration of CYP3A4 Metabolized Chemotherapy

MK-0869 is a *moderate inhibitor* of the CYP3A4 isoenzyme. Adverse experiences were tabulated according to the concomitant administration of chemotherapeutic agents metabolized by CYP3A4 (docetaxel, etoposide, paclitaxel, vinblastine sulfate, and vinorelbine tartrate).

One hundred sixty four patients (58%) in the MK-0869 group and 164 patients (57.5%) in the Standard Therapy group received chemotherapeutic agents that are metabolized by CYP3A4.

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Table 32

Number (%) of 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—Cycle 1

	MK-0869 Regimen (N=164)		Standard Therapy (N=164)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	26	(15.9)	14	(8.5)
Patients with no serious adverse experience	138	(84.1)	150	(91.5)
Body as a Whole/Site Unspecified	**14**	**(8.5)**	**4**	**(2.4)**
Abdominal pain	2	(1.2)	0	(0.0)
Abnormal consciousness	0	(0.0)	1	(0.6)
Dehydration	5	(3.0)	1	(0.6)
Fever	1	(0.6)	0	(0.0)
Fistula	1	(0.6)	0	(0.0)
Infection	0	(0.0)	1	(0.6)
Malignant neoplasm	2	(1.2)	0	(0.0)
Metastatic neoplasm of known primary	1	(0.6)	0	(0.0)
Septic shock	3	(1.8)	0	(0.0)
Syncope	0	(0.0)	1	(0.6)
Unknown cause of death	0	(0.0)	1	(0.6)
Upper respiratory infection	1	(0.6)	0	(0.0)
Cardiovascular System	**4**	**(2.4)**	**5**	**(3.0)**
Arterial thrombosis	0	(0.0)	1	(0.6)
Atrial fibrillation	1	(0.6)	1	(0.6)
Cardiac arrest	0	(0.0)	1	(0.6)
Cerebrovascular accident	1	(0.6)	0	(0.0)
Deep venous thrombosis	0	(0.0)	1	(0.6)
Pulmonary embolism	2	(1.2)	1	(0.6)
Venous thrombosis	1	(0.6)	1	(0.6)
Digestive System	**4**	**(2.4)**	**3**	**(1.8)**
Diarrhea	2	(1.2)	1	(0.6)
Gastrointestinal perforation	1	(0.6)	1	(0.6)
Paralytic ileus	1	(0.6)	0	(0.0)
Vomiting[†]	0	(0.0)	1	(0.6)
Endocrine System	**1**	**(0.6)**	**0**	**(0.0)**
Diabetes mellitus	1	(0.6)	0	(0.0)
Hemic and Lymphatic System	**7**	**(4.3)**	**3**	**(1.8)**
Anemia	1	(0.6)	0	(0.0)
Febrile neutropenia	1	(0.6)	1	(0.6)
Neutropenia	5	(3.0)	2	(1.2)

(Ref. Table 79 Protocol 054)

Table 32 (cont)

Number (%) of 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—Cycle 1

	MK-0869 Regimen (N=164)		Standard Therapy (N=164)	
	n	(%)	n	(%)
Metabolism and Nutrition	**0**	**(0.0)**	**2**	**(1.2)**
Hyperglycemia	0	(0.0)	1	(0.6)
Hypokalemia	0	(0.0)	1	(0.6)
Hyponatremia	0	(0.0)	1	(0.6)
Musculoskeletal System	**0**	**(0.0)**	**1**	**(0.6)**
Bone pain	0	(0.0)	1	(0.6)
Respiratory System	**12**	**(7.3)**	**3**	**(1.8)**
Chronic obstructive pulmonary disease	1	(0.6)	0	(0.0)
Dyspnea	3	(1.8)	1	(0.6)
Hemoptysis	0	(0.0)	1	(0.6)
Lung malignant neoplasm	2	(1.2)	0	(0.0)
Non-small cell lung carcinoma	2	(1.2)	0	(0.0)
Pneumonia	3	(1.8)	0	(0.0)
Pneumonitis	0	(0.0)	1	(0.6)
Pneumothorax	1	(0.6)	0	(0.0)
Respiratory insufficiency	5	(3.0)	1	(0.6)
Skin and Skin Appendages	**1**	**(0.6)**	**0**	**(0.0)**
Herpes zoster	1	(0.6)	0	(0.0)

Number (%) of 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—Cycle 1

	MK-0869 Regimen (N=164)		Standard Therapy (N=164)	
	n	(%)	n	(%)
Urogenital System	**2**	**(1.2)**	**1**	**(0.6)**
Breast cellulitis	1	(0.6)	0	(0.0)
Renal insufficiency	1	(0.6)	0	(0.0)
Testicular malignant neoplasm	0	(0.0)	1	(0.6)

(Ref. Table 79 Protocol 054)

Medical Officer Comment:
CYP3A4 substrates as well as inhibitors and inducers were part of the exclusion criteria. A large number of patients received chemotherapeutic agents metabolized by CYP3A4. However, several chemotherapeutic agents had too few patients to establish a safety profile. This will be discussed in the executive summary.

The incidence of serious adverse experiences was nearly twice as high in the MK-0869 regimen (15.9%) compared to the Standard Therapy (8.5%) for patients who received concomitant chemotherapeutic agents metabolized by CYP3A4. In particular, more patients in the MK-0869 group experienced serious adverse experiences in the following body systems: Body as a Whole/Site Unspecified (8.5% versus 2.4%), Respiratory System (7.3% versus 1.8%), and Hematologic and Lymphatic System (4.3% versus 1.8%)

The data from Table 79 is misleading. It shows that fever was reported as a serious adverse event in only one patient in the MK-0869 group and that no patients in the MK-0869 group reported infection as a serious adverse event. However, one patient in the MK-0869 group developed a serious respiratory infection and Septic Shock was reported in 3 patients in the MK-0869 group compared to no patients receiving Standard Therapy.

During Cycle 1 neutropenia was reported as a serious adverse experience in 5 patients in the MK-0869 regimen and 2 patients receiving Standard Therapy. However, the incidence of febrile neutropenia was the same for each treatment group, with one patient from each group.

Serious adverse events involving the respiratory system were reported four times as often in the MK-0869 group compared to Standard Therapy during Cycle 1.

The incidence of serious adverse experiences in patients treated with concomitant chemotherapy NOT metabolized by CYP3A4 was lower in the MK-0869 group (4.2%) compared to the Standard Therapy group (11.6%) during Cycle 1. In this subset of patients, there were no cases of septic shock in the MK-0869 group compared to two cases in the Standard Therapy group. Neutropenia was not reported as a serious adverse experience in the MK-0869 group compared to 4 patients in the Standard Therapy. Only one patient, in the Standard Therapy group, reported febrile neutropenia as an adverse event. Serious adverse events involving the respiratory system for this subset of patients were reported in four patients in the Standard Therapy group compared to no patients in the MK-0869 group.

The results are difficult to interpret. The MK-0869 regimen may have increased the toxicity of chemotherapeutic agents metabolized by CYP3A4.

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".

Table 33

Mean Changes From Baseline in Vital Signs—Cycle 1

Parameter	Units	Treatment	N[‡]	Baseline[†]		Posttreatment[‡]		Change	
				Mean	SD	Mean	SD	Mean	SD
Systolic BP	mm Hg	MK-0869 Regimen	277	123.84	17.04	117.51	19.33	-6.34	17.46
		Standard Therapy	277	124.42	16.86	117.12	18.65	-7.30	16.16
Diastolic BP	mm Hg	MK-0869 Regimen	277	76.86	9.84	74.81	10.26	-2.05	11.39
		Standard Therapy	276	77.09	10.48	73.96	9.99	-3.13	10.37
Heart rate	Beats/min	MK-0869 Regimen	277	81.09	12.59	83.60	13.25	2.51	14.47
		Standard Therapy	277	80.05	11.33	83.20	12.63	3.15	12.20

(Ref. Table 98 Protocol 054)

Table 34

Summary Statistics for 12-Lead Electrocardiogram (ECG)

ECG Parameter (Units)	Visit	Treatment Group	N[†]	Mean	SD
PR_Interval (msec)	Pre-Cisplatin	MK-0869 Regimen	277	142.16	22.94
		Standard Therapy	278	142.44	21.17
	Discontinuation Visit	MK-0869 Regimen	186	138.75	20.27
		Standard Therapy	193	139.65	22.26
QT_C_Interval (msec)	Pre-Cisplatin	MK-0869 Regimen	280	426.45	20.88
		Standard Therapy	281	427.50	21.55
	Discontinuation Visit	MK-0869 Regimen	187	425.93	20.45
		Standard Therapy	194	429.33	21.80

(Ref. Table 99 Protocol 054)

Medical Officer Comment:
Mean and standard deviation were calculated for the PR interval and QTc interval pre-cisplatin administration and at the patient discontinuation visit. No notable findings were revealed.

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

Medical Officer Comment:
Of the 567 randomized patients included in the safety analyses of Cycle 1, 3 patients (0.5%) were identified as having febrile neutropenia according to NCI definition (1 patient (0.4%) in the MK-0869 group and 2 patients (0.7%) in the Standard Therapy group, respectively)

Deaths

Cycle 1

Twenty-four deaths occurred during Cycle 1. There were 13 deaths (4.6%) in the MK-0869 regimen and 11 deaths (3.9%) in the Standard Therapy group. The most commonly reported adverse experiences resulting in death during Cycle 1 were in the Respiratory System, with 6 patients in the MK-0869 and 5 patients in the Standard Therapy group. Details of these cases are consistent with the insufficiency representing progression of underlying malignant disease (lung cancer); the temporal relationship to MK-0869 administration was variable and the investigator did not determine any of the cases to be drug related.

Table 35

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

Study Site Number	AN	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation[1]	Action Taken[1]	Outcome
Treatment Group: MK-0869 Regimen													
005	5341	M	Multi	65	Off drug 19 days		23	Septic shock	11.00 hrs	Severe	Prob not	Discontinued PRx	Fatal
006	5527	M	Multi	45	Off drug 16 days		20	Unknown cause of death	5.00 mins	Severe	Prob not	Discontinued PRx	Fatal
006	6507	F	Black	59	Off drug 17 days		21	Dyspnea	1.00 day	Severe	Prob not	Discontinued PRx	Fatal
006	6507	F	Black	59	Off drug 17 days		21	Non-small cell lung carcinoma	1.00 day	Mod	Prob not	Discontinued PRx	Fatal
015	5001	M	Hispanic	54	Off drug 34 days		38	Malignant neoplasm	19.00 days	Severe	Prob not	Discontinued PRx	Fatal
017	6216	F	Hispanic	73	Off drug 12 days		16	Arrhythmia	0.45 min	Severe	Def not	Discontinued PRx	Fatal
018	5097	M	White	74	MK-0869	80 mg	3	Respiratory insufficiency	2.00 days	Severe	Def not	Discontinued PRx	Fatal
018	5097	M	White	74	Dexamethasone	8 mg	3	Respiratory insufficiency	2.00 days	Severe	Def not	Discontinued PRx	Fatal
018	5097	M	White	74	Placebo	0 mg	3	Respiratory insufficiency	2.00 days	Severe	Def not	Discontinued PRx	Fatal
018	5097	M	White	74	Off drug 1 days		4	Chronic obstructive pulmonary disease	1.00 day	Severe	Def not	Discontinued PRx	Fatal

(Ref. Table 70 Protocol 054)

Table 35 (cont)

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

Study Site Number	AN	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation[1]	Action Taken[2]	Outcome
018	5097	M	White	74	Off drug 1 days		4	Lung malignant neoplasm	1.00 day	Severe	Def not	No action with test drug	Fatal
018	5097	M	White	74	Off drug 1 days		4	Malignant neoplasm	1.00 day	Severe	Def not	No action with test drug	Fatal
018	5109	M	Asian	70	Off drug 19 days		23	Respiratory insufficiency	248.00 mins	Severe	Def not	Discontinued PRx	Fatal
018	5114	M	Black	54	Off drug 7 days		11	Respiratory insufficiency	1.00 day	Severe	Def not	Discontinued PRx	Fatal
018	5119	M	White	62	Off drug 13 days		17	Pulmonary embolism	1.00 day	Severe	Def not	Discontinued PRx	Fatal
018	5119	M	White	62	Off drug 13 days		17	Respiratory insufficiency	1.00 day	Severe	Def not	Discontinued PRx	Fatal
018	5138	M	White	59	Off drug 6 days		10	Pulmonary embolism	1.00 day	Severe	Def not	Discontinued PRx	Fatal
018	5153	M	White	54	Off drug 17 days		21	Septic shock	2.00 days	Severe	Def not	Discontinued PRx	Fatal
018	6088	F	White	52	Off drug 24 days		28	Respiratory insufficiency	1.00 day	Severe	Def not	Discontinued PRx	Fatal
019	5086	M	White	71	Off drug 9 days		13	Neutropenia	2.00 days	Severe	Def not	No action with test drug	Fatal
019	5086	M	White	71	Off drug 10 days		14	Septic shock	1.00 day	Severe	Def not	Discontinued PRx	Fatal

(Ref. Table 70 Protocol 054)

Table 35 (cont)

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

Study Site Number	AN	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation[1]	Action Taken[2]	Outcome
Treatment Group: Standard Therapy													
006	5506	M	Multi	53	Off drug 18 days		22	Airway obstruction	2.00 days	Severe	Prob not	Discontinued PRx	Fatal
006	5507	M	Multi	71	Off drug 1 days		5	Dyspnea	7.40 hrs	Severe	Prob not	Discontinued PRx	Fatal
006	5507	M	Multi	71	Off drug 1 days		5	Hemoptysis	7.40 hrs	Severe	Def not	Discontinued PRx	Fatal
006	6534	F	Multi	37	Off drug 7 days		11	Dyspnea	2.00 days	Severe	Def not	Discontinued PRx	Fatal
006	6534	F	Multi	37	Off drug 8 days		12	Cardiac arrest	1.00 day	Severe	Prob not	Discontinued PRx	Fatal
007	6381	F	Multi	52	Off drug 12 days		16	Pulmonary hemorrhage	30.00 mins	Severe	Prob not	Discontinued PRx	Fatal
009	6263	F	Hispanic	19	Off drug 18 days		22	Metastatic neoplasm of known primary	3.00 days	Severe	Def not	Discontinued PRx	Fatal
015	5047	M	Hispanic	53	Off drug 8 days		12	Unknown cause of death	1.00 day	Severe	Prob not	Discontinued PRx	Fatal
017	5216	M	Hispanic	36	Off drug 4 days		8	Cardiac arrest	60.00 secs	Severe	Def not	Discontinued PRx	Fatal
017	5216	M	Hispanic	36	Off drug 4 days		8	Testicular malignant neoplasm	1.00 day	Severe	Def not	Discontinued PRx	Fatal

(Ref. Table 70 Protocol 054)

Table 35 (cont)

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

Study Site Number	AN	Gender	Race	Age	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation[1]	Action Taken[1]	Outcome
018	5095	M	White	62	Off drug 8 days		12	Pulmonary embolism	1.00 day	Severe	Def not	Discontinued PRx	Fatal
019	5121	M	White	57	Off drug 21 days		25	Respiratory insufficiency	210.00 mins	Severe	Prob not	Discontinued PRx	Fatal
019	5124	M	White	70	Off drug 8 days		12	Leukopenia	10.00 hrs	Severe	Prob not	Discontinued PRx	Fatal
019	5124	M	White	70	Off drug 8 days		12	Neutropenia	10.00 hrs	Severe	Prob not	No action with test drug	Fatal
019	5124	M	White	70	Off drug 8 days		12	Septic shock	10.00 hrs	Severe	Prob not	Discontinued PRx	Fatal
019	6102	F	White	41	Off drug 13 days		17	Septic shock	1.00 day	Severe	Prob not	Discontinued PRx	Fatal

(Ref. Table 70 Protocol 054)

Multiple Cycle

Twenty-five deaths occurred during the multiple-cycle extension period. Fourteen patients (6.3%) in the MK-0869 regimen and 11 patients (4.6%) in the Standard Therapy group died during the study.

The most commonly reported adverse experiences resulting in death in Cycles 2 to 6 were in the Body as a Whole/Site Unspecified Body System (7 patients [3.2%] and 4 patients [1.7%] in the MK-0869 group and Standard Therapy group, respectively). Within this Body System, septic shock (3 patients [1.4%] and 2 patients [0.8%] in the MK-0869 group and Standard Therapy group, respectively) was the most commonly reported adverse experience resulting in death.

Table 36

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

Study Site Number	AN	Gender	Race	Age	Cycle	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation[1]	Action Taken[1]	Outcome
Treatment Group: MK-0869 Regimen														
001	6365	F	Multi	52	3	Off drug 7 days		62	Pulmonary embolism	3.00 days	Severe	Def not	No action with test drug	Fatal
004	5224	M	Hispanic	72	2	Off drug 12 days		40	Metastatic neoplasm of unknown primary	12.00 hrs	Severe	Def not	Discontinued PRx	Fatal
005	5340	M	Multi	68	6	Off drug 8 days		167	Septic shock	2.00 days	Severe	Def not	No action with test drug	Fatal
005	6335	F	White	55	5	Dexamethasone	8 mg	116	Oral cavity malignant neoplasm	13.00 days	Severe	Def not	No action with test drug	Fatal
005	6335	F	White	55	5	Placebo	0 mg	116	Oral cavity malignant neoplasm	13.00 days	Severe	Def not	No action with test drug	Fatal
006	5531	M	Multi	54	6	Off drug 1 day		144	Dyspnea	12.00 hrs	Severe	Prob not	Discontinued PRx	Fatal
006	5531	M	Multi	54	6	Off drug 1 day		144	Respiratory insufficiency	1.00 day	Severe	Def not	Discontinued PRx	Fatal
007	5382	M	Multi	62	2	Off drug 9 days		47	Renal failure	2.00 days	Severe	Def not	Discontinued PRx	Fatal
007	5394	M	Multi	48	6	Off drug 10 days		162	Sepsis	2.00 days	Severe	Def not	No action with test drug	Fatal
007	5395	M	Multi	51	4	Off drug 14 days		102	Septic shock	1.00 hr	Severe	Def not	Discontinued PRx	Fatal
007	6383	F	Multi	41	3	Off drug 19 days		88	Sarcoma	4.00 days	Severe	Prob not	Discontinued PRx	Fatal
008	5440	M	Multi	67	3	Off drug 6 days		88	Unknown cause of death	1.00 day	Severe	Prob not	Discontinued PRx	Fatal

(Ref. Table 72 Protocol 054)

Table 36 (cont)

Study Site Number	AN	Gender	Race	Age	Cycle	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation*	Action Taken*	Outcome
014	5028	M	White	74	2	Off drug 3 days		34	Perforating duodenal ulcer	2.00 days	Severe	Prob	Discontinued PRx	Fatal
017	5215	M	Hispanic	62	3	Off drug 4 days		104	Septic shock	9.00 hrs	Severe	Def not	Discontinued PRx	Fatal
018	5093	M	White	72	3	Off drug 31 days		93	Respiratory insufficiency	2.00 days	Severe	Def not	No action with test drug	Fatal
018	5128	M	White	37	2	Off drug 33 days		66	Non-small cell lung carcinoma	6.00 days	Severe	Def not	Discontinued PRx	Fatal
Treatment Group: Standard Therapy														
002	5217	M	Hispanic	62	3	Off drug 5 days		67	Respiratory failure	17.00 hrs	Severe	Def not	Discontinued PRx	Fatal
005	5335	M	Multi	78	6	Off drug 2 days		159	Pneumonia	1.00 day	Severe	Prob not	No action with test drug	Fatal
005	6334	F	Black	45	2	Off drug 7 days		46	Pericardial effusion	3.00 days	Severe	Prob not	Discontinued PRx	Fatal
005	6336	F	Multi	51	2	Off drug 2 days		38	Septic shock	6.00 mins	Severe	Prob not	Discontinued PRx	Fatal
007	5396	M	Multi	70	3	Off drug 31 days		92	Renal failure	4.00 days	Mod	Def not	Discontinued PRx	Fatal
007	5402	M	Multi	72	4	Off drug 25 days		113	Septic shock	8.00 days	Severe	Prob not	Discontinued PRx	Fatal
007	6391	F	Multi	62	3	Off drug 10 days		75	Sepsis	1.00 day	Severe	Def not	Discontinued PRx	Fatal
012	6272	M	Hispanic	71	5	Dexamethasone	8 mg	97	Congestive heart failure	1.00 day	Severe	Def not	Discontinued PRx	Fatal

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

Study Site Number	AN	Gender	Race	Age	Cycle	Therapy	Total Daily Dose	Relative Day of Onset	Adverse Experience	Duration of Adverse Experience	Intensity	Drug Relation*	Action Taken*	Outcome
015	5005	M	Hispanic	58	6	Placebo	0 mg	136	Unknown cause of death	1.00 day	Severe	Prob not	Discontinued PRx	Fatal
015	5005	M	Hispanic	58	6	Dexamethasone	8 mg	136	Unknown cause of death	1.00 day	Severe	Prob not	Discontinued PRx	Fatal
018	5127	M	White	61	2	Off drug 27 days		61	Non-small cell lung carcinoma	1.00 day	Severe	Def not	Discontinued PRx	Fatal
018	6106	F	White	52	2	Placebo	0 mg	27	Pulmonary embolism	1.00 day	Severe	Def not	Discontinued PRx	Fatal
018	6106	F	White	52	2	Dexamethasone	20 mg	27	Pulmonary embolism	1.00 day	Severe	Def not	Discontinued PRx	Fatal
018	6106	F	White	52	2	Placebo	0 mg	27	Respiratory insufficiency	1.00 day	Severe	Def not	Discontinued PRx	Fatal
018	6106	F	White	52	2	Dexamethasone	20 mg	27	Respiratory insufficiency	1.00 day	Severe	Def not	Discontinued PRx	Fatal

* Determined by the investigator

(Ref. Table 72 Protocol 054)

Medical Officer Comment:
Although adverse experiences of respiratory insufficiency resulting in death were more common in the MK-0869 group compared with the Standard Therapy group in Cycle 1, this was not the case in the Multiple-Cycle extension period (Cycles 2 to 6) where 2 patients from each group died from respiratory insufficiency. None of the serious adverse experiences of respiratory insufficiency were determined by the investigator to be drug related and none of the fatal adverse experiences were considered to be drug related.

It should be noted that 5 of the 6 patients in the MK-0869 group who died of respiratory insufficiency were all randomized at the same study site (Site 018). Almost all patients recruited by this investigator had lung cancer and the majority (86.5%) were treated with vinorelbine in combination with high doses of cisplatin. In the identical, parallel Phase III study, Study 052, 53 patients (28 in the MK-0869 group and 25 in the Standard Therapy group) received vinorelbine in combination with high doses of cisplatin and no patients died of respiratory insufficiency.

Medical Officer Conclusions:

The purpose of this study was to compare the MK-0869 regimen with Standard Therapy for 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^2. 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^2 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 and 120 mg/m^2. The Anzemet label describes a highly emetogenic cisplatin dose as ≥70 mg/m^2. Recent literature, as well as the Hesketh Scale used in this study, support that Cisplatin ≥ 50 mg/m^2 is a highly emetogenic dose. The Agency performed analysis excluding patients who received less than 70 mg/m^2, 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.

Primary Endpoint

The primary endpoint of this study was Complete Response in the overall phase (0 to 120 hours post-cisplatin initiation) with patients defined as treatment failures if they had emesis or required rescue medication. The primary endpoint did not include evaluation of nausea.

The Sponsor was successful in demonstrating that the MK-0869 regimen was more effective than Standard Therapy in the prevention of CINV for 0 to 120 hours post-cisplatin administration with 62.7% versus 43.3% ($p<0.001$) 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 acute, delayed and overall time period for the following secondary endpoints: no emesis, complete response, complete protection, no use of rescue medication. The MK-0869 regimen was superior to Standard Therapy for the endpoint Total Control for the overall and delayed phase. It was numerically better for the acute phase but failed to reach statistical significance.

Unlike Study 052, which failed to reach statistical significance for the endpoints of nausea, this study demonstrated statistical significance for the endpoint No Nausea for both the overall and delayed phase. The MK-0869 group also had a significantly higher proportion of patients who did not use rescue medications, and significantly more rescue-free time than the Standard Therapy group. The Sponsor suggests 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 significantly more efficacious for all endpoints (complete response, no emesis, complete protection, and no use of rescue medication) with the exception of the most stringent endpoint of total control for which there was numerical superiority but no statistical significance.

Delayed Phase

During the delayed phase (25 to 120 hours post-cisplatin) the MK-0869 regimen was more efficacious for all endpoints, including the primary endpoint of Complete Response. The differences were statistically significant for complete response, no emesis, complete protection, total control, no use of rescue medication, and no nausea.

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 all other efficacy endpoints (no emesis, no use of rescue medication, no significant nausea, no nausea, complete protection, and total control) also supported superiority of the MK-0869 regimen.

For complete response, no emesis, complete protection, total control, and no nausea, the difference between the MK-0869 regimen versus Standard Therapy was statistically significant.

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. 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

Serious adverse experiences were slightly more common in the MK-0869 group compared to the Standard Therapy group. Serious adverse experiences occurred in 31 patients (11.0%) in the MK-0869 group and 28 patients (9.8%) in the Standard Therapy group. The most commonly reported serious adverse experiences in Cycle 1 were neutropenia (5 patients [1.8%] and 6 patients [2.1%]), dehydration (5 patients [1.8%] and 2 patients [0.7%]), respiratory insufficiency (5 patients [1.8%] and 1 patient [0.4%]), septic shock (3 patients [1.1%] and 2 patients [0.7%]), and dyspnea (3 patients [1.1%] and 2 patients [0.7%]) in the MK-0869 group and Standard Therapy group, respectively.

The incidence of serious adverse experiences during the Multiple-Cycle extension period was balanced between treatment groups with approximately 14% of the patients developing a serious adverse event. The most commonly reported serious adverse experiences in Cycles 2 to 6 were neutropenia (6 patients [2.7%] and 4 patients [1.7%]), diarrhea (7 patients [3.2%] and 0 patients [0.0%]), dehydration (3 patients [1.4%] and 2 patients [0.8%]), septic shock (3 patients [1.4%] and 2 patients [0.8%]), pneumonia (3 patients [1.4%] and 2 patients [0.8%]), and respiratory insufficiency (2 patients [0.9%] and 3 patients [1.3%]) in the MK-0869 group and Standard Therapy group, respectively. The incidence of infection related serious adverse experiences was slightly higher in the MK-0869 group.

Chemotherapeutic Agents

The incidence of serious adverse experiences was nearly twice as high in the MK-0869 regimen (15.9%) compared to the Standard Therapy (8.5%) for patients who received concomitant chemotherapeutic agents metabolized by the CYP3A4. In particular, more patients in the MK-0869 group experienced serious adverse experiences in the following body systems: Body as a Whole/Site Unspecified (8.5% versus 2.4%), Respiratory System (7.3% versus 1.8%), and Hematologic and Lymphatic System (4.3% versus 1.8%)

In contrast, the incidence of serious adverse experiences in patients treated with concomitant chemotherapy NOT metabolized by CYP3A4 was lower in the MK-0869 group (4.2%) compared with the Standard Therapy group (11.6%).

Laboratory

The protocol-specified laboratory data analyses revealed no notable trends. Analysis using the NCI common toxicity criteria data did not reveal any marked differences between the treatment groups for hematologic parameters.

Deaths

The incidence of deaths was slightly higher in the MK-0869 group compared with the Standard Therapy group. There were 24 deaths that occurred in Cycle 1 (13 [4.6%] in the MK-0869 regimen and 11 [3.9%] in the Standard Therapy group). During the multi-cycle extension there were 25 deaths (14 [6.3%] in the MK-0869 group and 11 [4.6%] in the Standard Therapy group).

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SAFETY UPDATE REVIEW

See Clinical Reviews dated March 14, 2003