CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-549

Clinical Pharmacology and Biopharmaceutics Review

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-549	Submission Date(s): 09 27/02, and 01/07/03
Brand Name	Emend
Generic Name	Aprepitant
Reviewer	Venkat Jarugula, Ph.D. Myong-Jin Kim, Pharm.D.
Team Leader	Suresh Doddapaneni, Ph.D.
OCPB Division	Division of Pharmaceutical Evaluation II
ORM division	Division of Gastrointestinal & Coagulation Drug Products
Sponsor	Merck Research Laboratories
Relevant IND(s)	[redacted]
Submission Type; Code	NME, 1P
Formulation; Strength(s)	Capsule, 125 mg and 80 mg
Dosing regimen	Aprepitant is given for 3 days as part of regimen that includes a corticosteroid and a 5-HT_3 antagonist. The recommended dose of Emend is 125 mg orally 1 hour prior to chemotherapy treatment on Day 1 and 80 mg once daily on Days 2 and 3.
Indication	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy

1. Executive Summary

Aprepitant is a novel substance P neurokinin 1 (NK1) receptor antagonist and has been investigated as antiemetic. Emend (aprepitant) in combination with other antiemetic agents is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high dose cisplatin. Emend is given for 3 days as part of a regimen that includes a corticosteroid and 5-HT_3 antagonist. The recommended dose of Emend is 125 mg orally 1 hour prior to chemotherapy treatment on Day 1 and 80 mg once daily on Day 2 and 3.

1.1. Review Comments

The NDA was discussed by Gastrointestinal Drugs Advisory Committee meeting on March 6, 2003. One of the main issues for the committee meeting was the potential drug interaction of aprepitant with cancer chemotherapy agents that are metabolized by cytochrome P450 3A4 (CYP3A4).

Clinical Pharmacology studies have shown that aprepitant is extensively metabolized, primarily via oxidation by CYP3A4 isozyme. Aprepitant at the recommended dose regimen is an inhibitor of CYP3A4 activity and resulted in more than three fold increase in the exposure of

concomitantly administered midazolam, a sensitive CYP3A4 substrate. There are many cancer chemotherapeutic agents that are metabolized by CYP3A4 isozyme and concomitant administration of aprepitant may inhibit the metabolism of these chemotherapy agents resulting in increased toxicity. Sponsor has not adequately characterized the drug interaction potential of aprepitant with chemotherapy agents. Currently there is an ongoing drug interaction study with intravenously administered docetaxel. Proposed label recommends caution when aprepitant is to be administered with drugs that are primarily metabolized by CYP3A4 and contraindicates pimozide, terfenadine, astemizole, and cisapride. However, there is no data in the NDA to assess the degree of interaction of aprepitant with chemotherapy agents and no dosage adjustments could be recommended at this time

Another issue at the AC meeting was the generalizability of 5-HT_3 antagonists for coadministration with aprepitant for prevention of chemotherapy induced nausea and vomiting (CINV). The Phase III clinical studies were conducted with intravenous ondansetron. Pharmacokinetic drug interaction studies have shown that aprepitant does not affect the pharmacokinetics of intravenous ondansetron and orally administered granisetron (both CYP 3A4 substrates). There is no data on PK interaction with oral ondansetron. However, the label for ondansetron states that since this drug is metabolized by multiple CYP450 isozymes, significant drug interactions are unlikely. Pharmacokinetic drug interaction with dolasetron is unlikely because this drug is metabolized by multiple pathways with carbonyl reductase and CYP2D6 being the main pathways and CYP3A4 plays a minor role. However, there is no clinical safety data on coadministration of aprepitant with dolasetron.

Recommendations of Gastrointestinal Drugs Advisory Committee

The GI Advisory Committee recommended the approval of aprepitant with Phase IV commitments by the sponsor to conduct drug interaction studies of aprepitant with dolasetron and chemotherapy agents metabolized by CYP3A4. The committee recommended restricted labeling to state that clinical data on coadministration of aprepitant with many chemotherapy agents metabolized via CYP3A4 is not available and appropriate warnings should be proposed in the labeling of this drug.

2. RECOMMENDATION

From the viewpoint of the Office of Clinical Pharmacology and Biopharmaceutics, Human Pharmacokinetics and Biopharmaceutics section of the NDA is acceptable provided that a satisfactory agreement can be reached between the Agency and the sponsor regarding the language in the Package Insert and Phase IV commitments as outlined below.

3. PHASE IV COMMITMENTS

***In Vitro* Studies:**

Please conduct *in vitro* metabolism interaction studies of aprepitant with various chemotherapy agents metabolized by CYP450 enzyme system.

Sponsor should be requested to provide data regarding the effect of concentrations) and different speeds of rotation) at each concentration with the capsule formulation. Meanwhile, Q=— % at 20 minutes with the proposed dissolution method is acceptable as an interim specification.

***In Vivo* Studies:**

Please conduct *in vivo* drug interaction studies to investigate the effect of aprepitant and the regimen (including corticosteriod and 5-HT_3 antagonist) on the safety, tolerability and pharmacokinetics of chemotherapy agents metabolized by CYP3A4.

Please conduct *in vivo* drug interaction study to investigate the effect of aprepitant on the safety, tolerability and pharmacokinetics of dolasetron (include patients who are poor metabolizers for CYP2D6 isozyme).

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5. Summary of Clinical Pharmacology and Biopharmaceutics Findings

5.1. Pharmacokinetics:

5.1.1. Absorption

The absolute bioavailability of aprepitant from the nanoparticle capsule formulation of 125 mg and 80 mg doses is 59% and 67%, respectively. Plasma concentrations of aprepitant reach peak levels at 4 hours. The pharmacokinetics are slightly nonlinear with approximately 25% higher AUC at the 125 mg dose compared to the 80 mg dose. The pharmacokinetics of aprepitant administered as a 3- or 5-day regimen (125 mg on Day 1 and 80 mg/day on subsequent days) show that plasma concentrations of aprepitant are similar (for 3–Day) or slightly higher (for 5-Day) on the last day of dosing compared to Day 1. Following multiple dosing of fixed doses (125 mg or 375 mg) over 28 days, the plasma concentrations of aprepitant accumulate over the first 7 days and then decline from Day 7 to Day 28. The later decline in plasma concentrations may be due to autoinduction of CYP3A4 enzyme by aprepitant.

Food effect

The capsule formulation did not have a significant food effect. Therefore, aprepitant can be administered without regard to food intake. The earlier tablet formulations with submicron particle size were shown to have significant food effect (a 3 to 4 –fold increase in bioavailability with food, due to poor solubility of the drug).

5.1.2. Distribution

Following intravenous administration, aprepitant had a mean apparent volume of distribution of 66 L. It is more than 95% bound to plasma proteins in healthy subjects.

5.1.3. Metabolism

Aprepitant undergoes extensive metabolism, primarily via CYP3A4 mediated oxidation. Seven metabolites have been identified in human plasma following oral administration of [^{14}C]-aprepitant. The metabolites are not likely to contribute significantly to the efficacy of aprepitant because these metabolites are either inactive or weakly active or are present at low levels relative to aprepitant.

5.1.4. Elimination

After IV administration of the prodrug, [^{14}C]-L-758298, in humans approximately 45% and 58% of total radioactivity was excreted in feces and urine, respectively, as metabolites of aprepitant. The prodrug was shown to be completely and rapidly converted to aprepitant, *in vivo*. No unchanged aprepitant was detected in urine. Overall, it appears that aprepitant undergoes extensive metabolism and is primarily eliminated via excretion of metabolites. Following intravenous administration, aprepitant had mean plasma clearance of 84 mL/minute, and terminal half-life of about 13 hours. The half-life is similar after oral administration.

5.1.5. Special Populations:

Elderly

Compared to young adults (≤ 45 years), elderly subjects (≥ 65 years) showed small increases of 36% and 24% in AUC and C_{max}, respectively.

Gender

Compared to men, women had slightly lower (up to 16%) AUC and slightly higher (up to 27%) C_{max}.

Race

Slightly higher (20 to 30%) plasma concentrations of aprepitant were noted in hispanic subjects compared to white or black subjects.

These differences in elderly, gender, and race were concluded as not clinically significant and no dosage adjustment is recommended in these groups.

Renal Insufficiency

Systemic exposure (AUC) of total aprepitant is lower (20 to 40%) in patients with severe renal insufficiency and end stage renal disease compared to healthy subjects with normal renal function. Since unbound drug concentrations of aprepitant are similar in patients with renal insufficiency compared to healthy subjects with normal renal function, dosage adjustment is not necessary.

Hepatic Insufficiency

An increase of up to 20% in AUC was noted in patients with moderate hepatic impairment compared to age matched control subjects with normal hepatic function. No dosage adjustment is recommended for patients with mild and moderate hepatic impairment. Pharmacokinetics of aprepitant in patients with severe hepatic impairment were not studied. Caution should be exercised when aprepitant is to be administered to patients with severe hepatic insufficiency.

5.2. Drug-Drug Interactions

Aprepitant is extensively metabolized by CYP3A4. *In vitro* metabolism studies and *in vivo* pharmacokinetic studies have shown that aprepitant inhibits CYP3A4 on short term dosing (up to 5 days) and induces CYP3A4 on chronic dosing (over 28 days).

Table. 1. Drug Interactions of aprepitant (AP).

Drug	Mean ratio of AUC*	Mean ratio of C_{max}*
Effect on aprepitant		
Ketoconazole (potent 3A4 inhibitor)	4.8 ↑	1.5 ↑
Diltiazem with 300 mg AP(moderate 3A4 inhibitor)	2.0 ↑	2.0 ↑
Diltiazem with 100 mg IV L-758298	1.5 ↑	1.2 ↑
Rifampin (potent inducer)	0.09 ↓	0.4 ↓
Dexamethasone (3A4 substrate)	1.3 ↑ (Day 1) 0.98 ↓ (Day 5)	
Effect of aprepitant		
On CYP3A4 substrates		
Midazolam	2.3 ↑ (Day 1) 3.3 ↑ (Day 5)	1.5 ↑ (Day 1) 1.9 ↑ (Day 5)
Diltiazem	1.7 ↑	1.5 ↑
Dexamethasone	2.2 ↑	
Methylprednisolone (oral)	2.5 ↑	1.5 ↑
Methylprednisolone (IV)	1.34↑	
Ethinyl estradiol (with 14 days of AP)	0.59 ↓	0.64 ↓
Norethindrone (with 14 days of AP)	0.91 ↓	0.81 ↓
Ondansetron (IV)	No effect**	No effect
Granisetron (oral)	No effect	No effect
Other isozymes		
Warfarin (CYP2C9 substrate)	0.66 ↓# (Day 8) 0.89↓ INR (Day 8)	
Paroxetine (CYP2D6 substrate)	0.75↓	
Digoxin (P-gp substrate)	No effect	No effect

*Ratio of AUC or Cmax with and without the interacting drug, ↑denotes increase, ↓denotes decrease.
Ratio of S-warfarin trough concentrations fold-change from baseline (warfarin + aprepitant/warfarin + placebo). ** No significant effect

The following are the main conclusions from the drug interaction studies:

Conclusions relevant to the short term administration (up to 5 days)

- Aprepitant, upon short term administration (for 5 days) is an inhibitor of CYP3A4 and results in 2 to 3 fold increase in mean AUC of orally coadministered midazolam, a sensitive CYP3A4 substrate. In contrast, ketoconazole, a potent inhibitor of CYP3A4 is known to increase the AUC of midazolam by 9 to 16 fold.

- Following oral administration of aprepitant regimen for 3-days, the AUC of intravenously administered midazolam was increased by 25% on Day 4 and decreased by 19% on Day 14 and was unchanged on Day 15 (since the beginning of 3-day aprepitant regimen).
- Aprepitant also increases the AUC of orally administered diltiazem and methylprednisolone by 1.7 and 2.5 fold, respectively. Based on the difference observed with oral versus intravenous administration of methylprednisolone, aprepitant appears to have greater inhibitory effect when the CYP3A4 substrate is administered orally than when it is administered intravenously.
- Concomitant administration of aprepitant regimen (125/80 mg) increased dexamethasone AUC by about 2 fold. Therefore, dexamethasone dose in the clinical trials for the aprepitant (active) treatment group was approximately half of that used in the standard therapy (comparator) group. Higher dose regimen of aprepitant (375/250 mg) resulted in greater increase in dexamethasone AUC by up to 4.5-fold indicating dose dependent CYP3A4 inhibition by aprepitant.
- Coadministration of aprepitant did not significantly affect the pharmacokinetics of intravenously administered ondansetron or orally administered granisetron. Drug interaction data with dolasetron is unavailable. However, dolasetron is known to be metabolized by multiple pathways including carbonyl reductase, CYP2D6 and CYP3A4. Blood levels of hydrodolasetron (active metabolite of dolasetron) increased 24% when dolasetron was coadministered with cimetidine (nonselective inhibitor of CYP450) for 7 days, and decreased 28% with coadministration of rifampin (potent inducer of CYP450) for 7 days.
- Potent CYP3A4 inhibitor, ketoconazole, inhibited the metabolism of aprepitant significantly resulting in a 5-fold mean increase in AUC of aprepitant, while a moderate CYP3A4 inhibitor, diltiazem resulted in about two fold increase. However, since the other two drugs (dexamethasone and ondansetron) coadministered with the aprepitant regimen are CYP3A4 substrates, CYP3A4 inhibitors may result in increased concentrations of these drugs.
- Potent CYP3A4 inducer, rifampin, reduced the plasma concentration of coadministered aprepitant by 90%. However, since the other two drugs (dexamethasone and ondansetron) coadministered with the aprepitant regimen are CYP3A4 substrates, CYP3A4 inducers may result in decreased concentrations of these drugs.
- Aprepitant is an inducer of CYP2C9; the ratio of International Normalized Ratio (INR) fold-change from baseline decreased by about 11% on Day 8 following concomitant administration of aprepitant 125 mg/80 mg three day regimen. The S-warfarin trough plasma concentration decreased by up to 34% by Day 8.
- Aprepitant does not have significant effect on P-gp mediated transport as evidenced by no change in the pharmacokinetics of coadministered digoxin, a substrate of P-gp transporter.

Conclusions relevant to the long term administration (more than 14 days)-

- Upon multiple administration for two weeks, aprepitant resulted in a 40% reduction in levels of ethinyl estradiol (CYP3A4 substrate). This interaction is relevant for chronic indications of aprepitant. However, since aprepitant regimen (3-Day) has not studied, sponsor has appropriately recommended a caution in the label to use backup or alternative contraceptive methods when aprepitant is coadministered with oral contraceptives.
- Following multiple administration of aprepitant (~70 mg) for two weeks, the AUC of orally administered midazolam by about two fold indicating that aprepitant has CYP3A4 inhibitory affect for as long as two weeks of dosing. Following multiple dosing for 4 weeks, aprepitant undergoes autoinduction, which was thought to be by CYP3A4 induction. For long-term administration of this drug, sponsor need to better characterize the induction potential both in terms of the mechanism and the time-course of induction.

- Concomitant administration of two weeks of aprepitant tablet formulation (approximately comparable to 85 to 170 mg of the market formulation), resulted in slightly decreased (25%) AUC of paroxetine (CYP2D6 substrate). Mechanism for lowering of paroxetine concentrations is not understood because CYP2D6 isozyme is not known to be inducible enzyme. However, these results indicate the aprepitant does not inhibit the metabolism of CYP2D6 substrates.

5.2.1. Potential of aprepitant to interact with chemotherapeutic agents that are metabolized by CYP3A4 isozyme:

The drug interaction study results in the NDA have shown that aprepitant is an inhibitor of CYP3A4 on short term administration. Aprepitant administered as 5 day regimen (125 mg on Day 1, 80 mg/day from Day 2 to 5) showed significant inhibition of CYP 3A4, as seen by 2 to 3 fold mean increase in midazolam (highly specific substrate) AUC. Aprepitant also resulted in a two fold increase in AUC of dexamethasone and diltiazem. Thus it is possible that aprepitant (at the doses recommended in Emend) may result in a two to three fold mean increase in the plasma levels of coadministered drugs that are primarily metabolized by CYP 3A4.

There are many chemotherapeutic agents for which CYP3A4 plays an important role in their metabolism. Increase in chemotherapeutic agent's plasma concentration due to inhibition of its metabolism by aprepitant may result in significant toxicity of these agents. Some of the chemotherapeutic agents that are known or suspected to be metabolized by CYP3A4 isozyme include: docetaxel, paclitaxel, irinotecan, etopsoide, vinorelbine, vinblastine, vincristine, ifosfamide, cyclophosphamide, and imatinib. Unfortunately, adequate information regarding drug–drug interactions is not available for many of these agents either from sponsor's studies or published literature. There is an ongoing drug interaction study which investigates the effect of aprepitant on docetaxel (given intravenously), a chemotherapeutic drug primarily metabolized by
Preliminary results with five patients suggest no clinically significant interaction.

One study reported in the literature showed that ketoconazole increased the exposure to SN-38, the active metabolite of irinotecan by 109% and the article recommends up to four-fold reduction in dosage. Due to lack of data from the controlled drug interaction study(ies) between Emend and chemotherapeutic drugs and lack of sufficient information in the literature about the effect of CYP3A inhibitors on chemotherapeutic drugs, it is difficult to recommend any dosage adjustments/appropriate precaution/warning in the label. However, clinical trial database consists of patients who were administered some of these chemotherapy agents metabolized by CYP3A4 and a discussion on the safety database in the Phase III clinical studies is contained in the clinical review.

5.3. QT analysis in Clinical Pharmacology studies:

There was no prospectively planned, controlled clinical study to evaluate the effect of aprepitant on QT interval. A comprehensive analysis of the effect of aprepitant on QT_c interval was performed on the EKG data collected in 15 clinical pharmacology studies and 6 clinical studies. Aprepitant to be marketed formulation doses up to 375 mg and the tablet formulations of up to 800 mg doses were administered in these studies.

Most of the QT interval readings consisted of automatic readings measured at either one to two time points (4, or 8 hours) with capsule formulation or more frequently with tablet or IV formulation (e.g., 0.5, 1, 2, 4, 8, and 24 hours).

The mean QTc interval changes for L-758298 (prodrug) and aprepitant were similar to those seen with placebo.

Only 4 subjects in each of the three treatments groups of clinical dose (4 of 86 subjects; 4.7%), higher than clinical dose (4 of 43 subjects, 9.3%) and placebo (4 of 43 subjects; 9.3%) had QT_c interval increases from baseline ≥30 and ≤60 msec.

QTc interval increases from baseline ≥30 and ≤60 msec were slightly higher (8 of 60 subjects, 11.6%) for the early tablet formulation compared to capsule formulation. For the L-758298 IV treatment, 9 subjects (of 80 subjects; 11.3%) and 1 subject (of 40; 2.5%) on placebo had QT_c interval changes ≥30 and ≤60 msec.

Only one subject had QTc interval >500 msec at 24 hours following administration of 800 mg tablet formulation. This subject also received a single dose of 1200 mg with no prolongation of QTc.

Based on the available data, there were few, if any, outliers of clinical concern and many of the subjects who are outliers had subsequent higher doses of L-758298 or oral aprepitant with no changes in QTc.

5.4. Exposure-Response (PK/PD) information:
There is good correlation between plasma trough concentrations of aprepitant and its binding to brain NK1 receptors. Based on the correlation, trough concentrations of 10 ng/ml and 100 ng/ml produce NK_1 receptor occupancy of about 50% and 90%, respectively.

In Phase IIb dose ranging studies of CINV, submaximal antiemetic efficacy was achieved at 40-mg 25 mg regimen, while maximum efficacy was achieved with 125 mg/80 mg regimen and there was no apparent benefit at the highest dose regimen of 375 mg/250 mg. Based on the pharmacokinetic pharmacodynamic (PK/PD) correlation, trough concentrations from 375mg /250 mg and 125-mg/80-mg regimens are predicted to provide >95% NK_1 receptor blockade, while 40 mg 25 mg results in approximately 80 to 89% receptor occupancy.

6. Question Based Review

6.1. General Attributes

What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

Physico-chemical properties
Aprepitant is a novel substance P neurokinine 1 receptor antagonist. The drug substance is isolated as a crystalline solid and is not hygroscopic. The molecular formula is $C_{23}H_{21}F_7N_4O_3$ with a molecular weight of 534.43. It has 3 chiral centers and is optically active. The molecular structure is given below:

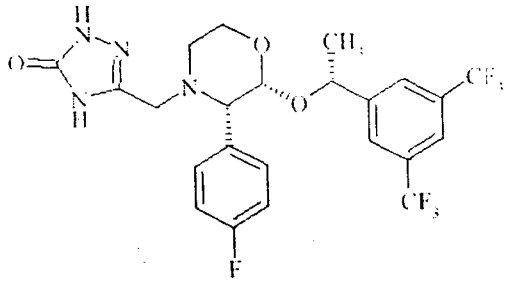


Figure 1: Structure of aprepitant

Aprepitant exists in two polymorphic forms (Form I and Form II). Form I is thermodynamically more stable than Form II. Form II was used only in Formulation A in very early phase I studies. Form I was used in all subsequent formulations including the to be marketed formulation. Aprepitant is practically insoluble in water, [redacted]. It is slightly soluble to soluble in commonly used organic solvents. Solubilities at 25°C in ethanol, isopropyl acetate, acetonitrile and methyl ethyl ketone were [redacted] respectively. Octanol : 0.1 M aqueous phosphate buffer (pH 7.0) partition coefficient at room temperature was 6.5 X 10^4 (log P =4.8 ± 0.1).

Formulation
The market formulation of aprepitant is a hard gelatin capsule containing the drug in a nanoparticle formulation. The development of the market formulation of aprepiatant evolved from preformulations studies to probe tablet and capsule to final hard gelatin capsule formulation. Four solid oral formulations of aprepitant, designated as A, B, C, and D have been developed during the course of development of this drug. Formulation A, B, and C are tablet formulations and Formulation D (to be marketed) is a nanoparticle capsule formulation. Tablet formulations were used in early clinical studies and have shown low oral bioavailability due to the poor solubility of aprepitant. In addition, early clinical studies also utilized a water soluble phosphate ester prodrug of aprepitant (L-758298) that was administered intravenously and is rapidly and completely converted into aprepitant in vivo. A nanoparticle capsule formulation (Formulation D) with particle size [redacted] was developed to enhance the bioavailability. This capsule formulation contains the nanoparticle drug substance coated on to microcystalline cellulose beads. The nanoparticle capsule formulation has superior bioavailability and reduced food effect

compared with tablet formulations used in earlier studies. This formulation was used in Phase IIb (protocol 040/042) and Phase III (Protocols 052 and 054) efficacy trials for CINV, and in key Clinical Pharmacology studies (see Table2).

Table 2. Aprepitant tablet and capsule formulations used in various clinical studies

Formulation	Study Number
A	002, 003, 004, 005, 006, 007
B	002, 005, 006, 008, 009, 010, 011, 012, 015, 016, 017
C	017, 019, 020, 021, 022, 023, 026, 027, 028, 029, 045
D	015, 026, 032, 039, 040/042, 041, 043, 044, 046, 047, 048, 049, 050, 052, 054, 056, 057, 064, 067

Table 3. Composition of tablet formulations used in early clinical studies

Formulation	A %	B %	C %
Component			
Aprepitant	8[1]	20[1]	50[1]
Total tablet weight (mg)	250 (20-mg dose) 625 (50-mg dose)	500 (100-mg dose) 750 (150-mg dose)	200 (100- , dose) 600 (300- mg dose)

particle size.

[1] Used only in Formulation C.

Table 4. Composition of final market formulation

Components	Unit Strength mg/Capsule	 mg/Capsule
Aprepitant[1]	80.00	125.0
Hydroxypropyl cellulose SL		
Sodium lauryl sulfate NF		
Microcrystalline cellulose NF		
Sucrose NF		
Sodium lauryl sulfate NF		
Purified water USP[2]		
Capsule fill weight (mg)		

Since the final market formulation is used in Phase II b and all Phase III studies and the key clinical pharmacology studies, no bioequivalence study is necessary. For studies where a tablet formulation was used, the calculated approximate equivalent dose of the nanoparticle capsule (based on plasma AUC) is provided to facilitate comparison to the market formulation.

What is the proposed mechanism of action?

The tachykinins (also known as neurokinins) are a family of peptides that are mainly found in neurons. The biological actions of tachykinins are mediated through specific cell surface receptors (neurokinin or NK receptors). Substance P and NK_1 receptors are critical for the regulation of vomiting reflex and are also highly expressed in brain. Aprepitant is a selective neurokinin 1 (NK_1) receptor antagonist, which has been shown preclinically to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin.

6.2. General Clinical Pharmacology

What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (also called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

In clinical pharmacology studies, binding to NK_1 receptors in brain was measured by positron emission tomography.
In clinical studies, efficacy endpoints were assessed based on number of emetic episodes, use of rescue therapy and nausea ratings.

Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. The active moiety, aprepitant was measured following administration of aprepitant and the prodrug, L-758298 (refer to analytical methods section).

6.2.1. Pharmacokinetics

What are the basic pharmacokinetic characteristics?
Pharmacokinetics of aprepitant 3-day regimen:

Pharmacokinetics of aprepitant 3-day regimen were studied following oral administration of 125 mg on Day 1 and 80 mg on Days 2 and 3.

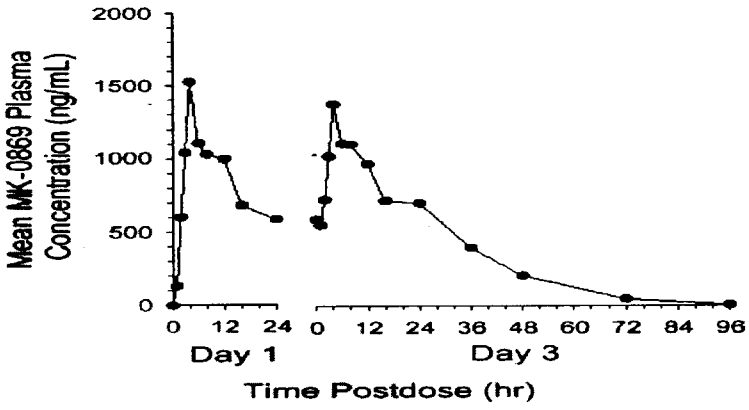


Figure 2. Mean Plasma Concentration (ng/mL) versus Time Profiles of MK-0869 (aprepitant) Following the Days 1 and 3 Doses of a 125-mg/80-mg/80-mg 3-Day Aprepitant Dosing Regimen.

Table 5. Summary Statistics for Aprepitant when Administered as 125-mg on Day 1 and 80-mg on Days 2 and 3 (n=12)

MK-0869 Pharmacokinetic Parameters			
PK Parameter	**Day 1**	**Day 3**	**Day 3/Day 1[†]**
$AUC_{(0\text{-}24\ hr)}$ (ng•hr/mL)	19,455[‡] (17,975; 21,057)	20,149[‡] (16,148; 25,141)	1.04[‡] (0.84, 1.28)
C_{max} (ng/mL)	1539[‡] (1339, 1769)	1356[‡] (1223, 1505)	–
T_{max} (hr)	4.0[§] (4.00, 5.00)[‖]	4.0[§] (4.00, 4.04)[‖]	–
Half-Life (hr)		8.63[¶] (7.26, 10.63)	–

[†] Accumulation ratio for the anti-CINV regimen where the dose changes from Days 1 to 3.
[‡] Geometric mean.
[§] Median.
[‖] Distribution-free confidence interval based on Wilcoxon sign-rank test.
[¶] Harmonic mean.
CINV = Chemotherapy-induced nausea and vomiting.

- The geometric mean accumulation ratio was 1.04 with 95% CI (0.84, 1.28) which was not significantly greater than 1.0
- The plasma levels of aprepitant on Day 3 (with 80 mg dose) are similar to those on Day 1 (with 125 mg dose).

Multiple Dose Pharmacokinetics:

The multiple dose pharmacokinetics of aprepitant were characterized in a double blind, parallel, randomized, placebo-controlled study conducted in 36 healthy male and female young subjects (Study # P043). The study consisted of two parts: Part 1 was single dose administration, and Part 2: Multiple dose administration. A total of 36 subjects received the following treatments in randomized fashion:

Treatment A: AP 125 mg /day, N= 16 (8 male and 8 female)
Treatment B: AP 375 mg/day, N= 16 (8 male and 8 female)
Treatment C: Matching placebo, N= 8 (4 male and 4 female)

On each day of dosing, the drug was administered within 15 minutes following a standard light breakfast. In each treatment all subjects finished both Part 1 (single dose) and Part 2 (multiple dose), which are separated by 1-week washout period.

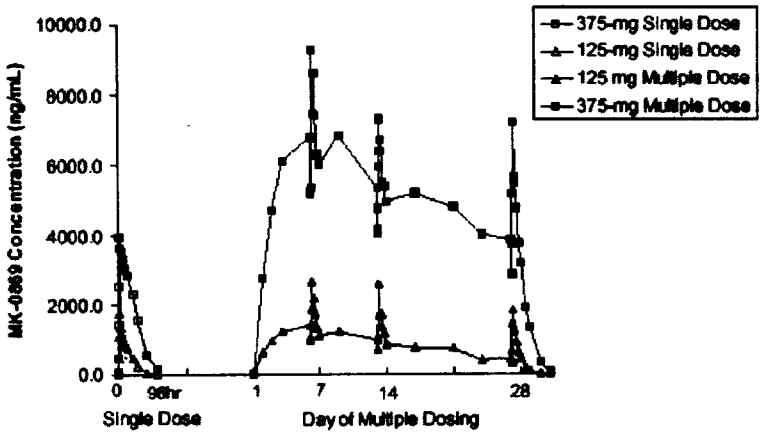


Figure 3. **Mean** plasma concentration of aprepitant following single and multiple dose administration in young healthy subjects.

Table 6. Pharmacokinetic data following single and multiple dose administration in young healthy subjects.

MK-0869 28-Day Multiple-Dose Regimen—Pharmacokinetic Summary
for MK-0869 Steady State $AUC_{0\text{-}24\ hr}$, Accumulation, and Gender Analysis

Variable	Dose	Gender	GM Day 1	GM Day 7	GM Day 14	GM Day 28* (90% CI)	Accum. GMR Day 7/Day 1 (90% CI)	Accum. GMR Day 14/Day 1 (90% CI)	Accum. GMR Day 28/Day 1 (90% CI)	Steady State GMR Day 14/Day 28 (90% CI)
AUC_{τ} (ng·hr/mL)	125 mg/day	Combined	22808.9	35877.4	29364.5	30009.8	1.63 (1.41, 1.89)	1.33 (1.15, 1.54)	0.91 (0.78, 1.05)	1.46 (1.26, 1.70)
		Male	18920.8	30753.6	25534.4	22121.5	2.15 (1.79, 2.59)	1.88 (1.56, 2.26)	1.17 (0.97, 1.41)	1.61 (1.34, 1.93)
		Female	26088.5	31703.3	24250.4	17905.6	1.22 (0.95, 1.55)	0.93 (0.73, 1.19)	0.69 (0.54, 0.88)	1.35 (1.06, 1.73)
		Female/ Male*	-	-	-	0.81 (0.59, 1.11)*	-	-	-	-
	375 mg/day	Combined	69231.8	154375.6	124257.6	101324.3	2.23 (1.93, 2.57)	1.79 (1.56, 2.07)	1.46 (1.27, 1.69)	1.23 (1.06, 1.41)
		Male	67274.8	139700.6	155338.2	68514.0	2.67 (2.19, 3.25)	2.31 (1.90, 2.81)	1.55 (1.28, 1.89)	1.49 (1.22, 1.81)
		Female	71829.5	132835.7	95556.9	97779.0	1.85 (1.49, 2.29)	1.39 (1.12, 1.72)	1.36 (1.10, 1.68)	1.02 (0.82, 1.26)
		Female/ Male*	-	-	-	0.94 (0.69, 1.26)*	-	-	-	-

MK-0869 28-Day Multiple-Dose Regimen—Pharmacokinetic Summary
for MK-0869 Steady State $AUC_{0\text{-}24\ hr}$, Accumulation, and Gender Analysis

Variable	Dose	Gender	GM Day 1	GM Day 7	GM Day 14	GM Day 28* (90% CI)	Accum. GMR Day 7/Day 1 (90% CI)	Accum. GMR Day 14/Day 1 (90% CI)	Accum. GMR Day 28/Day 1 (90% CI)	Steady State GMR Day 14/Day 28 (90% CI)
C_{max} (ng/mL)	125 mg/day	Combined	1711.6	2552.5	2417.6	1812.1	-	-	-	1.33 (1.13, 1.57)
		Male	1359.4	2361.3	2296.3	1644.4	-	-	-	1.40 (1.15, 1.69)
		Female	2214.3	2819.9	2614.0	1995.1	-	-	-	1.31 (1.09, 1.74)
		Female/ Male*	- -	-	-	1.21 (0.89, 1.65)*	-	-	-	-
	375 mg/day	Combined	4194.1	9244.3	7163.3	6905.5	-	-	-	1.04 (0.89, 1.21)
		Male	3965.8	9846.6	8013.1	6250.6	-	-	-	1.29 (1.09, 1.58)
		Female	4487.5	8789.0	6438.4	7627.6	-	-	-	0.84 (0.66, 1.08)
		Female/ Male*	-	-	-	1.22 (0.91, 1.64)*	-	-	-	-
Plasma trough level (ng/mL)	125 mg/day	Male	-	-	-	557.1	-	-	-	-
		Female	-	-	-	199.4	-	-	-	-
		Female/ Male*	-	-	-	0.36 (0.22, 0.59)*	-	-	-	-
	375 mg/day	Male	-	-	-	5888.2	-	-	-	-
		Female	-	-	-	3029.5	-	-	-	-
		Female/ Male*	-	-	-	0.51 (0.48, 1.45)*	-	-	-	-

* Gender analysis was exploratory and the ratio of geometric means and confidence interval (CI) for female/male comparisons are expressed.
GM = Geometric mean.
Accum. GMR = Accumulation geometric mean ratio.

As shown in the Figure 6, plasma concentrations of aprepitant accumulated up to Day 7 and began to decline after Day 7. The decline of concentrations after the first week administration is likely due to autoinduction of CYP3A4 enzyme.

Steady state was reached by Day 22 for combined (male and female) and by Day 25 for males and by Day 18 for females based on trough concentrations.

The accumulation ratio of AUC was 1.63 for Day 7 and lower 1.33 for Day 14 and 0.91 for Day 28 in comparison to Day 1 AUC (Table 6).

The AUC and trough concentration of aprepitant were slightly lower and the Cmax was slightly higher in females than the male subjects.

Metabolites of aprepitant, L-825678 and L-755446 were also measured in pooled plasma samples from 4 males and 4 females each. In general L-755446, L-825678 exposures ranged from 10 to 25 fold, and 8 to 10-fold lower than the parent, respectively.

Comparison of the AUC between doses 125 and 375 mg shows that the PK is slightly more than dose proportional (about 40 to 70% higher than dose proportional at 375 mg dose over four weeks of dosing).

6.2.2. Metabolism

In Vitro Metabolism

The in vitro metabolism of aprepitant (AP) is qualitatively similar in microsomes or hepatocytes of rats and humans. The primary metabolic events of aprepitant are N-dealkylation and O-dealkylation. In the presence of liver microsomes and primary hepatocyte cultures prepared from rats and humans, [^{14}C]aprepitant underwent metabolism to several nonpolar, polar, and very polar metabolites. A total of 14 metabolites (5 nonpolar, 3 polar and 6 very polar) were identified. In addition several glucuronides (L-863668, L-863665, L-863908, and a glucuronide of hydroxylated –L-755446) are detected when [^{14}C]aprepitant or [^{14}C]L-755446 is incubated with primary hepatocyte cultures prepared from rats or humans.

Identification of CYP450 isozymes responsible for the metabolism of aprepitant in human liver microsomes:

The relative contribution of various CYP450 isozymes to the metabolism of [^{3}H] or [^{14}C]aprepitant and two metabolites ([^{14}C]L-755446 and [^{14}C]L-809861) was characterized in vitro using CYP isozyme-selective inhibitors and microsomes expressing individual recombinant human CYP isozymes. The metabolism of AP in human liver microsomes was completely inhibited by ketoconazole (1 μM), a potent, selective CYP3A4 inhibitor. No inhibition was detected with inhibitors specific for other isozymes including quinidine for CYP2D6 (1 μM), sulfaphenazole for CYP2C9 (1 μM), furafylline for CYP1A2 (25 μM), and 4-methylpyrazole for CYP2E1 (100 μM). Separately, microsomes containing recombinant human CYP3A4, CYP1A2, or CYP2C19 were found to be capable of catalyzing the metabolism of AP. In summary, these results indicate that CYP3A4 is mainly responsible for the metabolism of AP in human liver microsomes with minor contributions from CYP1A2 and CYP2C19. CYP3A4 catalyzes a variety of metabolic reactions of aprepitant, including initial N-dealkylation and O-dealkylation reactions. The presence of L-858442 and L-858443 as major metabolites in human urine suggests that initial O-dealkylation reaction may be a more important pathway in humans than in the

nonclinical species. CYP3A4 was also primarily responsible for the metabolism of nonpolar metabolites [^{14}C]L-755446 and [^{14}C]L-80981.

Aprepitant as an inhibitor of CYP450 isozymes:

Pooled human liver microsomes were used to evaluate the potential of aprepitant to inhibit various CYP450 isozymes. Aprepitant (AP) was found to be moderate inhibitor of several CYP3A4-mediated probe reactions (midazolam 1'-hydroxylation, K_i = 10 μM; midazolam 4-hydroxylation, K_i = 10 μM; diltiazem N-demethylation, K_i = 11 μM; terfenadine metabolism, K_i = 21 μM; testosterone 6β-hydroxylation, IC_{50} = 2 to 4 μM). AP was a very weak inhibitor of the reactions mediated by other CYP isozymes: CYP1A2 (IC_{50} >100 μM), CYP2C9 (IC_{50} >100 μM), CYP2C19 (K_I = 66 μM), CYP2D6 (IC_{50} >100 μM) and CYP2E1 (IC_{50} >100 μM).
For comparison, the aprepitant regimen in vivo yields an average Cmax of 1539 ng/ml (~3μM), which is at least 20 to 30 times less than the IC_{50} or K_I observed for CYP isozymes except for CYP3A4, whose K_I is only about three times higher than the Cmax indicating the in vivo potential for inhibition of drugs metabolized by CYP3A4.
Overall, in vitro studies indicate that AP is a moderate inhibitor of CYP3A4 and a weak inhibitor other CYP450 mediated reactions in human liver microsomes.
Sponsor has conducted in vivo drug interaction studies with CYP3A4 substrates (midazolam, diltiazem, dexamethasone, methylprednisolone, ondansetrone and granisetron), CYP2C9 substrates (warfarin) and CYP2D6 substrates (paroxetine and dextromethorphan).

Aprepitant as a substrate and inhibitor of P-glycoprotein (P-gp):

The potential of AP as a substrate and inhibitor of P-gp has been studied in vitro using Caco-2 and cell lines which over expressed human MDR1 P-gp (KB-V1 and MDR1 transfected cells) or mouse mdr1 a P-gp (mdr1 a transfected cells). In Caco-2 cells, the permeability of [^{3}H]-AP (20 μM) from basolateral to apical (B to A) to that from apical to basolateral (A to B) was greater than unity (2.3 fold), but much less than that for [^{3}H]vinblastine (about 7-fold), a known P-gp substrate. In human MDR1 and mouse mdr1 a transfected cell lines, the amount of [^{3}H]-AP transported from B to A within 3 hr were greater than those from A to B by 7.4- and 13-fold, respectively, as compared with 11- and 19-fold for vinblastine in the two cell lines. In summary these results indicate that AP is substrate for human MDR1 and mouse mdr1 a transporter proteins, but it seems to be a weaker P-gp substrate than vinblastine.

AP (10 μM) resulted in 36% reduction of the B-to-A/A-to-B permeability ratio of vinblastine (1μM) in Caco-2 cells compared to 87% reduction by cyclosporine A (10 μM)and 60% reduction by verapamil (10 μM). Similar results were obtained at a higher vinbalstine concentration of 5 μM. In MDR1 over expressed KB-V1 cells, AP (2 and 10 μM) and verapamil (10 μM) showed no substantial inhibition of vinbalstine accumulation as compared with cyclosporine A at 10 μM. These results suggest that AP is weaker inhibitor of P-gp mediated transport of vinblastine than cyclosporine A and its inhibitory effect is either weaker or similar to that of verapamil.
An in vivo drug interaction study of AP with digoxin (P-gp substrate) showed no significant effect on digoxin pharmacokinetics confirming that AP has no significant inhibitory effect on P-gp mediated transport.

Mass-Balance

The disposition, metabolism and mass balance of aprepitant were investigated in two studies. In Protocol 013, 8 healthy subjects received a single oral dose of 300 mg [^{14}C]-aprepitant and an IV infusion of 100 mg [^{14}C]-L-758298. In protocol 010, 4 healthy subjects received IV 100 mg [^{14}C]-L-758298 with an extended postdose sampling collection period up to 28 days to further characterize mass balance.

Table 7. **Mean** (N=8) recovery radioactivity (%dose) following a single dose of 100 mg IV [^{14}C]-L-758298 and 300 mg oral [^{14}C]-aprepitant

	100 mg IV [^{14}C]L-758298				300 mg Oral [^{14}C]aprepitant			
Parameter	Urine (%)	Feces (%)	Fecal Wipe (%)	Total (%)	Urine (%)	Feces (%)	Fecal Wipe (%)	Total (%)
Geometric Mean	47.1	31.3	0.06	78.8	4.7	85.6	0.28	91.2
90% CI	(44.4, 50.0)	(29.1, 33.7)	NC	(75.2, 82.5)	(3.6, 6.0)	(79.5, 92.2)	NC	(85.5, 97.2)
NC = Not calculated. CI = Confidence interval.								

Table 8. **Mean** (N=4) recovery of radioactivity (% dose) over 28 days following a single dose of 100 mg [^{14}C]-L-758298

Parameter	Urine (%)	Feces (%)	Fecal Wipe (%)	Total (%)
Geometric Mean	57.0	45.0	0.07	102.5
90% CI	(48.1, 67.7)	(42.7, 47.4)	NC	(94.3, 111.3)
NC = Not calculated. CI = Confidence interval.				

Both studies showed that slightly greater elimination of radioactivity in urine (47 to 57%) compared to feces (31 to 45%) following IV [^{14}C]-L-758298.

Following oral dosing, a large proportion of radioactivity (~86%) was recovered in feces due to poor absorption of drug from this formulation. Oral bioavailability of this radiolabeled formulation was ~9%.

Unchanged drug was not detected in urine following IV or oral administration suggesting extensive metabolism. Excretion of 45% radioactivity in feces following IV administration suggests that biliary excretion contributes to clearance of aprepitant and metabolites. [^{14}C]-aprepitant and [^{14}C]-L-809771 were the major components in fecal extracts up to Day 3.

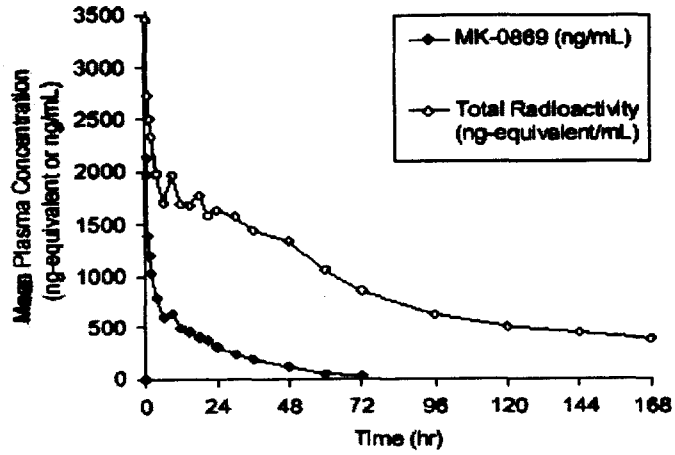


Figure 4. Mean (N=8) plasma concentration profiles of total radioactivity and aprepitant (MK-0869) following a single dose of 100 mg IV [^{14}C]-L-758298

Following IV administration, aprepitant accounted for ~20% of the total radioactivity in plasma while metabolites accounted for ~80% of total radioactivity. Twelve metabolites (5 nonpolar, 3 polar, 3 very polar and a glucuronide conjugate) in plasma were identified (see Figure 5). Major component in plasma up to at least 48 hours post dose was aprepitant, whereas 2 polar metabolites, L-829617 and L-829615 appeared to be the major components at 72 hours.

The metabolites are not likely to contribute significantly to the efficacy of aprepitant because these metabolites are either inactive or weakly active or are present at low levels relative to aprepitant.

Proposed Metabolic Pathways of [^{14}C]Aprepitant in Rats, Dogs, and Humans

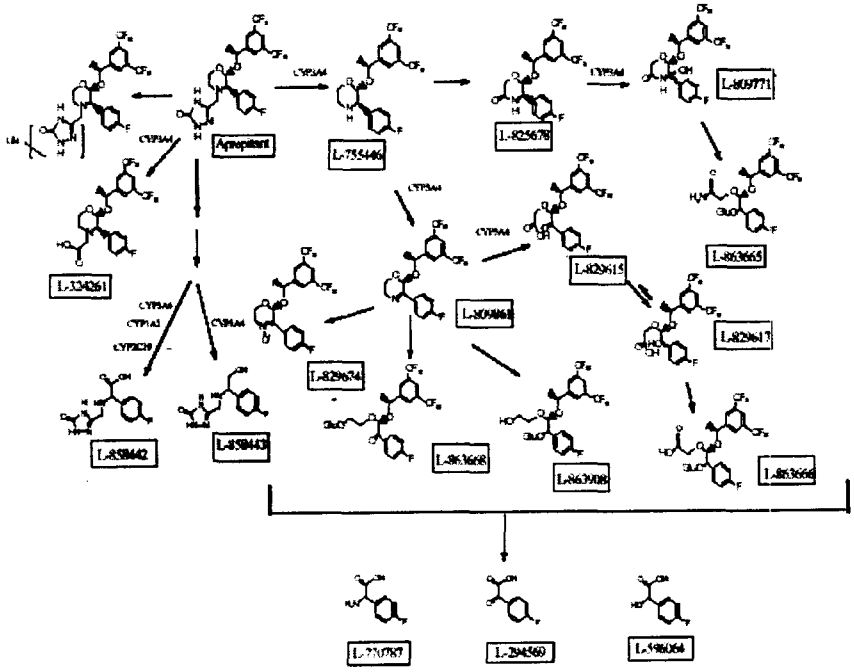


Figure 5. Metabolic pathways of aprepitant

6.2.3. Exposure-Response of Aprepitant

What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy and safety? Is there a PK/PD relationship for efficacy and safety parameters?

The correlation of plasma AP concentrations with binding of AP to brain NK_1 receptors was assessed in 2 studies in healthy young men using positron emission tomography (PET) scanning and a specific NK_1 receptor binding ligand (L-829165) as PET tracer. This ligand binds reversibly and quantitatively to human NK_1 receptors. The positron emitting isotope labeled ligand ^{18}F-L-829165 is readily brain penetrant and its binding to NK_1 receptors is quantitatively displaced both in vitro and in vivo by various NK_1 receptors antagonists including AP. Using ^{18}F-L-829165 as a PET tracer, the binding AP to brain NK_1 receptors was quantified by measuring blockade of binding of PET tracer to NK_1 receptors in the corpus striatum, the area of the brain with the highest concentration of NK_1 receptors.

The first study was single-blind, multiple dose, randomized, and placebo controlled study in which subjects received AP or placebo for 14 days shortly after breakfast at the doses 10 mg/day (n=2), 30 mg/day (n=3), 100 mg/day (n=3), 300 mg/day (n=2) of tablet formulation C and placebo (n=2). The second study was also similar in design and used formulation C with a dose of AP 30 mg/day (n=3) and placebo (n=1). Two PET scans were obtained for each subjects: the first scan (baseline) was taken within two weeks prior to the first dose and the second PET was at 24 hr after the last dose of AP. The receptor binding data from both the studies was combined and the relationship between plasma concentration of AP and the % binding of receptors is illustrated in the following figure.

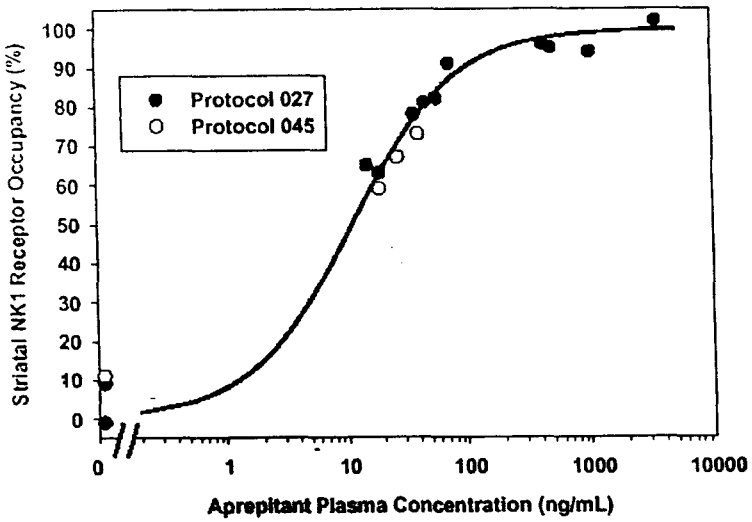


Figure 6. Correlation between plasma AP concentration and binding of AP to striatal NK_1 receptors in humans.

Based on the above figure, plasma concentrations of AP are well correlated with receptor binding with a curve described by Hill equation. Based on this relationship, AP concentrations of 10 and 100 ng ml produce NK_1 receptor occupancies of approximately 50 and 90%, respectively.

In phase II b dose ranging studies of CINV, submaximal antiemetic efficacy was achieved at 40-mg/25 mg regimen, while maximum efficacy was achieved with 125 mg/80 mg regimen and there was no apparent benefit at the highest dose regimen of 375 mg/250 mg. The upper portion of the fitted curve shown above is reproduced in the following figure with super imposed concentrations of AP that were expected from the doses used in Phase II b studies.

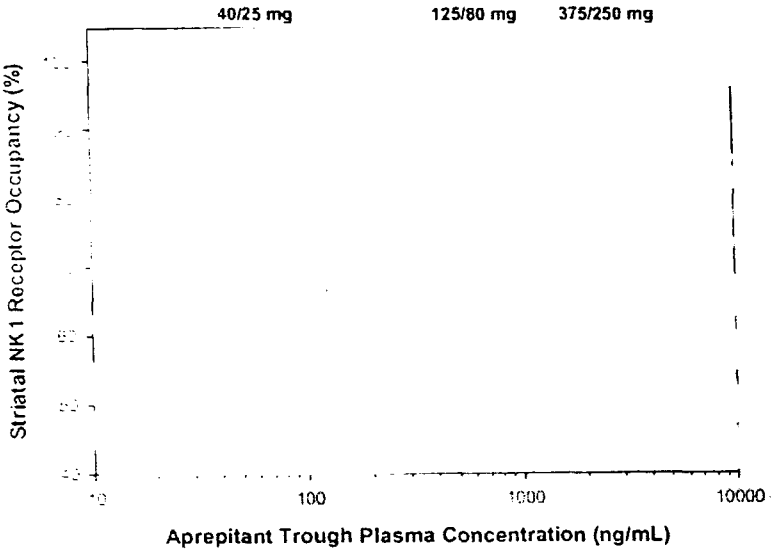


Figure 7. The relationship between plasma AP trough concentrations expected from different dosing regimens of AP and the striatal NK_1 receptor occupancy.

Based on the PK/PD correlation shown in the above figure, trough concentrations from 375mg /250 mg and 125-mg/80-mg regimens are predicted to provide >95% NK_1 receptor blockade, while 40 mg/25 mg results in approximately 80 to 89% receptor occupancy. Based on the phase II b dose ranging studies and the PK/PD relationship, sponsor concluded that nearly complete (>95%) NK_1 receptor blockade is required to obtain maximum antiemetic efficacy of aprepitant and NK_1 receptor blockade of 80 to 90% still provides significant but less than maximal antiemetic efficacy. Thus, the dose selection of 125/80 mg regimen for phase III studies seems to be appropriate based on the given data, although there was no data obtained with a regimen in between 125/80 mg and 40/25 mg regimens.

Effect of Aprepitant on QT prolongation:
There was no prospectively planned, controlled clinical study to evaluate the effect of aprepitant on QT interval. A comprehensive analysis of the effect of aprepitant on QT_c interval was performed on the EKG data collected in several clinical pharmacology studies.

Most of the QT interval readings consisted of automatic readings measured at either one to two time points (4 or 8 hours) with capsule formulation or more frequently with tablet or IV formulation (e.g., 0.5, 1, 2, 4, 8, and 24 hrs).

Only 4 subjects in each of the three treatments groups of clinical dose (4 of 86 subjects; 4.7%), higher than clinical dose (4 of 43 subjects, 9.3%) and placebo (4 of 43 subjects; 9.3%) had QT_c interval increases from baseline ≥30 and ≤60 msec.

The mean QTc interval changes for L-758298 (prodrug) and aprepitant were similar to those seen with placebo.

QTc interval increases from baseline ≥30 and ≤60 msec were slightly higher (8 of 60 subjects, 11.6%) for the early tablet formulation compared to capsule formulation.
For the L-758298 IV treatment, 9 subjects (of 80 subjects; 11.3%) and 1 subject (of 40; 2.5%) on placebo had QTc interval changes ≥30 and ≤60 msec.

Only one subject had QTc interval >500 msec at 24 hours following administration of 800 mg tablet formulation. This subject also received a single dose of 1200 mg tablet formulation with no prolongation of QTc.

There were few, if any, outliers of clinical concern and many of the subjects who are outliers had subsequent higher doses of L-758298 or oral aprepitant with no changes in QTc.

6.2.4. **Intrinsic Factors**
How does the systemic exposure change with various intrinsic and extrinsic factors?
Is there a need for dosage adjustment or contraindication/caution with these factors?

Rationale for clinically meaningful differences in systemic exposure of aprepitant:

In order to assess the clinical significance of the changes in exposure of aprepitant due to intrinsic and extrinsic factors, sponsor has provided a rationale for clinically meaningful difference based on the range of exposure data observed in phase I and phase II studies.
The aprepitant regimen for CINV (125 mg on Day 1, 80 mg on Days 2 and 3) results in plasma AUC up to ~24 μg.h/ml and C_{max} up to 2 μg/ml (Protocol 043). The highest exposure in clinical studies was a plasma AUC of ~154 μg.h/ml and Cmax of ~9.2 μg/ml on Day 7 with multiple dosing of 375 mg/day (Protocols 043 and 039), which was shown to be well tolerated in healthy subjects and patients. Therefore, sponsor concluded that increases in plasma concentrations up to ~5 to 6 fold above those seen with the recommended dose regimen are well tolerated. Conversely, a decrease in plasma AUC from ~24μg.h/ml (using the 125/80 mg regimen) to ~4 μg.h/ml (with the 40/25 mg regimen) resulted in a clinically important decrease in antiemetic efficacy based on Phase IIb dose ranging study (Protocols 040 and 042). Therefore, a reduction of plasma concentration of ~8 fold below those of recommended dose regimen will be associated with clinically meaningful decrease in efficacy.
Based on the above mentioned comparisons of exposures from the highest and lowest dose regimens tested in clinical studies in relation to the recommended dose regimen, sponsor proposed a relative conservative interval of 0.5 to 2.0 fold change in exposure of aprepitant as clinically significant change (with upper limit of CI equal or exceeding 3.0). This interval is generally acceptable, given the fact that no significant toxicities noted in phase III clinical studies (see Clinical Review). However, it should be noted that the higher multiples of exposure noted above are based on limited number patients in phase I and II studies and only one dose regimen (125/80 mg) was tested in Phase III. Furthermore, aprepitant is an inhibitor of CYP3A4 isozyme. So any increase in its plasma levels will likely result in greater inhibition of the metabolism of concomitantly administered CYP3A4 substrates.

6.2.4.1. Hepatic Insufficiency

An open label, single period, multiple dose study was conducted to investigate the effect hepatic insufficiency on the pharmacokinetics, safety and tolerability of Aprepitant. Ten patients with mild hepatic insufficiency (Child-Pugh score 5 to 6) and moderate hepatic insufficiency (Child-Pugh score 7 to 9) in comparison to 20 healthy control subjects (age-, gender-, and weight-matched) received the following treatments:

Day 1: A single oral dose of 125 mg aprepitant capsule (to be marketed formulation)
Days 2 and 3: A single oral dose of 80 mg aprepitant capsule (to be marketed formulation)
All doses were administered 15 minutes after the standard light breakfast in the morning.

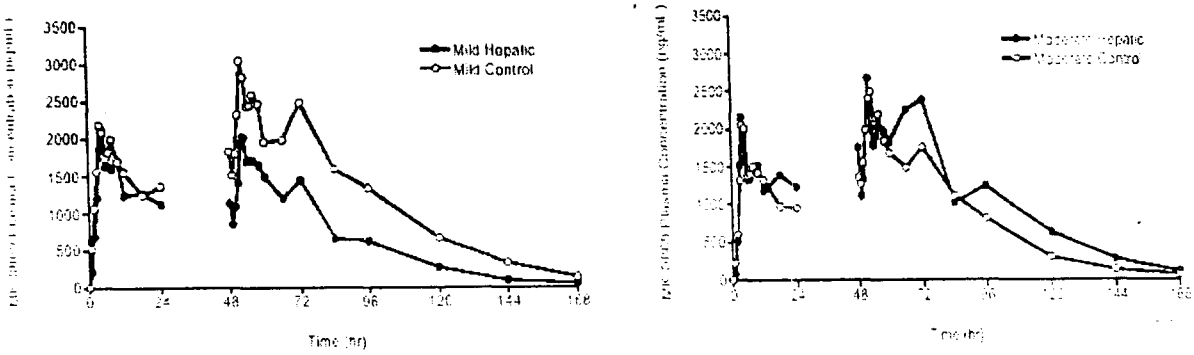


Figure 8. Mean plasma concentration profiles of AP in patients with mild and moderate hepatic insufficiency compared to healthy control subjects.

Table 9. Geometric mean PK parameters in patients with hepatic insufficiency compared to healthy controls

Disease state	Hepatic patient (A)	Healthy control (B)	Ratio (A/B)	90% CI
		$AUC_{0\text{-}24hr}$ (Day 1)		
Mild	30248	33934	0.89	(0.74, 1.08)
Moderate	33161^	30103^	1.10@	(1.00, 1.21)
		$AUC_{0\text{-}24hr}$ (Day 3)		
Mild	32604	50834	0.64	(0.50, 0.83)
Moderate	48182	40972	1.18	(0.99, 1.40)

^Geometric mean, back-transformed from least squares mean from analysis of covariance, performed on natural log-transformed data, estimated at the mean age (52 yr) and weight (82 kg) of all patients.
@ Estimated ratio at mean age and weight of all patients and subjects included in the analysis. Due to interactions, ratio may vary with age and weight.

Patients with mild hepatic insufficiency had 35% lower $AUC_{0\text{-}24hr}$ and moderate hepatic insufficiency had 18% higher $AUC_{0\text{-}24hr}$ compared to control healthy subjects. It is not known why plasma levels were lower in mild hepatic insufficiency patients compared to healthy subjects.

Overall, there was no clinically significant effect on the pharmacokinetics of aprepitant in patients with mild to moderate hepatic impairment. So, no dosage adjustment is recommended in these patients. Since the effect of severe hepatic insufficiency has not been studied, caution should be exercised when aprepitant is administered in these patients.

6.2.4.2. Effect of renal insufficiency

An open-label, 2-part study was conducted to evaluate the safety, tolerability, and pharmacokinetics of aprepitant in patients with severe renal insufficiency (CrCl<30 ml/min/1.73 m^2) and end stage renal disease (requiring hemodialysis) compared to healthy subjects (CrCl>80 ml/min/1.73 m^2). Serum creatinine clearance estimations for patients with severe renal insufficiency (SRI) were based on two baseline 24-hour urinary creatinine clearance determinations. For healthy control subjects, serum clearance was calculated using the Cockroft Gault Equation and then normalized to a body surface area of 1.73 m^2.

Part 1 was a 2-period, 2-panel study in 8 patients (panel A) with end stage renal disease (ESRD) and 8 healthy control subjects (panel B) matched by age (within 3 years), gender, and weight (within 5 kg). ESRD patients enrolled in Panel A participated in both treatment periods of Part 1. ESRD patients underwent hemodialysis 48 hours (in period 1) and 4 hours (in period 2) after dosing with 240 mg (3 x 80 mg) aprepitant nanoparticle capsules.
Part 2 was a 1-period, 2-panel study involving 8 patients with SRI (panel C) and 8 healthy control subjects (panel D) matched by age (within 3 years), gender, and weight (within 5 kg).

Table 10. Effect of renal insufficiency on mean pharmacokinetic parameters (n=8 per group).

Patient group	$AUC_{0-\infty}$ (ng.hr/ml)		Cmax (ng/ml)	
	Geometric Mean	Patients/subjects Geometric Mean ratio (90% CI)	Geometric Mean	Patients/subjects Geometric Mean ratio (90% CI)
Total plasma levels				
ESRD patients Healthy controls	42,072 72,993	0.58 (0.45, 0.74)	2005 2967	0.68 (0.55, 0.83)
SRI patients Healthy controls	77,206 97,987	0.79 (0.56, 1.10)	2561 3778	0.68 (0.47, 0.98)
Unbound plasma levels				
ESRD patients Healthy controls	1571 1879	0.84 (0.57, 1.22)		
SRI patients Healthy controls	2825 2660	1.06 (0.62, 1.82)		

The clearance of AP is mediated mainly by hepatic metabolism and the renal insufficiency is not expected to significantly alter pharmacokinetics of AP. However, unexpectedly systemic exposure to aprepitant (AUC) was lower in ESRD (40%↓) and SRI (20%↓) patients compared to the matched healthy control subjects. There was no apparent relationship between creatinine clearance and the plasma concentration of AP (AUC and Cmax).

There was a tendency to decreased protein binding in the ESRD and SRI patients compared to healthy control subjects. The geometric mean free fraction of AP at 4 hours post dose was 3.99% for SRI patients and 2.33% for healthy controls and was 3.06% for ESRD patients versus 2.00% for healthy controls. As a result the unbound concentrations of AP were not significantly different in ESRD and SRI patients compared to healthy control subjects. Since the pharmacological effect is likely to be more closely related to unbound concentrations (which did not change with renal function), no dosage adjustment is recommended in these patient populations.

Hemodialysis (at 4 and 48 hours after dosing) did not significantly effect the pharmacokinetics. Plasma clearance of AP by dialysis was about 1 ml/min, which is small compared to the total plasma clearance of about 70 ml/min. This also means that in the event of overdose, hemodialysis would not be effective mode of therapy to reduce plasma concentrations of AP.

6.2.4.3. Effects of gender, age, race, and weight

To evaluate the effects of gender, age, race, and body weight on pharmacokinetics of aprepitant, a comprehensive analysis of pharmacokinetic parameters across all appropriate phase I studies was conducted.

Gender

Men and women comprised of 59% and 41%, respectively, of the subjects in the comprehensive analysis. Compared to men, women had slightly lower (up to 16%) AUC and slightly higher (up to 27%) C_{max}. The half-life in women (9 to 11 h) was slightly shorter than men (11 to 13 h).

Age

Compared to young adults (≤ 45 years), elderly subjects (≥ 65 years) showed small increases of 36% and 24% in AUC and C_{max}, respectively.

Race

Slightly higher (20 to 30%) plasma concentrations of aprepitant were noted in hispanic subjects compared to white or black subjects. There was no difference between black and white subjects.

Body Weight

There was a small, statistically significant negative relationship between weight and $AUC_{0\text{-}24h}$ and C_{max}. For every 10 kilogram increase in weight, AUC would be expected to decrease, on average by 7%, and Cmax would be expected to decrease by 5%. Half-life was unaffected by weight.

These differences in pharmacokinetics of aprepitant with gender, elderly, race and weight are not clinically significant and no dosage adjustment is recommended in these groups.

6.2.5. Extrinsic Factors
Drug Interactions

6.2.5.1. Interaction with CYP3A4

Effect of Aprepitant on midazolam pharmacokinetics:

The effect of two aprepitant regimens on the pharmacokinetics of midazolam was investigated in study P041. This study was initially designed to investigate the potential PK interactions among high dose MK-0869 (Aprepitant) capsules when administered with and without standard antiemetic regimen for CIE (chemotherapy induced emesis) of dexamethasone and intravenous (IV) infusion of ondansetron. Dexamethasone dosage used in the study along with ondansetron is considered as one of the standard antiemetic regimens for CIE.

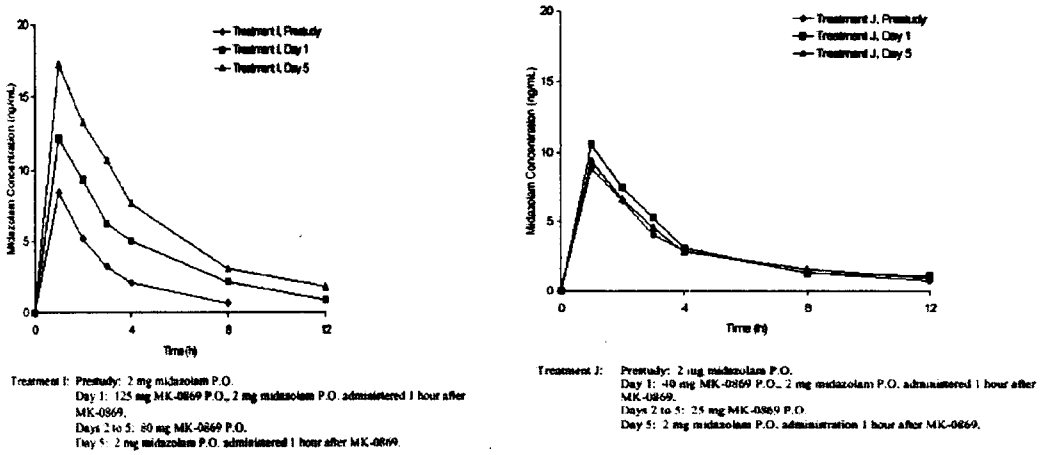
Plasma dexamethasone concentrations on Days 1 and 5 were significantly increased with concomitant administration of aprepitant and concentrations of aprepitant were slightly reduced on Day 5 suggesting inhibition of CYP3A4 by aprepitant and induction of CYP3A4 by dexamethasone, respectively. There was no effect of aprepitant on ondansetron plasma levels. Thus, the protocol was amended to study the interaction between lower doses of aprepitant and dexamethasone. In addition, the protocol was also amended to investigate the effect of low-dose and modified low-dose of aprepitant capsules (Formulation D, final market formulation) on midazolam plasma concentrations.

The midazolam evaluation portion of the study was an open-label, randomized, single-period crossover study conducted in 16 healthy male subjects, who received the following treatment regimens:

Table 11: Treatment regimens for midazolam evaluation

Treatment Regimen	Prestudy	Day 1	Days 2 to 5
Treatment I (Low-dose MK-0869)		MK-0869 (125 mg P.O.)	MK-0869 (80 mg/day P.O.)
Treatment J (Modified low-dose MK-0869)		MK-0869 (40 mg P.O.)	MK-0869 (25 mg/day P.O.)
Midazolam (2 mg P.O.) Treatments I and J	Days -7 to -3	Day 1, 1 hour after MK-0869	Day 5, 1 hour after MK-0869
P.O. = By mouth.			

In each treatment group, eight male subjects received 2 mg midazolam (po) prestudy and 3 to 7 days later subjects began a 5-treatment regimen with low dose (Treatment I) or modified low dose of aprepitant (Treatment J). Midazolam was also given on Days 1 and 5 during administration of both regimens of aprepitant.



Treatment I: Prestudy: 2 mg midazolam P.O.
Day 1: 125 mg MK-0869 P.O., 2 mg midazolam P.O. administered 1 hour after MK-0869.
Days 2 to 5: 80 mg MK-0869 P.O.
Day 5: 2 mg midazolam P.O. administered 1 hour after MK-0869.

Treatment J: Prestudy: 2 mg midazolam P.O.
Day 1: 40 mg MK-0869 P.O., 2 mg midazolam P.O. administered 1 hour after MK-0869.
Days 2 to 5: 25 mg MK-0869 P.O.
Day 5: 2 mg midazolam P.O. administration 1 hour after MK-0869.

Figure 9. Mean plasma concentrations of midazolam following low dose (left panel) and modified low dose regimen of aprepitant (right panel).

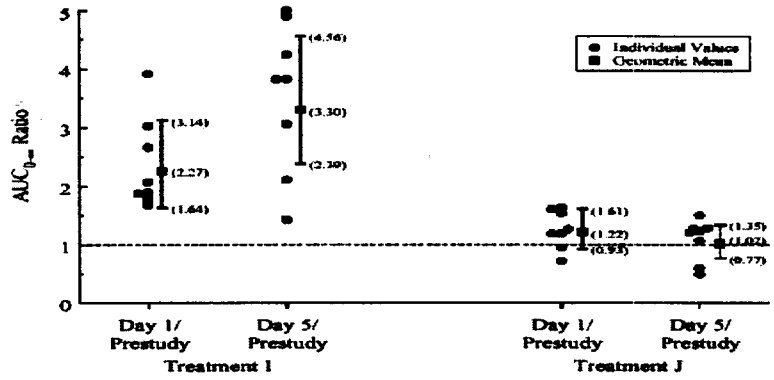


Figure 10. **Individual and geometric mean** AUC ratios midazolam

Table 12: **Mean PK** parameters of midazolam with and without concomitant aprepitant regimens

Effects on Midazolam $AUC_{0-\infty}$ (ng-h/mL)						
Day	Treatment Regimen Midazolam $AUC_{0-\infty}$*	Reference Regimen Midazolam $AUC_{0-\infty}$*	Ratio†	p-Value	95% CI	Hypothesized Interval
Midazolam Evaluation (Amendment 041-01)						
1	Low-dose MK-0869 with oral midazolam (I) 52.1	Oral midazolam alone (prestudy) 23.0	I/Prestudy 2.27	< 0.01	(1.64, 3.14)	N/A
5	Low-dose MK-0869 with oral midazolam (I) 75.7	Oral midazolam alone (prestudy) 23.0	I/Prestudy 3.30	< 0.01	(2.39, 4.56)	N/A
1	Modified low-dose MK-0869 with oral midazolam (J) 37.7	Oral midazolam alone (prestudy) 30.8	J/Prestudy 1.22	0.143	(0.93, 1.61)	N/A
5	Modified low-dose MK-0869 with oral midazolam (J) 31.4	Oral midazolam alone (prestudy) 30.8	J/Prestudy 1.02	> 0.25	(0.77, 1.35)	N/A

* Least squares geometric mean. For the amendment, estimates for treatment ratios were based on both paired and unpaired observations for these treatments.
CI = Confidence interval.
N/A = Not applicable. No hypothesis specified; estimation only.

*N= 8 per treatment.

The low dose regimen of aprepitant (125/80 mg) increased the mean $AUC_{0-\infty}$ of midazolam by 2.3 and 3.3-fold on Days 1 and 5, respectively and increased the mean Cmax of midazolam by 1.46 and 1.94 fold, respectively.

There were two individual subjects with a 5-fold increase in midazolam AUC on Day 5 of the low dose regimen of aprepitant.

The modified low dose regimen of aprepitant (40/25 mg) did not significantly affect midazolam plasma levels.

The larger change in midazolam AUC on Day 5 compared to Day 1 following low dose regimen may be associated with higher AUC values of aprepitant on Day 5 as a plot of fold-change in midazolam AUC versus aprepitant AUC showed a positive correlation.

Sponsor concluded that the effect of low-dose aprepitant regimen on midazolam are consistent with a weak (Day 1) to moderate (Day 5) inhibition of CYP3A4. Although sponsor concluded

that aprepitant has weak to moderate inhibitory effect on CYP3A4 in comparison to the potent effect of ketoconazole; a two to three fold mean change in AUC (up to 5-fold change in some individuals) may have significant safety concerns depending on therapeutic index of the drugs administered along with aprepitant.

The CYP 3A4 inhibitory effect of aprepitant and the resultant change in plasma levels of the coadministered drug may depend on the contribution CYP3A4 in the overall elimination of the drug.

Effect of aprepitant on dexamethasone

In the study mentioned above, sponsor also investigated the pharmacokinetic interaction between aprepitant and dexamethasone or ondansetron. Initially in the study, the effect of high dose aprepitant was studied with a 3-period, crossover design. Nineteen (19) healthy male and female subjects received the following treatment regimen:

Table 13. Treatment regimen for high dose aprepitant and standard antiemetic regimen for CIE evaluation:

Treatment Regimen	Day 1	Days 2 to 5
Treatment A (High-dose MK-0869 and standard antiemetic regimen for CIE)	MK-0869 (375 mg P.O.), dexamethasone (20 mg P.O.), and ondansetron (32 mg IV)	MK-0869 (250 mg/day P.O.) and dexamethasone (8 mg/day P.O.)
Treatment B (Standard antiemetic regimen for CIE alone)	Dexamethasone (20 mg P.O.) and ondansetron (32 mg IV)	Dexamethasone (8 mg/day P.O.)
Treatment C (High-dose MK-0869 alone)	MK-0869 (375 mg P.O.)	MK-0869 (250 mg P.O.)
CIE = Chemotherapy-induced emesis. IV = Intravenous. P.O. = By mouth.		

After noting that high dose regimen of aprepitant did interact with dexamethasone and did not affect ondansetron, the protocol was continued to investigate the effect of low dose and modified low dose regimens of aprepitant on dexamethasone concentrations in 20 healthy male and female subjects who received the following treatments in a randomized, incomplete block design:

Table 14. Treatment regimens for evaluation of aprepitant on dexamethasone

Treatment Regimen	Day 1	Days 2 to 5
Treatment D (Low-dose MK-0869 alone)	MK-0869 (125 mg P.O.)	MK-0869 (80 mg/day P.O.)
Treatment E (Standard antiemetic regimen for CIE alone)	Dexamethasone (20 mg P.O.) and ondansetron (32 mg IV)	Dexamethasone (8 mg/day P.O.)
Treatment F (Low-dose MK-0869 and standard antiemetic regimen for CIE)	MK-0869 (125 mg P.O.), dexamethasone (20 mg P.O.), and ondansetron (32 mg IV)	MK-0869 (80 mg/day P.O.) and dexamethasone (8 mg/day P.O.)
Treatment G (Low-dose MK-0869 and modified antiemetic regimen for CIE)	MK-0869 (125 mg P.O.), dexamethasone (12 mg P.O.), and ondansetron (32 mg IV)	MK-0869 (80 mg/day P.O.) and dexamethasone (4 mg/day P.O.)
Treatment H (Modified low-dose MK-0869 and standard antiemetic regimen for CIE)	MK-0869 (40 mg P.O.), dexamethasone (20 mg P.O.), and ondansetron (32 mg IV)	MK-0869 (25 mg/day P.O.) and dexamethasone (8 mg/day P.O.)
CIE = Chemotherapy-induced emesis. IV = Intravenous. P.O. = By mouth.		

Table 15. Effect of standard CIE regimen on high dose aprepitant PK

Treatment	Cmax (ng/ml)	Cmax Ratio, (95% CI)	AUC (ng.hr/ml)	AUC Ratio (95% CI)
Day 1				
High dose AP + St.CIE regimen (A)	4986	1.20 (1.03, 1.40)	63.512	1.12 (1.01, 1.24)
High Dose AP (C)	4142		56,941	
Day 5				
High dose AP + St.CIE regimen	6116	0.61 (0.52, 0.73)	103.291	0.75 (0.63, 0.89)
High Dose AP	9974		137.635	

Table 16. Effect of standard and modified CIE regimens on low dose aprepitant PK

Treatment	Cmax (ng/ml)	Ratio, (95% CI)	AUC (ng.hr/ml)	Ratio
Day 1				
Low dose AP + St.CIE regimen (F)	2036	1.46 (1.20, 1.79)	24.309	1.30* (1.15, 1.46)
Low Dose AP + Modified CIE regimen (G)	1820	1.31 (1.07, 1.61)	22.934	1.23^ (1.09, 1.38)
Low Dose AP (D)	1391		18.714	
Day 5				
Low dose AP + St.CIE regimen (F)	1649	1.04 (0.89, 1.22)	22.531	0.98 (0.85, 1.14)
Low Dose AP + Modified CIE regimen (G)	1518	0.96 (0.82, 1.12)	19.488	0.85 (0.73, 0.98)
Low Dose AP (D)	1586		23.005	

*Ratio for 6 subjects that received both F and D
^Ratios for 5 subjects that received both G and D

With the standard CIE regimen, the Day 1 AUC of high dose aprepitant was not significantly affected. However, the Day 5 AUC was reduced by about 25% (based on Geometric mean ratio of 0.75), possibly due to induction by dexamethasone.

With standard CIE regimen, the Day 1 AUC of low dose aprepitant was increased by a mean of 30%, while the Day 5 levels were not significantly affected.

The PK of low dose aprepitant was not significantly affected by concomitant administration of modified CIE regimen. It should be noted that the low dose regimen of aprepitant was selected for the phase III studies.

Table 17. Effect of aprepitant on dexamethasone

Effect of high dose AP on Dexamethasone PK parameters*						
Day	Treatment A AUC_{0-24h}	Treatment B AUC_{0-24h}	Ratio A/B (90% CI)	Treatment A Cmax	Treatment B Cmax	Ratio A/B (90% CI)
1	2305	899	2.56 (2.21, 2.97)	289	219	1.32 (1.14, 1.53)
5	1278	312	4.10 (3.63, 4.63)	132	72	1.82 (1.59, 2.09)

*Least square estimates based on analysis of variance.

Treatment A = Day 1: 375 mg AP, P.O + 20 mg dexamethasone P.O. + 32 mg ondansetron IV.
(Test) Day 2 to 5: 250 mg/day AP P.O. + 8 mg/day dexamethasone P.O.
Treatment B = Day 1: 20 mg dexamethasone P.O. + 32 mg ondansetron IV.
(Control) Day 2 to 5: 250 mg/day AP P.O. + 8 mg/day dexamethasone P.O.

Table 18. Effect of low dose and modified dose of aprepitant on dexamethasone PK parameters*

Day	Treatment	Geometric mean AUC_{0-24h}	Ratio versus E (90% CI)	Geometric mean Cmax	Ratio versus E (90% CI)
1	F	1943	2.17 (1.95, 2.40)	242	1.35 (1.12, 1.64)
	G	1160	1.29 (1.17,1.44)	152	0.85 (0.70, 1.03)
	H	1300	1.45 (1.31, 1.61)	224	1.25 (1.03, 1.52)
	E	897		179	
5	F	642	2.20 (1.89, 2.55)	88	1.52 (1.21, 1.90)
	G	302	1.03 (0.89, 1.20)	46	0.79 (0.63, 0.99)
	H	355	1.21 (1.05, 1.41)	64	1.10 (0.88, 1.38)
	E	292		58	

*Least squares estimates based on analysis of variance. Estimates for treatment ratios based on both paired and unpaired observation for those treatments.
Treatment E: Day 1: 20 mg dexamethasone P.O. + 32 mg ondansetron IV
Day 2 to 5: 8 mg/day dexamethasone P.O.
Treatment F: Day 1: 125 mg AP P.O. + 20 mg dexamethasone P.O. + 32 mg ondansetron IV
Day 2 to 5: 80 mg/day AP P.O. + 8 mg/day dexamethasone P.O.

Treatment G: Day 1: 125 mg AP P.O. + 12 mg dexamethasone P.O. + 32 mg ondansetron IV
Day 2 to 5: 80 mg/day AP P.O. + 4 mg/day dexamethasone P.O.
Treatment H: Day 1: 40 mg AP P.O. + 20 mg dexamethasone P.O. + 32 mg ondansetron IV
Day 2 to 5: 25 mg/day AP P.O. + 8 mg/day dexamethasone P.O.

With concomitant administration of high dose (375/250 mg) regimen of AP, plasma concentrations of dexamethasone were increased by 2.5 and 4 times on Days 1 and Day 5, respectively (Treatment A vs B).

With low dose AP (125/80 mg) regimen also, dexamethasone AUC was increased by about two fold on Days 1 and 5 (Treatment F vs E).

The PK of dexamethasone on Day 1 and 5 was not significantly affected following administration of a standard antiemetic regimen for CIE along with modified low dose of AP (Treatment H vs E).

The PK (AUC and Cmax) of dexamethasone was not significantly affected following administration of a modified antiemetic regimen along with low dose AP (Treatment G vs E)

Overall, the plasma levels of dexamethasone were increased following administration of standard antiemetic regimen for CIE along with high and low dose AP due to the CYP3A4 inhibition by

AP. It should be noted that that the CYP3A4 inhibition of dexamethasone metabolism by aprepitant was higher at the 375/250 mg regimen compared to 125/80 mg regimen of aprepitant.

Since there was about two fold increase in dexamethasone plasma levels when given with low dose AP (the regimen tested in Phase III), sponsor adopted the half of the usual dose of dexamethasone in standard regimen for the phase III studies.

In addition, the results of this study also showed that the pharmacokinetics of ondansetron (IV) were not affected by concomitant administration of high dose AP (325/250 mg). Based on this, no effect is anticipated at the proposed aprepitant dosage regimen (125/80 mg).

Drug Interaction between aprepitant and diltiazem

This was a double-blind, randomized, placebo-controlled, 3-period study consisting of an initial treatment period (Period 1) followed by 2 crossover treatment periods (Periods 2 and 3), to determine the PK and PD (ECG and vital signs) of IV dosing of L-758298 and of oral dosing of MK-0869 (aprepitant) with and without concurrent diltiazem in 10 mild-to-moderate hypertensive patients.

Prior to the start of Period 1, patients had a 1- to 2- week washout from prior hypertensive medication. There was at least a 1-week washout interval between Periods 1 and 2, and a 3- to 5-day washout between Periods 2 and 3. In Periods 2 and 3, treatments were administered according to a 2-period crossover design. Throughout each study period, a 100-mg IV L-758298 was infused over 15 minutes and a 300-mg oral aprepitant (Tablet formulation B) was administered 30 minutes after a standard breakfast.

Schematic of Study Design

Period 1			
N	Days 1 to 7	Day 8	Days 9 to 13
8	No Medication	L-758298 IV 100 mg	Oral MK-0869 300 mg once daily
2	No Medication	IV Placebo	Oral Placebo

Periods 2 and 3										
	Pre Period 2		Period 2[a]				Period 3[a]			Days Through Poststudy
N	Day -2	Day -1	Days 1 to 7	Day 8	Days 9 to 13	Washout	Days 1 to 7	Day 8	Days 9 to 13	
5	Diltiazem 60 mg t.i.d.	Diltiazem 90 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.
				L-758298 IV 100 mg	MK-0869 oral 300 mg			IV placebo	Oral placebo	
5	Diltiazem 60 mg t.i.d.	Diltiazem 90 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.	Diltiazem 120 mg t.i.d.
				IV placebo	Oral placebo			L-758298 IV 100 mg	MK-0869 oral 300 mg	

[a] Ten patients in a 2-period, crossover design.
Note: t.i.d. = 3 times daily

A) Effect of Diltiazem on aprepitant PK

Table. 19. PK Parameters for Aprepitant Following Administration of L-758298 100-mg IV With (Period 2 or 3) or Without (Period 1) Diltiazem 120-mg Orally 3 Times Daily.

	Geometric Mean or Median						
	L-758298 With Diltiazem (N=6)	L-758298 Without Diltiazem (N=6)	Geometric Mean Ratio (With/Without)	Median Difference (With - Without)	90% Confidence Interval	p-Value
AUC_{0-24hr} (ng•hr/mL)[1]	18843.00	13008.08	1.45		(1.17, 1.79)	0.017
C_{max} (ng/mL)[1]	1729.15	1439.07	1.20		(0.99, 1.46)	0.120
T_{max} (hr)	0.50[2]	0.50[2]		2.75[3]	(0.00, 5.50)[4]	0.500

[1] Geometric mean and geometric-mean ratio.
[2] Median.
[3] Hodges-Lehmann estimate of median difference.
[4] Approximate 90% Tukey confidence interval for median difference.
N = Number of hypertensive patients included in analysis.

Table 20. PK Parameters for Aprepitant (MK-0869) Following Administration ofMK-0869 in Hypertensive Patients (N=6) Following Administration of MK-0869 300-mg Orally Daily for 5 Days Either With (Period 2 or 3) or Without Diltiazem 120-mg Orally 3 Times Daily (Period 1).

	Geometric Mean or Median					
	MK-0869 With Diltiazem (N=6)	MK-0869 Without Diltiazem (N=6)	Geometric Mean Ratio (With/Without)	Median Difference (With - Without)	90% Confidence Interval	p-Value
$AUC_{0\text{-}24\ hr}$ (ng•hr/mL)[†]	106187.50	53139.86	2.00		(1.50, 2.66)	0.005
C_{max} (ng/mL)[†]	5681.02	2898.85	1.96		(1.50, 2.56)	0.004
T_{max} (hr)	6.00[‡]	6.00[‡]		0.00[§]	(-2.00, 9.00)[‖]	>0.999

† Geometric mean and geometric mean ratio.
‡ Median.
§ Hodges-Lehmann estimate of median difference.
‖ Approximate 90% Tukey confidence interval for median difference.
N = Number of hypertensive patients included in analysis.

Coadministration of diltiazem resulted in significant increase in the $AUC_{0\text{-}24}$ of MK-0869 by~45%, and 100% with intravenous administration of L-758298 (prodrug of aprepitant) and oral administration of aprepitant, respectively. There was a 100% increase in Cmax of aprepitant following oral administration aprepitant and diltiazem.

These changes are consistent with moderate CYP3A4 inhibition by diltiazem; no dose adjustment of MK-0869 is needed.

Table 21. PK Parameters for Diltiazem, Desacetyldiltiazem, and N-monodesmethyldiltiazem Following Administration of Diltiazem 120-mg Orally 3 Times Daily With MK-0869 300-mg or Placebo Orally Daily For 5 Days.

	Geometric Mean					
	Diltiazem With MK-0869[†]	Diltiazem Without MK-0869[†]	Geometric Mean Ratio (With/Without)	Median Difference (With - Without)	90% Confidence Interval	p-Value
Diltiazem						
$AUC_{0\text{-}24\ hr}$ (ng_hr/mL)	8496.53	5114.59	1.66		(1.44, 1.92)	<0.001
C_{max} (ng/mL)[‡]	472.49	306.58	1.54		(1.34, 1.77)	0.001
T_{max} (hr)[‡]	4.00[§]	4.00[§]		-0.50[¶]	(-1.00, 0.50)[#]	0.532
Desacetyldiltiazem						
$AUC_{0\text{-}24\ hr}$ (ng_hr/mL)	1084.03	505.89	2.14		(1.80, 2.55)	<0.001
AUC ratio[‖]	0.13	0.10	1.29		(1.08, 1.53)	0.027
C_{max} (ng/mL)[‡]	50.10	22.47	2.23		(1.97, 2.53)	<0.001
T_{max} (hr)[‡]	5.00[§]	5.00[§]		-0.25[¶]	(-1.50, 0.50)[#]	0.556
N-monodesmethyldiltiazem						
$AUC_{0\text{-}24\ hr}$ (ng_hr/mL)	1486.79	1640.40	0.91		(0.76, 1.09)	0.338
AUC ratio[‖]	0.25	0.34	0.74		(0.57, 0.97)	0.073
C_{max} (ng/mL)[‡]	64.85	75.13	0.86		(0.78, 0.96)	0.036
T_{max} (hr)[‡]	4.00[§]	5.00[§]		0.00[¶]	(-1.50, 0.50)[*]	0.929

† N=9; see Table 13 for details.
‡ After the first dose of diltiazem.
§ Median and median difference.
‖ Metabolite-to-parent AUC ratio.
¶ Hodges-Lehmann estimate of median difference.
# Approximate 90% Moses confidence interval for median difference.

- Significant increases in the $AUC_{0\text{-}24}$ of diltiazem by ~66%, and desacetyldiltiazem by ~114%. These changes are consistent with moderate CYP3A4 inhibition by MK-0869. N-monodesmethyldiltiazem is slightly decreased.
- The ratio of the AUC of desacetyldiltiazem/diltiazem is significantly (30%) higher with MK-0869.

- N-monodesmethyldiltiazem, which is formed from diltiazem via a CYP3A4-mediated pathway, the ratio of the AUC ratio (N-monodesmethyldiltiazem/diltiazem) is about 25% lower.

C) PD of Oral MK-0869 (Period 1)

Table 22. PD Parameters Following Administration of Oral MK-0869 (Day 13) or No Medication (Day 7) in Period 1.

	Mean Maximum Change From Baseline		Geometric Mean Ratio (MK-0869/No Med.)	Least Square Mean Difference (MK-0869 - No Med.)	90% CI	p-Value
	MK-0869[†]	No Medication[†]				
PR interval (msec)[‡]	1.06	1.01	1.05		(0.99, 1.10)	0.146
QTc interval (msec)[‡]	1.00	1.02	0.98		(0.94, 1.02)	0.397
Systolic BP (mm Hg)[§]	-13.33	-5.87		-7.46	(-18.06, 3.14)	0.224
Diastolic BP (mm Hg)[§]	-6.46	-5.65		-0.81	(-9.09, 7.46)	0.858
Heart rate (beats/min)[§]	-7.71	-9.19		1.48	(-2.04, 5.00)	0.452

[†] N=8; see Table 15 for details.
[‡] Geometric mean maximum relative change from baseline and geometric mean ratio.
[§] Least square mean maximum moving average change from baseline and least square mean difference.
CI = confidence interval; BP = blood pressure.

- There was a greater drop (-7.46 mm Hg) in mean maximum change in systolic BP from baseline with the administration of oral aprepitant when compared to no medication. The upper limit of the 90% CI (-18.06, -9.09) were higher than the protocol defined criteria of <10 and <8 mm Hg for systolic and diastolic BP, respectively. These changes in BP are small but clinically meaningful.

- No clinically meaningful change in HR or PR interval.

Table 23. PD Parameters Following Administration of Oral Diltiazem With or Without Oral MK-0869 on Day 13 of Periods 2 and 3.

	Mean Maximum Change From Baseline		Geometric Mean Ratio (With/Without)	Least Square Mean Difference (With - Without)	90% CI	p-Value
	Diltiazem With MK-0869[†]	Diltiazem Without MK-0869[†]				
PR interval (msec)[‡]	1.17	1.12	1.04		(1.00, 1.09)	0.102
QTc interval (msec)[‡]	1.00	1.02	0.98		(0.95, 1.01)	0.217
Systolic BP (mm Hg)[§]	-12.66	-18.80		6.14	(-3.11, 15.40)	0.249
Diastolic BP (mm Hg)[§]	-12.36	-12.72		0.36	(-6.17, 6.89)	0.920
Heart rate (beats/min)[§]	-5.53	-3.43		-2.09	(-7.43, 3.25)	0.482

[†] N=9; see Table 14 for details.
[‡] Geometric mean maximum relative change from baseline and geometric mean ratio.
[§] Least square mean maximum moving average change from baseline and least square mean difference.
CI = confidence interval; BP = blood pressure

- Oral MK-0869 given concurrently with diltiazem does not result in a clinically significant PR prolongation, or changes in HR, systolic or diastolic BP beyond those changes induced by diltiazem alone.

Overall, consistent with moderate inhibitory effect of CYP3A, diltiazem increased the plasma exposure of aprepitant by two fold. No dosage adjustment of aprepitant is recommended (see rationale for clinically meaningful difference).

Duration of effect of aprepitant regimen on CYP3A4 and CYP2C9

This was a double-blind, placebo-controlled, randomized, parallel-group, single-center study to evaluate the effect of MK-0869 on CYP3A4 and CYP2C9 activities as measured by co-administration of probe drugs, midazolam and tolbutamide, respectively. The effect of MK-0869 on CYP2C9 was investigated to assess when the CYP2C9 inductive effect of the MK-0869 regimen for CINV resolves. In addition, whether induction of CYP2C9 activity by MK-0869 differs between subjects homozygous for the wild-type CYP2C9 allele and subjects not homozygous for the wild-type CYP2C9 allele was evaluated. Twenty-four healthy non-smoking volunteers were randomized to receive MK-0869 3-day regimen (Treatment group I) or placebo (Treatment group II, n=12) on Days 1 (125 mg), 2 (80 mg), and 3 (80 mg). Subjects in each of these treatment groups also received co-administration of IV midazolam 2-mg dose infused over 2 minutes and oral tolbutamide 500-mg tablet at baseline (Days –7 to –5) and on Days 4, 8, and 15. On each day of dosing, subjects received a standard breakfast that was consumed within 30 minutes prior to dosing with study drugs. At prestudy, a 5-mL whole blood sample was collected from each subject for CYP2C9 genotyping (CYP2C9*1, CYP2C9*2, and CYP2C9*3).

Midazolam (CYP3A4)

Table 24. PK Variables for Midazolam Following an IV 2-mg Dose Given at Baseline (Days –7 to –5) and at Study Days 4, 8, and 15 Following Administration of the MK-0869 Regimen for CINV or Placebo on Days 1 through 3.

Variable	Day	Geometric Mean[†]		Mean Fold Change From Baseline (Day:Baseline)		Ratio of Geometric Mean Fold Change (MK-0869/ Placebo)	90% CI for Ratio of Geometric Mean Fold Change	p-Value
		MK-0869 Group (N=12)	Placebo Group (N=12)	MK-0869 Group (N=12)	Placebo Group (N=12)			
$AUC_{0-\infty}$ (ng•hr/mL)	Baseline	70.2[†]	72.7[†]	-	-			
	4	92.5	76.9	1.32[‡]	1.06[‡]	1.25	(1.09, 1.42)	0.007
	8	57.4	73.7	0.82	1.01	0.81	(0.71, 0.92)	0.008
	15	67.6	72.5	0.96	1.00	0.96	(0.85, 1.10)	0.646
C_{max} (ng/mL)	Baseline	116[†]	134[†]	-	-			
	4	85	124	0.74[‡]	0.92[‡]	0.80	(0.41, 1.54)	0.568
	8	105	112	0.90	0.84	1.08	(0.56, 2.08)	0.840
	15	113	120	0.98	0.90	1.09	(0.57, 2.10)	0.829
Clearance (mL/min)	Baseline	475[†]	458[†]	-	-			
	4	360	434	0.76[‡]	0.95[‡]	0.80	(0.70, 0.92)	0.007
	8	581	452	1.22	0.99	1.24	(1.09, 1.41)	0.008
	15	493	460	1.04	1.00	1.04	(0.91, 1.18)	0.648

Variable	Day	Geometric Mean		Mean Fold Change From Baseline (Day:Baseline)		Ratio of Geometric Mean Fold Change (MK-0869/ Placebo)	90% CI for Ratio of Geometric Mean Fold Change	p-Value
		MK-0869 Group (N=12)	Placebo Group (N=12)	MK-0869 Group (N=12)	Placebo Group (N=12)			
$t_{1/2}$ (hr)	Baseline	4.25[§]	4.15[§]	-	-			
	4	4.15	4.25	0.10[¶]	0.20[¶]	-0.10[†]	(-0.50, 0.50)[#]	-
	8	4.15	3.50	-0.25	-0.43	0.30	(-0.40, 0.80)	-
	15	4.15	3.95	0.05	-0.28	0.30	(-0.20, 0.80)	-

[†] Geometric mean at baseline and Days 4, 8, and 15 not based on ANOVA.
[‡] Back-transformed from least-squares mean from one-way ANOVA performed on natural log-transformed fold-change for Days 4, 8, and 15.
[§] Median at baseline and Days 4, 8, and 15.
[¶] Hodges-Lehmann estimate of median change between Day 4, 8, or 15 and baseline.
[†] Hodges-Lehmann estimate of the shift between the 2 treatment groups changes between Day 4, 8, or 15 and baseline.
[#] Moses' Confidence Interval based on Wilcoxon rank-sum test of Days 4, 8, and 15.
CINV = Chemotherapy-induced nausea and vomiting.
ANOVA = Analysis of variance.
CI = Confidence interval.

Following administration of 3-Day aprepitant regimen (Days 1 – 3), there was 25% increase in IV midazolam AUC on Day 4.
A two to three fold increase in midazolam AUC following its oral administration was noted during the 5-day regimen of aprepitant in a previous drug interaction study (P041). It should be noted that the effect on IV midazolam was not studied during aprepitant regimen. However, based

on the current study, after stopping the regimen, there was only a slight inhibition of CYP3A4 mediated metabolism.

On Day 8, there was a weak inductive effect on CYP3A4 activity as manifested by a 19% decrease in midazolam AUC and 24% increase in midazolam clearance with no significant change in C_{max} or $t_{1/2}$. The inductive effect was weak and was no longer present on Day 15 indicating that the inductive effect resolves at 2 weeks after initiation of the MK-0869 regimen for CINV.

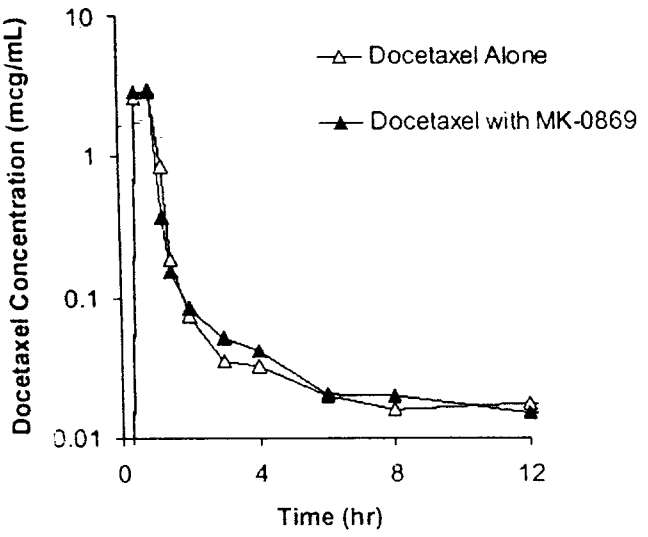
6.2.5.2. Interaction with cancer chemotherapy agents metabolized by CYP3A4.
Drug interaction with docetaxel:
Based on *in vitro* and *in vivo* studies, it has been shown that aprepitant inhibits CYP 3A4 activity. Since aprepitant may be coadministered with chemotherapy drug that are metabolized by CYP3A4, the exposure of these chemotherapy agents may be increased by coadministration of aprepitant leading to increased toxicity. Therefore, it is important to investigate the effect of aprepitant on the pharmacokinetics and safety of chemotherapy drugs metabolized by CYP3A4. A drug interaction study with docetaxel is ongoing. Sponsor stated that among chemotherapy agents, docetaxel appears to be the most sensitive to modulation of CYP3A4 activity and has less cycle-to-cycle variability in its pharmacokinetics than many other chemotherapy agents. As such the sponsor selected docetaxel as representative of other chemotherapy agents metabolized by CYP3A4.

This is an open-label, balanced, 2-period crossover study over 2 consecutive courses of chemotherapy with docetaxel. Male and female patients (target N=20) who are receiving docetaxel as their normal chemotherapy regimen are randomized to the following two treatments in randomized crossover fashion:

Treatment A (docetaxel without aprepitant): On Day 1of treatment A: docetaxel (60 to 100 mg m^2) as a single intravenous (IV) infusion administered over 1 hour.
Treatment B (docetaxel with aprepitant): On Day 1 of treatment B: a single oral dose of 125 mg aprepitant; at 1 hour after aprepitant dosing: docetaxel IV infusion (60 to 100 mg/m^2) administered over 1 hour. On Days 2 and 3: a single oral dose of aprepitant 80 mg/day

Plasma samples for docetaxel were taken over 30 hours following the docetaxel infusion and those for aprepitant were taken over 24 hours following docetaxel infusion and an additional is obtained on Day 4 of Treatment B. There was a minimum of 3 weeks washout between the first day of Period 1 and the first day of period 2.

A preliminary pharmacokinetic and safety data for the first 5 patients enrolled in the study was submitted in the 4 month Safety Update Report.



Concentrations were near or below LOQ for samples collected beyond 12 hours postdosing of docetaxel (at 24 and 30 hours).

Figure 11. **Mean** (N=5) plasma concentration profile of docetaxel (TAXOTERE™) with and without aprepitant.

Table 25. **Individual and mean** $AUC_{0-\infty}$ of docetaxel with and without coadministration of aprepitant.

Patient Allocation Number	Docetaxel $AUC_{0-\infty}$ Without MK-0869 (μg•hr mL)	Docetaxel $AUC_{0-\infty}$ With MK-0869 (μg•hr/mL)	Docetaxel $AUC_{0-\infty}$ Ratio (With MK-0869 Without MK-0869)
0004			
0005			
0014			
0015			
0019			
Arithmetic Mean (SD)	3.11 (0.75)	3.08 (0.89)	-
Geometric Mean*	3.05	2.98	0.98

*The geometric mean AUC excluding Allocation Number 0005 is 3.25 mcg•hr/mL without MK-0869 and 3.15 mcg•hr mL with MK-0869, and the geometric mean ratio (docetaxel with MK-0869/docetaxel without MK-0869) is 0.97.

SD = Standard deviation.

Table 26. Individual and mean Cmax of docetaxel with and without aprepitant.

Patient Allocation Number	Docetaxel C_{max} Without MK-0869 (µg/mL)	Docetaxel C_{max} With MK-0869 (µg/mL)	Docetaxel C_{max} Ratio (With MK-0869/ Without MK-0869)
0004			
0005			
0014			
0015			
0019			
Arithmetic Mean (SD)	3.06 (0.82)	3.10 (1.13)	-
Geometric Mean*	2.98	2.92	0.98

*The geometric mean C_{max} excluding Allocation Number 0005 is 3.15 mcg/mL without MK-0869 and 3.24 mcg/mL with MK-0869, and the geometric mean ratio (docetaxel with MK-0869/docetaxel without MK-0869) is 1.03.

SD = Standard deviation.

A minor dosing anomaly occurred for patient AN 0005 during treatment A (without aprepitant) in which the docetaxel infusion was temporarily halted and restarted after several minutes but was completed in 1 hour and 15 minutes (slightly longer than the specified 1 hour infusion time).

Based on the above data, it appears that docetaxel IV pharmacokinetics is not significantly affected by the coadministration of aprepitant. However, it should noted that docetaxel IV infusion was administered 1 hour after the Day 1 dosing of aprepitant and docetaxel was not administered on Day 2 or Day 3 following administration of aprepitant.

This finding of no affect of aprepitant (proven to be CYP3A4 inhibitor from other studies) on docetaxel plasma concentrations is rather unexpected. The results of this study raise the question as to whether the results of this study can be generalized to other chemotherapy drugs metabolized by CYP3A4.

Effect of ketoconazole and rifampin on aprepitant

This was a single-center, randomized, 2-part, 2-period, open-label, crossover study to evaluate the effect of a CYP3A4 inducer (rifampin) (Part I), and of a CYP3A4 inhibitor (ketoconazole) (Part II) on a single-dose of aprepitant pharmacokinetics. Part I was a 2-period crossover in 12 of the 24 subjects, and the treatments were as follows:

Treatment A = A single dose of aprepitant 375-mg (3 x 125-mg capsules) on Day 1 only
Treatment B = Open-label 600-mg rifampin given once daily on Days 1 to 14 and a single dose of aprepitant 375-mg (3 x 125-mg capsules) on Day 9

Part II was a 2-period crossover in the 12 remaining subjects and the treatments were as follows:

Treatment C = A single dose of aprepitant 125-mg on Day 1 only
Treatment D = Open-label 400-mg ketoconazole given once daily on Days 1 to 10 and a single dose of aprepitant 125-mg on Day 5

All doses were administered in the morning 30 to 60 minutes after a standard light breakfast.

A) Effect of rifampin on aprepitant PK:

Table 27. Geometric means, geometric mean ratios, and 95% CI for oral aprepitant 375 mg (3 x 125 mg) administered alone on day 1 and on day 9 of a 14-day regimen of rifampin 600 mg (2 x 300 mg) daily

Variable	N	MK-0869 With Rifampin (Treatment B)	MK-0869 Without Rifampin (Treatment A)	Geometric Mean Ratio (B/A)	95% Confidence Interval	Mean Square Error†
$AUC_{0-\infty}$ (ng•hr/mL)‡	11	9217	98652	0.09*	(0.07, 0.12)	0.0465
C_{max} (ng/mL)‡	11	1056	2792	0.38*	(0.30, 0.47)	0.0495
$t_{1/2}$§ (hr)	11	4.9	15.1*			
T_{max}¶ (hr)	11	3.0	4.0			

* Significant difference between treatments, $p<0.001$.
† Mean square errors associated with ratio analyses (within subject) are reported on the log scale.
‡ Analyses performed using geometric means.
§ Harmonic mean (back-transformed elimination rate constant treatment group mean based on statistical analysis).
¶ Median.
Treatment A = Three 125-mg MK-0869 capsules on Day 1.
Treatment B = Two 300-mg rifampin capsules once daily on Days 1 to 14 and three 125-mg MK-0869 capsules on Day 9.

The $AUC_{0-\infty}$ of aprepitant administered with rifampin was significantly less (10.7-fold decrease) than the $AUC_{0-\infty}$ of aprepitant administered alone. The C_{max} of aprepitant administered with rifampin was significantly less (2.6-fold decrease) than the C_{max} of aprepitant administered alone. The harmonic mean $t_{1/2}$ difference between aprepitant with rifampin (3.1-fold decrease) and aprepitant alone was statistically significant ($p \leq 0.001$).

B) Effect of ketoconazole on aprepitant PK:

Table 28. Geometric means, geometric mean ratios, and 95% CI for oral aprepitant 125-mg administered alone on day 1 and on day 5 of a 10-day regimen of ketoconazole once daily

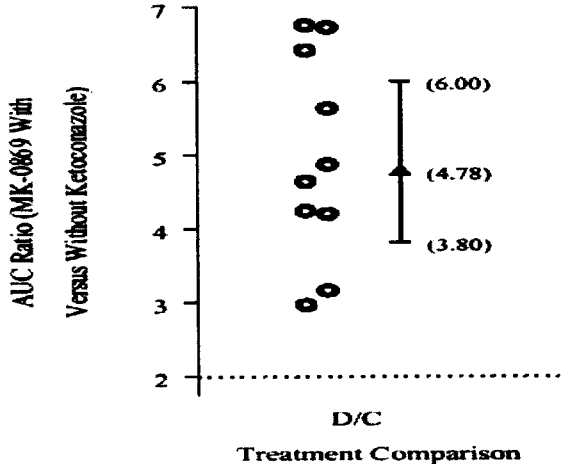
Variable	N	MK-0869 With Ketoconazole (Treatment D)	MK-0869 Without Ketoconazole (Treatment C)	Geometric Mean Ratio D/C	95% Confidence Interval	Mean Square Errors†
$AUC_{0-\infty}$ (ng•hr/mL)‡	10	151684	31747	4.78*	(3.80, 6.00)	0.0490
C_{max} (ng/mL)‡	11	1842	1211	1.52*	(1.28, 1.81)	0.0317
$t_{1/2}$§ (hr)	10	38.7	11.5*			
T_{max}¶ (hr)	11	8.0	8.0			

* Significant difference between treatments, $p<0.001$.
† Mean square errors (within subject) associated with ratio analyses (within subject) are reported on the log scale.
‡ Analyses performed using geometric means.
§ Harmonic mean (back-transformed elimination rate constant treatment group mean based on statistical analysis).
¶ Median.
Treatment C = Three 125-mg MK-0869 capsules on Day 1.
Treatment D = Two 200-mg ketoconazole tablets on Days 1 to 10 and one 125-mg MK-0869 capsule on Day 5.

The $AUC_{0-\infty}$ of aprepitant administered with ketoconazole was significantly greater (4.8-fold increase) than the $AUC_{0-\infty}$ of aprepitant administered alone. The C_{max} of aprepitant administered with ketoconazole was significantly less (1.5-fold increase) than the C_{max} of aprepitant

administered alone. The harmonic mean $t_{1/2}$ difference between aprepitant with ketoconazole (3.4-fold increase) and aprepitant alone was statistically significant ($p \leq 0.001$)

Figure 12. Individual $AUC_{0-\infty}$ ratios (°), geometric mean ratios (▲), and 95% CI (I) for oral aprepitant 125-mg administered alone (day 1) (C) and with ketoconazole (D) on day 5 of a 10-day regimen of ketoconazole 400-mg (2 x 200 mg) once daily.



6.2.5.3. Drug interaction with 5-HT_3 antagonists

For the current indication of prevention of CINV, aprepitant regimen is coadministered with a $5HT_3$ antagonist on Day 1. The efficacy and safety of aprepitant was studied in Phase II and Phase III clinical studies with concomitant dosing of intravenous ondansetron. It is likely that for the treatment of CINV, aprepitant will be coadministered with other 5-HT_3 antagonists such as granisetron and dolasetron. Therefore, it is important to investigate the effect of aprepitant on concomitantly administered 5-HT_3 antagonists.

Effect of aprepitant on Ondansetron pharmacokinetics

The potential for pharmacokinetic interaction between aprepitant and ondansetron was investigated as part of a larger study (P041). For details on study design, refer to section on interaction with midazolam (page 25).

Table 29. Pharmacokinetic parameters of ondansetron Day 1 following 375 mg/250 mg aprepitant with the standard dexamethasone regimen (treatment A) and the standard dexamethasone regimen alone (Treatment B).

Parameter	Treatment A	Treatment B	Ratio A/B (90% CI)	p-Value	MSE[†]
$AUC_{0-\infty}$ (ng-hr/mL)[‡]	1456.5	1268.3	1.15 (1.05, 1.26)	0.019	0.0194
C_{eoi} (ng/mL)[‡,§]	360.8	408.4	0.88 (0.70, 1.12)[‖]	>0.250	0.0900
Half-life (h)[¶]	5.04	4.49			

[†] Mean square error on natural log-scale.
[‡] Least squares geometric mean based on analysis of variance.
[§] Concentration at end of infusion.
[‖] 95% CI.
[¶] Harmonic mean.
CI = Confidence interval.

Based on the data from the above table, there is no clinically meaningful effect of aprepitant on the pharmacokinetics of intravenously administered ondansetron.
No PK interaction study was conducted with orally administered ondansetron. The results of the current study may not be extrapolated to orally administered ondansetron due to the first-pass metabolism after oral administration.

Effect of aprepitant on granisteron:
An open-label, randomized, 2-period crossover study to evaluate the effect of aprepitant on granisetron pharmacokinetics was conducted. In Treatment A, subjects were concomitantly administered single oral doses of 125 mg aprepitant and 2mg granisteron. At 24 and 48 hours later, each subject received a single oral dose of 80 mg aprepitant (i.e., 125mg/80 mg/80 mg regimen of aprepitant, capsule formulation D). In Treatment B, subjects received a single oral dose of 2 mg granisetron alone. All doses were given in the morning, 15 minutes after a standard breakfast.

Table 30. Mean PK parameters of granisteron following administration with and without aprepitant regimen for CINV (N=17).

Granisetron Pharmacokinetic Parameter	Granisetron With Aprepitant (Treatment A)	Granisetron Without Aprepitant (Treatment B)	Ratio (With/ Without)	90% CI	p-Value	MSE (Natural Log Scale)
$AUC_{0-\infty}$ (ng-hr/mL)[†]	101.4	92.2	1.10	(0.96, 1.26)	0.235	0.050
C_{max} (ng/mL)[†]	9.0	9.0	1.00	(0.87, 1.13)	>0.250	0.047
T_{max} (hr)[‡]	3.0	3.0	0[‖]	---	>0.250	---
Half-life (hr)[#]	6.5 (9.6)[‡]	6.9 (9.9)[‡]	-0.5[‖]	---	0.160	---

[†] Geometric mean, based on least squares estimate from analysis of variance.
[‡] Median.
[#] Harmonic mean.
[‖] Hodges-Lehmann estimate of median difference (A minus B).
CI = Confidence interval.
MSE = Mean square error.
"—" = Not applicable.

Based on the above data, it is clear that aprepitant does not significantly affect the pharmacokinetics of orally administered granisteron.

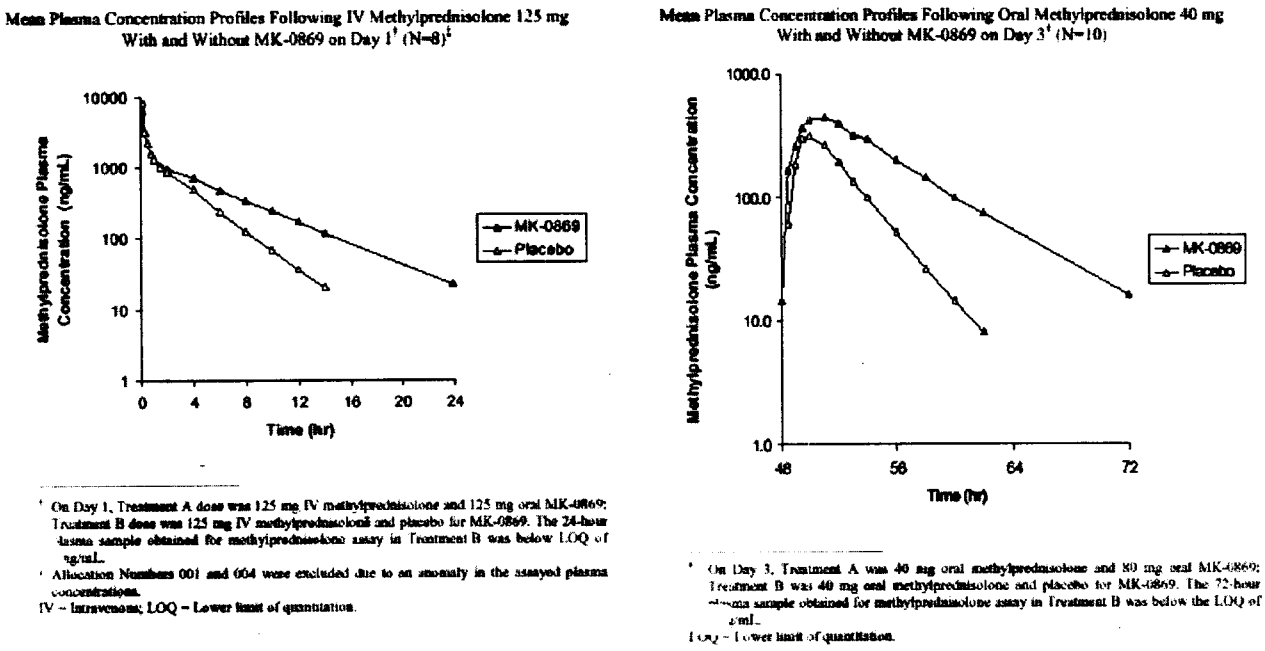
In summary, the regimen of aprepitant for prevention of CINV does not significantly affect the pharmacokinetics of intravenously administered ondansteron and orally administered granisteron. No data of interaction with oral ondansetron and no PK or clinical data with dolasetron. However, dolasetron has multiple metabolic pathways. Carbonyl ester and CYP2D6 being the main

pathways and CYP 3A4 plays only a minor role in its metabolism. Thus, aprepitant may not have pharmacokinetic interaction with dolasetron. However, dolasetron has been reported to have QT prolongation effect. There is no clinical data on coadministration of aprepitant with dolasetron.

Interaction with Methylprednisolone:
Since many clinicians incorporate oral and/or intravenous methylprednisolone in CINV regimen and methylprednisolone is a CYP3A4 substrate, sponsor conducted a drug interaction study to examine the effect of aprepitant on methylprednisolone pharmacokinetics. This was a double-blind, randomized, placebo-controlled, 2-period, crossover study in 8 healthy male (black) and 2 healthy female (black) subjects, who received the following treatments in a randomized order:

> Treatment A: aprepitant daily for 3 days (125 mg on Day 1, 80 mg on Days 2 and 3) with 125 mg methylprednisolone IV 30 minutes after the oral aprepitant dose on Day 1and 40 mg oral methylprednisolone coadministered on Days 2 and 3.
>
> Treatment B: Placebo for Emend on 3 days with 125 mg methylprednisolone IV 30 minutes after the oral placebo dose on Day 1and 40 mg oral methylprednisolone coadministered on Days 2 and 3.

On each day of dosing subjects consumed a standard light breakfast approximately 60 minutes prior to the oral dose of aprepitant/placebo. There was a 12-day minimum washout period between the last dose in Period 1 and the first dose in Period 2. The pharmacokinetic results are summarized below:



[1] On Day 1, Treatment A dose was 125 mg IV methylprednisolone and 125 mg oral MK-0869; Treatment B dose was 125 mg IV methylprednisolone and placebo for MK-0869. The 24-hour plasma sample obtained for methylprednisolone assay in Treatment B was below LOQ of ng/mL.
[2] Allocation Numbers 001 and 004 were excluded due to an anomaly in the assayed plasma concentrations.
IV = Intravenous; LOQ = Lower limit of quantitation.

[1] On Day 3, Treatment A was 40 mg oral methylprednisolone and 80 mg oral MK-0869; Treatment B was 40 mg oral methylprednisolone and placebo for MK-0869. The 72-hour plasma sample obtained for methylprednisolone assay in Treatment B was below the LOQ of ng/mL.
LOQ = Lower limit of quantitation.

Figure 13. Mean plasma concentration profiles of methylprednisolone with and without aprepitant

Table 31. The effect of aprepitant on mean PK parameters of methylprednisolone

Variable	Methylprednisolone with Emend (Treatment A)	Methylprednisolone with placebo (Treatment B)	Geometric Mean Ratio (Treatment A/ Treatment B)	95% Confidence Interval
IV Methylprednisolone on Day 1 (N=8)				
$AUC_{0\text{-}24hr}$ (ng.hr/ml)*	9123	6822	1.34	(1.17, 1.52)
C_{EO} (ng/ml)*	6646	8532	0.78	(0.64, 0.94)
$t_{1/2}$ (hr)#	3.5	2.0	----	
Oral Methylprednisolone on Day 3 (N=10)				
$AUC_{0\text{-}24hr}$ (ng.hr/ml)	3462	1405	2.46	(2.24, 2.72)
Cmax (ng/ml)	499	342	1.46	(1.31, 1.63)
$t_{1/2}$ (hr)#	3.7	2.1	----	----
Tmax (hr)**	2.5	2.0	-----	----

*Geometric mean, #Harmonic mean, **Median

Based on this study, aprepitant inhibits the metabolism of methylprednisolone (CYP3A4 substrate). The inhibitory effect seems to be greater for oral administration (2.5 fold increase in $AUC_{0\text{-}24hr}$) compared IV administration (1.34 fold increase in $AUC_{0\text{-}24hr}$) of methylprednisolone possibly due to the additional inhibition of first pass metabolism. These results are consistent with the CYP3A inhibitory potential of aprepitant (as noted with midazolam, dexamethasone, and diltiazem).

In contrast, ketoconazole, a potent CYP3A4 inhibitor increased the AUC of IV methylprednisolone by 2.4 times (*Glynn et al, Clin Pharmacol Ther 1986;39:654-9*) and itraconazole increased the AUC of orally administered methylprednisolone by 3.9 times (*Varis et al., Clin Pharmacol Ther 1998;64:363-8*).

Drug interaction with erythromycin (assessed by erythromycin breath test):
A single-blind, 2-period, randomized, crossover study was conducted to investigate whether aprepitant at a dose of 300 mg has any effect of on the CYP3A4 system (as measured by erythromycin breath test (EBT) and the oral midazolam hydroxylation and to investigate whether aprepitant has any effect on CYP2D6 as measured by the oral dextromethorphan test. Twelve healthy male subjects received the following two treatments:

Treatment A: single oral doses of three 100 mg placebo tablets for 4 days;
On Day 1, 1 hour following aprepitant/placebo dosing, a single oral dose 2.0 mg midazolam solution coadministered with an intravenous injection of 0.03 mg [^{14}C N-methyl] erythromycin for EBT; On Day 4, 1 hour following aprepitant/placebo dosing, a single oral dose of 30 mg dextromethorphan.

Treatment B: single oral doses of three 100 mg aprepitant tablets (Tablet formulation B) for 18 days; On Day 14, 1 hour following aprepitant/placebo dosing, a single oral dose 2.0 mg midazolam solution coadministered with an intravenous injection of 0.03 mg [^{14}C N-methyl] erythromycin for EBT; On Day 18, 1 hour following aprepitant/placebo dosing, a single oral dose of 30 mg dextromethorphan.

Table 32. Effect of aprepitant on midazolam and erythromycin

	Geometric Mean with aprepitant (Treatment B)	Geometric Mean with placebo (Treatment A)	Ratio of B/A (90% CI)
Midazolam (CYP3A4)			
AUC (ng.hr/ml)	38.3	18.0	2.13 (1.70, 2.66)
Cmax (ng/ml)	15.5	7.7	2.03 (1.58, 2.60)
Erythromycin breath test (EBT)			
% ^{14}C exhaled in 1 hr	2.99	2.75	1.09 (1.00, 1.18)

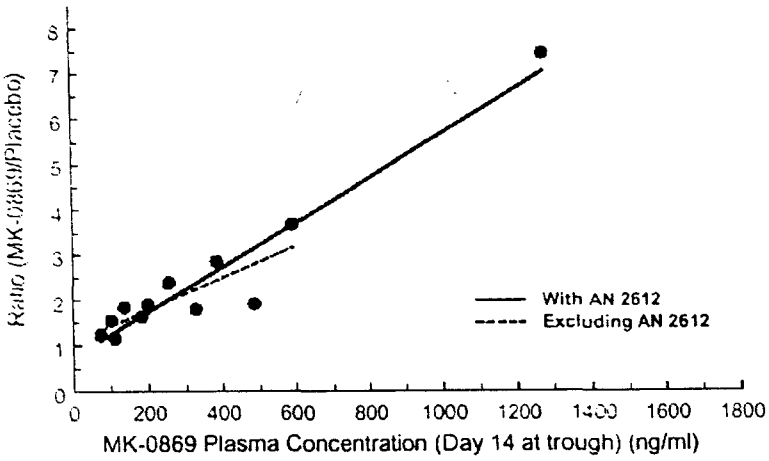


Figure 14. Relationship between midazolam AUC ratio with and without aprepitant and plasma concentrations of aprepitant.

Based on the results shown in the above table, multiple dosing of 300 mg aprepitant tablet formulation B for 14 days increased the AUC and Cmax of orally administered midazolam by about two fold consistent with the CYP3A4 inhibitory effect, which was seen in a previous study with 5 day regimen of aprepitant. In one subject, the AUC of midazolam increased by 7.4 fold and this subject also had the highest AUC of aprepitant. There is a positive linear correlation between the inhibitory effect and the plasma trough concentrations of aprepitant. Subjects with higher concentrations of aprepitant had higher increases in midazolam concentrations.

Midazolam results of this study are inconsistent with the CYP3A4 inductive effect by chronic dosing of aprepitant (14 days) seen in DDI study with ethinyl estradiol and with autoinduction

effect seen in multiple dose pharmacokinetic study. It should be noted that the dose of aprepitant used in this study is equivalent to 70 mg of the to be marketed capsule formulation. This study showed that aprepitant following two weeks of dosing inhibited the CYP3A4 metabolism of oral midazolam.

In the study, ^{14}C-erythromycin at tracer dose serves as a probe of systemic CYP3A4 activity as measured by erythromycin breath test. The amounts of % ^{14}C exhaled in 1 hour following administration of 300 mg tablet formulation (equivalent to 70 mg to be marketed capsule formulation) and placebo were similar. This result indicates that at this dose, aprepitant did not significantly affect the systemic CYP3A4 activity. Sponsor noted that in comparison, ketoconazole at a dose of 400 mg/day for 4 days decreased $^{14}CO_2$ in EBT by 65% and rifampin at 600 mg/day for 4 days increased $^{14}CO_2$ by 120% and glucocorticoids (including dexamethasone) have been reported to increase $^{14}CO_2$ by 55%. However, it should be noted that the erythromycin was administered after 14 days of ~70 mg aprepitant. So the result may be a net effect or balance of inhibition and induction and moreover the dose used (~70 mg) is less than the dose being recommended in the aprepitant regimen. In other words, the results of EBT in this study may not be relevant for the 3-day regimen of aprepitant, but could be applicable for indication with chronic administration.

Overall, this study showed that multiple dose administration of ~70 mg aprepitant for 14 days results in inhibition of first pass CYP3A4 activity (as noted with oral midazolam) and does not affect the systemic CYP3A4 activity (based on no change in EBT).

6.2.5.4. Interactions with other isozymes (CYP2C9, CYP2D6)

Effect of aprepitant on warfarin (CYP2C9 substrate)

Part I:
This was a double-blind, placebo-controlled, randomized, 2-period, parallel-group study to evaluate the effect of the 3-day MK-0869 on steady-state PK of $AUC_{0\text{-}24h}$ for the R(+) and S(-) warfarin and on steady-state PD of warfarin as assessed by daily trough INR. The secondary objective was to evaluate the effect of the 3-day MK-0869 on steady-state PK of C_{max} for the R(+) and S(-) warfarin.

Period 1 was an open-label warfarin "run-in" period where all healthy subjects received 5 mg/day of warfarin for the 1st 4 days followed by individualized dose-titration to reach an INR value of 1.3 to 1.8 based on daily trough INR determinations. Once the INR of each subject was within 1.3-1.8 for 4 consecutive days, the individualized maintenance dose of warfarin was fixed and that dosage was administered each day until a total of 10 to 12 consecutive days had accrued at a constant warfarin dose. Subjects were then randomized to receive either Treatment 1 (MK-0869 + warfarin) or Treatment 2 (placebo + warfarin) during Period 2. Subjects in Treatments 1 and 2 received a single oral dose of MK-0869 125 mg or a matching placebo on Day 1, and a single oral dose of MK-0869 80 mg or a matching placebo on Days 2 and 3. In addition, each subject in Treatments 1 and 2 received the individualized maintenance dose of warfarin concomitantly with the MK-0869 or placebo 15 minutes following a standard light breakfast (~640 calories). Warfarin dosing ceased after Day 7 of Period 2.

Part II:
A separate group of 12 subjects participated in Part II only. Part II was an open-label, 1-period study to evaluate the MK-0869 PK profile during the 3-day MK-0869 regimen for CINV. Subjects received a single oral dose of MK-0869 125-mg on Day 1 and a single oral dose of MK-

0869 80-mg on Days 2 and 3. All doses were administered 15 minutes following completion of a standard light breakfast. Blood samples were taken predose and at specified times up to 96 hours following the last MK-0869 dose.

Table 33. Geometric Mean Warfarin AUC0-24hr (ng•hr/mL) on Days –1 and 3 in Subjects Receiving Warfarin with MK-0869 or with Placebo (Part I, Period 2)

Treatment	AUC_{0-24hr} (ng•hr/mL) Day -1	Day 3	Fold-Change From Baseline (Day 3/Day -1) Fold-Change[†] (90% CI)	p-Value	Ratio of Fold-Change From Baseline (MK-0869/Placebo) Ratio (90% CI)	p-Value	MSE[‡]
S(-) Warfarin							
Warfarin + MK-0869 (n=11)	9523	9370	0.98 (0.95, 1.02)	>0.250	0.96 (0.92, 1.01)	0.151	0.00390
Warfarin + Placebo (n=12)	9789	9993	1.02 (0.99, 1.05)	0.231	–		
R(+) Warfarin							
Warfarin + MK-0869 (n=11)	14020	14547	1.04 (1.01, 1.07)	0.044	1.04 (1.00, 1.08)	0.137	0.00339
Warfarin + Placebo (n=12)	13173	13178	1.00 (0.97, 1.03)	>0.250	–		

† Back-transformed from least-squares mean from one-way ANOVA performed on natural log-transformed fold-change.
‡ Mean square error (MSE) from ANOVA performed on natural log-transformed fold-change.
CI = Confidence interval.
ANOVA – Analysis of variance.

The 90% CI for the ratio (warfarin + MK-0869/warfarin + placebo) for AUC_{0-24hr} of both S(-) and R(+) warfarin were all within the BE criterion of 0.80, 1.25.

Table 34. Summary of S(-) and R(+) Warfarin Trough Plasma Concentrations During and Following the 3-Day MK-0869 Regimen for CINV or Placebo in Period

Summary Statistics for S(-) Warfarin and R(+) Warfarin Trough Plasma Concentrations						
	Ratio of Warfarin Trough Plasma Concentration Fold-Change From Baseline[†] (Warfarin + MK-0869/Warfarin + Placebo)					
	S(-) Warfarin			R(+) Warfarin		
Treatment Day	Ratio	90% CI	p-Value	Ratio	90% CI	p-Value
Day 1	0.99	(0.93, 1.05)	>0.250	1.08	(1.00, 1.16)	0.057
Day 2	1.04	(0.95, 1.13)	>0.250	1.12	(1.00, 1.25)	0.094
Day 3	1.02	(0.94, 1.11)	>0.250	1.18	(1.09, 1.28)	<0.010
Day 4	0.94	(0.86, 1.03)	>0.250	1.08	(0.98, 1.18)	0.191
Day 5	0.81	(0.76, 0.87)	<0.010	1.03	(0.94, 1.12)	>0.250
Day 6	0.76	(0.70, 0.82)	<0.010	1.02	(0.94, 1.11)	>0.250
Day 7	0.67	(0.62, 0.73)	<0.010	0.91	(0.84, 0.98)	0.040
Day 8	0.66	(0.58, 0.74)	<0.010	0.96	(0.88, 1.05)	>0.250

† Day -1.
CI = Confidence interval.

For S(-) warfarin, the ratio of geometric mean fold-change from baseline (warfarin + MK-0869/warfarin + placebo) was significantly less than 1.0 on Days 5 through 8. Mean trough S(-) warfarin plasma concentrations were ~34% lower by Day 8 compared with placebo in the MK-0869 treated group.
For R(+) warfarin, the ratio of geometric mean fold-change from baseline showed small increase on Day 3 and a slight decrease on Day 7, but not on Day 8.

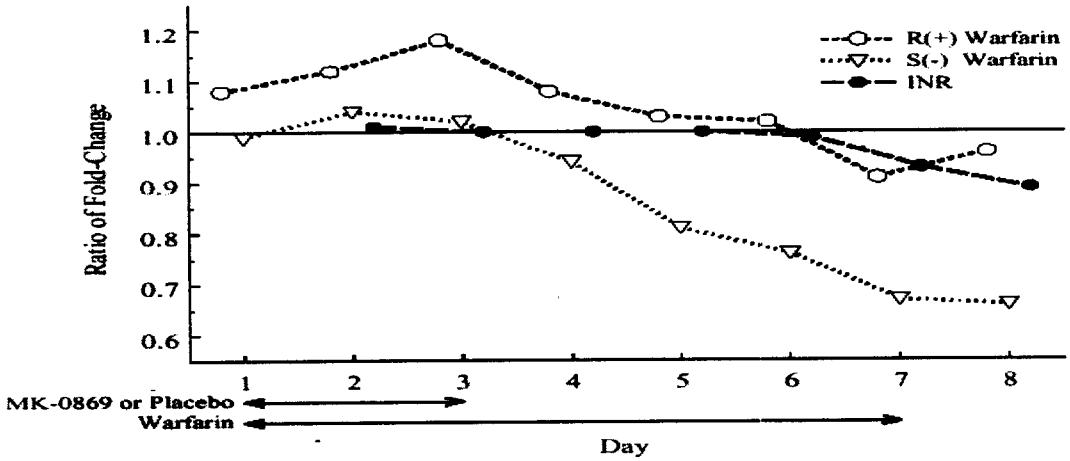
Effect of MK-0869 on Warfarin PD (INR):

Table 35. Summary of INR Fold-Change from Baseline on Days 2 to 8 When Warfarin was Administered with MK-0869 or with Placebo

	INR Fold-Change From Baseline						
	Warfarin + MK-0869		Warfarin + Placebo		Ratio (Warfarin + MK-0869/Warfarin + Placebo)		
Day	Geometric Mean[†]	p-Value	Geometric Mean[†]	p-Value	Ratio (95% CI)	p-Value	Variance[‡]
2	0.99	>0.250	0.98	>0.250	1.01 (0.95, 1.06)	>0.250	0.00406
3	1.01	>0.250	1.01	>0.250	1.00 (0.95, 1.06)	>0.250	0.00397
4	1.00	>0.250	1.00	>0.250	1.00 (0.92, 1.08)	>0.250	0.00803
5	1.00	>0.250	1.00	>0.250	1.00 (0.90, 1.11)	>0.250	0.01371
6	0.96	0.148	0.97	0.243	0.99 (0.92, 1.07)	>0.250	0.00806
7	0.90	<0.010	0.97	0.206	0.93 (0.86, 1.00)	0.050	0.00713
8	0.86	<0.010	0.96	0.150	0.89 (0.82, 0.97)	0.011	0.00934

† Back-transformed from least-squares mean from repeated measures ANOVA performed on natural log-transformed fold-change.
‡ Between-subject variance on natural log-scale for each day, from a repeated measures ANOVA, performed on natural log-transformed fold-change from baseline values.
CI = Confidence interval; ANOVA = Analysis of variance.

Figure 15. Ratios (Warfarin + MK-0869/Warfarin + Placebo) of Geometric Mean INR Fold-Change from Baseline and Geometric Mean R(+) and S(-) Warfarin Trough Concentration Fold-Change from Baseline on Days 2 Through 8 When Warfarin was Administered with MK-0869 or Placebo.



There was no significant change from baseline in INR on Days 2 through 6 in subjects receiving warfarin with MK-086, but a significant decrease was observed on days 7 and 8 (0.90 and 0.86, respectively).

The ratios (warfarin with MK-0869/warfarin with placebo) of geometric mean fold-changes from baseline on Days 7 and 8 were significantly less than 1.0. The Day 7 ratio was 0.93 with 95% CI (0.86, 1.00), and the Day 8 ratio was 0.89 with 95% CI (0.82, 0.97).

After completion of the 3-day MK-0869 regimen for CINV, INR time fold-change from baseline compared with placebo was lower by ~11% on Day 8.

Effect of MK-0869 on Tolbutamide (CYP2C9):

For details regarding study design, please refer to page # 34.

Table 37. PK Variables for Tolbutamide Following an Oral 500-mg Dose Given at Baseline (Days –7 to –5) and at Study Days 4, 8, and 15 Following Administration of the MK-0869 Regimen for CINV or Placebo on Study Days 1 through 3.

		Geometric Mean		Mean Fold Change From Baseline (Day/Baseline)				
Variable	Day	MK-0869 Group (N=12)	Placebo Group (N=12)	MK-0869 Group (N=12)	Placebo Group (N=12)	Ratio of Geometric Mean Fold Change (MK-0869/ Placebo)	90% CI for Ratio of Geometric Mean Fold Change	p-Value
$AUC_{0-\infty}$ (ng•hr/mL)	Baseline	624[†]	750[†]	-	-	-	-	
	4	471	738	0.76[‡]	0.98[‡]	0.77	(0.67, 0.88)	0.002
	8	432	722	0.69	0.96	0.72	(0.63, 0.82)	<0.001
	15	549	778	0.88	1.04	0.85	(0.74, 0.97)	0.050
C_{max} (ng/mL)	Baseline	43.3[†]	47.6[†]	-	-	-	-	
	4	42.2	44.9	0.97[‡]	0.94[‡]	1.03	(0.91, 1.16)	0.666
	8	40.9	48.3	0.94	1.01	0.93	(0.83, 1.05)	0.320
	15	41.3	47.4	0.95	1.00	0.96	(0.85, 1.08)	0.539
$t_{1/2}$ (hr)	Baseline	8.2[§]	10.2[§]	-	-	-	-	
	4	6.0	10.3	-2.63[¶]	-0.58[¶]	-2.05[#]	(-3.50, -0.90)[#]	-
	8	6.0	9.6	-3.10	-1.13	-1.65	(-3.70, -0.40)	-
	15	7.3	9.6	-1.28	-0.08	-0.65	(-2.60, 0.00)	-

		Geometric Mean		Mean Fold Change From Baseline (Day/Baseline)				
Variable	Day	MK-0869 Group (N=12)	Placebo Group (N=12)	MK-0869 Group (N=12)	Placebo Group (N=12)	Ratio of Geometric Mean Fold Change (MK-0869/ Placebo)	90% CI for Ratio of Geometric Mean Fold Change	p-Value
T_{max} (hr)	Baseline	4.0[§]	4.0[§]	-	-			
	4	5.0	6.0	0.5[¶]	1.0[¶]	-1.0[#]	(-3.0, 0.0)[#]	-
	8	4.0	4.0	-0.5	-5.0	0.0	(-1.0, 1.0)	-
	15	4.0	4.0	0.0	0.0	0.0	(-2.0, 1.0)	-

[†] Geometric mean at baseline and on Days 4, 8, and 15 not based on ANOVA.
[‡] Back-transformed from least-squares mean from one-way ANOVA performed on natural log-transformed fold-change on Days 4, 8, and 15.
[§] Median at baseline and on Days 4, 8, and 15.
[¶] Hodges-Lehmann estimate of median change between Day 4, 8, or 15 and baseline.
[#] Hodges-Lehmann estimate of the shift between the 2 treatment groups changes between Day 4, 8, or 15 and baseline.
[#] Moses' Confidence Interval based on Wilcoxon Rank-Sum Test.
CINV = Chemotherapy-induced nausea and vomiting.
CI = Confidence interval.
ANOVA = Analysis of variance.

CYP2C9 Genotype

Table 38. The Ratio of Geometric Mean Fold Change (MK-0869/Placebo) of Tolbutamide $AUC_{0-\infty}$ and C_{max} Excluding Subjects with At Least One CYP2C9*2 or CYP2C9*3 allele.

	Ratio of Geometric Mean Fold Change (MK-0869/Placebo)		Ratio 90% CI		p-value	
Study Day	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$	C_{max}	$AUC_{0-\infty}$	C_{max}
4	0.85	1.06	(0.72, 0.99)	(0.94, 1.20)	0.090	0.413
8	0.76	0.93	(0.64, 0.89)	(0.82, 1.05)	0.008	0.337
15	0.85	0.95	(0.72, 1.00)	(0.83, 1.07)	0.096	0.450

Subgroup Analysis: MK-0869 Treatment Group (n=9), Placebo Group (n=8)

The modest CYP2C9 inductive effect of the MK-0869 regimen for CINV is similar in the entire group (EM and PM) as well as the subgroup (EM only), probably because of small number of subjects for PM group.

Urinary Excretion of Tolbutamide and Metabolites

Table 39. The Mean Urinary Excretion (% of the administered dose excreted over 0 to 48 h) of Tolbutamide on Study Days 4, 8, and 15 for Subjects Receiving MK-0869 (N=12) or Placebo (N=12).

	MK-0869 Treatment Group		Placebo Group		
Study Day	Mean urinary excretion for tolbutamide	GM fold changes from baseline	Mean urinary excretion for tolbutamide	GM fold changes from baseline	Ratio (MK-0869/placebo) of GM for tolbutamide urine recovery fold change from baseline
Baseline	0.116%		0.133%		
4	0.095%	0.81	0.140%	1.03	0.78
8	0.095%	0.81	0.151%	1.08	0.76
15	0.116%	0.96	0.148%	1.09	0.88

GM: geometric mean

Table 40. The Mean Urinary Excretion (% of administered dose excreted over 0 to 48 h) of Hydroxytolbutamide and Carboxytolbutamide on Days 4, 8, and 15 for Subjects Receiving MK-0869 (N=12) or Placebo (N=12).

	MK-0869 Treatment Group		Placebo Group		
Study Day	Mean urinary excretion for the metabolites	GM fold changes from baseline	Mean urinary excretion for the metabolites	GM fold changes from baseline	Ratio (MK-0869/placebo) of GM for the metabolites urine recovery fold change from baseline
Baseline	83.9%		86.9%		
4	88.5%	1.05	83.6%	0.97	1.07
8	86.5%	1.03	85.3%	1.00	1.04
15	80.0%	0.95	81.9%	0.96	1.00

GM: geometric mean

The MK-0869 regimen for CINV produced modest induction of CYP2C9 activity on Days 4 and 8. The MK-0869 regimen for CINV resulted in decreases in the plasma $AUC_{0-\infty}$ of tolbutamide of 23% and 28% on Days 4 and 8, respectively, and were accompanied by increases in the urinary excretion of tolbutamide metabolites. On Day 15, the tolbutamide $AUC_{0-\infty}$ was slightly (15%) lower compared with placebo but urinary excretion of tolbutamide metabolites had returned to baseline.

Effect of aprepitant on digoxin (P-gp substrate)

This was a double-blind, placebo-controlled, randomized, 2-period, crossover study to investigate the influence of oral MK-0869 on the plasma concentration profile of immunoreactive digoxin and urinary immunoreactive digoxin excretion after multiple-dose oral digoxin administration in 12 healthy subjects. There were two 13-day treatment periods (A and B) and a 14-day washout period between treatment periods. During Treatments A and B, 12 subjects received daily oral doses of digoxin 0.25 mg on Days 1 through 13. In Treatment A, subjects received a single oral

dose of MK-0869 125 mg on Day 7 and single oral doses of MK-0869 80 mg/day on Days 8 through 11. Subjects received single oral daily doses of MK-0869 placebo capsule on Days 7 through 11 of Treatment B. All doses of MK-0869/placebo and/or digoxin were administered 15 minutes after a light breakfast.

Table 41. Comparison of PK Parameters and Urinary Excretion of Digoxin on Days 7 and 11 Following Co-administration with MK-0869 and Administration alone (n=11)

Immunoreactive Digoxin Pharmacokinetic Parameter	Study Day	N	Geometric Mean		Geometric Mean Ratio	p-Value[3]	Mean Square Error[4]
			Digoxin With MK-0869[1]	Digoxin With Placebo[2]	MK-0869/Placebo (90% CI)		
$AUC_{0\text{-}24\,hr}$ (ng-hr/mL)	7	11	10.5	10.6	0.99 (0.91, 1.09)	0.91	0.0121
	11	11	9.9	10.6	0.93 (0.83, 1.05)	0.32	0.0223
$U_{ae,0\text{-}24\,hr}$ (mg)	7	11	91.5	100.1	0.91 (0.80, 1.04)	0.24	0.0282
	11	11	96.8	97.1	1.00 (0.91, 1.09)	0.94	0.0128
C_{max} (ng/mL)	7	11	1.25	1.20	1.04 (0.89, 1.23)	0.64	0.0434
	11	11	1.17	1.15	1.02 (0.92, 1.14)	0.73	0.0187

On both Days 7 and 11, the 90% CI of digoxin $AUC_{0\text{-}24\,hr}$ were within the BE criterion of 0.80 to 1.25.
The 90% CI of digoxin 24-hour urinary excretion for both Days 7 and 11 were within the pre-specified bounds of 0.70 to 1.43.
Administration of MK-0869 after a standard light breakfast as a single daily oral dose of 125-mg followed by 4 consecutive single oral daily doses of 80-mg did not affect the PK or urinary excretion of digoxin.

Effect on Dextromethorphan (CYP2D6):
The effect of AP on CYP2D6 mediated metabolism was studied by measuring the urinary excretion ratio of dextromethorphan/dextrorphan (DM/DT) with and without coadministration of AP.

Table 42: Summary of dextromethorphan, dextrorphan and creatinine urinary excretion data following administration of 30 mg dextromethorphan with and without AP.

Parameter	Estimates		Geometric Mean Ratio or Mean Difference with Confidence Interval			
	With 300 mg MK-0869	With Placebo	300 mg MK-0869 vs. Placebo	p-Value	Confidence Interval	Within-subject MSE[1]
DM/DT [2]	0.0080	0.0038	2.09	<0.001	(1.69, 2.59)	0.144
DT/CR [3]	0.0067	0.0121	0.55	<0.001	(0.42, 0.73)	0.093
DM Excretion [4]	0.0490	0.0367	0.0123	0.074	(-0.0015, 0.0260)	0.0002
DT Excretion [5]	5.48	9.02	-3.54	<0.001	(-5.24, -1.85)	3.46
CR Excretion [5]	814.84	755.83	59.02	0.353	(-75.83, 193.86)	21976.24

[1] MSE for ratio analyses are reported on the natural log scale.
[2] Normal theory analysis on natural log-transformed data: Geometric Means; Geometric Mean Ratio; Two-sided 80% CI (of which the upper bound is equivalent to a one-sided 90% CI).
[3] DM values below the limit of quantitation were estimated to be 25 ng/mL (13 of 24 data points).
[4] Normal theory analysis on natural log-transformed data: Geometric Means; Geometric Mean Ratio; 95% CI.
[5] Normal theory analysis on original data: Least Squares Means; Least Squares Mean Difference; 95% CI.

Where:
DM = Dextromethorphan (ng/mL).
DT = Dextrorphan (ng/mL).
CR = Creatinine (ng/mL).
DM Excretion (mg) = DM x Urine volume.
DT Excretion (mg) = DT x Urine volume .
CR Excretion (mg) = CR x Urine volume.

Data Source: [2.1.1]

AP seemed to have increased the urinary ratio of DM/DT by about two fold suggesting inhibition of CYP2D6 metabolism. However, the interpretation of these results is somewhat limited because the assay used was not sensitive enough to measure urinary DM concentrations in most samples even though a standard 30 mg dose of DM was administered. Urinary DM values below LOQ were estimated as ~ ng/ml. On the average, the urinary DM excretion was increased by 30% and was below LOQ for 7 subjects. Therefore, the results of this study should be interpreted with caution.

To put these results in perspective, in vitro, the K_I for AP inhibition of CYP2D6 was >100 μM in comparison to known 2D6 inhibitor, quinidine with K_I value < 0.1 μM. Quinidine has been shown to increase the DM/DT ratio by about 24-fold, with an associated 20-fold increase in urinary DM excretion. Thus, according to the sponsor, the two fold increase in DM/DT noted in this study is not likely to be reflective of a clinically significant effect on CYP2D6 system. It should be noted that another drug interaction study with paroxetine did not show any inhibitory effect on CYP2D6.

Drug interaction with paroxetine (CYP2D6 substrate):

AP is under development for the treatment of depression. A double-blind, randomized, placebo-controlled, three-period crossover study was conducted in order to investigate the effects of concomitant administration of AP and the selective serotonin uptake inhibitor, paroxetine. There was at least a 14 day washout between treatment periods and the allocation to treatment sequence was stratified by gender. All doses were given in the morning, 20 minutes after a standard, light breakfast. All subjects were phenotyped for CYP2D6 activity using a single 60 mg dose dextromethorphan (urinary ratio of dextromethorphan to dextrorphan >0.3 = poor metabolizer) prior to dosing in Period 1. Subjects were also genotyped for the presence of 2D6*1 or 2D6*4 alleles, with the latter coding for an inactive protein (poor metabolizer genotype = *4/ *4). Only one subject (AN 4708) was clearly a poor metabolizer (Urinary DM/DT ratio = 4.36 and *4 / *4 genotype).

A total of 20 healthy volunteers (11 males and 9 females) entered the study and 18 subjects completed all treatment periods. Two subjects discontinued prior to the completion of the study. (one due to relocation and another subject due to adverse events, myocolonic jerks, disorientation and lethargy on paroxetine treatment).

Table 43. Geometric mean pharmacokinetic parameters of paroxetine with and without AP on Day 14 (N=18)

Paroxetine Pharmacokinetic Parameter	Geometric Mean Paroxetine With MK-0869	Geometric Mean Paroxetine With MK-0869 Placebo	Geometric Mean Ratio (90 % CI) Paroxetine With MK-0869/ Paroxetine With MK-0869 Placebo	p-Value	Within-Subject MSE[1]
$AUC_{0\text{-}24\ hr}$ (ng•hr/mL)	497.69	670.33	0.74 (0.62, 0.89)	0.012	0.098
C_{max} (ng/mL)	34.43	43.51	0.79 (0.68, 0.93)	0.020	0.073
T_{max} (hr)[2]	4.5 (5.0)	4.6 (4.0)	—	—	—

[1] Natural log scale.
[2] Arithmetic mean (median).

Concomitant administration of AP resulted in lower (about 20% for Cmax to 25% for AUC) paroxetine plasma concentrations. One subject (AN 4704) showed notably reduced plasma concentrations of paroxetine, particularly when given with AP. Sponsor stated that this subjects might have skipped that the dose of paroxetine on Day 14. After excluding this subject in the statistical analysis, the geometric mean AUC ratio (with and without AP) was a little higher (0.80 compared to 0.74, with new CI being 0.70, 0.92).
On subject, who was a poor metabolizer based on phenotyping and genotyping, did not differ much from the rest of subjects in terms of plasma concentration of paroxetine. In fact, his levels were lower than the mean for each treatment group.

Table 44. Geometric mean pharmacokinetic parameters of AP with and without concomitant administration of paroxetine.

MK-0869 Pharmacokinetic Parameters	Geometric Mean MK-0869 With Paroxetine	Geometric Mean MK-0869 With Paroxetine Placebo	Geometric Mean Ratio (90 % CI) MK-0869 With Paroxetine/ MK-0869 With Paroxetine Placebo	p-Value	Within-Subject MSE[1]
$AUC_{0\text{-}24\ hr}$ (ng•hr/mL)	20364	27973	0.73 (0.61, 0.87)	0.008	0.095
C_{max} (ng/mL)	1672	2156	0.78 (0.66, 0.92)	0.018	0.083
T_{max} (hr)[2]	4.7 (4.0)	4.9 (4.0)	—	—	—

[1] Natural log scale.
[2] Arithmetic mean (median).

The mean plasma concentrations of AP were lower when coadministered with paroxetine 20 mg daily for 14 days. The mean AUC was reduced by about 25% while the Cmax was lower by about 20% with coadministration of paroxetine. However, it should be noted that there was a large inter-subject variability in the plasma levels of AP, especially when it was given alone.
It should be noted that this study was conducted with tablet formulation C of AP and the dose used in this study (200 mg at steady state) is approximately equal to 150 mg of the to be marketed capsule formulation.

Overall, this study showed that there was a pharmacokinetic interaction between AP and paroxetine with $AUC_{0\text{-}24h}$ and Cmax of each drug reduced by 20 to 25% in the presence of the other. Based on the serial trough concentrations of either drug, this interaction was apparent by approximately one week of treatment. These results are consistent with the induction of the

metabolism of both drugs. The metabolism of AP by CYP3A4 is likely an inducible process. But, induction of CYP3A4 by paroxetine has not been reported in the literature. On the other hand, induction of paroxetine by CYP2D6 is also not reported. Thus the mechanism of pharmacokinetic interaction noted in this study is not clear. In any event, the magnitude of interaction seems to be small and the clinical relevance of this interaction needs to be evaluated for depression indication. However, for the current indication of CINV, this interaction is not relevant.

Interaction with oral contraceptives:

Since AP has been studied for other indications such as depression where chronic administration of AP in women who are on oral contraceptives (OC) may be recommended, sponsor has conducted two separate drug interaction studies with OC. Both studies examined the effects of AP on a monophasic OC, ORTHO-NOVUM™ 1/35, containing 35 µg ethinyl estradiol (EE) and 1 mg norethindrone (NET) using a double blind, randomized, two-period crossover design. The two periods consisted of two consecutive OC cycles with AP/placebo administered from Day 1 through 14 of each cycle. In protocol 022, Part 1 examined the effect of morning dosing of AP on the PK/PD of OC while Part 2 examined the effects of evening administration of AP (with 12 hr gap between OC and AP dosing). In this study 300 mg Formulation C was used and this is approximately comparable to a 180 mg dose of the market formulation. The other study (protocol 032) used the same design as Part 1 of protocol 022 except for a dose of 100 mg market formulation (Formulation D).

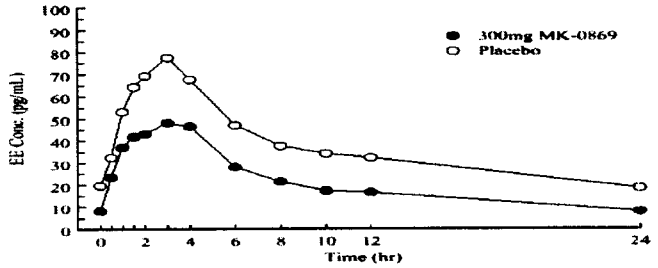


Figure 16. Median serum concentrations of ethinyl estradiol (N=15) on Day 14 following administration of OC in the morning with 300 mg aprepitant or placebo in the morning or evening for 14 days.

Table 45. Pharmacokinetic parameters of ethinyl estradiol and norethindrone following administration OC (Ortho-Novum 1/35) with aprepitant or placebo for 14 days.

Parameter	Treatment	Protocol 022 (N=15)* Median	Ratio (99% CI)**	p-Value	Protocol 032 (n=6) GM#	GMR## (90% CI)	p-Value
Ethinyl Estradiol							
AUC_{tau} (pg·hr/mL)	OC + Aprepitant	500.0	0.59 (0.53, 0.64)	<0.010	486.6	0.57 (0.51, 0.64)	NA
	OC + Placebo	907.1			855.0		
C_{max} (pg/mL)	OC + Aprepitant	39.2	0.64 (0.56, 0.72)	<0.010	54.1	0.80 (0.64, 1.01)	NA
	OC + Placebo	59.6			67.4		
Norethindrone							
AUC_{tau} (ng·hr/mL)	OC + Aprepitant	137.8	0.91 (0.83, 0.97)	0.014	145.3	0.92 (0.83, 1.02)	NA
	OC + Placebo	165.5			157.7		
C_{max} (ng/mL)	OC + Aprepitant	15.4	0.81 (0.72, 0.91)	<0.010	14.2	1.07 (0.89, 1.30)	NA
	OC + Placebo	18.9			13.2		

* n=6 subjects only in Part 1, n=3 subjects only in Part II, and n=5 subjects in both parts.
** Back-transformation of Hodges-Lehmann estimation applied to natural log-transformed values.
*** Distribution-free confidence interval for the true ratio, back-transformed from Hodges-Lehmann estimation applied to natural log-transformed values.
# Geometric mean based on least squares mean estimate on natural log scale.
Geometric mean ratio (OC with aprepitant/OC with placebo) corresponding to difference (aprepitant minus placebo) in least squares treatment means on natural log scale.
CI = Confidence interval.
OC = Oral contraceptive.
NA = Not reported because of small sample size.

The EE and NET pharmacokinetic data from Part I and Part II of protocol 022 (morning versus evening dosing of AP) were similar and hence the results were pooled. As shown in the figure, the median serum concentrations of EE on Day 14 were significantly reduced during AP administration. The median Day 14 $AUC_{0\text{-}24h}$ of EE was reduced by about 40 to 43% in both studies and the Cmax was reduced by 20 to 35%. However, the effect of NET seems to be small with 8 to 9% reduction in $AUC_{0\text{-}24h}$.
The pharmacokinetic interaction noted in these studies suggests induction of EE metabolism. Even though the metabolites of EE including EE sulfate, EE-glucuronide and 2-methoxy-EE were measured in a subset of subjects from these studies, these data did not provide explanation into the mechanism of the interaction.

A significant effect of AP on pharmacodynamics of OC in terms of abnormal bleeding profile was observed on both studies. All of the women in both studies who received AP experienced scant or absent withdrawal bleeding at the end of the OC cycles (Day 22 through 28). This effect is likely due to lower plasma concentration of EE in presence of AP.

Overall, it can be concluded that chronic administration of AP (two weeks) with OC results in reduced plasma levels of EE by about 40% along with abnormal bleeding profiles. These results are relevant to the chronic administration of AP. However, since the aprepitant regimen is not studied with OC, sponsor is proposing to use backup contraceptive method when aprepitant is to be coadministered with OC.

6.3. BIOPHARMACEUTICS

What are the differences between clinical formulation and to be marketed formulation? Is the to be marketed formulation bioequivalent to clinical trials formulation?

The to be marketed formulation (Formulation D) was used in Phase IIb and all Phase III Studies for CINV and in the key clinical pharmacology studies. The to be marketed formulation is a hard gelatin capsule containing nanoparticles —— with improved bioavailability and reduced food effect. Tablet formulations (Formulation A, B, and C) with larger particle size were used in early phase I studies and in some drug interactions studies and have low bioavailability and high food effect due to poor solubility (see Formulation section).

Since the final market formulation is used in Phase II b and all Phase III studies and the key clinical pharmacology studies, no bioequivalence study is necessary. For studies where a tablet formulation was used, the calculated approximate equivalent dose of the nanoparticle capsule (based on plasma AUC) is provided to facilitate comparison to the market formulation.

6.3.1. Effect of Food

Is there any effect of food on the pharmacokinetics of aprepitant? How is it addressed in the label?

The capsule formulation did not have a significant food effect. Therefore, aprepitant can be administered without regard to food intake. The earlier tablet formulations with particle size were shown to have significant food effect (a 3 to 4 –fold increase in bioavailability with food, due to poor solubility of the drug).

Absolute bioavailability and Food effect:

Effect of food on the to-be-marketed formulation was investigated in study 049, that had multiple objectives including absolute bioavailability, intravenous pharmacokinetics, and dose-proportionality of 80 mg and 125 mg oral doses.

This is a 2-part study in healthy young male and female subjects. Subjects participated in only 1 of the 2 parts of the study. A total of 32 subjects were planned to be enrolled (8 subjects for Part 1 of the study and 24 subjects for Part 2 of the study).

Part 1 of the study was a single-period, double-blind, placebo-controlled to investigate the safety and tolerability of the MK-0869 2-mg IV dose. Allocation to study treatment was stratified by sex to assure that 6 subjects (3 males and 3 females) received a 2-mg dose of MK-0869 IV infusion over 4 hours (Treatment A), and 2 subjects (1 male and 1 female) received a matching placebo IV infusion (Treatment B).

Part 2 of the study was an open-labeled, randomized, 4-period crossover study to evaluate the absolute BA and to determine the effect of food on the MK-0869 125-mg and 80-mg capsules. Twenty-four healthy young male (n=12) and female subjects (n=12) were enrolled. The 4 treatment periods of Part 2 were each separated by at least 7 days. Treatments C, D, E, and F oral doses were administered with 8 ounces of water.

Treatment C: Simultaneous administration of MK-0869 125-mg PO and an IV infusion of a 2-mg dose of stable isotope labeled MK-0869 in the fasted state
Treatment D: Simultaneous administration of MK-0869 80-mg PO and an IV infusion of a 2-mg dose of stable isotope labeled MK-0869 in the fasted state
Treatment E: MK-0869 125-mg PO 15 minutes following a standard breakfast
Treatment F: MK-0869 80-mg PO 15 minutes following a standard breakfast

During Part 2 of the study, the stable isotope-labeled MK-0869 IV dosing in Treatments C and D was terminated due to clinical adverse experiences of flushing, cyanosis, dyspnea, and chest discomfort in 2 female subjects within 2 minutes of the start of the stable isotope labeled MK-0869 IV dosing. Fourteen of the 24 planned subjects completed Treatments C, D, E, and F, including the IV dosing component of Treatments C and D. For the 4 remaining subjects, Treatments C and D were modified to eliminate the IV component and received only MK-0869

The composition of a standard breakfast consisted of the following: 2 scrambled eggs, 2 slices of toast with 2 pats of butter, 2 strips of bacon, 113 grams of hash brown potatoes, and 236 mL of whole milk. This is similar to FDA recommended high-fat, high-calorie breakfast.

Based on the tolerability and clinical activity of MK-0869, a difference of < 2-fold between fasted and fed $AUC_{0-\infty}$ was considered clinically insignificant and would support that these doses of formulation D capsule could be administered without regard to food intake [(geometric mean AUC0-∞ ratio of fed/fasted is within the interval (0.5, 2.0)].

In Part 1 of the study, the dosing of study drug was followed by a 72-hour PK assessment. In Part 2 of the study, the dosing of study drug within each treatment period was followed by a 96-hour PK assessment.

PK of IV MK-0869

Table 46. PK Parameters of MK-0869 Administration Following IV 2-mg Doses of Unlabeled and Stable Isotope Labeled MK-0869 in the Fasted State.

MK-0869	Treatment A[†] (Part 1)		Treatment C[‡] (Part 2)		Treatment D[#] (Part 2)	
Pharmacokinetic Parameters	N	Geometric Mean[!] (95% CI)	N	Geometric Mean[!] (95% CI)	N	Geometric Mean[!] (95% CI)
$AUC_{0-\infty}$ (ng•hr/mL)	6	394.8 (266.9, 583.9)	20	560.3 (481.4, 652.0)	18	461.9 (387.4, 550.7)
C_{max} (ng/mL)	6	38.0 (27.2, 53.1)	20	34.2 (28.3, 41.3)	18	31.3 (26.5, 37.1)
T_{max} (hr)	6	4.0	20	4.0	18	4.0
Half-life (hr)	6	13.2 (7.4, 19.0)	19	9.4 (8.6, 10.2)	18	9.8 (8.8, 10.7)
Cl_p (mL/min)	6	84.4 (57.1, 124.8)	20	59.5 (51.1, 69.3)	18	72.2 (60.5, 86.1)
Vd_{ss} (L)	6	66.1 (44.5, 98.2)	20	62.0 (54.3, 70.8)	18	69.9 (61.0, 80.1)

-Median for T_{max}, and harmonic mean and jack-knife 95% CI for half-life

Absolute BA of MK-0869 125-mg and 80-mg in the Fasted State

Table 47. Absolute BA (Oral Dose-Standardized $AUC_{0-\infty}$/IV Dose-Standardized $AUC_{0-\infty}$) of MK-0869 125-mg and 80-mg in the Fasted State by Sex and Combined.

	Genders Combined		Female		Male		
MK-0869 Oral Dose	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	N	Geometric Mean (95% CI)	Ratio (Female/Male) of Geometric Means (90% CI)
125 mg[$]	20	0.59 (0.53, 0.65)	9	0.52 (0.45, 0.62)	11	0.65 (0.57, 0.75)	0.80 (0.67, 0.96)
80 mg[$]	18	0.67 (0.62, 0.73)	7	0.65 (0.57, 0.74)	11	0.70 (0.63, 0.77)	0.93 (0.81, 1.06)

- The mean absolute BA of MK-0869 doses in the fasted state are 0.59 for the 125-mg dose, and 0.67 for the 80-mg dose

Effect of Food on Relative BA of MK-0869 125-mg and 80-mg

Table 48. Relative BA (Fed/Fasted) for MK-0869 125-mg and 80-mg Capsules

MK-0869 Pharmacokinetic Parameter	MK-0869 Dose†	Gender	Fed N‡	Fed Geometric Mean‡	Fasted N‡	Fasted Geometric Mean‡	Geometric Mean Ratio (Fed/Fasted)¶ (90% CI)
$AUC_{0-\infty}$ (ng•hr/mL)	125 mg	Combined	21	25897.9	21	21633.2	1.20 (1.10, 1.30)
		Female	10	25413.9	10	20580.0	1.23 (1.08, 1.41)
		Male	11	26460.8	11	22850.7	1.16 (1.05, 1.28)
	80 mg	Combined	20	13195.2	21	12135.5	1.09 (1.00, 1.18)
		Female	9	12602.3	10	11076.3	1.14 (0.99, 1.31)
		Male	11	13816.0	11	13257.7	1.04 (0.94, 1.15)
C_{max} (ng/mL)	125 mg	Combined	21	1254.7	21	1003.3	1.25 (1.11, 1.41)
		Female	10	1369.5	10	1137.4	1.20 (0.98, 1.49)
		Male	11	1163.3	11	893.9	1.30 (1.14, 1.49)
	80 mg	Combined	20	749.1	21	657.9	1.14 (1.01, 1.28)
		Female	9	759.3	10	663.6	1.14 (0.92, 1.42)
		Male	11	728.3	11	643.1	1.13 (0.99, 1.30)
T_{max} (hr)	125 mg	Combined	21	4.0	21	4.0	1.0 (1.0, 2.0)
		Female	10	4.5	10	4.0	2.0 (0.0, 3.0)
		Male	11	4.0	11	4.0	1.0 (-2.0, 3.0)
	80 mg	Combined	20	4.0	21	4.0	1.0 (-0.5, 1.5)
		Female	9	5.0	10	4.0	1.0 (-1.0, 2.0)
		Male	11	4.0	11	3.0	1.0 (-1.0, 2.0)
Half-Life (hr)	125 mg	Combined	21	10.3	21	11.1	
		Female	10	9.6	10	11.4	
		Male	11	11.1	11	10.8	
	80 mg	Combined	20	10.5	21	11.6	
		Female	9	9.3	10	10.3	
		Male	11	11.9	11	13.2	

-Median for T_{max} and harmonic mean for half-life
-For T_{max}, Hodges-Lehmann point estimate of median difference (fed minus fasted) and exact 95% CI

A 20% food effect for the MK-0869 125-mg capsule and a 9% food effect for the MK-0869 80-mg capsule as assessed by increase in plasma MK-0869 $AUC_{0-\infty}$ when dosed with food. There is no clinically important effect of food on the PK of MK-0869 125-mg and 80-mg capsules and thus these may be dosed without regard to food intake.

Dose Proportionality of MK-0869 125-mg and 80-mg Doses

Table 49. Dose Comparison (125 mg/80 mg) for Dose-Standardized MK-0869 $AUC_{0-\infty}$ and C_{max} of MK-0869 125-mg and 80-mg in the Fasted and Fed States

MK-0869 Pharmacokinetic Parameter	State	125-mg Capsule† N‡	125-mg Capsule† Geometric Mean	80-mg Capsule† N‡	80-mg Capsule† Geometric Mean	Geometric Mean Ratio (125 mg/80 mg) (90% CI)
Dose-Standardized $AUC_{0-\infty}$ (ng•hr/mL per mg)	Fasted	21	173.1	21	151.7	1.14 (1.05, 1.24)
	Fed	20	207.2	21	164.9	1.26 (1.16, 1.36)
Dose-Standardized C_{max} (ng/mL per mg)	Fasted	21	8.0	21	8.2	0.98 (0.87, 1.10)
	Fed	20	10.0	21	9.4	1.07 (0.95, 1.21)

- The plasma $AUC_{0-\infty}$ of MK-0869 increased in a slightly greater than dose-proportional fashion (i.e., 14% and 26% greater than if kinetics were linear following fasted and fed administration, respectively) at the 125-mg dose compared with the 80-mg dose.

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secret and/or

confidential

commercial

information

Therefore, sponsor should be requested to provide data regarding the effect of surfactant (at various concentrations) and different speeds of rotation at each surfactant concentration with capsule formulation.
Meanwhile, Q= —% at 20 minutes is acceptable as an interim specification until the sponsor provides justification for the use of with the capsule formulation.

6.3.3. Analytical Methods

Are the analytical methods used to quantify the active moieties adequately validated?

High-performance liquid chromatography (HPLC) method with tandem mass spectrometric detection was used to measure plasma concentrations of aprepitant and the prodrug, L-758298 following liquid-liquid or solid phase extraction for the isolation of aprepitant and L-758298, respectively. Two (2) standard concentration ranges of 1 to 500 ng/ml and 10 to 5000 ng/ml were used for quantification of both compounds. The limits of quantitation (LOQ) for aprepitant and L-758298 were 1 and 10 ng/ml, respectively. More sensitive assays with a linear range of 0.1 to 25 ng/ml of plasma for both aprepitant and stable isotope labeled [$^{13}C_2{}^{15}N_3$]-aprepitant were used in study that assessed the absolute bioavailability.

The limit of quantitation for measuring urine concentrations of aprepitant and L-758298 was 10 ng/ml with a linear range of 10 to 5000 ng/ml.

Aprepitant and L-758298 in plasma samples were stable during storage at -20^0C for at least 10 months

In general the assay methods including the accuracy and precision (under 10%) were adequate to characterize the pharmacokinetics of aprepitant in humans.

12 pages redacted from this section of the approval package consisted of draft labeling

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-549	Brand Name	EMEND
OCPB Division (I, II, III)	II	Generic Name	Aprepitant
Medical Division	180	Drug Class	NK1 receptor antagonist
OCPB Reviewer	Venkat Jarugula Myong-Jin Kim	Indication(s)	Prevention of acute and delayed nausea and vomiting associated with chemotherapy
OCPB Team Leader	Suresh Doddapaneni	Dosage Form	Capsule
		Dosing Regimen	Once daily- 125 mg on day 1 & 80 mg on days 2 & 3
Date of Submission	9/27/02	Route of Administration	Oral
Estimated Due Date of OCPB Review	3/13/03	Sponsor	Merck & Co.
PDUFA Due Date	3/27/02	Priority Classification	Priority
Division Due Date	3/13/03		

I. Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	A. X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:	X			
Isozyme characterization:				
Blood plasma ratio:	X			
Plasma protein binding:	X			
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	X			
multiple dose:	X			
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X			
In-vivo effects of primary drug:	X			
In-vitro:	X			
Subpopulation studies -				
ethnicity:	X			Composite analysis
gender:	X			Composite analysis
pediatrics:				
geriatrics:	X			
renal impairment:	X			Severe and ESRD patients
hepatic impairment:	X			Mild and moderate patients
PD:				
Phase 2:	X			
Phase 3:				
PK PD:				

Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. **Biopharmaceutics**				
Absolute bioavailability:	X			
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X			
Dissolution:	X			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. **Other CPB Studies**				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies				

Filability and QBR comments

	"X" if yes	B. Comments
Application filable ?	X	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	(1) Is there exposure response relationship? (2) Is the metabolism adequately described? (3) Is the pharmacokinetics in special populations adequately described?	
Other comments or information not included above	A total of 35 studies were submitted in the Human Pharmacokinetics and Bioavailability section of the NDA. Out these, 24 studies were conducted with the early tablet formulations (A, B, and C). The rest of the studies were conducted with the to-be-marketed capsule formulation D. All the studies conducted with capsule formulation and some of the relevant studies with early tablet formulations B and C were reviewed.	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Myong-Jin Kim
3/12/03 09:08:14 PM
PHARMACOLOGIST

Venkateswar Jarugula
3/13/03 12:05:49 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
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