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1. Introduction and Organization of the Document

Nausea and vomiting have been reported by patients, nurses, and physicians as the most distressing side effects of chemotherapy, and the disruptive effects of these symptoms on patients' daily lives have been well documented [1; 2]. In light of the need for continued routine use of emetogenic chemotherapy, effective prevention of chemotherapy-induced nausea and vomiting (CINV) is a central goal for physicians administering cancer chemotherapy.

Aprepitant (EMEND™[1], MK-0869) is a highly selective substance P neurokinin 1 (NK_1) receptor antagonist that has been developed for the prevention of acute and delayed chemotherapy-induced nausea and vomiting. Substance P and the NK_1-receptors that mediate its activity are present in the brain stem centers that elicit the emetic reflex. In preclinical models of emesis, brain-penetrant NK_1-receptor antagonists such as aprepitant, given alone, prevent both acute and delayed cisplatin-induced emesis as well as emesis evoked by a wide spectrum of peripherally and centrally acting emetogens. The overall objective of the clinical development plan for aprepitant is to evaluate the efficacy and safety of aprepitant, which is given concomitantly with an antiemetic regimen for CINV that includes a corticosteroid and a 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor antagonist.

This document focuses primarily on the research development program for aprepitant in the prevention of CINV in oncology patients receiving highly emetogenic chemotherapy (HEC). The study results described in this document confirm that a 3-day regimen of aprepitant is effective in the prevention of CINV in patients who receive highly emetogenic chemotherapy. The efficacy of aprepitant is due to its mechanism of action as a potent and highly selective nonpeptide NK_1-receptor antagonist with a duration of action that provides antiemetic coverage throughout the acute and delayed phases of CINV.

The study results described in this background document confirm that aprepitant demonstrates notable safety and efficacy in the prevention of acute and delayed CINV in patients receiving highly emetogenic therapy for the treatment of cancer. The overall safety and tolerability of aprepitant are favorable even in seriously ill patients with oncology diagnoses.

This document is organized as follows:

Section 1 Introduction and Organization of the Document.

Section 2 Synopsis.

[1] EMEND is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

Section 3 Nonclinical Development of NK_1-Receptor Antagonists for CINV. This section discusses the role of substance P and its blockade in chemotherapy-induced emesis. This section includes a description of NK_1-receptor activity in vitro and the aprepitant pharmacological profile in vivo.

Section 4 Nonclinical Pharmacokinetics and Drug Metabolism. Nonclinical pharmacokinetics and metabolism of aprepitant are outlined.

Section 5 Nonclinical Toxicology. This section details the findings of safety assessment toxicology studies.

Section 6 Human Pharmacokinetics, Bioavailability, and Pharmacodynamics. A description of formulation development and pharmacokinetic findings is presented.

Section 7 Clinical Efficacy. This section discusses the aprepitant CINV clinical development program and documents the efficacy data in patients in Phase II and Phase III trials. The rationale for efficacy endpoints, dose selection, and the CINV prevention regimen are discussed.

Section 8 Clinical Safety. This section covers the overall exposure and safety profile for aprepitant with a focus on the CINV Phase III studies.

Section 9 Benefits Versus Risks Relationship.

Section 10 Conclusions.

Section 11 List of References.

2. Synopsis

2.1 Introduction

CINV are common and well-recognized complications of cancer chemotherapy that impair patients' ability to carry out normal daily activities. Patients continue to rank CINV among the most distressing and disruptive side effects of chemotherapy. At present, for the prevention of symptoms associated with highly emetogenic chemotherapy (HEC), for which cisplatin is the reference, the most effective available therapy is the combined use of a 5-HT_3–receptor antagonist and a corticosteroid. The principal shortcoming of current therapy is suboptimal efficacy in the prevention of delayed phase CINV, though control of acute symptoms is also inadequate in many patients. Presently, there are no available antiemetic agents indicated for preventing the delayed symptoms that occur on subsequent days following chemotherapy administration. Additionally, current therapy often does not consistently maintain its efficacy over repeat cycles of chemotherapy.

This document focuses on the development program for aprepitant, which, when added to a current antiemetic regimen, prevents CINV in oncology patients receiving highly emetogenic chemotherapy. Aprepitant is first in a new class of medication that acts via a mechanism of action distinct from any antiemetic introduced into medical practice thus far. The study results described in this document confirm that aprepitant is effective in the prevention of CINV in patients who receive highly emetogenic chemotherapy. The efficacy of aprepitant is due to its mechanism of action as a potent and highly selective nonpeptide NK_1-receptor antagonist that provides antiemetic coverage throughout the acute and delayed phases of CINV.

Based on the findings summarized within this document, the proposed indication for aprepitant (EMEND™) is as follows:

> *EMEND, 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.*

In accordance with the clinical trials described herein, the recommended dosage information for this indication is as follows:

> *EMEND is given for 3 days as part of a regimen that includes a corticosteroid and 5-HT_3 receptor antagonist. The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3.*

The purpose of this synopsis is to highlight the key information and conclusions from the aprepitant development program that are summarized in this document.

2.2 Nonclinical Development of NK_1-Receptor Antagonists for CINV (Section 3)

The neurobiology of emetic signaling pathways has recently become better understood in an attempt to provide relief from the emesis and nausea associated with cancer chemotherapy. Emesis is a complex, highly organized process; and although there is no exact anatomical correlate of the vomiting center, emesis can be conceptualized as being centrally orchestrated by the interactions of several nuclei within the brain stem (medulla). These nuclei include the nucleus tractus solitarius (NTS), area postrema, and the dorsal motor nucleus of the vagus (DMNV), that together are referred to as the dorsal vagal complex. The dorsal vagal complex integrates the incoming emetic signals and coordinates the various sensory, somatic, and autonomic physiological responses that are associated with nausea and vomiting.

Therapy with cytotoxic agents such as cisplatin is thought to cause emesis through the release of emetogenic substances such as serotonin (5-HT) from enterochromaffin cells in the gut. Serotonin stimulates afferent nerve fibers by activating excitatory 5-HT_3 receptors on peripheral abdominal vagal nerve terminals. This action, in turn, initiates emetic signaling input to central vomiting centers. The 5-HT_3–receptor antagonists have been shown to decrease the initial acute phase of emesis that occurs in the 24-hour period following administration of anti-neoplastic drugs such as cisplatin by blocking the peripheral stimulation of receptors on abdominal vagal afferents. However, 5-HT_3–receptor antagonists are poorly effective against the delayed phase of emesis (>24 hours). To enhance the antiemetic activity of the 5-HT_3–receptor antagonists in clinical practice, attempts to vary the dosing intervals, routes of administration, as well as including dexamethasone in the antiemetic regimen, have met with limited success.

Acute antiemetic effects were demonstrated across a range of species: ferrets, dogs, pigs, and the house musk shrew. Of note, the preclinical discovery of and the elucidation of the mechanisms of action for the 5-HT_3–receptor antagonists in the treatment of CINV have been extensively derived from the study of emesis models in ferrets. This species has a profile of emetic responses similar to humans, and, most importantly, shows both acute and delayed emetic responses to cisplatin. Ferrets express NK_1 receptors with human-type pharmacology, facilitating evaluation of the clinical potential of aprepitant by using preclinical assays that were designed to mimic the acute and delayed time course of events that occur during CINV in humans.

Overall, the preclinical science indicated that substance P is likely to play a key role in CINV. Autoradiographic mapping studies showed that NK_1 receptors are present in high concentrations in brain stem nuclei of the dorsal vagal complex, which are critical for the regulation of the vomiting reflex to central and peripheral emetogenic stimuli. Preclinical studies have shown that NK_1-receptor antagonists prevent emesis by acting centrally within the NTS. In contrast, 5-HT_3–receptor antagonists have been shown to act mainly in the periphery on abdominal vagal afferent nerve terminals. The complementary profiles of these 2 classes of antiemetic agents, acting at distinct pharmacological and

anatomic sites within the emesis pathways, suggested that there could be additivity in their antiemetic effects. Ferret emesis models also indicated that NK_1-receptor antagonists were highly effective against the delayed phase of emesis caused by cisplatin.

Since the therapy available for the treatment of delayed chemotherapy-induced nausea and vomiting in humans is presently inadequate, this finding suggested that NK_1-receptor antagonists could be a novel opportunity to improve current clinical antiemetic standards of care by providing more complete and durable control of CINV.

Aprepitant administrated orally or intravenously (as its phosphoryl prodrug) was effective against acute cisplatin-induced emesis in ferret models. Aprepitant also blocked emesis produced by the centrally acting emetogens, morphine and apomorphine. Antiemetic effects were enhanced when suboptimal doses of both aprepitant and established antiemetic agents (ondansetron and dexamethasone) were coadministrated. The inhibition of delayed emesis by aprepitant was found to be independent of its effect in the acute phase.

Preclinical studies showed that aprepitant is a highly selective, competitive, brain-penetrant compound with a duration of central action suitable for once-daily dosing in clinical studies. Positron emission tomography (PET) studies confirmed the brain-penetrant nature of aprepitant and its access to central NK_1-receptor sites that mediate its antiemetic effects.

Preclinical studies in ferret emesis models indicate that:

(1) aprepitant, compared with 5-HT_3–receptor antagonists, has a broader spectrum of activity against acute and delayed cisplatin-induced emesis;

(2) additivity can be obtained with a concomitant use of aprepitant with a 5-HT_3–receptor antagonist or a corticosteroid to maximize protective benefits against CINV; and

(3) once-daily oral doses of aprepitant provide effective protection against acute and delayed cisplatin-induced emesis in ferrets.

2.3 Nonclinical Pharmacokinetics and Drug Metabolism (Section 4)

Three (3) animal species (CD-1 mouse, Sprague-Dawley rat, and Beagle dog) were selected for toxicological evaluation of aprepitant. In this background document, pharmacokinetic data collected from these species and from ferret studies as well as aprepitant metabolism characteristics compiled from mouse, rat, and dog studies are charted. The parent compound is the major drug component responsible for antiemetic activity. All major metabolites identified have lower human NK_1-receptor binding affinities relative to aprepitant.

Aprepitant has been observed to induce its own metabolism in rats, which resulted in both parent compound and metabolites being monitored in Safety Assessment studies (see Section 5). Although aprepitant is an inhibitor of P-glycoprotein (P-gp) in vitro, this

property was shown not to be clinically significant (see Section 6). Aprepitant is a moderate inhibitor of cytochrome P-450 (CYP3A4) in vitro, which prompted further examination of this property in the clinical setting.

Nonclinical pharmacokinetic and drug metabolism studies support the observations that:

(1) aprepitant has good oral bioavailability (16 to 46%) and a half-life of 3 to 10 hours in mice, rats, dogs, and ferrets;

(2) aprepitant is brain penetrant in ferrets and is the major drug-related component detected in the brain responsible for its antiemetic activity;

(3) metabolites of aprepitant observed in humans are also observed in nonclinical species, hence validating the use of the animal models selected for the Safety Assessment studies of aprepitant;

(4) metabolites have reduced affinity at human NK_1-receptor sites;

(5) aprepitant is a moderate inhibitor of CYP3A4 in vitro; and

(6) aprepitant is a very weak, not clinically relevant inhibitor of CYPs 1A2, 2C9, 2C19, 2C6, and 2E1 in vitro.

2.4 Nonclinical Toxicology (Section 5)

The potential toxicity of aprepitant was extensively evaluated in a series of single-dose studies in rats and mice, repeated-dose oral toxicity studies in rats and dogs, oral development and reproductive toxicity studies in rats and rabbits, and in vitro and in vivo genetic toxicity studies. The hepatic enzyme induction potential of aprepitant was also evaluated in rats and mice. Although regulatory guidance states that carcinogenicity studies are not required for indications such as CINV in which the nature of treatment is limited, short, and episodic, carcinogenicity studies in rats and mice were conducted with aprepitant to support other potential therapeutic indications.

To define the toxicity profile of aprepitant, dose levels for in vivo studies were selected to maximize systemic exposure to aprepitant, to establish no-effect levels for the treatment-related findings, and to determine margins of safety relative to the proposed clinical dose based on a comparison of systemic exposure.

The resultant safety assessment profile for aprepitant is summarized as follows:

(1) There are no contraindications for the therapeutic use of aprepitant in humans based on the data from nonclinical toxicology studies.

(2) Aprepitant has a low order of acute toxicity; in dogs, the no-effect level was ~6-fold in excess of the exposure at the intended clinical dose.

(3) Aprepitant has no effects on female or male fertility in rats; aprepitant is not teratogenic nor does it cause embryo-fetal toxicity in rats or rabbits at doses in which transplacental exposure occurs.

(4) Aprepitant is neither genotoxic nor mutagenic; and in the carcinogenicity study in mice, there was no evidence of an increased incidence of any tumor type. A species-specific hepatocellular tumor-promotion phenomenon was observed in rats, which is known to occur with other marketed drugs that induce hepatic cytochrome P-450 enzymes and has not been shown to occur in humans.

Based on the results of the nonclinical toxicology studies, there are no contraindications to the therapeutic use of aprepitant

2.5 Human Pharmacokinetics, Bioavailability, and Pharmacodynamics (Section 6)

Pharmacokinetics

The market composition of aprepitant is a capsule containing the drug in a nanoparticle formulation. This formulation, which has superior bioavailability and reduced food effect compared with formulations used earlier in the program, was used in Phase IIb and Phase III efficacy trials for CINV and in key Clinical Pharmacology studies. Aprepitant is well absorbed under fasting conditions from the nanoparticle capsule and may be dosed without regard to food intake. The time of maximum plasma concentration is ~4 hours and half-life is ~9 to 12 hours. The half-life of aprepitant is suitable to allow once-daily oral dosing. The pharmacokinetics of aprepitant are not significantly affected by race, gender, body weight, or age. Dose adjustment of aprepitant is not necessary in patients with renal insufficiency or mild to moderate hepatic insufficiency. Aprepitant is >95% bound to plasma protein in healthy humans.

PET studies in humans indicate that aprepitant crosses the blood-brain barrier. Nearly complete (>95%) NK_1-receptor blockade is required to obtain maximum antiemetic efficacy of aprepitant in humans.

Aprepitant undergoes extensive metabolism primarily via oxidation by CYP3A4. Up to 12 metabolites of aprepitant have been identified in plasma. All of these metabolites were also detected in rats and dogs. The resultant metabolites have been identified as having substantially lower receptor affinity, lower plasma concentrations relative to aprepitant, and poorer brain penetrance than aprepitant. Even after multiple doses of aprepitant to healthy humans, concentrations of metabolites with the greatest affinities for the human NK_1 receptor were 8- to 25-fold lower than aprepitant and are unlikely to contribute significantly to central nervous system (CNS) NK_1-antagonistic effects in humans.

In vitro experiments indicate that the major plasma metabolites in humans were all derived from stepwise oxidative metabolism of aprepitant, largely by CYP3A4 with minor contributions from CYP1A2 and CYP2C19. The importance of CYP3A4 in the metabolism of aprepitant in vivo was confirmed in clinical drug interaction studies (described in Sections 6.4.1 and 6.4.2).

Drug Interactions

The potential for drug interactions with aprepitant has been well characterized in Clinical Pharmacology studies. In vitro data indicated that aprepitant is a substrate as well as an inhibitor of CYP3A4 activity. Because aprepitant is a substrate of CYP3A4, the effects on aprepitant pharmacokinetics of drugs that inhibit (ketoconazole, diltiazem) or induce (rifampin, dexamethasone) CYP3A4 were delineated. Several clinical studies were also conducted to evaluate thoroughly the effect of aprepitant on CYP3A4 activity in humans. These included the effects of aprepitant on the CYP3A4 substrates midazolam, diltiazem, dexamethasone, methylprednisolone, ondansetron, and granisetron. In addition, an ongoing study is examining the potential effect of aprepitant on docetaxel, a chemotherapeutic agent that is also a CYP3A4 substrate.

During the course of the clinical program, data indicated that aprepitant also appeared to induce the activities of CYP2C9 and CYP3A4. Therefore, these effects were defined in clinical interaction studies of aprepitant with warfarin and tolbutamide (CYP2C9 substrates) and midazolam (CYP3A4 substrate). Since aprepitant may be coadministered with drugs (such as certain chemotherapeutic agents) that are substrates of the P-gp transporter, an interaction study of aprepitant with digoxin (a P-gp substrate) was conducted. Studies were also conducted to evaluate the effects of aprepitant on CYP2D6 substrates (dextromethorphan, paroxetine) and on an oral contraceptive.

The drug interaction profile of aprepitant can be summarized as follows:

(1) The pharmacokinetics of aprepitant are affected by drugs that modulate CYP3A4 activity.

    Coadministration of aprepitant with strong CYP3A4 inhibitors (e.g., ketoconazole) may result in clinically important elevations of plasma concentrations of aprepitant and should be approached cautiously. Concomitant administration of aprepitant with moderate CYP3A4 inhibitors (e.g., diltiazem) does not result in clinically meaningful changes in plasma concentrations of aprepitant.

    Coadministration of aprepitant and rifampin results in clinically important decreases in plasma concentrations of aprepitant that may result in decreased efficacy of aprepitant.

(2) The aprepitant regimen for CINV (125 mg on Day 1, 80 mg on Days 2 and 3) during dosing produces at most moderate inhibition of CYP3A4 activity (comparable to verapamil, diltiazem, and less than grapefruit juice) that results in increases (~2 fold) in the plasma concentrations of coadministered synthetic corticosteroids (dexamethasone and methylprednisolone). The CYP3A4 inhibitory effect of aprepitant is less for intravenously administered drugs (such as chemotherapy agents). Following completion of dosing, there is a small, transient inductive effect on CYP3A4.

(3) The aprepitant regimen for CINV produces slight induction of CYP2C9 activity that is nearly resolved within 12 days after completion of the regimen. Drugs with narrow therapeutic indices that are know to be metabolized by CYP2C9 (e.g., warfarin, phenytoin) may have transiently lower plasma concentrations when coadministered with aprepitant.

(4) Aprepitant had no clinically meaningful interactions with diltiazem, ondansetron, granisetron, digoxin, dextromethorphan, or paroxetine. The efficacy of oral contraceptives with 2 weeks of administration of aprepitant may be reduced. Although a 3-day regimen of aprepitant given concomitantly with oral contraceptives has not been studied, alternative or back-up methods of contraception should be used.

(5) Aprepitant does not affect P-glycoprotein activity (either inhibition or induction) as assessed using digoxin as a P-glycoprotein substrate. The aprepitant regimen for CINV is unlikely to result in clinically significant interactions with drugs that are P-glycoprotein substrates (e.g., some chemotherapeutic agents).

(6) Interaction studies with sensitive intravenously administered CYP3A4 substrates (erythromycin, methylprednisolone), a chemotherapeutic agent metabolized by CYP3A4 (docetaxel), and a P-glycoprotein substrate (digoxin) suggest that, overall, there is a low potential for aprepitant to produce clinically meaningful effects on the pharmacokinetics of intravenously administered chemotherapeutic agents.

(7) Aprepitant does not inhibit CYP2D6 activity in vivo.

2.6 Clinical Efficacy (Section 7)

The objective of the aprepitant clinical development program was to develop an oral NK_1-receptor antagonist 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.

Seven (7) clinical studies were completed in patients receiving highly emetogenic chemotherapy with cisplatin-based chemotherapy to assess the efficacy of aprepitant and L-758298, the intravenously administered prodrug for aprepitant, in preventing CINV. Two (2) Phase III studies of identical design, Protocol 052 and Protocol 054, evaluated the nanoparticle capsule formulation of aprepitant, which confirmed the efficacy and tolerability of a 3-day aprepitant regimen: 125 mg on Day 1 followed by 80 mg on Days 2 and 3.

All studies were double-blind, multicenter, randomized trials, in cisplatin-naïve male and female patients, with the primary evaluation coming from the initial cycle of chemotherapy with high-dose cisplatin. Phase IIb and Phase III studies also employed multiple-cycle extensions.

Clinical Efficacy Endpoints

In all Phase IIb/Phase III studies, efficacy was assessed using an endpoint that incorporated the use of rescue therapy: Complete Response (defined as no emetic episodes and no use of rescue medication to treat established nausea or emesis). Patients were defined as failures according to this endpoint if they either had emesis, irrespective of rescue therapy, or if they took rescue for established nausea. Therefore, this endpoint reflects both the prevention of emesis as well as the control of nausea in patients without emesis.

Complete response was also the primary endpoint in 2 of the 4 Phase IIa clinical studies in the program: Protocol 004 and Protocol 007. For the other 2 Phase IIa studies, no emesis was the primary endpoint. For consistency and to facilitate comparisons between studies, the data for complete response are highlighted in this document for all 7 studies in the program.

Efficacy parameters related to the control of nausea and emesis were assessed by patients recording their experiences after chemotherapy in self-report diaries in all studies. The endpoints assessed throughout the program were based on 3 components: emetic episodes, use of rescue therapy, and nausea ratings.

Use of Acute, Delayed, and Overall Phases for Efficacy Evaluations

When the clinical syndrome of CINV was initially described, the focus was on symptoms that occurred on the same day that chemotherapy was administered, and studies typically assessed symptoms for just 24 hours following chemotherapy. With the subsequent introduction of effective therapy for acute symptoms, it became apparent that many patients also had CINV symptoms that occurred more than 24 hours following chemotherapy. Accordingly, there was increasing interest in the prevention of delayed symptoms, which are typically defined as those that occur for up to ~4 to 6 days after the 24-hour acute phase. The overall phase includes both the acute and delayed phases (specifically, the 5 days after the administration of chemotherapy in the aprepitant Phase IIb/III program).

Aprepitant Dose Regimen

The Phase II program confirmed a dosing regimen of 125 mg on Day 1 followed by 80 mg on Days 2 and 3 as most desirable for further testing. Pharmacokinetic data demonstrated that this regimen provided consistent daily plasma exposure during the 3 days of dosing.

CINV Phase III Program

Two (2) Phase III studies were conducted following the same study design: Protocol 052 was conducted in the United States, Canada, South Africa, Europe, Australia, and Taiwan, and Protocol 054 was conducted solely in Latin America. Both were multicenter, randomized, double-blind, parallel-group, controlled trials with in-house blinding to assess the safety and efficacy of aprepitant in the prevention of CINV in

cisplatin-naïve patients who were treated with chemotherapy regimens that included cisplatin ≥70 mg/m^2 administered on a single day. A total of 1099 adult patients were enrolled in the 2 Phase III studies: 530 patients in Protocol 052 and 569 patients in Protocol 054. Efficacy analyses were performed on modified intention-to-treat populations. These populations included all enrolled patients who received cisplatin, took at least 1 dose of study drug, and had at least 1 posttreatment assessment: 521 patients in Protocol 052 and 525 patients in Protocol 054.

Summary of Aprepitant Efficacy in CINV Phase III Studies

The efficacy results from the Phase III program can be summarized as follows:

(1) Administration of aprepitant with Standard Therapy (ondansetron plus dexamethasone on Day 1, followed by dexamethasone on Days 2 to 4) provided protection against CINV throughout the acute and delayed phases.

(2) The aprepitant regimen was more effective than Standard Therapy in the prevention of CINV as assessed by the primary endpoint of complete response. Further, efficacy was superior to Standard Therapy when the acute phase (0 to 24 hours) and the delayed phase (25 to 120 hours) were analyzed separately.

(3) The aprepitant regimen was also significantly more effective than Standard Therapy using the component endpoints of the complete response endpoint (i.e., no emesis and no rescue) in all phases in both Phase III studies.

(4) Consistent with their symptom relief, patients who received the aprepitant regimen reported less impact of CINV on their daily lives compared with those who received Standard Therapy, as assessed by a validated nausea and vomiting specific patient questionnaire (The Functional Living Index—Emesis [FLIE]).

(5) Efficacy was maintained and was considerably better than Standard Therapy over 6 cycles of chemotherapy.

(6) The efficacy of the aprepitant regimen was independent of age, race, or gender.

2.7 Clinical Safety (Section 8)

The clinical development program revealed that aprepitant is generally well tolerated at doses that are clinically effective for the treatment of CINV.

Evaluation of safety in this document focuses on the Phase III CINV studies. These 2 pivotal studies utilized the aprepitant regimen proposed for market. In these studies, specific attention was paid to potential interaction between aprepitant and concomitant chemotherapy metabolized by CYP3A4 since aprepitant, as dosed for CINV, is a weak to moderate CYP3A4 inhibitor, similar to diltiazem.

In addition, data from studies in indications other than CINV are also included in this document in the Clinical Safety section, as these studies tested a broad range of

aprepitant doses administered for extended periods of time to patients/subjects not exposed to the side effects of chemotherapy.

Overall, 3342 adult patients/subjects were exposed to aprepitant, or L-758298 (the intravenous [IV] prodrug of aprepitant). Of these, 1459 adult cancer patients received aprepitant or L-758298 for prevention of CINV.

Key safety findings from the Phase I Clinical Pharmacology and the Phase II and Phase III CINV studies are located in Section 8 and are summarized as follows:

Key Safety Findings in Clinical Pharmacology Studies

Overall, a total of 808 subjects (generally healthy adults) were enrolled in Phase I Clinical Pharmacology studies in which they received aprepitant, L-758298, other drugs, or placebo. Subjects received single daily doses of aprepitant for up to 29 days.

Aprepitant was generally well tolerated. The incidences of clinical and laboratory adverse experiences were generally similar among all active treatment groups. Certain clinical adverse experiences (asthenia/fatigue, somnolence, dizziness, flushing, diarrhea, nausea, hiccups, menstrual disorder, and headache) tended to occur more frequently in the active treatment groups (including the group not receiving aprepitant) compared with placebo. Adverse experiences of hiccups were reported more commonly in the aprepitant groups, but only in patients treated with aprepitant plus dexamethasone; there were no reports of hiccups in subjects who received only aprepitant.

Key Safety Findings in CINV Phase II Studies

A total of 1375 cancer patients were treated with study drug (including 460 placebo-treated patients) in the CINV Phase II studies. Overall, the aprepitant regimens tested in the CINV Phase II program were generally well tolerated, although in the Phase IIb study (Protocol 040/42) a higher incidence of febrile neutropenia was observed in the aprepitant 125-mg/80-mg group (6.1%) compared with the Standard Therapy group (3.8%). A post hoc assessment suggested that infection-related serious adverse experiences were also reported more frequently in the aprepitant 125-mg/80-mg group (3.7%) compared with the Standard Therapy group (1.9%) in the Phase IIb study.

Differences observed in the Phase IIb study may reflect chance occurrence due to the low overall numbers of patients, and both febrile neutropenia and serious infections remained within the expected frequency range for this patient population. Alternatively, the differences may have been a consequence of higher exposure to dexamethasone in the aprepitant group compared with the Standard Therapy group during Phase IIb.

Safety in CINV Phase III Studies

The CINV Phase III studies (Protocol 052 and Protocol 054) evaluated the aprepitant regimen proposed for market. These trials had an identical study design and evaluated aprepitant for the prevention of CINV associated with highly emetogenic chemotherapy. Therefore, data from these 2 trials have been merged and represent the focus of the

evaluation of the safety of aprepitant for CINV. As discussed in Section 7.5, the regimen tested in the 2 Phase III studies differed from the regimen tested in Phase IIb studies; the dexamethasone dose was reduced (20 mg reduced to 12 mg) as was the duration of aprepitant dosing (5 days reduced to 3 days). Since these changes may have altered the overall safety profile of the aprepitant regimen, the CINV Phase III safety data have not been combined with the Phase II studies.

Based on the Phase II experience, certain adverse experiences were prespecified as being of special interest in Phase III. These included fever, febrile neutropenia, infections, leukopenia, neutropenia, anemia, thrombocytopenia, hypertension, hyperglycemia, hypokalemia, and dehydration. These adverse experiences potentially reflect hematologic toxicity, immunosuppression, and/or the effects of corticosteroids.

The Phase III studies provided an option to receive aprepitant for up to 6 cycles of chemotherapy. Safety data from Cycle 1 are presented in Section 8.5.2. Safety data from the optional Multiple-Cycle extension are summarized in Section 8.5.3. Overall, 1099 adult patients (547 and 552 in the aprepitant group and Standard Therapy group, respectively) were randomized into the Phase III studies and ~75% of the patients entered the optional Multiple-Cycle extension.

In general, the adverse experience profile was typical of a population of patients with cancer receiving high-dose cisplatin-based chemotherapy, and the overall incidence and profile of clinical and laboratory adverse experiences were comparable in both treatment groups. The most common side effects included hiccups, asthenia/fatigue, constipation, headache, and anorexia. The incidences of prespecified adverse experiences that reflect the toxicity of cancer chemotherapy, including neutropenia, leukopenia, and dehydration, were generally similar between treatment groups in the Phase III studies. In particular, the incidences of febrile neutropenia (1.7% and 1.3% in the aprepitant group and the Standard Therapy group, respectively) and serious infection-related adverse experiences (3.7% in the aprepitant group and 2.4% in the Standard Therapy group) in the 2 treatment groups were not statistically significantly different. In the CINV program, the adverse experience profile associated with aprepitant was carefully reviewed in order to assess whether aprepitant potentially had a clinically significant interaction with chemotherapy, specifically evaluating chemotherapy metabolized by CYP3A4 as well as chemotherapy not metabolized by CYP3A4. No evidence of such an interaction was seen.

Safety of Aprepitant in the Absence of Chemotherapy

In addition to CINV studies, the clinical development program of aprepitant included non-CINV indications not claimed in the original marketing application. These studies were conducted in patients with depression, schizophrenia, migraine, dental pain, and post-herpetic neuralgia, as well as in healthy subjects with motion-induced nausea and light-induced melatonin suppression. The safety data from these studies are of particular importance as they tested a broad range of aprepitant doses (up to 375 mg) administered

for extended periods of time (up to 8 weeks) to a large number (n=1095) of patients/subjects not exposed to the side effects of chemotherapy.

In these studies for non-CINV indications, the overall incidences and profiles of clinical and laboratory adverse experiences in patients treated with aprepitant (or its IV prodrug, L-758298) were generally similar to those in patients treated with the comparator and/or placebo. Non-CINV studies also revealed no evidence of adverse experiences suggestive of hematological toxicity and/or immunosuppression associated with aprepitant administration.

2.8 Benefits Versus Risks Relationship (Section 9)

Aprepitant represents a significant medical advance for patients receiving highly emetogenic chemotherapy. It is a breakthrough drug with a novel mechanism of action—the first antagonist of substance P (NK_1-receptor antagonist) to be entered into clinical use. The efficacy profile of aprepitant elegantly complements current therapy since its addition to a standard therapy regimen of a 5-HT_3–receptor antagonist plus a corticosteroid markedly improves the prevention of both acute and particularly delayed CINV symptoms and, importantly, the improvement appears to be maintained in subsequent cycles of chemotherapy. Aprepitant was generally well tolerated in a broad range of clinical studies. Drug interactions need to be considered when using aprepitant because it is a substrate, weak to moderate inhibitor and inducer of CYP3A4, and an inducer of CYP2C9. The drug-interaction profile of aprepitant was comprehensively characterized. Appropriate guidance on its use with other drugs in the target population will be provided in the label for the proposed indication 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.

2.9 Conclusions (Section 10)

Aprepitant has a favorable benefit/risk ratio when used for the prevention of CINV in accordance with its proposed labeling guidelines. Key efficacy and safety conclusions based on Phase III data are summarized below. For a complete compilation of aprepitant development program conclusions arranged by research discipline, refer to Section 10.

Efficacy of Aprepitant in CINV

Conclusions on efficacy derived from the aprepitant clinical development program in patients receiving highly emetogenic cancer chemotherapy with cisplatin are as follows:

- The efficacy of aprepitant in the prevention of CINV is dose related: 125 mg administered on Day 1 followed by 80 mg on subsequent days is effective as assessed by the overall complete response and consistently superior to 40 mg administered on Day 1 followed by 25 mg on subsequent days.
- Administration of the Phase III aprepitant regimen provides protection against CINV overall and throughout both the acute and delayed phases, and is superior to Standard

Therapy that includes a 5-HT_3–receptor antagonist plus dexamethasone on Day 1, followed by dexamethasone on Days 2 to 4.

- The efficacy of the aprepitant regimen is unaffected by age, race, or gender, or the concomitant administration of emetogenic chemotherapy in addition to cisplatin.
- The aprepitant regimen is also effective in reducing the impact of CINV on patients' daily lives.
- The efficacy advantage of the aprepitant regimen versus Standard Therapy observed in Cycle 1 appears to be maintained during subsequent cycles of chemotherapy.

Safety of Aprepitant in CINV

In patients receiving emetogenic chemotherapy for underlying malignancy:

- The aprepitant regimen for CINV is generally well tolerated, with incidences and overall pattern of clinical and laboratory adverse experiences generally similar to the Standard Therapy regimen.
- The aprepitant regimen for CINV does not significantly alter the toxicity of concomitant chemotherapy whether metabolized by CYP3A4 or not.
- There are no clinically important differences in the safety profile of aprepitant due to patient age, race, or gender.
- The safety profile of aprepitant is generally similar irrespective of primary cancer diagnosis; in clinical trials, most patients had lung, ovarian, or head and neck cancer.

3. Nonclinical Development of NK_1-Receptor Antagonists for CINV

3.1 Background

Emesis is a complex, highly organized process that is orchestrated centrally by the interactions of several nuclei in the brain stem. These nuclei include the nucleus tractus solitarius (NTS), area postrema, and the dorsal motor nucleus of the vagus (DMNV) that together are sometimes referred to as the dorsal vagal complex. The dorsal vagal complex integrates incoming emetic signals and coordinates and initiates the various (sensory, somatic, and autonomic) physiological responses that are associated with nausea and vomiting. The NTS is the primary central input point for emetic stimuli coming from the abdominal viscera (vagal and sympathetic afferent fibers) and also from the area postrema. Cells in the NTS lie behind the blood-brain barrier, while those in the area postrema, from a functional viewpoint, lie outside this barrier. Cells in the area postrema are activated primarily by emetogens circulating in plasma or cerebrospinal fluid. Emetic responses can also be produced by sensory stimuli (pain, sight, and smell) and by memory, anticipation, and fear. These sensory and emotional inputs to the vomiting center are presumed to be driven from higher cortical brain centers. These cortical components are likely to be more prominent in clinical emesis than in experimental animal models. After activation of the brain stem vomiting center, the emetic response is achieved through a highly coordinated efferent output to vagal, phrenic, and spinal abdominal motor pathways. This is usually preceded or accompanied by nausea through output to higher cortical CNS centers. The prelude to vomiting is reduction in gastric tone and peristalsis, and increased tone in the jejunum and duodenum that precipitates gastric reflux. Vomiting is achieved by relaxation of the stomach cardia and cardiac sphincter that is coordinated with contraction of the diaphragm and abdominal muscles against a closed pylorus.

The neurobiology of emetic signaling pathways has recently become better understood particularly due to the development of new agents to prevent emesis and nausea associated with cancer chemotherapy. Therapy with cytotoxic agents such as cisplatin is thought to cause emesis through the release of emetogenic substances such as serotonin (5-HT) from the enterochromaffin cells in the gut. High concentrations of 5-HT released in the gut stimulate abdominal vagal afferent fibers by activating excitatory 5-HT_3 receptors on peripheral abdominal vagal nerve terminals. This action initiates emetic signaling input to the central vomiting centers such as the NTS. The 5-HT_3–receptor antagonist drugs such as ondansetron and granisetron can inhibit this pathway [3]. Cytotoxic agents may also stimulate cells in the area postrema with input to the NTS and thereby also contribute to the emetic response.

The preclinical discovery and study of the mechanism of action of the 5-HT_3–receptor antagonists have most extensively involved ferrets. This species has a profile of emetic responses similar to humans and importantly, like clinical experience, demonstrates both acute and delayed emetic responses to cisplatin. Furthermore, experimental models in

ferrets have been generally predictive for clinically useful antiemetic drugs. Taken together, these observations indicate that ferret models are appropriate for the study of novel antiemetic therapies for CINV.

The use of 5-HT_3–receptor antagonists revolutionized the treatment of emesis induced by anti-neoplastic chemotherapy in humans. In the clinic, all the 5-HT_3–receptor antagonists so far tested have a similar profile of antiemetic action and, although their dosing regimens vary, there is no difference in their antiemetic efficacy [4].

There is currently no completely effective therapy for the treatment of acute or delayed chemotherapy-induced emesis in humans. Most notably, current therapies are limited in the protection that they afford during the delayed phase. The 5-HT_3–receptor antagonists have been shown to decrease markedly the initial acute phase of emesis that occurs in the 24-hour period after administration of anti-neoplastic drugs such as cisplatin. However, the 5-HT_3–receptor antagonists are only poorly effective as monotherapy against the delayed phase of chemotherapy-induced emesis (>24 hour) both in humans [5; 6] and ferrets [7]. Attempts have been made to enhance the antiemetic activity of the 5-HT_3–receptor antagonists clinically and experimentally by varying the dose, dosing intervals, and routes of administration [8], but these measures have met with limited success.

3.2 Role of Substance P and its Blockade in Chemotherapy-Induced Emesis

Substance P belongs to a family of neuropeptides known as tachykinins that share the common C-terminal sequence: Phe-X-Gly-Leu-Met-NH_2. The 3 most common mammalian tachykinins are substance P, neurokinin A (NKA), and neurokinin B (NKB). The biological actions of these 3 tachykinins are mediated through specific cell-surface receptors designated NK_1, NK_2, and NK_3, with substance P being the preferred agonist for NK_1 receptors. All the tachykinin receptors identified to date belong to the family of G-protein coupled receptors and are coupled to the inositol phosphate signal transduction pathway [9].

Substance P is the most abundant and widely distributed tachykinin in the mammalian CNS [9]. Extensive substance P-like immunoreactivity has been demonstrated in key brain stem areas associated with emesis such as the NTS and area postrema [10; 11; 12]. Substance P is excitatory when applied to neurons in the area postrema of the dog [13], and when injected directly into the brain stem, is able to evoke emesis in ferrets [14]. Autoradiographic mapping studies showed that substance P NK_1 receptors are present in high concentrations in brain stem nuclei of the dorsal vagal complex, such as the NTS, which are critical for the regulation of the vomiting reflex to central and peripheral emetogenic stimuli.

The first suggestion that an NK_1-receptor blockade strategy could have an antiemetic effect came from the observations that depletion of substance P in the NTS using resinferatoxin could prevent the responses to peripheral emetogenic stimuli such as radiation and copper sulphate as well as to the central emetogen loperamide [15]. This unique profile of effects against peripheral and central emetogenic stimuli is thought to

occur because substance P depletion reduces activation of neurons in the NTS, the key brain stem area where emetic signals from both the area postrema and peripheral abdominal vagal afferents converge [10].

The development of nonpeptide substance P NK_1-receptor antagonists increased the opportunity to investigate the role of substance P in emetic reflexes and define the therapeutic potential of its blockade using preclinical assays. Landmark studies showed that the human NK_1-receptor antagonist CP-99994, but not its NK_1-inactive enantiomer CP-100263, blocked emesis induced in ferrets by cisplatin. NK_1-receptor antagonists also blocked the emetogenic responses to morphine and apomorphine that act centrally and that are refractory to 5-HT_3–receptor antagonists [16; 17; 3; 18; 19]. Using peptide and nonpeptide molecules, Gardner et al. [20] and Tattersall et al. [21] showed that NK_1-receptor antagonists must penetrate the brain, particularly to the NTS region, in order to block cisplatin-induced emesis in ferrets. These observations indicated that NK_1-receptor antagonists suppress the response to central emetogens through an action at central sites in contrast to the 5-HT_3–receptor antagonists that act mainly in the periphery. The acute antiemetic effects of the NK_1-receptor antagonists were not limited to ferrets but were also demonstrated preclinically across a range of species including dogs [19], pigs [22], and the house musk shrew (*Suncus murinus*) [14; 23].

In addition to the acute antiemetic effects, preclinical studies with CP-99994 [24] showed that NK_1-receptor antagonists were highly effective against the delayed phase emetic response to cisplatin in ferrets. This finding was unique since neither 5-HT_3–receptor antagonists nor dexamethasone had clear activity in this model [7; 25]. These observations, taken together with the activity of NK_1-receptor antagonists against acute emetic stimuli, suggested that NK_1-receptor antagonists might provide a novel opportunity to improve current clinical practice by providing a more complete and sustained control of CINV.

Overall, the preclinical science indicated that substance P is likely to play a key role in CINV. Experiments with NK_1-receptor antagonists showed that they have a broader spectrum of antiemetic activity than the 5-HT_3–receptor antagonists probably because they act centrally within the NTS, whereas the 5-HT_3–receptor antagonists act mainly in the periphery. The finding that these agents act at distinct pharmacological and anatomic sites within emetic pathways suggested that there could be additivity in their actions. It was therefore hypothesized that coadministration of NK_1-receptor antagonists and 5-HT_3–receptor antagonists might provide increased benefits over current antiemetic drug regimens especially if clinical protection is incomplete with either agent alone.

3.3 NK_1-Receptor Activity of Aprepitant In Vitro

Aprepitant was shown to be a high-affinity competitive human NK_1-receptor antagonist that dissociates slowly from human NK_1 receptors in vitro.

Aprepitant inhibited the binding of [^{125}I]-Tyr^8-substance P to the human NK_1 receptor with an IC_{50} of 0.12 nM giving an apparent Kd of 86 pM with a Hill coefficient of 1.1,

indicating a single site of action. The affinity of aprepitant at the NK_1 receptors of preclinical species used for the in vivo assessment of its central and antiemetic activity was very similar to its affinity at human receptors (gerbil [IC_{50}=0.46 nM], ferret [IC_{50}=0.51 nM]).

In radioligand binding assays, aprepitant was approximately 3000-fold selective for the human cloned NK_1 receptor (IC_{50} = 0.1 nM) versus the human cloned NK_3 receptor (IC_{50} = 300 nM) and 45,000-fold selective over the human cloned NK_2 receptor (IC_{50} = 4500 nM). In a range of assays at other human cloned G-protein coupled receptors, aprepitant retained >50,000-fold selectivity for the human cloned NK_1 receptor. It is particularly noteworthy that aprepitant is highly selective (>80,000 fold) for human NK_1 receptors over previously recognized sites (serotonin 5-HT_3, dopamine D_2, corticosteroid and opiate) relevant to other mechanisms of antiemetic activity (IC_{50} NK_1 of 0.12 nM compared with >10 μM). These data support the proposition that the antiemetic activity seen with aprepitant may be attributed specifically to NK_1-receptor blockade.

3.4 Pharmacological Profile In Vivo

Brain Penetration and Central Activity of Aprepitant

In the aprepitant development program, a novel assay system was designed to study central NK_1-receptor antagonist activity in vivo [26]. In this assay, repetitive hindfoot tapping was evoked in gerbils by intracerebroventricular (ICV) infusion of an NK_1-receptor agonist (GR73632). The ability of NK_1-receptor antagonists administered intravenously to block the foot tapping was taken as a measure of their brain penetrability and central NK_1-receptor antagonist activity. By varying the pretreatment time of the antagonist before the NK_1 agonist challenge, a measure of central duration of activity could also be obtained. This assay was a reliable predictor for the antiemetic activity of NK_1-receptor antagonists in ferret emesis models [26].

The gerbil behavior studies showed that aprepitant was a brain-penetrant compound with a central duration of action that could be suitable for once-daily dosing. Aprepitant produced a dose-dependent and essentially complete inhibition of the foot tapping (ID_{50} of 0.32 mg/kg IV, when given immediately before the agonist challenge). The inhibition of foot tapping remained pronounced even when aprepitant was administered 4 or 24 hours before challenge with the NK_1 agonist (ID_{50} of 0.04 mg/kg IV and 0.33 mg/kg IV, respectively). The same assay system was used to show that the central NK_1-antagonist activity of aprepitant's metabolites (see Section 4) was clearly less than that of the parent molecule itself, indicating that their contribution to the antiemetic activity of aprepitant in vivo was likely to be relatively minor.

Brain Positron Emission Tomography (PET) Studies with Aprepitant

The occupancy of central NK_1 receptors by aprepitant was also investigated by the development of a novel highly selective NK_1-receptor PET radiotracer [^{18}F] SPA-RQ to enable studies of NK_1 receptors in living animal and human brain. PET imaging studies in rhesus monkeys, after IV infusion to achieve constant plasma concentrations, showed

that central NK_1-receptor occupancy by aprepitant was clearly related to its plasma levels with 50% receptor occupancy at 51 ng/mL and >80% at >120 ng/mL. The plasma concentration versus occupancy curve had a Hill slope of 1, consistent with the hypothesis that aprepitant binds to a single population of central NK_1 receptors. The PET studies confirmed the brain-penetrant nature of aprepitant and its availability to central NK_1-receptor sites.

Antiemetic Activity of Aprepitant

The antiemetic activity of aprepitant was evaluated preclinically in vivo using ferrets. Ferrets express NK_1 receptors with human-type pharmacology, facilitating evaluation of clinical potential. The assays were designed to mimic the acute and delayed time course of events that occur during CINV in humans in order to assess the potential therapeutic profile of aprepitant [24].

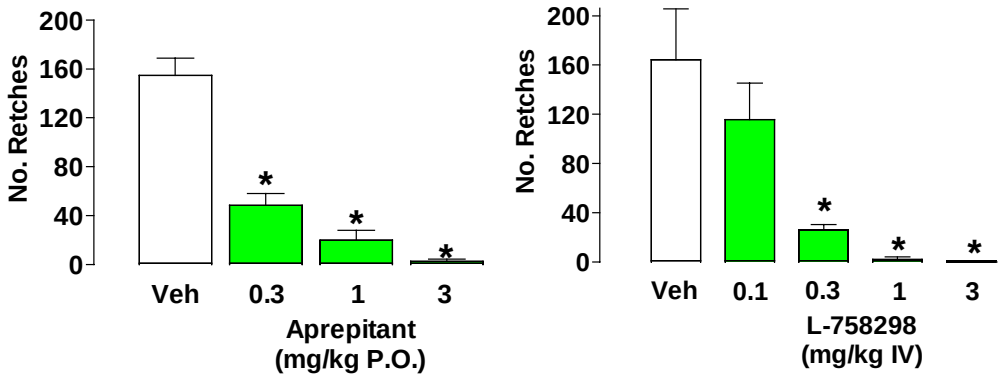
Acute Emesis Studies

In acute studies, aprepitant was administered orally (P.O.) or intravenously to ferrets 60 min or 3 min, respectively, before cisplatin 10 mg/kg IV. In coadministration studies, all treatments were given intravenously 3 min before cisplatin. The ferrets were monitored continuously by trained observers for a 4-hour period after dosing cisplatin to record the incidence of retching and vomiting. The profile of response was the same whether retching or vomiting was used for evaluation of drug effect.

The acute studies showed that aprepitant administered P.O. or intravenously (as its phosphoryl prodrug) was effective against acute cisplatin-induced emesis (Figure 1). The ID_{90} (dose giving 90% inhibition) for inhibition of retching or vomiting was 1 mg/kg IV and 3 mg/kg P.O. Aprepitant also distinguished itself from 5-HT_3–receptor antagonists by blocking (ID_{90} = 3 mg/kg P.O.) emesis produced by morphine and apomorphine (data not shown). These findings, together with the activity of aprepitant in the gerbil brain penetration assay (see above), supported the proposal that aprepitant's antiemetic effects are centrally mediated.

Figure 1

Prevention of Cisplatin-Induced (10 mg/kg IV) Retching in Ferrets by Aprepitant and L-758298 (Phosphoryl Prodrug of Aprepitant)

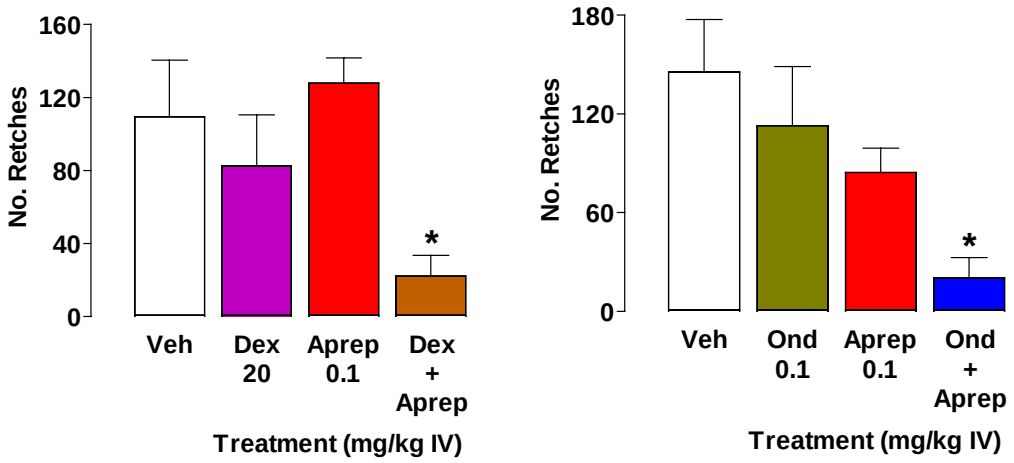


Data shown are the mean (± Standard Error of Mean) number of retches in a 4-hour observation period after cisplatin dosing. Significant differences from vehicle pretreated ferrets are shown as * $p<0.05$ Dunnett's test (n = 4 per group). IV = Intravenous; P.O. = Orally; Veh = Vehicle.

Coadministration studies in ferrets (Figure 2) using a suboptimal dose of aprepitant showed that its antiemetic effects were enhanced when given with suboptimal doses of established antiemetic agents such as dexamethasone or 5-HT_3–receptor antagonists such as ondansetron [24]. These findings supported the hypothesis that additivity could be obtained between these classes of agents that act at different (central versus peripheral) sites in the emesis pathways. The data suggested that if protection with either agent alone was incomplete in the clinic then a coadministration strategy in the clinic might increase the level of antiemetic protection during chemotherapy.

Figure 2

Prevention of Acute Cisplatin-Induced Retching (10 mg/kg IV) in Ferrets by Coadministration of Suboptimal Doses of Dexamethasone or a 5-HT_3–Receptor Antagonist (Ondansetron) With a Suboptimal Dose of Aprepitant



Data shown are the mean (± Standard Error of Mean) number of retches in a 4-hour observation period after cisplatin administration. Significant differences from vehicle pretreated ferrets are shown as * $p<0.05$ Dunnett's test (n=6 per group). Doses for coadministered treatments were the same as when agents were given alone. IV = Intravenous; Aprep = Aprepitant; Dex = Dexamethasone; Ond = Ondansetron.

Delayed Emesis Studies

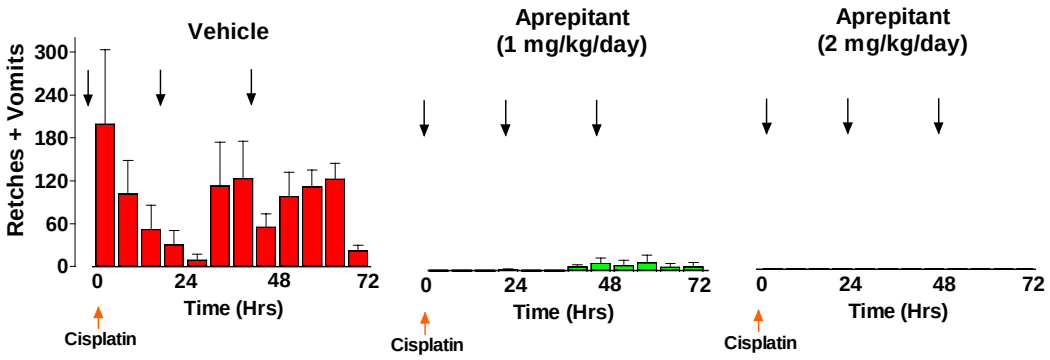
Cisplatin-induced delayed emesis was modeled in the ferret using a lower dose of cisplatin (5 mg/kg given intraperitoneally) than used in the acute studies. Three (3) study designs were used. First, in daily dosing experiments, aprepitant was given 2 hours before cisplatin and then at 24 hours and 48 hours after the initial dose. Second, a single dose of aprepitant was given 2 hours before cisplatin. Third, aprepitant administration was withheld until 24 hours and 48 hours after cisplatin, when the acute phase of emesis was complete. In all studies, the ferrets were monitored continuously by trained observers for retching and vomiting responses for 72 hours. The effects of aprepitant in the delayed emesis models were evaluated using the combined score for retching and vomiting.

In the ferret delayed cisplatin-induced emesis model, once-daily dosing of aprepitant was able to block both the acute and delayed phases. At the low oral daily dose of 1 mg/kg/day, aprepitant markedly inhibited the retching and vomiting response to cisplatin (Figure 3). When administered orally at 2 mg/kg/day or 4 mg/kg/day, aprepitant completely inhibited the acute (first 24 hours) and delayed (24 to 72 hours) emetic

responses to cisplatin with no episodes being observed over the entire 72-hour observation period (Figure 3). In contrast, higher single oral doses of aprepitant (4, 8, or 16 mg/kg) blocked only the acute phase and dose-dependently decreased but did not abolish the delayed phase of emesis (Figure 4). These observations indicated that low once-daily oral doses of aprepitant could provide effective protection against acute and delayed cisplatin-induced emesis in ferrets.

Figure 3

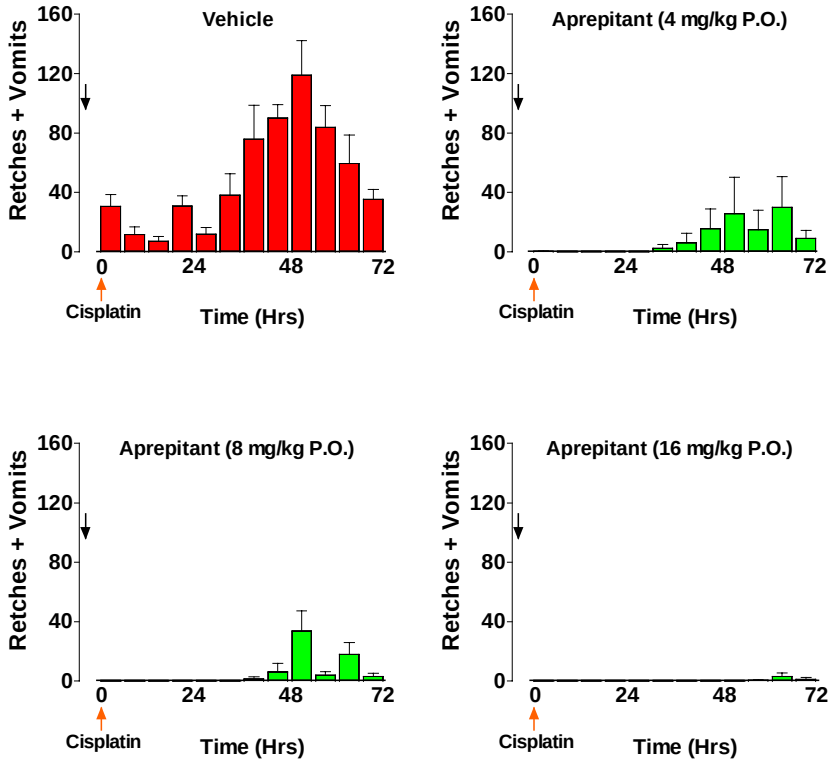
Prevention of Acute and Delayed Cisplatin-Induced (5 mg/kg IP) Retching and Vomiting in Ferrets by Once-Daily Oral Dosing of Aprepitant Compared With Vehicle



Data shown are the mean (± Standard Error of Mean) numbers of retches + vomits occurring in 6-hour time intervals (n=4 per group). IP = Intraperitoneal. Vehicle or aprepitant was dosed at 2 hours before cicplatin and then 24 hours and 48 hours later.

Figure 4

Prevention of Acute and Delayed Cisplatin-Induced (5 mg/kg IP) Retching and Vomiting in Ferrets by a Single Dose of Aprepitant Compared With Vehicle

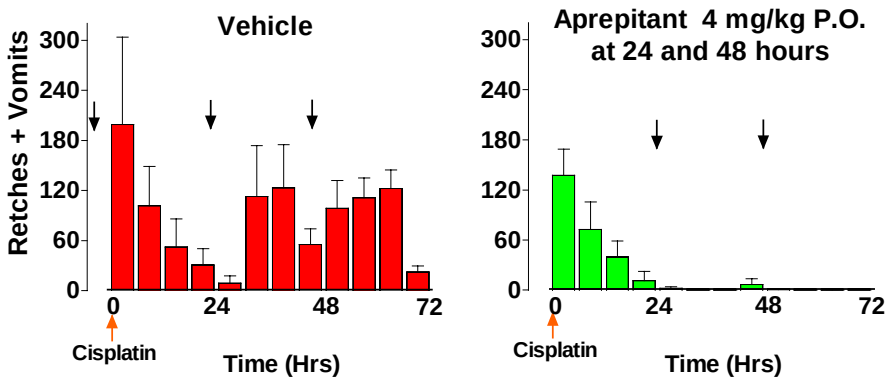


Data shown are the mean (± Standard Error of Mean) numbers of retches + vomits occurring in 6-hour intervals (n=4 to 8 per group). Arrows indicate the time of dosing. IP = Intraperitoneal; P.O. = Orally.

In order to examine whether the action of aprepitant against the delayed phase of cisplatin-induced emesis was simply a consequence of its effectiveness in the acute phase, the first administration of aprepitant was withheld until 24 hours after dosing with cisplatin, when the acute phase of emesis had already occurred (Figure 5). Aprepitant (4 mg/kg P.O.) administered 24 hours and 48 hours after cisplatin) produced a profound inhibition of the delayed phase of emesis. This finding indicated that the inhibition of delayed cisplatin-induced emesis by aprepitant is independent of its effects in the acute phase.

Figure 5

Prevention of Delayed Retching and Vomiting in Ferrets by Treatment With Aprepitant at 24 Hours and 48 Hours After Cisplatin (5 mg/kg IP) Compared With Vehicle



Data shown are the mean (± Standard Error of Mean) numbers of retches + vomits occurring in 6-hour intervals (n=4 per group). The left panel shows the acute and delayed response profile that is unaffected by vehicle treatment (arrows indicate times of dosing). The right panel indicates 2 aprepitant doses (arrows) given at 24 hours and 48 hours after the acute emetic phase. IP = Intraperitoneal; P.O. = Orally.

3.5 Conclusions

- Aprepitant is a highly selective, competitive, brain-penetrant NK_1-receptor antagonist.
- The antiemetic effects of aprepitant in ferrets are centrally mediated.
- Coadministration studies showed that the protective effects of aprepitant can be additive with 5-HT_3–receptor antagonists (ondansetron) or corticosteroids (dexamethasone) against cisplatin-induced emesis in ferrets.
- Aprepitant is unique compared with other agents used to control CINV (5-HT_3–receptor antagonists and dexamethasone) as it is effective against both acute and delayed cisplatin-induced emesis in ferrets.
- The activity of aprepitant against delayed cisplatin-induced emesis in ferrets is independent of its effects in the acute phase.
- Low once-daily oral doses of aprepitant provide effective protection against acute and delayed cisplatin-induced emesis in ferrets.

4. Nonclinical Pharmacokinetics and Drug Metabolism

4.1 Summary

This section describes the pharmacokinetics of aprepitant in 3 animal species selected for the toxicological evaluation of this compound, namely the CD-1 mouse, Sprague-Dawley rat, and Beagle dog. Pharmacokinetic data in the ferret are also presented since this is the species in which the antiemetic properties of aprepitant were initially characterized. The metabolism of aprepitant in mouse, rat, and dog is also described. It is concluded that aprepitant is well absorbed and is brain penetrant. The parent compound is the major drug-related component in ferret brain responsible for the antiemetic activity of aprepitant. All major metabolites identified had lower human NK_1-receptor binding affinities relative to aprepitant. Aprepitant induced its own metabolism in rats, which resulted in both parent compound and metabolites being monitored in toxicology studies. The metabolites observed in animals and humans validate the usage of the animal models selected for the toxicology studies. Aprepitant is a weak to moderate inhibitor of CYP3A4 in vitro, and this property was evaluated thoroughly in the clinic (Section 6). While aprepitant is an inhibitor of P-gp in vitro, this property was not evident in vivo in humans (Section 6).

4.2 Pharmacokinetics

Aprepitant is well absorbed and its oral bioavailability ranges from 16 to 46% in mice, rats, dogs, and ferrets (Table 1). Aprepitant exhibits a moderate (rat) to slow (mouse, dog, and ferret) clearance with a terminal half-life of 3 to 10 hours. The reversible binding of aprepitant to plasma proteins determined in vitro is ≥95% in rat, dog, and human. When dosed intravenously to rats, [^{14}C]aprepitant distributes rapidly and extensively to tissues, including the brain, and the radioactivity levels decline with time with no apparent retention in any organ.

Intact [^{14}C]aprepitant is the predominant radioactive component in ferret brain 48 hours following oral dosing, suggesting a major role for the parent compound as a mediator of the antiemetic efficacy of aprepitant in this animal model. This conclusion is further substantiated by the observation that all major metabolites have ~4- to 7000-fold lower human NK_1-receptor binding affinities relative to aprepitant (Table 2).

Table 1

Pharmacokinetics of Aprepitant in Male Sprague-Dawley Rats, Male Beagle Dogs, Male CD-1 Mice, and Male Ferrets Following a Single IV or P.O. Administration of Aprepitant[†]

Dose/Route (mg/kg)	CL_p (mL/min/kg)	Vd_{ss} (L/kg)	$t_{1/2}$ (hr)	C_{max} (ng/mL)	T_{max} (hr)	F (%)
Rat						
0.2/IV	17.6±5.3	3.2±0.5	2.7±0.4			
2/IV/P.O.	12.7±1.7	2.8±0.1	3.2±0.4	232±53	1 to 2	39
5/IV/P.O.	13.4±2.6	2.5±0.2	2.4±0.4	392±89	2	46
25/P.O.				1386±514	2 to 6	
125/P.O.				1616±426	1 to 4	
Dog						
0.2/IV	2.6±0.2	1.0±0.3	5.7±1.4	-	-	-
0.5/IV	2.3±0.7	1.1±0.1	7.3±2.6	-	-	-
2/IV/P.O.	0.9±0.2	0.9±0.1	ND[‡]	485±77	1 to 2	16
32 /P.O.	-	-	-	1464±764	4	
Mouse						
2 /IV; 10 P.O.	4.9	1.2	2.6	2175.7	4	42.4
Ferret						
0.5/IV; 10/P.O.	1.5±0.1	1.3±0.1	9.7±0.9	326.7±69.2	3.3±1.2	45.4±11.3

[†] The pharmacokinetic parameters CL_p, Vd_{ss}, and $t_{1/2}$ were obtained from the IV doses and C_{max}, T_{max}, and bioavailability (F%) from oral doses. Values shown are the mean (± SD) of n=3 for rats, dogs, and ferrets, and n=3 at each time point for mice. Dogs and ferrets were studied in crossover study designs with a 2-week washout period; one exception was the IV dose in dogs at 2 mg/kg where 3 different dogs were used.

[‡] ND: Not determined.

IV = Intravenous; P.O. = By mouth; SD = Standard deviation.

Table 2

Binding Affinities of Aprepitant and its Metabolites
in the NK_1-Receptor Binding Assay

Parent/Metabolite	IC_{50} (nM)
Aprepitant	0.12
L-755446	0.5
L-809861	10
L-829674	3.6
L-825678	1.7
L-809771	30
L-829617	18
L-829615	880
L-596064	>1000
L-294569	>1000
L-770787	>1000
L-858442	240
L-858443	>1000

4.3 Metabolism

[^{14}C]Aprepitant is eliminated primarily by metabolism followed by excretion of Phase I and Phase II metabolites in urine, bile, and feces. Unchanged parent drug is not detected in urine, and accounts for only 3 to 7% of the IV dose recovered in rat and dog bile. Unlike in humans, glucuronidation represents a significant metabolic pathway in rats and dogs. A glucuronide conjugate of [^{14}C]aprepitant is the major metabolite in rat bile, accounting for ~18% of the radioactive oral dose. In dog bile, several glucuronide conjugates of polar and nonpolar metabolites of aprepitant are observed, in addition to a glucuronide conjugate of aprepitant itself, and together these account for ~14% of the IV dose. Metabolite profiles are similar qualitatively in all of the species studied. Aprepitant is an inducer of hepatic CYP enzymes in rodents (Section 5), which resulted in aprepitant and several nonpolar (L-755446, L-809861, L-829674, L-825678, and L-809771), polar (L-829615 and L-829617), and very polar (L-294569, L-596064, L-770787, L-858442, and L-858443) metabolites being assayed in toxicology studies (Table 3). Metabolites of aprepitant observed in human plasma were also observed in nonclinical safety species.

CYP3A4 is primarily responsible for the metabolism of aprepitant in human liver microsomes. Aprepitant is a weak to moderate inhibitor (IC_{50} 2 to 21 µM) of metabolic reactions catalyzed by CYP3A4 and a very weak inhibitor of reactions mediated by CYP1A2, CYP2C9, CYP2C19, CYP2D6, or CYP2E1 (IC_{50} values >66 µM). Aprepitant is a substrate for P-gp-mediated transport in vitro, but appears to be a weaker substrate than vinblastine. It is a weaker inhibitor of the P-gp-mediated transport of vinblastine than either cyclosporin A or verapamil. Drug interaction studies for aprepitant with

probe drug substrates of CYP3A4 (midazolam) and P-gp (digoxin) were subsequently undertaken in the clinic (Section 6).

Table 3

The Presence of [^{14}C]Aprepitant and its Metabolites in Biological Matrices in Nonclinical Species and in Humans Following P.O. Administration of [^{14}C]Aprepitant†

Species	**Rat**				**Dog**				**Human**		
Compound	Plasma	Urine	Bile	Feces	Plasma	Urine	Bile	Feces	Plasma	Urine	Feces
Aprepitant	√‡	ND‡	√	√	√	ND	√	√	√	ND	√
Metabolites Present in Plasma and Excreta											
Nonpolar											
L-755446	√	ND	√	√	√	ND	√	√	√	ND	√
L-809861	√	ND	√	√	ND	ND	√	√	√	ND	√
L-829674	√	ND	√	√	√	ND	√	√	√	ND	√
L-825678	√	ND	√	√	√	ND	√	√	√	ND	√
L-809771	√	ND	√	√	√	ND	√	√	√	ND	√
Polar											
L-829617	√	ND	√	√	√	ND	√	√	√	ND	√
L-829615	√	ND	√	√	√	ND	√	√	√	ND	√
Very Polar											
L-596064	√	√	√	NS	√	√	ND	ND	√	√	ND
L-294569	√	√	√	NS	ND	√	ND	ND	√	√	ND
L-770787	√	ND	ND	NS	√	ND	ND	ND	√	√	ND
L-858442	ND	√	ND	NS	ND	√	ND	ND	ND	√	ND
L-858443	ND	√	ND	NS	ND	√	ND	ND	ND	√	ND

† All metabolites presented are Phase I products. For human only, this table also contains metabolite profiling data following IV dosing of [^{14}C]L-758298.

‡ √: Detected by either LC-MS/MS or HPLC/radioactivity; ND: Not detected by either LC-MS/MS or HPLC/radioactivity; NS: Not studied.

Note: Following a 100 mg/kg P.O. dose to the mouse, the following components were observed in the 5 hours postdose plasma: aprepitant, L-755446, L-825678, L-809771, L-809861, L-829617, in addition to some very polar metabolites not characterized in this study.

P.O. = By mouth; IV = Intravenous.

4.4 Conclusions

- Aprepitant has good oral bioavailability (16 to 46%) and has a half-life of 3 to 10 hours in mice, rats, dogs, and ferrets.
- Aprepitant is brain penetrant in ferrets and is the major drug-related component detected in the brain responsible for antiemetic activity.
- Metabolites of aprepitant observed in humans are also observed in nonclinical species, validating the use of the animal models selected for the toxicology studies of aprepitant. All metabolites have reduced affinity at human NK_1 receptors, relative to aprepitant itself.

- Aprepitant is a weak to moderate inhibitor of CYP3A4 in vitro (IC_{50} 2 to 21 µM). Aprepitant is a very weak inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, and 2E1 (IC_{50} >66 µM) in vitro.
- Aprepitant is a substrate and a weak inhibitor of human P-glycoprotein in vitro.

5. Nonclinical Toxicology

5.1 Background

The potential toxicity of aprepitant was extensively evaluated in a series of single-dose studies in rats and mice, repeated-dose oral toxicity studies in rats and dogs, oral developmental and reproductive toxicity studies in rats and rabbits, and in vitro and in vivo genetic toxicity studies. In addition, the hepatic enzyme induction potential of aprepitant was evaluated in rats and mice.

The recommended clinical dose of aprepitant is 125 mg administered orally 1 hour prior to chemotherapy (Day 1) and 80 mg once daily on Days 2 and 3. Patients typically receive up to 6 cycles of chemotherapy at intervals of ~3 weeks. Although regulatory guidances (61FR8153) do not require carcinogenicity studies for indications such as CINV due to the limited, short, and episodic duration of patient treatment, carcinogenicity studies in rats and mice were conducted with aprepitant to support other potential therapeutic indications and are summarized here for completeness.

To define the toxicity profile of aprepitant, dose levels for the in vivo studies were selected to maximize systemic exposure to aprepitant, to establish no-effect levels for the treatment-related findings, and to determine margins of safety relative to the proposed clinical dose based on a comparison of systemic exposure. Based on the results of the nonclinical toxicology studies, there are no contraindications to the therapeutic use of aprepitant.

Aprepitant is poorly soluble in aqueous media. The initial nonclinical toxicology studies were conducted using a micron particle size formulation of aprepitant that was administered once daily. In an attempt to increase and maximize systemic exposure to aprepitant, a twice-a-day (b.i.d.) dosing regimen and/or a second formulation (submicron particle size of aprepitant) were used in an extensive series of toxicity and toxicokinetic studies. Further, comprehensive studies were conducted to define a plateau in systemic exposure to aprepitant and 12 polar, nonpolar, and very polar circulating metabolites.

5.2 Acute and Repeated-Dose Toxicology

5.2.1 Acute Toxicology in Rats and Mice

Acute administration of aprepitant to female rats and mice indicated that the compound has a low potential for toxicity via the intended clinical route. The approximate oral lethal $dose_{50}$ was >2000 mg/kg in both rats and mice.

5.2.2 Repeated-Dose Toxicology

5.2.2.1 Repeated-Dose Toxicology in Rats

Aprepitant induces hepatic cytochrome P-450 enzymes in rodents. Specifically, in a 16-day study in rats at doses up to 125 mg/kg/day, aprepitant induced 7-ethoxy-4-trifluoromethyl coumarin O-deethylase (EFCOD) activity, CYP2B, and CYP3A. The

primary toxicologic findings in the repeated-dose studies in rats were associated with hepatic enzyme induction.

Aprepitant was evaluated in a series of repeated-dose toxicity studies in rats that ranged in dose from 0.2 mg/kg/day to 1000 mg/kg b.i.d (the maximum feasible dose based on viscosity and dosability of the drug formulation). A plateau in plasma systemic exposure to aprepitant and its circulating metabolites was established at 125 mg/kg b.i.d. (aprepitant mean $AUC_{0\text{-}24\ hr}$=approximately 27 μg•hr/mL and 6 μg•hr/mL in female and male rats, respectively). These plasma systemic exposures are approximately equivalent to (females) or 3-fold less than (males) the exposure in humans at the intended clinical dose.

The primary treatment-related changes in rats included liver weight increases, hepatocellular centrilobular hypertrophy, thyroid weight increases, thyroid follicular cell hyperplasia, pituitary cell vacuolation, and slight alterations in serum cholesterol and triglycerides. The changes in the liver were considered adaptive responses to the increased metabolic load secondary to hepatic enzyme induction. The changes in the thyroid were considered compensatory responses to the increased rate of thyroxine clearance stimulated by the enzyme induction. Vacuolation of the pituitary cells likely represented a degeneration or exhaustion of TSH-producing cells. Similar findings have been observed in rats with structurally and pharmacologically dissimilar marketed drugs that have been shown to induce hepatic cytochrome P-450 enzymes. These findings, which are well described to be rodent-specific, are of limited toxicological significance to human risk assessment. The remaining changes in the liver noted at doses ≥125 mg/kg b.i.d. represented perturbations of hepatocellular function due to the exaggerated hepatic enzyme induction. The no-effect level in rats following chronic administration (0.25 mg/kg/day) was based on liver and thyroid changes associated with hepatic enzyme induction.

5.2.2.2 Repeated-Dose Toxicology in Dogs

Aprepitant was generally well tolerated in a series of repeated-dose toxicity studies in dogs that ranged in dose from 2 mg/kg/day to 750 mg/kg b.i.d. A plateau in systemic exposure to aprepitant and its circulating metabolites was established at 500 mg/kg b.i.d. (aprepitant mean $AUC_{0\text{-}24\ hr}$=1430 μg•hr/mL; ~70-fold in excess of the exposure at the intended clinical dose).

The no-effect level in the dog studies was 32 mg/kg/day (mean $AUC_{0\text{-}24\ hr}$=approximately 113 μg•hr/mL; ~6-fold greater than the human exposure). Slight increases in serum alkaline phosphatase activity and decreases in the A/G ratio occurred at systemic exposures ≥13-fold greater than the human exposure. Significantly decreased body weight gain, testicular degeneration, and prostatic atrophy were observed at systemic exposures ≥31-fold greater than the human exposure. Although the mechanism for the changes in the testis and prostate are unknown, the findings were present at systemic

exposures greatly in excess of the exposure at the intended clinical dose and are of minimal toxicological significance for human risk assessment.

A slight treatment-related increase in liver weight (+22% relative to control, expressed as a percent of brain weight) was noted at a systemic exposure 70-fold greater than the human exposure. There were no gross or microscopic findings that correlated with the liver weight change. The increase in liver weight at this high systemic exposure is of minimal toxicological significance for human risk assessment.

5.3 Reproductive Toxicology in Rats

The potential effects of aprepitant on fertility were evaluated in female and male rats at doses up to 1000 mg/kg b.i.d. In the female fertility study, the no-effect level for effects of aprepitant on mating performance, fertility, and embryonic/fetal survival in F_0 female rats was ≥1000 mg/kg b.i.d. in the presence of a transient and treatment-related decrease in mean food consumption. Systemic exposure at this dose is approximately equivalent to exposure in humans at the recommended dose. In the male fertility study, the no-effect level for effects on mating performance, fertility, embryonic/fetal survival, sperm count and motility, testicular weights, and the microscopic appearance of the testes and epididymides was ≥1000 mg/kg b.i.d. Systemic exposure at this dose in male rats was ~3-fold less than the exposure in humans at the intended clinical dose.

5.4 Embryo-Fetal and Perinatal Toxicology in Rats and Rabbits

In rats, there was no evidence of maternotoxicity as assessed by body weight gain, food consumption, physical signs, and length of gestation up to the highest dose evaluated (1000 mg/kg b.i.d; systemic exposure to aprepitant=1.5-fold greater than the human exposure). There was no evidence of developmental toxicity in fetuses as assessed by embryonic/fetal survival, fetal body weights, and fetal external, visceral, and skeletal morphology or in the F_1 generation as assessed by survival, external morphology, physical signs, body weight gain, behavior, sexual maturation, and reproductive performance. No treatment-related effects were noted at birth in the F_2 generation as evaluated by survival, body weight, and external morphology. Based on the results of this study, the no-observed-adverse-effect level (NOAEL) for maternal and developmental toxicity in rats was ≥1000 mg/kg b.i.d. In a toxicokinetic study in which pregnant and lactating rats were administered 1000 mg/kg b.i.d., transplacental and lactational exposures to the F_1 generation were demonstrated (fetal aprepitant concentrations were up to 27% of the mean maternal plasma drug concentration; milk concentrations were ~90% of the mean maternal plasma drug concentration).

In rabbits, the highest dose evaluated in the developmental toxicity study (25 mg/kg/day; systemic exposure equivalent to the human exposure) was limited by effects on maternal body weight gain and food consumption established in a range-finding study. In the developmental toxicity study, treatment-related maternal findings included transient maternal body weight loss and decreased food consumption in the 25-mg/kg/day group. There was no evidence of developmental toxicity in any drug-treated group as assessed

by embryonic/fetal survival, fetal body weights, and fetal external, visceral, and skeletal morphology. Based on these results, the NOAEL of aprepitant for maternal toxicity in rabbits was 5 mg/kg/day. The NOAEL for developmental toxicity was ≥25 mg/kg/day. Placental transfer was demonstrated in a toxicokinetic study in which aprepitant was administered to pregnant rabbits at doses up to 25 mg/kg/day (fetal aprepitant concentrations were up to 56% of the mean maternal plasma drug concentrations).

5.5 Genetic Toxicology

Aprepitant was shown to be neither mutagenic nor genotoxic in assays conducted to detect mutagenicity, DNA strand breaks, and chromosomal aberrations.

5.6 Carcinogenic Potential in Mice and Rats

A mouse carcinogenicity study was conducted at doses of 2.5, 25, 125, and 500 mg/kg/day. In previous toxicokinetic studies, a plateau in systemic exposure to aprepitant and its circulating metabolites was demonstrated at 500 mg/kg/day in mice (mean $AUC_{0\text{-}24\ hr}$=approximately 36 μg•hr/mL; approximately 2-fold greater than the human exposure). There were no treatment-related or statistically significant ($p>0.05$) effects on mortality. There were no treatment-related neoplastic changes. There was no statistically significant ($p>0.05$) evidence of a trend in the incidence of any tumor type. Non-neoplastic changes were limited to centrilobular hepatocellular hypertrophy in female mice in the 125- and 500-mg/kg/day groups and in male mice in the 25-, 125-, and 500-mg/kg/day groups. These changes were considered secondary to hepatic cytochrome P-450 enzyme induction. This finding, which is well documented to be rodent-specific, is of limited toxicological significance to human risk assessment [27; 28; 29].

Two (2) carcinogenicity studies were conducted in rats at doses that ranged from 0.05 to 125 mg/kg b.i.d. A plateau in plasma systemic exposure to aprepitant and its circulating metabolites was established at 125 mg/kg b.i.d. (aprepitant mean $AUC_{0\text{-}24\ hr}$=approximately 27 μg•hr/mL and 6 μg•hr/mL in female and male rats, respectively; approximately equivalent to [females] or 3-fold less than [males] the exposure in humans at the intended clinical dose). There were no treatment-related or statistically significant ($p>0.05$) effects on mortality. Treatment-related neoplastic changes included an increased incidence of hepatocellular adenoma in female rats (25 mg/kg b.i.d. and 125 mg/kg b.i.d.) and in male rats (125 mg/kg b.i.d.), thyroid follicular cell adenoma in female and male rats (125 mg/kg b.i.d.), and thyroid follicular cell carcinoma in male rats (125 mg/kg b.i.d). A trend of increasing incidence of hepatocellular adenoma through the high dose only was observed in female rats (adjusted $p=0.044$). No other tumor type had a statistically significant increase after multiplicity adjustment. The increased incidences of hepatocellular adenoma and of hepatocellular centrilobular hypertrophy (≥5 mg/kg b.i.d.) were considered secondary to hepatic cytochrome P-450 enzyme induction. Similar neoplastic and non-neoplastic liver changes have been described in rats treated with marketed drugs known to have potent cytochrome P-450 enzyme induction potential. The thyroid follicular cell adenomas and

carcinomas and associated follicular cell hyperplasia were consistent with an altered thyroid hormone milieu, a phenomenon well described in rats treated with compounds known to have cytochrome P-450 enzyme inducing potential. The tumor promotion phenomenon observed in rodents caused by hepatic cytochrome P-450 enzyme induction has not been shown to occur in humans and is of limited toxicological significance to human risk assessment [30]. There were no other treatment-related or statistically significant ($p>0.05$) increases in tumor incidences in rats treated with aprepitant. Non-neoplastic treatment-related changes noted in the liver (≥5 mg/kg b.i.d.) represented perturbations of hepatocellular function due to the exaggerated hepatic cytochrome P-450 enzyme induction.

5.7 Conclusions

- There are no contraindications to the therapeutic use of aprepitant in humans based on the results of the nonclinical toxicology studies.
- Aprepitant has a low order of acute toxicity.
- The principal findings observed in the liver, thyroid, and/or pituitary in the rat studies were considered rodent-specific, were consistent with changes reported for structurally and pharmacologically dissimilar marketed drugs that have been shown to induce hepatic cytochrome P-450 enzymes in rodents, and are of limited toxicological significance to human risk assessment.
- In dogs, the no-effect level was approximately 6-fold in excess of the exposure at the intended clinical dose.
- Aprepitant has no effects on female or male fertility in rats.
- Aprepitant is not teratogenic nor does it cause embryo-fetal toxicity in rats or rabbits at doses in which transplacental exposure occurs.
- Aprepitant is neither genotoxic nor mutagenic.
- In the carcinogenicity study in mice, there was no evidence of an increased incidence of any tumor type. In the carcinogenicity studies in rats, the increased incidences of hepatocellular adenomas and thyroid follicular cell adenomas and carcinomas were consistent with hepatic enzyme induction. This rodent-specific tumor promotion phenomenon has been observed with other marketed drugs that induce hepatic cytochrome P-450 enzymes, has not been shown to occur in humans, and is of limited toxicological significance to human risk assessment.

6. Human Pharmacokinetics, Bioavailability, and Pharmacodynamics

This section summarizes the pharmacokinetics, biopharmaceutics, and pharmacodynamics of aprepitant in humans. The pharmacokinetics of aprepitant in healthy subjects and in special populations (the elderly, patients with renal or hepatic insufficiency) are presented first followed by descriptions of relevant drug interactions. Finally, a brief description of pharmacokinetic/receptor occupancy correlations is provided.

The pharmacokinetics of aprepitant can be summarized as follows. Aprepitant has a favorable pharmacokinetic profile in humans that supports once daily oral dosing. The pharmacokinetics of aprepitant are not significantly affected by race, gender, or age, and dose adjustment is not necessary in patients with renal insufficiency or mild to moderate hepatic insufficiency. Aprepitant is brain penetrant and the regimen for CINV is anticipated to provide a high level of blockade of CNS NK_1 receptors.

Several drug interaction studies with aprepitant were conducted throughout the course of the development program. Some of these studies were conducted to support the use of aprepitant for chronic dosing indications, and, due to differences in dose levels or duration of dosing of aprepitant, they are not relevant to the short-term dosing proposed for prevention of CINV. The studies relevant to administration of aprepitant for CINV indicate that drug interactions with the aprepitant regimen for CINV are generally modest. Of particular importance is that aprepitant has a low potential for interaction with chemotherapy with which it would be coadministered.

6.1 Formulation Development

The market formulation of aprepitant is a capsule containing the drug in a nanoparticle formulation. This formulation has superior bioavailability and reduced food effect compared with formulations used earlier in the program. 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 (Protocols 041, 046, 047, 048, 049, 050, 051, 056, 057, 064, 067, and 076). Some of the earlier studies in the aprepitant clinical development program evaluated tablet formulations that had lower bioavailability and a larger food effect relative to the nanoparticle capsule, and thus were not developed for market use. 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. This prodrug was not developed for marketed use. A stable isotope-labeled aprepitant formulation was also developed for IV administration as a tracer dose (2 mg) to evaluate the bioavailability of the final market composition capsules and to estimate the apparent volume of distribution and plasma clearance of aprepitant.

The summary of pharmacokinetic data presented below focuses on studies using the market composition nanoparticle capsules. For studies where a tablet formulation was used, the calculated approximately equivalent dose of the nanoparticle capsule (based on

pharmacokinetic exposures as measured by plasma AUC) is provided to facilitate comparison to the market composition capsule.

6.2 Analytical Methods for the Determination of Aprepitant and L-758298

Methods utilizing liquid-liquid or solid-phase extraction for the isolation of aprepitant or L-758298, respectively, followed by high-performance liquid chromatography (HPLC) with tandem mass spectrometric detection were developed to support the analysis of plasma samples for aprepitant and L-758298. Two (2) standard concentration ranges of 1 to 500 and 10 to 5000 ng/mL were used for both the quantification of aprepitant and L-758298. The limits of quantification (LOQ) of these methods 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 a study that assessed the absolute bioavailability of aprepitant. A separate method was developed to analyze aprepitant in kidney dialysate fluid with an LOQ of 1 ng/mL of kidney dialysate and a linear range of 1 to 500 ng/mL.

Methods for the determination of aprepitant and L-758298 in urine samples had an LOQ of 10 ng/mL of analyte with a linear range of 10 to 5000 ng/mL.

Aprepitant in plasma was stable during storage at -20^{o}C for at least 10 months. L-758298 in plasma was stable during storage at -70^{o}C for at least 6 months. All concentration data in clinical study samples reported in this document were based on assays conducted within the time frames of sample storage for which the analytes have been demonstrated to be stable.

6.3 Pharmacokinetics in Humans

6.3.1 Absorption

Aprepitant is well absorbed under fasting conditions from the market composition nanoparticle capsules. The absolute bioavailability of 80-mg and 125-mg capsule doses administered under fasting conditions was 67% and 59%, respectively. Administering the capsule doses with a high-fat meal resulted in 9% higher AUC and 14% higher C_{max} for the 80-mg capsule, and 20% higher AUC and 25% higher C_{max} for the 125-mg capsule. This represents a slight enhancement of absorption of aprepitant with food. The magnitude of these differences is small enough to conclude that food does not affect systemic exposure to aprepitant to a clinically meaningful extent following administration of the 80-mg and 125-mg capsules. Hence, aprepitant capsules may be dosed without regard to food intake.

6.3.2 Distribution

Aprepitant is greater than 95% bound to plasma protein in healthy humans. The apparent volume of distribution of aprepitant in healthy young adult subjects is ~66 L. PET

studies in humans indicate that aprepitant crosses the blood-brain barrier (see Section 6.5).

6.3.3 Metabolism

Aprepitant undergoes extensive metabolism primarily via oxidation by CYP3A4. Up to 12 metabolites of aprepitant have been identified in plasma following administration of single doses of [^{14}C]-aprepitant or its prodrug (L-758298) (see Table 3 in Section 4.3). All of these metabolites were also detected in rats and dogs (species used for toxicological studies). All of the metabolites of aprepitant found in human plasma have much reduced human NK_1-receptor in vitro binding affinities compared with aprepitant. The 2 metabolites with the greatest affinities for the human NK_1 receptor, L-755446 and L-825678, have ~4.2-fold and ~14-fold lower affinity than aprepitant, respectively. After administration of multiple doses of aprepitant to healthy young humans, the plasma concentrations of these 2 metabolites relative to that of aprepitant were 8- to 25-fold lower than aprepitant. In addition, in an animal model of CNS NK_1-receptor antagonism, these metabolites show poor brain penetration compared with aprepitant. Based on substantially lower receptor affinity, lower plasma concentrations relative to aprepitant, and poorer brain penetrance, it is unlikely that aprepitant metabolites contribute significantly to CNS NK_1-antagonistic effects in humans.

In vitro experiments indicate that the major plasma metabolites in humans were all derived from stepwise oxidative metabolism of aprepitant largely by CYP3A4 with minor contributions from CYP1A2 and CYP2C19. The importance of CYP3A4 in the metabolism of aprepitant in vivo was confirmed in clinical drug interaction studies (described in Sections 6.4.1 and 6.4.2).

6.3.4 Excretion

After IV administration of [^{14}C]-L-758298 to humans, ~45% of total radioactivity was excreted in feces and ~58% of total radioactivity was excreted in urine (entirely as metabolites of aprepitant). Oral administration of [^{14}C]-aprepitant resulted in ~86% of total radioactivity excreted in feces and ~5% in urine. The larger excretion of aprepitant in feces in this study was likely due to poor absorption of drug from the formulation that was used. This formulation consisted of micron-sized drug particles that were subsequently shown to have lower oral bioavailability than submicron (nanoparticle) sized drug particles that are used in the market composition formulation. Unchanged aprepitant was not detected in urine, suggesting that aprepitant underwent extensive metabolism and was eliminated primarily via excretion of metabolites.

6.3.5 Intravenous Pharmacokinetics

Although the market formulation of aprepitant is administered orally, it was important to obtain a complete understanding of the pharmacokinetics of aprepitant when it was administered intravenously because certain pharmacokinetic parameters (plasma clearance, volume of distribution) can only be determined following IV dosing. Other parameters (AUC, C_{max}) are presented below for oral dosing (Section 6.3.6). Following

IV dosing of aprepitant, the apparent plasma clearance of aprepitant was 84 mL/min, 72 mL/min, and 60 mL/min when IV aprepitant was administered alone, with the 80-mg capsule, and with the 125-mg capsule, respectively. This indicates slight non-linearity in aprepitant IV pharmacokinetics, presumably due to saturable metabolism (i.e., clearance decreases slightly as plasma concentration of aprepitant increases). The aprepitant apparent volume of distribution was ~66 L and apparent plasma terminal half-life was 13.2 hours.

6.3.6 Single-Dose Oral Pharmacokinetics

The pharmacokinetics of the market composition formulation of aprepitant were determined following single oral doses of 80 mg or 125 mg. The plasma $AUC_{0-\infty}$ and C_{max} of aprepitant increased slightly greater than proportional to dose for the 125-mg compared with the 80-mg dose. A separate study also indicated slightly greater than dose proportional increases in plasma concentration of aprepitant for a 375-mg dose compared with the 125-mg dose. The time of maximum plasma concentration was ~4 hours and half-life was ~9 to 12 hours. The half-life of aprepitant is acceptable to allow once-daily oral dosing.

6.3.7 Multiple-Dose Oral Pharmacokinetics

The proposed regimen of aprepitant for prevention of CINV is a loading dose of 125 mg on Day 1 and 80 mg/day on Days 2 and 3 and was the regimen used in Phase III studies. A 5-day regimen of aprepitant (125 mg on Day 1 and 80 mg on Days 2 through 5) was also evaluated in some Clinical Pharmacology and Phase II studies. In the remainder of Section 6, these will be referred to as either the 3-day regimen or 5-day regimen for CINV. The pharmacokinetics of aprepitant administered as a 3- or 5-day regimen are shown in Table 4. These results show that plasma concentrations of aprepitant with these regimens are similar or slightly higher on the last day of dosing (Day 3 or 5) compared with Day 1. Thus, the 3-day regimen used in Phase III provides relatively constant daily exposure (AUC) to aprepitant over the dosing period.

Table 4

Mean Pharmacokinetic Parameters of Aprepitant in Healthy Young Adults

Dose (mg)[†]	$AUC_{0-24\ hr}$ (ng•hr/mL)	C_{max} (ng/mL)
	Day 1	Day 1
125 mg[‡]	18715	1391
	19455	1539
	Day 3 or 5	Day 3 or 5
80 mg Days 2 to 5	23005	1585
80 mg Days 2 to 3	20149	1356

[†] All doses administered shortly after breakfast.
[‡] Data from 2 separate studies (Protocols 041 and 067).

6.3.8 Effects of Gender, Body Weight, Age, and Race on the Pharmacokinetics of Aprepitant

The effects of gender, body weight, age, and race on the pharmacokinetics of aprepitant were examined in a composite analysis of pharmacokinetic parameters across several Phase I studies.

Minor gender differences were noted for C_{max} (16% higher in females compared with males) and half-life (25% lower in females compared with males). These small differences are not considered clinically meaningful and the same dose of aprepitant may be used in men and women.

There was a small, negative relationship between weight and $AUC_{0\text{-}24\ hr}$ and C_{max}. For every 10-kg increase in weight, $AUC_{0\text{-}24\ hr}$ decreases 7% and C_{max} decreases 5%. Half-life was unaffected by weight. Therefore, adjustment of aprepitant dose on the basis of body weight in adults is not necessary.

Slight effects of age on aprepitant pharmacokinetics were detected. Generally, for every 10-year increase in age over the age range of 18 to 85 years, the $AUC_{0\text{-}24\ hr}$ increases ~8% and the C_{max} increases ~7%. A study in which elderly subjects (≥65 years) were specifically evaluated also showed small increases in aprepitant AUC and C_{max} of 36% and 24%, respectively, compared with young adult subjects (≤45 years). These differences are not clinically meaningful and dose adjustment of aprepitant is not needed in the elderly.

The analysis of race included Caucasians, Blacks, and Hispanics. There were too few Asian subjects to provide meaningful comparisons. There were no significant differences between Black and Caucasian subjects in any of the aprepitant pharmacokinetic parameters. For Hispanic subjects, the $AUC_{0\text{-}24\ hr}$ was ~25% higher compared with Caucasians and 29% higher compared with Blacks, and the C_{max} was 22% higher compared with Caucasians and 31% higher compared with Blacks. These differences are not considered clinically meaningful. Therefore, dose adjustment of aprepitant is not needed for patients of different races.

Rationale for Clinically Meaningful Differences in Aprepitant Exposure

The safety and tolerability data obtained with aprepitant indicate that there is a wide upper therapeutic margin for this drug when used to treat CINV. The aprepitant regimen for CINV resulted in plasma AUC up to ~23 µg•hr/mL (see Section 6.3.7). To provide perspective, the highest exposure of aprepitant documented in non-CINV clinical studies was a plasma AUC of ~154 µg•hr/mL, determined on Day 7 of a study in which aprepitant was administered as a dose of 375 mg/day for 28 days (Protocol 043). This dose of aprepitant was shown to be well tolerated in subjects in Protocol 043, and also in patients treated with this dose for up to 6 weeks (Protocol 039). Therefore, increases in plasma concentration of aprepitant ~5- to 6-fold above those achieved with the regimen for CINV are well tolerated. Conversely, a decrease in aprepitant plasma AUC from

~23 μg•hr/mL (using the 125-mg/80-mg regimen) to ~4 μg•hr/mL (using the 40-mg/25-mg regimen) resulted in a clinically important decrease in antiemetic efficacy in Protocol 040/042. Thus, a reduction in plasma concentration of aprepitant of ~6-fold resulted in a clinically meaningful decrease in efficacy. It can be concluded that increases in plasma concentrations of aprepitant less than 2-fold are well tolerated.

6.3.9 Pharmacokinetics in Patients With Renal Insufficiency

Elimination of aprepitant occurs primarily through metabolism. Although renal insufficiency would not be expected to have any direct effect on the elimination of aprepitant, it was important to examine the effect of renal insufficiency on the pharmacokinetics of aprepitant since cancer patients may have renal insufficiency. Additionally, for patients undergoing hemodialysis, establishing the extent to which this procedure contributes to the removal of aprepitant from the circulation was important.

The effect of renal insufficiency on the pharmacokinetics of aprepitant (administered as a single dose of 240-mg market composition capsule formulation) was evaluated in patients with severe renal insufficiency (SRI, creatinine clearance <30 mL/min/1.73m^2) and patients with end-stage renal disease (ESRD).

Compared with healthy controls, ESRD patients had 42% lower $AUC_{0-\infty}$, 32% lower C_{max}, and 22% shorter half-life for aprepitant. Compared with healthy controls, SRI patients had 21% lower $AUC_{0-\infty}$, 32% lower C_{max}, and 1% shorter half-life for aprepitant.

The effect of renal insufficiency on plasma protein binding of aprepitant showed a trend for aprepitant protein binding to decrease with decreasing renal function. Comparison of unbound aprepitant AUC revealed no significant differences between patients and subjects (unbound aprepitant AUC was 16% lower in ESRD patients and 6% higher in SRI patients compared with their healthy control subjects). Therefore, the plasma concentration of unbound aprepitant is not significantly affected by renal insufficiency. Consequently, dose adjustment of aprepitant in renal insufficiency patients is not necessary.

Hemodialysis does not affect the pharmacokinetics of aprepitant and thus adjustment of aprepitant dose to compensate for hemodialysis is not necessary in ESRD patients, and hemodialysis would not be an effective remedy for an aprepitant overdose.

6.3.10 Pharmacokinetics in Patients With Hepatic Insufficiency

Aprepitant is cleared via metabolism and thus it was anticipated that patients with hepatic insufficiency might have impaired capacity to eliminate aprepitant from the plasma. The pharmacokinetics of aprepitant were examined in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), and healthy (age-, gender-, and weight-matched) control subjects. Each participant received the aprepitant 3-day regimen for CINV (125 mg on Day 1, 80 mg on Days 2 and 3).

Mild hepatic insufficiency patients had aprepitant $AUC_{0\text{-}24\ hr}$ 11% and 36% lower on Day 1 and Day 3, respectively, compared with healthy control subjects. Moderate hepatic insufficiency patients had aprepitant $AUC_{0\text{-}24\ hr}$ 10% and 18% higher on Day 1 and Day 3, respectively, compared with healthy control subjects. Half-life was slightly shorter in mild hepatic insufficiency patients (9.8 hours) than in their corresponding healthy controls (14.7 hours). There was no significant difference in half-life for moderate hepatic insufficiency patients (14.1 hours) versus their corresponding healthy controls (12.6 hours). There were no clinically important differences in C_{max} between mild or moderate hepatic insufficiency patients and healthy controls. Plasma total protein, albumin, and binding of aprepitant to plasma proteins were similar in patients with hepatic insufficiency and healthy subjects. These small differences between patients with hepatic insufficiency and healthy controls are not clinically meaningful. Therefore, adjustment of the aprepitant regimen for CINV is not required for patients with mild or moderate hepatic insufficiency. There are no aprepitant pharmacokinetic data or clinical experiences in patients with severe hepatic insufficiency (Child-Pugh score >9).

6.4 Drug Interactions

The potential for drug interactions with aprepitant has been well characterized in Clinical Pharmacology studies. Several drug interaction studies with aprepitant were conducted throughout the course of the development program. However, some of these studies (diltiazem, dextromethorphan, paroxetine, and oral contraceptive interaction studies) were conducted to support the use of aprepitant for chronic dosing indications, and, due to differences in dose levels or duration of dosing of aprepitant, they generally are not relevant to the short-term dosing proposed for prevention of CINV. Nevertheless, all of the drug interaction studies are described here for completeness.

In vitro data indicated that aprepitant is a substrate as well as an inhibitor of CYP3A4 activity. Because aprepitant is a substrate of CYP3A4, the effects on aprepitant pharmacokinetics of drugs that inhibit (ketoconazole, diltiazem) or induce (rifampin, dexamethasone) CYP3A4 were delineated. Several clinical studies were also conducted to evaluate thoroughly the effect of aprepitant on CYP3A4 activity in humans. These included the effects of aprepitant on the CYP3A4 substrates midazolam, erythromycin, diltiazem, dexamethasone, methylprednisolone, ondansetron, and granisetron. In addition, an ongoing study is examining the potential effect of aprepitant on docetaxel, a chemotherapeutic agent that is also a CYP3A4 substrate.

During the course of the clinical program, data indicated that aprepitant also appeared to induce the activities of CYP2C9 and CYP3A4. Therefore, these effects were defined in clinical interaction studies of aprepitant with warfarin and tolbutamide (CYP2C9 substrates) and midazolam (CYP3A4 substrate). Since aprepitant may be coadministered with drugs (such as certain chemotherapeutic agents) that are substrates of the P-gp transporter, an interaction study of aprepitant with digoxin (a P-gp substrate) was conducted. Studies were also conducted to evaluate the effects of aprepitant on CYP2D6 substrates (dextromethorphan, paroxetine), and on an oral contraceptive.

The drug interaction profile of aprepitant can be summarized as follows: The pharmacokinetics of aprepitant are affected by drugs that modulate CYP3A4 activity. The aprepitant regimen for CINV produces at most moderate inhibition of orally administered CYP3A4 substrates during dosing (comparable to verapamil, diltiazem, or grapefruit juice), which results in increases in the plasma concentrations of orally coadministered synthetic corticosteroids (dexamethasone and methylprednisolone). This effect of aprepitant was offset by dose adjustment of dexamethasone in the Phase III studies, to provide similar exposures of dexamethasone in the 2 treatment groups (Section 7). The CYP3A4 inhibitory effect of aprepitant is less for intravenously administered drugs (such as chemotherapeutic agents). Following completion of dosing, there is a small, transient inductive effect on CYP3A4.

The aprepitant regimen for CINV produces slight, transient induction of CYP2C9 activity that necessitates closer monitoring of narrow therapeutic index drugs metabolized by CYP2C9 (such as warfarin and phenytoin) when coadministered with aprepitant. The efficacy of oral contraceptives with 2 weeks of administration of aprepitant may be reduced.

Aprepitant had no clinically meaningful interactions with erythromycin, diltiazem, ondansetron, granisetron, digoxin, dextromethorphan, or paroxetine. Preliminary data in 5 patients indicate that coadministration of the aprepitant regimen for CINV had little effect on intravenously administered docetaxel pharmacokinetics, suggesting that aprepitant has low potential to affect the pharmacokinetics of chemotherapeutic agents metabolized by CYP3A4.

6.4.1 Effects of CYP3A4 Inhibitors on Aprepitant

In vitro data indicate that aprepitant is metabolized mostly by CYP3A4. Thus, it was anticipated that drugs that inhibit CYP3A4 would inhibit the metabolism of aprepitant leading to increased plasma concentrations of aprepitant. The potential for drugs that inhibit CYP3A4 activity to affect the pharmacokinetics of aprepitant was assessed in 2 different studies.

The effect of ketoconazole (a strong inhibitor of CYP3A4) on the pharmacokinetics of aprepitant was evaluated in a study in which subjects were administered a single dose of the 125-mg aprepitant market composition nanoparticle capsule alone or on Day 5 of a 10-day course of ketoconazole 400 mg/day. The $AUC_{0-\infty}$ of aprepitant administered with ketoconazole was almost 5-fold greater than the $AUC_{0-\infty}$ of aprepitant administered alone. The corresponding increases in C_{max} and half-life were ~1.5- and 3-fold, respectively. These pharmacokinetic effects were well tolerated in healthy subjects. These results confirm that CYP3A4 contributes substantially to the metabolism of aprepitant in vivo, and that concomitant administration of aprepitant with strong CYP3A4 inhibitors results in increased plasma concentrations of aprepitant.

The effect of a moderate CYP3A4 inhibitor (diltiazem) on aprepitant pharmacokinetics was evaluated in an early study in the program. Hypertensive patients were titrated to a

diltiazem dose of 120 mg 3 times daily, and were then administered a single 100-mg IV dose of L-758298 (prodrug of aprepitant) or placebo, followed by an aprepitant tablet formulation (300 mg/day) or placebo for 5 days (also discussed in Section 6.4.3.2). These doses of L-758298 and aprepitant tablet are approximately comparable to 121 mg and 234 mg, respectively, of the market composition capsule formulation based on human exposure data. Thus this interaction study evaluated doses substantially higher than those of the aprepitant regimen for CINV (125 mg and 80 mg).

The plasma $AUC_{0\text{-}24\ hr}$ of aprepitant was 45% higher and the C_{max} was 20% higher following dosing of L-758298 with diltiazem versus L-758298 alone. The plasma AUC and C_{max} of aprepitant following oral dosing for 5 days were also higher (~2-fold) when coadministered with diltiazem. These results confirmed that concomitant dosing of a moderate inhibitor of CYP3A4 (diltiazem) results in increases in the plasma concentration of aprepitant that are not considered clinically important.

As noted previously in Section 6.3.8, plasma concentrations of aprepitant ~5- to 6-fold above those achieved with the regimen for CINV are well tolerated; thus, the effect of CYP3A4 inhibitors on aprepitant is unlikely to pose a clinical safety concern. Nevertheless, coadministration of aprepitant with strong CYP3A4 inhibitors (e.g., ketoconazole) may result in clinically important elevations of plasma concentrations of aprepitant and should be approached cautiously. Concomitant administration of aprepitant with moderate CYP3A4 inhibitors (e.g., diltiazem) does not result in clinically meaningful changes in plasma concentration of aprepitant.

6.4.2 Effects of CYP3A4 Inducers on Aprepitant

Inducers of CYP3A4 would be expected to decrease plasma concentrations of aprepitant. The effect of rifampin (a strong inducer of CYP3A4 and other CYPs) on the pharmacokinetics of aprepitant was evaluated after subjects were administered a single 375-mg dose of aprepitant market composition capsules alone and on Day 9 of a 14-day course of rifampin 600 mg/day. The $AUC_{0\text{-}\infty}$ of aprepitant administered with rifampin was ~11-fold lower than the $AUC_{0\text{-}\infty}$ of aprepitant administered alone. The corresponding decreases in C_{max} and half-life of aprepitant were ~2.5- and 3-fold, respectively. Coadministration of strong CYP3A4 inducers with aprepitant would be expected to decrease plasma concentrations (and potentially decrease the antiemetic efficacy) of aprepitant.

Dexamethasone is also an inducer of CYP3A4. A study (Protocol 041) examined the pharmacokinetics of aprepitant administered as the 5-day regimen for CINV concomitantly with dexamethasone (20 mg P.O. on Day 1 followed by 8 mg/day P.O. on Days 2 through 5) and ondansetron (32 mg IV on Day 1). Administration of dexamethasone and ondansetron did not affect the AUC of aprepitant to a clinically meaningful extent (aprepitant AUC was 30% higher on Day 1 and 2% lower on Day 5 when aprepitant was coadministered with dexamethasone and ondansetron). Thus,

although dexamethasone induces CYP3A4, an inductive effect was not apparent when coadministered with ondansetron and the aprepitant regimen for CINV.

In summary, coadministration of aprepitant and rifampin results in clinically important decreases in plasma concentrations of aprepitant that may result in decreased efficacy of aprepitant. Since CYP3A4 contributes significantly to the metabolism of aprepitant, concomitant therapy of aprepitant with strong CYP3A4 inducers (e.g., rifampin) should be approached cautiously. However, less strong inducers of CYP3A4 (e.g., dexamethasone) do not affect the pharmacokinetics of aprepitant administered as the regimen for CINV.

6.4.3 Effects of Aprepitant as a CYP3A4 Inhibitor

6.4.3.1 Effect of Aprepitant on Probe CYP3A4 Substrates: Midazolam and Erythromycin

Midazolam is a benzodiazepine and CYP3A4 substrate whose metabolism is highly sensitive to the modulation of CYP3A4 activity in vivo. Consequently, it is frequently used as a sensitive probe to assess the effects of other drugs on CYP3A4 activity in vivo, and when administered orally it provides an assessment of systemic and first pass CYP3A4 activity combined. Erythromycin is also a substrate of CYP3A4, which, when given intravenously as small radiolabeled probe doses that do not inhibit CYP3A4 activity, provides an index of only systemic CYP3A4 activity via a test called the erythromycin breath test (EBT) [31].

In Protocol 016, aprepitant was administered once daily for 2 weeks at a dose of a tablet formulation that was approximately comparable to a dose of 72 mg of the aprepitant market formulation nanoparticle capsule. Subjects received a single 2-mg oral dose of midazolam coadministered with an IV injection of [^{14}C *N*-methyl] erythromycin prior to aprepitant dosing and 1 hour after the last dose of aprepitant on Day 14. The midazolam AUC increased 2.1-fold and C_{max} increased 2-fold on the last day of aprepitant dosing (Day 14). There was a 9% increase in the EBT (% ^{14}C exhaled/hour) with aprepitant, which was not statistically significant. For reference, inhibitors of CYP3A4 such as ketoconazole cause as much as a 76% decrease in the EBT, and inducers of CYP3A4 such as rifampin increase the EBT by as much as 86% [32]. This result indicated that aprepitant inhibited mostly first pass CYP3A4 activity with little effect on systemic CYP3A4 activity, and suggested that aprepitant would have little effect on CYP3A4 substrates administered intravenously.

The effect of aprepitant on CYP3A4 activity using the aprepitant 5-day regimen for CINV was evaluated as part of Protocol 041 with oral midazolam as a probe (also described in Section 6.4.2). Subjects received a single oral dose of midazolam prior to Day 1 dosing and on Days 1 and 5 (1 hour after aprepitant dosing). Dexamethasone and ondansetron were not coadministered with aprepitant and midazolam to the subjects in this part of Protocol 041. The $AUC_{0-\infty}$ of midazolam was increased 2.3-fold on Day 1 and 3.3-fold on Day 5 when midazolam was orally coadministered with the aprepitant 5-day

regimen in Protocol 041. The effect of the 5-day aprepitant regimen for CINV on oral midazolam AUC (2.3- to 3.3-fold increase) is comparable to or less than the CYP3A4 inhibitory effects of commonly prescribed drugs such as verapamil (2.9-fold increase), fluconazole (3.5-fold increase), or diltiazem (3.7-fold increase), and is similar to that of grapefruit juice (2.4-fold increase).

A separate study (Protocol 076) evaluated the effect of aprepitant on systemic CYP3A4 activity using IV midazolam, in which healthy young subjects received either the aprepitant 3-day regimen for CINV (without dexamethasone and ondansetron) or placebo with a single IV dose of midazolam prior to Day 1 dosing and at 3 time points after completion of aprepitant dosing (Days 4, 8, and 15). On Day 4, 24 hours after the last dose of the 3-day regimen, aprepitant (relative to placebo) had a weak inhibitory effect on CYP3A4 activity manifested as a 25% (1.25-fold) increase in IV midazolam $AUC_{0-\infty}$ and a 20% decrease in clearance. Data on the potential inductive effect of aprepitant on CYP3A4 are discussed in Section 6.4.4.1.

The inhibitory effect of aprepitant on CYP3A4 activity is unlikely to be clinically important for most drugs with which it might be coadministered (see diltiazem interaction in Section 6.4.3.2). The relative lack of effect of aprepitant on an intravenously administered CYP3A4 probe substrate (erythromycin) indicates that the moderate inhibition of CYP3A4 by aprepitant results from a significant first pass inhibition that would affect orally administered drugs, and that intravenously administered CYP3A4 substrates (such as many chemotherapeutic agents) are likely to be affected less by aprepitant. This conclusion is supported by the minimal effects of aprepitant on intravenously administered drugs that are CYP3A4 substrates (methylprednisolone, ondansetron, docetaxel) described in subsequent Sections 6.4.3.3, 6.4.3.4, and 6.4.3.5.

Although the effect of aprepitant on orally administered CYP3A4 substrates is moderate and would not pose a clinical safety concern for most drugs, such an effect may have serious clinical consequences for a few drugs that are orally administered CYP3A4 substrates and for which increased plasma concentrations could result in significant toxicity (e.g., QT_c interval prolongation with pimozide, terfenadine, astemizole, or cisapride). However, it should be noted that terfenadine, astemizole, and cisapride are no longer marketed in the United States. The potential effects of increased plasma concentrations of midazolam or other benzodiazepines that are sensitive CYP3A4 substrates with relatively narrow therapeutic margins (alprazolam, triazolam) should be considered when orally coadministering these agents with aprepitant.

6.4.3.2 Effect of Aprepitant on Diltiazem

Diltiazem is both a substrate and an inhibitor of CYP3A4. Therefore, it was also of interest to determine the effect of aprepitant on the pharmacokinetics and pharmacodynamics (blood pressure and electrocardiogram [ECG] effects) of diltiazem as part of Protocol 011 (also described in Section 6.4.1).

Consistent with the CYP3A4 inhibitory effect of aprepitant observed with midazolam (see Section 6.4.3.1), the $AUC_{0\text{-}24\ hr}$ of diltiazem was increased up to 2-fold when diltiazem was coadministered with IV L-758298 or oral aprepitant. Concurrent administration of aprepitant and diltiazem did not result in clinically meaningful PR interval prolongation, changes in heart rate, or systolic or diastolic blood pressure beyond those changes induced by diltiazem alone. The doses and duration of dosing of aprepitant used in this study provided aprepitant exposures higher than those that would be achieved by the regimen for CINV. It is likely that the effect of the aprepitant regimen for CINV on diltiazem would be less than that observed in Protocol 011. Therefore, no dose adjustments of aprepitant or diltiazem are needed when these are coadministered.

6.4.3.3 Effect of Aprepitant on Corticosteroids: Dexamethasone and Methylprednisolone

Dexamethasone and methylprednisolone are 2 corticosteroids commonly used for the treatment of CINV; both are likely be used as antiemetic therapy in conjunction with aprepitant, and both are sensitive substrates of CYP3A4. Therefore, investigations of the effect of aprepitant on the pharmacokinetics of these corticosteroids were undertaken.

The effect of the aprepitant 5-day regimen for CINV on dexamethasone pharmacokinetics was examined as part of Protocol 041 (also described in Section 6.4.3.1). Dexamethasone was orally coadministered either as standard antiemetic doses (20 mg on Day 1 and 8 mg/day on Days 2 to 5) or with lower dexamethasone doses (dexamethasone 12 mg on Day 1 and 4 mg/day on Days 2 to 5). Ondansetron was administered in each regimen (32 mg IV on Day 1 only). Coadministration of the aprepitant 5-day regimen for CINV with the standard dexamethasone doses resulted in a ~2-fold increase in dexamethasone AUC on both Day 1 and Day 5. This effect is consistent with inhibition by aprepitant of dexamethasone metabolism via CYP3A4.

The lower dexamethasone doses coadministered with the aprepitant 5-day regimen produced plasma concentrations of dexamethasone (dexamethasone AUC of 1160 ng•hr/mL on Day 1 and 303 ng•hr/mL on Day 5) that were similar to those of the standard antiemetic doses of dexamethasone without aprepitant (dexamethasone AUC of 897 ng•hr/mL on Day 1 and 292 ng•hr/mL on Day 5). Therefore, an approximate 2-fold reduction of dexamethasone doses, when coadministered with the aprepitant regimen for CINV, provides similar dexamethasone exposure compared with the administration of dexamethasone without aprepitant. This effect provided the basis for use of the modified dexamethasone doses coadministered with aprepitant in Phase III studies to facilitate interpretation of efficacy results (see Section 7.5.2).

A separate study (Protocol 064) examined the effect of aprepitant on orally and intravenously administered methylprednisolone. Administration of the 3-day aprepitant regimen for CINV with methylprednisolone (125 mg IV on Day 1 and 40 mg taken orally on Days 2 and 3) resulted in an increase in the AUC of methylprednisolone of 34% (1.34-fold) on Day 1 and 150% (2.5-fold) on Day 3. When coadministered with the aprepitant regimen for CINV, the IV methylprednisolone dose should be reduced by

~25% and the oral methylprednisolone dose should be reduced by ~50% to achieve exposures of methylprednisolone similar to those obtained when it is given without aprepitant.

This effect is consistent with inhibition by aprepitant of methylprednisolone metabolism via CYP3A4. The effect of aprepitant on oral methylprednisolone (2.5-fold AUC increase) was similar in magnitude to the effect of aprepitant on oral midazolam (2.3- to 3.3-fold increase, see Section 6.4.3.1) indicating that methylprednisolone is a sensitive CYP3A4 substrate. The extent of CYP3A4 inhibition is less for intravenously versus orally administered methylprednisolone.

6.4.3.4 Effect of Aprepitant on Serotonin Receptor Type 3 (5-HT_3) Antagonists: Ondansetron and Granisetron

Ondansetron and granisetron are 5-HT_3–receptor antagonists used frequently to treat CINV. Both of these drugs are metabolized in part by CYP3A4 [33; 34]. Therefore, it was important to characterize the potential pharmacokinetic interactions between aprepitant and these drugs because they may be frequently coadministered to treat CINV.

The potential for interaction between aprepitant and ondansetron was examined as part of Protocol 041 (also described in Sections 6.4.3.1 and 6.4.3.3) in which aprepitant was administered as a high-dose regimen of market composition capsules (375 mg on Day 1, 250 mg/day on Days 2 through 5). Note that these doses of aprepitant are at least 3-fold higher than the doses of aprepitant that are recommended for clinical use in the treatment of CINV. Ondansetron was administered as 32 mg IV on Day 1 only, and dexamethasone was coadministered orally as 20 mg on Day 1 and 8 mg/day on Days 2 through 5.

The plasma ondansetron $AUC_{0-\infty}$ was 15% higher when ondansetron was coadministered with the high-dose aprepitant regimen compared with administration without aprepitant. There were no significant differences in maximum plasma concentrations or half-life of ondansetron. This slight difference in ondansetron AUC is considered clinically unimportant. Therefore, adjustment of the IV dose of ondansetron is not necessary when it is coadministered with aprepitant.

In a separate study (Protocol 050), the potential for interaction between aprepitant and granisetron was examined. Aprepitant was administered as the 3-day regimen for CINV with a single oral dose of granisetron 2 mg on Day 1 or a single oral dose of granisetron 2 mg alone in a separate period (dexamethasone was not administered in this study). There was no significant effect of aprepitant on granisetron $AUC_{0-\infty}$, C_{max}, or half-life. Thus, adjustment of the dose of granisetron is not necessary when it is coadministered with the aprepitant regimen for CINV.

The only other 5-HT_3–receptor antagonist currently available for use in the United States is dolasetron. CYP3A4 does not contribute substantially to the metabolism of dolasetron or its active metabolite, and moderate CYP3A4 inhibitors (verapamil, diltiazem) do not

affect the clearance of the active metabolite of dolasetron. Thus it is unlikely that aprepitant would significantly affect the pharmacokinetics of dolasetron.

In summary, aprepitant does not significantly affect the pharmacokinetics of ondansetron or granisetron and thus adjustment of the doses of these 2 antiemetic drugs is not necessary when they are coadministered with aprepitant. Since both ondansetron and granisetron are CYP3A4 substrates, these results suggest that aprepitant does not substantially inhibit the overall disposition of all CYP3A4 substrates.

6.4.3.5 Effect of Aprepitant on the Pharmacokinetics of Docetaxel

A number of cancer chemotherapeutic agents are metabolized to various degrees via CYP3A4. These include etoposide, vinca alkaloids (vinblastine, vincristine, and vinorelbine tartrate), taxanes (docetaxel and paclitaxel), irinotecan, and ifosfamide (see Table 5 in Section 6.4.8) [35]. Coadministration of these agents with drugs that inhibit CYP3A4 (such as aprepitant) might result in decreased metabolic clearance of these agents and could result in increased exposure and increased toxicity of these compounds.

Of these agents, docetaxel has been noted to be particularly susceptible to alterations of CYP3A4 activity. In vitro data indicate that docetaxel is metabolized predominantly by CYP3A4 [36]. Studies in cancer patients receiving docetaxel showed that the in vivo activity of CYP3A4 (assessed using sensitive and specific probes for hepatic CYP3A4 activity) correlated with docetaxel clearance, and patients with the lowest CYP3A4 activity exhibited lower docetaxel clearance and greater docetaxel toxicity [37; 38]. Coadministration of oral docetaxel with oral cyclosporine A (an inhibitor of CYP3A4 activity and P-gp) resulted in a 7.3-fold increase in the plasma AUC of docetaxel [39]. Thus, both in vitro and in vivo data confirm that docetaxel is metabolized via CYP3A4, and it is an appropriate agent to determine if aprepitant affects to a clinically important extent the pharmacokinetics of a chemotherapeutic agent metabolized by CYP3A4.

An ongoing study (Protocol 051) is being conducted in patients receiving IV docetaxel as single-agent chemotherapy. In each of 2 consecutive chemotherapy cycles, patients receive the same dose of docetaxel (60 to 100 mg/m^2) and in 1 of the cycles (randomly assigned), they receive open label aprepitant 125 mg 1 hour prior to IV infusion of docetaxel followed on Days 2 and 3 with single oral doses of aprepitant 80 mg/day. In the other cycle, the patients receive docetaxel alone. Patients are allowed to receive other antiemetic medications with their treatment but they must receive the same concomitant medications at the same dose in each treatment period.

A total of 5 patients have so far completed the study. Preliminary pharmacokinetic data show that the geometric mean $AUC_{0-\infty}$ of docetaxel was 2.98 µg•hr/mL and 3.05 µg•hr/mL when administered with and without aprepitant, respectively. The geometric mean (range) AUC ratio (with aprepitant/without aprepitant) was 0.98 (0.77 to 1.10). The harmonic mean observed terminal half-life of docetaxel was 8.8 hours and 9.4 hours and the mean (range) plasma clearance of docetaxel was 27.2 (18.0 to 37.0) $L/h/m^2$ and 26.6 (17.2 to 36.0) $L/h/m^2$ when administered with and without aprepitant,

respectively. The geometric mean (range) plasma clearance ratio (with aprepitant/without aprepitant) was 1.02 (0.91 to 1.30).

In summary, coadministration of the aprepitant 3-day regimen for CINV had little, if any, effect on docetaxel pharmacokinetics and was generally well tolerated in these 5 patients.

6.4.4 Effects of Aprepitant as a CYP Inducer

6.4.4.1 Aprepitant Induction of CYP3A4

During the course of the clinical program, data from a multiple-dose study (Protocol 043) in which aprepitant was administered as single oral doses of either 125-mg or 375-mg market composition capsules once daily for 28 days became available. Trough plasma concentrations of aprepitant initially rose up to approximately Day 7 and then decreased beyond Day 7 suggesting that aprepitant induces its own metabolism when dosed over several weeks. Since aprepitant is metabolized mostly by CYP3A4, these data suggest that aprepitant induces CYP3A4 activity. However, it was unclear what relevance this finding had for the aprepitant 3-day regimen for CINV.

To characterize the potential for CYP3A4 inductive effects of the aprepitant regimen for CINV, Protocol 076 was conducted (also described in Section 6.4.3.1) in which subjects received the aprepitant 3-day regimen for CINV or placebo, and they also received a single IV dose of midazolam prior to Day 1 dosing and at 3 time points after completion of aprepitant dosing (Days 4, 8, and 15). As noted in Section 6.4.3.1, the aprepitant regimen for CINV produced a small net inhibitory effect of CYP3A4 on Day 4 followed on Day 8 (i.e., 5 days after completion of aprepitant dosing) by a weak inductive effect on CYP3A4 activity manifested by a 19% decrease in midazolam $AUC_{0-\infty}$ and 24% increase in midazolam clearance with no significant change in midazolam C_{max} or half-life, relative to placebo. There was no effect of the aprepitant 3-day regimen for CINV on CYP3A4 activity at Day 15 (i.e., 12 days after completion of aprepitant dosing). The effect at Day 8 represents weak CYP3A4 induction and is clinically unimportant. Note for comparison that rifampin (a strong inducer) produces a decrease in midazolam AUC of 96% [40].

Summary of Aprepitant Effects on CYP3A4 Substrates

In summary, aprepitant is both an inhibitor and inducer of CYP3A4. When aprepitant is present in the plasma (e.g., during Days 1 through 3 and on the day after completion of dosing of the regimen for CINV), the net effect of aprepitant is inhibition of CYP3A4 manifested by increased plasma concentration of the CYP3A4 substrate probe, midazolam. Inhibition of CYP3A4 by aprepitant is less for intravenously administered substrates. After aprepitant has been cleared from the plasma (e.g., 5 days after completion of the aprepitant regimen for CINV), the inhibitory effect of aprepitant is no longer present and a small inductive effect on CYP3A4 activity becomes apparent (manifested as a slight decrease in plasma concentration of midazolam). The small,

clinically unimportant inductive effect is no longer present 12 days after completion of the regimen.

6.4.4.2 Aprepitant Induction of CYP2C9

Aprepitant may be coadministered with warfarin in cancer patients. Since warfarin has a narrow therapeutic index, it was necessary to assess the potential effect of aprepitant on warfarin pharmacokinetics and pharmacodynamics (International Normalized Ratio of prothrombin time or INR). This was accomplished in a study in which healthy young subjects received single daily oral doses of warfarin titrated to achieve a stable INR. After attainment of a stable INR, the warfarin dose was kept constant and subjects then received either the aprepitant 3-day regimen for CINV or placebo on Days 1, 2, and 3. Ondansetron and dexamethasone were not administered in this study.

Treatment with aprepitant had no significant effect on plasma concentrations of either R(+)- or S(-)-warfarin isomers on Day 3. However, following completion of the aprepitant regimen for CINV, there was a statistically significant decrease (by as much as 34%) of S(-)-warfarin trough plasma concentration from Days 5 through 8. There was a small (7%) decrease in R(+)-warfarin trough plasma concentrations only on Day 8. This was accompanied by a small (up to 14%) but statistically significant decrease in the INR on Days 7 and 8. Since S(-)-warfarin is metabolized almost exclusively by CYP2C9, this result suggested that aprepitant induces CYP2C9 activity. It is noteworthy that aprepitant did not substantially affect the pharmacokinetics of R(+)-warfarin, which is metabolized by several CYPs (3A4, 1A2, 2C19). This suggests that the aprepitant regimen for CINV does not substantially affect the metabolism of drugs metabolized via multiple CYPs, as noted previously for ondansetron and granisetron (see Section 6.4.3.4).

The time course of aprepitant induction of CYP2C9 activity and its recovery was assessed in Protocol 076 (also described in Sections 6.4.3.1 and 6.4.4.1). In this study, healthy young subjects received either the aprepitant 3-day regimen for CINV or placebo, and also received single oral 500-mg doses of tolbutamide (a specific CYP2C9 substrate) prior to Day 1 and at 3 time points after completion of aprepitant dosing (Days 4, 8, and 15). The aprepitant regimen for CINV (relative to placebo) resulted in decreases in the plasma $AUC_{0-\infty}$ of tolbutamide of 23% and 28% on Days 4 and 8, respectively, indicative of slight CYP2C9 induction. There were slight decreases in tolbutamide half-life without change in C_{max} on Days 4 and 8. On Day 15, the tolbutamide $AUC_{0-\infty}$ was approaching baseline (15% lower compared with placebo), a difference that is not clinically relevant.

These results are consistent with transient, modest induction of CYP2C9 activity by the aprepitant regimen for CINV. Coadministration of aprepitant with drugs that are known to be metabolized by CYP2C9 may result in slightly lower plasma concentrations of these drugs for up to 12 days after completion of the regimen for CINV. This effect is not of clinical importance for most drugs that are CYP2C9 substrates (e.g., nonsteroidal anti-inflammatory drugs such as diclofenac). However, for drugs metabolized by CYP2C9 that have a narrow therapeutic index (e.g., warfarin, phenytoin), this small

effect could be clinically important. Accordingly, in patients on chronic warfarin therapy, after completion of the 3-day regimen of aprepitant for each chemotherapy cycle, the prothrombin time (INR) should be closely monitored to establish and maintain the required dose of warfarin. There are no chemotherapeutic agents that are known to be predominantly metabolized by CYP2C9 (although the metabolic pathways are not well characterized for all chemotherapeutic agents), and thus the slight inductive effect of aprepitant on CYP2C9 activity likely would not significantly affect the pharmacokinetics of coadministered chemotherapeutic agents.

6.4.5 P-glycoprotein (P-gp)

In vitro data indicate that aprepitant is a substrate and weak inhibitor of P-gp (Section 4.3) raising the possibility that aprepitant might affect other drugs, such as some chemotherapeutic agents, that are P-gp substrates (see Table 5 in Section 6.4.8). Therefore, it was important to evaluate the effect of the aprepitant 5-day regimen for CINV on P-gp activity in Protocol 047 using digoxin as a specific P-gp substrate. The aprepitant regimen administered to healthy subjects who had been dosed with digoxin to steady state had no significant effect on digoxin pharmacokinetics either during coadministration or for 3 days after completion of the aprepitant regimen. This finding supports the conclusion that aprepitant is not an inhibitor of the P-gp transporter. Also of importance, these data indicate that this dosing regimen of aprepitant does not induce the activity of P-gp.

The lack of effect of aprepitant on P-gp activity, as assessed using digoxin as a P-gp substrate, indicates that the aprepitant regimen for CINV is unlikely to result in clinically significant interactions with other drugs that are P-gp substrates.

6.4.6 CYP2D6 Substrates

Aprepitant is not a substrate but is a very weak inhibitor of CYP2D6 in vitro (IC_{50} >66 μM), and thus an interaction in vivo between aprepitant and drugs metabolized by CYP2D6 is unlikely. However, as part of a Phase II study in depression (Protocol 028), aprepitant was coadministered with paroxetine, a CYP2D6 substrate. Therefore, to ensure that a pharmacokinetic interaction would not confound interpretation of data from Protocol 028, the potential effect of aprepitant on in vivo CYP2D6 activity was investigated. The potential for aprepitant to affect CYP2D6 activity was assessed in 2 studies using the CYP2D6 substrates dextromethorphan or paroxetine. The first study (Protocol 016) showed no significant effect of aprepitant (dosed for 18 days at a dose approximately comparable to 72 mg of market composition capsules) on CYP2D6 assessed using dextromethorphan as a probe. The second study (Protocol 021) showed that concomitant dosing of aprepitant (dosed for 2 weeks as daily tablet doses approximately comparable to 85 to 170 mg of the market composition capsule) and paroxetine (20 mg/day) resulted in slightly (~25%) decreased plasma AUC of both aprepitant and paroxetine. The mechanism for the reduction in paroxetine level is yet to be determined but is unlikely to represent induction of CYP2D6 activity since CYP2D6

is not known to be an inducible enzyme [41]. These results indicate that aprepitant does not inhibit the metabolism of CYP2D6 substrates in vivo.

6.4.7 Oral Contraceptive

Aprepitant has been studied for other indications in which it is administered chronically in patient populations that include women taking oral contraceptives (OC). Therefore, 2 interaction studies of aprepitant and an OC were conducted. Administration of aprepitant (either as a tablet dose approximately comparable to 180 mg of market composition capsule or a market composition capsule dose of 100 mg) for the first 2 weeks of the OC cycle in women taking ORTHO-NOVUM™ 1/35 (35 µg ethinyl estradiol [EE] and 1 mg norethindrone [NET]) resulted in significant pharmacokinetic and pharmacodynamic effects. Coadministration of aprepitant with the OC resulted in a 41 to 43% reduction in EE AUC and a smaller reduction (8 to 9%) in NET AUC.

In both studies, a significant pharmacodynamic interaction was observed. All of the women in both studies who received aprepitant experienced abnormal withdrawal bleeding at the end of their OC cycles (Days 22 through 28) in which aprepitant had been administered. The abnormalities consisted largely of scant or absent withdrawal bleeding at the end of the cycle. In light of the effect of aprepitant on the pharmacokinetics of EE, it is likely that this pharmacodynamic effect was a consequence of decreased serum concentrations of EE. The effect of aprepitant on EE and NET pharmacokinetics is consistent with induction of their metabolism (EE > NET) although the precise mechanism is yet to be defined. The efficacy of OCs during chronic administration of aprepitant may be reduced. Although a 3-day regimen of aprepitant given concomitantly with OCs has not been studied, alternative or back-up methods of contraception should be used.

6.4.8 Potential for Interaction With Chemotherapeutic Agents

Aprepitant will be administered with a variety of chemotherapeutic agents. Thus to assess the potential for effects of aprepitant on chemotherapy, it is important to consider the metabolism and disposition of these agents. All patients in the Phase III studies received cisplatin as part of their treatment. Cisplatin is not metabolized by cytochrome P-450 enzymes and thus its pharmacokinetics as well as those of similar drugs (carboplatin) are unlikely to be affected by aprepitant [35].

The disposition of most chemotherapeutic agents involves metabolism and/or transport. Although the metabolic pathways may not be well characterized for all chemotherapeutic agents, it has been demonstrated that the cytochrome P-450 enzymes play a predominant role in the metabolism of many chemotherapeutic agents, and CYP3A4 is involved in the metabolism of many agents [35]. In addition, P-gp has been identified as a key transporter involved in the disposition of these drugs. Table 5 describes commonly used chemotherapeutic agents and CYPs predominantly involved in their metabolism. The compounds transported by P-gp are also indicated. Note that for most of these compounds, CYP3A4 and/or P-gp play a major role in their disposition. CYP2C9 is not

known to be predominantly involved in the metabolism of any of these compounds. Therefore, the potential for aprepitant to affect the pharmacokinetics of chemotherapeutic agents can be defined based on its effects on CYP3A4 and P-gp.

The drug interaction profile of aprepitant described in previous sections indicates that it had a weak inhibitory effect (34% increase in AUC) on a sensitive CYP3A4 substrate (methylprednisolone) administered intravenously on Day 1 (when IV chemotherapy would be administered). The lack of clinically meaningful effects of aprepitant on other IV CYP3A4 substrates (erythromycin, ondansetron) and an IV chemotherapy CYP3A4 substrate (docetaxel) suggests that there is low potential for aprepitant to affect the pharmacokinetics of intravenously administered chemotherapeutic agents metabolized by CYP3A4. The lack of effect of aprepitant on P-gp (see digoxin interaction in Section 6.4.5) indicates that there is also low potential for interactions of aprepitant with chemotherapeutic agents handled by P-gp.

The modest inductive effects of aprepitant on CYP3A4 and CYP2C9 (Section 6.4.4) would not be expected to affect coadministered chemotherapy because: (1) they occur several days after chemotherapy is given and are transient (resolving within 2 weeks); (2) HEC typically is administered every 3 to 4 weeks (therefore cumulative induction with repeated cycles would not occur); (3) the effects are relatively modest; and (4) CYP2C9 is not known to be predominantly involved in the metabolism of any chemotherapeutic agents.

In summary, CYP3A4 and P-gp are the most common pathways known to affect the pharmacokinetics of chemotherapeutic agents. Interaction studies with sensitive IV CYP3A4 substrates (erythromycin, methylprednisolone), a chemotherapeutic agent metabolized by CYP3A4 (docetaxel), and a P-gp substrate (digoxin) suggest that, overall, there is a low potential for aprepitant to produce clinically meaningful effects on the pharmacokinetics of intravenously administered chemotherapeutic agents. Safety results from Phase III studies support this conclusion (Section 8).

Table 5

Involvement of Cytochrome P-450 (CYP) Enzymes and P-Glycoprotein (P-gp) in the Disposition of Commonly Used Chemotherapeutic Agents

Chemotherapeutic Agent	Metabolized/Transported By:
Cyclophosphamide	CYP2B6
Ifosfamide	CYP3A4
Doxorubicin	P-gp
Irinotecan	CYP3A4, CYP3A5, P-gp
Etoposide	CYP3A4, P-gp
Docetaxel	CYP3A4, P-gp
Paclitaxel	CYP2C8, CYP3A4, P-gp
Vinblastine	CYP3A4, P-gp
Vincristine	CYP3A4, CYP3A5-7, P-gp
Vinorelbine	CYP3A4, P-gp

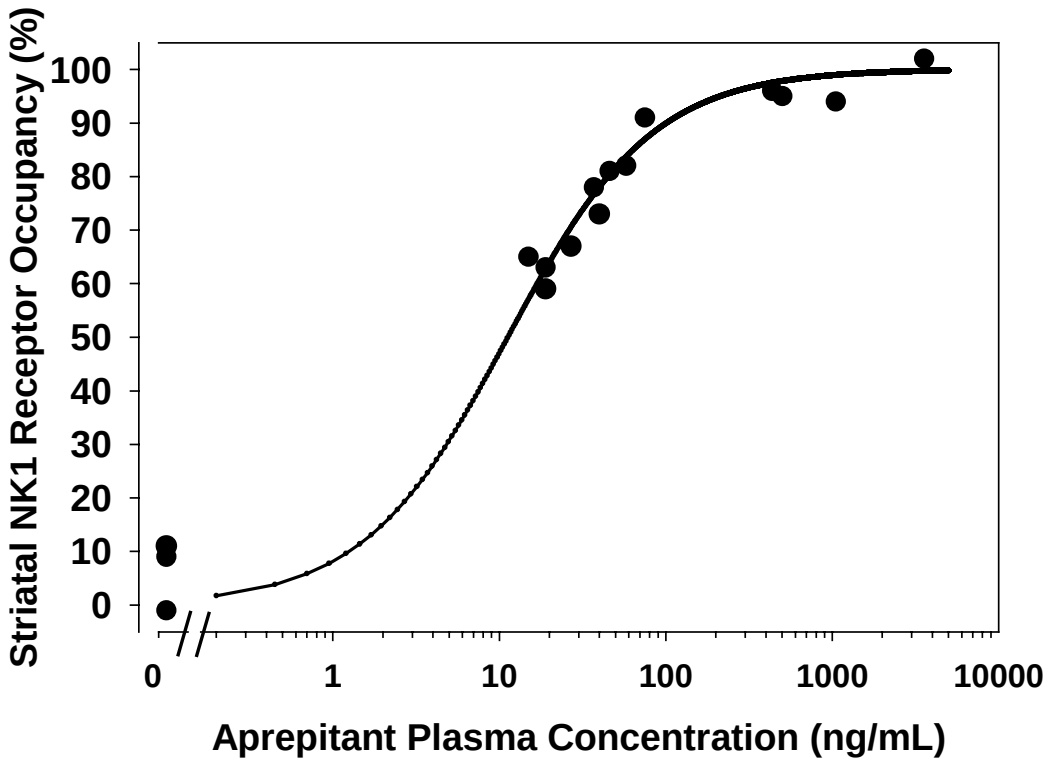
6.5 Pharmacokinetic/CNS NK_1-Receptor Occupancy Correlations

The assessment of the pharmacology of CNS active drugs is greatly facilitated by the ability to measure quantitatively CNS-receptor pharmacology using PET. To enable measurement of binding of aprepitant to brain NK_1 receptors in vivo in humans, a specific NK_1-receptor binding ligand was developed (L-829165, see Section 3.4). This compound binds reversibly and quantitatively to human NK_1 receptors with high affinity, and can be easily labeled with a positron emitting isotope (^{18}F). The resultant ^{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-receptor antagonists including aprepitant. The correlation of plasma aprepitant levels with the binding of aprepitant to brain NK_1-receptors was assessed in 2 studies in healthy young men.

Using ^{18}F-L-829165 as a PET tracer, the binding of aprepitant to brain NK_1 receptors was quantified by measuring blockade of binding of the PET tracer to NK_1 receptors in the corpus striatum (the area of the brain with the highest concentration of NK_1 receptors). Aprepitant was administered as various tablet doses to healthy young men for 2 weeks. By comparing PET scans before and at the end of the dosing period, it was possible to determine the extent of binding of aprepitant to brain NK_1 receptors (occupancy), and it was also possible to correlate the occupancy of brain NK_1 receptors with plasma trough concentrations of aprepitant (Figure 6). Based on these PET data, aprepitant plasma concentrations of ~10 ng/mL and ~100 ng/mL are predicted to produce brain (corpus striatum) NK_1-receptor occupancies of ~50% and ~90%, respectively.

Figure 6

Correlation of Aprepitant Plasma Trough Concentration With Binding of Aprepitant to Striatal NK_1 Receptors



Each point represents binding in an individual subject

Correlation of NK_1-receptor blockade and antiemetic efficacy of aprepitant can be estimated indirectly by comparisons of efficacy in the Phase IIb CINV dose-range finding study, plasma pharmacokinetics at these doses in healthy subjects, and the pharmacokinetic/occupancy relationship. In the Phase IIb study of CINV, antiemetic efficacy was observed at all of the aprepitant dose levels (Day 1/Days 2 through 5) studied, with submaximal efficacy at the 40-mg/25-mg dose, and maximal efficacy at the 125-mg/80-mg dose with no apparent benefit of increasing the dose to 375 mg/250 mg.

Pharmacokinetics were obtained from healthy subjects who received treatments similar to those received by patients in the Phase IIb study (administered as market composition nanoparticle capsule with concomitant dexamethasone and ondansetron). Plasma concentrations after the 375-mg/250-mg and 125-mg/80-mg regimens are predicted to

provide >95% NK_1-receptor blockade throughout each of Days 1 through 5. The mean trough plasma concentrations of aprepitant for the aprepitant 40-mg/25-mg regimen would result in NK_1-receptor occupancies ranging from ~80 to 89% at trough on each of Days 1 through 5. Thus, it is concluded that, on average, nearly complete (>95%) NK_1-receptor blockade provides maximum antiemetic efficacy of aprepitant, and NK_1-receptor blockade of ~80 to 90% provides significant but less than maximal antiemetic efficacy.

6.6 Conclusions—Aprepitant Pharmacokinetics/Pharmacodynamics

- Aprepitant is well absorbed after oral administration with minimal food effect. Bioavailability of the market formulation is 59 to 67% (fasting).
- The plasma half-life of aprepitant is consistent with once-daily dosing and the regimen for CINV provides approximately constant daily plasma exposure of aprepitant.
- Aprepitant is eliminated by metabolism via CYP3A4 and its metabolites do not contribute to its activity in vivo.
- The pharmacokinetics of aprepitant are not significantly affected by race, gender, body weight, or age.
- Dose adjustment of aprepitant is not necessary in patients with renal insufficiency or mild to moderate hepatic insufficiency.
- Nearly complete (>95%) brain NK_1-receptor blockade provides maximum antiemetic efficacy of aprepitant in humans.

6.7 Conclusions—Aprepitant Drug Interactions

- Coadministration of aprepitant with strong CYP3A4 inhibitors (e.g., ketoconazole) may result in clinically important elevations of plasma concentrations of aprepitant and should be approached cautiously; but concomitant administration of aprepitant with moderate CYP3A4 inhibitors (e.g., diltiazem) does not result in clinically meaningful changes in plasma concentrations of aprepitant.
- Coadministration of aprepitant and rifampin results in clinically important decreases in plasma concentrations of aprepitant that may result in decreased efficacy of aprepitant.
- The aprepitant regimen for CINV produces at most moderate inhibition of CYP3A4 activity (comparable to verapamil, diltiazem, or grapefruit juice) during dosing followed by a small, transient, clinically unimportant inductive effect on CYP3A4 following completion of dosing. The inhibition of CYP3A4 by aprepitant is less for intravenously administered substrates.
- Moderate inhibition of CYP3A4 by the aprepitant regimen for CINV increases the plasma concentrations of orally coadministered synthetic corticosteroids

(dexamethasone and methylprednisolone). Dose adjustment of dexamethasone was implemented in Phase III studies to facilitate interpretation of antiemetic efficacy.

- Aprepitant has a pharmacokinetic effect, but is without clinically important pharmacodynamic effects, on diltiazem. Adjustment of diltiazem doses is not necessary.
- The aprepitant regimen for CINV does not significantly affect the pharmacokinetics of ondansetron or granisetron. Adjustment of the doses of these 2 antiemetic drugs is not necessary.
- Preliminary data in 5 patients indicate that coadministration of the aprepitant regimen for CINV had little effect on docetaxel pharmacokinetics. Overall, there is a low potential for aprepitant to produce clinically meaningful effects on the pharmacokinetics of IV chemotherapeutic agents.
- The aprepitant regimen for CINV produces slight induction of CYP2C9 activity that is nearly resolved within 12 days after completion of the regimen. Drugs with narrow therapeutic indices that are known to be metabolized by CYP2C9 (e.g., warfarin, phenytoin) may have transiently lower plasma concentrations when coadministered with aprepitant. For patients on warfarin, INR should be appropriately monitored during the period immediately following administration of the regimen.
- Aprepitant does not affect P-glycoprotein activity (either inhibition or induction) as assessed using digoxin as a P-glycoprotein substrate. The aprepitant regimen for CINV is unlikely to result in clinically significant interactions with drugs that are P-glycoprotein substrates (e.g., some chemotherapeutic agents).
- Aprepitant does not inhibit CYP2D6 activity in vivo, and is a very weak inhibitor of CYPs 1A2, 2C9, 2C19, and 2E1 in vitro.
- The efficacy of oral contraceptives during chronic administration of aprepitant may be reduced. Although a 3-day regimen of aprepitant given concomitantly with oral contraceptives has not been studied, alternative or back-up methods of contraception should be used.

7. Clinical Efficacy

7.1 CINV Background

Nausea and vomiting have been reported by patients, nurses, and physicians as the most distressing side effects of chemotherapy, and the disruptive effects of CINV on patients' daily lives have been well documented [1; 2]. In light of the need for continued routine use of emetogenic chemotherapy, effective prevention of CINV is a central goal for physicians administering cancer chemotherapy.

In current practice, cisplatin is the single most emetogenic chemotherapeutic agent [42; 43]. In the absence of preventive therapy, cisplatin at doses ≥50 mg/m^2 predictably evokes acute vomiting (vomiting that occurs within 24 hours of administration) in ~100% of patients [44] and delayed vomiting (vomiting that occurs from 2 to 7 days postadministration) in ~70 to 90% of patients [45]. Chemotherapeutic agents have been categorized in several different classification schemes, according to their capacity to induce emesis [46; 45], and in each, a cisplatin dose of >50 mg/m^2 exemplifies the class of chemotherapy defined as highly emetogenic. Other commonly used emetogenic chemotherapeutic agents include cyclophosphamide, carboplatin, and doxorubicin. Cisplatin is a component of chemotherapy regimens used to treat common cancers such as lung, head and neck, and ovarian. Cisplatin is frequently coadministered with chemotherapeutic agents such as fluorouracil, gemcitabine, etoposide, cyclophosphamide, vinca alkaloids, and taxanes. The emetogenicity of a chemotherapeutic agent appears to be enhanced when it is coadministered with another emetogenic agent [47].

Efficacy in the prevention of CINV associated with cisplatin has been used as the benchmark to evaluate the efficacy of other antiemetic therapies, notably the various 5-HT_3–receptor antagonists (ondansetron, granisetron, and dolasetron) and the dopamine D_2-receptor antagonist, metoclopramide [48]. Also, efficacy in the prevention of symptoms associated with cisplatin has been predictive of antiemetic efficacy associated with other chemotherapeutic agents such as cyclophosphamide and doxorubicin [45].

7.1.1 Current CINV Therapy

When cisplatin was first introduced, patients had a median of 12 acute emetic episodes following its administration. Subsequently, high-dose metoclopramide therapy was shown to prevent cisplatin-induced acute emesis in 30 to 40% of patients; however, the use of such high-dose regimens was limited because of anti-dopaminergic side effects (e.g., extrapyramidal reactions, anxiety, and depression).

The development and introduction of 5-HT_3–receptor antagonists was a major advance in the prevention of CINV, because these agents prevented cisplatin-induced acute emesis in ~50% of patients and were very well tolerated [49]. The available 5-HT_3–receptor antagonists (ondansetron, granisetron, and dolasetron) appear to have a comparable efficacy and tolerability profile [48]. Though clearly effective for the prevention of cisplatin-induced acute emesis, 5-HT_3–receptor antagonists have not been confirmed to

have efficacy in the prevention of delayed CINV symptoms associated with HEC such as cisplatin [6]. For HEC, the 5-HT_3–receptor antagonists are approved in the United States only for single-day use in the prevention of nausea and vomiting associated with HEC.

Corticosteroids as single agents reduce the incidence of delayed emesis by 10 to 20 percentage points [6]. Coadministration of corticosteroids improves the effect of 5-HT_3–receptor antagonist therapy in the prevention of acute emesis by 10 to 20 percentage points [48]. Hence, the most effective current therapy for prevention of symptoms associated with HEC is a regimen of a 5-HT_3–receptor antagonist (administered prior to chemotherapy only) and a corticosteroid (administered prior to chemotherapy and continued for a total of 4 to 5 days). Consensus treatment guidelines published by the American Society of Clinical Oncology (ASCO) [48] recommend administering 5-HT_3–receptor antagonists during the delayed phase; however, several large, well-designed studies have failed to demonstrate a benefit of 5-HT_3–receptor antagonist therapy during the delayed phase when corticosteroids are coadministered [50; 51; 52].

Despite appropriate use of currently available antiemetic therapy, many patients still experience CINV following HEC such as cisplatin: ~25% have acute CINV and ~50% have delayed CINV [48]. Cancer chemotherapy treatment generally consists of several cycles of therapy: typical regimens consist of 4 to 6 cycles. The assessment of efficacy of antiemetic therapy has almost exclusively been derived from studies of the initial cycle (Cycle 1) of chemotherapy. The evaluation of antiemetic therapy during repeat cycles is considerably more complex than for the first cycle because of the potentially variable response between different cycles, "carryover" effects (including anticipatory symptoms), and attrition as patients discontinue therapy. Patients discontinue therapy for various reasons including lack of efficacy of chemotherapy and side effects of chemotherapy. The percentage of patients with CINV symptoms has been reported to increase during repeat cycles of chemotherapy [53]. Therefore, a preponderance of patients receiving HEC over multiple cycles still experience CINV at some point during their chemotherapy treatment, despite the best available antiemetic therapy. Approximately 20% of the patients receiving chemotherapy in the United States receive a highly emetogenic regimen.

In summary, despite effective therapy, most patients receiving HEC still experience CINV, which explains why patients continue to rank nausea and vomiting as the most distressing symptoms associated with chemotherapy treatment [1]. A new therapeutic approach that improves prevention of CINV, particularly throughout both the acute and delayed phases, is highly desirable.

7.2 Overview of Aprepitant CINV Clinical Development Program

7.2.1 Overview of the Aprepitant CINV Clinical Studies

The objective of the aprepitant clinical program was to develop an oral NK_1-receptor antagonist 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.

Seven (7) clinical studies were completed in patients receiving HEC including cisplatin, to assess the efficacy of aprepitant and L-758298, its intravenously administered prodrug, in preventing CINV (Table 6). Four (4) Phase IIa studies were performed to define the components of the regimen; a Phase IIb study was performed to optimize the dose of aprepitant; and 2 Phase III studies were performed to confirm the dose regimen. Table 6 also lists the primary endpoints and the time frames of their assessment, which are discussed further in Sections 7.2.2 and 7.2.3.

Table 6

Summary of Clinical Studies in Aprepitant CINV Program

Phase	Protocol Number	Formulation	Primary Endpoint[†]
IIa	004	L-758298	Complete response (acute phase)
IIa	CN-007	L-758298 and Aprepitant Tablet	No emesis (acute phase)
IIa	007	Aprepitant Tablet	Complete response (delayed phase)
IIa	012	Aprepitant Tablet	No emesis (acute phase)
IIb	040/042	Aprepitant Nanoparticle	Complete response (overall)
III	052	Aprepitant Nanoparticle	Complete response (overall)
III	054	Aprepitant Nanoparticle	Complete response (overall)

[†] Definitions in Section 7.2.2.

A tablet formulation of aprepitant was the only oral formulation used in the Phase IIa studies. The doses of the tablet formulation administered, 400 mg prior to cisplatin and 300 mg on subsequent days, were equivalent to ~310 mg and ~230 mg of the nanoparticle capsule formulation used in the later Phase IIb and Phase III studies. Hence, the Phase IIa aprepitant tablet regimen provided somewhat higher plasma levels of aprepitant than the aprepitant nanoparticle capsule regimen that was evaluated in Phase IIb and Phase III (125 mg administered prior to cisplatin and 80 mg administered on subsequent days). These Phase IIa studies established that optimal control of CINV is obtained when aprepitant is administered for multiple days, in conjunction with a 5-HT_3–receptor antagonist and dexamethasone.

The single Phase IIb study, Protocol 040/042, conducted using a nanoparticle capsule formulation of aprepitant, established that 375 mg of aprepitant on Day 1, followed by 250 mg on subsequent days, achieved maximal efficacy, as did 125 mg of aprepitant followed by 80 mg daily on subsequent days. Both these aprepitant regimens were more effective than aprepitant 40 mg on Day 1 followed by 25 mg on subsequent days. The 125-mg/80-mg regimen was therefore selected for Phase III.

Two (2) Phase III studies of identical design, Protocol 052 and Protocol 054, evaluated the nanoparticle capsule formulation of aprepitant, and confirmed the efficacy and tolerability of a 3-day aprepitant regimen: 125 mg on Day 1 followed by 80 mg on Days 2 and 3.

7.2.2 Clinical Efficacy Endpoints—Definitions and Rationale

Efficacy parameters related to the control of nausea and emesis were assessed by patients recording their experiences after chemotherapy in self-report diaries in all studies. The endpoints assessed throughout the program were based on 3 components: emetic episodes, use of rescue therapy, and nausea ratings.

Emesis: An emetic episode was defined as one or more continuous vomits (expulsion of stomach contents through the mouth) or retches (an attempt to vomit that is not productive of stomach contents). Emetic episodes were considered distinct if separated by the absence of vomiting and retching for at least 1 minute. The time and date of each emetic episode was recorded by the patient in the diary.

Rescue Therapy: Rescue therapy was permitted on an as-needed basis for all protocols. The definition of rescue therapy was any medication taken to alleviate established nausea or vomiting. Although no therapy is of proven efficacy for either established nausea or vomiting, rescue therapy was permitted to treat established nausea or vomiting.

Nausea Assessment: A 100-mm horizontal visual analogue scale (VAS) was used to measure nausea in all CINV studies, except the initial proof of concept study Protocol 004, which used a 4-point categorical scale. The VAS was used to record patient self-assessment of nausea for the preceding 24 hours. The reliability and validity of the VAS have been established for a variety of conditions [54], including the assessment of chemotherapy-induced nausea [55]. In patients undergoing chemotherapy, measurement of the intensity of nausea by VAS has revealed good concordance with a 4-point categorical scale, but the VAS is more sensitive to changes over time [56].

No Emesis Endpoint: The No Emesis endpoint was defined as no emetic episodes, without regard to use of rescue medication and was assessed in all studies. The no emesis endpoint was the primary endpoint for 2 Phase IIa studies, Protocol 012 and Protocol CN-007.

Complete Response Endpoint (Primary Endpoint in Phase IIb/Phase III): In all studies, efficacy was assessed using an endpoint that incorporated whether rescue therapy was used: Complete Response (defined as no emetic episodes and no use of rescue medication to treat established nausea or emesis). Patients were defined as failures according to this endpoint if they either had emesis, irrespective of rescue therapy or if they took rescue for established nausea. Therefore, this endpoint reflects both the prevention of emesis and nausea control in patients without emesis.

The complete response endpoint was chosen as the primary endpoint for the Phase IIb and Phase III studies, following discussions with the Agency, because it reflects control

of both nausea and emesis, and also because it was the primary endpoint used in the development of the 5-HT_3–receptor antagonists: ondansetron and dolasetron.

Complete response was also the primary endpoint in 2 of the 4 Phase IIa clinical studies in the program: Protocol 004 and Protocol 007. For the other 2 Phase IIa studies, no emesis was the primary endpoint. For consistency and to facilitate comparisons between studies, the data for complete response are highlighted in this document for all 7 studies in the program.

7.2.3 Rationale for Use of Acute, Delayed, and Overall Phases for Efficacy Evaluations

When the clinical syndrome of CINV was initially described, the focus was on symptoms that occurred on the same day that chemotherapy was administered [48], and studies typically assessed symptoms for just 24 hours following chemotherapy. The choice of 24 hours as the period of observation was not driven by pathophysiologic considerations. With the subsequent introduction of effective therapy for acute symptoms, it became apparent that many patients also had CINV symptoms that occurred more than 24 hours following chemotherapy [6]. Accordingly, there was increasing interest in the prevention of delayed symptoms, which are typically defined as those that occur for up to ~4 to 6 days after the 24-hour acute phase [6]. Because of the desirability of improving the prevention of both acute and delayed CINV symptoms, the Phase IIa studies focused on separate assessments of efficacy during these phases in order to clarify the efficacy profile of aprepitant.

From a clinical perspective, prevention of CINV is desirable throughout both the acute and delayed phases. The Phase IIa studies focused on separate assessments of the acute phase and the delayed phase of emesis to comprehensively understand the efficacy profile of aprepitant. Once the Phase IIa studies confirmed that aprepitant provided benefit in both the acute phase and the delayed phase, it was clear that the most clinically relevant endpoint for the assessment of efficacy should reflect an "overall" time frame that simply merges the acute and the delayed phases. Hence, the primary hypothesis in both the Phase IIb and Phase III studies was based on an "overall" time frame, which represents the acute and delayed phases merged together, and specific secondary hypotheses assessed the prevention of symptoms in the acute and delayed phases independently.

7.2.4 Clinical Study Design of HEC Studies and Patient Selection Criteria

This section provides a description of the study designs and patient selection criteria for the 7 clinical studies in the development program.

All studies were double-blind, multicenter, randomized trials, in cisplatin-naïve male and female patients with cancer, who were studied during an initial cycle of HEC, defined as a regimen that included high-dose cisplatin-based chemotherapy. The dose of cisplatin required for enrollment was >50 mg/m^2 in the initial study, Protocol 004, and was >70 mg/m^2 in the 6 subsequent studies. Cisplatin was administered during a single

infusion of ≤3 hours duration on Day 1. Patients were allowed to enroll if they were receiving other chemotherapy, though emetogenic chemotherapy could only be administered on the same day as cisplatin, Day 1. More than 90% of patients received other chemotherapy in addition to cisplatin in the studies: the agents most frequently coadministered with cisplatin included etoposide, vinorelbine, gemcitabine, taxanes, doxorubicin, cyclophosphamide, and fluorouracil.

Randomization in all trials was stratified according to gender and whether emetogenic chemotherapy was given in addition to cisplatin. A chemotherapeutic agent was defined as emetogenic if it was categorized as either Level 3, 4, or 5 using the Hesketh classification of emetogenicity [47].

In general, inclusion and exclusion criteria were applied to allow enrollment of patients without serious complicating illnesses or concomitant therapy that could have potentially confounded the evaluation of the study regimen. The criteria were similar in all studies and were consistent with those employed in the pivotal trials for the 5-HT_3–receptor antagonists.

7.2.5 Evolution of Study Designs

The initial Phase IIa study, Protocol 004, was a proof-of-concept study to establish whether aprepitant had any activity in the prevention of emesis associated with cisplatin-based HEC, and if it did, how its activity compared with that of a 5-HT_3–receptor antagonist, ondansetron.

Once evidence of efficacy of aprepitant was obtained in Protocol 004, the remaining Phase IIa studies were planned to address what other antiemetic therapy should be used concomitantly with aprepitant and the duration of aprepitant therapy to maximize the prevention of CINV.

The collective Phase IIa data provided the rationale for selection of a regimen to be evaluated in the Phase IIb study. The Phase IIb data, in turn, provided the rationale for both dose selection and further refinement of the aprepitant regimen for Phase III including duration of therapy.

7.2.6 Statistical Methodology

All 7 studies consisted of evaluation of aprepitant during an initial single cycle of chemotherapy. The Phase IIb and Phase III studies also had optional multiple-cycle extensions. The primary focus in all studies was on the initial cycle of chemotherapy.

For all studies, the statistical analyses focused on a modified-intention-to-treat (MITT) population of patients. To be included in the MITT population, a patient must have received cisplatin chemotherapy, received at least 1 dose of study drug, and have had at least 1 posttreatment efficacy assessment.

7.3 Phase IIa Program

7.3.1 Monotherapy Proof of Concept—Protocol 004: L-758298

This initial proof-of-concept study, Protocol 004, involved a comparison of ondansetron (32 mg IV) with L-758298, the intravenously administered prodrug of aprepitant. Test medications were given as a single dose prior to administration of >50 mg/m^2 cisplatin (mean dose 78 mg/m^2). This was the only study to evaluate aprepitant as monotherapy in direct comparison with a 5-HT$_3$–receptor antagonist. In this study, the delayed phase was defined as the 6 days following Day 1 (i.e., a total of 144 hours, from 24 to 168 hours following initiation of cisplatin). In all subsequent studies, the delayed phase was defined as 4 days (96 hours, from 24 to 120 hours following initiation of cisplatin). The first 9 patients assigned to the L-758298 group received 60 mg. Because less than complete control was observed, the dose of L-758298 was increased to 100 mg for the 21 subsequent patients while maintaining the study blind for the investigators and patients. A placebo control group could not be included for ethical reasons, as historical data show that the proportion of patients with complete response in the absence of antiemetic therapy would be 0% overall (0% during the acute phase, and 10 to 30% during the delayed phase) [6; 44].

Statistical Methods

For all Phase IIa studies, the proportions of patients with complete response were compared using a Fisher's exact test. All statistical comparisons were two-tailed with a significance level of 5%.

Results

Fifty-three (53) patients were randomized and all were included in the MITT analyses.

Table 7 presents the proportions of patients with complete response during the acute (Day 1) and delayed (Days 2 to 7) phases post-cisplatin.

Table 7

Number (%) of Patients With Complete Response
by Treatment Group and Phase—L-758298 Protocol 004

	Treatment Group			
	L-758298 60 mg/100 mg IV		Ondansetron 32 mg IV	
Phase	N	n (%)	N	n (%)
Acute (Day 1)	30	11 (36.7)	23	11 (47.8)
Delayed (Days 2 to 7)	29	14 (48.3)*	23	4 (17.4)

* p=0.04 compared with ondansetron.
N = Number of patients included in the MITT analyses.
n = Number of patients with complete response.
IV = Intravenous.

Acute Phase (Primary Hypothesis): The proportion of patients with complete response was numerically smaller in the L-758298 group than in the ondansetron group, although the difference was not statistically significant. A similar outcome was seen for the no emesis primary endpoint: 36.7% following L-758298 versus 52.2% following ondansetron therapy, which was also not statistically significant.

Delayed Phase: The proportion of patients with complete response was higher in the L-758298 treatment group than in the ondansetron group (Table 2) (48.3% versus 17.4%, p=0.04).

The difference in the no emesis endpoint (not presented in Table 7) was more pronounced: 72.4% of patients had no delayed emesis in the L-758298 treatment group compared with 30.4% in the ondansetron group (p=0.005). The efficacy in the L-758298 treatment group observed in the delayed phase could not be attributed to superior prevention of emesis during the acute phase, as more patients in this treatment group had acute symptoms compared with those receiving ondansetron.

The data in this pilot study demonstrated that L-758298 was a clinically effective antiemetic, with efficacy in the prevention of both acute and delayed CINV symptoms. The efficacy in the prevention of delayed symptoms was particularly distinctive. Neither drug was maximally effective as monotherapy, however.

The differential time course of symptoms in the 2 treatment groups implied that there may be 2 primary mechanisms responsible for CINV: a 5-HT_3–receptor dependent mechanism that is especially important during the acute phase, and an NK_1-receptor dependent mechanism that is particularly prominent during the delayed phase but which is also present during the acute phase. This suggested that it would be worthwhile to evaluate the efficacy of a regimen that included both a 5-HT_3–receptor antagonist and an NK_1-receptor antagonist. The Phase IIa program was therefore expanded to define an aprepitant regimen that would potentially provide enhanced efficacy relative to currently available regimens in the prevention of CINV.

7.3.2 Rationale for Concomitant Therapy—Protocols 007, 012, and CN-007

The following data from Phase IIa Protocols 007, 012, and CN-007 provide the rationale for selection of the aprepitant regimen that was later evaluated in Phase IIb. The intravenously administered formulation of the aprepitant prodrug, L-758298, was not developed further because of technical issues associated with its administration. However, data from the Phase IIa study, Protocol CN-007, that focused on this formulation are presented here, as they provide additional support for the efficacy of aprepitant as an antiemetic, especially in the prevention of delayed symptoms.

For aprepitant, a loading-dose strategy was used in all Phase II studies to optimize occupancy of CNS NK_1 receptors at the time of the maximum emetic stimulus; a higher dose was administered on Day 1 followed by a lower dose on Days 2 to 5. Four hundred

(400) mg of a tablet formulation of aprepitant was administered prior to cisplatin and 300 mg of the same formulation was administered on subsequent days. Based on the pharmacokinetics of aprepitant, this would allow approximately similar plasma concentrations throughout the treatment period.

The aprepitant Phase IIa studies were designed and initiated prior to the recommendation by the American Society of Oncology that corticosteroids be routinely used for the prevention of delayed symptoms associated with HEC [46]. Therefore, corticosteroids were not administered during the delayed phase in the control arms in Phase IIa, though they were administered on Day 1 to all patients. The Standard Therapy regimen in these studies consisted of the combination of a 5-HT_3–receptor antagonist (granisetron or ondansetron) and dexamethasone administered on Day 1 prior to cisplatin.

Protocol 007:

In Protocol 007, all patients were administered a Standard Therapy regimen of a 5-HT_3–receptor antagonist (granisetron) and a corticosteroid (dexamethasone) prior to cisplatin. The study was designed (Table 8) to address 2 questions:

- Whether a 5-day aprepitant regimen provided benefit when coadministered with Standard Therapy (Treatment Group A versus C).
- Whether a 5-day aprepitant regimen was more effective than a 1-day aprepitant regimen when both were coadministered with Standard Therapy (Treatment Group A versus B).

Table 8

Summary of Study Design for Aprepitant Protocol 007

Group	Day 1	Days 2 to 5
A $G/D/A_1 \rightarrow A_{2-5}$	Granisetron 10 µg/kg IV Dexamethasone 20 mg P.O. Aprepitant 400 mg P.O.	Aprepitant 300 mg P.O. daily
B $G/D/A_1 \rightarrow PBO_{2-5}$	Granisetron 10 µg/kg IV Dexamethasone 20 mg P.O. Aprepitant 400 mg P.O.	Placebo to match aprepitant P.O. daily
C $G/D_1 \rightarrow PBO_{2-5}$ (Standard Therapy)	Granisetron 10 µg/kg IV Dexamethasone 20 mg P.O. Placebo to match aprepitant P.O.	Placebo to match aprepitant P.O. daily
G = Granisetron; D = Dexamethasone; A = Aprepitant; PBO = Placebo; → = Followed by. IV = Intravenous; P.O. = Taken orally.		

Results

One hundred sixty-one (161) patients were randomized and 158 were included in the MITT analyses.

Table 9 presents the number and percent of patients with complete response by treatment group and phase.

Table 9

Number (%) of Patients With Complete Response
by Treatment Group and Phase—Aprepitant Protocol 007

Phase	Treatment Group					
	A $G/D/A_1 \rightarrow A_{2-5}$		**B** $G/D/A_1 \rightarrow PBO_{2-5}$		**C** $G/D_1 \rightarrow PBO_{2-5}$ (Standard Therapy)	
	N	n (%)	N	n (%)	N	n (%)
Acute (Day 1 post-cisplatin)	53	41 (77.4)*	54	45 (83.3)**	51	29 (56.9)
Delayed (Days 2 to 5 post-cisplatin)	50	26 (52.0) **	54	23 (42.6)	51	8 (15.7)

* $p<0.05$ compared with Group C.
** $p<0.01$ compared with Group C.
G = Granisetron; D = Dexamethasone; A = Aprepitant; PBO = Placebo; $\rightarrow$ = Followed by.
N = Number of randomized patients who were included in the analysis.
n = Number of randomized patients who were included in the analysis with complete response for the specific time period.

- The 5-day aprepitant regimen (A) was superior to Standard Therapy (C) during **both** the acute (primary hypothesis) and delayed phases when analyzed separately; each comparison was statistically significant (Treatment Group A versus C).
- The 5-day aprepitant regimen (A) was numerically superior to the 1-day aprepitant regimen (B) during the delayed phase (Treatment Group A versus B).
- The 1-day aprepitant regimen (B) was numerically superior to Standard Therapy (C) during both the acute and delayed phases when analyzed separately; since this comparison was post hoc, statistical testing was not done (Treatment Group B versus C).

Table 10 shows the percentage of patients with complete response by treatment group and day. There was a consistent numerical advantage for the 5-day over the 1-day aprepitant regimen after Day 1 (Treatment Group A versus B), which increased toward the end of the 5-day observation period, indicating that continued treatment was beneficial. This was a post hoc analysis and statistical testing was not done.

Table 10

Number (%) of Patients With Complete Response
by Treatment Group and Day—Aprepitant Protocol 007

	Treatment Group		
	A $G/D/A_1 \rightarrow A_{2-5}$	**B** $G/D/A_1 \rightarrow PBO_{2-5}$	**C** $G/D_1 \rightarrow PBO_{2-5}$ (Standard Therapy)
Day Post-Cisplatin	n/N (%)	n/N (%)	n/N (%)
Day 1	41/53 (77.4)	45/54 (83.3)	29/51 (56.9)
Day 2	38/50 (76.0)	37/54 (68.5)	16/51 (31.4)
Day 3	33/50 (66.0)	32/54 (59.3)	17/51 (33.3)
Day 4	35/50 (70.0)	32/54 (59.3)	16/51 (31.4)
Day 5	42/50 (84.0)	37/54 (68.5)	29/51 (56.9)

G = Granisetron; D = Dexamethasone; A = Aprepitant; PBO = Placebo; → = Followed by.
N = Number of randomized patients who were included in the analysis.
n = Number of randomized patients who were included in the analysis with complete response for the specific time period.
Days are defined as multiples of 24 hours following the initiation of cisplatin.

Protocol 012:

In Protocol 012, all patients were administered a corticosteroid (dexamethasone) prior to cisplatin, though only 2 of the 4 treatment groups received a 5-HT_3–receptor antagonist (granisetron).

The study was designed (Table 11) to address the following questions:

- Whether a 6-day aprepitant regimen, with the extra dose of aprepitant administered on the day prior to cisplatin (Day –1), administered with dexamethasone (Day 1 only), was more effective than Standard Therapy in the prevention of acute emesis (Treatment Group C versus A). The comparison of acute phase efficacy using the no emesis endpoint was the primary hypothesis for the study.
- Whether a 5-day aprepitant regimen (administered with Standard Therapy) was more effective than Standard Therapy alone (Treatment Group B versus A) (this comparison was also included in the preceding study, Protocol 007).
- Whether a 5-day aprepitant regimen (administered with Standard Therapy) was more effective than a 5-day aprepitant regimen administered with dexamethasone (Day 1 only) (Treatment Group B versus D).
- Whether a 6-day aprepitant regimen, with the extra dose of aprepitant administered on the day prior to cisplatin (Day –1), was more effective than a 5-day aprepitant

regimen, when both were coadministered with dexamethasone (Day 1 only) (Treatment Group C versus D).

Table 11

Summary of Study Design for Aprepitant Protocol 012

Group	Day –1	Day 1	Days 2 to 5
A $PBO_{-1} \rightarrow G/D_1 \rightarrow PBO_{2-5}$ (Standard Therapy)	Placebo matched to aprepitant P.O.	Granisetron 10 µg/kg IV, dexamethasone 20 mg P.O., and placebo matched to aprepitant P.O.	Placebo matched to aprepitant P.O. daily
B $PBO_{-1} \rightarrow A/G/D_1 \rightarrow A_{2-5}$	Placebo matched to aprepitant P.O.	Granisetron 10 µg/kg IV, dexamethasone 20 mg P.O., and aprepitant 400 mg P.O.	Aprepitant 300 mg P.O. daily
C $A_{-1} \rightarrow D/A_1 \rightarrow A_{2-5}$	Aprepitant 400 mg P.O.	Placebo matched to granisetron IV, dexamethasone 20 mg P.O., and aprepitant 400 mg P.O.	Aprepitant 300 mg P.O. daily
D $PBO_{-1} \rightarrow D/A_1 \rightarrow A_{2-5}$ $D/A \rightarrow A$	Placebo matched to aprepitant P.O.	Placebo matched to granisetron IV, dexamethasone 20 mg P.O., and aprepitant 400 mg P.O.	Aprepitant 300 mg P.O. daily
G = Granisetron; D = Dexamethasone; A = Aprepitant; PBO = Placebo; → = Followed by. IV = Intravenous; P.O. = Taken orally.			

Results

Three hundred fifty-four (354) patients were randomized and 347 were included in the MITT analyses.

Table 12 presents the number and percent of patients with complete response by treatment group and phase.

Table 12

Number (%) of Patients With Complete Response
by Treatment Group and Phase—Aprepitant Protocol 012

	Treatment Group							
	A $PBO_{-1} \rightarrow G/D_1 \rightarrow PBO_{2-5}$ (Standard Therapy)		**B** $PBO_{-1} \rightarrow A/G/D_1 \rightarrow A_{2-5}$		**C** $A_{-1} \rightarrow D/A_1 \rightarrow A_{2-5}$		**D** $PBO_{-1} \rightarrow D/A_1 \rightarrow A_{2-5}$	
Phase	N	n (%)	N	n (%)	N	n (%)	N	n (%)
Acute (Day 1)	90	46 (51.1)	84	63 (75.0) **	89	39 (43.8)	84	34 (40.5)
Delayed (Days 2 to 5)	90	20 (22.2)	84	34 (40.5) *	88	34 (38.6)	84	33 (39.3)
* $p<0.05$ compared with Group A (specific p=0.014). ** $p<0.01$ compared with Group A (specific p=0.002 for acute phase; p=0.005 overall). G = Granisetron; D = Dexamethasone; A = Aprepitant; PBO = Placebo; → = Followed by. N = Number of patients included in the analysis. n = Number of patients with complete response.								

- A 6-day aprepitant regimen administered with dexamethasone (Day 1) was numerically inferior to Standard Therapy in the prevention of acute CINV, but was numerically superior in the prevention of delayed CINV (Treatment Group C versus A). The better delayed efficacy in the aprepitant treatment group could not be attributed to superior prevention of emesis during the acute phase, as more patients in this treatment group (C) had acute symptoms compared with those receiving Standard Therapy (A). A similar outcome was seen with the no emesis endpoint for the primary comparison: 46.1% of patients had no acute emesis in Treatment Group C versus 56.7% in Treatment Group A.
- A 5-day aprepitant regimen administered with Standard Therapy significantly improved the control of CINV during **both** the acute and delayed phases (Treatment Group B versus A), relative to Standard Therapy.
- A 5-day aprepitant regimen administered with Standard Therapy was more effective than a 5-day aprepitant regimen coadministered with dexamethasone in the prevention of acute CINV, but had almost identical efficacy in the prevention of delayed CINV (Treatment Group B versus D).
- A 6-day aprepitant regimen had similar efficacy to a 5-day aprepitant regimen when both regimens were coadministered with dexamethasone (Day 1 only) (Treatment Group C versus D). The acute efficacy of aprepitant and dexamethasone was not enhanced by aprepitant dosing on Day -1.

Protocol CN-007: L-758298

In Protocol CN-007, all patients were administered a corticosteroid, dexamethasone 20 mg IV, prior to cisplatin. The study (Table 13) addressed 2 questions:

- Whether a 5-day aprepitant regimen provided benefit when coadministered with dexamethasone (Treatment Group A versus C): The 5-day aprepitant regimen consisted of the aprepitant prodrug L-758298 administered intravenously on Day 1 followed by P.O. aprepitant on Days 2 to 5.
- Whether a 5-day aprepitant regimen was more effective than a 1-day aprepitant regimen when both were coadministered with dexamethasone (Treatment Group A versus B): The 1-day aprepitant regimen consisted of the aprepitant prodrug L-758298 administered intravenously on Day 1.

The primary hypothesis for the study was for the no emesis endpoint during the acute phase for the combined Treatment Group A and B versus Treatment Group C.

Table 13

Summary of Study Design for L-758298 Protocol CN-007

Group	Day 1	Days 2 to 5
A $L/D_1 \rightarrow A_{2-5}$	L-758298 100 mg IV and dexamethasone 20 mg IV	Aprepitant 300 mg P.O. daily
B $L/D_1 \rightarrow PBO_{2-5}$	L-758298 100 mg IV and dexamethasone 20 mg IV	Placebo to match aprepitant P.O. daily
C $O/D_1 \rightarrow PBO_{2-5}$ (Standard Therapy)	Ondansetron 32 mg IV and dexamethasone 20 mg IV	Placebo to match aprepitant P.O. daily

L = L-758298 (aprepitant prodrug); D = Dexamethasone; A = Aprepitant; PBO = Placebo; → = Followed by.
IV = Intravenous; P.O. = Taken orally.

Results

One hundred seventy-seven (177) patients were randomized and 175 were included in the MITT analyses.

Table 14 presents the number and percent of patients with complete response by treatment group and phase.

Table 14

Number (%) of Patients With Complete Response by Treatment Group and Phase—
L-758298 Protocol CN-007

	Treatment Group					
	A $L/D_1 \rightarrow A_{2-5}$		**B** $L/D_1 \rightarrow PBO_{2-5}$		**C** $O/D_1 \rightarrow PBO_{2-5}$ (Standard Therapy)	
Phase	N	n (%)	N	n (%)	N	n (%)
Acute (Day 1)	60	27 (45.0)	57	20 (35.1)	58	48 (82.8)
Delayed (Days 2 to 5)	59	35 (59.3)*	56	25 (44.6)	58	22 (37.9)

* $p<0.05$ compared with Group C.
L = L-758298 (aprepitant prodrug); D = Dexamethasone; A = Aprepitant; PBO = Placebo; → = Followed by.
N = Number of patients randomized and included in the analysis.
n = Number of patients with complete response for the specific time period.
IV = Intravenous; P.O. = By mouth.

- The 5-day aprepitant regimen administered with dexamethasone (Day 1) was numerically superior to Standard Therapy in the prevention of delayed CINV, but was numerically inferior in the prevention of acute CINV (Treatment Group A versus C). The comparison of acute phase efficacy using the no emesis endpoint was the primary hypothesis for the study, and a similar outcome was seen with this endpoint: 84.5% of patients had no acute emesis in Treatment Group C versus 47.9% in the combined Treatment Group A and B.
- The 1-day aprepitant regimen administered with dexamethasone (Day 1) was numerically superior to Standard Therapy in the prevention of delayed CINV, but was numerically inferior in the prevention of acute CINV (Treatment Group B versus C).
- The consistent superiority of both aprepitant regimens versus Standard Therapy in the prevention of delayed CINV, could not be attributed to superior control of acute CINV.
- The 5-day aprepitant regimen was numerically superior to the 1-day aprepitant regimen in the prevention of delayed CINV (Treatment Group A versus B).

Table 15 shows the percentage of patients with complete response by treatment group and day.

- There was a consistent numerical advantage for the 5-day aprepitant regimen over the 1-day regimen after Day 1, particularly during the last 3 days of the observation period, indicating that continued treatment was beneficial (Treatment Group A versus B).

Table 15

Number (%) of Patients With Complete Response by Treatment Group and Day—
L-758298 Protocol CN-007

Day Post-Cisplatin	**A** $L/D_1 \rightarrow A_{2-5}$		**B** $L/D_1 \rightarrow PBO_{2-5}$		**C** $O/D_1 \rightarrow PBO_{2-5}$ (Standard Therapy)	
	n/N	(%)	n/N	(%)	n/N	(%)
Day 1	27/60	(45.0)	20/57	(35.1)	48/58	(82.8)
Day 2	40/59	(67.8)	34/56	(60.7)	33/58	(56.9)
Day 3	47/59	(79.7)	34/56	(60.7)	27/58	(46.6)
Day 4	48/59	(81.4)	35/56	(62.5)	32/58	(55.2)
Day 5	52/59	(88.1)	40/56	(71.4)	44/58	(75.9)

L = L-758298 (aprepitant prodrug); D = Dexamethasone; A = Aprepitant; PBO = Placebo; → = Followed by.
n/N = Number of patients with complete response/number of patients included in analysis.
Days are defined as multiples of 24 hours following the initiation of cisplatin.

7.3.3 Overall Conclusions From Phase IIa Program

- Aprepitant as monotherapy, or coadministered with corticosteroids, demonstrates efficacy in the prevention of acute CINV, but is less effective than 5-HT_3–receptor antagonists (Protocols 004, 012, and CN-007).
- Aprepitant as monotherapy, or coadministered with corticosteroids, demonstrates efficacy in the prevention of delayed CINV, and is more effective than 5-HT_3–receptor antagonists (Protocols 004, 012, and CN-007).
- The differential time course of 5-HT_3–receptor dependent (acute) and NK_1-receptor dependent (acute and delayed) symptoms implies 2 distinct mechanisms for CINV and provides a rationale for coadministering therapies that operate through these mechanisms (Protocols 004, 012, and CN-007).
- The coadministration of aprepitant, dexamethasone, and a 5-HT_3–receptor antagonist on Day 1, followed by aprepitant on subsequent days, provides consistently better control of both acute and delayed CINV compared with the Standard Therapy regimen consisting of a 5-HT_3–receptor antagonist and dexamethasone on Day 1 (Protocols 007 and 012).
- The coadministration of aprepitant, dexamethasone, and a 5-HT_3–receptor antagonist on Day 1, followed by aprepitant on subsequent days, provides better control of acute CINV compared with the coadministration of aprepitant and dexamethasone (Protocols 007 and 012).
- Continued daily dosing with aprepitant after Day 1 improves control of delayed phase CINV compared with aprepitant dosing on Day 1 only (Protocols 007 and CN-007).
- The delayed phase efficacy of aprepitant is not solely a consequence of the prevention of symptoms in the acute phase (Protocols 004, 012, and CN-007).
- The efficacy of aprepitant in the prevention of CINV is not enhanced by an additional dose given the day before chemotherapy (Protocol 012).

7.3.4 Rationale for Use of Overall Phase for Primary Efficacy Evaluations in Phase IIb and Phase III

From a clinical perspective, prevention of CINV is desirable throughout both the acute and delayed phases. Once the Phase IIa studies confirmed that aprepitant provided benefit in both the acute phase and the delayed phase, and that its efficacy in the prevention of delayed symptoms could not be attributed to superior acute control, it was clear that the most clinically relevant endpoint for the assessment of efficacy should reflect an "overall" time frame that merged the acute and the delayed phases. Hence, the primary hypothesis in both the Phase IIb and Phase III studies was based on an "overall" time frame (Days 1 to 5), which represents a simple fusion of acute and delayed phases together, and specific secondary hypotheses assessed the prevention of symptoms in the acute and delayed phases independently.

7.4 Dose Finding: Phase IIb Study

The regimen that was most effective in the Phase IIa program consisted of aprepitant dosed for 5 days, and coadministered on Day 1 with a 5-HT_3–receptor antagonist and a corticosteroid. Hence, this was the regimen chosen for further evaluation in Phase IIb, with the refinement that corticosteroids were coadministered for 5 days in both treatment groups to optimize efficacy. This regimen is consistent with ASCO guidelines for the use of corticosteroids during the delayed phase that were published following the initiation of the Phase IIa program [46]. The Phase IIb study (Protocol 040/042) evaluated 3 dose regimens of aprepitant. A new nanoparticle aprepitant capsule was utilized because this formulation had improved bioavailability relative to the Phase IIa tablet, particularly in the fasting state. The Day 1 loading dose strategy for aprepitant was continued. All patients were treated with a 5-HT_3–receptor antagonist (ondansetron IV) on Day 1 and a corticosteroid (dexamethasone P.O.) on Days 1 to 5 (Table 16).

The study was initiated with 2 aprepitant regimens: 375 mg (Day 1)/250 mg (Days 2 to 5) and 125 mg (Day 1)/80 mg (Days 2 to 5). The 375-mg/250-mg regimen was predicted to be maximally effective, whereas the 125-mg/80-mg regimen was expected to have limited efficacy.

The 375-mg/250-mg dose was subsequently replaced by a 40-mg/25-mg aprepitant dose after 35 patients were treated in the aprepitant 375-mg/250-mg group. This modification was made when pharmacokinetic data became available, after initiation of the study, that demonstrated higher than expected plasma levels with the aprepitant nanoparticle capsule formulation. These new data implied that contrary to the original prediction both the 125-mg/80-mg and the 375-mg/250-mg aprepitant regimens would provide >95% occupancy of CNS NK_1 receptors, and should therefore each demonstrate clinical efficacy. Thus, the 2 aprepitant dose regimens assessed during the latter part of the study were 125 mg/80 mg and 40 mg/25 mg.

The pivotal dose-response relationships of interest were the comparisons of the aprepitant 125-mg/80-mg and 40-mg/25-mg regimens with Standard Therapy and are displayed in Table 17.

For administrative purposes only, 2 distinct but identical protocols were used for this single Phase IIb study. The patient cohort in the United States was identified as Protocol 040, and Protocol 042 was used for all other countries. The primary endpoint was the overall complete response on Days 1 to 5.

Table 16

Summary of Study Design for Protocol 040/042

Treatment Regimen	Day 1	Days 2 to 5
Aprepitant 375 mg/250 mg	Aprepitant 375 mg P.O. Ondansetron 32 mg IV Dexamethasone 20 mg P.O.	Aprepitant 250 mg P.O. daily Dexamethasone 8 mg P.O. daily
Aprepitant 125 mg/80 mg	Aprepitant 125 mg P.O. Ondansetron 32 mg IV Dexamethasone 20 mg P.O.	Aprepitant 80 mg P.O. daily Dexamethasone 8 mg P.O. daily
Aprepitant 40 mg/25 mg	Aprepitant 40 mg P.O. Ondansetron 32 mg IV Dexamethasone 20 mg P.O.	Aprepitant 25 mg P.O. daily Dexamethasone 8 mg P.O. daily
Standard Therapy	Aprepitant placebo P.O. Ondansetron 32 mg IV Dexamethasone 20 mg P.O.	Aprepitant placebo P.O. daily Dexamethasone 8 mg P.O. daily
P.O. = Given orally. IV = Intravenous.		

Statistical Methods

Treatment comparisons were performed between the aprepitant regimens and the Standard Therapy regimen. Treatment comparisons were made in the context of a logistic regression that included terms for treatment, gender, use of concomitant emetogenic chemotherapy, and geographic region (U.S. versus non-U.S.). Time to first emesis or rescue was displayed using Kaplan-Meier curves for each treatment regimen. The time interval for this display was 0 to 120 hours. A log-rank test was used for treatment comparisons.

Results

Three hundred eighty-one (381) patients were randomized into Protocol 040/042 following the addition of the 40-mg/25-mg aprepitant treatment group and 377 of these patients were included in the MITT analysis.

Table 17 presents the number and percent of patients with complete response by treatment group and phase.

Table 17

Number (%) of Patients With Complete Response
by Treatment Group and Phase—Protocol 040/042

	Aprepitant Regimen Plus Standard Therapy				Standard Therapy	
	125 mg/80 mg		40 mg/25 mg			
	n/m	(%)	n/m	(%)	n/m	(%)
Overall (0 to 120 hours)	93/131	(71.0)**	70/119	(58.8)*	55/126	(43.7)
Acute phase (0 to 24 hours)	109/131	(83.2)*	90/119	(75.6)	90/126	(71.4)
Delayed phase (25 to 120 hours)	96/132	(72.7)**	76/119	(63.9)**	57/126	(45.2)

* $p<0.05$ when compared with Standard Therapy.
** $p<0.01$ when compared with Standard Therapy.
n/m = Number of patients with complete response/number of patients included in analysis.

- The 375-mg/250-mg (35 patients treated prior to discontinuation) and 125-mg/80-mg aprepitant regimens had generally similar efficacy (i.e., both appeared to provide the full benefit obtainable with aprepitant): the overall complete response in the 33 patients treated with the 375-mg/250-mg regimen for whom efficacy data were available was 69.7% (data not included in the table).
- The aprepitant 125-mg/80-mg regimen was significantly more effective than the Standard Therapy regimen in the prevention of CINV overall (primary analysis), and also during the acute and delayed phases (key secondary analyses) when analyzed individually.
- The aprepitant 40-mg/25-mg regimen was significantly more effective than the Standard Therapy regimen in the overall prevention of CINV, and also during the delayed phase. The aprepitant 40-mg/25-mg regimen was numerically more effective than Standard Therapy in the prevention of acute CINV.
- The aprepitant 125-mg/80-mg regimen showed consistent numerical advantages over the aprepitant 40-mg/25-mg regimen, both in the overall prevention of CINV and during the acute and delayed phases. The analysis of the dose-response was a secondary analysis.

The assessment of nausea also demonstrated the consistent advantage of the aprepitant 125-mg/80-mg regimen over both the aprepitant 40-mg/25-mg regimen and Standard Therapy.

Table 18 presents the number and percent of patients protected from nausea, as defined by the No Significant Nausea endpoint (maximum nausea VAS rating <25 mm), by treatment group and phase (secondary analysis).

Table 18

Number (%) of Patients With No Significant Nausea
(Maximum VAS <25 mm) by Treatment Group and Phase—
Protocol 040/042

	Aprepitant Regimen Plus Standard Therapy				Standard Therapy	
	125 mg		40 mg			
	n/m	(%)	n/m	(%)	n/m	(%)
Overall (0 to 120 hours)	107/131	(81.7)*	82/119	(68.9)	74/126	(58.7)
Acute phase (0 to 24 hours)	119/131	(90.8)	103/119	(86.6)	110/126	(87.3)
Delayed phase (25 to 120 hours)	110/132	(83.3)*	82/119	(68.9)	79/126	(62.7)

* $p<0.01$ when compared with Standard Therapy.
VAS = Visual analogue scale.
n/m = Number of patients with complete response/number of patients included in analysis.

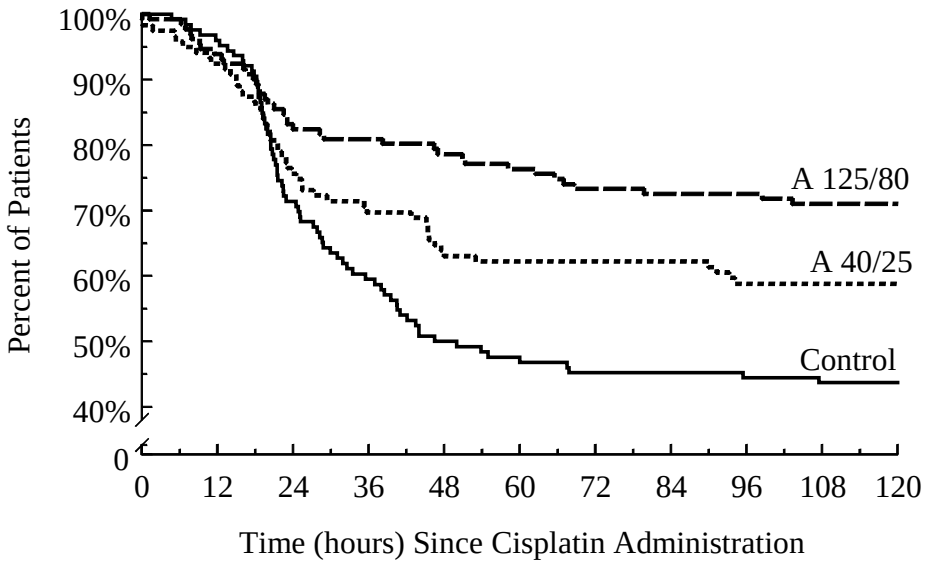
- The aprepitant 125-mg/80-mg regimen was significantly more effective than the Standard Therapy regimen in the prevention of significant nausea overall, and also during the delayed phase when analyzed separately. It was numerically superior during the acute phase.
- The aprepitant 40-mg/25-mg regimen was numerically more effective than the Standard Therapy regimen in the prevention of significant nausea overall and also during the delayed phase; however, there was no advantage during the acute phase.

Time to First Emesis or Rescue (Exploratory Analysis Post Hoc)

Kaplan-Meier curves for the time to first emesis or rescue overall are plotted in Figure 7. The Kaplan-Meier curves show that both aprepitant groups had significantly better protection against emesis and the use of rescue therapy than the Standard Therapy group ($p\leq0.001$). For the first 16 hours approximately, the cumulative percentages of patients who first experienced emesis or took rescue were similar at each time point for all 3 treatment groups. Thereafter, the advantage of the aprepitant groups became evident. Almost all first emetic episodes or use of rescue occurred within the first 72 hours of the 120-hour observation period post-cisplatin administration in all 3 treatment groups. The advantage of the 125-mg/80-mg dose regimen over the 40-mg/25-mg dose regimen is also evident in this display.

Figure 7

Time to First Emesis or Rescue
(Protocol 040/042)



A = Aprepitant regimen.
Control = Standard Therapy.

7.5 Rationale for the Phase III Aprepitant Regimen

Table 19 presents the treatment regimens utilized in both Phase III CINV studies: Protocol 052 and Protocol 054.

Table 19

Treatment Regimens in Phase III CINV Studies

Group	Day 1	Days 2 to 3	Day 4
Aprepitant Regimen	Aprepitant P.O. (125 mg) Ondansetron IV (32 mg) Dexamethasone P.O. (12 mg)	Aprepitant P.O. (80 mg once daily) Dexamethasone P.O. (8 mg)	Dexamethasone P.O. (8 mg)
Standard Therapy	Ondansetron IV (32 mg) Dexamethasone P.O. (20 mg)	Dexamethasone P.O. (16 mg)	Dexamethasone P.O. (16 mg)
IV = Intravenous; P.O. = Taken orally.			

7.5.1 Aprepitant Dose Regimen

The efficacy profile of the aprepitant 125-mg/80-mg dosing regimen in the Phase IIb study identified it as maximally effective, and most appropriate for further evaluation in Phase III.

As noted, 2 Phase IIa studies, Protocol 007 and Protocol CN-007, provided consistent evidence that 5-day aprepitant dosing was more effective in the prevention of delayed CINV, especially on Days 4 and 5, than single-day dosing. Because few initial emetic events occurred after Day 3 in any of the treatment groups in the Phase IIb study (see Section 7.4), a 3-day dosing regimen was used in Phase III; this duration of dosing was predicted to provide most if not all of the benefit attainable during the 5-day evaluation period.

The loading-dose strategy used in Phase II, to maximize occupancy of CNS NK_1 receptors at the time of the maximum emetic stimulus, was continued in Phase III, with a reduced dose administered on Days 2 and 3. Pharmacokinetic data demonstrated that this regimen provided consistent daily plasma exposure during the 3 days of dosing. Therefore, a 3-day aprepitant regimen, 125 mg on Day 1 followed by 80 mg on Days 2 and 3, was selected for Phase III.

7.5.2 Dexamethasone Regimen

All patients enrolled in the Phase III studies were to receive dexamethasone daily on Days 1 through 4. The Standard Therapy group received 1 dose of oral dexamethasone 20 mg on Day 1 and dexamethasone 8 mg twice daily on Days 2, 3, and 4. This regimen is consistent with published guidelines [46]. Because of the pharmacokinetic interaction between dexamethasone and the aprepitant 125-mg/80-mg regimen, a lower dose of dexamethasone was administered to the aprepitant treatment group; the dexamethasone regimen administered to patients in the aprepitant treatment group consisted of oral dexamethasone 12 mg on Day 1 and single 8-mg doses each morning on Days 2 to 4. With this adjustment, based on data from pharmacokinetic studies (see Section 6.4.3.3), the dexamethasone plasma exposure would be generally similar in both Phase III treatment groups.

7.5.3 5-HT_3–Receptor Antagonist Regimen

Ondansetron was chosen as the 5-HT_3–receptor antagonist for the Phase III program because it is the most widely used 5-HT_3–receptor antagonist and its properties and dose-response relationship are well understood. The various 5-HT_3–receptor antagonists are generally regarded as having such similar efficacy and safety profiles that the American Society of Clinical Oncology has recommended that decisions on clinical use can appropriately be based on factors such as convenience, availability, and cost [48]. Worldwide, various doses of ondansetron are approved for administration prior to high-dose cisplatin to prevent CINV.

As in earlier studies, the Phase III studies used the dose regimen approved in the United States (ondansetron 32 mg IV on Day 1, 30 minutes prior to cisplatin) in accordance with the lack of data supporting the efficacy of these agents during the delayed phase [50; 51; 52]. Additionally, they are only approved for single-day use in the prevention of nausea and vomiting associated with HEC.

7.6 Phase III Program

Two (2) Phase III international studies were conducted according to the same study design: Protocol 052 and Protocol 054. Both were multicenter, randomized, double-blind, parallel-group, active controlled trials with in-house blinding to assess the safety and efficacy of aprepitant in the prevention of CINV in cisplatin-naïve patients who were treated with chemotherapy regimens that included cisplatin ≥70 mg/m^2 administered on a single day: other chemotherapy was permitted, though emetogenic chemotherapy such as doxorubicin or cyclophosphamide could only be administered on Day 1 with cisplatin to ensure that a consistent emetogenic stimulus was provided on a single day. Randomization was stratified according to both gender and coadministration of emetogenic chemotherapy to ensure balance in the distribution of these known risk factors for nausea and vomiting.

A total of 1099 adult patients were enrolled in the 2 Phase III studies: 530 patients were randomized in Protocol 052 and 569 were randomized in Protocol 054. The MITT populations included all enrolled patients who received cisplatin, took at least 1 dose of study drug, and had at least 1 posttreatment assessment: 521 patients in Protocol 052 and 524 patients in Protocol 054. Efficacy data for all 40 patients from a single study site in Protocol 054 were excluded from the analyses because of concerns that good clinical practices were not followed at the site. However, analyses including these data yielded similar conclusions.

Both Phase III studies had optional multiple-cycle extensions: patients could continue to receive the same blinded study therapy that they received in Cycle 1 during Cycles 2 to 6, provided they continued to receive cisplatin chemotherapy. In accordance with feedback from investigators and an agreement with the Agency, data collection during the Multiple-Cycle extension was limited to key efficacy and safety measures. Therefore, the detailed patient diary that recorded efficacy data in Cycle 1 was not used in the Multiple-Cycle extension. Instead, patients were asked 2 questions at the Days 6 to 8 clinic visit: Have you had any episodes of vomiting or retching since your chemotherapy started in this cycle? Have you had any nausea since your chemotherapy started in this cycle that interfered with normal daily life?

Primary Objectives for Both Protocol 052 and 054

Cycle 1

1. To demonstrate that aprepitant triple therapy is superior to Standard Therapy in the control of CINV as measured by the proportion of patients with complete response in the 120 hours following the initiation of high-dose cisplatin chemotherapy.
2. To evaluate the safety and tolerability of triple therapy with aprepitant.

Primary Hypotheses for Both Protocol 052 and 054

Cycle 1

1. Compared with Standard Therapy, aprepitant triple therapy will provide superior control of CINV as measured by the proportion of patients with complete response in the 120 hours following the initiation of cisplatin chemotherapy. The expected difference between the triple therapy regimen and Standard Therapy is assumed to be ~15 percentage points (e.g., 60% and 45% following triple therapy and Standard Therapy, respectively).
2. Aprepitant triple therapy will be well tolerated.

7.6.1 Statistical Methods—Cycle 1

Efficacy

The primary efficacy hypothesis for the Phase III studies was that the proportion of patients reporting an overall complete response (no emesis and no rescue) in Cycle 1 during the 5 days (120 hours) postinitiation of cisplatin following treatment with the aprepitant regimen would be superior to Standard Therapy. Efficacy assessments were recorded in the patient diary beginning just prior to cisplatin infusion through the morning of Day 6. The key secondary hypotheses assessed the complete response during the acute and delayed phases analyzed separately. Several other secondary efficacy measures were also assessed in terms of the proportion of patients responding: No Emesis, Time to First Emesis, No Significant Nausea, and No Nausea (Section 7.6.3.2). Additionally, the proportion of patients reporting "No impact on daily life" derived from the FLIE questionnaire Total Score was also evaluated (Section 7.6.3.4). For each of these parameters treatment comparisons were made in the context of a logistic regression model that included terms for treatment, gender, use of concomitant emetogenic chemotherapy, and geographic region (U.S. versus non-U.S.).

7.6.2 Patient Baseline Characteristics

The patient populations enrolled were generally similar in both Protocol 052 and Protocol 054, though patients in Protocol 054 were slightly younger and relatively more were women (Table 20). In both protocols, the distribution of known risk factors for CINV (age, female gender, morning sickness, motion sickness, and cisplatin dose) and proportion of patients receiving emetogenic chemotherapy in addition to cisplatin were generally similar between treatment groups, though patients in Protocol 054 drank alcohol less. The baseline data and CINV risk factors are presented for each protocol separately because the efficacy data are presented subsequently for each study separately also.

Table 20

Baseline Patient Demographics and Characteristics by Study and Treatment Group—(Cycle 1) Adult Patients—Protocols 052 and 054

	Protocol 052				Protocol 054			
	Aprepitant Regimen (N=264)		Standard Therapy (N=266)		Aprepitant Regimen (N=283)		Standard Therapy (N=286)	
	n	(%)	n	(%)	n	(%)	n	(%)
Gender								
Male	166	(62.4)	166	(61.9)	148	(52.3)	146	(51.0)
Female	98	(36.8)	100	(37.3)	135	(47.7)	140	(49.0)
Age (Years)								
Mean	58.8		57.7		54.2		53.1	
SD	12.45		11.94		13.45		14.11	
Median	61.0		59.0		56.0		54.0	
Range	18-84		19 to 83		18 to 82		18 to 81	
Alcohol Intake								
No consumption per week	152	(57.1)	153	(57.1)	237	(83.7)	248	(86.7)
1 to 10 drinks per week	63	(23.7)	62	(23.1)	41	(14.5)	36	(12.6)
>10 drinks per week	44	(16.5)	41	(15.3)	5	(1.8)	2	(0.7)
Null	7	(2.6)	12	(4.5)	-	-	-	-
History of Morning Sickness								
Yes	19	(7.1)	13	(4.9)	29	(10.2)	19	(6.6)
No	247	(92.9)	254	(94.8)	254	(89.8)	267	(93.4)
Null	0	(0.0)	1	(0.4)	-	-	-	-
History of Motion Sickness								
Yes	20	(7.5)	12	(4.5)	11	(3.9)	10	(3.5)
No	246	(92.5)	255	(95.1)	272	(96.1)	276	(96.5)
Null	0	(0.0)	1	(0.4)	-	-	-	-
Other Concurrent Emetogenic Chemotherapy								
(Hesketh Level ≥3)								
With[†]	40	(15.0)	44	(16.0)	49	(17.3)	48	(16.8)
Without[‡]	226	(85.0)	224	(84.0)	234	(82.7)	238	(83.2)
Cisplatin Dose								
Mean Dose (mg/m^2)	80.6		79.8		80.2		80.2	

[†] "With" includes patients who received other concurrent emetogenic chemotherapy (Hesketh Level ≥3) excluding cisplatin [47].

[‡] "Without" includes patients who received other concurrent emetogenic chemotherapy (Hesketh Level <3) excluding cisplatin, and patients with no other concurrent emetogenic chemotherapy [47].

The proportions of patients with specific primary cancer diagnoses and the proportions of patients receiving specific concomitant chemotherapy were similar in both treatment groups (Table 21 and Table 22, respectively). The data in Table 21 and Table 22 are presented for Protocol 052 and Protocol 054 combined because the safety data are presented for the combined protocols in Section 8. The specific primary cancer diagnoses were similar in both protocols and the specific concomitant chemotherapy was also similar in both protocols except that gemcitabine was more frequently administered in Protocol 052.

Table 21

Percent of Patients With Specific Primary Cancer Diagnoses by Treatment Group—Protocols 052 and 054 Combined

Primary Cancer Diagnoses	Aprepitant Regimen (N=547)	Standard Therapy (N=552)
Lung	40.0	38.0
Ovarian	9.5	11.1
Head and neck	9.3	6.7
Esophageal	4.2	2.9
Gastric	3.7	2.4
Testicular	3.8	5.3
Bladder	3.1	4.0

Table 22

Percent of Patients Treated With Specific Concomitant Chemotherapy by Treatment Group—Protocols 052 and 054 Combined

Chemotherapeutic Agents	Aprepitant Regimen (N=547)	Standard Therapy (N=552)
Etoposide	19.4	16.7
Fluorouracil	18.3	16.8
Gemcitabine	16.3	18.3
Vinorelbine tartrate	15.4	14.5
Paclitaxel	9.5	10.5
Cyclophosphamide	9.1	7.8
Doxorubicin	6.9	8.0
Docetaxel	2.0	2.5
Cisplatin only	4.9	4.0

7.6.3 Efficacy of Aprepitant in CINV

7.6.3.1 Effect of Aprepitant: Complete Response Endpoint

Table 23 presents the number and percent of patients with complete response by treatment group and phase (overall, acute, and delayed) for Protocols 052 and 054 individually. The results for both studies appear highly consistent.

Overall (Primary Hypothesis): Overall (0 to 120 hours following initiation of cisplatin infusion) both individual Phase III Protocols 052 and 054 showed significant superiority for the aprepitant regimen (72.7% and 62.7%, respectively) for the complete response endpoint compared with Standard Therapy (52.3% and 43.3%, respectively) ($p<0.001$ for both studies adjusted for gender, region, and use of concomitant emetogenic chemotherapy).

Acute Phase (Secondary Hypothesis): During the acute phase (0 to 24 hours following initiation of cisplatin infusion) both individual Phase III Protocols 052 and 054 showed significant superiority for the aprepitant regimen (89.2% and 82.8%, respectively) for the complete response endpoint compared with Standard Therapy (78.1% and 68.4%, respectively) ($p<0.001$ for both studies).

Delayed Phase (Secondary Hypothesis): During the delayed phase (25 to 120 hours following initiation of cisplatin infusion) both individual Phase III Protocols 052 and 054 showed significant superiority for the aprepitant regimen (75.4% and 67.7%, respectively) for the complete response endpoint compared with Standard Therapy (55.8% and 46.8%, respectively) ($p<0.001$ for both studies).

Table 23

Number (%) of Patients With Complete Response
by Treatment Group and Phase—Protocols 052 and 054

	Aprepitant Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Protocol 052				
Overall	189/260	(72.7)**	136/260	(52.3)
Acute phase	231/259	(89.2)**	203/260	(78.1)
Delayed phase	196/260	(75.4)**	145/260	(55.8)
Protocol 054				
Overall	163/260	(62.7)**	114/263	(43.3)
Acute phase	216/261	(82.8)**	180/263	(68.4)
Delayed phase	176/260	(67.7)**	123/263	(46.8)

** $p<0.001$ when compared with Standard Therapy.
n/m = Number of patients with desired response/number of patients included in analysis.

7.6.3.2 Efficacy of Aprepitant: Other Endpoints

In addition to complete response, other endpoints were used to comprehensively define the aprepitant efficacy profile in Phase III.

- No Emesis
- Time to First Emesis or Rescue
- No Significant Nausea—defined as a maximum VAS rating <25 mm
- No Nausea—defined as a maximum VAS rating <5 mm
- Complete Protection—defined as complete response plus no significant nausea, which was defined as a maximum nausea VAS score of <25 mm
- Total Control—defined as complete response plus no nausea, which was defined as a maximum nausea VAS score of <5 mm

The choice of <25 mm on the nausea VAS as "no significant" nausea was based on a published comparison of a 100-mm VAS with a standard CINV categorical scale, which demonstrated that patients recording VAS ratings of <25 mm generally recorded either no or mild nausea on the categorical scale [56]. Mild nausea on a categorical scale is defined as nausea that does not interfere with normal activities, whereas significant nausea is defined as nausea that does interfere with normal activities [56].

The data for the additional efficacy endpoints are presented in Table 24 and Table 25 for Protocol 052 and Protocol 054, respectively.

Table 24

Number (%) of Patients With Favorable Response
by Treatment Group and Phase—Protocol 052

Post-Cisplatin Phase	Aprepitant Regimen n/m	(%)	Standard Therapy n/m	(%)
No Emesis (No Emetic Episodes) (Secondary)				
Overall	202/260	(77.7)**	143/260	(55.0)
Acute phase	234/260	(90.0)**	207/261	(79.3)
Delayed phase	210/260	(80.8)**	153/260	(58.8)
No Use of Rescue Medication (For Established Emesis or Nausea) (Post Hoc)				
Overall (0 to 120 hours)	210/260	(80.8)**	184/260	(70.8)
Acute phase (0 to 24 hours)	244/259	(94.2)*	231/260	(88.8)
Delayed phase (25 to 120 hours)	211/260	(81.2)*	191/260	(73.5)
Complete Protection (No Emesis, No Rescue, and Maximum Nausea VAS <25mm) (Exploratory)				
Overall (0 to 120 hours)	163/257	(63.4)**	128/260	(49.2)
Acute phase (0 to 24 hours)	217/256	(84.8)**	194/260	(74.6)
Delayed phase (25 to 120 hours)	172/259	(66.4)**	134/260	(51.5)
Total Control (No Emesis, No Rescue, and Maximum Nausea VAS <5mm) (Exploratory)				
Overall (0 to 120 hours)	117/257	(45.5)	104/260	(40.0)
Acute phase (0 to 24 hours)	181/256	(70.7)	167/260	(64.2)
Delayed phase (25 to 120 hours)	127/259	(49.0)	111/260	(42.7)
No Significant Nausea (Maximum VAS <25 mm) (Secondary)				
Overall (0 to 120 hours)	188/257	(73.2)	171/259	(66.0)
Acute phase (0 to 24 hours)	232/256	(90.6)	224/259	(86.5)
Delayed phase (25 to 120 hours)	195/259	(75.3)	178/260	(68.5)
No Nausea (Maximum VAS <5 mm) (Secondary)				
Overall (0 to 120 hours)	122/257	(47.5)	115/260	(44.2)
Acute phase (0 to 24 hours)	185/256	(72.3)	179/259	(69.1)
Delayed phase (25 to 120 hours)	132/259	(51.0)	124/260	(47.7)

* $p<0.05$ when compared with Standard Therapy.
** $p<0.01$ when compared with Standard Therapy.
VAS = Visual analogue scale.
n/m = Number of patients with a given response/number of patients in the analysis.

Table 25

Number (%) of Patients With Favorable Response
by Treatment Group and Phase—Protocol 054

Post-Cisplatin Phase	Aprepitant Regimen n/m	(%)	Standard Therapy n/m	(%)
No Emesis (No Emetic Episodes) (Secondary)				
Overall (0 to 120 hours)	172/260	(66.2)**	117/263	(44.5)
Acute phase (0 to 24 hours)	218/261	(83.5)**	181/263	(68.8)
Delayed phase (25 to 120 hours)	186/260	(71.5)**	127/263	(48.3)
No Use of Rescue Medication (For Established Emesis or Nausea) (Post Hoc)				
Overall (0 to 120 hours)	214/260	(82.3)**	191/263	(72.6)
Acute phase (0 to 24 hours)	251/261	(96.2)**	236/263	(89.7)
Delayed phase (25 to 120 hours)	216/260	(83.1)*	195/263	(74.1)
Complete Protection (No Emesis, No Rescue, and Maximum Nausea VAS <25mm) (Exploratory)				
Overall (0 to 120 hours)	145/261	(55.6)**	107/263	(40.7)
Acute phase (0 to 24 hours)	208/260	(80.0)**	170/263	(64.6)
Delayed phase (25 to 120 hours)	159/261	(60.9)**	116/263	(44.1)
Total Control (No Emesis, No Rescue, and Maximum Nausea VAS <5mm) (Exploratory)				
Overall (0 to 120 hours)	116/261	(44.4)**	84/263	(31.9)
Acute phase (0 to 24 hours)	166/261	(63.6)	149/263	(56.7)
Delayed phase (25 to 120 hours)	130/261	(49.8)**	89/263	(33.8)
No Significant Nausea (Maximum VAS <25 mm) (Secondary)				
Overall (0 to 120 hours)	185/260	(71.2)	168/263	(63.9)
Acute phase (0 to 24 hours)	235/260	(90.4)*	218/263	(82.9)
Delayed phase (25 to 120 hours)	189/260	(72.7)	172/263	(65.4)
No Nausea (Maximum VAS <5mm) (Secondary)				
Overall (0 to 120 hours)	127/260	(48.8)*	102/263	(38.8)
Acute phase (0 to 24 hours)	176/260	(67.7)	174/263	(66.2)
Delayed phase (25 to 120 hours)	137/260	(52.7)**	105/263	(39.9)

* $p<0.05$ when compared with Standard Therapy.
** $p<0.01$ when compared with Standard Therapy.
VAS = Visual analogue scale.
n/m = Number of patients with a given response/number of patients in the analysis.

Both components of the primary endpoint of complete response (i.e., the no emesis endpoint and the no rescue endpoint) showed a significant advantage for the aprepitant regimen versus Standard Therapy in both studies throughout all phases. Since patients took rescue to treat either established emesis or nausea, the use of rescue reflects control of nausea. Patients treated with the aprepitant regimen used rescue less frequently, indicating the beneficial effect of aprepitant on the alleviation of nausea.

In both protocols, the aprepitant regimen showed numerical or statistically significant advantages over Standard Therapy on all specific nausea assessments, which were prespecified secondary analyses. The aprepitant regimen was significantly better than Standard Therapy for the no significant nausea endpoint during the acute phase and for the no nausea endpoint overall and during the delayed phase in Protocol 054. In Protocol 052, numerical but not statistical advantages were observed.

There was also a significant advantage for the aprepitant regimen as measured by the exploratory complete protection endpoint overall, and also throughout the acute and delayed phases. Since this composite endpoint includes a nausea assessment (maximum VAS score <25 mm), in addition to control of emesis and no use of rescue therapy, the significant advantage seen for the aprepitant regimen in both studies, is also indicative of the aprepitant regimen controlling both nausea and vomiting.

The other prespecified composite endpoint, total control, which includes a different nausea criterion (maximum VAS <5 mm), also favored the aprepitant regimen throughout all phases, providing further support of control of both nausea and vomiting. However, the differences were not significant for this very rigorous endpoint.

In a post hoc analysis of the data merged from both Protocol 052 and Protocol 054 for both the no nausea and no significant nausea endpoints, the aprepitant regimen was significantly superior to Standard Therapy during both the delayed and overall phases ($p<0.05$) (Table 26).

Table 26

Number (%) of Patients With No Significant Nausea and No Nausea by Treatment Group—Protocols 052 and 054 Combined—Cycle 1

	Aprepitant Regimen	Standard Therapy
	n/m (%)	n/m (%)
No Significant Nausea (Maximum VAS <25 mm) (Secondary)		
Delayed	373/517 (72.1)*	339/522 (64.9)
Overall	383/519 (74.0)*	350/523 (66.9)
No Nausea (Maximum VAS <5 mm) (Secondary)		
Delayed	249/517 (48.2)*	217/523 (41.5)
Overall	269/519 (51.8)**	229/523 (43.8)

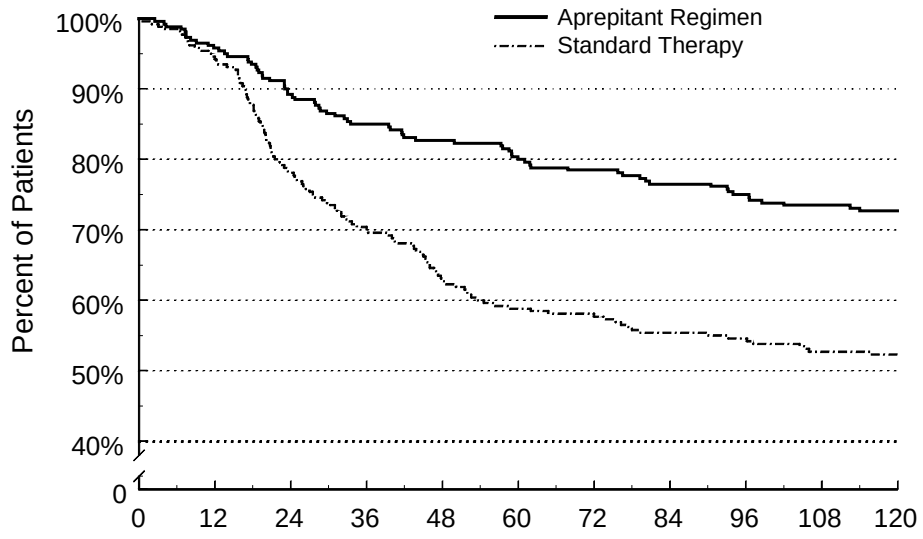
* p <0.05 when compared with Standard Therapy.
** p <0.01 when compared with Standard Therapy.
VAS = Visual analogue scale.
n/m = Number of patients with a given response/number of patients in the analysis.

7.6.3.3 Time to First Emesis or Rescue (Overall Phase) (Post Hoc)

Figure 8 and Figure 9 display the Kaplan-Meier curves for time to first emesis or rescue in the overall phase for Protocol 052 and Protocol 054, respectively. The curves depict the cumulative percentage of patients who remained emesis free and rescue free since the initiation of cisplatin therapy and show that the overall time to first emesis or rescue was significantly longer in the aprepitant treatment group ($p<0.001$) in both studies. The curves up to ~16 hours post-initiation of cisplatin appear to be similar but diverge after that time point as the advantages provided by aprepitant become evident. The onset of most first emetic episodes or use of rescue was in the first 72 hours of the 120-hour observation period.

Figure 8

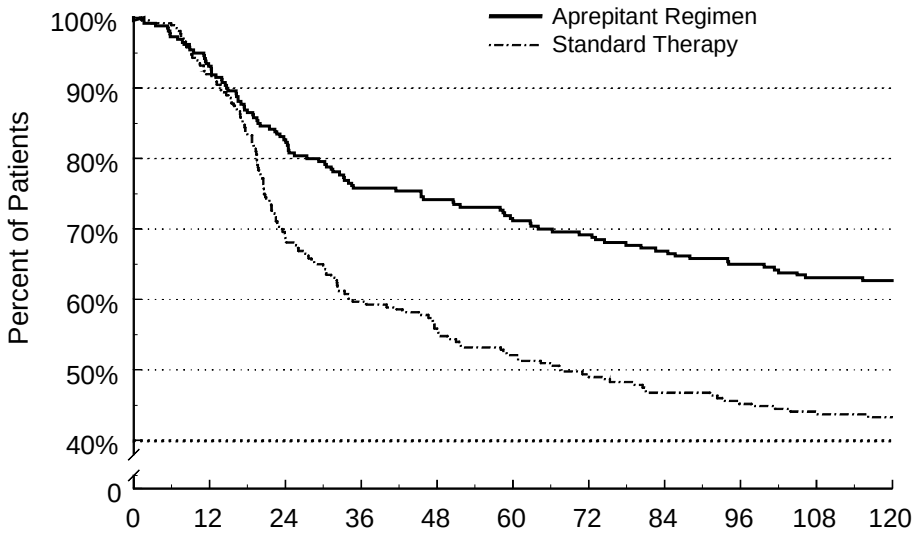
Percent of Patients Who Remain Emesis and Rescue Free Over Time From Start of Aprepitant Administration—Cycle 1 (Protocol 052)



Time (hours) Since Cisplatin Administration

Figure 9

Percent of Patients Who Remain Emesis and Rescue Free Over Time From Start of Aprepitant Administration—Cycle 1 (Protocol 054)



Time (hours) Since Cisplatin Administration

7.6.3.4 Impact of CINV on Daily Life (FLIE Total Score)—Effect of Aprepitant

Symptom relief alone does not fully describe the benefits of effective antiemetic therapy to patients because it does not assess the impact of CINV on patients' daily lives. The FLIE is a validated, 18-question nausea- and vomiting-specific questionnaire that was included in the aprepitant clinical development program to assess the impact of CINV on patients' daily lives [57]. Patients are asked to rate the extent to which nausea (Questions 1 to 9) and vomiting (Questions 10 to 18) impact the following aspects of their daily life: daily functioning, ability to enjoy meals, enjoy liquids, perform household tasks, perform recreation/leisure activities, spend time with family/friends, personal hardship, and hardship on others. Responses for each item are marked on a 1- to 7-point VAS with 1 corresponding to "a great deal" and 7 corresponding to "none"/"not at all." "No impact of CINV on daily life" is defined in the FLIE Scoring Manual as a response falling within the category anchored by "none"/"not at all." For the FLIE total score, "no impact on daily life" corresponds to an average item score >6 on the 7-point scale. Patients completed the questionnaire 5 days after receiving cisplatin chemotherapy (Day 6) in Cycle 1.

Table 27 shows the observed proportions of patients with no impact of CINV on daily life by treatment group for Cycle 1 of Protocols 052 and 054 as assessed by the FLIE total score, which was a prespecified secondary endpoint. Significantly more patients in the aprepitant group reported "no impact of CINV on daily life" relative to patients in the Standard Therapy group in both Protocols 052 and 054.

Table 27

Number (%) of Patients With "No Impact of CINV on Daily Life[†]" by Treatment Group in Protocols 052 and 054—Cycle 1

	Aprepitant Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
Protocol 052				
FLIE Total Score	188/254	(74.0)*	162/252	(64.3)
Protocol 054				
FLIE Total Score	189/253	(74.7)**	162/255	(63.5)

* $p<0.05$ when compared with Standard Therapy.
** $p<0.01$ when compared with Standard Therapy.
[†] "No Impact of CINV on Daily Life" is defined as an average item score of >6 on the 7-point scale.
n/m = Number of patients with "No Impact of CINV on Daily life"/number of patients included in the analysis.
CINV = Chemotherapy-induced nausea and vomiting.

7.6.3.5 Summary of Aprepitant Efficacy in Cycle 1 of CINV Phase III Studies

The 2 studies consistently demonstrated that the Phase III aprepitant regimen was more effective than Standard Therapy in the prevention of CINV. This was shown on the primary endpoint of overall complete response, as well as in separate analyses of the acute and delayed phases. The aprepitant regimen was also shown to be significantly more effective than Standard Therapy using the component endpoints of the complete response endpoint (i.e., no emesis and no rescue) in both Phase III studies overall and also for the acute and delayed analyses.

All of the other endpoints assessed consistently favored the aprepitant regimen over Standard Therapy, though not all comparisons attained statistical significance in the individual studies (e.g., for some of the nausea endpoints). Furthermore, patients who received the aprepitant regimen reported less impact of CINV on their daily lives compared with those who received Standard Therapy as reflected by the data obtained using the FLIE questionnaire.

7.6.3.6 Efficacy of Aprepitant by Age, Gender, Race, and Additional Emetogenic Chemotherapy

Table 28 shows the subgroup summaries for age (<65 years versus ≥65 years, <75 years versus ≥75 years), gender, race (Asian, Black, Hispanic American, Multi-Racial, and White), and additional emetogenic chemotherapy for the number and percent of patients reporting complete response overall (primary hypothesis) when Protocols 052 and 054 were combined.

The efficacy advantage of the aprepitant regimen compared with Standard Therapy was independent of gender, age group, and racial group, except that in the small numbers of Black patients, the advantage was not apparent on the primary complete response endpoint. However, even in this small subgroup, there was a numerical advantage for the aprepitant regimen on the no emesis endpoint. There were no significant differences in the pharmacokinetics of aprepitant in Black and Caucasian subjects noted (see Section 6.3.8).

Consistent with the literature, the complete response rates in the subset of patients treated with emetogenic chemotherapy in addition to cisplatin (either cyclophosphamide or doxorubicin) were lower in both treatment groups. However, the beneficial effect of the aprepitant regimen was clearly seen suggesting that aprepitant is also effective in preventing symptoms in patients receiving emetogenic chemotherapeutic agents with cisplatin.

Table 28

Number (%) of Patients With Overall Complete Response by Gender, Age Group, Race, and Additional Emetogenic Chemotherapy and Treatment Group—Protocols 052 and 054 Combined—Cycle 1

	Aprepitant Regimen		Standard Therapy	
	n/m	(%)	n/m	(%)
All Patients	352/520	(67.7)	250/523	(47.8)
Gender				
Female	143/216	(66.2)	89/219	(40.6)
Male	209/304	(68.8)	161/304	(53.0)
Age Group (years)				
Age <65	228/357	(63.9)	170/375	(45.3)
Age ≥65	124/163	(76.1)	80/148	(54.1)
Age <75	327/492	(66.5)	236/500	(47.2)
Age ≥75	25/28	(89.3)	14/23	(60.9)
Race Group				
Asian	11/16	(68.8)	7/11	(63.6)
Black	15/25	(60.0)	13/21	(61.9)
Hispanic American	39/64	(60.9)	29/70	(41.4)
Multi-Racial	57/98	(58.2)	41/104	(39.4)
White	230/317	(72.6)	160/317	(50.5)
Additional Emetogenic Chemotherapy				
Cyclophosphamide and/or Doxorubicin	41/70	(58.6)	19/72	(26.4)

n/m = Number of patients with complete response response/number of patients included in analysis.

7.6.3.7 Effect of Aprepitant in Multiple Cycles

Statistical Methods

Using the Yes or No outcomes recorded for the No Emesis and No Significant Nausea questions that were asked at the Days 6 to 8 clinic visit in the Multiple-Cycle extension, Kaplan-Meier curves for the time (cycle) to first emesis and to first report of significant nausea were plotted for both studies as prespecified exploratory analyses. The curves display the percentage of patients emesis free (Figure 10 and Figure 12) and free of significant nausea (Figure 11 and Figure 13) during the Multiple-Cycle extension for the respective protocols.

An additional analysis using a model with 3 potential outcomes was created post hoc for the multiple-cycle data merged from both Phase III protocols: "favorable" response (no emesis and no significant nausea), "partial" response (no emesis and significant nausea or emesis and no significant nausea), and "failure" (emesis and significant nausea). This

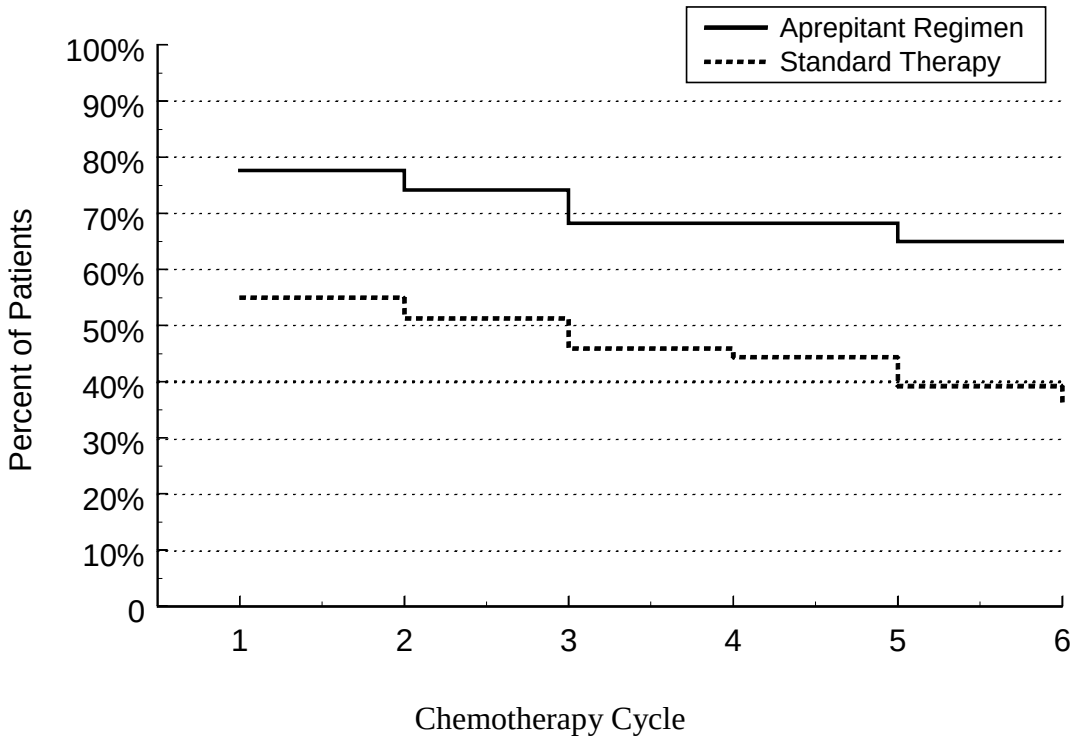
3-state model, employing transitional probabilities, was used to calculate the probability of having a "favorable" response at a given cycle, without being a "failure" during a prior cycle. This approach takes into consideration the variable response between cycles and the attrition rate and has been reported to provide a more comprehensive assessment of efficacy during a Multiple-Cycle extension [53]. The probability of having a favorable response using this model was calculated and displayed graphically for data combined from both Protocol 052 and Protocol 054 (Figure 14).

Results Protocol 052

The Kaplan-Meier curves for time to first emesis show that of the patients who continued in the Multiple-Cycle extension, those receiving the aprepitant regimen maintained consistently better responses over the 6 cycles of chemotherapy compared with those in the Standard Therapy group. The difference was significant in a post hoc analysis ($p<0.001$) (Figure 10).

Figure 10

Kaplan-Meier Curves of Continued Success Rate for
Time (Cycle) to First Emesis in Protocol 052—Cycles 1 to 6



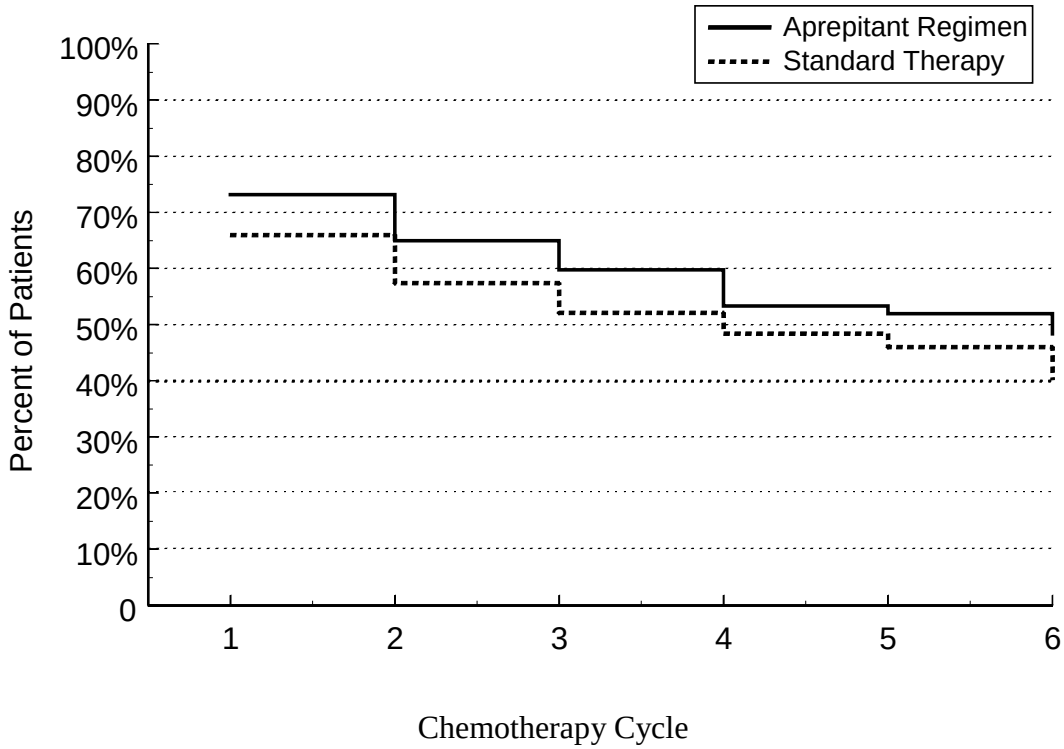
Patients in Each Cycle

Aprepitant Regimen:	N = 260	N = 132	N = 101	N = 61	N = 42	N = 31
Standard Therapy:	N = 260	N = 104	N = 66	N = 32	N = 17	N = 12

The Kaplan-Meier curves for time to first significant nausea also show that, of the patients who continued in the Multiple-Cycle extension, those receiving the aprepitant regimen maintained consistently better responses over the 6 cycles of chemotherapy compared with those in the Standard Therapy group (Figure 11).

Figure 11

Kaplan-Meier Curves of Continued Success Rate for Time (Cycle) to First Significant Nausea in Protocol 052—Cycles 1 to 6



Patients in Each Cycle

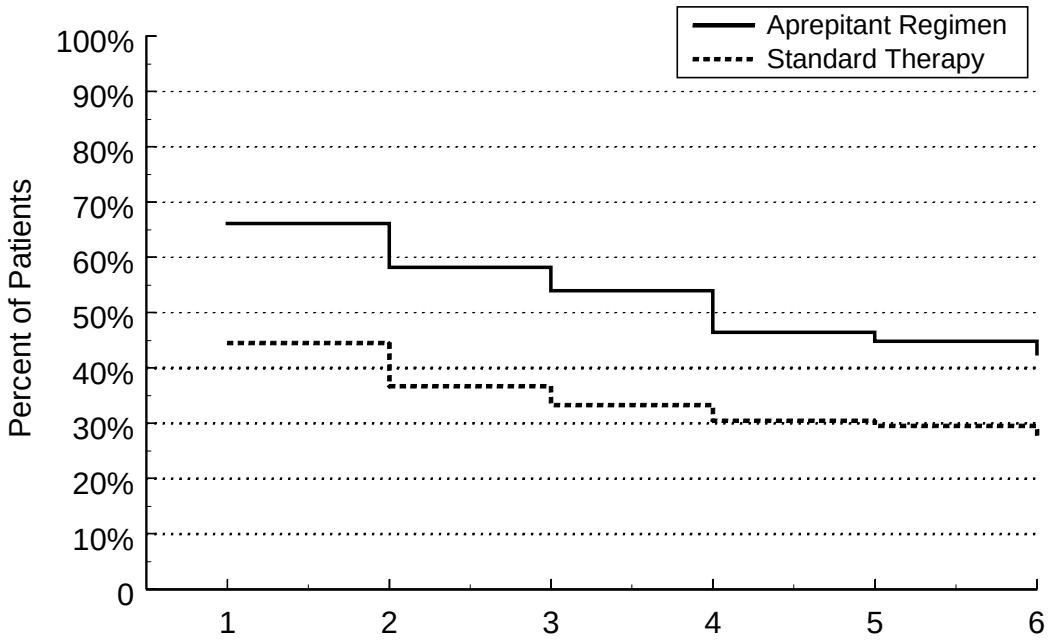
Aprepitant Regimen:	N = 257	N = 125	N = 89	N = 56	N = 36	N = 29
Standard Therapy:	N = 259	N = 123	N = 76	N = 42	N = 20	N = 16

Results Protocol 054

The Kaplan-Meier curves for time to first emesis show that, of the patients who continued in the Multiple-Cycle extension, those receiving the aprepitant regimen maintained consistently better responses over the 6 cycles of chemotherapy compared with those in the Standard Therapy group. The difference was significant in a post hoc analysis ($p<0.001$) (Figure 12).

Figure 12

Kaplan-Meier Curves of Continued Success Rate for
Time (Cycle) to First Emesis in Protocol 054—Cycles 1 to 6



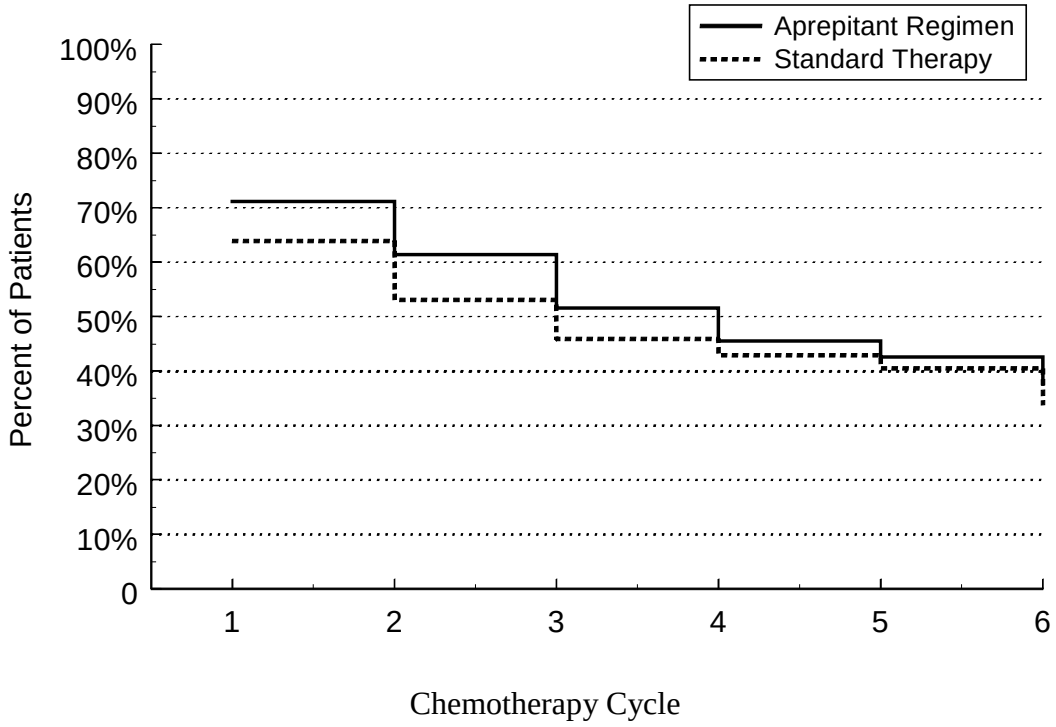
Patients in Each Cycle

Aprepitant Regimen:	N = 260	N = 124	N = 84	N = 58	N = 28	N = 20
Standard Therapy:	N = 263	N = 97	N = 65	N = 48	N = 29	N = 17

The Kaplan-Meier curves for time to first significant nausea show that, of the patients who continued in the Multiple-Cycle extension, those receiving the aprepitant regimen maintained consistently better responses over the 6 cycles of chemotherapy compared with those in the Standard Therapy group (Figure 13).

Figure 13

Kaplan-Meier Curves of Continued Success Rate for Time (Cycle) to First Significant Nausea in Protocol 054—Cycles 1 to 6



Patients in Each Cycle

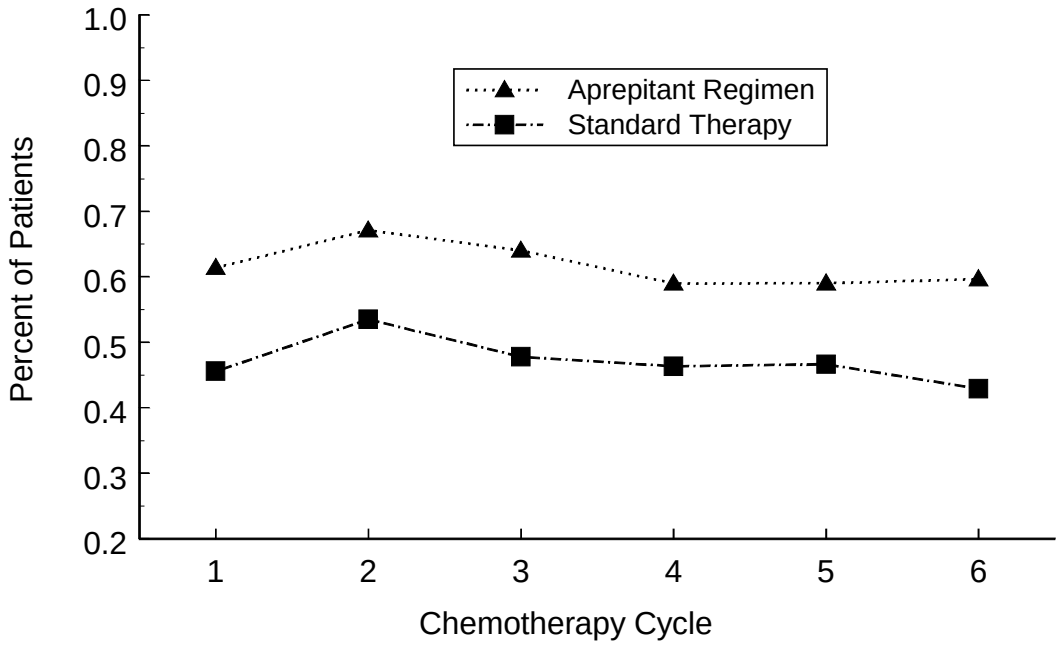
Aprepitant Regimen:	N = 260	N = 139	N = 94	N = 59	N = 31	N = 17
Standard Therapy:	N = 263	N = 136	N = 89	N = 61	N = 36	N = 18

Protocol 052 and Protocol 054 Combined (Transitional Probability Approach; Post Hoc Display)

Figure 14 displays the probability of patients having a favorable response (i.e., no emesis and no significant nausea) without failing during a prior cycle (i.e., reporting both emesis and significant nausea) for Protocol 052 and Protocol 054 combined using the transitional probability approach. The data show that over the 6 cycles, the probability of a favorable response was consistently higher in the aprepitant group compared with the Standard Therapy group, and that the efficacy advantage of the aprepitant regimen versus Standard Therapy evident in Cycle 1 appeared to be maintained in repeated cycles.

Figure 14

Probability of a Favorable Response (No Emesis and No Significant Nausea) by Cycle and Treatment Group—Protocol 052 and Protocol 054 Combined—Cycles 1 to 6



Patients in Each Cycle

Aprepitant Regimen:	N=516	N=290	N=216	N=140	N=86	N=60
Standard Therapy:	N=522	N=274	N=182	N=115	N=65	N=43

7.7 Phase IIb/Phase III Conclusions—Efficacy of Aprepitant in CINV

The following efficacy conclusions were derived from the aprepitant Phase IIb and Phase III clinical studies in patients receiving highly emetogenic cancer chemotherapy with cisplatin:

- The efficacy of aprepitant in the prevention of CINV is dose related: 125 mg administered on Day 1 followed by 80 mg on subsequent days is effective as assessed by the overall complete response and consistently superior to 40 mg administered on Day 1 followed by 25 mg on subsequent days.

- Administration of the Phase III aprepitant regimen provides protection against CINV overall and throughout both the acute and delayed phases, and is superior to Standard Therapy that includes a 5-HT_3–receptor antagonist plus dexamethasone on Day 1, followed by dexamethasone on Days 2 to 4.
- The efficacy of the aprepitant regimen is unaffected by age, race, gender, or the concomitant administration of emetogenic chemotherapy in addition to cisplatin.
- The aprepitant regimen is effective in reducing the impact of CINV on patients' daily lives.
- The efficacy advantage of the aprepitant regimen versus Standard Therapy observed in Cycle 1 appears to be maintained during subsequent cycles of chemotherapy.

8. Clinical Safety

8.1 Overview

Based on a favorable profile in nonclinical studies, the aprepitant clinical development program was designed to test the hypothesis that aprepitant prevents CINV while demonstrating good safety and tolerability in patients with cancer receiving emetogenic chemotherapy.

The safety and tolerability assessments reported here focus primarily on the Phase III CINV studies because these 2 pivotal studies evaluated the aprepitant regimen proposed for market in comparison with current standard antiemetic therapy (see Section 8.5). In these studies, specific attention was paid to the potential interaction between aprepitant and concomitant chemotherapy metabolized by CYP3A4, since aprepitant, as dosed for CINV, is a weak to moderate CYP3A4 inhibitor, similar to diltiazem.

Key findings from the Clinical Pharmacology studies and the Phase II CINV studies relevant to the further development of aprepitant are also summarized in this section (see Sections 8.3 and 8.4). In addition, data from studies in indications other than CINV are included, as these studies tested a broad range of aprepitant doses administered for extended periods of time to patients/subjects not exposed to the side effects of chemotherapy (see Section 8.6).

Overall, the pattern of clinical and laboratory adverse experiences observed in Clinical Pharmacology and Clinical Research studies shows that aprepitant is generally well tolerated at doses that are clinically effective for the treatment of CINV, and at doses up to 3-fold higher than the proposed regimen for CINV, for up to 8 weeks.

8.2 Overall Exposure to Aprepitant

The clinical development program for aprepitant included Phase I Clinical Pharmacology studies and Phase II and Phase III CINV studies. Other clinical studies were conducted in non-CINV indications that are not proposed for market at this time. Aprepitant was evaluated in different formulations. Tablet formulations used in early studies were well tolerated, but are not proposed for market because their bioavailability was somewhat lower than the later-developed nanoparticle capsule, and markedly influenced by food. An IV prodrug of aprepitant, L-758298, was used in some studies. The Phase III studies used the nanoparticle capsule formulation, which is the Final Market Image (FMI).

Table 29 summarizes the total number of adult patients/subjects who received aprepitant or L-758298 throughout the development program. Overall, 3342 adult patients/subjects were exposed to aprepitant or L-758298. Of these, 1459 adult cancer patients received aprepitant or L-758298 for prevention of CINV. The great majority of these patients received aprepitant with other antiemetics.

Table 29

Total Number of Adult Patients/Subjects on Aprepitant or L-758298
in the Development Program

	Aprepitant Capsules (FMI)	Aprepitant Tablets	L-758298	Total
Clinical Pharmacology	368	229	114	711
CINV Phase IIa	29	369	149	547
CINV Phase IIb	368	0	0	368
CINV Phase III	544	0	0	544
Total CINV	**941**	**369**	**149**	**1459**
Non-CINV Studies	180	926	66	1172
Total	**1489**	**1524**	**329**	**3342**

FMI = Final Market Image.

8.3 Key Safety Findings in Clinical Pharmacology Studies

Overall, a total of 808 subjects (generally healthy adults) were enrolled in Phase I Clinical Pharmacology studies in which they received aprepitant, L-758298 (the IV prodrug of aprepitant), other drugs, or placebo. In this set of studies, subjects received single daily doses of aprepitant for up to 29 days.

Aprepitant was generally well tolerated. The incidences of clinical and laboratory adverse experiences were generally similar among all active treatment groups. Certain clinical adverse experiences (asthenia/fatigue, somnolence, dizziness, flushing, diarrhea, nausea, hiccups, menstrual disorder, and headache) tended to occur more frequently in the active treatment groups (including the group not receiving aprepitant) compared with placebo. Adverse experiences of hiccups were reported more commonly in the aprepitant groups, but only in patients treated with aprepitant plus dexamethasone; there were no reports of hiccups in subjects who received only aprepitant. The adverse experiences that occurred slightly more frequently in the active groups did not affect the overall good tolerability of aprepitant in healthy subjects.

8.4 Key Safety Findings in CINV Phase II Studies

A total of 1375 cancer patients were treated with study drug in the CINV Phase II studies: 915 with aprepitant and 460 with Standard Therapy. Overall the aprepitant regimens tested in the CINV Phase II program were generally well tolerated. In the Phase IIb study, febrile neutropenia occurred more frequently in the aprepitant group as compared with Standard Therapy. Incidences of febrile neutropenia in this study were 6.1% in the aprepitant 125-mg/80-mg group and 3.8% in the Standard Therapy group. In addition, a post hoc assessment suggested that infection-related serious adverse experiences were

also reported more frequently in the aprepitant 125-mg/80-mg group (3.7%) compared with the Standard Therapy group (1.9%) in the Phase IIb study.

The differences in the incidences of febrile neutropenia and infections between treatment groups observed in the Phase IIb study may have been due to chance as the overall numbers were low and remained within the expected frequency for this patient population. Alternatively, the differences may have been a consequence of higher exposure to dexamethasone in the aprepitant group compared with the Standard Therapy group during Phase IIb (see Sections 6.4.3.3 and 7.5.2). These and other potential adverse events were carefully evaluated in the Phase III safety database.

8.5 Safety in CINV Phase III Studies

The CINV Phase III studies (Protocol 052 and Protocol 054) evaluated the aprepitant regimen proposed for market. These trials had an identical study design and evaluated aprepitant for the prevention of CINV associated with HEC. Safety data from these 2 trials have been merged and represent the focus of the evaluation of the safety of aprepitant for CINV. As discussed in Section 7.5, the regimen tested in the Phase III studies differed from the one tested in Phase IIb with respect to the dexamethasone dosing and the duration of aprepitant dosing. Since these changes may have altered the overall safety profile of the aprepitant regimen, the CINV Phase III safety data have not been merged with the Phase II studies.

8.5.1 Evaluation of Safety in CINV Phase III Studies

The safety of aprepitant in Phase III was evaluated by monitoring patients for adverse experiences, vital signs measurements, physical examinations, 12-lead ECGs, and laboratory safety tests (hematology, blood chemistry, and urinalysis). All laboratory tests were performed by a central laboratory and graded according to the National Cancer Institute (NCI) Common Toxicity Criteria on a scale of 0 to 4, with 0 representing no toxicity and 4 representing life-threatening toxicity. Clinical adverse experiences (reported by the patient or observed by the investigator) were also graded by the investigators using the NCI Common Toxicity Criteria. These criteria were used to assess the severity of toxic effects that are predictably associated with the specific chemotherapy regimens in accordance with standard practice in oncology studies.

Based on the Phase II experience, certain adverse experiences were prespecified as being of special interest in Phase III. These included fever, febrile neutropenia, infections, leukopenia, neutropenia, anemia, thrombocytopenia, hypertension, hyperglycemia, hypokalemia, and dehydration. These adverse experiences potentially reflect either hematologic toxicity, immunosuppression, and/or the effects of corticosteroids.

The Phase III studies included an option for patients to receive aprepitant for up to 6 cycles of chemotherapy. During the Multiple-Cycle extension, as agreed with the Agency, the reporting conventions for adverse experiences were modified compared with Cycle 1: only adverse experiences that caused discontinuation of study therapy or that were determined by the investigator to be serious or drug related were reported.

8.5.1.1 Statistical Analysis

The incidences of febrile neutropenia and serious infection-related adverse experiences in Cycle 1 were prespecified in the Data Analysis Plan as requiring statistical analyses for each individual Phase III study and for the 2 studies combined.

To be included in the safety analyses, patients must have received cisplatin and at least 1 dose of study drug. Two (2) patients in the Phase III studies received at least 1 dose of study drug, but did not receive cisplatin. These 2 patients were included in all safety displays, but they were not included in the statistical analyses of safety. For these prespecified safety outcomes, the Fisher's exact test was used to compare the treatment groups. The risk differences of the aprepitant group relative to the Standard Therapy group were calculated along with their associated exact 95% confidence intervals.

8.5.2 Cycle 1

8.5.2.1 Clinical Adverse Experiences

8.5.2.1.1 Clinical Adverse Experience Summary (Cycle 1)

Table 30 summarizes the total number of clinical adverse experiences during Cycle 1 of the merged CINV Phase III studies.

Table 30

Clinical Adverse Experience Summary—CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Number (%) of patients:				
With one or more adverse experiences	376	(69.1)	372	(67.6)
With drug-related† adverse experiences	93	(17.1)	70	(12.7)
With serious adverse experiences	73	(13.4)	75	(13.6)
Who died	20	(3.7)	21	(3.8)
Discontinued due to adverse experiences	42	(7.7)	32	(5.8)

† Determined by the investigator to be possibly, probably, or definitely drug related.
CINV = Chemotherapy-induced nausea and vomiting.
N = Number of adult patients who received at lest 1 dose of study therapy.

8.5.2.1.2 Clinical Adverse Experiences by Body System (Cycle 1)

As shown in Table 31, the incidences and profiles of the specific clinical adverse experiences by body system were similar in the 2 treatment groups in Cycle 1 of the CINV Phase III studies combined. The most frequently reported adverse experiences in Cycle 1 of the CINV Phase III studies in the aprepitant group and the Standard Therapy group, respectively, were asthenia/fatigue, nausea, and constipation. Adverse experiences

that occurred slightly more frequently in the aprepitant group compared with the Standard Therapy group included dizziness, diarrhea, cough, and hiccups. The great majority of these adverse experiences were graded as mild or moderate by the investigators.

Table 31

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

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Patients with one or more adverse experiences	376	(69.1)	372	(67.6)
Patients with no adverse experience	168	(30.9)	178	(32.4)
Body as a Whole/Site Unspecified	**200**	**(36.8)**	**169**	**(30.7)**
Abdominal pain	25	(4.6)	18	(3.3)
Asthenia/fatigue	97	(17.8)	65	(11.8)
Dehydration	32	(5.9)	28	(5.1)
Dizziness	36	(6.6)	24	(4.4)
Fever	16	(2.9)	19	(3.5)
Malaise	12	(2.2)	9	(1.6)
Mucous membrane disorder	14	(2.6)	17	(3.1)
Cardiovascular System	**48**	**(8.8)**	**43**	**(7.8)**
Digestive System	**234**	**(43.0)**	**223**	**(40.5)**
Constipation	56	(10.3)	67	(12.2)
Diarrhea	56	(10.3)	41	(7.5)
Dyspepsia	16	(2.9)	11	(2.0)
Epigastric discomfort	22	(4.0)	17	(3.1)
Gastritis	23	(4.2)	17	(3.1)
Heartburn	29	(5.3)	27	(4.9)
Nausea	69	(12.7)	65	(11.8)
Stomatitis	11	(2.0)	14	(2.5)
Vomiting	41	(7.5)	42	(7.6)
Eyes, Ears, Nose, and Throat	**52**	**(9.6)**	**47**	**(8.5)**
Pharyngitis	12	(2.2)	11	(2.0)
Tinnitus	20	(3.7)	21	(3.8)

Table 31 (Cont.)

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

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Hemic and Lymphatic System	**38**	**(7.0)**	**36**	**(6.5)**
Anemia	13	(2.4)	10	(1.8)
Neutropenia	17	(3.1)	16	(2.9)
Metabolism and Nutrition	**75**	**(13.8)**	**69**	**(12.5)**
Anorexia	55	(10.1)	52	(9.5)
Musculoskeletal System	**49**	**(9.0)**	**47**	**(8.5)**
Muscular weakness	14	(2.6)	12	(2.2)
Myalgia	12	(2.2)	6	(1.1)
Nervous System	**77**	**(14.2)**	**84**	**(15.3)**
Headache	46	(8.5)	48	(8.7)
Insomnia	16	(2.9)	17	(3.1)
Psychiatric Disorder	**19**	**(3.5)**	**10**	**(1.8)**
Respiratory System	**101**	**(18.6)**	**65**	**(11.8)**
Cough	13	(2.4)	3	(0.5)
Dyspnea	16	(2.9)	7	(1.3)
Hiccups	59	(10.8)	31	(5.6)
Skin and Skin Appendages	**33**	**(6.1)**	**25**	**(4.5)**
Alopecia	11	(2.0)	7	(1.3)
Urogenital System	**27**	**(5.0)**	**28**	**(5.1)**

Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
CINV = Chemotherapy-induced nausea and vomiting.
P.O. = By mouth.
IV = Intravenous.
N = Number of adult patients who received at least 1 dose of study therapy.

8.5.2.1.3 Drug-Related Clinical Adverse Experiences (Cycle 1)

As shown in Table 32, the incidences of adverse experiences that the investigators considered possibly, probably, or definitely drug related were slightly higher in the aprepitant group compared with Standard Therapy group. The most frequent drug-related clinical adverse experiences were hiccups, asthenia/fatigue, constipation, headache, and anorexia. All were slightly more frequent in the aprepitant group compared with the Standard Therapy group.

Table 32

Number (%) of Patients With Drug-Related Clinical Adverse Experiences (Incidence >0.5% in One or More Treatment Groups) by Body System—CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Patients with one or more drug-related† adverse experiences	93	(17.1)	70	(12.7)
Patients with no drug-related adverse experience	451	(82.9)	480	(87.3)
Body as a Whole/Site Unspecified	**28**	**(5.1)**	**20**	**(3.6)**
Abdominal pain	5	(0.9)	3	(0.5)
Asthenia/fatigue	16	(2.9)	9	(1.6)
Dizziness	5	(0.9)	4	(0.7)
Digestive System	**43**	**(7.9)**	**28**	**(5.1)**
Constipation	12	(2.2)	11	(2.0)
Diarrhea	6	(1.1)	5	(0.9)
Dyspepsia	8	(1.5)	4	(0.7)
Heartburn	6	(1.1)	7	(1.3)
Nausea	4	(0.7)	0	(0.0)
Eyes, Ears, Nose, and Throat	**3**	**(0.6)**	**3**	**(0.5)**
Hemic and Lymphatic System	**3**	**(0.6)**	**1**	**(0.2)**
Anemia	3	(0.6)	0	(0.0)
Metabolism and Nutrition	**12**	**(2.2)**	**7**	**(1.3)**
Anorexia	11	(2.0)	3	(0.5)
Musculoskeletal System	**1**	**(0.2)**	**4**	**(0.7)**
Nervous System	**14**	**(2.6)**	**16**	**(2.9)**
Headache	12	(2.2)	10	(1.8)
Insomnia	2	(0.4)	3	(0.5)
Respiratory System	**25**	**(4.6)**	**16**	**(2.9)**
Hiccups	25	(4.6)	16	(2.9)
Skin and Skin Appendages	**5**	**(0.9)**	**3**	**(0.5)**

† Determined by the investigator to be possibly, probably, or definitely drug related.
Although a patient may have had 2 or more drug-related clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
CINV = Chemotherapy-induced nausea and vomiting.
N = Number of adult patients who received at least 1 dose of study therapy.

8.5.2.1.4 Serious Clinical Adverse Experiences (Cycle 1)

In Cycle 1 of the CINV Phase III studies combined, serious clinical adverse experiences occurred with similar incidences in the 2 treatment groups (Table 33). Only 6 patients experienced serious adverse experiences considered to be drug related by the investigators: 2 (0.4%) in the aprepitant group and 4 (0.7%) in the Standard Therapy group.

The most frequently reported serious clinical adverse experiences were dehydration, febrile neutropenia, and neutropenia. Serious clinical adverse experiences that occurred slightly more frequently in the aprepitant group compared with the Standard Therapy group included dehydration, neutropenia, and respiratory insufficiency. Despite a slightly higher incidence of neutropenia in the aprepitant group, other indices of hematological toxicity, such as febrile neutropenia and leukopenia, were similar in the 2 treatment groups, or higher in the Standard Therapy group. Also, the pattern of abnormal laboratory tests of neutropenia, as graded according to the NCI Common Toxicity Criteria, was comparable across both treatment groups (see Table 37 in Section 8.5.2.3).

Clinical details of the respiratory insufficiency cases are consistent with the hypothesis that respiratory insufficiency represented progression of underlying malignant disease (lung cancer for all 5 patients in the aprepitant group); these events did not present a common temporal association with aprepitant administration and none was determined to be drug related by the investigators.

Serious adverse experiences of leukopenia occurred slightly more frequently in the Standard Therapy group compared with the aprepitant group.

Serious adverse experiences of the Cardiovascular System occurred with similar incidence in the 2 treatment groups. Within this system, myocardial infarction occurred slightly more frequently in the aprepitant group, while cardiac arrest occurred slightly more frequently in the Standard Therapy group.

Table 33

Number (%) of Patients With Serious Clinical Adverse Experiences (Incidence >0.5% in One or More Treatment Groups) by Body System—CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Patients with one or more serious adverse experiences	73	(13.4)	75	(13.6)
Patients with no serious adverse experience	471	(86.6)	475	(86.4)
Body as a Whole/Site Unspecified	**27**	**(5.0)**	**21**	**(3.8)**
Cardiopulmonary failure	1	(0.2)	3	(0.5)
Dehydration	10	(1.8)	5	(0.9)
Fever	3	(0.6)	2	(0.4)
Septic shock	3	(0.6)	2	(0.4)
Cardiovascular System	**17**	**(3.1)**	**18**	**(3.3)**
Cardiac arrest	2	(0.4)	4	(0.7)
Deep venous thrombosis	3	(0.6)	2	(0.4)
Myocardial infarction	3	(0.6)	0	(0.0)
Pulmonary embolism	4	(0.7)	3	(0.5)
Digestive System	**10**	**(1.8)**	**16**	**(2.9)**
Diarrhea	3	(0.6)	2	(0.4)
Vomiting	1	(0.2)	3	(0.5)
Endocrine System	**2**	**(0.4)**	**3**	**(0.5)**
Hemic and Lymphatic System	**22**	**(4.0)**	**16**	**(2.9)**
Febrile neutropenia	7	(1.3)	7	(1.3)
Leukopenia	1	(0.2)	4	(0.7)
Neutropenia	12	(2.2)	6	(1.1)
Pancytopenia	1	(0.2)	3	(0.5)
Thrombocytopenia	4	(0.7)	1	(0.2)
Metabolism and Nutrition	**3**	**(0.6)**	**6**	**(1.1)**
Hyponatremia	1	(0.2)	3	(0.5)
Musculoskeletal System	**1**	**(0.2)**	**4**	**(0.7)**
Nervous System	**0**	**(0.0)**	**3**	**(0.5)**
Respiratory System	**14**	**(2.6)**	**15**	**(2.7)**
Dyspnea	3	(0.6)	3	(0.5)
Pneumonia	4	(0.7)	3	(0.5)
Respiratory insufficiency	5	(0.9)	1	(0.2)
Urogenital System	**9**	**(1.7)**	**9**	**(1.6)**
Renal insufficiency	3	(0.6)	1	(0.2)

Although a patient may have had 2 or more serious clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
CINV = Chemotherapy-induced nausea and vomiting.
N = Number of adult patients who received at least 1 dose of study therapy.

8.5.2.1.5 Serious Clinical Adverse Experiences Resulting in Death (Cycle 1)

In total, 41 out of 1094 adult patients (3.7%) enrolled in 1 of the 2 CINV Phase III studies died during Cycle 1. By treatment category, they were distributed as follows: 20 patients (3.7%) in the aprepitant group and 21 patients (3.8%) in the Standard Therapy group (Table 34).

Slight differences in the incidences of fatal adverse experiences between the 2 treatment groups were observed in the following body systems: Hemic and Lymphatic, Digestive, and Urogenital. The incidences of fatal adverse experiences in the Hemic and Lymphatic System were slightly higher in the aprepitant group (0.7%) compared with the Standard Therapy group (0.2%).

On the other hand, the incidences of fatal adverse experiences in the Digestive and Urogenital Systems were slightly higher in the Standard Therapy group compared with the aprepitant group: 0.2% in the aprepitant group versus 0.5% in the Standard Therapy group for the Digestive System, and 0.0% in the aprepitant group versus 0.5% in the Standard Therapy group for the Urogenital System.

Even though the incidences of fatal adverse experiences in the Respiratory System were similar in the 2 treatment groups (1.3% in the aprepitant group and 1.5% in the Standard Therapy group), the specific adverse experience of respiratory insufficiency resulting in death was more common in the aprepitant group (5 patients [0.9%]) compared with the Standard Therapy group (1 patient [0.2%]); this was offset by various Respiratory System adverse experiences in the Standard Therapy group. In the aprepitant group, the deaths categorized as respiratory insufficiency (n=5) were attributed to the following specific adverse experiences: respiratory insufficiency, chronic obstructive pulmonary disease, and lung malignant neoplasm (n=1); respiratory insufficiency and pulmonary embolism (n=1); and respiratory insufficiency (n=3). In the Standard Therapy group, one patient died due to respiratory insufficiency. Clinical details of these cases are consistent with the hypothesis that respiratory insufficiency represented progression of underlying malignant disease (lung cancer); the temporal relationship to aprepitant administration was variable, none was associated with neutropenia, and the investigator did not consider any of the cases to be drug related.

Table 34

Number (%) of Adult Patients With Adverse Experiences Resulting in Death (Incidence >0% in One or More Treatment Groups) by Body System—
CINV Phase III Studies Combined—Cycle 1

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Patients with one or more adverse experiences resulting in death	20	(3.7)	21	(3.8)
Patients with no adverse experience resulting in death	524	(96.3)	529	(96.2)
Body as a Whole/Site Unspecified	**8**	**(1.5)**	**7**	**(1.3)**
Cardiopulmonary failure	1	(0.2)	3	(0.5)
Malignant neoplasm	2	(0.4)	0	(0.0)
Metastatic neoplasm of known primary	0	(0.0)	1	(0.2)
Sepsis	1	(0.2)	0	(0.0)
Septic shock	3	(0.6)	2	(0.4)
Unknown cause of death	1	(0.2)	1	(0.2)
Cardiovascular System	**6**	**(1.1)**	**7**	**(1.3)**
Arrhythmia	1	(0.2)	1	(0.2)
Cardiac arrest	2	(0.4)	4	(0.7)
Cardiogenic shock	0	(0.0)	1	(0.2)
Cerebrovascular accident	0	(0.0)	1	(0.2)
Hemorrhage	0	(0.0)	1	(0.2)
Myocardial infarction	1	(0.2)	0	(0.0)
Pulmonary embolism	2	(0.4)	2	(0.4)
Digestive System	**1**	**(0.2)**	**3**	**(0.5)**
Esophageal malignant neoplasm	0	(0.0)	1	(0.2)
Gastrointestinal perforation	0	(0.0)	1	(0.2)
Necrotizing enterocolitis	1	(0.2)	0	(0.0)
Stomatitis	0	(0.0)	1	(0.2)
Upper gastrointestinal hemorrhage	0	(0.0)	1	(0.2)
Hemic and Lymphatic System	**4**	**(0.7)**	**1**	**(0.2)**
Febrile neutropenia	1	(0.2)	0	(0.0)
Leukopenia	0	(0.0)	1	(0.2)
Neutropenia	2	(0.4)	1	(0.2)
Pancytopenia	1	(0.2)	0	(0.0)
Thrombocytopenia	1	(0.2)	0	(0.0)
Metabolism and Nutrition	**1**	**(0.2)**	**0**	**(0.0)**
Hypokalemia	1	(0.2)	0	(0.0)

Table 34 (Cont.)

Number (%) of Adult Patients With Adverse Experiences Resulting in Death (Incidence >0% in One or More Treatment Groups) by Body System—
CINV Phase III Studies Combined—Cycle 1

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Respiratory System	**7**	**(1.3)**	**8**	**(1.5)**
Airway obstruction	0	(0.0)	1	(0.2)
Aspiration pneumonia	1	(0.2)	0	(0.0)
Chronic obstructive pulmonary disease	1	(0.2)	0	(0.0)
Dyspnea	1	(0.2)	2	(0.4)
Hemoptysis	0	(0.0)	1	(0.2)
Lung carcinoma	0	(0.0)	1	(0.2)
Lung malignant neoplasm	1	(0.2)	0	(0.0)
Non-small cell lung carcinoma	1	(0.2)	1	(0.2)
Pulmonary hemorrhage	0	(0.0)	1	(0.2)
Respiratory failure	0	(0.0)	1	(0.2)
Respiratory insufficiency	5	(0.9)	1	(0.2)
Urogenital System	**0**	**(0.0)**	**3**	**(0.5)**
Renal insufficiency	0	(0.0)	1	(0.2)
Testicular malignant neoplasm	0	(0.0)	1	(0.2)
Uremia	0	(0.0)	1	(0.2)

Although a patient may have had 2 or more clinical adverse experiences resulting in death, the patient was counted only once within a category. The same patient may appear in different categories.
CINV = Chemotherapy-induced nausea and vomiting.
N = Number of adult patients who received at least 1 dose of study therapy.

8.5.2.1.6 Discontinuations Due to Clinical Adverse Experiences (Cycle 1)

As shown in Table 35, the patterns of distribution of the adverse experiences causing discontinuation of study therapy by body system were generally similar in the 2 treatment groups.

Table 35

Number (%) of Patients With Clinical Adverse Experiences Resulting in Discontinuation of Study Therapy (Incidence >0.5% in One or More Treatment Groups) by Body System—CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Patients with one or more adverse experiences resulting in discontinuation of study therapy	42	(7.7)	32	(5.8)
Patients with no adverse experience resulting in discontinuation of study therapy	502	(92.3)	518	(94.2)
Body as a Whole/Site Unspecified	**15**	**(2.8)**	**8**	**(1.5)**
Septic shock	3	(0.6)	2	(0.4)
Cardiovascular System	**11**	**(2.0)**	**8**	**(1.5)**
Cardiac arrest	2	(0.4)	4	(0.7)
Myocardial infarction	3	(0.6)	0	(0.0)
Digestive System	**4**	**(0.7)**	**4**	**(0.7)**
Psychiatric Disorder	**3**	**(0.6)**	**0**	**(0.0)**
Respiratory System	**8**	**(1.5)**	**7**	**(1.3)**
Respiratory insufficiency	5	(0.9)	1	(0.2)
Urogenital System	**0**	**(0.0)**	**3**	**(0.5)**

Although a patient may have had 2 or more clinical adverse experiences resulting in discontinuation of study drug, the patient is counted only once within a category. The same patient may appear in different categories.
CINV = Chemotherapy-induced nausea and vomiting.
P.O. = By mouth.
IV = Intravenous.
N = Number of adult patients who received at least 1 dose of study therapy.

8.5.2.2 Laboratory Adverse Experiences (Cycle 1)

During Cycle 1 of the CINV Phase III studies, laboratory safety tests were performed at baseline, at the clinic visit that occurred between Day 6 and Day 8 post-cisplatin, and also at the clinic visit between Day 19 and Day 28 post-cisplatin.

8.5.2.2.1 Laboratory Adverse Experience Summary (Cycle 1)

Table 36 presents a summary of laboratory adverse experiences in Cycle 1 of the 2 CINV Phase III studies combined. Overall, the incidences of laboratory adverse experiences were generally similar.

Table 36

Laboratory Adverse Experience Summary—
CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)[†]	n	(%)[†]
Number (%) of patients:				
With at least one laboratory test postbaseline	539	(99.1)	543	(98.7)
With one or more adverse experiences	120	(22.3)	106	(19.5)
With drug-related[‡] adverse experiences	22	(4.1)	14	(2.6)
With serious adverse experiences	1	(0.2)	1	(0.2)
Discontinued[§] due to adverse experiences	2	(0.4)	4	(0.7)

[†] The percent = Number of randomized patients who received study drug within the laboratory adverse experience category/number of randomized patients with one or more laboratory tests postbaseline.
[‡] Determined by the investigator to be possibly, probably, or definitely drug related.
[§] Discontinued refers to discontinuation from study drug therapy.
CINV = Chemotherapy-induced nausea and vomiting.
N = Number of adult patients who received at least 1 dose of study therapy.

8.5.2.2.2 Laboratory Adverse Experiences by Laboratory Test Category (Cycle 1)

The incidences of laboratory adverse experiences by laboratory test category in Cycle 1 were similar in the aprepitant group (22.3%) and in the Standard Therapy group (19.5%). The most frequently reported laboratory adverse experiences in Cycle 1 of the 2 CINV Phase III studies were proteinuria, increased alanine aminotransferase, and increased blood urea nitrogen. Laboratory adverse experiences that occurred more frequently in the aprepitant group compared with the Standard Therapy group included alkaline phosphatase increased (2.1% and 0.2% in the aprepitant group and the Standard Therapy group, respectively) and aspartate aminotransferase increased (3.0% and 1.3% in the aprepitant group and the Standard Therapy group, respectively). The great majority of these abnormalities were graded as 1 (mildly abnormal) or 2 (moderately abnormal), according to the NCI Common Toxicity Criteria. Adverse experiences of decreased neutrophils occurred more frequently in the Standard Therapy group (3.0%) compared with the aprepitant group (1.7%).

8.5.2.2.3 Drug-Related Laboratory Adverse Experiences (Cycle 1)

In total, 36 patients in Cycle 1 of the 2 CINV Phase III studies had one or more drug-related laboratory adverse experiences: 4.1% in the aprepitant group and 2.6% in the Standard Therapy group. Drug-related laboratory adverse experiences of increased alanine aminotransferase were slightly more frequent in the aprepitant group (2.8%) compared with the Standard Therapy group (1.5%).

8.5.2.2.4 Serious Laboratory Adverse Experiences (Cycle 1)

Serious laboratory adverse experiences were infrequent in Cycle 1 of the 2 CINV Phase III studies and were reported in 1 patient (0.2%) in the aprepitant group (hypokalemia and hyponatremia) and 1 patient (0.2%) in the Standard Therapy group (decreased hemoglobin).

8.5.2.2.5 Discontinuations Due to Laboratory Adverse Experiences (Cycle 1)

Six (6) patients discontinued study therapy due to laboratory adverse experiences in Cycle 1 of the 2 CINV Phase III studies: 2 patients (0.4%) in the aprepitant group (both due to serum creatinine increased) and 4 patients (0.7%) in the Standard Therapy group. These latter 4 patients in the Standard Therapy group discontinued study therapy due to the following laboratory adverse experiences: serum creatinine increased (n=2), serum creatinine increased and BUN increased (n=1), and decreased neutrophils (n=1).

8.5.2.3 Laboratory Analytes by NCI Common Toxicity Criteria (Cycle 1)

In Cycle 1 of the 2 CINV Phase III studies, laboratory analytes obtained at protocol-specified clinic visits were routinely categorized according to the NCI Common Toxicity Criteria. The possible toxicity grades were on a scale of 1 to 4, with 1 indicating mild; 2 indicating moderate; 3 indicating severely abnormal; and 4 indicating life threatening. These grades were assigned by a central laboratory, independent of whether or not the investigator reported the abnormality as a clinically relevant adverse experience.

The pattern of abnormal laboratory analytes as categorized by the NCI Common Toxicity Criteria was comparable across both treatment groups. In particular, hematological toxicity, hepatotoxicity, and nephrotoxicity occurred with similar frequency in the 2 treatment groups (Table 37). Similar incidences and patterns of severity of hypercreatinemia between the 2 treatment groups indicate that aprepitant does not affect the renal dysfunction associated with cisplatin treatment.

Table 37

Percent of Patients With Specific Laboratory Tests Graded by National Cancer Institute (NCI) Common Toxicity Criteria—CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=544)				Standard Therapy (N=550)			
	NCI Toxicity Grade				NCI Toxicity Grade			
	1	2	3	4	1	2	3	4
Analyte	%	%	%	%	%	%	%	%
White Blood Cell (WBC) Count (/mm^3) **1: ≥3000 - <LLN; 2: ≥2000 - <3000; 3: ≥1000 -<2000; 4: <1000**								
Days 6 to 8 Visit	6.4	3.1	1.5	0.2	3.5	3.3	0.4	0.6
Days 19 to 29 Visit	9.7	7.8	2.2	0.2	13.4	10.7	1.9	0.2
Hemoglobin (g/dL) **1: ≥10.0 - <LLN; 2: ≥8 - <10; 3: ≥6.5 - <8.0; 4: <6.5**								
Days 6 to 8 Visit	16.8	1.9	0.0	0.2	15.7	4.3	0.2	0.0
Days 19 to 29 Visit	38.2	5.6	0.9	0.0	36.4	8.6	0.2	0.4
Neutrophil Count (/mm^3) **1: ≥1500 <2000; 2: ≥1000 - <1500; 3: ≥500 - <1000; 4: <500**								
Days 6 to 8 Visit	3.1	2.3	1.0	0.2	2.5	1.4	0.4	0.6
Days 19 to 29 Visit	10.8	6.3	5.6	1.5	13.4	7.5	5.9	1.5
Platelet Count (/mm^3) **1: ≥75,000 - <LLN; 2: ≥50,000 - <75,000; 3: ≥10,000 - <50,000; 4: <10,000**								
Days 6 to 8 Visit	6.2	0.4	0.2	0.0	5.4	0.4	0.6	0.0
Days 19 to 29 Visit	1.3	0.0	0.2	0.0	2.4	0.7	0.0	0.0
Serum Alanine Aminotransferase **1: > ULN - 2.5 x ULN; 2: > 2.5 - 5.0 x ULN; 3: > 5.0 - 20.0 x ULN; 4: > 20.0 x ULN**								
Days 6 to 8 Visit	35.4	5.7	0.8	0.0	32.4	6.5	0.4	0.0
Days 19 to 29 Visit	11.0	1.1	0.0	0.0	11.2	1.7	0.6	0.0
Serum Aspartate Aminotransferase **1: > ULN - 2.5 x ULN; 2: > 2.5 - 5.0 x ULN; 3: > 5.0 - 20.0 x ULN; 4: > 20.0 x ULN**								
Days 6 to 8 Visit	18.2	0.8	0.6	0.0	13.0	1.0	0.2	0.0
Days 19 to 29 Visit	8.1	0.4	0.0	0.0	9.6	0.8	0.2	0.0
Total Serum Bilirubin **1: > ULN - 1.5 x ULN; 2: > 1.5 - 3.0 x ULN; 3: > 3.0 - 10.0 x ULN; 4: > 10.0 x ULN**								
Days 6 to 8 Visit	2.2	0.6	0.2	0.0	2.8	1.0	0.0	0.0
Days 19 to 29 Visit	0.0	0.0	0.0	0.0	0.6	0.4	0.0	0.0

Table 37 (Cont.)

Percent of Patients With Specific Laboratory Tests Graded by National Cancer Institute (NCI) Common Toxicity Criteria—CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=544)				Standard Therapy (N=550)			
	NCI Toxicity Grade				NCI Toxicity Grade			
	1	2	3	4	1	2	3	4
Analyte	%	%	%	%	%	%	%	%
Total Serum Creatinine **1: > ULN - 1.5 x ULN; 2: > 1.5 - 3.0 x ULN; 3: > 3.0 - 6.0 x ULN; 4: > 60 x ULN**								
Days 6 to 8 Visit	11.0	3.2	0.2	0.0	12.6	3.2	0.4	0.0
Days 19 to 29 Visit	6.8	0.6	0.0	0.0	6.3	1.2	0.2	0.0

NCI toxicity grades: 1 = mildly abnormal; 2 = moderately abnormal; 3 = severely abnormal; 4 = life threatening.
When multiple laboratory results were graded within a time frame, the most severe grade was counted.
CINV = Chemotherapy-induced nausea and vomiting.
N = Number of adult patients who received at least 1 dose of study therapy. Not all patients had all laboratory tests performed at both visits.
LLN = Lower limit of normal.
ULN = Upper limit of normal.

8.5.2.4 Prespecified Adverse Experiences of Special Interest (Cycle 1)

Adverse experiences of special interest were prespecified for the CINV Phase III studies in order to assess whether there was evidence of enhanced toxicity of chemotherapy and/or corticosteroids that might be a consequence of a clinically significant pharmacokinetic interaction with aprepitant. The prespecified adverse experiences were selected to reflect potential chemotherapy-induced hematologic toxicity (anemia, leukopenia, neutropenia, and thrombocytopenia), potential corticosteroid-induced toxicity (dehydration, hypertension, hyperglycemia, and hypokalemia), and also toxicity potentially related to chemotherapy and/or corticosteroids (fever, febrile neutropenia, and infection). The prespecified adverse experiences include those that meet the criteria for classification as a serious adverse experience (such as hospitalization) as well as those that do not.

Synonymous terms (such as decreased neutrophils and neutropenia) were combined. Therefore, the display of adverse experiences in this section integrates adverse experiences reported as laboratory adverse experiences (such as decreased neutrophils) and clinical adverse experiences (such as neutropenia). The category "Infections" includes adverse experiences collected based on a review of all adverse experiences occurring during Cycle 1 of the Phase III CINV studies by 2 Merck Research Laboratory (MRL) physicians who were blinded to treatment allocation.

The incidences of these prespecified adverse experiences in Cycle 1 of the 2 CINV Phase III studies are presented in Table 38 by treatment group; 28.1% and 27.1% of the patients in the aprepitant and Standard Therapy group, respectively, had one or more prespecified adverse experiences.

Febrile neutropenia was diagnosed in 9 patients (1.7%) in the aprepitant group and 7 patients (1.3%) in the Standard Therapy group. The difference in the incidences of febrile neutropenia between the aprepitant group and the Standard Therapy group was not statistically significant (p=0.625).

Prior to unblinding, MRL physicians reviewed the investigator-provided data in Cycle 1 to assess whether the investigator diagnosis of febrile neutropenia was consistent with the NCI Common Toxicity Criteria: 1) absolute neutrophil count $<1.0 \times 10^9$ /L; 2) fever $\geq 38.5^{o}$ C; and 3) no clinically or microbiologically documented infection. Twelve (12) patients had febrile neutropenia according to these criteria: 4 (0.7%) in the aprepitant group and 8 (1.5%) in the Standard Therapy group. The difference in the incidences of febrile neutropenia according to the NCI Common Toxicity Criteria between the aprepitant group and the Standard Therapy group was not statistically significant (p=0.385).

Overall, 125 patients experienced an infection (serious, or nonserious): 68 and 57 patients in the aprepitant and Standard Therapy groups, respectively. A total of 33 patients had an infection that met the criteria for seriousness. By treatment group, 20 patients (3.7%) in the aprepitant group and 13 patients (2.4%) in the Standard Therapy group had an infection-related serious adverse experience. The difference in incidences of infection-related serious adverse experiences between the aprepitant group and the Standard Therapy group was not statistically significant (p=0.220). It should be noted that the diagnoses of infection and febrile neutropenia are mutually exclusive.

Overall, the incidences of prespecified adverse experiences of special interest were generally similar between treatment groups. Therefore, addition of aprepitant did not alter the toxicity of chemotherapy and/or corticosteroids observed when coadministered with Standard Therapy.

Table 38

Number (%) of Patients With Prespecified Adverse Experiences of Special Interest (Incidence >0% in One or More Treatment Groups) by Body System—
CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=544)		Standard Therapy (N=550)	
	n	(%)	n	(%)
Patients with one or more prespecified adverse experiences	153	(28.1)	150	(27.3)
Patients with no prespecified adverse experience	391	(71.9)	400	(72.7)
Body as a Whole/Site Unspecified	**102**	**(18.8)**	**92**	**(16.7)**
Dehydration	32	(5.9)	28	(5.1)
Fever	16	(2.9)	19	(3.5)
Infections	68	(12.5)	58	(10.5)
Cardiovascular System	**10**	**(1.8)**	**7**	**(1.3)**
Hypertension	10	(1.8)	7	(1.3)
Hemic and Lymphatic System	**63**	**(11.6)**	**61**	**(11.1)**
Anemia	17	(3.1)	14	(2.5)
Febrile neutropenia	9	(1.7)	7	(1.3)
Leukocytosis	5	(0.9)	1	(0.2)
Leukopenia	12	(2.2)	13	(2.4)
Neutropenia	27	(5.0)	32	(5.8)
Thrombocytopenia	22	(4.0)	19	(3.5)
Metabolism and Nutrition	**22**	**(4.0)**	**24**	**(4.4)**
Hyperglycemia	9	(1.7)	10	(1.8)
Hypokalemia	14	(2.6)	15	(2.7)

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

CINV = Chemotherapy-induced nausea and vomiting.
N = Number of adult patients who received at least 1 dose of study therapy.

8.5.3 Multiple-Cycle Extension (Cycles 2 to 6)

After completion of Cycle 1, patients had the option to participate in a Multiple-Cycle extension for a maximum of 5 subsequent cycles, if they fulfilled the multiple-cycle enrollment criteria. Overall, a total of 851 patients (413 in the aprepitant group and 438 in the Standard Therapy group) participated in the Multiple-Cycle extension (including patients who entered Cycle 2, but were discontinued prior to receiving study therapy). The baseline demographics of patients entering the Multiple-Cycle extension were generally similar to those of the patients in Cycle 1. Also, the incidences of primary

cancer diagnoses for patients continuing in Cycles 2 to 6 were generally similar to those of the Cycle 1 patients.

8.5.3.1 Clinical Adverse Experiences (Cycles 2 to 6)

During the Multiple-Cycle extension of the CINV Phase III studies, as agreed with the Agency, the reporting conventions for adverse experiences were modified compared with Cycle 1: only adverse experiences that caused discontinuation of study therapy or that were determined by the investigator to be serious or drug related were reported. Overall, the pattern of distribution of these adverse experiences in Cycles 2 to 6 was generally similar to Cycle 1 (Table 39).

In Cycles 2 to 6 of the 2 CINV Phase III studies combined, the incidences of clinical adverse experiences considered by the investigators as possibly, probably, or definitely drug related were 5.6% and 4.1% in the aprepitant and Standard Therapy groups, respectively. Drug-related adverse experiences that occurred more frequently in the aprepitant group in Cycle 1, such as asthenia/fatigue and hiccups, did not occur more frequently in the aprepitant group in Cycles 2 to 6.

The incidences of serious adverse experiences in Cycles 2 to 6 were 19.1% and 18.3% in the aprepitant and Standard Therapy groups, respectively. In multiple cycles, the same number of patients in the 2 treatment groups experienced serious dehydration, an adverse experience that occurred more frequently in the aprepitant group compared with the Standard Therapy group in Cycle 1. The incidences of serious adverse experiences in each cycle of chemotherapy were generally similar between the 2 treatment groups (Table 40).

The incidence of adverse experiences resulting in death was slightly higher in the aprepitant group (6.8%) compared with the Standard Therapy group (5.3%). Fatal adverse experiences that occurred more frequently in the aprepitant group included septic shock and respiratory insufficiency. Overall, 7 patients experienced fatal septic shock: 5 (1.2%) in the aprepitant group and 2 (0.5%) in the Standard Therapy group. Clinical details of these cases do not demonstrate a consistent pattern with respect to primary cancer diagnoses, concomitant chemotherapy in addition to cisplatin, temporal relationship with aprepitant administration, chemotherapy cycle in which death occurred, and/or concomitant causes of death.

Overall, 5 patients experienced fatal respiratory insufficiency: 4 (1.0%) in the aprepitant group and 1 (0.2%) in the Standard Therapy group. Clinical details of these cases are consistent with the hypothesis that respiratory insufficiency represented progression of the underlying malignant disease (lung carcinoma [n=4] and laryngeal malignant neoplasm [n=1]). Also, there was no consistent pattern with respect to concomitant chemotherapy in addition to cisplatin, temporal relationship with aprepitant administration, chemotherapy cycle in which death occurred, and/or concomitant causes of death. None of the fatal adverse experiences of respiratory insufficiency was associated with neutropenia.

The incidences of fatal adverse experiences in each cycle of chemotherapy were generally similar between the 2 treatment groups (Table 41).

Overall, the safety data from the Multiple-Cycle extension are consistent with the safety and tolerability profile of aprepitant in Cycle 1.

Table 39

Clinical Adverse Experience Summary—CINV Phase III Studies Combined
(Cycles 2 to 6)

	Aprepitant Regimen (N=413)		Standard Therapy (N=438)	
	n	(%)	n	(%)
Number (%) of patients[†]				
With drug-related[‡] adverse experiences	23	(5.6)	18	(4.1)
With serious adverse experiences	79	(19.1)	80	(18.3)
Who died	28	(6.8)	23	(5.3)
Discontinued due to adverse experiences	50	(12.1)	42	(9.6)

[†] Only clinical adverse experiences that were serious, drug-related, or resulted in discontinuation of study therapy were collected in the Multiple-Cycle extension (Cycles 2 to 6).
[‡] Determined by the investigator to be possibly, probably, or definitely drug related.
CINV = Chemotherapy-induced nausea and vomiting.
N = Patients who entered Cycle 2 (including patients who were discontinued prior to receiving study therapy in Cycle 2).

Table 40

Incidences of Serious Clinical Adverse Experiences by Cycle—
CINV Phase III Studies Combined (Cycles 2 to 6)

	Aprepitant Regimen	Standard Therapy
	n/m (%)	n/m (%)
Cycle 2	32/413 (7.7)	31/438 (7.1)
Cycle 3	22/337 (6.5)	21/347 (6.1)
Cycle 4	24/250 (9.6)	20/255 (7.8)
Cycle 5	6/184 (3.3)	8/189 (4.2)
Cycle 6	9/148 (6.1)	10/152 (6.6)

CINV = Chemotherapy-induced nausea and vomiting.
n/m = Patients with serious clinical adverse experiences in the specific cycle/patients who entered each cycle (including patients who were discontinued prior to receiving study therapy in the specific cycle).

Table 41

Incidences of Adverse Experiences Resulting in Death by Cycle—
CINV Phase III Studies Combined (Cycles 2 to 6)

	Aprepitant Regimen	Standard Therapy
	n/m (%)	n/m (%)
Cycle 2	6/413 (1.5)	6/438 (1.4)
Cycle 3	8/337 (2.4)	5/347 (1.4)
Cycle 4	8/250 (3.2)	6/255 (2.4)
Cycle 5	2/184 (1.1)	2/189 (1.1)
Cycle 6	4/148 (2.7)	4/152 (2.6)

CINV = Chemotherapy-induced nausea and vomiting.
n/m = Patients who died in the specific cycle/patients who entered each cycle (including patients who were discontinued prior to receiving study therapy in the specific cycle).

8.5.4 Drug-Drug Interactions

Clinical adverse experiences in the CINV Phase III program were analyzed carefully for evidence of drug-drug interactions. Due to the weak to moderate inhibitory effect of aprepitant on the CYP3A4 enzyme, specific attention was directed to the assessment of interactions potentially mediated by CYP3A4.

In Cycle 1 of the combined CINV Phase III studies, the incidences of all adverse experiences, as well as the incidences of the prespecified adverse experiences of special interest, were reviewed to determine whether there was any difference between treatment groups related to the concomitant administration of aprepitant with chemotherapy metabolized by CYP3A4 (etoposide [58], vinca alkaloids [59], taxanes [60; 61], irinotecan [62], and ifosfamide [63]). The incidences of serious adverse experiences and prespecified adverse experiences of special interest were also reviewed to determine how these incidences were affected by concomitant administration of individual chemotherapeutic agents most frequently coadministered with cisplatin (etoposide, fluorouracil, gemcitabine, vinorelbine, docetaxel, paclitaxel cyclophosphamide, and doxorubicin), irrespective of their route of metabolism. If the pharmacokinetics of these agents were significantly altered when coadministered with aprepitant, then an increased incidence of adverse experiences reflecting hematologic toxicity would be anticipated, as hematologic toxicity is the dose-limiting toxicity for the vast majority of these chemotherapeutic agents [64].

As described previously, adverse experiences of special interest were prespecified to assess potential chemotherapy-induced hematologic toxicity (anemia, leukopenia, neutropenia, and thrombocytopenia), potential corticosteroid-induced toxicity (dehydration, hypertension, hyperglycemia, and hypokalemia), and also toxicity potentially related to chemotherapy and/or corticosteroids (fever, febrile neutropenia, and infection).

For the purpose of all displays in this section on drug-drug interactions, concomitant therapy was defined as any therapy administered on Days 1 to 3 post-cisplatin because this was the period of aprepitant administration.

8.5.4.1 Safety Profile According to the Concomitant Administration of Any Chemotherapy Metabolized by CYP3A4

Overall, 1094 adult patients received study drug in Cycle 1 of the 2 Phase III studies and 517 of these patients were treated with concomitant chemotherapy metabolized by CYP3A4 in addition to cisplatin. The following chemotherapies were considered CYP3A4 substrates: etoposide, vinca alkaloids (vinblastine, vincristine, and vinorelbine tartrate), taxanes (docetaxel and paclitaxel), irinotecan, and ifosfamide.

Table 42 presents the incidences of clinical, laboratory, and prespecified adverse experiences in patients treated with concomitant chemotherapy metabolized by CYP3A4, and in patients who were not treated with concomitant chemotherapy metabolized by

CYP3A4. In both treatment groups, coadministration of cisplatin and chemotherapy metabolized by CYP3A4 resulted in a slight increase in the incidence of adverse experiences compared to administration of cisplatin as sole chemotherapy, or with chemotherapy not metabolized by CYP3A4 [65; 66; 67]. However, the incidences remained very similar between the aprepitant and Standard Therapy groups, indicating that the safety profile of aprepitant was not generally altered by coadministration of chemotherapy metabolized by CYP3A4.

Table 42

Number (%) of Patients With Adverse Experiences According to Concomitant Administration of Chemotherapy Metabolized by CYP3A4—Days 1 to 3—CINV Phase III Studies Combined (Cycle 1)

Adverse Experience	Concomitant Chemotherapy CYP3A4 Substrate	Aprepitant Regimen N=544		Standard Therapy N=550	
		n/m	%	n/m	%
Clinical Adverse Experiences	With CYP3A4	197/266	74.1%	187/251	74.5%
	Without CYP3A4	179/278	64.4%	183/299	61.2%
Serious Clinical Adverse Experiences	With CYP3A4	40/266	15.0%	34/251	13.5%
	Without CYP3A4	33/278	11.9%	40/299	13.4%
Laboratory Adverse Experiences	With CYP3A4	60/263	22.8%	49/246	19.9%
	Without CYP3A4	59/276	21.4%	57/297	19.2%
Serious Laboratory Adverse Experiences	With CYP3A4	0/263	0.0%	0/246	0.0%
	Without CYP3A4	1/276	0.4%	1/297	0.3%
Prespecified Adverse Experiences	With CYP3A4	80/266	30.1%	71/251	28.3%
	Without CYP3A4	73/278	26.3%	78/299	26.1%

Incidences of laboratory adverse experiences include only patients with at least one laboratory test postbaseline.
Prespecified Adverse Experiences include: dehydration, fever, infections, hypertension, anemia, febrile neutropenia, leukopenia, thrombocytopenia, hyperglycemia, and hypokalemia.
N = Number of adult patients who received at least 1 dose of study therapy.
n/m = Number of patients with adverse experiences/number of patients within the specified subgroup with or without concomitant chemotherapy CYP34A substrate.
CINV = Chemotherapy-induced nausea and vomiting.

As an index of hematologic toxicity, the incidence of neutropenia graded according to the NCI Common Toxicity Criteria was assessed. The incidence of neutropenia at the posttreatment clinic visit was generally similar in both treatment groups in Cycle 1 of the 2 CINV Phase III studies, irrespective of the concomitant administration of chemotherapy metabolized via CYP3A4. The incidence of Grade 3 and Grade 4 neutropenia in the subgroup of patients who received concomitant chemotherapy metabolized by CYP3A4 was similar in the aprepitant group (5.6% and 0.9%, respectively) and in the Standard Therapy group (5.0% and 1.4%, respectively). The incidence of Grade 3 and Grade 4

neutropenia in the subgroup of patients who did not receive concomitant chemotherapy metabolized by CYP3A4 was similar in the aprepitant group (5.7% and 2.2%, respectively) and in the Standard Therapy group (6.7% and 1.6%, respectively).

8.5.4.2 Safety Profile According to the Concomitant Administration of Specific Chemotherapy Agents

The incidences of serious clinical adverse experiences and prespecified adverse experiences potentially reflecting the toxicity of chemotherapy and/or corticosteroids were also reviewed according to the concomitant administration of the individual chemotherapy agents that were most commonly used with cisplatin in Phase III: etoposide, fluorouracil, gemcitabine, vinorelbine, docetaxel, paclitaxel cyclophosphamide, and doxorubicin. Some of these agents are primarily metabolized by CYP3A4 (etoposide, vinorelbine, docetaxel, and paclitaxel) and some are not (fluorouracil, gemcitabine, cyclophosphamide, and doxorubicin).

8.5.4.2.1 Adverse Experience Profile With Specific Chemotherapy Agents Metabolized by CYP3A4: Etoposide, Vinorelbine, Paclitaxel, and Docetaxel

Overall, the safety profile of aprepitant was not generally altered by coadministration of individual chemotherapy agents that are CYP3A4 substrates and are commonly used with cisplatin (Table 43). Only 24 patients (11 in the aprepitant group and 13 in the Standard Therapy group) received cisplatin with docetaxel. In this small cohort of patients, serious adverse experiences occurred more frequently in the Standard Therapy group, while prespecified adverse experiences occurred more frequently in the aprepitant group. These findings do not support a clinically significant interaction between aprepitant and docetaxel and are consistent with the preliminary results of an ongoing Clinical Pharmacology study indicating that concomitant administration of aprepitant does not increase the plasma concentrations of docetaxel, a CYP3A4 substrate, to a clinically meaningful degree.

In particular, the Phase III aprepitant CINV safety database suggested no patterns of prespecified adverse experiences of hematologic toxicity that would indicate clinically significant changes in the toxicity of chemotherapeutic agents metabolized via CYP3A4, as hematologic toxicity is the dose-limiting toxicity for these chemotherapeutic agents (Table 44, Table 45, Table 46, and Table 47) [64].

Table 43

Number (%) of Patients With Serious and Prespecified Adverse Experiences According to Concomitant Administration of Specific Chemotherapy Metabolized by CYP3A4—CINV Phase III Studies Combined (Cycle 1)

Specific Concomitant Chemotherapy	Adverse Experience	Aprepitant Regimen N=544		Standard Therapy N=550	
		n/m	%	n/m	%
Etoposide	Serious Clinical Adverse Experiences	16/106	15.1%	14/91	15.4%
	Prespecified Adverse Experiences	33/106	31.1%	25/91	27.5%
Vinorelbine	Serious Clinical Adverse Experiences	13/82	15.9%	8/76	10.5%
	Prespecified Adverse Experiences	32/82	39.0%	29/76	38.2%
Paclitaxel	Serious Clinical Adverse Experiences	7/52	13.5%	6/58	10.3%
	Prespecified Adverse Experiences	8/52	15.4%	11/58	19.0%
Docetaxel	Serious Clinical Adverse Experiences	3/11	27.3%	5/13	38.5%
	Prespecified Adverse Experiences	5/11	45.5%	3/13	23.1%

Prespecified Adverse Experiences include: Dehydration, fever, infections, hypertension, anemia, febrile neutropenia, leukopenia, thrombocytopenia, hyperglycemia, and hypokalemia.
N = Number of adult patients who received at least 1 dose of study therapy.
n/m = Number of patients with adverse experiences/number of patients within the specific subgroup.
CINV = Chemotherapy-induced nausea and vomiting.

Table 44

Number (%) of Patients Treated With Etoposide With Specific Prespecified Adverse Experiences (Incidence >0% in One or More Treatment Groups) of the Hemic and Lymphatic System—CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=106)		Standard Therapy (N=91)	
	n	(%)	n	(%)
Hemic and Lymphatic System	**19**	**(17.9)**	**16**	**(17.6)**
Anemia	3	(2.8)	4	(4.4)
Febrile neutropenia	5	(4.7)	2	(2.2)
Leukopenia	2	(1.9)	7	(7.7)
Neutropenia	11	(10.4)	8	(8.8)
Thrombocytopenia	6	(5.7)	2	(2.2)

CINV = Chemotherapy-induced nausea and vomiting.
N = Number of randomized Cycle 1 patients who received etoposide.

Table 45

Number (%) of Patients Treated With Vinorelbine Tartrate With Specific Prespecified Adverse Experiences (Incidence >0% in One or More Treatment Groups) of the Hemic and Lymphatic System—CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=82)		Standard Therapy (N=76)	
	n	(%)	n	(%)
Hemic and Lymphatic System	5	(6.1)	9	(11.8)
Anemia	0	(0.0)	4	(5.3)
Leukocytosis	1	(1.2)	0	(0.0)
Leukopenia	3	(3.7)	0	(0.0)
Neutropenia	3	(3.7)	3	(3.9)
Thrombocytopenia	1	(1.2)	2	(2.6)

CINV = Chemotherapy-induced nausea and vomiting.
N = Number of randomized Cycle 1 patients who received vinorelbine tartrate.

Table 46

Number (%) of Patients Treated With Paclitaxel With Specific Prespecified Adverse Experiences (Incidence >0% in One or More Treatment Groups) of the Hemic and Lymphatic System—CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=52)		Standard Therapy (N=58)	
	n	(%)	n	(%)
Hemic and Lymphatic System	4	(7.7)	3	(5.2)
Anemia	2	(3.8)	0	(0.0)
Febrile Neutropenia	1	(1.9)	1	(1.7)
Leukocytosis	0	(0.0)	1	(1.7)
Leukopenia	0	(0.0)	1	(1.7)
Neutropenia	1	(1.9)	2	(3.4)

CINV = Chemotherapy-induced nausea and vomiting.
N = Number of randomized Cycle 1 patients who received paclitaxel.

Table 47

Number (%) of Patients Treated With Docetaxel With Specific Prespecified Adverse Experiences (Incidence >0% in One or More Treatment Groups) of the Hemic and Lymphatic System—CINV Phase III Studies Combined (Cycle 1)

	Aprepitant Regimen (N=11)		Standard Therapy (N=13)	
	n	(%)	n	(%)
Hemic and Lymphatic System	2	(18.2)	3	(23.1)
Anemia	1	(9.1)	1	(7.7)
Febrile neutropenia	1	(9.1)	1	(7.7)
Neutropenia	1	(9.1)	1	(7.7)

CINV = Chemotherapy-induced nausea and vomiting.
N = Number of randomized Cycle 1 patients who received docetaxel.

8.5.4.2.2 Adverse Experience Profile With Specific Chemotherapy Agents Not Metabolized by CYP3A4: Fluorouracil, Gemcitabine, Cyclophosphamide, and Doxorubicin

Overall, the safety profile of aprepitant was not generally altered by coadministration of individual chemotherapy agents that are not CYP3A4 substrates and are commonly used with cisplatin (Table 48).

Table 48

Number (%) of Patients With Serious and Prespecified Adverse Experiences According to Concomitant Administration of Specific Chemotherapy Not Metabolized by CYP3A4—CINV Phase III Studies Combined (Cycle 1)

Specific Concomitant Chemotherapy	Adverse Experience	Aprepitant Regimen N=544		Standard Therapy N=550	
		n/m	%	n/m	%
Fluorouracil	Serious Clinical Adverse Experiences	14/100	14.0%	21/93	22.6%
	Prespecified Adverse Experiences	28/100	28.0%	24/93	25.8%
Gemcitabine	Serious Clinical Adverse Experiences	16/89	18.0%%	14/101	13.9%
	Prespecified Adverse Experiences	23/89	25.8%	28/101	27.7%
Cyclophosphamide	Serious Clinical Adverse Experiences	3/50	6.0%	3/43	7.0
	Prespecified Adverse Experiences	11/50	22.0%	12/43	27.9%
Doxorubicin	Serious Clinical Adverse Experiences	1/38	2.6%	5/43	11.6%
	Prespecified Adverse Experiences	14/38	36.8%	15/43	34.9%

Prespecified Adverse Experiences include: Dehydration, fever, infections, hypertension, anemia, febrile neutropenia, leukopenia, thrombocytopenia, hyperglycemia, and hypokalemia.
N = Number of adult patients who received at least 1 dose of study therapy.
n/m = Number of patients with adverse experiences/number of patients within the specific subgroup.
CINV = Chemotherapy-induced nausea and vomiting.

8.5.5 Drug-Demographic Interactions

8.5.5.1 Adverse Experiences by Age

Overall, the pattern of distribution of clinical and laboratory adverse experiences across age categories was generally similar in both treatment groups in Cycle 1 of the CINV Phase III studies. As expected, in both groups the incidence of adverse experiences increased somewhat with age (Table 49). No dose adjustment of aprepitant is necessary for age.

Table 49

Number (%) of Patients With Adverse Experiences by Age Groups—
CINV Phase III Studies Combined—Cycle 1

	Aprepitant Regimen				Standard Therapy			
	<65		≥65		<65		≥65	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Patients with clinical adverse experiences	254/375	(67.7)	122/169	(72.2)	260/398	(65.3)	110/152	(72.4)
Patients with laboratory adverse experiences	75/373	(20.1)	44/166	(26.5)	76/394	(19.3)	30/149	(20.1)

Incidences of laboratory adverse experiences are calculated in patients with at least one laboratory test postbaseline.
n/N = Number of patients with adverse experiences/number of patients within the specific subgroup.
CINV = Chemotherapy-induced nausea and vomiting.

8.5.5.2 Adverse Experiences by Race

Overall, the pattern of distribution of clinical and laboratory adverse experiences across race categories was generally similar in both treatment groups in Cycle 1 of the 2 CINV Phase III studies (Table 50). The incidence of laboratory adverse experiences in Black patients was higher in the aprepitant group, but the Black population in the studies was too small to draw meaningful conclusions.

Table 50

Number (%) of Patients With Adverse Experiences by Race—
CINV Phase III Studies Combined—Cycle 1

By Race	Aprepitant Regimen						Standard Therapy					
	White		Black		Other		White		Black		Other	
	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Patients with clinical adverse experiences	214/320	(66.9)	19/25	(76.0)	143/199	(71.9)	206/323	(63.8)	16/23	(69.6)	148/204	(72.5)
Patients with laboratory adverse experiences	67/317	(21.1)	11/25	(44.0)	41/197	(20.8)	61/318	(19.2)	6/23	(26.1)	39/202	(19.3)

Incidences of laboratory adverse experiences include only patients with at least one laboratory test postbaseline.
n/N = Number of patients with adverse experiences/number of patients within the specific subgroup.
CINV = Chemotherapy-induced nausea and vomiting.

8.5.5.3 Adverse Experiences by Gender

Overall, the incidences of adverse experiences were generally similar between genders in both treatment groups (Table 51). Anorexia occurred more frequently in males (12.9%) than females (4.6%) in the Standard Therapy group. Vomiting occurred more frequently in females (11.6%) than males (4.5%) in the aprepitant group.

Table 51

Number (%) of Patients With Adverse Experiences by Gender—
CINV Phase III Studies Combined—Cycle 1

	Aprepitant Regimen				Standard Therapy			
	Female		Male		Female		Male	
By Gender	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Patients with clinical adverse experiences	158/233	(67.8)	218/311	(70.1)	161/239	(67.4)	209/311	(67.2)
Patients with laboratory adverse experiences	48/233	(20.6)	71/306	(23.2)	46/239	(19.2)	60/304	(19.7)

Incidences of laboratory adverse experiences include only patients with at least one laboratory test postbaseline.
n/N = Number of patients with adverse experiences/number of patients within the specific subgroup.
CINV = Chemotherapy-induced nausea and vomiting.

8.5.6 Drug-Disease Interactions

The 3 most common cancer categories in the Phase III studies were lung, ovarian, and head and neck cancer. Overall, the cancer-specific incidences of adverse experiences were generally similar in the 2 treatment groups (Table 52). In patients with ovarian cancer, diarrhea was more common in the aprepitant group compared with the Standard Therapy group.

The incidences of prespecified adverse experiences of special interest were also generally similar between treatment groups irrespective of primary cancer diagnosis.

Table 52

Number (%) of Patients With Adverse Experiences by Primary Cancer Diagnosis—
CINV Phase III Studies Combined—Cycle 1

	Aprepitant Regimen						Standard Therapy					
	Lung		Ovarian		Head and Neck		Lung		Ovarian		Head and Neck	
By Primary Cancer Diagnosis	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)	n/N	(%)
Patients with clinical adverse experiences	155/215	(72.1)	39/52	(75.0)	43/66	(65.2)	152/202	(75.2)	35/60	(58.3)	31/52	(59.6)
Patients with laboratory adverse experiences	49/212	(23.1)	8/52	(15.4)	16/66	(24.2)	42/198	(21.2)	6/60	(10.0)	8/52	(15.4)

Incidences of laboratory adverse experiences include only patients with at least one laboratory test postbaseline.
n/N = Number of patients with adverse experiences/number of patients within the specific subgroup.
CINV = Chemotherapy-induced nausea and vomiting.

8.5.7 Summary and Discussion of Safety in CINV Phase III Studies

Overall, 1099 adult patients (547 and 552 in the aprepitant and Standard Therapy groups, respectively) were randomized into the Phase III studies, and ~75% of the patients entered the optional Multiple-Cycle extension.

In general, the adverse experience profile was typical of a population of patients with cancer receiving high-dose cisplatin-based chemotherapy [65; 66; 67], and the overall incidence and profile of clinical and laboratory adverse experiences were comparable in both treatment groups. The incidences of prespecified adverse experiences that reflect the toxicity of cancer chemotherapy, including neutropenia, leukopenia, and dehydration, were generally similar between treatment groups in the Phase III studies. In particular, the incidences of febrile neutropenia and serious infection-related adverse experiences in the 2 treatment groups were not statistically significantly different.

Adverse experiences of asthenia/fatigue and hiccups determined by the investigator to be drug related were more frequent in the aprepitant group than in the Standard Therapy group in Cycle 1. However, this was not the case in the Multiple-Cycle extension. Adverse experiences of hiccups were likely due to dexamethasone, as this is an adverse experience known to occur with dexamethasone, and in Clinical Pharmacology studies, hiccups occurred in 7 subjects who received concomitant aprepitant and dexamethasone, while there were no reports of hiccups in subjects who received only aprepitant in any Clinical Pharmacology study. Asthenia/fatigue is a known consequence of chemotherapy, and is frequently present in patients with cancer.

The incidences of serious clinical adverse experiences were similar in the 2 treatment groups in Cycle 1 (13.4% and 13.6% in the aprepitant group and the Standard Therapy group, respectively) and in the Multiple-Cycle extension (19.1% and 18.3% in the aprepitant group and the Standard Therapy group, respectively). Serious adverse experiences of dehydration occurred more frequently in the aprepitant group compared with the Standard Therapy group in Cycle 1. However, the same number of patients experienced this adverse experience in the 2 treatment groups in multiple cycles. Serious adverse experiences of respiratory insufficiency were uncommon, but more frequent in the aprepitant group compared with the Standard Therapy group during Cycle 1 and Cycles 2 to 6. Clinical details of these cases are consistent with the hypothesis that respiratory insufficiency represented progression of underlying malignant disease. Serious adverse experiences of neutropenia were also more frequent in the aprepitant group compared with the Standard Therapy group during Cycle 1 and Cycles 2 to 6. However, this finding contrasted with the distribution of other indices of hematological toxicity, such as serious adverse experiences of febrile neutropenia and leukopenia that were similar or slightly more common in the Standard Therapy group. Also, the patterns of abnormal laboratory tests of neutropenia, as graded according to the NCI Common Toxicity Criteria, were comparable across both treatment groups.

In the CINV studies, the range of causes of deaths was consistent with this patient population receiving high-dose chemotherapy including cisplatin, and the incidences of death were generally similar between the treatment groups in each cycle of chemotherapy.

The patterns of distribution of adverse experiences that resulted in discontinuation of study therapy were generally similar across both treatment groups in Cycle 1 and in Cycles 2 to 6.

The protocol-specified laboratory data analyses revealed no notable trends. Categorization of protocol-specified laboratory analytes using the NCI Common Toxicity Criteria data did not reveal any differences between the treatment groups for hematologic parameters, including neutropenia. Though the protocol-specified laboratory tests were not necessarily timed to capture the peak of hematologic toxicity [64], the data obtained at the clinic visit that occurred between Day 19 and Day 29 post-cisplatin provided an adequate signal for the assessment of the frequency and severity of these abnormalities, since the incidence of neutropenia (NCI Grades 1 to 4 inclusive) was ~20 to 25% in both treatment groups at this visit.

Overall, coadministration of cisplatin with chemotherapy metabolized by CYP3A4 resulted in a slight increase in the incidence of adverse experiences in both treatment groups, but the incidences remained very similar across groups, indicating that the safety profile of aprepitant, a weak to moderate inhibitor of CYP3A4, was not generally altered by coadministration of chemotherapy metabolized by CYP3A4. In particular, analysis of the Phase III aprepitant CINV safety database suggested no patterns of adverse experiences related to hematologic toxicity that would indicate clinically significant changes in the toxicity of chemotherapeutic agents metabolized via CYP3A4. These findings are consistent with the preliminary results of an ongoing Clinical Pharmacology study indicating that concomitant administration of aprepitant does not increase the plasma concentrations of docetaxel (a chemotherapy agent primarily metabolized via the CYP3A4 pathway) to a clinically meaningful extent. Of note, interactions of chemotherapy metabolized by CYP3A4 have been reported with strong CYP3A4 inhibitors [68], but not with moderate inhibitors. This may reflect in part the fact that most of the chemotherapeutic agents are given parenterally and thus are not subject to the first pass metabolic effects of orally administered CYP3A4 substrates. In the Phase III CINV studies, there was also no evidence that aprepitant altered the toxicity of any of the chemotherapeutic agents most commonly coadministered with cisplatin.

There were also no clinically important differences in the safety profile of aprepitant due to patient cancer diagnosis, age, race, or gender.

In conclusion, the aprepitant regimen tested in the CINV Phase III studies was generally well tolerated, with incidences and overall pattern of clinical and laboratory adverse experiences similar to those of the Standard Therapy group. Overall, the safety profile

was not suggestive of aprepitant enhancing the toxicity of chemotherapy, and/or increasing the risk of infections.

8.6 Safety of Aprepitant in the Absence of Chemotherapy

In addition to CINV studies, the clinical development program of aprepitant included non-CINV indications not claimed in the original marketing application. These studies were conducted in patients with depression, schizophrenia, migraine, dental pain, and post-herpetic neuralgia, as well as in healthy subjects with motion-induced nausea and light-induced melatonin suppression. The safety data from these studies are of particular importance as they tested a broad range of aprepitant doses (up to 375-mg capsules) administered for extended periods of time (up to 8 weeks) to a large number (n=1095) of patients/subjects not exposed to the side effects of chemotherapy.

In these studies for non-CINV indications, the overall incidences and profiles of clinical and laboratory adverse experiences in patients treated with aprepitant (or its IV prodrug, L-758298 at doses up to 100 mg) were generally similar to those in patients treated with the active comparator and/or placebo. Incidences of asthenia/fatigue, dizziness, headache, and somnolence in the aprepitant or L-758298 group were generally similar to those in the active comparator group, though slightly higher than those in the placebo group. Hiccups were very infrequently reported as an adverse experience. Notably, corticosteroids were not coadministered with aprepitant in these studies. Serious adverse experiences occurred in 0.9% and 0.8% of the patients in the aprepitant or L-758298 group and in the placebo group, respectively. No patients died in any of the studies for non-CINV indications.

The pattern of clinical and laboratory adverse experiences in studies for non-CINV indications was not suggestive of hematological toxicity or immunosuppression associated with the administration of aprepitant at daily doses up to 3-fold higher than the regimen for CINV, for up to 8 weeks.

8.7 Assessment of Potential Effects of Aprepitant on the QT_c Interval

8.7.1 Nonclinical Assessment

The potential of aprepitant for cardiovascular or autonomic effects was studied using anesthetized dogs in vivo. No meaningful changes in blood pressure or heart rate were observed after administration of aprepitant at 1.0 mg IV (a dose that fully inhibits the vasodepressor effects of exogenous substance P). There were no remarkable changes in ECG Lead II activity including no changes in the QTc interval that could be attributed to aprepitant treatment. Moreover, the compound showed no anti-cholinergic, anti-adrenergic, or ganglionic-blocking activity since responses to autonomic stimuli were unchanged after aprepitant administration.

8.7.2 Clinical Assessment

A comprehensive analysis of the effect of aprepitant on the QT_c interval as it relates to the risk of QT_c interval prolongation was performed with data in the Clinical

Pharmacology and Clinical Research databases. The potential for QT_c interval prolongation by aprepitant was evaluated in those studies that included on-drug ECGs. On-drug was defined as approximately the time of maximal plasma concentration (T_{max}) for aprepitant (within 2 to 4 hours after dosing of the nanoparticle or tablet formulations of aprepitant or L-758298 [the IV prodrug of aprepitant]). Fifteen (15) Clinical Pharmacology studies and 9 Clinical Research studies (3 CINV studies and 6 studies in other indications) included subjects/patients who met these criteria. Of those, 7 Clinical Pharmacology studies and 2 Clinical Research studies (1 CINV study and 1 study in patients with depression) used aprepitant nanoparticle formulation (FMI). In the depression study (Protocol 039) aprepitant FMI was administered at doses of up to 375 mg daily for up to 8 weeks. In total, 160 subjects and 250 patients in the Clinical Pharmacology and Clinical Research studies, respectively, received doses of or equivalent to ≥125 mg of the nanoparticle formulation.

The assessment of QT_c interval changes was based on the Committee for Proprietary Medicinal Products (CPMP) categorical levels of clinical concern. The CPMP categories identify QT_c interval prolongations of ≥30 to 60 msec as of potential clinical concern and prolongations >60 msec as of significant clinical concern. In addition to these changes from baseline and in accordance with the CPMP guidance, the numbers of subjects or patients with absolute QT_c intervals ≥500 msec were also assessed. As a third additional approach, reports of adverse experiences related to QT_c interval (QT or QT_c interval prolongation, ventricular tachycardia or fibrillation, or torsade de pointes) were also reviewed and compared between treatment groups.

This extensive review of the Clinical Pharmacology and Clinical Research databases showed no findings of clinical concern. The mean QT_c interval changes from baseline were similar in the L-758298, aprepitant, and corresponding placebo treatment groups and there appeared to be no trend related to the aprepitant dose. The proportions of subjects and patients with QT_c interval prolongations meeting the CPMP criteria for potential or significant clinical concern were overall small and similar between treatment groups. Most of the subjects and patients meeting the CPMP criteria had absolute QT_c interval values within normal limits. Clinical adverse experiences related to QT_c interval prolongation were infrequent and similarly distributed between treatment groups (6 in the aprepitant groups and 6 in comparator groups). In summary, the aprepitant nanoparticle capsule formulation at doses of up to 375 mg administered daily for up to 8 weeks was similar to placebo in its effect on QT_c interval prolongation and frequency of QT_c interval-related adverse experiences.

The following 3 tables present key findings related to the effect of aprepitant on the QT_c interval in the CINV studies . Table 53 presents QT_c interval prolongations of ≥30 to 60 msec and prolongations >60 msec observed in the CINV studies (Protocols 004, CN-007, and 040/042). Table 54 presents the numbers of patients with absolute QT_c intervals ≥500 msec in the CINV studies (Protocols 004, CN-007, and 040/042). Table 55 presents the summary statistics for QT_c interval (msec) data in the CINV Phase IIb study (Protocol 040/042); aprepitant (40, 125, or 375 mg FMI) in this study was coadministered with ondansetron and dexamethasone on Day 1.

Table 53

Counts of Patients With Changes From Baseline in the CPMP[†]-Defined Categories of Increasing Clinical Concern for QT_c Interval Prolongation—CINV Studies (Protocols 004, CN-007, and 040/042)

QT_c Interval Change From Baseline	Ondansetron (N = 23)		L-758298 60 mg/100 mg (N = 30)		Placebo for L-758298[‡] (N = 50)		L-758298 100 mg[‡] (N = 97)		Placebo for Aprepitant[§] (N = 149)		Aprepitant 40 mg[§] (N = 100)		Aprepitant 125 mg[§] (N = 152)		Aprepitant 375 mg[§] (N = 8)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
<30	21	(91.3)	27	(90.0)	32	(64.0)	61	(62.9)	108	(72.5)	77	(77.0)	124	(81.6)	8	(100)
[30, 60]	0	(0.0)	3	(10.0)	14	(28.0)	27	(27.8)	30	(20.1)	15	(15.0)	20	(13.2)	0	(0.0)
>60	2	(8.7)	0	(0.0)	4	(8.0)	9	(9.3)	11	(7.4)	8	(8.0)	8	(5.3)	0	(0.0)

[†] CPMP = Committee for Proprietary Medicinal Products. Categories obtained from its points to consider document: The assessment of the potential for QT interval prolongation by non-cardiovascular medicinal products.
[‡] Patients also received dexamethasone 20 mg IV.
[§] Patients also received ondansetron 32 mg IV and dexamethasone 20 mg P.O.
CINV = Chemotherapy-induced nausea and vomiting.
IV = Intravenous; P.O. = By mouth.
N = The number of patients who had a QT_c interval measurement in the treatment group.
N = The number of patients in the particular category.

Table 54

Counts of Patients With a QT_c Interval ≤500 or >500 msec—CINV Studies (Protocols 004, CN-007, and 040/042)

QT_c Interval (msec)	Ondansetron (N = 23)		L-758298 60 mg/100 mg (N = 30)		Placebo for L-758298[†] (N = 50)		L-758298 100 mg[†] (N = 99)		Placebo for Aprepitant[‡] (N = 177)		Aprepitant 40 mg[‡] (N = 111)		Aprepitant 125 mg[‡] (N = 181)		Aprepitant 375 mg[‡] (N = 19)	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
≤500	21	(91.3)	30	(100)	47	(94.0)	96	(97.0)	175	(98.9)	109	(98.2)	174	(96.1)	18	(94.7)
>500	2	(8.7)	0	(0.0)	3	(6.0)	3	(3.0)	2	(1.1)	2	(1.8)	7	(3.9)	1	(5.3)

[†] Patients also received dexamethasone 20 mg IV.
[‡] Patients also received ondansetron 32 mg IV and dexamethasone 20 mg P.O.
CINV = Chemotherapy-induced nausea and vomiting.
IV = Intravenous; P.O. = By mouth.
N = The number of patients who had a QT_c interval measurement in the treatment group.
N = The number of patients in the particular category.

Table 55

Summary Statistics for QT_c Interval (msec) Data—
CINV Phase IIb Study (Protocol 040/042)

Trial	Aprepitant Dose	Days on Treatment	Time of ECG Measurement (Hours Postdose)	N	QT_c Interval at Baseline Mean	QT_c Interval Postdose				
						Mean	Median	Min	Max	SD
040/042	Aprepitant 40 mg	1	2 to 4	100	403.8	414.3	417.9	249.2	516.4	43.9
	Aprepitant 125 mg	1	2 to 4	152	411.6	413.2	413.3	284.0	516.4	42.8
	Aprepitant 375 mg	1	2 to 4	8	445.7	436.6	437.6	380.0	505.7	46.3
	Standard Therapy	1	2 to 4	149	401.0	413.8	413.1	302.4	513.0	40.7

N = Number of patients with a baseline and post baseline QT_c interval value.
SD = Standard deviation.
ECG = Electrocardiogram.
CINV = Chemotherapy-induced nausea and vomiting.
Standard Therapy = Ondansetron 32 mg intravenously and Dexamethasone 20 mg orally on Day 1.

8.8 Discussion of Aprepitant Safety Profile

The aprepitant clinical development program was designed to test the hypothesis that aprepitant, a selective NK_1-receptor antagonist, would prevent CINV while demonstrating good safety and tolerability.

The extensive experience with aprepitant in the Clinical Pharmacology program and also in the non-CINV clinical studies demonstrates the excellent safety and tolerability of the compound. Non-CINV studies also revealed no evidence of adverse experiences suggestive of hematologic toxicity and/or immunosuppression associated with aprepitant administration.

In the CINV program, the adverse experience profile associated with aprepitant was carefully reviewed in order to assess whether aprepitant potentially had a clinically significant interaction with chemotherapy metabolized by CYP3A4. No evidence of such an interaction was seen.

In general, aprepitant was well tolerated, with incidences of clinical and laboratory adverse experiences similar to those in the comparator groups.

8.9 Overall Safety Conclusions

Based on the clinical and pharmacological data generated in the development program, in patients receiving emetogenic chemotherapy for underlying malignancy:

- The aprepitant regimen for CINV is generally well tolerated, with incidences and overall pattern of clinical and laboratory adverse experiences generally similar to the Standard Therapy regimen.
- The aprepitant regimen for CINV does not significantly alter the toxicity of concomitant chemotherapy whether metabolized by CYP3A4 or not.
- There are no clinically important differences in the safety profile of aprepitant due to patient age, race, or gender.
- The safety profile of aprepitant is generally similar irrespective of primary cancer diagnosis; in clinical trials, most patients had either lung, ovarian, or head and neck cancer.

9. Benefits Versus Risks Relationship

9.1 Introduction

CINV are common, potentially disabling complications of cancer chemotherapy that impair patients' ability to carry out normal daily activities [57].

At present, the most effective therapy for prevention of the CINV symptoms associated with HEC, which is exemplified by cisplatin, is a combination of a 5-HT_3–receptor antagonist (administered prior to chemotherapy) and a corticosteroid (administered prior to chemotherapy and continued for a total of 4 to 5 days). Consensus treatment guidelines published by the American Society of Clinical Oncology (ASCO) [48] recommend that 5-HT_3–receptor antagonists be administered during the delayed phase; however, several large, well-designed studies have failed to demonstrate a benefit of 5-HT_3–receptor antagonist therapy during the delayed phase when corticosteroids are administered [50; 51; 52]. 5-HT_3–receptor antagonists are approved in the United States only for single-dose administration prior to HEC and are not approved to treat delayed phase symptoms.

The principal shortcoming of current therapy is suboptimal efficacy in the prevention of acute and delayed phase CINV, especially delayed symptoms. Importantly, current therapy may not maintain its efficacy during repeated cycles of chemotherapy [53]. The deficiencies of current antiemetic therapy are further demonstrated by a recent study of patient perceptions regarding chemotherapy: patients ranked nausea and vomiting and hair loss among the most distressing symptoms associated with chemotherapy, despite administration of 5-HT_3–receptor antagonists [1]. Therefore, there is still an unmet medical need for a therapy that improves prevention of CINV, particularly during the delayed phase.

9.2 Potential Benefits of Aprepitant

Phase II clinical trials with aprepitant, or its intravenously administered prodrug (L-758298), in patients undergoing HEC with cisplatin, demonstrated that aprepitant is effective in the prevention of both acute and delayed CINV when administered as a single agent. Greater efficacy was achieved in a variety of different regimens involving coadministration with corticosteroids and 2 frequently prescribed 5-HT_3–receptor antagonists (granisetron and ondansetron). The efficacy in prevention of delayed symptoms was not solely derived from improved control of acute symptoms. These 5 Phase II studies also established that the best control of symptoms occurred when aprepitant was dosed for more than 1 day and given as part of a regimen that also included a corticosteroid and a 5-HT_3–receptor antagonist. This regimen was utilized in the Phase III clinical trials.

The aprepitant regimen, as tested in 2 Phase III studies, protected most patients from emesis and enabled them to avoid the use of rescue therapy throughout the 5 days following highly emetogenic cisplatin-based chemotherapy. The best currently available

standard therapy prevented overall CINV in only 48% of patients ($p<0.001$) in these studies compared to 68% receiving the aprepitant regimen. Separate assessments of the acute and delayed phases also demonstrated a significant benefit. The aprepitant regimen also provided a significant improvement over Standard Therapy in the prevention of acute symptoms: CINV symptoms were prevented in 86% of patients treated with the aprepitant regimen compared to 73% of patients treated with Standard Therapy; $p<0.001$), and a very marked improvement in the prevention of delayed symptoms of CINV (72% versus 51%; $p<0.001$) was observed. The prevention of delayed CINV is particularly important, as current therapy provides protection for only about half of the patients undergoing HEC and because these symptoms are significant factors in perturbing patients' daily lives [69; 57]. The benefit of aprepitant as an effective antiemetic therapy was reinforced by the observation in both Phase III studies that significantly more patients treated with the aprepitant regimen reported "no impact of CINV on daily life" compared with those treated with Standard Therapy (74.0% versus 64.3%, $p<0.05$; 74.7% versus 63.5%, $p<0.01$) based on data obtained using the FLIE questionnaire. The advantage of the aprepitant regimen over Standard Therapy demonstrated during the initial cycle of chemotherapy was well maintained during repeat cycles.

The efficacy of the aprepitant regimen was unaffected by age, race, or gender and the concurrent administration of emetogenic chemotherapy in addition to cisplatin.

9.3 Risks of Aprepitant Regimen

The toxicity potential of aprepitant was evaluated in a series of preclinical repeated-dose oral toxicity studies in dogs and rats up to 1 year. These studies have demonstrated that aprepitant has little potential for toxicity.

The adverse experience profile of the 544 patients in the aprepitant treatment group who received at least 1 dose of study therapy in Cycle 1 of the combined Phase III studies was generally typical of patients receiving chemotherapy. These patients had a variety of primary cancer diagnoses, the most frequent of which included lung (40%), ovarian (9.5%), and head and neck (9.3%). In addition to cisplatin, these patients received concomitant therapy with numerous different commonly administered chemotherapeutic agents, the most frequent of which included etoposide (19.4%), fluorouracil (18.3%), gemcitabine (16.3%), vinorelbine (15.4%), paclitaxel (9.5%), cyclophosphamide (9.1%), doxorubicin (6.9%), and docetaxel (2.0%).

The most common reported adverse effects of the aprepitant regimen (when comparing the aprepitant treatment group with the Standard Therapy group, respectively) were asthenia/fatigue (18% versus 12%), nausea (13% versus 12%), constipation (10% versus 12%), diarrhea (10% versus 7%), and hiccups (11% versus 6%) (see Section 8). The most common drug-related adverse effects of the aprepitant regimen (when comparing the aprepitant treatment group with the Standard Therapy group, respectively) were hiccups (5% versus 3%), asthenia/fatigue (3% versus 2%), constipation (2% versus 2%),

and headache (2% versus 2%). The incidences of serious adverse experiences and deaths were similar between the aprepitant treatment group and the Standard Therapy group.

Drug interactions of aprepitant were carefully evaluated because aprepitant as used in the treatment of CINV is a substrate, weak to moderate inhibitor and very weak inducer of CYP3A4, and an inducer of CYP2C9. Aprepitant is unlikely to interact with drugs that are substrates for the P-gp transporter, as demonstrated by the lack of interaction of aprepitant with digoxin in a clinical drug-interaction study.

Of note, the interaction studies conducted with aprepitant indicate a low potential for aprepitant to produce clinically meaningful effects on the pharmacokinetics of intravenously administered chemotherapeutic agents, including those metabolized by CYP3A4. In accordance with this prediction, careful analysis of the Phase III aprepitant CINV safety database suggested no patterns of adverse experiences, notably those related to hematologic toxicity, that would indicate clinically significant changes in the toxicity of chemotherapeutic agents metabolized via CYP3A4.

Aprepitant is a substrate for CYP3A4; therefore, coadministration of aprepitant with drugs that inhibit CYP3A4 activity may result in increased plasma concentrations of aprepitant. Consequently, concomitant administration of aprepitant with strong CYP3A4 inhibitors (e.g., ketoconazole) should be approached cautiously. This is not expected to be a significant clinical issue because strong CYP3A4 inhibitors are infrequently used due to the availability of other therapeutic options. In addition, aprepitant plasma exposures 5- to 6-fold greater than the clinical exposure produced with the aprepitant regimen for CINV have been well tolerated when aprepitant was administered daily for up to 6 weeks in non-CINV studies. Concomitant administration of aprepitant with moderate CYP3A4 inhibitors (e.g., diltiazem) does not result in clinically meaningful changes in plasma concentrations of aprepitant.

Aprepitant has been shown to induce the metabolism of S(-)-warfarin, which is metabolized predominantly through CYP2C9. In patients on chronic warfarin therapy, after completion of the 3-day regimen of aprepitant with each chemotherapy cycle, the prothrombin time (International Normalized Ratio or INR) should be monitored closely to establish and maintain the required dose of warfarin. Coadministration of aprepitant with drugs that are known to be metabolized by CYP2C9 may result in lower plasma concentrations of these drugs, although there are no chemotherapeutic agents that are known to be CYP2C9 substrates.

The efficacy of oral contraceptives following administration of aprepitant may be reduced; therefore, alternative or back-up methods of contraception should be used.

In clinical drug-interaction studies, aprepitant did not have clinically important effects on the pharmacokinetics of the 5-HT_3–receptor antagonists ondansetron or granisetron.

There are no adequate well-controlled studies of aprepitant in pregnant women. Aprepitant should be used during pregnancy only if the potential benefit justifies the potential risk to the mother and the fetus.

9.4 Benefit/Risk Summary

Aprepitant represents a significant medical advance for patients receiving HEC. It is a breakthrough drug with a novel mechanism of action—the first NK_1-receptor antagonist to be entered into clinical use. The efficacy profile of aprepitant complements current therapy since its addition to a standard therapy regimen markedly improves the prevention of both acute and particularly delayed CINV symptoms and, importantly, the improvement appears to be maintained in subsequent cycles of chemotherapy. Aprepitant was generally well tolerated in clinical studies. As with many marketed drugs, potential drug interactions need to be considered when using aprepitant. Relevant statements in the proposed product label provide appropriate guidance on its use in the target population, which consists of cancer patients under close medical supervision. It is intended for the following indication: the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

9.5 Conclusions

Clinical evaluation of aprepitant demonstrates that it has a highly favorable benefit/risk ratio when used for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy.

10. Conclusions

Conclusions—Nonclinical Development of NK_1-Receptor Antagonists for CINV

- Aprepitant is a highly selective, competitive, brain-penetrant NK_1-receptor antagonist.
- The antiemetic effects of aprepitant in ferrets are centrally mediated.
- Coadministration studies showed that the protective effects of aprepitant can be additive with 5-HT_3–receptor antagonists (ondansetron) or corticosteroids (dexamethasone) against cisplatin-induced emesis in ferrets.
- Aprepitant is unique compared with other agents used to control CINV (5-HT_3-receptor antagonists and dexamethasone) as it is effective against both acute and delayed cisplatin-induced emesis in ferrets.
- The activity of aprepitant against delayed cisplatin-induced emesis in ferrets is independent of its effects in the acute phase.
- Low once-daily oral doses of aprepitant provide effective protection against acute and delayed cisplatin-induced emesis in ferrets.

Conclusions—Aprepitant Nonclinical Pharmacokinetics and Drug Metabolism

- Aprepitant has good oral bioavailability (16 to 46%) and has a half-life of 3 to 10 hours in mice, rats, dogs, and ferrets.
- Aprepitant is brain penetrant in ferrets and is the major drug-related component detected in the brain responsible for antiemetic activity.
- Metabolites of aprepitant observed in humans are also observed in nonclinical species, validating the use of the animal models selected for the toxicology studies of aprepitant. All metabolites have reduced affinity at human NK_1 receptors, relative to aprepitant itself.
- Aprepitant is a weak to moderate inhibitor of CYP3A4 in vitro (IC_{50} 2 to 21 μM). Aprepitant is a very weak inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, and 2E1 (IC_{50} >66 μM) in vitro.
- Aprepitant is a substrate and a weak inhibitor of human P-glycoprotein in vitro.

Conclusions—Aprepitant Nonclinical Toxicology

- There are no contraindications to the therapeutic use of aprepitant in humans based on the results of the nonclinical toxicology studies.
- Aprepitant has a low order of acute toxicity.
- The principal findings observed in the liver, thyroid, and/or pituitary in the rat studies were considered rodent-specific, were consistent with changes reported for

structurally and pharmacologically dissimilar marketed drugs that have been shown to induce hepatic cytochrome P-450 enzymes in rodents, and are of limited toxicological significance to human risk assessment.

- In dogs, the no-effect level was ~6-fold in excess of the exposure at the intended clinical dose.
- Aprepitant has no effects on female or male fertility in rats.
- Aprepitant is not teratogenic nor does it cause embryo-fetal toxicity in rats or rabbits at doses in which transplacental exposure occurs.
- Aprepitant is neither genotoxic nor mutagenic.
- In the carcinogenicity study in mice, there was no evidence of an increased incidence of any tumor type. In the carcinogenicity studies in rats, the increased incidences of hepatocellular adenomas and thyroid follicular cell adenomas and carcinomas were consistent with hepatic enzyme induction. This rodent-specific tumor promotion phenomenon has been observed with other marketed drugs that induce hepatic cytochrome P-450 enzymes, has not been shown to occur in humans, and is of limited toxicological significance to human risk assessment.

Conclusions—Aprepitant Pharmacokinetics/Pharmacodynamics

- Aprepitant is well absorbed after oral administration with minimal food effect. Bioavailability of the market formulation is 59 to 67% (fasting).
- The plasma half-life of aprepitant is consistent with once-daily dosing and the regimen for CINV provides approximately constant daily plasma exposure of aprepitant.
- Aprepitant is eliminated by metabolism via CYP3A4 and its metabolites do not contribute to its activity in vivo.
- The pharmacokinetics of aprepitant are not significantly affected by race, gender, body weight, or age.
- Dose adjustment of aprepitant is not necessary in patients with renal insufficiency or mild to moderate hepatic insufficiency.
- Nearly complete (>95%) brain NK_1-receptor blockade provides maximum antiemetic efficacy of aprepitant in humans.

Conclusions—Aprepitant Drug Interactions

- Coadministration of aprepitant with strong CYP3A4 inhibitors (e.g., ketoconazole) may result in clinically important elevations of plasma concentrations of aprepitant and should be approached cautiously; but concomitant administration of aprepitant with moderate CYP3A4 inhibitors (e.g., diltiazem) does not result in clinically meaningful changes in plasma concentrations of aprepitant.

- Coadministration of aprepitant and rifampin results in clinically important decreases in plasma concentrations of aprepitant that may result in decreased efficacy of aprepitant.
- The aprepitant regimen for CINV produces at most moderate inhibition of CYP3A4 activity (comparable to verapamil, diltiazem, or grapefruit juice) during dosing followed by a small, transient, clinically unimportant inductive effect on CYP3A4 following completion of dosing. The inhibition of CYP3A4 by aprepitant is less for intravenously administered substrates.
- Moderate inhibition of CYP3A4 by the aprepitant regimen for CINV increases the plasma concentrations of orally coadministered synthetic corticosteroids (dexamethasone and methylprednisolone). Dose adjustment of dexamethasone was implemented in Phase III studies to facilitate interpretation of antiemetic efficacy.
- Aprepitant has a pharmacokinetic effect, but is without clinically important pharmacodynamic effects, on diltiazem. Adjustment of diltiazem doses is not necessary.
- The aprepitant regimen for CINV does not significantly affect the pharmacokinetics of ondansetron or granisetron. Adjustment of the doses of these 2 antiemetic drugs is not necessary.
- Preliminary data in 5 patients indicate that coadministration of the aprepitant regimen for CINV had little effect on docetaxel pharmacokinetics. Overall, there is a low potential for aprepitant to produce clinically meaningful effects on the pharmacokinetics of IV chemotherapeutic agents.
- The aprepitant regimen for CINV produces slight induction of CYP2C9 activity that is nearly resolved within 12 days after completion of the regimen. Drugs with narrow therapeutic indices that are known to be metabolized by CYP2C9 (e.g., warfarin, phenytoin) may have transiently lower plasma concentrations when coadministered with aprepitant. For patients on warfarin, INR should be appropriately monitored during the period immediately following administration of the regimen.
- Aprepitant does not affect P-glycoprotein activity (either inhibition or induction) as assessed using digoxin as a P-glycoprotein substrate. The aprepitant regimen for CINV is unlikely to result in clinically significant interactions with drugs that are P-glycoprotein substrates (e.g., some chemotherapeutic agents).
- Aprepitant does not inhibit CYP2D6 activity in vivo, and is a very weak inhibitor of CYPs 1A2, 2C9, 2C19, or 2E1 in vitro.
- The efficacy of oral contraceptives during chronic administration of aprepitant may be reduced. Although a 3-day regimen of aprepitant given concomitantly with oral contraceptives has not been studied, alternative or back-up methods of contraception should be used.

Conclusions—Clinical Efficacy of Aprepitant in CINV

Phase IIa

- Aprepitant as monotherapy, or coadministered with corticosteroids, demonstrates efficacy in the prevention of acute CINV, but is less effective than 5-HT_3–receptor antagonists (Protocols 004, 012, and CN-007).
- Aprepitant as monotherapy, or coadministered with corticosteroids, demonstrates efficacy in the prevention of delayed CINV, and is more effective than 5-HT_3–receptor antagonists (Protocols 004, 012, and CN-007).
- The differential time course of 5-HT_3–receptor dependent (acute) and NK_1-receptor dependent (acute and delayed) symptoms implies 2 distinct mechanisms for CINV and provides a rationale for coadministering therapies that operate through these mechanisms (Protocols 004, 012, and CN-007).
- The coadministration of aprepitant, dexamethasone, and a 5-HT_3–receptor antagonist on Day 1, followed by aprepitant on subsequent days, provides consistently better control of both acute and delayed CINV compared with the Standard Therapy regimen consisting of a 5-HT_3–receptor antagonist and dexamethasone on Day 1 (Protocols 007 and 012).
- The coadministration of aprepitant, dexamethasone, and a 5-HT_3–receptor antagonist on Day 1, followed by aprepitant on subsequent days, provides better control of acute CINV compared with the coadministration of aprepitant and dexamethasone (Protocols 007 and 012).
- Continued daily dosing with aprepitant after Day 1 improves control of delayed phase CINV compared with aprepitant dosing on Day 1 only (Protocols 007 and CN-007).
- The delayed phase efficacy of aprepitant is not solely a consequence of the prevention of symptoms in the acute phase (Protocols 004, 012, and CN-007).
- The efficacy of aprepitant in the prevention of CINV is not enhanced by an additional dose given the day before chemotherapy (Protocol 012).

Phase IIb/III

- The efficacy of aprepitant in the prevention of CINV is dose related: 125 mg administered on Day 1 followed by 80 mg on subsequent days is effective as assessed by the overall complete response and consistently superior to 40 mg administered on Day 1 followed by 25 mg on subsequent days.
- Administration of the Phase III aprepitant regimen provides protection against CINV overall and throughout both the acute and delayed phases, and is superior to Standard Therapy that includes a 5-HT_3–receptor antagonist plus dexamethasone on Day 1, followed by dexamethasone on Days 2 to 4.

- The efficacy of the aprepitant regimen is unaffected by age, race, gender, or the concomitant administration of emetogenic chemotherapy in addition to cisplatin.
- The aprepitant regimen is effective in reducing the impact of CINV on patients' daily lives.
- The efficacy advantage of the aprepitant regimen versus Standard Therapy observed in Cycle 1 appears to be maintained during subsequent cycles of chemotherapy.

Conclusions—Clinical Safety of Aprepitant in CINV

- The aprepitant regimen for CINV is generally well tolerated, with incidences and overall pattern of clinical and laboratory adverse experiences generally similar to the Standard Therapy regimen.
- The aprepitant regimen for CINV does not significantly alter the toxicity of concomitant chemotherapy whether metabolized by CYP3A4 or not.
- There are no clinically important differences in the safety profile of aprepitant due to patient age, race, or gender.
- The safety profile of aprepitant is generally similar irrespective of primary cancer diagnosis; in clinical trials, most patients had either lung, ovarian, or head and neck cancer.

Conclusion—Aprepitant Benefits Versus Risks Relationship

- Clinical evaluation of aprepitant demonstrates that it has a highly favorable benefit/risk ratio when used for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy.

11. List of References

1 de Boer-Dennert M, de Wit R, Schmitz PIM, et al. Patient perceptions of the side-effects of chemotherapy: the influence of 5HT3 antagonists. Br J Cancer 1997;76(8):1055-61.

2 Griffin AM, Butow PN, Coates AS, et al. On the receiving end V: patient perceptions of the side effects of cancer chemotherapy in 1993. Ann Oncol 1996;7:189-95.

3 Andrews PLR, Bhandari P. The 5-hydroxytryptamine receptor antagonists as antiemetics: preclinical evaluation and mechanism of action. Eur J Cancer 1993;29A(Suppl. 1):S11-S16.

4 Gregory RE, Ettinger DS. 5-HT_3 receptor antagonists for the prevention of chemotherapy-induced nausea and vomiting: a comparison of their pharmacology and clinical efficacy. Drugs 1998;55(2):173-89.

5 de Mulder PHM, Seynaeve C, Vermorken JB, et al. Ondansetron compared with high-dose metoclopramide in prophylaxis of acute and delayed cisplatin-induced nausea and vomiting: a mulitcenter, randomized, double-blind, crossover study. Ann Intern Med 1990;113:834-40.

6 Tavorath R, Hesketh PJ. Drug treatment of chemotherapy-induced delayed emesis. Drugs 1996;52(5):639-48.

7 Rudd JA, Naylor RJ. Effects of 5-HT_3 receptor antagonists on models of acute and delayed emesis induced by cisplatin in the ferret. Neuropharmacology 1994;33(12):1607-8.

8 Gralla RJ. The clinical approach to chemotherapy-induced emesis. In: Reynolds DJM, Andrews PLR, Davis CJ, eds. Serotonin and the scientific basis of anti-emetic therapy. Oxford: Clinical Communications, 1995:60-7.

9 Otsuka M, Yoshioka K. Neurotransmitter functions of mammalian tachykinins. Physiol Rev 1993;73(2):229-308.

10 Leslie RA. Neuroactive substances in the dorsal vagal complex of the medulla oblongata: nucleus of the tractus solitarius, area postrema, and dorsal motor nucleus of the vagus. Neurochem Int 1985;7(2):191-211.

11 Dockray GJ, Sharkey KA. Neurochemistry of visceral afferent neurones. In: Cervero F, Morrison JFB, eds. Progress in brain research: visceral sensation. Volume 67. Amsterdam: Elsevier Science Publishers, 1986:133-48.

12 Dockray GJ, Green T, Varro A. The afferent peptidergic innervation of the upper gastrointestinal tract. In: Singer MV, Goebell H, eds. Falk Symposium. Volume 50 ed. Dordrecht: Kluwer Academic Publishers, 1989:105-22.

13 Carpenter DO, Briggs DB, Strominger N. Responses of neurons of canine area postrema to neurotransmitters and peptides. Cell Mol Neurobiol 1983;3(2):113-26.

14 Gardner CJ, Twissell DJ, Dale TJ, et al. The broad-spectrum anti-emetic activity of the novel non-peptide tachykinin NK_1 receptor antagonist GR203040. Br J Pharmacol 1995;116:3158-63.

15 Andrews PLR, Bhandari P. Resinferatoxin, an ultrapotent capsaicin analogue, has anti-emetic properties in the ferret. Neuropharmacology 1993;32(8):799-806.

16 Bountra C, Bunce K, Dale T, et al. Anti-emetic profile of a non-peptide neurokinin NK_1 receptor antagonist, CP-99,994 in ferrets. Eur J Pharmacol 1993;249:R3-R4.

17 Tattersall FD, Rycroft W, Hargreaves RJ, Hill RG. The tachykinin NK_1 receptor antagonist CP-99,994 attenuates cisplatin induced emesis in the ferret. Eur J Pharmacol 1993;250:R5-R6.

18 Tattersall FD, Rycroft W, Hill RG, Hargreaves RJ. Enantioselective inhibition of apomorphine-induced emesis in the ferret by the neurokinin$_1$ receptor antagonist CP-99,994. Neuropharmacology 1994;33(2):259-60.

19 Watson JW, Gonsalves SF, Fossa AA, et al. The anti-emetic effects of CP-99,994 in the ferret and the dog: role of the NK_1 receptor. Br J Pharmacol 1995;115:84-94.

20 Gardner CJ, Bountra C, Bunce KT, et al. Anti-emetic activity of neurokinin NK_1 receptor antagonists is mediated centrally in the ferret [Abstract]. Br J Pharmacol 1994;112:516P.

21 Tattersall FD, Rycroft W, Francis B, et al. Tachykinin NK_1 receptor antagonists act centrally to inhibit emesis induced by the chemotherapeutic agent cisplatin in ferrets. Neuropharmacol 1996;35(8):1121-9.

22 Grélot L, Dapzol J, Estève E, et al. Potent inhibition of both the acute and delayed emetic responses to cisplatin in piglets treated with GR205171, a novel highly selective tachykinin NK_1 receptor antagonist. Br J Pharmacol 1998;124:1643-50.

23 Tattersall FD, Rycroft W, Marmont N, Cascieri M, Hill RG, Hargreaves RJ. Enantiospecific inhibition of emesis induced by nicotine in the house musk shrew (*Suncus murinus*) by the neurokinin$_1$ (NK_1) receptor antagonist CP-99,994. Neuropharmacology 1995;34(12):1697-9.

24 Rudd JA, Jordan CC, Naylor R.J. The action of the NK_1 tachykinin receptor antagonist, CP 99,994, in antagonizing the acute and delayed emesis induced by cisplatin in the ferret. Br J Pharmacol 1996;119:931-6.

25 Rudd JA, Naylor R.J. An interaction of ondansetron and dexamethasone antagonizing cisplatin-induced acute and delayed emesis in the ferret. Br J Pharmacol 1996;118:209-14.

26 Rupniak NMJ, Tattersall FD, Williams AR, et al. In vitro and in vivo predictors of the anti-emetic activity of tachykinin NK_1 receptor antagonists. Eur J Pharmacol 1997;326:201-9.

27 McClain RM. The significance of hepatic microsomal enzyme induction and altered thyroid function in rats: implications for thyroid gland neoplasia. Toxicol Pathol 1989;17(2):294-306.

28 Curran PG, DeGroot LJ. The effect of hepatic enzyme-inducing drugs on thyroid hormones and the thyroid gland. Endocr Rev 1991;12(2):135-50.

29 Amacher DE, Schomaker SJ, Burkhardt JE. The relationship among microsomal enzyme induction, liver weight and histological change in rat toxicology studies. Food Chem Toxicol 1998;36:831-9.

30 Whysner J, Ross PM, Williams GM. Phenobarbital mechanistic data and risk assessment: enzyme induction, enhanced cell proliferation, and tumor promotion. Pharmacol Ther 1996;71(1/2):153-91.

31 Lown KS, Thummel KE, Benedict PE, et al. The erythromycin breath test predicts clearance of midazolam. Clin Pharm Ther 1995;57:16-24.

32 Jamis-Dow CA, Pearl ML, Watkins PB, Blake DS, Klecker RW, Collins JM. Predicting drug interactions in vivo from experiments in vitro: human studies with paclitaxel and ketoconazole. Am J Clin Oncol 1997;20(6):592-9.

33 Bloomer JC, Baldwin SJ, Smith GJ, Ayrton AD, Clarke SE, Chenery RJ. Characterisation of the cytochrome P450 enzymes involved in the *in vitro* metabolism of granisetron. Br J Clin Pharmac 1994;38:557-66.

34 Villikka K, Kivistö KT, Neuvonen PJ. The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron. Clin Pharmacol Ther 1999;65(4):377-81.

35 Grochow LB, Ames MM, Pine JW, Jr., eds. A clinician's guide to chemotherapy pharmacokinetics and pharmacodynamics. Baltimore: Williams & Wilkins, 1998.

36 Marre F, Sanderink G-J, de Sousa G, Gaillard C, Martinet M, Rahmani R. Hepatic biotransformation of docetaxel (Taxotere®) in vitro: involvement of the CYP3A subfamily in humans. Cancer Res 1996;56:1296-302.

37 Goh B-C, Lee S-C, Wang L-Z, et al. Explaining interindividual variability of docetaxel pharmacokinetics and pharmacodynamics in asians through phenotyping and genotyping strategies. J Clin Oncol 2002;20(17):3683-90.

38 Hirth J, Watkins PB, Strawderman M, Schott A, Bruno R, Baker LH. The effect of an individual's cytochrome CYP3A4 activity on docetaxel clearance. Clin Cancer Res 2000;6:1255-8.

39 Malingré MM, Richel DJ, Beijnen JH, et al. Coadministration of cyclosporine strongly enhances the oral bioavailability of docetaxel. J Clin Oncol 2001;19(4):1160-6.

40 Backman JT, Olkkola KT, Neuvonen PJ. Rifampin drastically reduces plasma concentrations and effects of oral midazolam. Clin Pharmacol Ther 1996;59(1):7-13.

41 Rae JM, Johnson MD, Lippman ME, Flockhart DA. Rifampin is a selective, pleiotropic inducer of drug metabolism genes in human hepatocytes: studies with cDNA and oligonucleotide expression arrays. J Pharmacol Exp Ther 2001;299(3):849-57.

42 Grunberg SM, Hesketh PJ. Control of chemotherapy-induced emesis. N Engl J Med 1993;329(24):1790-6.

43 Bender CM, McDaniel RW, Murphy-Ende K, et al. Chemotherapy-induced nausea and vomiting. Clin J Oncol Nursing 2002;6(2):94-102.

44 Kris MG, Cubeddu LX, Gralla RJ, et al. Are more antiemetic trials with a placebo necessary? Report of patient data from randomized trials of placebo antiemetics with cisplatin. Cancer 1996;78(10):2193-8.

45 Gralla RJ. The evolution of antiemetic treatment. In: Dicato MA, ed. Medical management of cancer treatment induced emesis. St. Louis: Mosby, 1998:1-7.

46 Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC). Prevention of chemotherapy-and radiotherapy-induced emesis: Results of the Perugia Consensus Conference. Ann Oncol 1998;9:811-9.

47 Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15(1):103-9.

48 Gralla RJ, Osoba D, Kris MG, et al. Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. J Clin Oncol 1999;17(9):2971-94.

49 Hesketh PJ. Treatment of chemotherapy-induced emesis in the 1990s: impact of the 5-HT_3 receptor antagonists. Support Care Cancer 1994;2:286-92.

50 Tsukada H, Hirose T, Yokoyama A, Kurita Y. Randomised comparison of ondansetron plus dexamethasone with dexamethasone alone for the control of delayed cisplatin-induced emesis. Eur J Cancer 2001;37:2398-404.

51 Latreille J, Pater J, Johnston D, et al. Use of dexamethasone and granisetron in the control of delayed emesis for patients who receive highly emetogenic chemotherapy. J Clin Oncol 1998;16(3):1174-8.

52 Goedhals L, Heron JF, Kleisbauer J-P, Pagani O, Sessa C. Control of delayed nausea and vomiting with granisetron plus dexamethasone or dexamethasone alone in patients receiving highly emetogenic chemotherapy: a double-blind, placebo-controlled, comparative study. Ann Oncol 1998;9:661-6.

53 de Wit R, Schmitz PIM, Verweij J, et al. Analysis of cumulative probabilities shows that the efficacy of $5HT_3$ antagonist prophylaxis is not maintained. J Clin Oncol 1996;14(2):644-51.

54 Folstein MF, Luria R. Reliability, validity, and clinical application of the visual analogue mood scale. Psychol Med 1973;3:479-86.

55 Fetting JH, Grochow LB, Folstein MF, Ettinger DS, Colvin M. The course of nausea and vomiting after high-dose cyclophosphamide. Cancer Treat Rep 1982;66(7):1487-93.

56 Börjeson S, Hursti TJ, Peterson C, et al. Similarities and differences in assessing nausea on a verbal category scale and a visual analogue scale. Cancer Nurs 1997;20(4):260-6.

57 Lindley CM, Hirsch JD, O'Neill CV, Transau MC, Gilbert CS, Osterhaus JT. Quality of life consequences of chemotherapy-induced emesis. Qual Life Res 1992;1:331-40.

58 Relling MV, Nemec J, Schuetz EG, Schuetz JD, Gonzalez FJ, Korzekwa KR. *O*-demethylation of epipodophyllotoxins is catalyzed by human cytochrome P450 3A4. Mol Pharmacol 1993;45:352-8.

59 Tobe SW, Siu LL, Jamal SA, Skorecki KL, Murphy GF, Warner E. Vinblastine and erythromycin: an unrecognized serious drug interaction. Cancer Chemother Pharmacol 1995;35:188-90.

60 U.S.A.*TAXOL*® (paclitaxel) Injection (Patient Information Included).: July 2000.

61 Clarke SJ, Rivory LP. Clinical Pharmacokinetics of docetaxel. Clin Pharmacokinet 1999;36(2):99-114.

62 U.S.A. Package Product Label: Camptosar® irinotecan hydrochloride injection (Pharmacia) For Intravenous Use Only.: May 2002.

63 Kerbusch T, de Kraker J, Keizer J, et al. Clinical Pharmacokinetics and pharmacodynamics of ifosfamide and its metabolites. Clin Pharmacokinet 2001;40(1):41-62.

64 Haskell CM, Rosen L. Antineoplastic Agents. In: Berek JS, ed. Cancer Treatment. 5th ed. Philadelphia (PA): W.B. Saunders Company, 2001:104-215.

65 Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Ramdomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group study. J Clin Oncol 1998;16(7):2459-65.

66 Klastersky J, .Sculier JP, Bureau G, et al. Cisplatin versus cisplatin plus etoposide in the treatment of advanced non-small-cell lung cancer. J Clin Oncol 1989;7(8):1087-92.

67 Cardenal F, López-Cabrerizo MP, Antón A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 1999;17(1):12-8.

68 Kehrer DFS, Mathijssen RHJ, Verweij J, de Bruijn P, Sparreboom A. Modulation of irinotecan metabolism by ketoconazole. J Clin Oncol 2002;20(14):3122-9.

69 Osoba D, Zee B, Warr D, et al. Effect of postchemotherapy nausea and vomiting on health-related quality of life. Support Care Cancer 1997;5:307-13.