

CENTER FOR DRUG EVALUATION AND RESEARCH

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Statistical Review(s)



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OFFICE OF BIostatISTICS
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STATISTICAL REVIEW AND EVALUATION

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INDICATION: Prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy.
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1.0 EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

1.1 Overview of Clinical Program and Studies Reviewed

In this NDA submission, two-phase III studies, Study P052 and Study P054, were submitted to support the use of aprepitant regimen in the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy.

The primary objective for both studies was to demonstrate that MK-0869 triple therapy (Aprepitant) is superior to standard therapy (Table 1.1.1) in the control of chemotherapy-induced nausea and vomiting (CINV) as measured by the proportion of patients with complete response (no emesis and no rescue medication) in the 120 hours following the initiation of high-dose cisplatin chemotherapy and to evaluate the safety and tolerability of MK-0869 triple therapy.

Table 1.1.1 (Sponsor's) Treatment Regimen

Treatment Regimen	Day 1	Days 2 to 4
MK-0869	MK-0869 125 mg P.O. Dexamethasone 12 mg P.O. Ondansetron 32 mg IV or 3 doses of 0.15 mg/kg IV †	MK-0869 80 mg P.O. Daily (Days 2 and 3 only) Dexamethasone 8 mg P.O. Daily (morning) Dexamethasone Placebo P.O. Daily (evening)
Standard Therapy	MK-0869 Placebo P.O. Dexamethasone 20 mg P.O. Ondansetron 32 mg IV or 3 doses of 0.15 mg/kg IV †	MK-0869 Placebo P.O. Daily (Days 2 and 3 only) Dexamethasone 8 mg P.O. Daily (morning) Dexamethasone 8 mg P.O. Daily (evening)

† Dosing for adolescents =12 and <18 years of age and =40 kg body weight per site-specific amendment: ondansetron 3 doses of 0.15 mg/kg IV on Day 1.
P.O. = By mouth.
IV = Intravenous.

Both clinical trials (Studies P052 and P054) were multi-center, randomized, double-blind, parallel-group, controlled trials with in-house blinding to assess the safety and efficacy of MK-0869 in the prevention of CINV in patients with confirmed solid malignancies who were treated with a chemotherapy regimen that included cisplatin ≥ 70 mg/m². For Study P052, patients were enrolled from fifty-eight (58) centers located in the United States, Australia, Belgium, Canada, Denmark, France, Germany, Greece, Hungary, Italy, Russia, South Africa, Spain, Sweden, Switzerland, and Taiwan. Nevertheless, for Study P054, patients were enrolled from 18 centers located in Argentina, Brazil, Chile, Colombia, Guatemala, Mexico, Peru, and Venezuela.

1.2 Principal Findings

1.2.1 Study P052

Based on the sponsor's and this reviewer's analyses through the sponsor's study data, the following three consequences are demonstrated:

- The efficacy of MK-0869 regimen, assessed from complete response (no emesis and without rescue therapy), is superior to that of standard therapy in prevention of acute and delayed

vomiting associated with cancer therapy.

- The efficacy of MK-0869 regimen, assessed from complete protection, is superior to that of standard therapy in prevention of acute and delayed significant nausea and vomiting (but not for significant nausea alone) associated with emetogenic cancer therapy.
- However, the efficacy of MK-0869 regimen, assessed from no nausea and no significant nausea, is not superior to that of standard therapy in prevention of acute and delayed nausea associated with emetogenic cancer therapy.
- Similarly, the efficacy of MK-0869 regimen, assessed from total control, is also not superior to that of standard therapy in prevention of acute and delayed nausea and vomiting associated with emetogenic cancer therapy.

1.2.2 Study P054

Based on the sponsor's and this reviewer's analyses through the sponsor's study data, the following two results are acknowledged:

- The efficacy of MK-0869 regimen, assessed from complete response (no emesis and without rescue therapy), is superior to that of standard therapy in prevention of acute and delayed vomiting associated with cancer therapy.
- The efficacy of MK-0869 regimen, assessed from complete protection (no emesis, no rescue and maximum nausea VAS < 25 mm), is superior to that of standard therapy in prevention of acute and delayed significant nausea and vomiting (but not for significant nausea alone) associated with cancer therapy.

In addition, based on this reviewer's analyses through the sponsor's study data, the following two results are noted:

- The efficacy of MK-0869 regimen, assessed from no nausea and no significant nausea, is superior to that of standard therapy only in prevention of delayed nausea associated with cancer therapy.
- Similarly, the efficacy of MK-0869 regimen, assessed from total control (no emesis, no rescue and maximum nausea VAS < 5 mm), is superior to that of standard therapy only in prevention of delayed nausea and vomiting associated with cancer therapy.

1.3 Conclusions and Recommendations

From the results of the two Studies P052 and P054, the conclusions/recommendations on the efficacy of MK-0869 regimen, from statistical perspective, are made as follows:

- ◆ The efficacy of Mk-0869 is superior to that of standard therapy in prevention of acute and delayed vomiting associated with cancer therapy.

- ◆ The efficacy of Mk-0869 is superior to that of standard therapy in prevention of acute and delayed nausea and vomiting associated with cancer therapy (for logic leading to this conclusion/recommendation, refer to section 2.2.3 – Conclusions and Recommendations).
- ◆ However, the efficacy of Mk-0869 is not superior to that of standard therapy in prevention of acute and delayed nausea associated with cancer therapy.

2.0 STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

2.1 Introduction and Background

In this NDA submission, the sponsor made the following observations with regard to Aprepitant:

Cancer chemotherapy is associated with a predictable spectrum of dose-related toxic effects, which include nausea and vomiting. Nausea and vomiting are still regarded by cancer patients as among the most feared complications of chemotherapy with a demonstrated impact on quality of life despite recent advances in their prevention, notably the introduction of the 5-HT₃ receptor antagonists. Therefore, there is still a need for improved therapy to prevent chemotherapy-induced nausea and vomiting (CINV).

Aprepitant is a highly selective Substance P neurokinin 1 (NK₁) receptor antagonist that has demonstrated notable safety and efficacy in the prevention of acute and delayed chemotherapy-induced nausea and vomiting (CINV). Substance P and the NK₁ receptors that mediate its activity are present in the brainstem centers that elicit the emetic reflex. In pre-clinical models of emesis, brain-penetrant NK₁ receptor antagonists such as aprepitant given alone prevent both acute and delayed cisplatin-induced emesis as well as emesis evoked by a wide spectrum of peripherally and centrally acting emetogens. Aprepitant occupancy of central nervous system (CNS) NK₁ receptors has been demonstrated in positron emission tomographic (PET) studies in primates and man. The efficacy of EMENDTM is due to its mechanism of action as a potent and highly selective non-peptide NK₁ receptor antagonist with a long duration of action that provides anti-emetic coverage throughout the acute and delayed phases of CINV.

Two-phase III studies, Study P052 and Study P054, were submitted to support the use of aprepitant regimen in the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy.

The primary objective for both studies was to demonstrate that MK-0869 triple therapy (shown in Table 1.1.1) 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 and to evaluate the safety and tolerability of triple therapy with MK-0869.

Both clinical trials (Studies P052 and P054) were multi-center, randomized, double-blind, parallel-group, controlled trial to assess the safety and efficacy of MK-0869 in the prevention of CINV in patients with confirmed solid malignancies who were treated with a chemotherapy regimen that included cisplatin ≥ 70 mg/m². For Study P052, patients were enrolled from fifty-eight (58) centers located in the United States, Australia, Belgium, Canada, Denmark, France, Germany, Greece, Hungary, Italy, Russia, South Africa, Spain, Sweden, Switzerland, and Taiwan. Nevertheless, for Study P054, patients were enrolled from 18 centers located in Argentina, Brazil, Chile, Colombia, Guatemala, Mexico, Peru, and Venezuela.

Total 534 eligible patients for Study P052 and 569 for Study P054 were randomized to receive either treatment MK-0869 regimen or standard therapy (Table 1.1.1). The two studies employed a double stratification procedure: patients were stratified according to gender and within each gender stratum, patients were further stratified according to the administration of emetogenic chemotherapy in addition to cisplatin. Patients were first stratified by gender and assigned an appropriate range of allocation numbers (Ans). Patients were then stratified again based on additional emetogenic chemotherapy using the Hesketh classification. If patients were to receive chemotherapy of a Hesketh level 3 or greater they received the highest AN available within their stratum. If they were to receive a lower Hesketh level chemotherapy, then they received the lowest number available. It was assumed that randomization would balance the groups for other factors affecting the nausea and emesis response to cisplatin, e.g., age, alcohol intake, susceptibility to motion sickness, and history of emesis during pregnancy.

During chemotherapy Cycle 1, patients reported episodes of vomiting, daily nausea assessments, and use of rescue therapy in a diary from the initiation of cisplatin infusion (0 hours in Day 1) until the morning of Day 6 (~ 120 hours). After completion of Cycle 1, patients had the option to participate in a multiple-cycle extension for a maximum of 5 subsequent cycles if they fulfilled the multiple-cycle enrollment criteria.

During the multiple-cycle phase, the patient diary was replaced by the Emetic Episodes and Nausea Assessment worksheet, which was a simple questionnaire (2 questions) that assessed nausea and vomiting during the 120-hour period post cisplatin infusion in each of the subsequent cycles.

Clinical response was evaluated with a patient diary that was completed daily for 5 days after the administration of cisplatin (this was done during Cycle 1 only). The diary captured all emetic episodes, all use of rescue therapy (only taken for treatment of established nausea or emesis), and a daily nausea severity assessment. Patients were monitored for adverse experiences and tolerability at scheduled visits that occurred between Days 6 and 8 and Days 19 and 29 post cisplatin.

Unless stated otherwise, all tests of hypotheses were to use a 2-sided significance level of 5%. All the analyses described below would use data from the first cycle of chemotherapy. The efficacy and safety data from the multiple cycle extension will be summarized by descriptive statistics. Since the sponsor mainly used data from the first cycle of chemotherapy to support MK-0869 regimen in the use of the proposed indication, the efficacy analyses on the first cycle of chemotherapy are the focus of this review.

Two patient populations were considered for the efficacy analysis: the modified-intention-to-treat (MITT) population and the per-protocol population. The MITT population included all patients who received cisplatin, took a dose of study drug, and had at least one post-treatment assessment during Cycle 1. This was the primary population used to assess efficacy. The per-protocol population (PP) is the MITT population without those patients who were identified as protocol

violators prior to unblinding. This population was considered a supportive evaluation of the primary efficacy hypothesis.

For both studies, Studies P052 and P054, there were three phases in Cycle 1: overall phase - 0 to 120 hours following initiation of cisplatin infusion, acute phase - 0 to 24 hours following initiation of cisplatin infusion, and delayed phase - 25 to 120 hours following initiation of cisplatin infusion. In addition, the complete response was defined as no emesis and no use of rescue therapy for treatment of either nausea or emesis.

Firstly, the primary efficacy endpoint was the complete response in the overall phase in Cycle 1. It means no emetic episodes and no use of rescue medication to treat established nausea or emesis (complete response) during the 5 days following cisplatin chemotherapy (overall phase) in Cycle 1.

Then, in the amended protocol, the secondary endpoints proposed by the sponsor were:

- Complete Response in acute and delayed phases;
- No Emesis in overall, acute, and delayed phases;
- No Significant Nausea (VAS < 25 mm) in overall phase;
- No Nausea (VAS < 5mm) in overall phase;
- No Impact on Daily Life (FLIE total scores > 108) in overall phase;
- Time to First Emesis in overall phase.

Finally, in the protocol, the exploratory endpoints pre-specified by the sponsor were:

- No Significant Nausea (VAS < 25 mm) in delayed phase;
- No Nausea (VAS < 5mm) in delayed phase;
- Complete Protection (no emesis, no rescue and maximum nausea VAS < 25 mm) in overall, acute, and delayed phases;
- Total Control (no emesis, no rescue and maximum nausea VAS < 5 mm) in overall, acute, and delayed phases;
- Severity of nausea (comparing the distributions of the average VAS scores) in the overall and delayed phases.

The primary efficacy analysis was to compare MK-0869 triple therapy to the standard therapy with respect to the proportion of patients reporting Complete Response 0 to 120 hours following initiation of cisplatin. The treatment comparisons were to be made using logistic regression models that included terms for region (US versus non-US), gender, use of concomitant chemotherapy, and treatment. Treatment interactions with region, gender, and use of concomitant emetogenic chemotherapy were to be also assessed in the context of logistic regression models.

The treatment comparisons with respect to the secondary efficacy variables was to be made in the same fashion as that described for the primary efficacy analyses using logistic regression models. For analysis of time to first vomiting episode, Kaplan-Meier (K-M) curves would be plotted by treatment group to depict the percentage of patients who were vomiting-free since the initiation of cisplatin therapy. Treatment comparisons were to be made using unstratified log-rank tests.

Additionally, the frequency of vomiting episodes during the entire Cycle 1 diary data collection period was to be summarized by treatment group.

The sample size was determined to have 90% and 52% of power to detect 15% and 8%, of complete response differences respectively in the overall phase (60% for MK-0869 regimen versus 45% for standard therapy) and acute phase between MK-0869 triple therapy regimen and standard therapy at .05 significance level. Thus, a total of 500 patients (approximately 250 patients per treatment group) were to be enrolled in the study to yield a total of 470 evaluable patients (approximately 235 patients per treatment group) with at least 1 post-treatment rating.

For the efficacy analyses using the MITT approach, the missing data were imputed by carrying forward the preceding data that were not missing in the same phase (acute or delayed). Acute phase represents only one efficacy measurement, so no carrying forward is 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 Day1, 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. For the per-protocol analysis, no imputation for missing data was made.

The dispositions of Cycle 1 patients for Studies P052 and P054 are presented in Table 2.1.1 and Table 2.1.2, respectively.

Table 2.1.1 Overall disposition of patients for Cycle 1 for Study P052

Time Frame	MK-0869 Regimen	Standard Therapy	Total
ENTERED: Total	266 [†]	268 [†]	534
Male (age range—years)	168 (15 to 82)	168 (14 to 83)	336 (14 to 83)
Female (age range—years)	98 (18 to 84)	100 (30 to 79)	198 (18 to 84)
SCREENING FAILURES:			32
COMPLETED:	16	12	28
CONTINUING (multiple cycles):	181	195	376
DISCONTINUED: Total	69	61	130
Clinical adverse experience	23 [‡]	15	38 [§]
Laboratory adverse experience	1	3	4
Treatment failure	7	9	16
Other *	38	34	71

[†] Includes 3 patients who were randomized but did not receive study drug.

[‡] Includes one patient who was randomized but did not receive study drug.

[§] Includes 2 patients who were randomized but took no study drug and were discontinued due to clinical adverse experiences.

* Includes no response to or refusal of chemotherapy, non-compliance with study drug, ineligibility, protocol deviation, loss to follow-up, completion of chemotherapy, or withdrawal of consent.

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 for adults (or 3 doses of Ondansetron 0.15 mg/kg IV for adolescents) 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.

Table 2.1.2 Overall disposition of adult patients for Cycle 1 for Study P054

Time Frame	MK-0869 Regimen	Standard Therapy	Total
ENTERED: Total	283 [†]	286 [‡]	569
Male (age range—years)	148 (18 to 82)	146 (18 to 81)	294
Female (age range—years)	135 (19 to 80)	140 (19 to 81)	275
SCREENING FAILURES:			55
CONTINUING (multiple cycles):	234	246	480
DISCONTINUED: Total	49	40	89
Clinical adverse experience	21 [§]	16	37
Laboratory adverse experience	1	1	2
Treatment failure	1	2	3
Other *	26	21	47

[†] Includes 3 patients who were randomized but did not receive study drug.
[‡] Includes one patient who was randomized but did not receive study drug.
[§] Includes 2 patients who were randomized but took no study drug and were discontinued due to clinical adverse experiences.
* Includes no response to or refusal of chemotherapy, non-compliance with study drug, ineligibility, protocol deviation, loss to follow-up, completion of chemotherapy, or withdrawal of consent.
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 for adults (or 3 doses of Ondansetron 0.15 mg/kg IV for adolescents) 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.

For Study P052, of total 534 patients, 4 were adolescents: 2 for each treatment group. Based on Table 2.1.2, the sponsor indicated that the number of patients who discontinued from the study was similar in both treatment groups. The status “completed” was assigned to 28 patients (16 in the MK-0869 group and 12 in the Standard Therapy group). These patients were enrolled at 4 study sites (Site Numbers 017, 020, 034, and 037), which participated in the protocol with the agreement to enroll patients for Cycle 1 only. In addition, a higher incidence of patients withdrew consent in the MK-0869 regimen as compared to the Standard Therapy group.

Similar to Study P052, Table 2.2.3 showed that the number of patients who discontinued from Study P054 was similar in both treatment groups but MK-0869 regimen had a higher incidence of patients to withdraw consent.

2.2 Statistical Evaluation of Evidence on Efficacy/Safety

2.2.1 Detail Review of Individual Studies

2.2.1.1 Study P052

Baseline Demographics and Characteristics

In cycle 1, the demographic and other baseline characteristics reported by Table 22 of Volume 25 were gender, age, race, alcohol intake, history of morning sickness, history of motion sickness, history of chemotherapy, history of chemotherapy-induced vomiting, other concurrent emetogenic chemotherapy, and cisplatin dose. Based on Table 22, the sponsor indicated that the

two treatment groups were generally similar with respect to baseline demographics and characteristics.

In addition, five (5) patients (ANs 8054, 8114, 8206, 8373, and 9049) were randomized but received no cisplatin; these patients were excluded from the MITT analyses. A total of 108 patients who received cisplatin (52 patients in the MK-0869 group and 56 in the Standard Therapy group) were administered less than the protocol-mandated 70 mg/m² dose. Of the 108 patients, one hundred and two (102) patients received a cisplatin dose above 65 mg/m². The other 6 patients received a cisplatin dose between 50 mg/m² and 64 mg/m².

The distribution of known risk factors for CINV (female gender; history of alcohol use, morning sickness, motion sickness, and prior chemotherapy-induced vomiting) and the number of patients with and without prior chemotherapy was similar between two treatment groups.

Efficacy analysis Results and Conclusions

The sponsor indicated that of total 530 adult patients received an allocation number (AN), 4 patients did not receive study medication and cisplatin chemotherapy, and 1 did not receive cisplatin chemotherapy. From the remaining 525 patients, 4 patients did not provide any post-treatment evaluations in the patient diary (no efficacy data). Therefore, 521 patients are included in the Modified-Intent-to-Treat (MITT) efficacy analyses.

Table 2.2.1.1.1 presented the number of patients with complete response by treatment group and phase using MITT patient population. The three phases in Table 2.2.1.1.1 were defined as follows: overall phase - 0 to 120 hours following initiation of cisplatin infusion, acute phase - 0 to 24 hours following initiation of cisplatin infusion, and delayed phase - 25 to 120 hours following initiation of cisplatin infusion. The p-values in Table 2.2.1.1.1 were for the efficacy comparisons between MK-0869 regimen and Standard Therapy, calculated using sponsor's submitted SAS programs and data sets.

Table 2.2.1.1.1 (Sponsor's) Complete response[†] by treatment group and phase using MITT patient population

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
Overall Phase	189/260 (73)** (p < 0.0001)	136/260 (52)
Acute Phase	231/259 (89)** (p = 0.0009)	203/260 (78)
Delayed Phase	196/260 (75)** (p < 0.0001)	145/260 (56)

** : p < 0.001 when compared with Standard Therapy; † : Complete Response = No emesis with no rescue therapy;
n/m = Number of patients with desired response/number of patients included in time point.

From Table 2.2.1.1.1, the sponsor indicated that in the overall phase (the primary endpoint), during the 5 days post-cisplatin administration, 73% of patients in the MK-0869 group and 52% of the patients in the standard therapy group reported complete response. It led that the MK-0869 group had significantly higher percentages than the Standard Therapy group (p < 0.0001, adjusted for gender, region, and use of concomitant chemotherapy).

As for the acute phase (the secondary endpoint), 89% and 78% of the patients in the MK-0869 group and standard therapy group, respectively, had a complete response. The percentage for the MK-0869 group was significantly higher than that of the standard therapy group ($p = 0.0009$). Similarly, for the delayed phase (the secondary endpoint), the complete response rate for the MK-0869 regimen (75.4%) was significantly higher than that (55.8%) of Standard Therapy ($p < 0.0001$).

Based on above results, the sponsor concluded that for the overall, acute, and delayed phases, the MK-0869 regimen is more effective than standard therapy in the prevention of vomiting when assessed by complete response endpoint.

However, this reviewer notes that for the three phases, the interaction tests at significance level of 10% using logistic model, showed that the interactions between treatment and gender were all significant ($p = 0.001$). The impact of the treatment and gender interaction on the treatment comparisons is assessed by this reviewer and reported in the section of Statistical Reviewer's Findings.

Furthermore, at .05 significance level, the results from per protocol population analysis also showed that the complete response rates of the MK-0869 regimen were significantly higher than that of standard therapy in overall, acute, and delayed phases.

Finally, Table 2.2.1.1.2 presented the sponsor's analysis results on the other secondary and exploratory endpoints: no emesis, complete protection, total control, no use of rescue medication, no nausea and no significant nausea. The p-values in Table 2.2.1.1.2 were for the efficacy comparisons between MK-0869 regimen and Standard Therapy, calculated using sponsor's submitted SAS programs and data sets.

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Table 2.2.1.1.2 (Sponsor's) Number of patients by treatment group and phase using MITT patient population

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
No Emesis		
Overall Phase	202/260 (78)** (P < 0.0001)	143/260 (55)
Acute Phase	234/260 (90)** (P = 0.001)	207/261 (79)
Delayed Phase	210/260 (81)** (P < 0.0001)	153/260 (59)
Complete Protection		
Overall Phase	163/257 (63)** (P = 0.001)	128/260 (49)
Acute Phase	217/256 (85)** (P = 0.005)	94/260 (75)
Delayed Phase	172/259 (66)** (P = 0.0006)	134/260 (52)
Total Control		
Overall Phase	117/257 (46) (P = 0.21)	104/260 (40)
Acute Phase	181/256 (71) (P = 0.13)	167/260 (64)
Delayed Phase	127/259 (49) (P = 0.15)	111/260 (43)
No Use of Rescue Medication		
Overall Phase	210/260 (81)** (P = 0.009)	184/260 (71)
Acute Phase	244/259 (94)* (P = 0.035)	231/260 (89)
Delayed Phase	211/260 (81)* (P = 0.039)	191/260 (74)
No Nausea		
Overall Phase	122/257 (48) (P = 0.48)	115/260 (44)
Acute Phase	185/256 (72) (P = 0.48)	179/259 (69)
Delayed Phase	132/259 (51) (P = 0.46)	124/260 (48)
No Significant Nausea		
Overall Phase	188/257 (73) (P = 0.09)	171/259 (66)
Acute Phase	232/256 (91) (p=0.16)	224/259 (87)
Delayed Phase	195/259 (75) (P = 0.09)	178/260 (69)

*: p<0.05 when compared with Standard Therapy; **: p<0.01 when compared with Standard Therapy;

VAS = Visual analogue scale; n/m = Number of patients with desired response/number of patients included in time point.

At .05 significance level, Table 2.2.1.1.2 indicated that for no emesis, complete protection, and no use of rescue medication, the MK-0869 regimen has significantly higher response rates than standard therapy in the overall, acute, and delayed phases.

In addition, the analysis on the impact of CINV on daily life indicated that 74% of the patients in the MK-0869 group reported “no impact on daily life” relative to 64% of the patients in the standard therapy group. The treatment difference was significant (p=0.021).

Finally, using the sponsor's SAS program, the mean survival time (mean as the area under the survival curve) to the first emesis from start of cisplatin administration in the overall phase was 96 hours for the MK-0869 regimen versus 79 hours for the standard therapy. Furthermore, Log-rank test showed that time to the first emesis was significantly longer for patients in the MK-0869 group when compared with the standard therapy group (p<0.0001).

Since several secondary and exploratory endpoints were analyzed, the nominally significant results may not be taken quite at face value due to multiple comparisons. The multiplicity issue is further commented in the section of 2.2.2 - Statistical Reviewer's Findings.

Results of Adverse Events

In cycle 1, Clinical adverse experiences were reported by 333 of 526 patients (63.3%) who received study drug or control. Of the 333 patients, 170 patients (65.1%) in the MK-0869 group

and 163 patients (61.5%) in the standard therapy group reported one or more clinical adverse experiences. The sponsor indicated that the overall incidence of clinical adverse experiences was similar between both treatment groups. The most commonly reported clinical adverse experiences were asthenia/fatigue (17.2% and 9.4%), hiccups (13.8% and 6.8%), constipation (8.0% and 12.1%), nausea (10.7% and 8.7%), and diarrhea (8.4% and 3.8%) in the MK-0869 group and standard therapy group, respectively. In addition, sixty-seven (67) of the 526 patients (8.9%) who received study drug had one or more drug-related clinical adverse experiences (determined by the investigator to be possibly, probably, or definitely study drug related): 38 patients (14.6%) and 29 patients (10.9%) in the MK-0869 group and the standard therapy group, respectively.

Serious clinical adverse experiences occurred in eighty-eight (16.7%) of 526 randomized adult patients who received study drug or control: 42 (16.1%) and 46 (17.4%) of patients in the MK-0869 group and the standard therapy group, respectively. Drug-related serious clinical adverse experiences (determined by the investigator to be study drug related) occurred in 3 patients: 1 (0.4%) in the MK-0869 group and 2 (0.8%) in the standard therapy group.

Thirty-six (36) patients (6.8%) discontinued study drug therapy due to clinical adverse experiences. Two (2) patients (0.8%) in each treatment group discontinued study drug therapy due to a drug-related clinical adverse experience: 21 patients (8.0%) in the MK-0869 group and 15 (5.7%) in the standard therapy group. In addition, two patients (0.8%) who received standard therapy were discontinued from study due to serious drug-related clinical adverse experiences. Finally, 16 deaths occurred in this study: 7 patients (2.7%) in the MK-0869 group and 9 patients (3.4%) in the standard therapy group.

2.2.1.2 Study P054

Baseline Demographics and Characteristics

In cycle 1, the demographic and other baseline characteristics reported by Table 21 of Volume 27 were gender, age, race, alcohol intake, history of morning sickness, history of motion sickness, history of chemotherapy, history of chemotherapy-induced vomiting, other concurrent emetogenic chemotherapy, and cisplatin dose. Based on Table 21, the sponsor indicated that the two treatment groups were generally similar with respect to baseline demographics.

The baseline patient characteristics, including known risk factors for CINV (female gender; history of alcohol use, morning sickness, motion sickness, and prior chemotherapy-induced vomiting), were generally similar. However, there was a slightly higher incidence of a history of morning sickness in the MK-0869 group (10.2%) versus that in the standard therapy group (6.6%). In contrast, the standard therapy group had a higher incidence of a prior history of chemotherapy (10.1%) as compared with that in the MK-0869 group (7.4%).

Efficacy analysis Results and Conclusions

The sponsor indicated that a total of 569 adult patients were randomized into the study and received an allocation number (AN). Of the 569 patients, 1 patient did not receive study medication and cisplatin chemotherapy, 1 received study medication but did not receive cisplatin chemotherapy, and 2 received study medication and cisplatin but patient diaries were not available. Of the remaining 565 patients, 40 were randomized at Study Site 001

where, through monitoring visits and an audit, the efficacy data were determined to be unreliable. Thus, the sponsor excluded the efficacy data from these patients in the efficacy analysis. As a result, 525 patients were included in the MITT efficacy analyses. From the total of 525 patients, 1 patient from the MK-0869 group did not provide emesis and rescue data for the acute phase, and 2 patients from the MK-0869 group did not provide any emesis and rescue data for delayed and overall phases. Therefore, the MITT analysis included 524 patients in the acute phase, and 523 in the delayed and overall phases.

Table 2.2.1.2.1 presented the number of patients with complete response by treatment group and phase using MITT patient population. The three phases in Table 2.2.1.2.1 were defined as follows: overall phase - 0 to 120 hours following initiation of cisplatin infusion, acute phase - 0 to 24 hours following initiation of cisplatin infusion, and delayed phase - 25 to 120 hours following initiation of cisplatin infusion. The p-values in Table 2.2.1.2.1 were for the efficacy comparisons between MK-0869 regimen and Standard Therapy, calculated using sponsor's submitted SAS programs and data sets.

Table 2.2.1.2.1 (Sponsor's) Complete response¹ by treatment group and phase using MITT patient population

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
Overall Phase	163/260 (63)** (p < 0.0001)	114/263 (43)
Acute Phase	216/261 (83)** (p = 0.0001)	180/263 (68)
Delayed Phase	176/260 (68)** (p < 0.0001)	123/263 (47)

** : p<0.001 when compared with Standard Therapy; ¹ : Complete Response = No emesis with no rescue therapy;
n/m = Number of patients with desired response/number of patients included in time point.

From Table 2.2.1.2.1, the sponsor indicated that in the overall phase (the primary endpoint), during the 5 days post-cisplatin administration, 63% of patients in the MK-0869 group and 43% of the patients in the standard therapy group reported complete response. It followed that the MK-0869 group had significantly higher percentages than the standard therapy group (p<0.0001).

As for the acute phase (the secondary endpoint), 83% and 68% of the patients in the MK-0869 group and standard therapy group, respectively, had a complete response. The percentage for the MK-0869 group was significantly higher than that of the standard therapy group (p=0.0001). Similarly, for the delayed phase (the secondary endpoint), the complete response rate for the MK-0869 regimen (68%) was significantly higher than that (47%) of standard therapy (p<0.0001).

Based on the above results, the sponsor concluded that for the overall, acute, and delayed phases, the MK-0869 regimen is more effective than standard therapy in the prevention of vomiting when assessed by complete response endpoint.

Furthermore, at .05 significance level, the results from per protocol population analysis also showed that the complete response rate of the MK-0869 regimen was significantly higher than that of standard therapy for overall, acute, and delayed phases.

Finally, Table 2.2.1.2.2 presented the analysis results on the other secondary and exploratory endpoints: no emesis, complete protection, total control, no use of rescue medication, no nausea and no significant nausea. The p-values in Table 2.2.1.2.2 were for the efficacy comparisons between MK-0869 regimen and standard therapy, calculated using sponsor's submitted SAS programs and data sets.

Table 2.2.1.2.2 (Sponsor's) Number of patients by treatment group and phase using MITT patient population

	MK-0869 Regimen	Standard Therapy
	N/m (%)	n/m (%)
No Emesis		
Overall Phase	172/260 (66)** (P < 0.0001)	117/263 (45)
Acute Phase	218/261 (84)** (P < 0.0001)	181/263 (69)
Delayed Phase	186/260 (72)** (P < 0.0001)	127/263 (48)
Complete Protection		
Overall Phase	145/261 (56)** (P = 0.0006)	107/263 (41)
Acute Phase	208/260 (80)** (P < 0.0001)	170/263 (65)
Delayed Phase	159/261 (61)** (P = 0.0001)	116/263 (44)
Total Control		
Overall Phase	116/261 (44) ** (P = 0.003)	84/263 (32)
Acute Phase	166/261 (64) (P = 0.10)	149/263 (57)
Delayed Phase	130/261 (50) ** (P = 0.0002)	89/263 (34)
No Use of Rescue Medication		
Overall Phase	214/260 (82)** (P = 0.008)	191/263 (73)
Acute Phase	251/261 (96)** (P = 0.006)	236/263 (90)
Delayed Phase	216/260 (83)* (P = 0.013)	195/263 (74)
No Nausea		
Overall Phase	127/260 (49) * (P = 0.021)	102/263 (39)
Acute Phase	176/260 (68) (P = 0.71)	174/263 (66)
Delayed Phase	137/260 (53) ** (P = 0.003)	105/263 (40)
No Significant Nausea		
Overall Phase	185/260 (71) (P = 0.08)	168/263 (64)
Acute Phase	235/260 (90)* (P = 0.011)	218/263 (82)
Delayed Phase	189/260 (73) (P = 0.07)	172/263 (65)

*: p<0.05 when compared with Standard Therapy; **: p<0.01 when compared with Standard Therapy;

VAS = Visual analogue scale; n/m = Number of patients with desired response/number of patients included in time point.

At .05 significance level, Table 2.2.1.2.2 indicated that for no emesis, complete protection, and no use of rescue medication, the MK-0869 regimen had significantly higher response rates than standard therapy in the overall, acute, and delayed phases. However, for total control and no nausea, the MK-0869 regimen had significantly higher response rates than standard therapy only in the overall and delayed phases.

In addition, the analysis on the impact of CINV on daily life indicated that 75% of the patients in the MK-0869 group reported “no impact on daily life” relative to 64% of the patients in the Standard Therapy group. The treatment difference was significant ($p=0.007$).

Finally, using the sponsor’s SAS program, the mean survival time (mean as the area under the survival curve) to the first emesis from start of cisplatin administration in the overall phase was 89 hours for the MK-0869 regimen versus 70 hours for the standard therapy. Furthermore, Log-rank test showed that time to the first emesis was significantly longer for patients in the MK-0869 group when compared with the standard therapy group ($p<0.0001$).

Since several secondary and exploratory endpoints were analyzed, the nominally significant results may not be taken quite at face value due to multiple comparisons. The multiplicity issue is further commented in the section of 2.2.2 - Statistical Reviewer’s Findings.

Results of Adverse Events

In cycle 1, of the 569 patients randomized, 568 patients (283 patients in the MK-0869 group and 285 patients in the Standard Therapy group) were included in the assessment of safety and tolerability. Clinical adverse experiences were reported by 413 of 568 patients (72.7%) who received study drug or Standard Therapy: 206 patients (72.8%) in the MK-0869 group and 207 patients (72.6%) in the Standard Therapy group reported one or more clinical adverse experiences. The sponsor indicated that the overall incidence of clinical adverse experiences was similar between the two treatment groups.

Drug-related clinical adverse experiences (determined by the investigator to be possibly, probably, or definitely drug related) occurred in 96 of 568 patients (16.9%) who received study drugs: 55 patients (19.4%) in the MK-0869 group and 41 patients (14.4%) in the Standard Therapy group.

In addition, serious clinical adverse experiences occurred in 59 of 568 patients (10.4%) who received study drugs: 31 patients (11.0%) in the MK-0869 group and 28 patients (9.8%) in the Standard Therapy group. However, there was no statistically significant risk difference between the MK-0869 group and the Standard Therapy group for the incidence of patients with serious clinical adverse experiences in Cycle 1.

Finally, of 568 patients, thirty-six (6.3%; 36/568) discontinued study drug therapy due to a clinical adverse experience: 21 (7.4%; 21/283) and 15 (5.3%; 15/285) patients in the MK-0869 group and Standard Therapy group, respectively. Of these 36 patients, thirty-two discontinued study drug therapy due to a serious clinical adverse experience: 18 (6.4%; 18/283) and 14 (4.9%; 14/285) patients in the MK-0869 group and Standard Therapy group, respectively. It was also noted that one patient (0.4%; 1/283) in the MK-0869 group discontinued study drug therapy due to a serious drug-related clinical adverse experience (AN 5255).

2.2.2 Statistical Reviewer's Findings

2.2.2.1 Study P052

2.2.2.1.1 Reviewer's Statistical Analysis

In order to validate the sponsor's efficacy claim, this reviewer performs the following four analyses: 1) Exploratory analysis to assess the impact of the significant interaction between treatment and gender on treatment efficacy comparison, 2) Multiplicity p-value adjustments, 3) Complete response analysis for individual site, and 4) Subgroup analyses.

1) Impact assessment of the gender and treatment interaction

In order to assess the impact of the significant interaction between treatment and gender on the treatment efficacy comparison, this reviewer performs Mantel-Haenszel tests on complete response to compare treatment effects first by gender and then, by gender at each level of region using MITT patient population. The analysis by gender at each level of region tries to further explore if treatment differences by gender are affected by region (US versus Non-US).

Table 2.2.2.1.1 and Table 2.2.2.1.2 present the results using Mantel-Haenszel tests for the treatment comparisons respectively, by gender and by gender at each level of region using MITT patient population.

Table 2.2.2.1.1 (Reviewer's) Treatment comparison on complete response[†] in three phases by gender

Female

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
Overall Phase	76/98 (78)**	38/98 (39)
Acute Phase	88/97 (91)**	66/98 (67)
Delayed Phase	77/98 (79)**	41/98 (42)

Male

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
Overall Phase	113/162 (70)	98/162 (61)
Acute Phase	143/162 (88)	137/162 (85)
Delayed Phase	119/162 (74)	104/162 (64)

** : p<0.01 when compared with Standard Therapy; [†] : Complete Response = No emesis with no rescue therapy; n/m = Number of patients with desired response/number of patients included in time point.

Table 2.2.2.1.2 (Reviewer's) Treatment comparison on complete response[†] for three phases by gender at each level of region

Female in US

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
Overall Phase	20/26 (77)*	10/25 (40)
Acute Phase	25/26 (96)*	18/25 (72)
Delayed Phase	20/26 (77)*	11/25 (44)

Male in US

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
Overall Phase	22/35 (63)	20/35 (57)
Acute Phase	31/35 (89)	30/35 (86)
Delayed Phase	23/35 (66)	20/35 (57)

Female in Non-US

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
Overall Phase	56/72 (78)**	28/73 (38)
Acute Phase	63/71 (89)*	48/73 (66)
Delayed Phase	57/72 (79)**	30/73 (41)

Male in Non-US

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
Overall Phase	91/127 (72)	78/127 (61)
Acute Phase	112/127 (88)	107/127 (84)
Delayed Phase	96/127 (76)	84/127 (66)

** $p < 0.001$ when compared with Standard Therapy; * $p < 0.05$ when compared with Standard Therapy;

†: Complete Response = No emesis with no rescue therapy;

n/m = Number of patients with desired response/number of patients included in time point.

Firstly, Table 2.2.2.1.1 indicates that at significance level of 0.05, although for all three phases, the efficacy of MK-0869 regimen superior to that of standard therapy only shows in females, the efficacy of MK-0869 regimen demonstrates numerically better than that of standard therapy in males. Since the treatment differences are in the same direction across gender in favor of study drug MK-0869 regimen, the efficacy analysis using pooled patients from males and females is adequate.

Then, Table 2.2.2.1.2 shows that the effects of MK-0869 regimen are superior to that of standard therapy in females for both US and Non-US patients. Plus, in males, the effects of MK-0869 regimen are consistently numerically better than that of standard therapy for both US and Non-US patients. Thus, it indicates that for females and males, the efficacy patterns of MK-0869 regimen versus standard therapy are similar when compared between the US and Non-US patients. As a result, one may deduce that the treatment differences for MK-0869 regimen versus standard therapy by gender are not affected by region.

As noted by Table 2.2.2.1.1, for males, the efficacy of MK-0869 therapy is not superior to that of the standard therapy in three phases. The issue of non-superiority of MK-0869 therapy to the standard therapy in males is further assessed together with the information of Study P054 in the sub-section of 2.2.2.3 - Issue on the efficacy analysis by gender.

2) Multiplicity p-value adjustments

As noted by this reviewer, the indication for the use of Emend (MK0869 regimen) is to prevent the acute and delayed nausea and vomiting associated with initial and repeated courses of highly emetogenic cancer chemotherapy. However, the endpoints (complete response, no nausea, no significant nausea, complete protection, and total control) used to measure nausea and vomiting in the acute and delayed phases were pre-specified as the secondary and exploratory endpoints during the protocol stage.

Therefore, in order to adjust the false positive results for MK-0869 regimen versus standard therapy induced by the multiple comparisons for the secondary and exploratory endpoints pre-specified in the protocol, this reviewer employs Hochberg step-up procedure to deal with the multiplicity issue. The endpoints involved in this analysis are as follows: complete response, no vomiting, no significant nausea, no nausea, no impact on daily life, time to first vomiting episode, complete protection, total control, and severity of nausea. Table 2.2.2.1.3 presents the results. The original p-values listed in Table 2.2.2.1.3 are calculated using data set and SAS programs submitted by the sponsor while the adjusted p-values are calculated using SAS Multtest procedure.

Table 2.2.2.1.3 (Reviewer's) Adjusted p-values for the secondary and exploratory endpoints

Secondary /Exploratory Endpoint	Original P-value	Adjusted P-value	Secondary /Exploratory Endpoint	Original P-value	Adjusted P-value
CompR [#] in acute phase	0.0009	0.014*	Impact on daily life in overall phase	0.021	0.25
in delayed phase	<0.0001	0.002*	Time to first vomiting in overall phase	<0.0001	0.002*
Vomiting in overall phase	<0.0001	0.002*	Complete protection in overall phase	0.001	0.014*
in acute phase	0.001	0.014*	in acute phase	0.005	0.065
in delayed phase	<0.0001	0.002*	in delayed phase	0.0006	0.01*
Sig. [†] nausea in overall phase	0.09	0.48	Total control in overall phase	0.21	0.48
In acute phase	0.16	0.48	in acute phase	0.13	0.48
In delayed phase	0.09	0.48	in delayed phase	0.15	0.48
Nausea in overall phase	0.48	0.48	Severity of nausea in overall phase	0.12	0.48
in acute phase	0.48	0.48	Severity in delayed phase	0.20	0.48
in delayed phase	0.46	0.48			

[#]: Complete Response; [†]: Significant; *: Significance at .05 level.

Table 2.2.2.1.3 shows that after Hochberg step-up multiplicity adjustments, at 0.05 significance level, in prevention of vomiting (assessed by the complete response) for acute and delayed phases, the efficacy of MK-0869 regimen is superior to that of standard therapy. In addition, the efficacy of MK-0869 also shows significantly better than that of standard therapy on complete protection (no emesis, no rescue, and maximum nausea VAS < 25 mm) in the overall and delayed phases. However, at 0.05 significance level, for total control (no emesis, no rescue, and maximum nausea VAS < 5 mm), no nausea, and no significant nausea in acute and delayed

phases, the effects of MK-0869 regimen are not significantly better than those of standard therapy.

Nevertheless, noted by this reviewer, in the multiplicity adjustment analysis, several endpoints (for example: complete response, vomiting, significant nausea, nausea, complete protection, .. , etc.) appeared in three phases seemed to be highly correlated. Thus, the Hochberg multiplicity adjustment is possibly conservative for those endpoints with smaller original p-values. It is noted that although after Hochberg P- value adjustment, for complete protection in acute phase, the efficacy of MK-0869 regimen is not significantly better than that of standard therapy, the original p-value 0.005 for the two-treatment efficacy comparison is small. In addition, after Hochberg multiplicity adjustment, in the overall and delayed phases, the effects on complete protection for MK-0869 regimen have shown superior to that of the standard therapy. As a consequence, one should be able to recognize that the effect of MK-0869 on complete protection is significantly better than that of the standard therapy beginning in the acute phase and keeps going to the delayed phase.

3) Complete response analysis for individual site

In order to investigate if the efficacy of MK-0869 regimen superior to that of standard therapy dominated by large sites, this reviewer computes the percentage of complete response by site for the overall phase (the primary endpoint) using MITT patient population. Appendix A presents the results.

The results indicate that the largest site in Study P052 was number one but only has 7.5% (39/520) of MITT patients. Therefore, no huge site is noted to dominate the efficacy results.

However, noted by this reviewer, the complete response rates of four sites (050, 056, 003, and 010) in the standard therapy group are higher than those in the MK0869 regimen group. In order to assess the site effect on the efficacy treatment comparisons, this reviewer employs the sponsor's analysis model using MITT population to perform the treatment comparisons but replacing covariate REGION (US and Non-US) with variable UNIT. Total 13 Units are established by classifying sites with the same country into one Unit. Table 2.2.2.1.4 presents the results of treatment comparisons assessed by complete responses in the overall, acute, and delayed phases, using Mantel-Haenszel test with UNIT as the strata.

Table 2.2.2.1.4 (Reviewer's) Complete response[†] by treatment group and phase using UNIT as strata (MITT)

	MK-0869 Regimen	Standard Therapy
	n/m (%)	n/m (%)
Overall Phase	189/260 (73)* (p < 0.0001)	136/260 (52)
Acute Phase	231/259 (89)* (p = 0.001)	203/260 (78)
Delayed Phase	196/260 (75)* (p < 0.0001)	145/260 (56)

*: Significant at .05 level; †: Complete Response = No emesis with no rescue therapy;
n/m = Number of patients with desired response/number of patients included in time point.

Comparing the results from Table 2.2.2.1.4 to that from Table 2.2.1.1.1, one notes that these two results are similar. It indicates that the efficacy results perhaps are not significantly affected by allocating these four sites into different types of groupings.

4) Subgroup analysis

In order to assess the consistency of the treatment effect of MK0869 regimen over standard therapy across subgroups, this reviewer performed the subgroup analysis on the primary endpoint (complete response in overall phase) and two secondary endpoints (complete response in acute and delayed phases) using MITT patient population. The subgroups analyzed are Gender (Male and Female), Race (Caucasian and non-Caucasian), and Age group (age ≤ 65 and age > 65). Since the analysis by gender is already discussed in the sub-section of 2.2.2.1.1 – Reviewer’s Statistical Analysis, this analysis is not repeated here.

Race

Since more than 90% of patients recruited were Caucasian (White), no race analysis is performed.

Age group

Table 2.2.2.1.6 presents the results of treatment efficacy comparisons for MK0869 regimen versus standard therapy by age group (age ≤ 65 and age > 65).

Table 2.2.2.1.6 (Reviewer’s) Treatment comparisons on complete response¹ in three phases by age group

Age ≤ 65

	MK-0869 Regimen (MK)	Standard Therapy (ST)	P-Value for MK vs. ST
	n/m (%)	n/m (%)	
Overall Phase	119/171 (70)*	91/185 (49)	0.0001
Acute Phase	147/170 (87)*	139/185 (75)	0.01
Delayed Phase	124/171 (73)*	100/185 (54)	0.0004

Age > 65

	MK-0869 Regimen (MK)	Standard Therapy (ST)	P-Value for MK vs. ST
	n/m (%)	n/m (%)	
Overall Phase	70/89 (79)*	45/75 (60)	0.007
Acute Phase	84/89 (94)	64/75 (85)	0.054
Delayed Phase	72/89 (81)*	45/75 (60)	0.003

*: $p < 0.05$ when compared with Standard Therapy using Logistic regression adjusted by gender, region, and concomitant chemotherapy;

¹: Complete Response = No emesis with no rescue therapy;

n/m = Number of patients with desired response/number of patients included in time point.

Table 2.2.2.1.6 indicates that except for patients with age greater than 65 in the acute phase, the efficacy of the MK-0869 regimen is superior to that of the standard therapy in the three phases for both age groups. Although the effect of MK-0869 is not showing significantly better than that of the standard therapy for patients with age greater than 65 in the acute phase, the p-value 0.054

for the treatment comparison is borderline significant. As a result, the superiority of MK-0869 to that of the standard therapy can be considered independent of age group.

2.2.2.1.2 Finding Remarks

Based on the sponsor's and this reviewer's analyses through the sponsor's study data, the following three consequences are demonstrated:

- ◆ The efficacy of MK-0869 regimen, assessed from complete response (no emesis and without rescue therapy), is superior to that of standard therapy in prevention of acute and delayed vomiting associated with emetogenic cancer therapy.
- ◆ The efficacy of MK-0869 regimen, assessed from complete protection, is superior to that of the standard therapy in prevention of acute and delayed significant nausea and vomiting (but not for significant nausea alone) associated with emetogenic cancer therapy.
- ◆ However, the efficacy of MK-0869 regimen, assessed from no nausea and no significant nausea, is not superior to that of standard therapy in prevention of acute and delayed nausea associated with emetogenic cancer therapy.
- ◆ Similarly, the efficacy of Mk-0869 regimen, assessed from total control, is also not superior to that of the standard therapy in prevention of acute and delayed nausea and vomiting associated with emetogenic cancer therapy.

2.2.2.2 Study P054

2.2.2.2.1 Reviewer's Statistical Analysis

In order to validate the sponsor's efficacy claim, this reviewer performs the following three analyses: 1) Multiplicity p-value adjustments, 2) Complete response analysis for individual site, and 3) Subgroup analysis.

1) Multiplicity p-value adjustments

As the reason stated in the sub-section of Multiplicity p-value adjustments in Study P052 at page 19, in order to cope with the false positive results for MK-0869 regimen versus the standard therapy due to multiple comparisons, this reviewer employs Hochberg step-up procedure to deal with the multiplicity issue.

Table 2.2.2.2.1 presents the results of applying Hochberg step-up procedure to adjust the false positive results induced by the multiple comparisons for the secondary and exploratory endpoints pre-specified in the protocol, which are the same as those analyzed in Study P052. The original p-values listed in Table 2.2.2.2.1 are calculated using data set and SAS programs submitted by the sponsor while the adjusted p-values are calculated using SAS Multtest procedure.

Table 2.2.2.2.1 (Reviewer's) Adjusted p-values for the secondary and exploratory endpoints

Secondary /Exploratory Endpoint	Original P-value	Adjusted P-value	Secondary /Exploratory Endpoint	Original P-value	Adjusted P-value
CompR [#] in acute phase	0.0001	0.0014*	Impact on daily life in overall phase	0.007	0.063
in delayed phase	<0.0001	0.0014*	Time to first vomiting in overall phase	<0.0001	0.0014*
Vomiting in overall phase	<0.0001	0.0014*	Complete protection in overall phase	0.0006	0.007*
in acute phase	<0.0001	0.0014*	in acute phase	<0.0001	0.0014*
in delayed phase	<0.0001	0.0014*	in delayed phase	0.0001	0.0014*
Sig. [‡] nausea in overall phase	0.08	0.2	Total control in overall phase	0.003	0.03*
In acute phase	0.011	0.084	in acute phase	0.10	0.2
In delayed phase	0.07	0.2	in delayed phase	0.0002	0.0026*
Nausea in overall phase	0.021	0.11	Severity of nausea in overall phase	0.022	0.11
in acute phase	0.71	0.71	Severity in delayed phase	0.012	0.084
in delayed phase	0.003	0.03*			

[#]: Complete Response; [‡]: Significant; *: Significance at .05 level.

Table 2.2.2.2.1 shows that after Hochberg step-up multiplicity adjustments, at 0.05 significance level, in prevention of vomiting (assessed by the complete response) for acute and delayed phases, the efficacy of MK0869 regimen is superior to that of standard therapy. In addition, for the complete protection (no emesis, no rescue, and maximum nausea VAS < 25 mm), the efficacy of MK-0869 also shows significantly better than that of standard therapy in the acute and delayed phases while for the total control, the superiority of MK-0869 regimen is only demonstrated in the delayed phase. Finally, at 0.05 significance level, in prevention of nausea assessed by no nausea and no significant nausea for both acute and delayed phases, the efficacy of MK0869 regimen is not superior to that of standard therapy, with the exception of nausea in delayed phase.

As noted by the definitions of no nausea and no significant nausea, the symptom of significant nausea is much stronger than that of nausea and therefore, is more recognizable and easier for patients to capture. In another words, the patient's assessment on nausea symptom is more based on the psychological and subjective feeling. It follows that no significant nausea is more objective/important than no nausea in the assessment of nausea prevention. Now, the efficacy of MK-0869 regimen assessed by the more objective/important measurement, significance nausea, is not significant better than that of standard therapy for both acute and delayed phases. Consequently, the superiority of MK0869 regimen to standard therapy in the prevention of delayed nausea is not statistically/clinically persuasive.

2) Complete response analysis for individual site

In order to investigate if the efficacy of MK-0869 regimen superior to that of standard therapy dominated by large sites, this reviewer computes the percentage of complete response by site for the overall phase (the primary endpoint) using MITT patient population. Appendix B presents the results.

The results indicate that there are four sites (site numbers 018, 006, 007, and 009) with patients greater than 50, especially for site 103. However, the percentages of complete responses for MK-0869 regimen in the overall phase for the four sites are not abnormally higher than that of

standard therapy when compared with other sites. Thus, one may conclude that no huge site dominated the efficacy results. In addition, the percentages of the complete responses for MK-0869 regimen are not less than that of the standard therapy for all studied sites. Therefore, it is no reason to perform analysis on different types of site groupings to assess the site effect on the treatment efficacy comparisons.

3) Subgroup analysis

In order to assess the consistency of the treatment effect of MK0869 regimen over standard therapy across subgroups, this reviewer performed the subgroup analysis on the primary endpoint (complete response in overall phase) and two secondary endpoints (complete response in acute and delayed phases) using MITT patient population. The subgroups analyzed are Gender (Male and Female), Race (Caucasian and non-Caucasian), and Age group (age \leq 65 and age $>$ 65).

Gender

Table 2.2.2.2.2 presents the results of treatment efficacy comparisons for MK0869 regimen versus standard therapy by gender.

Table 2.2.2.2.2 (Reviewer's) Treatment comparisons on complete response[†] in three phases by gender
Female

	MK-0869 Regimen (MK)	Standard Therapy (ST)	P-Value for MK vs. ST
	n/m (%)	n/m (%)	
Overall Phase	67/118 (57)*	51/121 (42)	0.024
Acute Phase	96/118 (81)*	75/121 (62)	0.001
Delayed Phase	73/118 (62)*	57/121 (47)	0.023

Male

	MK-0869 Regimen (MK)	Standard Therapy (ST)	P-Value for MK vs. ST
	n/m (%)	n/m (%)	
Overall Phase	96/142 (68)*	63/142 (44)	<0.0001
Acute Phase	120/143 (84)*	105/142 (74)	0.042
Delayed Phase	103/142 (73)*	66/142 (47)	<0.0001

*: $p < 0.05$ when compared with Standard Therapy using Logistic regression adjusted by concomitant chemotherapy;

[†]: Complete Response = No emesis with no rescue therapy;

n/m = Number of patients with desired response/number of patients included in time point.

Table 2.2.2.2.2 indicates that at significance level of 0.05, the efficacy of the MK-0869 regimen is superior to that of the standard therapy in the three phases for both female and male subgroups.

Race

Table 2.2.2.2.3 presents the results of treatment efficacy comparisons for MK-0869 regimen versus standard therapy by race.

Table 2.2.2.2.3 (Reviewer's) Treatment comparisons on complete response[†] in three phases by race**Non-White**

	MK-0869 Regimen (MK)	Standard Therapy (ST)	P-Value for MK vs. ST
	n/m (%)	n/m (%)	
Overall Phase	105/176 (60) [*]	81/186 (44)	0.002
Acute Phase	142/177 (80) [*]	128/186 (69)	0.012
Delayed Phase	116/176 (66) [*]	86/186 (46)	0.0002

White

	MK-0869 Regimen (MK)	Standard Therapy (ST)	P-Value for MK vs. ST
	n/m (%)	n/m (%)	
Overall Phase	58/84 (69) [*]	33/77 (43)	0.0004
Acute Phase	74/84 (88) [*]	52/77 (68)	0.001
Delayed Phase	60/84 (71) [*]	37/77 (48)	0.002

*: p<0.05 when compared with Standard Therapy using Logistic regression adjusted by gender and concomitant chemotherapy;

†: Complete Response = No emesis with no rescue therapy;

n/m = Number of patients with desired response/number of patients included in time point.

Table 2.2.2.2.3 indicates that at significance level of 0.05, the efficacy of the MK-0869 regimen is superior to that of the standard therapy in the three phases for both White (Caucasian) and Non-White (Non-Caucasian) sub-groups.

Age group

Table 2.2.2.2.4 presents the results of treatment efficacy comparisons for MK0869 regimen versus standard therapy by age group (age ≤ 65 and age > 65).

Table 2.2.2.2.4 (Reviewer's) Treatment comparisons on complete response[†] in three phases by age group**Age ≤ 65**

	MK-0869 Regimen (MK)	Standard Therapy (ST)	P-Value for MK vs. ST
	n/m (%)	n/m (%)	
Overall Phase	121/200 (61) [*]	84/202 (42)	0.0002
Acute Phase	159/200 (80) [*]	129/202 (64)	0.0006
Delayed Phase	133/200 (67) [*]	91/202 (41)	<0.0001

Age > 65

	MK-0869 Regimen (MK)	Standard Therapy (ST)	P-Value for MK vs. ST
	n/m (%)	n/m (%)	
Overall Phase	42/60 (70.0) [*]	30/61 (49.2)	0.02
Acute Phase	57/61 (93.4)	51/61 (83.6)	0.07
Delayed Phase	43/60 (71.7) [*]	32/61 (52.5)	0.03

*: p<0.05 when compared with Standard Therapy using Logistic regression adjusted by gender and concomitant chemotherapy;

†: Complete Response = No emesis with no rescue therapy;

n/m = Number of patients with desired response/number of patients included in time point.

Table 2.2.2.2.4 indicates that at significance level of 0.05, except for patients with age greater

than 65 in the acute phase, the efficacy of the MK-0869 regimen is superior to that of the standard therapy in the three phases for both age groups. Although the effect of MK-0869 is not showing significantly better than that of the standard therapy for patients with age greater than 65 in the acute phase, the p-value 0.07 for the treatment comparison is close to the 0.05 significant level. As a result, the superiority of MK-0869 to that of the standard therapy can be considered independent of age group.

2.2.2.2.2 Finding Remarks

Based on the sponsor's and this reviewer's analyses through the sponsor's study data, the following two results are acknowledged:

- ◆ The efficacy of MK-0869 regimen, assessed from complete response (no emesis and without rescue therapy), is superior to that of standard therapy in prevention of acute and delayed vomiting associated with emetogenic cancer therapy.
- ◆ The efficacy of MK-0869 regimen, assessed from complete protection, is superior to that of standard therapy in prevention of acute and delayed significant nausea and vomiting (but not for significant nausea alone) associated with emetogenic cancer therapy.

In addition, based on this reviewer's analyses through the sponsor's study data, the following two results are established:

- ◆ The efficacy of MK-0869 regimen, assessed from no nausea and no significant nausea, is superior to that of standard therapy only in prevention of delayed nausea associated with emetogenic cancer therapy.
- ◆ Similarly, the efficacy of MK-0869 regimen, assessed from total control, is superior to that of standard therapy only in prevention of delayed nausea and vomiting associated with emetogenic cancer therapy.

2.2.2.3 Issue on the efficacy analysis by gender

In order to be more effectively explore the issue on the non-superiority of MK-0869 therapy to the standard therapy for males demonstrated by Study P052, the results for the two treatment comparisons on complete response in three phases by gender are presented by Table 2.2.2.3.1 and Table 2.2.2.3.2 respectively for Studies P052 and P054.

Table 2.2.2.3.1 (Reviewer's) Treatment comparisons on complete response[†] in three phases by gender (Study P052)

Female			
	MK-0869 Regimen (MK)	Standard Therapy (ST)	Difference (MK – ST) %
	n/m (%)	n/m (%)	
Overall Phase	76/98 (78)* (p < 0.0001)	38/98 (39)	39
Acute Phase	88/97 (91)* (p = 0.0002)	66/98 (68)	23
Delayed Phase	77/98 (79)* (p < 0.0001)	41/98 (42)	37

Male			
	MK-0869 Regimen (MK)	Standard Therapy (ST)	Difference (MK – ST) %
	n/m (%)	n/m (%)	
Overall Phase	113/162 (70) (p = 0.11)	98/162 (61)	11
Acute Phase	143/162 (88) (p = 0.39)	137/162 (85)	3
Delayed Phase	119/162 (74) (p = 0.09)	104/162 (64)	10

*: p<0.05 when compared with Standard Therapy using Logistic regression adjusted by region and concomitant chemotherapy;

†: Complete Response = No emesis with no rescue therapy;

n/m = Number of patients with desired response/number of patients included in time point.

Table 2.2.2.3.2 (Reviewer's) Treatment comparisons on complete response[†] in three phases by gender (Study P054)

Female			
	MK-0869 Regimen (MK)	Standard Therapy (ST)	Difference (MK – ST) %
	n/m (%)	n/m (%)	
Overall Phase	67/118 (57)* (p = 0.024)	51/121 (42)	15
Acute Phase	96/118 (81)* (p = 0.001)	75/121 (62)	19
Delayed Phase	73/118 (62)* (p = 0.023)	57/121 (47)	15

Male			
	MK-0869 Regimen (MK)	Standard Therapy (ST)	Difference (MK – ST) %
	n/m (%)	n/m (%)	
Overall Phase	96/142 (68)* (p<0.0001)	63/142 (44)	24
Acute Phase	120/143 (84)* (p=0.042)	105/142 (74)	10
Delayed Phase	103/142 (73)* (p<0.0001)	66/142 (47)	26

*: p<0.05 when compared with Standard Therapy using Logistic regression adjusted by concomitant chemotherapy;

†: Complete Response = No emesis with no rescue therapy;

n/m = Number of patients with desired response/number of patients included in time point.

For Study P052, Table 2.2.2.3.1 shows that the percentage differences of MK-0869 therapy minus standard therapy on complete response in three phases for males are much smaller than that of females and are not significant. However, for Study P054, Table 2.2.2.3.2 indicates the opposite results to that of Study P052, showing that the percentage differences of MK-0869 therapy minus standard therapy on complete response in overall and delayed phases for males are around 10% larger than that of females and are highly significant. The non-superiority of MK-0869 regimen to the standard therapy in males is not replicated in Study P054. Accordingly, the non-significant results for males shown by Study P052 are not considered critical. However, to be aware of the concern on the non-significant results for MK0869 versus the standard therapy for males, the efficacy comparisons between the two treatment groups on complete response in

three phases are recommended presented by gender separately for each of the two-phase III studies in labeling package.

2.2.3 Conclusions and Recommendations

From the finding remarks of the two Studies P052 and P054, the conclusions/recommendations on the efficacy of MK-0869 regimen are made as follows:

- ◆ Prevention of vomiting: the efficacy of MK-0869 regimen is shown superior to that of standard therapy in prevention of acute and delayed vomiting associated with emetogenic cancer therapy.
- ◆ Prevention of significant nausea and vomiting: the efficacy of MK-0869 regimen is superior to that of standard therapy in prevention of acute and delayed significant nausea and vomiting associated with emetogenic cancer therapy.
- ◆ Prevention of nausea and vomiting: it is noted that only for Study P054, the efficacy of MK-0869 is shown superior to that of standard therapy in prevention of delayed nausea and vomiting associated with emetogenic cancer therapy. However, as indicated by this reviewer in the section of multiplicity p-value adjustments in Study P054, the assessment of significant nausea is more objective/important than that of nausea symptom. Now, the efficacy of MK-0869 regimen is superior to that of standard therapy in prevention of acute and delayed significant nausea and vomiting associated with emetogenic cancer therapy. Therefore, the efficacy of MK-0869 regimen is also considered superior to that of standard therapy in prevention of acute and delayed nausea and vomiting associated with emetogenic cancer therapy.
- ◆ Prevention of significant nausea: it is noted that for Study P052, the efficacy of MK-0869 is not superior to that of standard therapy in prevention of acute and delayed significant nausea associated with emetogenic cancer therapy, assessed by original p-values. In addition, for Study P054, after multiplicity p-value adjustments, the efficacy of MK-0869 regimen is not shown superior to that of standard therapy in prevention of acute and delayed significant nausea associated with emetogenic cancer therapy. Accordingly, the efficacy of MK-0869 regimen is not considered superior to that of standard therapy in prevention of acute and delayed significant nausea associated with emetogenic cancer therapy.
- ◆ Prevention of nausea: it is noted that for Study P052, the efficacy of MK-0869 is not superior to that of standard therapy in prevention of acute and delayed nausea associated with emetogenic cancer therapy, assessed by original p-values. At the same time, for Study P054, the efficacy of MK-0869 is shown superior to that of standard therapy only in prevention of delayed nausea associated with emetogenic. However, as commented by this reviewer in the section of multiplicity p-value adjustments in Study P054, nausea symptom is less objective/important than significant nausea. Now, the efficacy of MK-0869 regimen is not superior to that of standard therapy in prevention of acute and delayed significant nausea associated with emetogenic cancer therapy. Consequently, the efficacy of MK-0869 is not considered superior to that of standard therapy in prevention of acute and delayed nausea associated with emetogenic cancer therapy.

In summary, the overall conclusions are made as follows:

- ◆ The efficacy of MK-0869 is superior to that of standard therapy in prevention of acute and delayed vomiting associated with emetogenic cancer therapy.
- ◆ The efficacy of MK-0869 is superior to that of standard therapy in prevention of acute and delayed nausea and vomiting associated with emetogenic cancer therapy.
- ◆ However, the efficacy of MK-0869 regimen is also not superior to that of standard therapy in prevention of acute and delayed nausea associated with emetogenic cancer therapy.

**APPEARS THIS WAY
ON ORIGINAL**

2.2.4 Appendix A: Percentage of complete response in overall phase for STUDY P052

Site Number	Number of Patients in MK-0869	Number of Patients in Standard	% of Complete Response in MK-0869	% of Complete Response in Standard	Total Patients in Site
001	18	21	66.667	28.571	39
002	6	5	50.000	40.000	11
003	6	6	50.000	66.667	12
006	2	2	50.000	100.000	4
007	3	2	0.000	50.000	5
008	2	3	100.000	66.667	5
009	3	5	100.000	40.000	8
010	7	4	71.429	100.000	11
012	6	5	100.000	20.000	11
013	6	4	83.333	75.000	10
014	0	2	0.000	100.000	2
015	10	10	90.000	50.000	20
016	1	2	100.000	50.000	3
017	3	2	33.333	50.000	5
018	6	7	50.000	42.857	13
019	5	5	80.000	40.000	10
020	4	4	100.000	50.000	8
021	3	4	100.000	50.000	7
022	2	2	0.000	100.000	4
023	12	12	75.000	41.667	24
024	6	4	66.667	50.000	10
025	3	4	66.667	25.000	7
026	4	3	100.000	66.667	7
027	0	1	0.000	100.000	1
028	1	0	100.000	0.000	1
029	6	5	66.667	20.000	11
030	5	3	20.000	66.667	8
031	2	2	50.000	100.000	4
032	17	16	94.118	93.750	33
033	4	4	100.000	75.000	8
034	4	4	75.000	75.000	8
035	7	6	71.429	66.667	13
036	3	5	66.667	0.000	8
037	7	7	85.714	28.571	14
038	1	2	0.000	0.000	3
039	6	6	66.667	0.000	12
040	2	3	50.000	66.667	5
041	1	1	100.000	0.000	2
042	9	10	77.778	20.000	19
043	3	3	66.667	66.667	6
044	2	3	50.000	33.333	5
045	5	3	80.000	66.667	8
046	2	3	50.000	66.667	5
048	2	2	50.000	50.000	4
050	12	13	58.333	84.615	25
051	3	3	66.667	66.667	6
052	5	5	60.000	60.000	10
054	6	7	66.667	14.286	13
056	10	10	70.000	80.000	20
057	15	14	100.000	57.143	29
060	1	0	100.000	0.000	1
061	1	1	100.000	100.000	2

2.2.5 Appendix B: Percentage of complete response in overall phase for STUDY P054

Site Number	Number of Patients in MK-0869	Number of Patients in Standard	% of Complete Response in MK-0869	% of Complete Response in Standard	Total Patients in Site
002	4	6	75.000	66.6667	10
003	2	2	50.000	50.0000	4
004	6	7	83.333	57.1429	13
005	15	17	60.000	29.4118	32
006	40	41	70.000	56.0976	81
007	28	28	42.857	28.5714	56
008	25	25	52.000	32.0000	50
009	5	5	80.000	40.0000	10
010	9	9	33.333	33.3333	18
011	6	6	100.000	66.6667	12
012	8	8	71.429	50.0000	16
014	21	20	52.381	35.0000	41
015	9	9	66.667	66.6667	18
016	9	9	44.444	22.2222	18
017	11	12	54.545	25.0000	23
018	53	50	76.923	54.0000	103
019	11	9	63.636	33.3333	20

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