Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Aprepitant

Proprietary Product Name: Emend

Sponsor: Merck Sharp & Dohme (Australia) Pty Ltd

November 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	Major variation: New dosage regimen and New dosage
Decision:	Approved
Date of Decision:	25 May 2012
Active ingredient(s):	Aprepitant
Product Name(s):	Emend
Sponsor's Name	Merck Sharp & Dohme (Australia) Pty Limited Locked Bag 2234 North Ryde NSW 1670
Dose form(s):	Capsules
Strength(s):	165 mg
Container(s):	Blister pack
Pack size(s):	1 or 6 capsules
Approved Therapeutic use:	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. · moderately emetogenic cancer chemotherapy Emend is indicated for the prevention of postoperative nausea and vomiting.
Route(s) of administration:	Oral
Dosage:	165 mg once daily
ARTG Number (s)	182320

Product Background

This AusPAR describes the application for the registration of:

· an additional strength of Emend (aprepitant) 165 mg capsule blister pack;

· an alternative single dose regimen of Emend (aprepitant) consistent with the proposed 165 mg presentation and

- amendments to the product information document for AUST R 123271 Emend aprepitant 40 mg capsules blister pack, AUST R 95773 Emend aprepitant 80 mg capsule blister pack, AUST R 95774 Emend aprepitant 125 mg capsule blister pack, AUST R 95775 Emend aprepitant 80 mg and 125 mg tri-pack capsule blister pack[1].

Aprepitant is an antagonist of the human substance P neurokinin 1 (NK_1) receptor. Substance P is a neurotransmitter thought to be involved in emesis through binding to the NK1 receptor in the brain. The drug is currently registered for:

- the prevention of nausea and vomiting associated with cancer chemotherapy (in combination with other antiemetic agents); and
- the prevention of postoperative nausea and vomiting.

Emend is currently registered as 40, 80 and 125 mg capsules.

Aprepitant is insoluble in water and hence an intravenous (IV) formulation cannot be produced. Fosaprepitant is a pro-drug for aprepitant which after IV administration is rapidly converted to aprepitant *in vivo* by phosphatase enzymes. Fosaprepitant is also registered in Australia (under the tradename Emend IV) for the prevention of nausea and vomiting associated with cancer chemotherapy. It is currently registered as a powder for injection in 115 and 150 mg vials.

In the oncology setting, both aprepitant and fosaprepitant were initially registered with dosage regimens that involved aprepitant/fosaprepitant being administered once daily for 3 days with each chemotherapy cycle. At its December 2010 meeting, the Advisory Committee on Prescription Medicines (ACPM) recommended approval of an application for a *single dose* regimen of fosaprepitant. The current application now seeks approval of a single dose regimen of aprepitant and a new presentation (165 mg capsule) consistent with the proposed new regimen.

The proposed dose is 165 mg orally given one hr prior to chemotherapy on Day 1 of each cycle for the prevention of chemotherapy induced nausea and vomiting. It is proposed that Emend 165 mg be taken in combination with dexamethasone and ondansetron.

The proposed 1 day, single dose oral Emend 165 mg regimens for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) are summarised below in Table 1.

Table 1: A. Highly Emetogenic Chemotherapy

(i) Original comparator regimen used in pivotal studies

		Day 1	Day 2	Day 3	Day 4
Ondansetron	IV	32 mg	-	-	-
Dexamethasone	PO	20 mg	16 mg	16 mg	16 mg

[1] Amendments to the product information document are beyond the scope of this AusPARs.

(ii) Currently Approved regimens

3 day regimen Aprepitant

		Day 1	Day 2	Day 3	Day 4
Aprepitant	PO	125 mg	80 mg	80 mg	-
Ondansetron	IV	32 mg	-	-	-
Dexamethasone	PO	12 mg	8 mg	8 mg	8 mg

3 day regimen Fosaprepitant

		Day 1	Day 2	Day 3	Day 4
Fosaprepitant	IV	115 mg	-	-	-
Aprepitant	PO	-	80 mg	80 mg	-
Ondansetron	IV	32 mg	-	-	-
Dexamethasone	PO	12 mg	8 mg	8 mg	8 mg

Single dose regimen Fosaprepitant

		Day 1	Day 2	Day 3	Day 4
Fosaprepitant	IV	150 mg	-	-	-
Ondansetron	IV	32 mg	-	-	-
Dexamethasone	PO	12 mg	8 mg	16 mg	16 mg

(iii) Proposed regimen

Single dose regimen Aprepitant

		Day 1	Day 2	Day 3	Day 4
Aprepitant	PO	165 mg	-	-	-
Ondansetron	IV	32 mg	-	-	-
Dexamethasone	PO	12 mg	8 mg	16 mg	16 mg

B. Moderately Emetogenic Chemotherapy

(i) Original comparator regimen used in pivotal studies

		Day 1	Day 2	Day 3	Day 4
Ondansetron	PO	16 mg	16 mg	16 mg	-
Dexamethasone	PO	20 mg	-	-	-

(ii) Currently Approved regimens

3 day regimen Aprepitant

		Day 1	Day 2	Day 3	Day 4
Aprepitant	PO	125 mg	80 mg	80 mg	-
Ondansetron	PO	16 mg	-	-	-
Dexamethasone	PO	12 mg	-	-	-

3 day regimen Fosaprepitant

		Day 1	Day 2	Day 3	Day 4
Fosaprepitant	IV	115 mg	-	-	-
Aprepitant	PO	-	80 mg	80 mg	-
Ondansetron	PO	16 mg	-	-	-
Dexamethasone	PO	12 mg	-	-	-

Single dose regimen Fosaprepitant

		Day 1	Day 2	Day 3	Day 4
Fosaprepitant	IV	150 mg	-	-	-
Ondansetron	PO	16 mg	-	-	-
Dexamethasone	PO	12 mg	-	-	-

(iii) Proposed regimen

Single dose regimen Aprepitant

		Day 1	Day 2	Day 3	Day 4
Aprepitant	PO	165 mg	-	-	-
Ondansetron	PO	16 mg	-	-	-
Dexamethasone	PO	12 mg	-	-	-

Regulatory Status

Oral Emend Capsules (aprepitant 40, 80, and 125 mg) are currently approved in 3 day treatment regimens for the prevention of chemotherapy induced nausea and vomiting (CINV) due to HEC and MEC for the treatment of cancer. Emend IV (fosaprepitant 115 and 150 mg) is also currently approved for these indications. Emend IV 115 mg can be substituted for oral Emend 125 mg on Day 1 only of the 3 day regimen, with oral Emend 80 mg being administered on Days 2 and 3. Emend IV 150 mg is administered on Day 1 only with no oral Emend administration on Days 2 and 3.

Table 2 summaries the international regulatory status of this product.

Table 2: International regulatory history

COUNTRY	DATE	Indication
European Union	Submitted: 31 December 2010 Approved: 28 November 2011	Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based cancer chemotherapy in adults. Prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy in adults. EMEND 165 mg is given as part of combination therapy.
Switzerland	Submitted: 17 June 2011	EMEND, in combination with a $5HT_3$ antagonist and dexamethasone, is indicated for the prevention of acute and delayed nausea and vomiting induced by highly emetogenic cancer chemotherapy, including high-dose cisplatin and moderately emetogenic cancer chemotherapy in adults.
Colombia	Submitted: 22 July 2011	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 chemotherapy - moderately emetogenic cancer chemotherapy

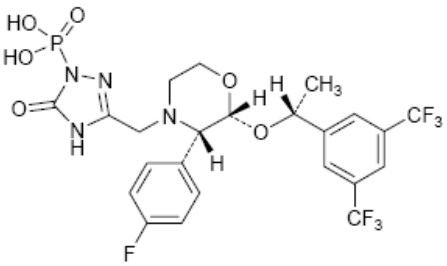
Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Aprepitant is a synthetic drug. The following diagrams show the chemical structure of aprepitant and fosaprepitant (Figure 1).

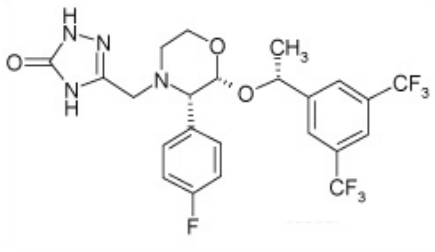
Figure 1: Chemical structures of aprepitant and fosaprepitant



fosaprepitant

C23H22F7N4O6P

MW 614.41



aprepitant

C23H21F7N4O3

MW 534.43

Drug Substance (active ingredient)

Aprepitant has 3 chiral centres presented a single stereoisomer (see structure above). It is practically insoluble in water so that control of particle size is important. Impurity levels are low. Drug substance details are unchanged from the registered strengths.

Drug Product

The proposed 165 mg Emend product is presented as opaque, size 0, hard gelatin capsules with a white body and light blue cap; the capsule has "466" and "165 mg" printed radially in black ink on one side of the body, with a Merck logo on opposite side. The strengths are distinguished by capsule shell size, different colours and the strength printed on each.

During capsule manufacture, the drug substance is milled, as a dispersion in water, then coated onto microcrystalline beads. Beads are screened then filled into capsule shells. Excipients are conventional. The capsule fill for the 165 mg strength is just a proportionally greater amount of the *same* capsule fill used in the registered Emend 40, 80 and 125 mg capsules.

With the exception of appearance the 165 mg capsule has the same specifications as the 40, 80 and 125 mg products (assay limits are controlled as percentages of the label claim). The specifications for the capsules include a dissolution test.

Stability data has been provided to support a shelf life of 4 years, store below 30ºC in aluminium (Al)/Al blisters, in keeping with the registered strengths.

Biopharmaceutics

The absolute bioavailability of aprepitant from the registered 80 and 125 mg capsules is approximately 60 to 65%. The pharmacokinetics are non-linear. Aprepitant undergoes extensive metabolism, which is the primary route of elimination. Food increased bioavailability by approximately 20% but this was considered not clinical meaningful, and the PI recommends dosing with or without food.

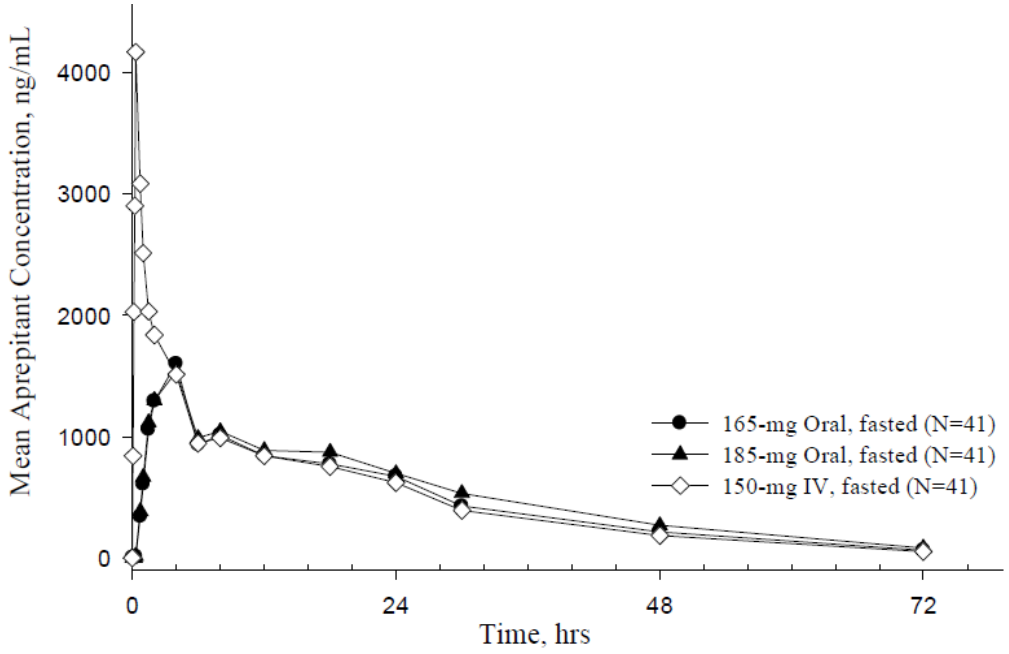
Fosaprepitant is very rapidly converted to aprepitant by phosphatase enzymes *in vivo*.

One bioavailability study was submitted in support of the current application. *Study 165* was an open, randomised, 3+1 period crossover study in 42 healthy young male and females. Three treatments were compared as fasting doses: 165 mg capsules (as proposed), a very closely related 185 mg aprepitant capsule, a 150 mg fosaprepitant intravenous dose (20 minute infusion; ≡ 130 mg aprepitant). In the fourth period there were comparisons of different fed doses: half the subjects received 165 mg capsule doses and half received 185 mg capsule doses. In both cases doses were given to a subgroup with a light breakfast and to another subgroup with a high fat breakfast. The fourth period thus provides two parallel group comparisons of low and high fat meals, and also allows (small group) crossover comparisons with fasting doses.

Plasma concentrations of aprepitant were measured after each of the doses; bioanalytical aspects were considered acceptable.

The difference between the 165 mg and 185 mg capsule doses studied here is small (12%). Systemic exposure was higher for the higher dose capsules, as expected but *both* were bioequivalent to the 150 mg fosaprepitant intravenous dose (that is, without dose adjustment: area under the concentration time response curve from time 0 to infinity ($AUC_{0-\infty}$) 95% CI 0.84-1.02 [165 mg dose] and 0.96-1.15 [185 mg dose]). Mean plasma profiles are shown in Figure 2 below.

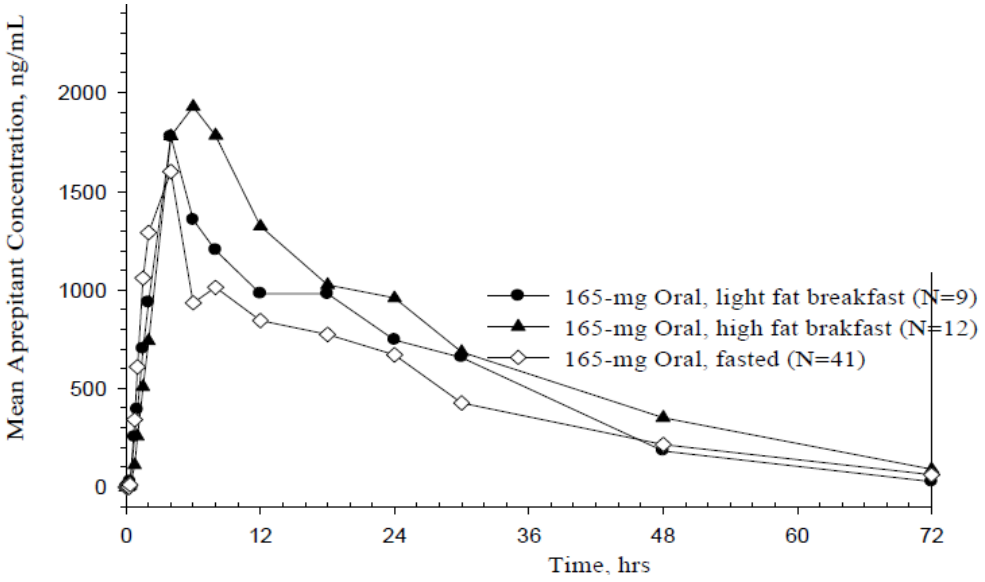
Figure 2: Mean aprepitant plasma concentrations after 165 mg and 185 mg capsule doses and 150 mg fosaprepitant IV doses



The mean absolute bioavailability (taking intravenous fosaprepitant as fully bioavailable as aprepitant) was 77.5% (standard deviation (SD) 27%; 165 mg dose) and 77.5% (SD 25%; 185 mg dose), which is higher than that measured at lower doses, perhaps consistent with some dose non-linearity.

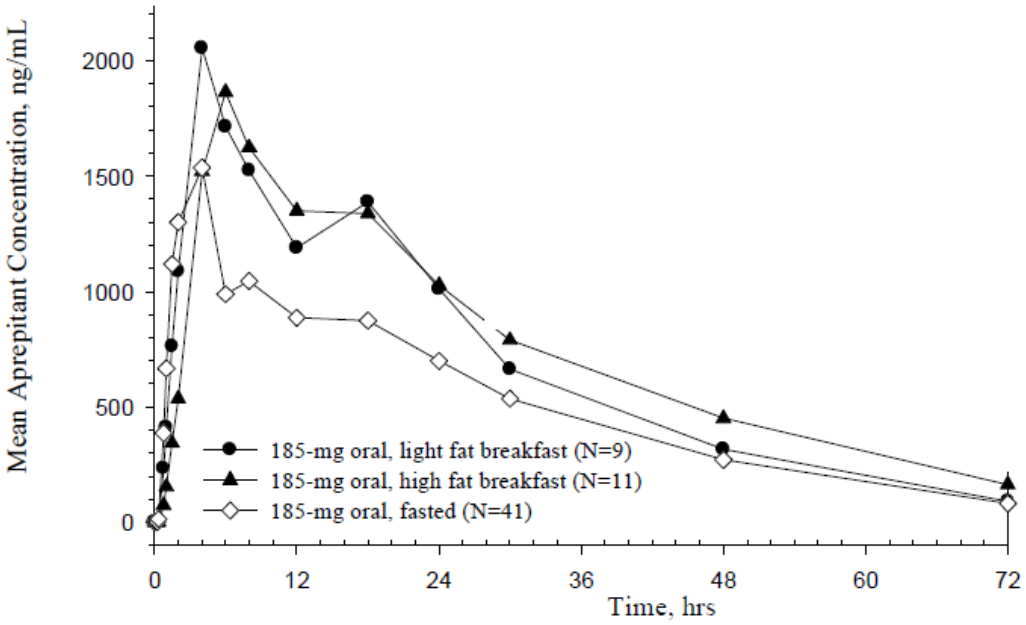
As in earlier studies, food increased aprepitant plasma levels. For the 165 mg doses a low fat breakfast had little effect on the peak plasma concentration (C_{max}) and increased $AUC_{0-\infty}$ by 8% (90% confidence interval (CI) 0.88-1.32). A high fat breakfast significantly increased both C_{max} (increased by 33%; 90% CI 1.13-1.56) and $AUC_{0-\infty}$ (increased by 47%; 90% CI 1.23-1.76).

Figure 3: Mean aprepitant plasma concentrations after 165 mg capsule doses



The 185 mg results were complicated by an extraordinarily low set of plasma levels for one subject found after dosing with a high fat breakfast (results for this subject following other doses were unremarkable). If this subject is excluded, a low fat breakfast had little effect on C_{max} and increased $AUC_{0-\infty}$ by 7% (90% CI 0.93-1.24). A high fat breakfast significantly increased both C_{max} (increased by 32%; 90% CI 1.15-1.51) and $AUC_{0-\infty}$ (increased by 45%; 90% CI 1.27-1.65). These results are very similar to those summarised above for the 165 mg doses. The mean profiles shown below include all subjects (Figure 4).

Figure 4: Mean aprepitant plasma concentrations after 185 mg capsule doses



The results show dietary fat aiding the absorption of aprepitant, which is pharmaceutically plausible. Nevertheless, dosing with or without food is still proposed.

Advisory Committee Considerations

The current application has not been referred to the Pharmaceutical Subcommittee of ACPM (PSC) because of the very close relationship to registered strengths.

Quality Summary and Conclusions

Registration is recommended with respect to chemistry, quality control and bioavailability aspects. The food effect was drawn to the attention of the Delegate.

III. Nonclinical Findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

The clinical submission consisted of an abridged submission consisting of pharmacodynamic (PD) and pharmacokinetic (PK) data primarily aimed at linking the proposed oral Emend 165 mg capsule one dose regimen with the approved single Emend IV 150 mg infusion regimen for the same indications. The aim of this approach was to demonstrate that the single dose oral 165 mg aprepitant capsule regimen and the single IV 150 mg fosaprepitant infusion regimen result in equivalent aprepitant AUC exposure (the PK bridge) and similar brain NK_1-receptor occupancy (the PD bridge). The single IV fosaprepitant 150 mg infusion regimen has been previously shown to be efficacious and well tolerated for the prevention of CINV in patients receiving chemotherapy [Study P017]. The sponsor states that the bridging strategy was discussed in principle with the European Medicines Agency Rapporteur (Sweden) and co-Rapporteur (The Netherlands). Study P017 (a Phase III, non-inferiority clinical efficacy and safety study) has been previously evaluated by the TGA and considered by the ACPM and supports the recommended single IV fosaprepitant 150 mg infusion regimens in the currently approved Emend IV PI.

No pre submission meeting appears to have been undertaken for this submission. However, the sponsor states that the submission is consistent with the updated Pre submission planning form submitted to the TGA by email on 3 February 2011, apart from two items: application forms have now been provided for each of the products impacted by the PI update; and the clinical part of the submission now consists of 31 volumes rather than 26 volumes.

The submission contained the following clinical information:

- 4 clinical pharmacology studies, including 3 providing PK data and 1 providing PD data.
- the 3 PK studies included: 1 definitive bioequivalence and food effect study with oral aprepitant (165 mg and 185 mg) and IV fosaprepitant (150 mg) [P165]; 1 CYP3A4 PK interaction (midazolam and dexamethasone) study with aprepitant 250 mg in the fasted state [P155]; and 1 CYP3A4 PK interaction (midazolam and dexamethasone) study with aprepitant 200 mg, 250 mg and 375 mg in the fed state [P175].
- the 1 PD study was a time-on-target (NK_1-occupancy) positron emission tomography (PET) study comparing IV fosaprepitant 150 mg with oral aprepitant 165 mg [P183].

Good Clinical Practice

The 4 submitted clinical pharmacology studies were undertaken in accordance with the principles of Good Clinical Practice (GCP).

Pharmacokinetics

None of the PK studies had deficiencies that excluded their results from consideration.

Study Summaries

Study P165. Single Dose Bioequivalence and Food Effect. Phase I

Objectives

The *primary objectives* were:

- to assess the aprepitant $AUC_{0-\infty}$ equivalence of single oral doses of aprepitant 165 mg and 185 mg Final Market Composition (FMC) capsules and that of a single IV dose of 150 mg fosaprepitant infused over 20 minutes in healthy young adult subjects; and
- to investigate the effect of food on the relative bioavailability of the oral aprepitant 165 mg and 185 mg FMC capsules in healthy young adult subjects.

The *secondary objective* was to assess the safety and tolerability of oral single dose administration of the aprepitant 165 mg and 185 mg FMC capsules and a 150 mg fosaprepitant intravenous dose infused over 20 minutes in healthy young adult subjects.

> *Comment*: Study P165 is the pivotal bioequivalence supporting the registration of the aprepitant 165 mg capsule as a single oral dose for the prevention of CINV associated with HEC and MEC. The sponsor indicated that comparison of historical PK data from aprepitant and fosaprepitant studies with various doses, and data extrapolations from Study PO12L1 (IV to oral comparisons) suggested that either a 165 mg or a 185 mg dose of oral aprepitant should provide a plasma aprepitant AUC similar to that resulting from an IV infusion of 150 mg fosaprepitant over 20 minutes. Therefore, the plasma aprepitant AUCs for both 165 mg and 185 mg aprepitant capsules were compared with the plasma aprepitant AUC resulting from the 150 mg intravenous dose of fosaprepitant (fosaprepitant is a prodrug of aprepitant). The sponsor indicates that the formulation of the aprepitant 165 mg FMC capsules used in this study is identical to the formulation proposed for registration, and that the formulation IV fosaprepitant 150 mg is identical to that approved in Australia. In this study, the IV fosaprepitant 150 mg infusion was administered over 20 minutes which is consistent with the approved duration of 20 to 30 minutes. Therefore, the IV comparator dose is considered to be clinically relevant.

Hypothesis and Estimation

Hypothesis: That the plasma $AUC_{0-\infty}$ of aprepitant following a single oral dose of either 165 mg or 185 mg aprepitant is equivalent to the plasma $AUC_{0-\infty}$ of aprepitant following a single 150 mg dose of fosaprepitant infused intravenously over 20 minutes in healthy young adult subjects (that is, the true GMR [oral aprepitant/IV fosaprepitant] of the $AUC_{0-\infty}$ is within the interval of 0.80 to 1.25).

Estimation: The effect of a standard high fat breakfast and a standard light breakfast on aprepitant plasma PKs ($AUC_{0-\infty}$ and C_{max}) following single 165 mg and 185 mg oral doses of aprepitant will be estimated in healthy young adult subjects.

Ethics

The final protocol, applicable amendment, and consent forms were reviewed and approved by the relevant Institutional Review Board (IRB). The study was conducted in accordance with GCP and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. Each subject gave written informed consent and were free to withdraw from the study at any time.

Study Site and Study Dates

The study was conducted at a single site in the USA. The primary treatment period was 20 February 2009 to 15 March 2009. The frozen file date was 14 September 2009.

Design

This was an open label, randomised bioequivalence study consisting of 4 treatment periods in healthy young adult and female subjects. In the first 3 treatment periods (randomised cross-over design) all enrolled subjects received single dose administration of the study drug after a 10 hr fast (oral aprepitant 165 mg capsule, oral aprepitant 185 mg capsule, and IV fosaprepitant 150 mg infused over 20 minutes). In treatment period 4 (fixed single dose), half of the subjects were randomised to oral aprepitant 165 mg in the fed state and half of the subjects were randomised to oral 185 mg in the fed state, with dosing occurring within 15 minutes after either a standard high fat breakfast or a standard light breakfast. The wash-out period between dosing in each treatment period was at least 7 days.

In each treatment period, subjects were required to drink 240 mL of water when the dose of study drug was administered. Also, on the day of dosing within each treatment period, water was withheld for 1 hr prior to dosing and for 1 hr after dosing. At all other times, subjects were allowed to drink water without restriction.

There were 5 separate, open label study drug treatments (A through E):

Treatment A: 165 mg aprepitant capsule in the fasted state.

Treatment B: 185 mg aprepitant capsule in the fasted state.

Treatment C: 150 mg fosaprepitant intravenous infusion in the fasted state.

Treatment D: 165 mg aprepitant with either a standard light breakfast or a standard high fat breakfast.

Treatment E: 185 mg aprepitant capsule with either a standard light breakfast or a standard high fat breakfast.

In each treatment period, subjects were admitted to the clinical research unit (CRU) the evening prior to dosing on Day 1 and remained in the unit for blood sampling for aprepitant plasma assays over 30 hrs following study drug administration. The subjects were then discharged from the CRU at the discretion of the investigator. Subjects were instructed to return to the CRU for aprepitant plasma sampling at 48 and 72 hrs postdose in each treatment period. Subjects returned to the CRU 14 days after the last dose of study drug for completion of the post study procedures.

Complete physical examinations (including vital signs), 12-lead electrocardiograms (ECGs) and laboratory safety tests (haematology, blood chemistry, and urinalysis) were conducted pre and post study. In each treatment period, vital signs were measured pre dose and at 4 and 24 hrs post dose on Day 1. For Treatment C, IV infusion site evaluations were done post start of the infusion at 0, 5, 10, 20 and 60 minutes and 4, 8 and 24 hrs. Adverse experiences were monitored throughout the course of the study.

> *Comment*: The study design was satisfactory and is consistent with BE/BA studies of this type. The washout period of 7 days is adequate as the apparent terminal half-life of

aprepitant ranges from approximately 9 to 13 hrs (that is, washout period was greater than 5 half-lives).

Inclusion and Exclusion Criteria

The intended study population was 42 healthy young, non smoking male and female subjects between 18 and 45 years of age with a body mass index (BMI) between 18 to 30 kg/m^2. The study included criteria allowing premature withdrawal (adverse experience that jeopardized the subject's safety and/or wellbeing; deviation from the dosing regimen as outlined in the protocol compromising the PK or PD results; violation of the study plan; or for administrative or other safety reasons).

Comment: The inclusion, exclusion and withdrawal criteria were satisfactory and consistent with Bioavailability (BA)/Bioequivalence (BE) studies of this type in healthy young male and female subjects.

Treatments

The study enrolled 42 subjects who were randomised using a computer generated allocation schedule to the treatment sequences shown below in Table 3. All doses were administered at the CRU and were witnessed by the study investigator and/or their staff.

No prescription and non prescription drugs or herbal remedies were to be taken beginning within 14 days (or 5 half-lives, whichever is longer) of dosing and throughout the entire study until post study visit. This restriction applied particularly to drugs known to influence the activity of CYP3A4 or drugs known to be metabolised by this enzyme. Concurrent therapy with any medication during the course of the study must have been discussed with the sponsor's medical monitor prior to administration, unless appropriate medical care required that therapy begin before the sponsor's medical monitor could be consulted.

Table 3: Study P165. Allocation of subjects to treatment.

Treatment Group Number	N	Subjects (Allocation Number)	Period 1	Period 2	Period 3	Period 4
1	7	0001, 0008, 0017, 0023, 0029, 0032, 0038	A	B	C	D High-fat breakfast: 0001, 0008, 0017, 0023 Standard light breakfast: 0029, 0032, 0038
2	7	0005, 0010, 0013, 0021, 0028, 0036, 0040	B	C	A	D High-fat breakfast: 0005, 0010, 0013, 0021 Standard light breakfast: 0028, 0036, 0040
3	7	0002, 0011, 0015, 0020, 0026, 0034, 0042	C	A	B	D High-fat breakfast: 0002, 0011, 0015, 0020 Standard light breakfast: 0026, 0034, 0042
4	7	0006, 0012, 0014, 0019, 0030, 0033, 0037	A	C	B	E High-fat breakfast: 0006, 0012, 0014, 0019 Standard light breakfast: 0030, 0033, 0037
5	7	0003†, 0007, 0018, 0024, 0025, 0035, 0041	B	A	C	E High-fat breakfast: 0003†, 0007, 0018, 0024 Standard light breakfast: 0025, 0035, 0041
6	7	0004, 0009, 0016, 0022, 0027, 0031, 0039	C	B	A	E High-fat breakfast: 0004, 0009, 00162, 0022 Standard light breakfast: 0027, 0031, 0039

Treatment A: 165 mg aprepitant FMC capsule in the fasted state.
Treatment B: 185 mg aprepitant FMC capsule in the fasted state.
Treatment C: 150 mg fosaprepitant dimeglumine IV infusion in the fasted state.
Treatment D: 165 mg aprepitant FMC capsule in the fed state. (High-fat breakfast or Standard light breakfast).
Treatment E: 185 mg aprepitant FMC capsule in the fed state. (High-fat breakfast or Standard light breakfast).
†AN0003 actually received 925 mg of aprepitant (5 x 185 mg) as a result of the accidental overdose that occurred when he was dosed in Treatment Period 1 and then subsequently discontinued from the study. His aprepitant plasma kinetic parameters were obtained from his Period 1 plasma PK sample, but because they reflect resulting PK values from and aprepitant exposure after oral dosing of 925 mg, the values for AN0003 are not included in the summary.

Primary Response Parameters

The primary response variables were aprepitant $AUC_{0-\infty}$ and C_{max} following single fasted or fed oral doses of aprepitant 165 mg and 185 mg, and an IV dose of fosaprepitant 150 mg.

Pharmacokinetic Assessments

The plasma concentration profile of aprepitant was determined within each of the 4 treatment periods at the following time points: pre dose and then post dose at 5, 10, 15, 20, 45 minutes and 1, 1.5, 2, 4, 6, 8, 12, 18, 24, 30, 48 and 72 hrs after oral aprepitant and after the initiation of the IV infusion of fosaprepitant. Plasma samples collected following administration of aprepitant and fosaprepitant were analysed for aprepitant concentration. The validated analytical method involved liquid-liquid extraction for analyte isolation followed by High-performance liquid chromatography (HPLC) using a reverse phase column and detected with tandem mass spectrometric detection employing a heater nebulizer (HN) interface in the positive ion mode. The lower limit of quantification (LLOQ) for aprepitant in plasma was 10 ng/mL and the linear calibration range was 10.0 to 2500 ng/mL.

Plasma aprepitant concentrations from the bioanalytical report and actual sampling times, converted to elapsed time relative to aprepitant or fosaprepitant dosing times, were used to determine the plasma PK parameters ($AUC_{0\text{-}24hr}$, $AUC_{0\text{-}\infty}$, C_{max}, time to peak concentration (T_{max}), apparent terminal t½, clearance (CL_p) and volume of distribution at steadt state (V_{ss})). Values below the LLOQ were replaced with zero. The $AUC_{0\text{-}24hr}$, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}\infty}$ were determined using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. The C_{max} and T_{max} were obtained by inspection of the plasma concentration data. The apparent terminal rate constant (λ) was estimated by regression of the terminal log-linear portion of the plasma concentration-time profile (using quantifiable concentrations only); t½ was calculated as the quotient of ln(2) and λ. The Cl_p was estimated from the relationship Clp = Dose/ $AUC_{0\text{-}\infty}$. The V_{ss} was estimated using the relationship V_{ss} = ($AUMC_{0\text{-}\infty}$ / $AUC_{0\text{-}\infty}$) x Dose / $AUC_{0\text{-}\infty}$, where $AUMC_{0\text{-}\infty}$ is the area under the first moment curve. Potency adjusted PK parameters ($AUC_{0\text{-}24hr}$, $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max}) were calculated by multiplying the unadjusted parameter by the nominal dose divided by actual dose.

Statistical Analysis and Sample Size

Equivalence (Oral versus IV Based on $AUC_{0\text{-}\infty}$ - Primary Hypothesis

The primary hypothesis was assessed using potency unadjusted data. A linear mixed-effects model using data from the first 3 treatment periods was applied to ln-transformed aprepitant $AUC_{0\text{-}\infty}$ values. The model contained fixed effects for treatment (A, B, C) and period (1, 2, 3) and a random effect for subject. The covariance structure used in this model was compound symmetry. The first order carryover effect was tested and found to be insignificant for $AUC_{0\text{-}\infty}$. Therefore the final model did not adjust for carryover.

A "two one-sided tests" procedure was used to evaluate the primary hypotheses relating to the geometric mean ratio (GMR) of the $AUC_{0\text{-}\infty}$ (Oral / IV). The first procedure tested the null hypothesis that the GMR was ≤ 0.80 versus the alternative that the GMR was > 0.80. The second procedure tested the null hypothesis that the GMR was ≥ 1.25 versus the alternative that the GMR was < 1.25. For each comparison, p-values for the GMR (Oral / IV) were calculated for each oral formulation from the linear mixed-effects model. To account for the two one-sided tests, this was taken as the largest of the p-values from the "two one-sided tests". Hochberg's step-up method for multiplicity was applied to preserve the overall alpha level for the primary hypothesis at 0.05. The p-values obtained were ranked across the two capsule dose levels in an ascending order p(2) ≤ p(1). Since the p(1) value was ≤ 0.05, the test procedure was stopped and it was concluded that the alternative hypotheses GMR > 0.80 and GMR< 1.25 were supported for both oral doses. The 95% CIs for the true GMRs (Oral/IV) at each dose level was provided for estimation purposes.

Assuming a true within-subject variance of 0.0471 for ln-AUC, with 36 subjects completing the study, there is a 97.7% probability that the 95% CI for the true GMR for AUC (Oral/ IV) will lie within the bounds 0.8 to 1.25, if the true ratio is 1.0. The true ratio can be as high as 1.05 or as low as 0.95 and will still have 90% probability that the 95% CI will lie within the equivalence bounds.

> *Comment: The equivalence of the oral and IV formulations was based on a "two one sided tests" (TOST) procedure. This is acceptable as rejection of the TOST (that is, GMR ≤ 0.80 and GMR ≥ 1.25) at the 0.5 level is the same as the capture of the 90% CI of the GMR within the limits 0.80 to 1.25. In addition, more than 36 subjects completed the equivalence assessment as planned which means that the study satisfied the estimated power calculations.*

Food Effect Estimation

The effect of food on the bioavailability of the two oral doses of aprepitant was evaluated using a linear mixed model with data from all 4 treatment periods. Since treatment and period were

confounded in the food effect assessment, the model included treatments [A, B, C, D (high-fat breakfast), D (light breakfast), E (high-fat breakfast), E (light breakfast)] and a random effect of subject. The covariance structure used in this model was compound symmetry. The 90% CIs for the true GMRs (high-fat breakfast fed/fasted; light breakfast fed/fasted) at each aprepitant dose were calculated from the model. There was one subject who had substantial outlying observations for AUC and C_{max} following a single 185 mg oral dose of aprepitant administered with a high-fat breakfast. Therefore, the study report included a supplementary sensitivity analysis excluding the results from this subject.

The precision of the estimates of food effect can be assessed by calculating the half-width of the 90% CIs expected for the given sample size and assumed variability. Assuming a true within-subject variance of 0.0471 for ln-AUC, then with 18 subjects receiving a dose both fasted and fed, the half-width of the 90% CI for the arithmetic mean difference (fed - fasted) on the log scale will be 0.126 log ng.hr/mL. The lower and upper bound 90% CI for the true GMR (fed/fasted) will be given by OBS[2]/1.13 and OBS x 1.13, where OBS is the observed GMR. For example, if the observed GMR for the $AUC_{0\text{-}24h}$ was 1.3 then the 90% CI would be 1.14 to 1.48.

Other Issues

The 95% CIs were constructed for the geometric means of the aprepitant PK parameters ($AUC_{0\text{-}\infty}$, $AUC_{0\text{-}24hr}$, $AUC_{0\text{-}t}$, C_{max}) for each treatment. In addition, the median, minimum and maximum were calculated for T_{max} and for $t_{1/2}$, harmonic mean and pseudo standard deviation (using jack-knife technique) were calculated. A supplemental analysis of potency adjusted data was also done for the bioequivalence assessment.

Subjects

The study enrolled 42 subjects (32 males and 10 females): 40 subjects completed the study as planned and 2 subjects discontinued the study prematurely. One male subject was discontinued after failing to report to the CRU for the post study visit and one male subject was discontinued after receiving an overdose of aprepitant of 925 mg (185 mg x 5 capsules) in Period 1 of the study. The 2 discontinued subjects were not replaced as the protocol was powered such that only 36 subjects had to complete as planned for statistical analysis to be performed. There was one protocol deviation in this study which involved the subject previously mentioned who was discontinued following an overdose of aprepitant. All 42 subjects were included in the evaluation of safety. Of the 42 subjects, 41 were included in the PK analysis (excluding the subject discontinued due to an aprepitant overdose).

The demographic characteristics of the 42 enrolled subjects are summarised below in Table 4. Of the 42 enrolled subjects, 23 (54.8%) were White, 16 (38.1%) were Black and 3 (7.1%) were of another racial origin. No subjects had pre existing conditions that prevented participation. Of the 42 enrolled subjects, 19 (45%) reported secondary diagnoses as part of their medical history, none of which were considered to be relevant as regards participation (list examined but not included in the CER). Of the 42 enrolled subjects, 4 (9.5%) reported use of prior drug therapy within 14 days of the start of the study, none of which were considered to be relevant as regards participation (list examined but not included in the CER). Of the 42 enrolled subjects, 8 (19%) took medication (exclusively paracetamol primarily for headache) other than test drugs during the study.

[2] OBS=observed GMR

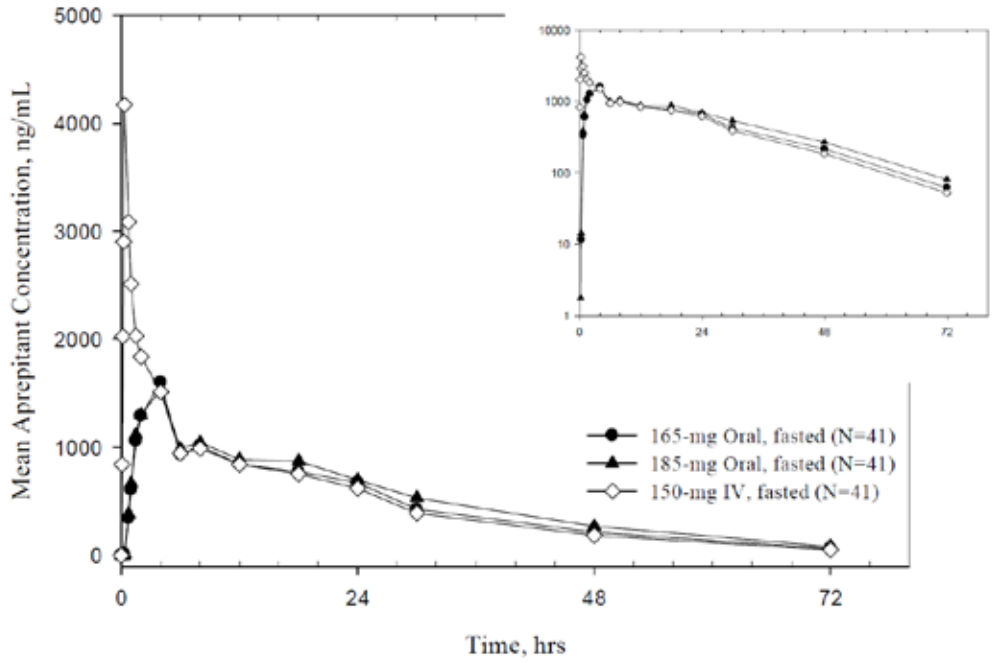
Table 4: Study P165. Basic demographics.

Study Summary	Age (yr)	Height (cm)	Weight (kg)	
N	42	42	42	
Range:	18 to 43	151.1 to 190.5	44.9 to 91.2	
Mean:	27.8	172.9	74.2	
Male N	32	32	32	
Male Range:	18 to 43	165.1 to 190.5	58.1 to 91.2	
Male Mean:	27.3	176.6	77.3	
Female N:	10	10	10	
Female Range:	21 to 42	151.1 to 167.6	44.9 to 78.9	
Female Mean:	29	161.3	64.3	

Bioequivalence Results

The arithmetic mean aprepitant plasma concentration-time profiles after administration of single oral doses of aprepitant (165 mg or 185 mg) or IV fosaprepitant (150 mg) in healthy male and female subjects for potency un-adjusted data are shown below in Figure 5.

Figure 5: Study P165. Arithmetic mean aprepitant plasma concentration (ng/mL) following single dose administration of the three treatments; potency unadjusted data.



The bioequivalence result of interest for the purposes of this submission was the single dose comparison between the oral aprepitant 165 mg capsule and the IV fosaprepitant 150 mg infusion. The results of this analysis for the $AUC_{0-\infty}$, AUC_{0-t}, and C_{max} parameters are provided below in Table 5. The within subject CV% was 21.5% for the $AUC_{0-\infty}$, 20.4% for the AUC_{0-t} and 23.8% for the C_{max}. The complete summary statistics for the comparisons between the two oral doses of aprepitant (165 mg and 185 mg) and the IV dose of fosaprepitant 150 mg for potency unadjusted data showed that they were similar to those for the potency adjusted results.

Table 5: Study P165. PK aprepitant results for single IV infusion of fosaprepitant 150 mg and single oral dose of aprepitant 165 mg capsule; potency unadjusted data.

		Fosap IV (n=41) 150 mg	Aprep PO (n=41) 165 mg	GMR [nominal 95% CI] PO / IV	Adjusted p-value
$AUC_{0-\infty}$	ng•hr/mL	35031 [a]	32508 [a]	0.93 [0.84, 1.02] [b]	p = 0.001 [c]
AUC_{0-t}	ng•hr/mL	33658 [a]	31178 [a]	0.93 [0.85, 1.01] [b]	
AUC_{0-24h}	ng•hr/mL	24444 [a]	20589 [a]	0.84 [0.78, 0.92] [b]	
C_{max}	ng/mL	4005 [a]	1666 [a]		

[a] Back-transformed least squares mean on natural log-transformed values.

[b] GMR = geometric least-squares mean ratio; the nominal 95% CIs provided for GMRs are for estimation purposes only.

[c] Adjusted p-value testing the null hypothesis that GMR ≤ 0.80 or GMR ≥1.25 versus the alternative that 0.80<GMR<1.25. If adjusted p-value ≤ 0.05, then the corresponding null hypothesis is rejected.

Comment: The single oral aprepitant 165 mg dose was considered by the sponsor to be the most appropriate dose for development for the prevention of CINV. The "two one-sided tests" procedure adjusted for multiplicity demonstrated that oral aprepitant 165 mg and IV fosaprepitant 150 mg were bioequivalent as regards the potency unadjusted $AUC_{0-\infty}$ (that is, 0.80 < GMR and GMR < 1.25); p=0.001). In addition, the nominal 95% CI of the GMR [oral/IV] of the $AUC_{0-\infty}$ was within the standard bioequivalence interval of 0.8 to 1.25. The potency unadjusted $AUC_{0-\infty}$ also showed that oral aprepitant 185 mg capsule and IV fosaprepitant 150 mg were bioequivalent. The bioequivalence of the two oral aprepitant capsules was not formally tested. However, the aprepitant plasma concentration - time profiles for the two oral capsule doses of 165 mg and 185 mg are similar, suggesting that the increased systemic exposure observed with the higher dose compared with the smaller dose is unlikely to be clinically significant (that is, LSM $AUC_{0-\infty}$ = 36775 and 32508 ng.hr/mL, respectively). Sampling time to 72 hrs was greater than 5 half-lives of aprepitant (that is, 45 to 65 hrs) indicating that the duration of sampling was sufficient to adequately characterise the aprepitant plasma concentration – time curves for the three treatments. Furthermore, the aprepitant $AUC_{0-t}/AUC_{0-\infty}$ ratios for all three treatments were greater than 80% indicating that the duration of sampling was sufficient to satisfactorily describe the elimination phase of the analyte.

The potency unadjusted $AUC_{0-\infty}$ GMR (oral/IV) data showed that, although exposure to aprepitant was bioequivalent following single oral dose aprepitant 165 mg and IV fosaprepitant 150 mg, the geometric mean exposure was 7% lower with the oral formulation relative to the IV formulation. Inspection of the aprepitant plasma concentration – time curves for the two formulations shows that exposure following the oral formulation was lower than that following the IV formulation over the first 4 hrs, while from 4 hrs through to 72 hrs the two curves are similar. However, the observed PK difference between the two treatments will be mitigated in clinical practice to some extent as oral aprepitant therapy will be started 1 hr before emetogenic chemotherapy. This still leaves a 3 hr window of uncertainty before aprepitant T_{max} is reached following oral administration (T_{max} = 4 hrs). In this 3 hr window, aprepitant plasma concentrations will be lower following oral aprepitant 165 mg compared with IV fosaprepitant 150 mg.

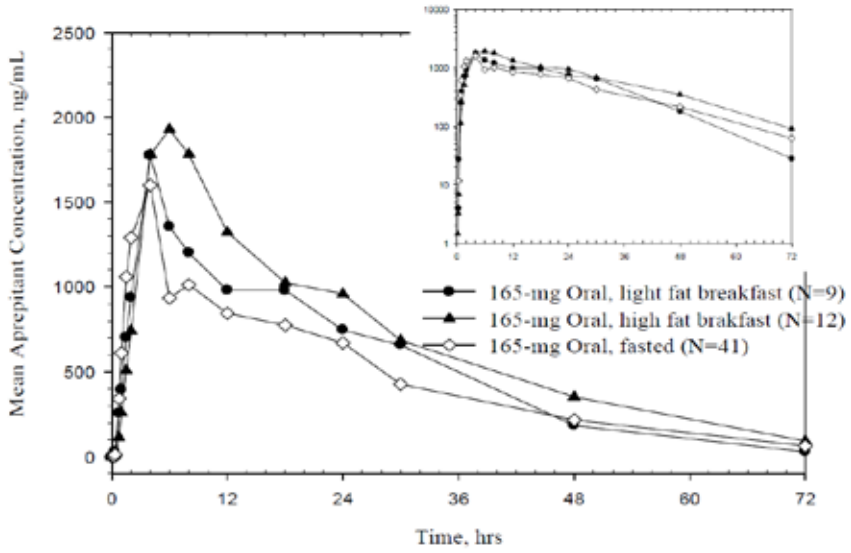
There are no clinical efficacy and safety data comparing oral aprepitant 165 mg with IV fosaprepitant 150 mg. However, there are data from the previously evaluated clinical efficacy and safety Study P017 which suggest that clinically significant differences in

efficacy between oral aprepitant 165 mg and IV fosaprepitant 150 mg are unlikely, despite the difference between the two treatments in aprepitant exposure over the first 4 hrs following administration. In Study P017, the efficacy of a regimen including aprepitant 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 was compared with a single fosaprepitant 150 mg IV infusion regimen on Day 1 in subjects scheduled to receive a first course of the highly emetogenic medicine cisplatin (70 mg/m^2) for treatment of a solid malignancy. The study included exploratory outcomes assessed in the acute phase of the study (0-24 hrs) which are considered to be relevant to the current submission. These acute phase outcomes allowed comparison between a single oral dose of aprepitant 125 mg and IV fosaprepitant on Day 1 of treatment. The results of the acute phase efficacy outcomes were similar for IV fosaprepitant 150 mg versus oral aprepitant 125 mg, respectively, for the following outcomes: complete response of no vomiting and no use of rescue medication (89.0% [963/1082] versus 88.0% [974/1107], difference = 1.1 [95%CI: -1.6, 3.8]); no vomiting (89.4% [966/1080] versus 89.0% [983/1105]; difference = 0.6 [95%CI: -2.0, 3.2]); and no use of rescue medication (97.5% [1081/1109] versus 97.1% [1105/1138], difference = 0.4 [95%CI: -1.0, 1.8]). In addition, the Kaplan-Meier curves for time to first vomiting episode from start of chemotherapy over the first 24 hrs were similar for the two treatments. The acute phase (0-24 hr) efficacy data from Study PO17 suggest that the difference in aprepitant exposure between oral aprepitant 165 mg and IV fosaprepitant 150 mg observed in Study P165 over the first 4 hrs of treatment is unlikely to be clinically significant. The results for Study PO17 have been obtained from the relevant clinical evaluation report from a previous submission.

Food Effect Results

The arithmetic mean aprepitant plasma concentration - time profiles after administration of single oral doses of aprepitant 165 mg in the fed state (low-fat or high-fat meal) and the fasted state in healthy male and female subjects are shown below in Figure 6.

Figure 6: Study P165. Arithmetic mean aprepitant (ng/ml) plasma concentration following administration of a 165 mg oral dose of aprepitant in the fed (high-fat or low-fat) and fasted states.



The effect of food on aprepitant PK parameters following a single oral dose of aprepitant 165 mg for the potency unadjusted data is summarised below in Table 6. The corresponding results following a single oral dose of aprepitant 185 mg were also summarised.

Table 6: Study 165. Plasma aprepitant PK parameters following single oral dose of 165 mg in the fed (high-fat and low-fat) and fasted state; potency unadjusted data.

Pharmacokinetic Parameter	Geometric Least-squares Mean (95% CI)[†]			GMR (90% CI)[†]		Within-subject CV % [‡]
	Fasted (n=41)	Low-fat (n=9)	High-fat (n=12)	Low-fat vs. Fasted	High-fat vs. Fasted	
$AUC_{0-\infty}$ (ng•hr/mL)	32520 (28570, 37016)	35149 (27706, 44593)	47785 (38760, 58911)	1.08 (0.88, 1.32)	1.47 (1.23, 1.76)	30.9
AUC_{0-24hr} (ng•hr/mL)	20586 (18636, 22741)	22882 (18765, 27903)	28713 (24153, 34133)	1.11 (0.93, 1.32)	1.39 (1.19, 1.63)	27.1
AUC_{0-t} (ng•hr/mL)	31184 (27611, 35219)	34291 (27293, 43085)	45949 (37608, 56139)	1.10 (0.90, 1.34)	1.47 (1.24, 1.75)	30.0
C_{max} (ng/mL)	1666 (1506, 1843)	1728 (1406, 2123)	2210 (1848, 2643)	1.04 (0.86, 1.25)	1.33 (1.13, 1.56)	28.6
T_{max} (hr)[§]	4.0 (1.5, 8.0)	4.0 (4.0, 6.0)	5.0 (2.0, 8.0)			
$t_{1/2}$ (hr)[¶]	12.8 (3.6)	8.8 (1.5)	12.6 (5.3)			

† Back-transformed least squares mean and CI on natural log-transformed values; GM= geometric mean; GMR = geometric least-squares mean ratio; the 90% CIs provided for GMRs
§ Median (minimum, maximum) reported for T_{max}.
‡ within-subject CV; within-subject coefficient of variation, approximated by the within-subject SD on the log-scale from mixed effect model*100%;
¶ Harmonic mean and Jack-knife SD reported for apparent $t_{1/2}$.
CI = Confidence Interval.

Comment: Food increased exposure to aprepitant following a single oral dose of aprepitant 165 mg by 8% (low-fat meal) and 47% (high fat meal) as assessed by the $AUC_{0-\infty}$, while the corresponding increases in C_{max} were 4% and 33%, respectively. However, the results for the aprepitant 185 mg capsule were the reverse of those observed for the 165 mg capsule with regard to both the AUC and C_{max} (that is, the high-fat meal resulted in smaller increases in exposure compared with the low-fat meal). This discrepancy appeared to be due to outlying PK results observed for one subject following administration of the 185 mg capsule with a high-fat meal. In this subject, following a single 185 mg oral dose of aprepitant the $AUC_{0-\infty}$ was about 13 fold higher in the fasted state than in the high-fat fed state (36927 versus 2766 ng.hr/mL, respectively).

The sponsor undertook a supplementary sensitivity analysis of the food effect on the 165 mg and 185 mg capsules by excluding the results from the subject with anomalous outcomes. The results showed that food (both low-fat and high-fat) increased exposure to aprepitant ($AUC_{0-\infty}$ and C_{max}) relative to fasting to a greater extent for the 185 mg dose compared with the 165 mg dose. In the supplementary sensitivity analysis exposure to aprepitant was notably higher when the 185 mg capsule was administered with a high-fat meal compared with the protocol specified analysis, while exposure did not notably differ between the two analyses when the 185 mg capsule was administered with a low-fat meal. The protocol specified and supplementary sensitivity analyses did not notably differ as regards the effect of food (high and low fat meal) on exposure to aprepitant following administration of the 165 mg capsule.

Overall, the data suggest that increased exposure ($AUC_{0-\infty}$ and C_{max}) to aprepitant following administration of the aprepitant 165 mg capsule with a low-fat meal is unlikely to be clinically significant. However, the increased systemic exposure to aprepitant following administration of the aprepitant 165 mg capsule with a high-fat meal is more problematical. Administration of the 165 mg capsule with a high-fat breakfast increased the $AUC_{0-\infty}$ by 47% and the C_{max} by 33%, relative to fasting administration and delayed the T_{max} by 1 hr. The PI states that Emend can be taken with or without food. The P165 study report states that the "moderate" increase in exposure to aprepitant when the 165 mg capsule was administered with a high-fat breakfast (that is, 47% increase in $AUC_{0-\infty}$) would not warrant a reduction in dosage given the wide therapeutic window of Emend. In addition, the P165 study report states that the standard of care for antiemetic administration for prevention of CINV is a light meal prior to administration of chemotherapy, consistent with the low-fat breakfast administered in the study. The P165 study report considers that if the aprepitant 165 mg single dose is approved for the prevention of CINV then it "would be reasonable to assert" that the labelling could state that the dose could be administered with or without

food. The issue of administration of aprepitant 165 mg with or without food is discussed further below.

Study P155. PK Interaction

Objectives

The *primary* objective had three parts:

Part 1: To evaluate the effect of a single 250 mg oral dose of aprepitant on CYP3A4 activity in healthy young adult subjects as measured by the PKs of dexamethasone following oral administration.

Part 2: To evaluate the effect of a single 250 mg oral dose of aprepitant on CYP3A4 activity in healthy young adult subjects as measured by the PKs of midazolam following oral administration.

Part 3: To assess the effect of food (a standard light breakfast) on the plasma PKs ($AUC_{0-\infty}$ and C_{max}) of a single 250 mg oral dose of aprepitant.

The secondary *objective* also had three parts:

Part 1: To assess the safety and tolerability of a single 8 mg oral daily dose of dexamethasone co-administered with a single 250 mg oral dose of aprepitant.

Part 2: To assess the safety and tolerability of a single 2 mg oral daily dose of midazolam co-administered with a single 250 mg oral dose of aprepitant.

Part 3: To assess the safety and tolerability of a single 250 mg oral dose of aprepitant administered without and with food.

> *Comment*: Aprepitant is a dose dependent inhibitor of CYP3A4 and both dexamethasone and midazolam are CYP3A4 substrates. The submission proposes that dexamethasone be administered as part of the single oral dose aprepitant 165 mg regimens for the prevention of CINV with HEC (that is, dexamethasone 12 mg orally on Day 1, 8 mg orally on Day 2 and 8 mg orally twice a day (bd) on Days 3 and 4), and for the prevention of CINV with MEC (that is, dexamethasone 12 mg orally on Day 1). The sponsor chose to investigate the effect of co-administration of midazolam with aprepitant as it considered that midazolam "is widely accepted as the appropriate CYP3A4 substrate 'probe" for investigating possible drug-drug interaction" with this isoenzyme.

Ethics

The protocol and informed consent form were reviewed and approved by the relevant IRB. The study was conducted in conformance with GCP and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent and the protection of human subjects participating in biomedical research.

Study Site and Study Dates

The study was conducted at a single site between 19 August 2008 and 30 October 2008. The date of the last patient out was 13 November 2008 and the frozen file date was 13 May 2009.

Hypothesis and Estimations

Hypothesis: Part 2: A single 250 mg oral dose of aprepitant is not a potent inhibitor of CYP3A4 metabolism when co-administered with a single oral 2 mg dose of midazolam on Day 1 (that is, the true geometric mean midazolam $AUC_{0-\infty}$ ratio (with/without aprepitant) on Day 1 is <5.0).

Estimations: Part 1: The GMR (with/without aprepitant) of oral dexamethasone AUC_{0-24h} on each of Days 1, 2 and 3 following administration of 8 mg oral daily doses of dexamethasone on Days 1, 2 and 3 with a single 250 mg oral dose of aprepitant on Day 1 will be estimated. *Part 2:* The

GMR (with/without aprepitant) of oral midazolam $AUC_{0-\infty}$ on Day 8 following administration of 2 mg oral daily doses of midazolam on Days 1 and 8 with a single 250 mg oral dose of aprepitant on Day 1 will be estimated. *Part 3:* The effect of a standard light breakfast on the plasma PKs ($AUC_{0-\infty}$ and C_{max}) following a single 250 mg oral dose of aprepitant will be estimated.

Design

This was a Phase I, open label, randomised, 3-part, 2-period, cross-over study deigned to evaluate the effect of a single 250 mg oral dose of aprepitant on the PKs of oral dexamethasone (Part 1), on the PKs of oral midazolam (Part 2) and the food effect on the PKs of a single 250 mg oral dose of aprepitant (Part 3) in healthy young adult subjects. The intended population of 50 healthy young adult male and female subjects were to be divided such that 12 subjects participated in Part 1, 26 subjects participated in Part 2 and 12 subjects participated in Part 3. In Part 1, each subject was randomised to receive 1 of 2 different treatments (A and B) in each study period. In Part 2, each subject was randomised to receive 1 of 2 different treatments (C and D) in each study period. In Part 3, each subject was randomised to receive 1 of 2 different treatments (E and F) in each study period. The 6 open label study drug treatments were:

Treatment A: Single 8 mg oral daily dose of dexamethasone alone on Days 1, 2 and 3.

Treatment B: Single 8 mg oral daily dose of dexamethasone on Days 1, 2 and 3, co-administered with a single 250 mg oral dose of aprepitant on Day 1.

Treatment C: Single 2 mg oral daily dose of midazolam alone on Days 1 and 8.

Treatment D: Single 2 mg oral daily dose of midazolam on Days 1 and 8, co-administered with a single 250 mg oral dose of aprepitant on Day 1.

Treatment E: Single 250 mg oral dose of aprepitant on Day 1 in the fasted state.

Treatment F: Single 250 mg oral dose of aprepitant on Day 1 in the fed state (approximately 30 minutes after a standard light breakfast).

All doses of study drug were administered at the clinical research unit (CRU) with subjects being admitted the evening prior to the first day of dosing and being discharged at the discretion of the investigator 24 hrs after last dosing. The majority of blood collections and vital sign measurements were undertaken in the CRU, with subjects returning to the unit for assessments required more than 24 hrs after discharge. In Part 1, subjects were required to fast (no food or liquid except water) for a minimum of 8 hrs before dosing on Days 1, 2 and 3. In Part 2, subjects were required to fast for a minimum of 8 hrs before dosing on Days 1 and 8. In Part 3, subjects were required to fast for a minimum of 8 hrs before dosing in the fasted state or before consuming a standard light breakfast about 30 minutes prior to dosing in the fed state. There was a minimum 14-day washout interval between dosing in each treatment period.

Complete physical examination (including vital signs), 12-lead ECGs and laboratory safety tests (haematology, blood chemistry, and urinalysis) were conducted at pre and post study. In each treatment period in Part 1, vital signs were measured pre dose and then at 4 and 24 hrs post dose on Day 1, and at 24 hrs post dose on Days 2 and 3. In each treatment period in Part 2, vital signs were measured pre dose and then at 24 hrs post dose on Days 1 and 8, and at 4 hrs post dose on Day 1. In each treatment period in Part 3, vital signs were measured pre dose and then at 4 and 24 hrs post dose on Day 1. Adverse experiences were monitored throughout the study.

Inclusion and Exclusion Criteria

The intended study population was 50 healthy male and female subjects between 18 and 45 years of age; subjects up to 55 years of age may have been enrolled with prior approval from the sponsor. The study also included criteria allowing premature withdrawal (that is, adverse experiences that jeopardized the subject's safety and/or wellbeing; deviation from the dosing

regimen as outlined in the protocol compromising the PK or PD results; violation of the study plan; or for administrative or other safety reasons).

> *Comment*: The inclusion, exclusion and withdrawal criteria were satisfactory and consistent with BA/BE studies of this type in healthy young male and female subjects.

Treatments

The summary of treatment allocation is provided below in Table 7. In each part of the study, subjects were randomised (1:1) into 1 of the 2 treatment sequences using allocation numbers. The restrictions on prior use of medicines and concurrent therapy during the course of the study were consistent with those described previously for Study P165.

The 250 mg dose of aprepitant was achieved using two x 125 mg capsules and the products were supplied by the sponsor. The investigator was responsible for supplying dexamethasone 4 mg tablets and midazolam oral syrup (2 mg/mL). The investigator was required to obtain supplies of dexamethasone and midazolam syrup from a single lot for each product with a single expiration date for each product that was acceptable for use throughout the duration of the study.

Table 7: Study 155. Treatment allocation.

Part of Study	No. of Subjects	Treatment Period		Allocation Numbers
		1	2	
1	6	A	B	0002, 0003, 0005, 0008, 0009, 0010
	6	B	A	0001, 0004, 0006, 0007, 0011, 0012
2	13	C	D	0013, 0015, 0018, 0020, 0022, 0024, 0025, 0027, 0030, 0031, 0034, 0035, 0037
	13	D	C	0014, 0016, 0017, 0019, 0021, 0023, 0026, 0028, 0029, 0032, 0033, 0036, 0038
3	6	E	F	0039, 0042, 0043, 0044, 0047, 0050
	6	F	E	0040, 0041, 0045, 0046, 0048, 0049

See above for identification of treatments A, B, C, D, E and F.

Primary Response Parameters

The primary variables of interest were the dexamethasone $AUC_{0\text{-}24h}$ and C_{max} on Days 1, 2 and 3 in Part 1, and the midazolam $AUC_{0\text{-}\infty}$ and C_{max} on Day 1 and Day 8 in Part 2, with and without the co-administration of a single 250 mg oral dose of aprepitant.

Pharmacokinetic Assessments

Blood sampling times for plasma dexamethasone assay in Part 1 of the study were as follows: Day 1: Pre dose (within -1 hr), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hr post dose; Day 2: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hr post dose; and Day 3: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hr post dose. Plasma dexamethasone concentrations were analysed using liquid-liquid extraction for analyte isolation followed by hydrophilic interaction liquid chromatography coupled with tandem mass spectrometric detection. The LLOQ for dexamethasone in plasma was 0.500 ng/mL and the linear calibration range was 0.500 to 500 ng/mL.

Blood sampling times for plasma midazolam assay in Part 2 of the study were as follows: Day 1: Pre dose (within -1 hr), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hr post dose; and Day 8: Pre dose (within -1 hr), 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 18 and 24 hr post dose. Plasma midazolam concentrations were analysed using liquid-liquid extraction for analyte isolation followed by hydrophilic interaction liquid chromatography coupled with tandem mass spectrometric detection. The LLOQ for midazolam in plasma was 0.100 ng/mL and the linear calibration range was 0.100 to 100 ng/mL.

Blood sampling times for plasma aprepitant (Treatment B in Part 1, Treatment D in Part 2 and Treatments E and F in Part 3) were as follows: Day 1: Pre dose (within -1 hr), 0.5, 1, 1.5, 2, 3, 4,

6, 8, 12, 18, 24, 48 and 72 hr post dose. Plasma aprepitant concentrations were analysed using liquid-liquid extraction for analyte isolation followed by HPLC using a reverse phase column and detected with tandem mass spectrometric detection employing a heater nebulizer (HN) interface in the positive ion mode. The LLOQ for aprepitant in plasma was 10 ng/mL and the linear calibration range was 10.0 to 2500 ng/mL.

Plasma dexamethasone, midazolam and aprepitant concentrations from the bioanalytical report and actual sampling times, converted to elapsed time relative to dexamethasone dosing times, were used to determine the plasma PK parameters (for example, $AUC_{0\text{-}24h}$, $AUC_{0\text{-}\infty}$, C_{max}, and apparent terminal $t_{½}$), with the exception of $T_{max.}$ Values below the plasma assay limit of quantification were replaced with zero. $AUC_{0\text{-}24h}$ or $AUC_{0\text{-}\infty}$ values were determined using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations. C_{max} and T_{max} were obtained by inspection of the plasma concentration data. Provided that the actual observed time of T_{max} did not differ in a meaningful way from the nominal plasma sampling time, nominal plasma sampling times were used to determine T_{max}. The apparent terminal rate constant (λ) was estimated by regression of the terminal log-linear portion of the plasma concentration-time profile (using quantifiable concentrations only); $t_{½}$ was calculated as the quotient of ln(2) and λ.

Statistical Analysis and Sample Size

Part 1 (Dexamethasone PKs)

Dexamethasone $AUC_{0\text{-}24h}$ and C_{max} on Days 1, 2 and 3 with or without aprepitant were estimated using a linear mixed-effects model with fixed effects terms of sequence, period, day (1, 2, 3), treatment and treatment by day interaction, and a random effect term of subject within sequence. An Ln-transformation was applied to the $AUC_{0\text{-}24h}$ and C_{max}. The 90% CI and estimates for the true GMRs for dexamethasone $AUC_{0\text{-}24h}$ and C_{max} (dexamethasone + aprepitant/ dexamethasone alone) were provided.

The precision of the estimates of the dexamethasone $AUC_{0\text{-}24hr}$ and C_{max} GMRs can be assessed by calculating the half-width of the 90% CIs expected for the given sample size and assumed variability. The variance estimates for dexamethasone $AUC_{0\text{-}24h}$ and C_{max} were obtained from Study P041. Assuming a true within-subject standard deviation of 0.1381for ln-$AUC_{0\text{-}24h}$, then with n = 12 subjects the half-width of the 90% CI for the $AUC_{0\text{-}24h}$ difference (dexamethasone + aprepitant minus dexamethasone alone) on the log scale will be 0.102. The lower and upper bound 90% CI for the true AUC GMR (dexamethasone + aprepitant/dexamethasone alone) on any given day will be given by OBS/1.108 and OBSx1.108, where OBS is the observed GMR. For example, if the observed GMR for the $AUC_{0\text{-}24h}$ was 1.0 then the 90% CI would be 0.90 to 1.11.

Similarly, assuming a true within-subject standard deviation of 0.2236 for ln-C_{max}, then with n=12 subjects, the half-width of the 90% CI for the C_{max} difference (dexamethasone + aprepitant minus dexamethasone alone) on the log scale will be 0.165. The lower and upper bound 90% CI for the true C_{max} GMR (dexamethasone + aprepitant/ dexamethasone alone) will be given by OBS/1.179 and OBSx1.179, where OBS is the observed GMR. For example, if the observed GMR for the C_{max} was 1.0 then the 90% CI would be 0.85 to 1.18.

Part 2 (Midazolam PKs)

The effect of a single dose of 250 mg aprepitant on midazolam $AUC_{0\text{-}\infty}$ and C_{max} was evaluated using a linear mixed-effects model with fixed effects terms of sequence, period, day (1, 8), treatment and treatment by day interaction, and a random effect term of subject within sequence. An Ln-transformation was applied to the $AUC_{0\text{-}\infty}$ and C_{max}. Two-sided 90% CIs for the true GMR for the $AUC_{0\text{-}\infty}$ (midazolam + aprepitant / midazolam alone) were calculated. If the upper bound of the 90% CI of the GMR for midazolam $AUC_{0\text{-}\infty}$ on Day 1 was no greater than 5.0, then the primary hypothesis would be supported.

Assuming a true within-subject standard deviation of 0.3115 for ln-$AUC_{0-\infty}$, then with n = 26 subjects, the half-width of the 90% CI for the $AUC_{0-\infty}$ difference (midazolam + aprepitant minus midazolam alone) on the log scale will be 0.1478. The lower and upper bound 90% CI for the true $AUC_{0-\infty}$ GMR (midazolam + aprepitant / midazolam alone) on Day 8 will be given by OBS/1.159 and OBSx1.159, where OBS is the observed GMR. For example, if the observed GMR for $AUC_{0-\infty}$ was 1.0, then the 90% CI would be 0.86 to 1.16.

Part 3 (Food effect on aprepitant)

The food effect on the PKs of aprepitant were assessed by evaluating Ln-transformed $AUC_{0-\infty}$ values using a mixed effects linear model containing fixed effect factors for period, sequence, and treatment, and subject within sequence as a random effect. Two-sided 90% CIs for the true GMR for the AUC (fed / fasted) were calculated. C_{max} was analysed in similar fashion.

The precision of the estimates of the aprepitant $AUC_{0-\infty}$ and C_{max} GMRs (with food/without food) can be assessed by calculating the half-width of the 90% CIs expected for the given sample size and assumed variability. The variance estimates for aprepitant $AUC_{0-\infty}$ and C_{max} were obtained from the pooled data across panels in Study P057. Assuming a true within-subject standard deviation of 0.3063 for ln-$AUC_{0-\infty}$, then with n = 12 subjects, the half-width of the 90% CI for the AUC_{0-24h} difference (with food – without food) on the log scale will be 0.2266. The lower and upper 90% CIs for the true GMR of the AUC (with food/without food) will be given by OBS/1.25 and OBSx1.25, where OBS is the observed GMR. For example, if the observed GMR for AUC_{0-24h} was 1.0, then the 90% CI would be 0.80 to 1.25.

Similarly, assuming a true within-subject standard deviation of 0.3109 for ln-C_{max}, then with n=12 subjects, the half-width of the 90% CI for the C_{max} difference (with food – without food) on the log scale will be 0.23. The lower and upper bound 90% CI for the true GMR for the C_{max} (with food/without food) will be given by OBS/1.26 and OBSx1.26, where OBS is the observed GMR. For example, if the observed GMR for C_{max} was 1.0, then the 90% CI would be 0.79 to 1.26.

> *Comment*: The statistical methods and sample size calculations were acceptable and represent well recognised approaches for studies of this type. However, no pre specified hypotheses were stated for Part 1 or Part 3 of the study (that is, no hypotheses [null, alternative] defining a significant effect of aprepitant on the PKs of dexamethasone and no hypotheses [null, alternative] defining a significant food effect on the PKs of aprepitant). No multiplicity adjustments were made since there was only one formal testable hypothesis.

Subjects

The study enrolled a total of 50 subjects: 12 (8 males and 4 females) in Part 1; 26 (20 males and 6 females) in Part 2; and 12 (8 males and 4 females) in Part 3. Of the 50 enrolled subjects, 46 completed the study as planned. The 4 subjects who discontinued prematurely all came from Part 2 of the study: one female discontinued after completing Treatment C due to a clinical adverse experience of back/flank pain, kidney stone occurring on Day 8, which prevented her from completing each of the protocol specified post dose PK blood samples; one male subject withdrew consent and discontinued for personal reasons after completing only Treatment C; one female withdrew consent and discontinued for personal reasons after completing both Treatments C and D; one female withdrew consent and discontinued for personal reasons after completing only Treatment C in Period 1. The 4 discontinued subjects were not replaced because as Part 2 of the study was adequately powered to meet the study objectives without replacement. In each part of the study, all subjects with at least 1 period of valid PK data were included in the PK evaluation. No major protocol deviations occurred during the study.

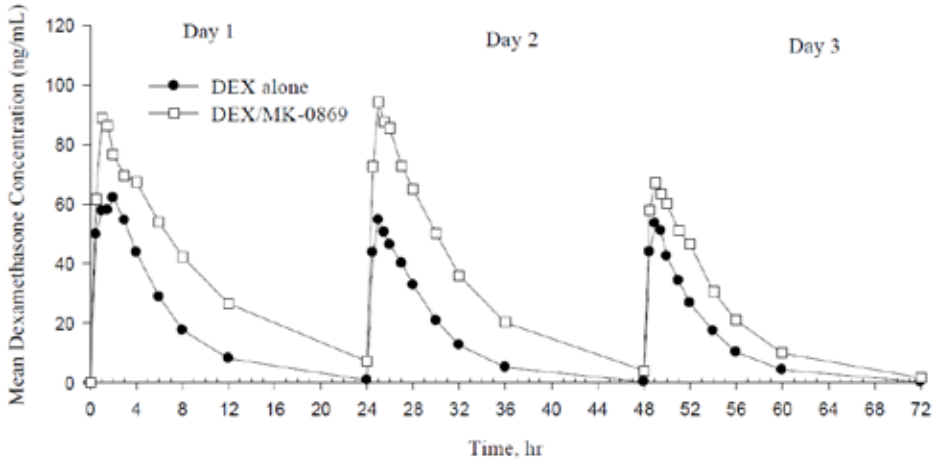
Of the 50 enrolled subjects, 31 (62%) reported secondary diagnoses. None of the pre existing conditions prevented participation in the study. Of the 50 enrolled subjects, 5 (10%) reported the use of prior drug therapy within 14 days prior to the start of the study and 7 (14%) took

medication other than test drugs (protocol specified study drugs) during the study. Neither prior, nor concomitant therapies were considered likely to have affected the PK and safely evaluations. Paracetamol generally taken for headache was the most commonly used prior and/or concomitant medication.

Pharmacokinetic Results Part 1. Aprepitant/Dexamethasone Interaction

Mean plasma dexamethasone concentrations following study drug administration on Days 1, 2 and 3 are shown below in Figure 7.

Figure 7: Study 155. Dexamethasone plasma concentration – time curves (linear scale).



Note: Oral dexamethasone 8 mg administered on Day 1, 2 and 3 (alone or co-administered with oral aprepitant 250 mg on Day 1).

The statistical summary of dexamethasone PK parameters ($AUC_{0\text{-}24h}$, C_{max}, T_{max}, and $t_{1/2}$) following administration oral dexamethasone 8 mg alone or co-administered with oral aprepitant 250 mg are summarised below in Table 8.

Table 8: Study 155. Dexamethasone PK parameters.

Pharmacokinetic Parameter	Day	Dexamethasone with Aprepitant		Dexamethasone Alone		(Dexamethasone + Aprepitant / Dexamethasone Alone)		
		Geometric Mean [‡]	95% CI for Geometric Mean	Geometric Mean [‡]	95% CI for Geometric Mean	Geometric Mean Ratio	90% CI for Geometric Mean Ratio	rMSE [†]
$AUC_{0\text{-}24hr}$ (ng•hr/mL)	1	794	(682, 924)	405	(348, 472)	1.96	(1.83, 2.10)	0.103
	2	698	(599, 812)	305	(262, 355)	2.29	(2.13, 2.45)	
	3	435	(374, 507)	270	(232, 315)	1.61	(1.50, 1.73)	
C_{max} (ng/mL)	1	104	(90, 119)	89	(77, 102)	1.16	(1.01, 1.34)	0.210
	2	102	(89, 118)	63	(55, 72)	1.63	(1.41, 1.88)	
	3	78	(68, 89)	63	(54, 72)	1.24	(1.07, 1.43)	
T_{max} (hr) [§]	1	1.00	(0.50 , 3.00)	1.33	(0.50 , 3.00)			
	2	1.00	(0.50 , 2.00)	1.00	(0.50 , 4.00)			
	3	1.00	(0.50 , 4.00)	1.00	(0.50 , 3.00)			
$t_{1/2}$ (hr) [#]	1	5.95	1.05	3.35	0.84			
	2	4.53	0.90	3.00	0.63			
	3	3.74	1.02	3.13	0.76			

[†] Root Mean square error on log-scale.
[‡] Geometric mean computed from a linear mixed-effects model performed on the natural-log transformed values.
[§] Median (minimum, maximum) reported for T_{max}.
[#] Harmonic mean and pseudo SD reported for apparent $t_{1/2}$.
CI = Confidence Interval.

Comment: Co-administration of dexamethasone 8 mg and aprepitant 250 mg on Day 1 increased exposure to dexamethasone on Days 1, 2 and 3. Increases in dexamethasone $AUC_{0\text{-}24h}$ were approximately 96%, 129% and 61% higher on Days 1, 2 and 3, respectively, when dexamethasone was co-administered with aprepitant compared with when dexamethasone was administered alone. The corresponding increases in dexamethasone C_{max} were approximately 16%, 63%, 24% on Days 1, 2 and 3, and all increases in C_{max} were smaller in magnitude than increases in $AUC_{0\text{-}24h}$. The 90% CI for the GMR of both $AUC_{0\text{-}24h}$ and C_{max} on Days 1, 2 and 3 were outside the standard

bioequivalence range of 0.80 to 1.25. The results indicate that a single oral dose of aprepitant 250 mg administered in the fasting state inhibits CYP3A4 metabolism of dexamethasone. The single oral dose of aprepitant (250 mg) administered in this study was greater than that being proposed for approval (165 mg) and the dexamethasone dose used in this study was lower than that being proposed for co-administration with single dose aprepitant.

Pharmacokinetic Results Part 2. Aprepitant/Midazolam Interaction

Mean plasma midazolam concentrations following study drug administration on Days 1 and 8 are shown below in Figures 8 and 9, respectively.

Figure 8: Study 155 Plasma midazolam Day 1 (n=26). 11

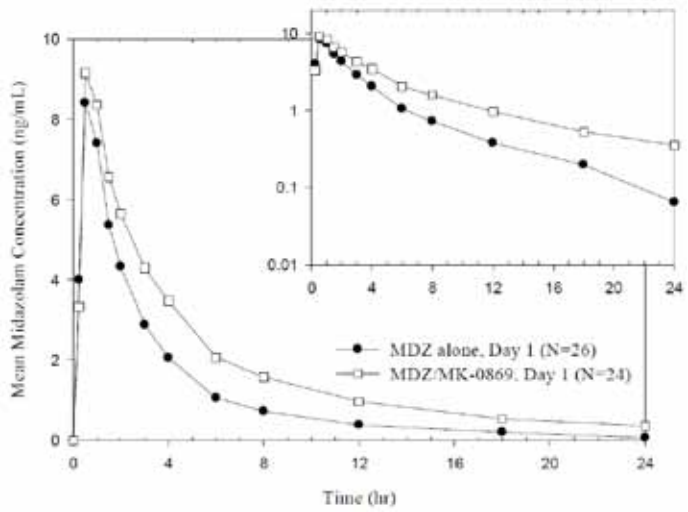
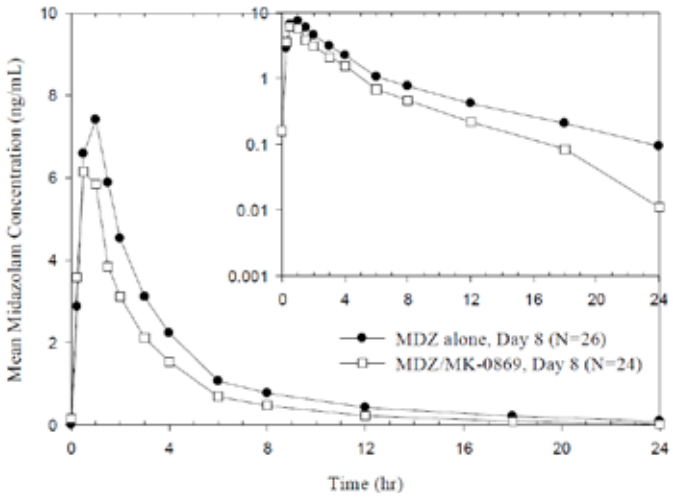


Figure 9: Study 155 Plasma midazolam Day 8 (n=26).



Midazolam PK parameters ($AUC_{0-\infty}$, C_{max}, T_{max}, and $t_{1/2}$) on Days 1 and 8 following Treatments C and D are summarised below in Table 9.

Table 9: Study P155 . Midazolam PK parameters, with and without co-administration of aprepitant.

Pharmacokinetic Parameter	Day	Midazolam with Aprepitant (N=24)		Midazolam Alone (N=26)		(Midazolam + Aprepitant / Midazolam Alone)		
		Geometric Mean ‡	95% CI for Geometric Mean	Geometric Mean ‡	95% CI for Geometric Mean	Geometric Mean Ratio	90% CI for Geometric Mean Ratio	r MSE †
$AUC_{0-\infty}$ (ng•hr/mL)	1	38.7	(33.5, 44.7)	23.7	(20.6, 27.4)	1.63	(1.50, 1.77)	0.173
	8	16.6	(14.4, 19.2)	24.1	(20.9, 27.8)	0.69	(0.63, 0.75)	
C_{max} (ng/mL)	1	9.5	(8.4, 10.8)	9.0	(8.0, 10.2)	1.06	(0.94, 1.18)	0.235
	8	6.6	(5.8, 7.5)	8.3	(7.3, 9.4)	0.80	(0.72, 0.89)	
T_{max} (hr) ♯	1	0.500	(0.25 , 1.50)	0.500	(0.25 , 1.00)			
	8	0.500	(0.25 , 1.00)	0.780	(0.50 , 1.50)			
$t_{1/2}$ (hr) #	1	6.53	2.68	3.96	2.19			
	8	3.53	1.96	3.79	2.49			

† Root Mean square error on log-scale.
‡ Geometric mean computed from a linear mixed-effects model performed on the natural-log transformed values.
♯ Median (minimum, maximum) reported for T_{max}.
# Harmonic mean and pseudo SD reported for apparent $t_{1/2}$.
CI = Confidence Interval.

Note: Single 2 mg oral daily dose of midazolam alone on Days 1 and 8; and single 2 mg oral daily dose of midazolam on Days 1 and 8, co-administered with a single 250 mg oral dose of aprepitant on Day 1.

Comment: On Day 1, the GMR (midazolam + aprepitant / midazolam alone) for the $AUC_{0-\infty}$ was less than 5 as was the upper bound 90% CI of the GMR. These results support the primary hypothesis that a single oral fasting dose of aprepitant 250 mg is not a potent inhibitor of CYP3A4 and suggest that the drug is a weak inhibitor of CYP3A4 activity (≤ 2 fold increase in $AUC_{0-\infty}$) when administered in the fasting state. Co-administration of midazolam and aprepitant on Day 1 increased midazolam $AUC_{0-\infty}$ and C_{max} by 63% and 6%, respectively, relative to midazolam alone. On Day 8, the midazolam $AUC_{0-\infty}$ and C_{max} GMRs (midazolam + aprepitant / midazolam alone) suggest that the single oral fasting dose of aprepitant 250 mg administered on Day 1 induced CYP3A4 formation resulting in increased metabolism of midazolam reflected by reductions of 31% and 20% in midazolam $AUC_{0-\infty}$ and C_{max}, respectively. The study report notes that "while there is no current classification system for qualifying the degree of CYP3A4 induction" the degree of induction observed on Day 8 can be described as modest and is unlikely to be of any clinical significance.

Pharmacokinetic Results Part 3. Food Effect

The effects of food (light standard breakfast) on the single dose PKs of oral aprepitant 250 mg are summarised below in Table 10.

Table 10: Study P155. Effect of food on the PK parameters of oral aprepitant 250 mg.

	Fed State		Fasted State		(Fed / Fasted)		
Pharmacokinetic Parameter	Geometric Mean ‡	95% CI for Geometric Mean	Geometric Mean ‡	95% CI for Geometric Mean	Geometric Mean Ratio	90% CI for Geometric Mean Ratio	rMSE †
$AUC_{0-\infty}$ (ng•hr/mL)	102643	(84030, 125379)	47383	(38790, 57878)	2.17	(1.73, 2.71)	0.301
C_{max} (ng/mL)	3156	(2483, 4012)	1973	(1552, 2509)	1.60	(1.26, 2.02)	0.319
T_{max} (hr) ♦	6.00	(4.00 , 18.00)	3.00	(1.50 , 4.00)	.		.
$t_{1/2}$ (hr) *	15.13	8.05	12.78	4.30	.		.

† Root Mean square error on log-scale.
‡ Geometric mean computed from a linear mixed-effects model performed on the natural-log transformed values.
♦ Median (minimum, maximum) reported for T_{max}.
* Harmonic mean and pseudo SD reported for apparent $t_{1/2}$.
CI = Confidence Interval.

Comment: Food had a significant effect on the PKs of aprepitant following a single oral dose of aprepitant 250 mg. The aprepitant $AUC_{0-\infty}$ increased by 117% and the C_{max} by 60% when aprepitant 125 mg was administered with a standard light breakfast compared with fasting administration. This result suggests that increased exposure to dexamethasone (Days 1, 2, 3) observed in Part 1 and increased exposure to midazolam (Day 1) observed in Part 2 of this study when the drugs were co-administered with oral aprepitant 250 mg in the fasted state could be significantly higher if co-administered with oral aprepitant in the fed state. In addition, increased exposure to aprepitant in the fed state might increase the effect of the drug on CYP3A4 induction resulting in further reductions in exposure to midazolam to those observed on Day 8 of Part 2 of the study.

Study P175. Aprepitant (fed state) Interaction with CYP3A4 Substrates

Objectives

The *primary objective* had three parts: (1) to evaluate the effect of single dose oral aprepitant (200 mg, 250 mg and 375 mg) administered in the fed state on Day 1 on CYP3A4 activity in healthy young adult subjects as assessed by the PKs of dexamethasone following oral administration of 12/8/8/8 mg over Days 1/2/3/4, respectively, in Part 1; (2) to evaluate the effect of single dose oral aprepitant (200 mg, 250 mg and 375 mg) administered in the fed state on Day 1 on CYP3A4 activity in healthy young adult subjects as assessed by the PKs of midazolam following oral administration of 2 mg on Days 1, 4 and 8 in Part 2; and (3) to assess the plasma aprepitant concentration profiles following single dose oral aprepitant (200 mg, 250

mg and 375 mg) administered in the fed state on Day 1 in healthy young adult subjects when co-administered with oral dexamethasone 12/8/8/8 mg over Days 1/2/3/4, respectively, in Part 1 and when co-administered with oral midazolam 2 mg on Days 1, 4 and 8 in Part 2.

The secondary objective had two parts: (1) to assess the safety and tolerability of single dose daily oral administration of dexamethasone 12/8/8/8 mg over Days 1/2/3/4, respectively, with single dose oral administration of aprepitant (200 mg, 250 mg and 375 mg) in the fed state on Day 1 in healthy young adult subjects in Part 1; and (2) to assess the safety and tolerability of single dose daily oral administration of midazolam 2 mg on Days 1, 4 and 8 with single dose oral administration of aprepitant (200 mg, 250 mg and 375 mg) in the fed state on Day 1 in healthy young adult subjects in Part 2.

Ethics

The protocol and informed consent form were reviewed and approved by the relevant IRB. The study was conducted in accordance with GCP and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent and the protection of human subjects participating in biomedical research.

Study Site and Study Dates

The study was a single-centre study undertaken at Buffalo, New York, USA. The study was initiated on 31 March 2009 and completed on 2 July 2009. The frozen file date was 23 March 2010.

Hypothesis and Estimation

Hypothesis: Part 2: A single oral dose of aprepitant (200 mg, 250 mg or 375 mg) in the fed state is not a potent inhibitor of CYP3A4 metabolism when co administered with a single oral dose of midazolam (2 mg) on Day 1 (the true GMR [with/without aprepitant] for the midazolam $AUC_{0-\infty}$ on Day 1 is <5.0)

Estimations: Part 1: The GMR (with /without aprepitant) of dexamethasone AUC_{0-24h} on each of Days 1, 2, 3, and 4 following administration of a single 12 mg oral dose of dexamethasone on Day 1, and single 8 mg oral daily doses of dexamethasone on Days 2, 3, and 4 with a single oral dose of aprepitant (200 mg, 250 mg, and 375 mg) in the fed state on Day 1 will be estimated; *Part 2:* The GMR (with /without aprepitant) of oral midazolam $AUC_{0-\infty}$ on Day 4 and on Day 8 following administration of 2 mg oral daily doses of midazolam on Days 1, 4 and 8 with a single oral dose of aprepitant (200 mg, 250 mg, and 375 mg) in the fed state on Day 1 will be estimated.

Design

This was a Phase I, 2-part, open label, randomised, 2-period, crossover, single centre study consisting of 8 study drug treatments (A, B, C, and D in Part 1 of the study, and E, F, G, and H in Part 2 of the study). The study evaluated the effect of single dose oral administration of aprepitant doses (200 mg, 250 mg, and 375 mg) in the fed state on the PKs of oral dexamethasone in Part 1, and on the PKs of oral midazolam in Part 2. Subjects participated in only one part of the study.

The intended study population of 60 healthy young adult male and female subjects were to be divided equally into Part 1 and Part 2. In Part 1, each subject was randomised to receive 1 of 3 different treatments (A and B, or A and C, or A and D) in each study period. In Part 2, each subject was randomised to receive 1 of 3 different treatments (E and F, or E and G, or E and H) in each study period. The 8 open label study drug treatments were:

Treatment A: Single 12 mg oral dose of dexamethasone on Day 1 and single 8 mg oral daily doses of dexamethasone on Days 2, 3 and 4.

Treatment B: Single 12 mg oral dose of dexamethasone on Day 1 and single 8 mg oral daily doses of dexamethasone on Days 2, 3 and 4 co-administered 30 minutes after a single 200 mg oral dose of aprepitant in the fed state on Day 1.

Treatment C: Single 12 mg oral dose of dexamethasone on Day 1 and single 8 mg oral daily doses of dexamethasone on Days 2, 3 and 4, co-administered 30 minutes after a single 250 mg oral dose of aprepitant in the fed state on Day 1.

Treatment D: Single 12 mg oral dose of dexamethasone on Day 1 and single 8 mg oral daily doses of dexamethasone on Days 2, 3 and 4, co-administered 30 minutes after a single 375 mg oral dose of aprepitant in the fed state on Day 1.

Treatment E: Single 2 mg oral daily dose of midazolam alone on Days 1, 4 and 8.

Treatment F: Single 2 mg oral daily dose of midazolam on Days 1, 4 and 8 co-administered 1 hr after a single 200 mg oral dose of aprepitant in the fed state on Day 1.

Treatment G: Single 2 mg oral daily dose of midazolam on Days 1, 4 and 8 co-administered 1 hr after a single 250 mg oral dose of aprepitant in the fed state on Day 1.

Treatment H: Single 2 mg oral daily dose of midazolam on Days 1, 4 and 8 co-administered 1 hr after a single 375 mg oral dose of aprepitant in the fed state on Day 1.

All doses of study drug were administered at the clinical research unit (CRU) and witnessed by the investigator and/or his staff. There was a minimum 14 day washout between dosing of study drug in each treatment period. In Part 1, subjects reported to the CRU in the evening prior to dosing on Day 1 and fasted overnight for a minimum of 8 hrs before consuming a standard light breakfast in the morning prior to dosing of study drugs on Days 1, 2, 3, and 4. In Part 2, subjects reported to the CRU in the evening prior to dosing on Day 1, in the evening prior to dosing on Day 4 and in the evening prior to dosing on Day 8, and fasted overnight for a minimum of 8 hrs before consuming a standard light breakfast in the morning prior to dosing of study drugs on Days 1, 4, and 8. The standard light breakfast consisted of the following (items of similar calorie content could be substituted): 1 cup of unsweetened cereal with ½ cup of skim milk; 2 slices of buttered toast with grape jelly; and 1 to 2 cups of decaffeinated coffee with half and half, with no more than 2 teaspoons (tsps) of sugar.

Complete physical examination (including vital signs), 12-lead ECGs and laboratory safety tests (haematology, blood chemistry, and urinalysis) were conducted pre study and post study. In each treatment period in Part 1, vital signs were measured at pre dose, at 4 and 24 hrs post dose on Day 1 and at 24 hrs post dose on Days 2, 3 and 4. In each treatment period in Part 2, vital signs were measured at pre dose, at 4 and 24 hrs post dose on Day 1 and at pre dose and at 24 hrs post dose on Days 4 and 8. Adverse experiences were monitored throughout the course of the study.

Inclusion and Exclusion Criteria

The study population included healthy male and female subjects between 18 and 45 years of age, with subjects up to 55 years being enrolled with the prior approval of the sponsor. The inclusion and exclusion were identical to those previously described for Study P155, as were the discontinuation criteria.

Treatments

There were 8 open label study drug treatments (A, B, C, and D in Part 1; and E, F, G, and H in Part 2) and these have been are outlined above under *Design*. Each subject participated in only Part 1 (dexamethasone interaction) or Part 2 (midazolam interaction). Subjects were randomised to the treatment sequences using a computer generated allocation schedule (see Table 11 below). The restrictions on prior use of medicines and concurrent therapy during the course of the study were consistent with those described previously for Studies P165 and P155.

The aprepitant 200 mg dose consisted of 2 x 80 mg plus 1 x 40 mg capsules, the 250 mg dose consisted of 2 x 125 mg capsules and the 375 mg dose consisted of 3 x 125 mg capsules. The aprepitant capsules were supplied by the sponsor. The investigator was responsible for supplying dexamethasone 4 mg tablets and midazolam oral syrup 2 mg/mL. The investigator was required to obtain supplies of dexamethasone and midazolam syrup from a single lot for each product with a single expiration date for each product that was acceptable for use throughout the length of the study.

Table 11: Study 175. Allocation of subjects to treatment.

Part of Study	No. of Subjects	Treatment Period		Allocation Numbers
		1	2	
1	5	A	B	0005; 0010; 0018; 0024; 0025
	5	B	A	0006; 0011; 0015; 0021; 0029
	5	A	C	0004; 0012; 0013; 0022; 0028
	5	C	A	0002; 0008; 0016; 0023; 0027
	5	A	D	0003; 0007; 0017; 0019; 0030
	5	D	A	0001; 0009; 0014; 0020; 0026
	30			
2	5	E	F	0034; 0040; 0045; 0053; 0060
	5	F	E	0036; 0041; 0047; 0052; 0057
	5	E	G	0032; 0042; 0044; 0051; 0055
	5	G	E	0035; 0037; 0048; 0049; 0056
	5	E	H	0031; 0038; 0043; 0050; 0059
	5	H	E	0033; 0039; 0046; 0054; 0058
	30			

Primary Pharmacokinetic Parameters of Interest

The primary PK parameters of interest in the study were the dexamethasone $AUC_{0\text{-}24h}$ and C_{max} on Days 1, 2, 3, and 4 in Part 1 and the midazolam $AUC_{0\text{-}\infty}$ and C_{max} on Days 1, 4, and 8 in Part 2, with and without the co-administration of aprepitant single oral doses (200 mg, 250 mg, and 375 mg) in the fed state (standard light breakfast) on Day 1.

> *Comment*: For the purposes of the current submission the pivotal PK parameters relate to the interaction data for the single oral aprepitant dose of 200 mg. The 200 mg dose is closest in strength to the 165 mg dose being proposed for approval.

Pharmacokinetic Assessments

In both parts of the study, blood for plasma drug assay was collected for up to 24 hrs post dose in each treatment period for dexamethasone (daily for 4 days) and midazolam (on Days 1, 4, and 8), respectively, and up to 96 hrs post dose for aprepitant.

The bioanalytical methods for measuring plasma concentrations of dexamethasone, midazolam and aprepitant were identical to those described previously for Study P155, as were the methods used to calculate the PK parameters.

Statistical Analysis and Sample Size

Primary Hypothesis Testing

Midazolam PK Interaction Part 2

The effect of single oral aprepitant doses (200 mg, 250 mg and 375 mg) in the fed state on Day 1 on midazolam $AUC_{0\text{-}\infty}$ was evaluated using a linear mixed-effects (LME) model with fixed effects terms of square, sequence within square, period, day, treatment and treatment by day interaction, and a random effect term of subject within sequence within square. The covariance structure of compound symmetry was used for this model. A log transformation was applied to $AUC_{0\text{-}\infty}$.

The primary hypothesis that the GMR of midazolam $AUC_{0-\infty}$ (with/without aprepitant) on Day 1 is < 5.00 was tested using the following stepwise procedure. At the lowest dose (200 mg), a two-sided 90% CI for the true mean difference (midazolam + aprepitant versus midazolam alone) in midazolam $AUC_{0-\infty}$ in the log scale was calculated for Day 1 using the LME model described above. This CI was then exponentiated to obtain a CI for the true GMR for midazolam $AUC_{0-\infty}$ (midazolam + aprepitant / midazolam alone). If the upper limit of the 90% CI of the GMR on Day 1 was not greater than 5.00 then it would be claimed that a single oral dose of 200 mg aprepitant in the fed state is not a potent inhibitor of CYP3A4 metabolism when co-administered with a single oral 2 mg dose of midazolam on Day 1 and the testing procedure continued to the next higher dose (250 mg). The procedure continues in this stepwise fashion until the upper bound of the 90% CI of GMR on Day 1 at a particular dose exceeds 5.00. For estimation purposes, 90% CIs were constructed for all doses and at all days.

Dexamethasone PKs (Estimation); Part 1

The same LME model as specified above for Part 2 was also used to Part 1. A two-sided 90% CI for the true mean difference (dexamethasone + aprepitant versus dexamethasone alone) in dexamethasone AUC_{0-24h} in the log scale was calculated for Days 1, 2, 3, and 4, respectively. These CIs were then exponentiated to obtain a CI for the true GMR for dexamethasone AUC_{0-24h} (dexamethasone + aprepitant/ dexamethasone alone). C_{max} of dexamethasone on Days 1 to 4 was analysed in a similar fashion as for AUC. Summary statistics were provided for other pharmacokinetic parameters (T_{max} and apparent terminal $t_{1/2}$).

Midazolam PKs (Estimation); Part 2

Similar analyses were conducted for Part 2 as those for Part 1 for both midazolam $AUC_{0-\infty}$ Days 4 and 8) and C_{max} (Days 1, 4 and 8). C_{max} of midazolam on Days 1, 4 and 8 was analysed in a similar fashion as for AUC. Summary statistics were provided for other pharmacokinetic parameters (T_{max} and apparent terminal $t_{1/2}$).

Power

Primary Hypothesis (Part 2); Midazolam

The midazolam $AUC_{0-\infty}$ variance estimate used in the calculations was obtained from Study P155. Assuming a within-subject standard deviation of 0.174 for ln-$AUC_{0-\infty}$, then with n = 10 subjects, there is at least 99% probability that the hypothesis will be supported that the true GMR (midazolam + aprepitant / midazolam alone) is less than 5.00. [that is, the upper bound 90% CI of the GMR is less than 5.00], given that the true ratio is 1.00. The true GMR can be as high as 4.00 and still have at least 80% power to support the hypothesis.

Estimation (Part 1); Dexamethasone:

Assuming a within-subject standard deviation of 0.109 for dexamethasone ln-AUC_{0-24h}, then with n = 10 subjects, the half-width of the 90% CI for the AUC_{0-24h} difference (dexamethasone + aprepitant minus dexamethasone alone) on the log scale will be 0.091. The lower and upper bound 90% CI for the true AUC GMR (dexamethasone + aprepitant /dexamethasone alone) on any given day will be given by OBS/1.10 and OBSx1.10, where OBS is the observed GMR. For example, if the observed AUC_{0-24h} GMR was 1.00 then the 90% CI would be 0.91 to 1.10.

Estimation (Part 2); Midazolam

With n = 10 subjects, the half-width of the 90% CI for the ln- $AUC_{0-\infty}$ difference (midazolam + aprepitant minus midazolam alone) on the log scale will be 0.145. The lower and upper bound 90% CI for the true $AUC_{0-\infty}$ GMR (midazolam + aprepitant / midazolam alone) will be given by OBS/1.156 and OBSx1.156, where OBS is the observed GMR. For example, if the observed C_{max} GMR was 1.00 then the 90% CI would be 0.86 to 1.16.

Comment: The statistical methods and sample size calculations were acceptable and represent well recognised approaches for studies of this type. A closed stepwise testing procedure was employed to control the overall Type I error rate at 0.05 across the comparisons at the multiple dose levels when testing the primary hypothesis.

Subjects; Demographics and Other Characteristics

The study enrolled a total of 62 subjects: 32 (20 males and 12 females) in Part 1 and 30 (16 males and 14 females) in Part 2. Of these 62 subjects, 59 (30 in Part 1 and 29 in Part 2) completed the study as planned and 3 discontinued prematurely. Of the 3 subjects discontinuing prematurely, 1 female in Part 1 withdrew consent, 1 female in Part 1 withdrew due to clinical adverse experiences (maculopapular rash, pruritus and fungal skin infection) and 1 female in Part 2 withdrew consent and discontinued. Both subjects withdrawing in Part 1 were replaced and both replacements completed the study as planned. The subject withdrawing in Part 2 was not replaced as it was determined that this part of the study was adequately powered to meet the study objectives without replacement. No major protocol deviations occurred during the study. All available date from the 62 subjects enrolled in the study was used in PK and safety analyses.

Of the 62 enrolled subjects, 32 (52%) reported secondary diagnoses as part of their medical history. However, none of these conditions prevented participation of any of the subjects in the study. Of the 62 enrolled subjects, 5 (8%) reported use of therapy within 14 days prior to the start of treatment and 20 (32%) took medication other than test drugs (protocol-specified study drugs) during the study. The most commonly used drugs during the study period were antacids for heartburn and paracetamol for headache. Neither prior nor concomitant therapies were considered to be clinically significant as regards interpretation of the PK and safety results.

Results for Primary Hypothesis; Midazolam PK Interaction Day 1 Part 2

The midazolam PK parameter values on Day 1 following administration of a single 2 mg oral dose of midazolam with and without co-administration of a single 200 mg, 250 mg and 375 mg oral dose of aprepitant in the fed state (standard light breakfast) are summarised below in Table 12.

Table 12: Study 175. Midazolam PKs (Day 1) with and without aprepitant.

Pharmacokinetic Parameter	MK-0869 Dose	Midazolam with Aprepitant			Midazolam Alone[&]			(Midazolam + Aprepitant / Midazolam Alone)		
		N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE [§]
$AUC_{0-\infty}$ (ng·hr/mL) [†]	200-mg	10	81.56	(66.74, 99.67)	30	25.93	(22.03, 30.53)	3.15	(2.76, 3.58)	0.198
	250-mg	10	85.83	(70.23, 104.89)				3.31	(2.91, 3.77)	.
	375-mg	10	91.04	(74.49, 111.25)				3.51	(3.08, 4.00)	.
AUC_{0-24hr} (ng·hr/mL) [†]	200-mg	10	74.59	(61.42, 90.59)	30	25.12	(21.46, 29.41)	2.97	(2.62, 3.37)	0.193
	250-mg	10	77.33	(63.68, 93.92)				3.08	(2.71, 3.49)	.
	375-mg	10	78.93	(65.00, 95.86)				3.14	(2.77, 3.56)	.
C_{max} (ng/mL) [†]	200-mg	10	16.25	(13.28, 19.89)	30	8.91	(7.54, 10.52)	1.83	(1.61, 2.07)	0.195
	250-mg	10	15.76	(12.87, 19.28)				1.77	(1.56, 2.01)	.
	375-mg	10	15.89	(12.98, 19.44)				1.78	(1.57, 2.03)	.
T_{max} (hr) [‡]	200-mg	10	0.75	(0.30 , 1.00)	30	0.50	(0.30 , 1.50)	.		.
	250-mg	10	0.50	(0.50 , 1.50)				.		.
	375-mg	10	0.75	(0.50 , 1.50)				.		.
Half-life (hr) [¶]	200-mg	10	6.26	2.58	30	3.84	2.18	.		.
	250-mg	10	7.12	2.63				.		.
	375-mg	10	8.18	2.74				.		.

[†] Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log-transformed values.
[§] rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. For log-transformed variables, rMSE*100% approximates the within-subject % CV on the raw scale.
[‡] Median, minimum, maximum.
[¶] Harmonic mean, jack-knife SD.
[&] Midazolam alone data (Treatment E) were pooled across 3 squares.

Comment: The most relevant results for the purposes of the current submission relate to the 200 mg dose of aprepitant co-administered with midazolam 2 mg in the fed state, as the 200 mg dose of aprepitant is closest to the 165 mg dose being proposed for approval. The GMR of the midazolam $AUC_{0-\infty}$ (midazolam + aprepitant / midazolam alone) was less than 5.00, as was the upper bound 90% CI for the ratio. Consequently, the pre specified null hypothesis has not been rejected (that is, in the fed state a single oral dose of aprepitant 200 mg is not a potent inhibitor of CYP3A4 when co-administered with a single oral dose of midazolam 2 mg on Day 1). Overall, single dose oral co-administration of aprepitant 200 mg and midazolam 2 mg on Day 1 increased the midazolam $AUC_{0-\infty}$ by approximately 3.2 fold and the midazolam C_{max} by 1.83 fold, relative to midazolam alone. There was a small dose response relationship for the three doses of aprepitant as regards the GMR but not as regards the C_{max}. The Day 1 increases in midazolam $AUC_{0-\infty}$ following co-administration with the 200 mg, 250 mg and 375 mg aprepitant doses were ~3.2, ~3.3, and ~3.5-fold, respectively. These results suggest that when administered in the fed state these three doses of aprepitant have a moderate inhibitory effect on CYP3A4 activity (that is, ≥ 2-fold to < 5-fold increase in AUC exposure).

Results Dexamethasone PKs Part 1 (Estimation)

The most relevant results relate to the co-administration of single oral dose aprepitant 200 mg on Day 1 with dexamethasone 12/8/8/8 mg on Days 1/2/3/4, respectively. The results for these analyses are summarised below in Table 13.

Table 13: Study P175. Dexamethasone $AUC_{0\text{-}24hr}$ and C_{max}, with and without aprepitant.

$AUC_{0\text{-}24hr}$

Pharmacokinetic Parameter	MK-0869 Dose	Day	Dexamethasone with Aprepitant			Dexamethasone Alone‡			(Dexamethasone + Aprepitant / Dexamethasone Alone)		
			N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE
$AUC_{0\text{-}24hr}$ (ng·hr/mL) †	200-mg	1	10	1289.77	(1117.72, 1488.29)	32	618.40	(554.04, 690.23)	2.09	(1.88, 2.31)	0.161
		2	10	724.99	(628.28, 836.58)	32	311.19	(278.80, 347.33)	2.33	(2.10, 2.58)	.
		3	10	400.47	(347.05, 462.11)	32	281.79	(252.47, 314.52)	1.42	(1.28, 1.57)	.
		4	10	310.20	(268.83, 357.95)	32	294.02	(263.43, 328.18)	1.06	(0.95, 1.17)	.

C_{max}

Pharmacokinetic Parameter	MK-0869 Dose	Day	Dexamethasone with Aprepitant			Dexamethasone Alone‡			(Dexamethasone + Aprepitant / Dexamethasone Alone)		
			N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE
C_{max} (ng/mL) †	200-mg	1	10	164.50	(141.66, 191.02)	32	134.27	(119.86, 150.43)	1.23	(1.10, 1.36)	0.168
		2	10	108.09	(93.09, 125.52)	32	65.36	(58.35, 73.23)	1.65	(1.49, 1.84)	.
		3	10	74.11	(63.82, 86.06)	32	65.19	(58.19, 73.04)	1.14	(1.02, 1.27)	.
		4	10	69.67	(59.99, 80.90)	32	66.45	(59.32, 74.44)	1.05	(0.94, 1.17)	.

† Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on Ln-transformed values.

§ rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. For log-transformed variables, rMSE*100% approximates the within-subject % CV on the raw scale.

‡ Dexamethasone alone data (Treatment A) were pooled across 3 squares.

Comment: The results indicate that a single dose of aprepitant 200 mg in the fed state co-administered with dexamethasone 12 mg on Day 1 increased dexamethasone $AUC_{0\text{-}24h}$ and C_{max} by ~2.1 and ~1.2 fold, respectively, on Day 1. The respective increases in dexamethasone $AUC_{0\text{-}24h}$ on Days 1, 2, 3, and 4 were ~2.1, ~2.3, ~1.4, and ~0.6-fold when dexamethasone was co-administered with aprepitant in the fed state relative to dexamethasone administered alone. Single dose aprepitant 200 mg in the fed state resulted in a ~2-fold increase in dexamethasone $AUC_{0\text{-}24h}$ on Days 1 and 2. Based on the results of this study, the draft PI (*Precautions*) recommends that the daily dose of dexamethasone on Days 1 and 2 should be reduced by approximately 50% when co-administered with aprepitant 165 mg on Day 1 to achieve exposures of dexamethasone similar to those when dexamethasone is given without aprepitant 165 mg. However, this recommendation is not reflected in the *Dosage and Administration* section of the draft PI. Furthermore, the recommendation is considered to relate to aprepitant 165 mg administered in the fed state rather than in the fasted state. This matter is discussed further below.

The results showed that the GMR and $AUC_{0\text{-}24h}$ C_{max} ratios (dexamethasone + aprepitant / dexamethasone) were highest on the second day of dexamethasone administration when co-administered with aprepitant 200 mg in the fed state on Day 1 and then fell on Days 3 and 4 to levels below those observed on Days 1 and 2. The higher GMR $AUC_{0\text{-}24h}$ and C_{max} values on Day 2 compared with Day 1 are likely due to a combination of an inhibitory effect on dexamethasone metabolism due to aprepitant and to carry-over of plasma dexamethasone concentrations from Day 1 to Day 2. The dexamethasone $t_{1/2}$ was 6.1 hrs on Day 1 when dexamethasone 12 mg was administered with aprepitant 200 mg in the fed state on Day 1 compared with 3.2 hrs when administered alone. The dexamethasone T_{max} was 1.5 hrs on Days 1, 2 and 3 irrespective of whether dexamethasone was administered alone or with aprepitant 200 mg (fed-state) on Day 1 and on Day 4 the dexamethasone T_{max} was 2.0 hrs when dexamethasone was administered with aprepitant 200 mg (fed-state) on Day 1 and 1.5 hrs when dexamethasone was administered alone.

Results Midazolam PKs (Interaction) Part 2

The midazolam $AUC_{0-\infty}$ and C_{max} on Days 4 and 8 following co-administration of a single oral dose of aprepitant 200 mg in the fed state and oral daily doses of midazolam 2 mg on Days 1, 4, and 8 are summarised below in Table 14.

Table 14: Study P175. Midazolam $AUC_{0-¥}$ and C_{max}, with and without aprepitant.

$AUC_{0-\infty}$

Pharmacokinetic Parameter	MK-0869 Dose	Day	Midazolam with Aprepitant			Midazolam Alone†			(Midazolam + Aprepitant / Midazolam Alone)		
			N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE §
$AUC_{0-\infty}$(ng·hr/mL) †	200-mg	4	10	30.60	(25.04, 37.40)	30	24.70	(20.99, 29.07)	1.24	(1.09, 1.41)	0.198
		8	10	18.32	(14.99, 22.39)	30	28.20	(23.96, 33.19)	0.65	(0.57, 0.74)	.

C_{max}

Pharmacokinetic Parameter	MK-0869 Dose	Day	Midazolam with Aprepitant			Midazolam Alone†			(Midazolam + Aprepitant / Midazolam Alone)		
			N	GM	95% CI	N	GM	95% CI	GMR	90% CI	rMSE §
C_{max} (ng/mL) †	200-mg	4	10	10.44	(8.53, 12.77)	30	8.69	(7.36, 10.26)	1.20	(1.06, 1.36)	0.195
		8	10	7.17	(5.86, 8.78)	30	9.75	(8.25, 11.51)	0.74	(0.65, 0.84)	.

† Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on ln-transformed values.

§ rMSE: Square root of conditional mean squared error (residual error) from the linear mixed effect model. For log-transformed variables, rMSE*100% approximates the within-subject % CV on the raw scale.

‡ Midazolam alone data (Treatment E) were pooled across 3 squares.

> *Comment*: The results indicate that a single oral dose of aprepitant 200 mg co-administered with midazolam 2 mg on Day 1 had a weak inhibitory effect on CYP3A4 on Day 4 as evidenced by increased midazolam exposure (that is, a 24% increase in midazolam $AUC_{0-\infty}$), and a modest effect on CYP3A4 induction on Day 8 as evidenced by reduced midazolam exposure (that is, a 35% reduction in midazolam $AUC_{0-\infty}$).

Evaluator's Comments on the PK Data

The pivotal PK Study P165 satisfactorily demonstrated that a single oral fasting dose of aprepitant 165 mg in the fasting state and a single IV infusion of fosaprepitant 150 mg over 20 minutes were bioequivalent as regards the $AUC_{0-\infty}$. The GMR [PO/IV] of the aprepitant $AUC_{0-\infty}$ was 0.93 [95% CI: 0.84, 1.02]; p=0.001. The aprepitant $AUC_{0-\infty}$ was 7% lower following oral aprepitant than following IV fosaprepitant due to lower aprepitant plasma concentrations over the first 4 hrs after administration. However, the aprepitant plasma concentration time curves were similar from 4 to 72 hrs. The clinical efficacy data from the previously evaluated clinical Study PO17 relating to acute phase (0-24 hrs) cisplatin induced nausea and vomiting suggest that lower exposure to aprepitant over the first 24 hrs following administration of single oral fasting aprepitant 165 mg compared with IV fosaprepitant 150 mg is unlikely to be clinically significant.

The draft Emend PI indicates that oral aprepitant can be administered with or without food but the pivotal PK Study P165 showed that administration of a single oral dose of aprepitant 165 mg with food increased exposure to aprepitant compared with fasting administration. Administration of a single oral dose of aprepitant 165 mg with low-fat and high-fat meals increased the aprepitant $AUC_{0-\infty}$ by 8% and 47%, respectively. These results suggest that if a single oral dose of aprepitant 165 mg is administered in the fed state then this should be with a low-fat rather than a high-fat meal.

The major clinical problem associated with increased exposure to aprepitant when a single oral dose of aprepitant 165 mg is administered with food relates to the increased inhibitory effect of aprepitant on CYP3A4 compared with fasting administration. The interaction PK data from Study P175 indicates that co-administration of a single oral dose of aprepitant 200 mg (taken with a standard light breakfast) and a single oral dose of midazolam 2 mg results in an approximately 3.2 fold increase in midazolam $AUC_{0\text{-}24h}$ compared with midazolam 2 mg alone. While this result indicates that a 200 mg dose of aprepitant taken with food is a moderate inhibitor of CYP3A4, it is considered that an approximately 3.2 fold increase in exposure of an emetogenic agent which is a substrate of CYP3A4 would represent a significant safety issue if the agent was co-administered with aprepitant 165 mg in the fed state.

The PK interaction data (midazolam) from Study P175 indicated that a single dose of aprepitant 200 mg in the fed state on Day 1 had a weak inhibitory effect on CYP3A4 on Day 4, while the Day 8 data indicated that the drug had a modest effect on CYP3A4 induction. The PK interaction data from Study P155 showed that co-administration of a single oral fasting dose of aprepitant 250 mg in the fasting state and a single oral dose of midazolam 2 mg resulted in a 1.63 fold increase in midazolam $AUC_{0\text{-}\infty}$ on Day 1 compared with midazolam 2 mg alone (a weak inhibitory effect on CYP3A4). Overall, the data from studies P175 and P155 shows that oral aprepitant administered in the fed state has a greater effect on CYP3A4 inhibition than oral aprepitant administered in the fasting state.

The proposed oral aprepitant 165 mg treatment regimens include co-administration with dexamethasone (a CYP3A4 substrate). The PK interaction data from Study P175 showed that co-administration of a single oral dose of aprepitant 200 mg (taken with a standard light breakfast) and oral doses of dexamethasone (12 mg on Day 1 and 8 mg on Days 2, 3, and 4) increased exposure to dexamethasone on Days 1, 2, 3, and 4 relative to dexamethasone administered alone. Dexamethasone $AUC_{0\text{-}24h}$ values were 2.09, 2.33, 1.42 and 1.06 fold higher on Days 1, 2, 3, and 4, respectively, when single dose oral aprepitant 200 mg (fed state) on Day 1 was co-administered with dexamethasone compared with dexamethasone alone. The absence of PK interaction data between the proposed single oral 165 mg dose of aprepitant in the fed state and the proposed doses of dexamethasone in the HEC and MEC regimens is considered to be a significant deficiency in the submitted data.

Pharmacodynamics

Introduction

The submission included one, Phase 1, pharmacodynamic study.

Study P183

Objectives

1. To evaluate the duration of brain NK_1-receptor occupancy over 5 days, as assessed by positron emission tomography (PET) using radiolabelled [F^{18}] MK-0999 as a PET tracer, after single dose IV administration of 150 mg fosaprepitant, and single dose oral administration of aprepitant 165 mg, and possibly after single dose oral administration of 250 mg aprepitant (depending on the results of the IV fosaprepitant 150 mg and oral aprepitant 165 mg comparison).
2. To investigate the relationship between plasma concentrations of aprepitant and brain NK_1-receptor occupancy.

   Comment: 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 now known as MK-0999. The previous aprepitant PET studies [P027 and P045] utilised PET ligand MK-0999 which

is readily brain penetrant. MK-099 binds with high affinity and specificity to NK_1-receptors and is quantitatively displaced from these receptors by NK_1-antagonists such as aprepitant (a selective high-affinity antagonist at human NK_1-receptors).

Ethics

The protocol and informed consent were reviewed and approved by the relevant IRB. The study was conducted in accordance with GCP and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Study Site and Study Dates

The study was conducted at a single centre (in Belgium). The primary treatment period was 12 May 2010 to 10 September 2010 and the last patient visit was on 6 October 2010. The frozen file date was 22 October 2010.

Hypothesis and Estimation

Primary Hypothesis: The mean value of brain NK_1-receptor occupancy for subjects in at least one of the Treatment Groups, B (oral aprepitant 165 mg) or C (oral aprepitant 250 mg), will be no less than 90% of the mean value of brain NK_1-receptor occupancy for subjects in Treatment Group A (IV fosaprepitant 150 mg) when assessed by PET at 24 and 48 hrs after dosing on Day 1. That is, at least one of the true geometric mean brain NK_1-receptor occupancy ratios (B/ A or C/A) will be ≥ 0.90 at the 24 hr post dose time point and at the 48 hr post dose time point.

Estimation: The brain NK_1-receptor occupancy for subjects in Treatment Group A (IV fosaprepitant 150 mg), Treatment Group B (oral aprepitant 165 mg) and if evaluated Treatment Group C (oral aprepitant 250 mg), will be estimated by PET at T_{max}, and 120 hrs after dosing on Day 1.

Design

The study was a Phase I, open label, parallel group study in healthy adults of both sexes designed to evaluate the duration of brain NK_1-receptor occupancy over 5 days within 2 study drug treatment groups (A and B) and possibly with a third study drug treatment group (Treatment C) using PET. The study planned to assign up to 24 subjects (8 per treatment group) to one the following treatment groups: single dose IV fosaprepitant 150 mg [Treatment A]; single dose oral aprepitant 165 mg [Treatment B], and if necessary, single dose oral aprepitant 250 mg [Treatment C]. In addition, subjects in treatment groups A, B and C (if necessary) were to receive oral dexamethasone on Days 1, 2, 3 and 4, and IV ondansetron on Day 1. Administration of the study drug on Day 1 was in the fed state following a standard light breakfast within 15 minutes prior to dosing.

It was planned that all subjects were to undergo 3 PET scans. In addition, a pre study brain magnetic resonance imaging (MRI) scan was also to be performed on each subject. The protocol allowed that, in the case of technical failure preventing PET tracer administration, a subject could repeat the scheduled study drug administration and PET scan after a minimum washout period of 7 days. For all subjects, the first PET scan (baseline) was to be obtained within 3 weeks prior to the first dose of study drug. The 2 subsequent PET scans were to be conducted at 2 of the following possible post dose time points for each subject: (a) at T_{max} (4 hrs after oral aprepitant on Day 1 or 30 minutes after the end of the 20 minute IV fosaprepitant infusion on Day 1); (b) 24 hrs post dosing; (c) 48 hrs post dosing; or (d) 120 hrs post- osing (relative to the start of the IV fosaprepitant infusion or time of oral aprepitant dosing). Blood was also to be collected for plasma aprepitant assay at pre dose and at selected time points over 120 hrs post dose in each treatment group and immediately prior to starting and immediately following stopping of each post dose PET scan. Within each treatment group, PET scans at T_{max} and 120

hrs post dose were to be obtained in 3 subjects and PET scans at 24 and 48 hrs post dose were to be obtained in 5 subjects.

> *Comment:* The primary hypothesis and design of this Phase 1 "time-on-target" PD study was considered satisfactory. The oral aprepitant 165 mg dose [Treatment B] was that proposed for approval and the IV fosaprepitant 150 mg infusion [Treatment A] was an approved dose. The co-administration of dexamethasone and ondansetron mimics the proposed aprepitant antiemetic regimens. In addition, aprepitant dosing following a standard light breakfast was done in an attempt to mimic patient treatment when receiving chemotherapy. The time points for the post dose PET scans (T_{max}, 24, 48, and 120 hrs post dose) were selected to evaluate brain NK_1-receptor occupancy in treatment groups A and B, as they represent post dose time points in both the acute and delayed phases of CINV and were thought to be the most practical time points to determine whether the 2 treatment groups have similar levels of brain NK_1-receptor occupancy. The study was also designed to further elucidate the PK/PD relationship between aprepitant plasma concentration and brain NK_1-receptor occupancy. The open label design is considered to be satisfactory, given that the outcomes of NK_1-receptor occupancy and aprepitant plasma concentrations are objectively determined and not subject to bias.
>
> Treatment C was not pursued as it was found to be unnecessary following assessment of Treatments A and B. Treatment C (aprepitant 250 mg) was only to be evaluated if the real-time assessment (during the conduct of the study) of the NK_1-receptor occupancy values from the PET scans at 24 hrs and 48 hrs post dose Treatment A (fosaprepitant 150 mg) and Treatment B (aprepitant 165 mg) showed that the primary hypothesis was not supported.

Inclusion and Exclusion Criteria

The intended study population was healthy, non smoking, young adult male and female subjects (of non childbearing potential) between 18 and 55 years of age who had a BMI ≤30 kg/m^2. The inclusion and exclusion criteria were considered to be satisfactory. The protocol also included standard criteria allowing subjects to be withdrawn from the study. Subjects who discontinued from the study for a serious adverse experience were to be followed up for outcome and subjects who discontinued from the study for any reason were to complete follow-up procedures at the post study visit.

Treatments

According to an open label, computer generated allocation schedule, enrolled subjects (8 per Treatment Group) were to be assigned to one of the three Treatment Groups (A, B or C) as listed below. Subjects could only participate in one treatment group during the study. The total number of subjects was 16 (8 per treatment group A and B); it was not necessary to evaluate Treatment C. All doses of study drug were to be administered in the fed state.

Treatment A: Single IV infusion of 150 mg (1 mg/mL) fosaprepitant over 20 minutes.

Treatment B: Single oral 165 mg aprepitant capsule.

Treatment C: Single oral 250 mg aprepitant dose (2 x 125 mg aprepitant capsules).

Subjects in Treatment Groups A, B and C (if necessary) were to concomitantly receive oral dexamethasone 12/8/8 bd/8 bd mg on Days 1/2/3/4, respectively, with or without a meal and IV ondansetron (32 mg on Day 1) with their respective study drug treatment. All doses of study drug on Day 1 were administered at the CRU and were witnessed by the study investigator and/or staff. Thereafter, on Days 2, 3, and 4 the initial dose of oral dexamethasone was administered within the CRU, while the second daily dose of oral dexamethasone on Days 3 and 4 could be administered outside of the CRU.

Pharmacodynamic and Pharmacokinetic Procedures

PET procedures: The timing of these procedures has been outline above under *Design.* For each PET scan, individual subjects received an IV bolus dose of [^{18}F] MK-0999. The average injected doses (±SD) in Treatments A and B were 93±20 MBq (n=22) and 102±15 MBq (n=24), respectively. PET acquisition started ~210 min after [^{18}F] MK-0999 administration and had a total duration of 60 min (6 x 10 min frames). Timing of the [^{18}F] MK-0999 dose and the PET scan for each subject could be modified at the discretion of the investigator in consultation with the Clinical Monitor. The NK_1-receptor central occupancy was estimated in the striatum, the brain region with highest [^{18}F] MK-0999 uptake. Since the cerebellum is known to have negligible NK_1-receptor expression, [^{18}F] MK-0999 specific binding to NK_1-receptors (or tracer binding potential) was estimated using this region to estimate the non-specific binding of the tracer. The binding potential (BP) was estimated using the ratio of the average activity in the striatum to the average activity in the cerebellum during the scanning session.

PK procedures: Blood collections for plasma aprepitant assay were obtained as follows: Day 1; pre dose (within -1 hr), and then 30 and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96 and 120 hrs after the initiation of the IV infusion of fosaprepitant, or after the time of oral administration of aprepitant. Separate blood collections were also planned for immediately before starting and stopping PET scans at T_{max}, 24 hrs, 48 hrs and 120 hrs. The aprepitant plasma PK parameters included $AUC_{0-\infty}$, C_{max}, T_{max}, and $t_{1/2}$. The assay for determining the aprepitant plasma concentration involved liquid-liquid extraction for analyte isolation followed by HPLC using a reverse phase column with tandem mass spectrometry employing a heater nebulizer (HN) interface in the positive ion mode. The lower limit of quantification (LLOQ) for the aprepitant plasma concentration was 10 ng/mL and the linear calibration range was 10.0 to 2500 ng/mL.

PK/PD procedures: The relationship between brain NK_1-receptor occupancy and plasma aprepitant concentration was examined using pre and post PET scan plasma concentrations to determine the average time-matched plasma concentrations. Individual values for receptor occupancy at all time points were plotted against the time-matched average plasma aprepitant concentrations.

Primary Response Parameters

The primary variables of interest were brain NK_1-receptor occupancy measured at T_{max}, 24 hrs, 48 hrs and 120 hrs post dose and plasma aprepitant concentrations assessed pre dose and over 120 hrs post dose.

Statistical Methods and Sample Size

PKs: Descriptive statistics were provided for $AUC_{0-\infty}$, AUC_{0-24hr}, C_{max}, T_{max}, $t_{½}$, CL and Vss for each treatment.

PDs: Data from Treatment A (IV fosaprepitant 150 mg) and Treatment B (oral aprepitant 165 mg) were analysed using a linear mixed effect (LME) model. The model contained treatment, time (T_{max}, 24, 48 and 120 hrs) and treatment-by-time interaction as fixed effects and subject nested within treatment as a random effect. An unstructured covariance structure was used. Analyses were carried out in the log scale and final results were back-transformed for reporting purposes. The point estimate and 90% CI were calculated for the GMR [B/A] of brain NK_1-receptor occupancy at 24 and 48 hrs after dosing on Day 1. The point estimates and 95% CIs for brain NK_1-receptor occupancy between Treatment B versus Treatment A at T_{max} and 120 hrs were also provided. Since the oral aprepitant 250 mg treatment was not explored in this study, no multiplicity adjustments were required

In each treatment group, all subjects with at least 1 successful post dose PET scan were included in the evaluation of PDs. Two subjects in Treatment A discontinued due to tracer synthesis

failure, resulting in only one of their 2 planned post dose PET scans being obtained with only partial data from these two subjects being included in the PD evaluation.

Power: It was estimated that the log-scale between-subject standard deviation was about 0.028 (log %) based on the previous PET Study PO27. The type-I error of 0.025 was used for power calculation. If the true GMRs (aprepitant / fosaprepitant) of brain NK_1-receptor occupancy at 24 and 48 hrs are 1.00 and the correlation between brain NK_1-receptor occupancy at 24 and 48 hrs is 0.5, with 5 subjects per arm at a specific time point, then there is at least 99.9% probability that both lower bounds of the 95% CIs for the GMRs are greater than 0.90. If the true GMRs (aprepitant / fosaprepitant) of brain NK_1-receptor occupancy at 24 and 48 hrs are no less than 0.96, then there is at least 85.9% probability that both lower bounds of the 95% CIs for the GMR are greater than 0.90.

Populations Analysed

Of the 16 enrolled subjects, 14 completed the study as planned and 2 were discontinued due to one of their planned post dose PET scans being unobtainable. All available brain NK_1-receptor occupancy data from the 16 subjects were used in the evaluation of PDs. All 16 subjects had available PK data and were included in the primary analysis of PKs.

All 16 subjects were White males with a mean age of 28.3 years [range: 20-44], mean height of 180.2 cm [range: 163.0 to 194.0] and mean weight of 78.0 kg [range: 62.2 to 94.4]. There were no pre existing conditions that prevented participation of any of the subjects in the study. Of the 16 subjects, 10 (63%) reported a history of previous medical conditions, none of which prevented participation in the study. Neither prior therapies (reported by 4/16 subjects) nor concomitant therapies (reported by 1/16 subjects) were considered relevant as regards conduct or interpretation of the study.

Brain NK1-Receptor Occupancy - Results

Following IV fosaprepitant 150 mg, NK_1-receptor occupancy at T_{max} (~ 30 min) and 24 hrs was ≥ 100%, at 48 hrs post drug administration was ≥ 97%, and at 120 hrs post drug administration was 62% (range: 41% to 75%).

Following oral aprepitant 165 mg, NK_1-receptor occupancy at T_{max} (~ 4 hrs) and 24 hrs was ≥99%, at 48 hrs post drug administration it was ≥ 97% and at 120 hrs post drug administration it was 57% (range: 37% to 76%).

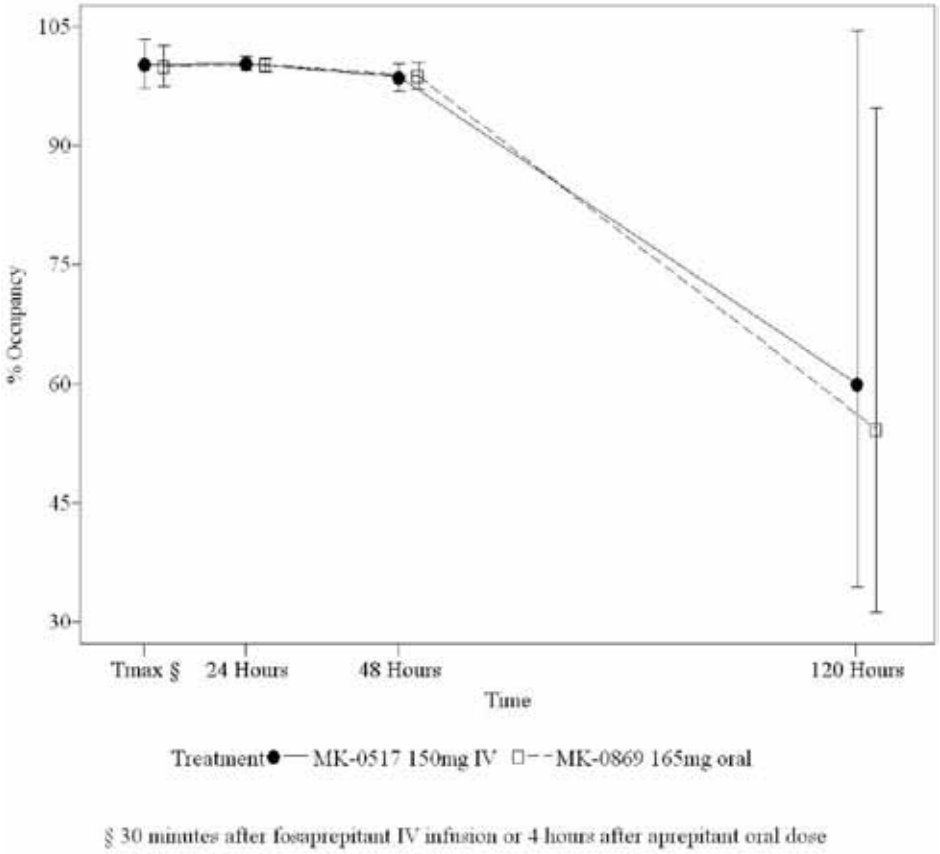
The statistical comparison of brain NK_1-receptor occupancy over 5 days following administration of 150 mg IV fosaprepitant infused over 20 minutes [Treatment A] and 165 mg oral aprepitant [Treatment B] by time post dose is summarised below in Table 15.

Table 15: Study 183. Brain NK_1-receptor occupancy.

Time of PET Scan	Treatment A		Treatment B		Treatment B / Treatment A
	150 mg IV MK-0517		165 mg Oral MK-0869		MK-0869 / MK-0517
	N	GM (95% CI)†	N	GM (95% CI)†	GMR‡ (90% CI)
T_{max} §	2	100.25 (97.22, 103.39)	3	99.99 (97.47, 102.58)	1.00 (0.97, 1.03)
24 Hours	5	100.40 (99.51, 101.29)	5	100.20 (99.31, 101.09)	1.00 (0.99, 1.01)
48 Hours	4	98.62 (96.91, 100.37)	5	98.79 (97.19, 100.42)	1.00 (0.98, 1.02)
120 Hours	3	59.93 (34.37, 104.49)	3	54.32 (31.15, 94.71)	0.91 (0.50, 1.66)
† Back-transformed least squares mean and 95% confidence interval from mixed effects model performed on natural log-transformed values.					
‡ GMR = Geometric Mean Ratio of the LS means.					
§ T_{max} is 30 minutes after the end of the 20-minute infusion of IV fosaprepitant (MK-0517) on Day 1, or at 4 hours after oral dosing of aprepitant (MK-0869) on Day 1.					

The geometric means with 95% CIs for the 150 mg IV fosaprepitant and 165 mg oral aprepitant treatment groups at T_{max}, 24, 48 and 120 hrs post dose are displayed below in Figure 10.

Figure 10: Brain NK1-receptor occupancy, geometric means and 95% CIs.



§ 30 minutes after fosaprepitant IV infusion or 4 hours after aprepitant oral dose

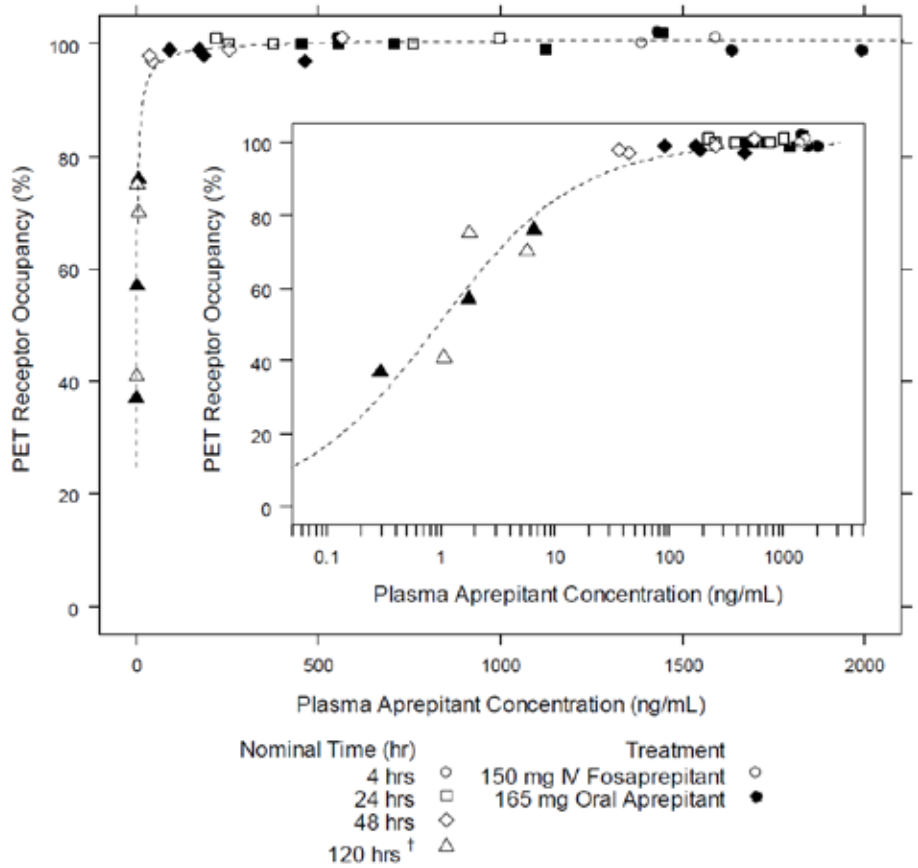
Comment: The results support the primary hypothesis that the true mean value of brain NK_1-receptor occupancy in the 165 mg oral aprepitant group is no less than 90% of the mean value of brain NK_1-receptor occupancy in the 150 mg IV fosaprepitant group at the 24 and 48 hr post dose time points since both the lower bounds of the 90% CIs for the GMRs at these time points are greater than 0.90. The NK_1-receptor occupancy at 24 hrs post dose was ≥100% for IV fosaprepitant 150 mg and ≥ 99% for oral aprepitant 165 mg and at 48 hrs postdose it was ≥97% for both treatments. The 95% CIs for the mean GMR at both the 24 and 48 hr post-dost time points for both treatments were narrow,

suggesting little inter-subject variability in NK_1-receptor occupancy at these post dose time points for both treatments.

PK/PD Relationship. Results

Individual values for receptor occupancy at all time points were pooled across all subjects and both treatments, then plotted against the average of the pre and postscan aprepitant plasma concentrations (see Figure 11 below). In subjects with PET scans obtained at 120 hrs, the time matched plasma concentrations were below the limit of detection of the bioanalytical assay (LLOQ: 10 ng/mL). These scans however had substantial receptor occupancy as measured by PET. Therefore, the expected concentrations at 120 hrs post dose were extrapolated from the individual plasma concentration-time curves by use of the terminal elimination half life. The extrapolated concentrations at 120 hrs for those subjects who had PET scans at that time, receiving either IV fosaprepitant 150 mg or oral aprepitant 165 mg, ranged from ~0.3 to 7 ng/mL.

Figure 11: Study 183. NK_1-receptor occupancy versus plasma aprepitant concentration (ng/ml) following administration of 150 mg IV fosaprepitant or 165 mg oral aprepitant (inset: semi-log plot).



Comment: The PK/PD analysis is considered to be exploratory due to limited data. The PK data were summarised descriptively. The PET NK_1-receptor occupancy (%)v ersus time curve showed no apparent hysteresis and appeared to be described by a sigmoidal model. However, with a maximum of only 2 post dose PET scans per individual, it was not possible to definitively assess hysteresis or whether NK_1-binding demonstrates slow kinetics as has been observed in nonclinical experiments. Therefore, a saturable binding model (Hill model) based on limited sampling was fitted to the data using non-linear least squares regression, with Maximum Occupancy (Occmax) fixed to 100% and Baseline fixed to 0%. The fitted values in this exploratory analysis were an Occ50 of

2.27± 0.99 ng/mL (concentration at 50% receptor occupancy), and Hill slope value (γ) of 0.84 ± 0.20 (parameter value ± standard error). Based on these parameter estimates, 90% receptor occupancy would be achieved with aprepitant plasma concentrations of ~21 ng/mL. The estimated occupancy at 72 hrs for IV fosaprepitant 150 mg and oral fosaprepitant 165 mg at average aprepitant concentrations of 92.5 and 142 ng/mL would be ~ 96% and ~ 97%, respectively.

Dosage Selection for the Pivotal Studies

There are no clinical efficacy and safety studies involving the proposed oral single dose of aprepitant 165 mg. The sponsor stated that comparison of historical PK data from aprepitant and fosaprepitant studies with various doses and data extrapolations from Study PO12L1 (IV to PO comparisons) suggested that either a 165 mg or a 185 mg dose of oral aprepitant would provide a plasma aprepitant AUC similar to that resulting from an IV infusion of 150 mg fosaprepitant over 20 minutes. Therefore, the plasma aprepitant AUC for both the 165 mg and 185 mg aprepitant capsules were compared with the plasma aprepitant AUC for the 150 mg IV infusion dose of fosaprepitant [Study P165]. Based on the results of Study P165, the sponsor considered that the aprepitant 165 mg dose capsule was the most appropriate dose for single dose oral treatment for CINV.

Efficacy

No new clinical efficacy studies in the proposed patient population were submitted. The approval of the single dose oral aprepitant 165 is based on the newly submitted PK and PD studies in healthy volunteers, and a previously submitted clinical efficacy and safety study.

Safety

Studies Providing Evaluable Safety Data

No new clinical safety studies in the proposed patient population were submitted. The submission included safety data following oral aprepitant administered at various doses and IV fosaprepitant 150 mg in healthy volunteers. The exposure data relating to aprepitant and fosaprepitant from the four Phase I clinical pharmacology studies are summarised below in Table 16:

Table 16: Summary of aprepitant and fosaprepitant exposure in healthy adult subjects.

Prot. No.	Abbreviated Title	Number of Subjects Exposed to:					
		Aprepitant (MK-0869) †					Fosaprepitant (MK-0517)
		165 mg	185 mg	200 mg	250 mg	375 mg	150 mg
P155	Fasted State CYP3A4 Interaction	--	--	--	48	--	--
P165	Definitive Bioequivalence / Food Effect Evaluation	41	41	--	--	--	41
P175	Fed State CYP3A4 Interaction	--	--	20	20	21	--
P183	Time-on-Target PET	8	--	--	--	--	8
	Total:	49	41	20	68	21	49

† One male subject in P165 had an accidental overdose of 925 mg aprepitant (5 X 185-mg) which was reported as a serious clinical adverse experience.

Demographic data for 170 healthy young adult subjects enrolled in the four Phase I clinical pharmacology studies are summarised below in Table 17.

Table 17: Demographic data for healthy adult subjects in the four, Phase 1 clinical pharmacology studies.

Protocol No.		P155	P165	P175	P183	Total
No. of Subjects Enrolled		50	42	62	16	170
Mean Age (years)		31.9	27.8	28.6	28.3	29.2
	Range	18 to 49	18 to 43	18 to 49	20 to 44	18 to 49
	Males	36	32	36	16	120
	Females	14	10	26	0	50
Race	Asian	2	2	3	0	7
	Black	22	16	23	0	61
	Caucasian	26	23	33	16	98
	Other	0	1	3	0	4

In the four Phase I clinical pharmacology studies, safety and tolerability was assessed using adverse event reporting, laboratory safety tests, physical examination findings, and standard 12-lead ECGs.

Extent of Exposure in Individual Studies

Study P165

A total of 42 healthy young adult subjects (32 males and 10 females) were enrolled in this study and 41 completed all 4 periods. These 41 subjects each received a single oral dose of 165 mg and 185 mg of aprepitant in the fasted state and a 150 mg IV infusion of fosaprepitant in treatment Periods 1, 2 or 3. In addition, they also received either a single oral dose of 165 mg or 185 mg of aprepitant with either a standard light-fat breakfast or a standard high-fat breakfast in treatment Period 4. Due to an accidental overdose, one subject was exposed to 925 mg of oral aprepitant. Of the 42 subjects who enrolled in the study, 40 completed the study per protocol but 2 subjects did not complete the study as planned. All 42 subjects enrolled in the study were included in the assessment of safety and tolerability.

Study P155

A total of 50 healthy young adult subjects (36 males and 14 females) were enrolled in this 3-part study and their respective exposure to study drug(s) was determined by which part of the study they participated in and whether or not they completed both treatment periods within that specified part of the study. All 50 subjects enrolled in the study were included in the assessment of safety and tolerability.

In Part 1 (dexamethasone interaction), 12 subjects were enrolled in the study and each completed the study as planned. All 12 subjects in Part 1 of the study received the 8 mg oral daily dose of dexamethasone on Days 1, 2 and 3 within 2 treatment periods and they also received on Day 1 in one of the 2 treatment periods a single 250 mg oral dose of aprepitant in the fasted state.

In Part 2 (midazolam interaction), 26 subjects were enrolled and 22 of these completed the study as planned. Four subjects discontinued prematurely (3 due to withdrawn consent and 1 due an adverse experience). In Part 2 of the study, 24 of the 26 enrolled subjects received the 2 mg oral daily dose of midazolam on Days 1 and 8 within both of the 2 treatment periods along with a single 250 mg oral dose of aprepitant on Day 1 within one of the 2 treatment periods.

Two subjects completed only the first treatment period in which they received the 2 mg oral daily dose of midazolam on Days 1 and 8 but were never exposed to aprepitant.

In Part 3 (food effect), 12 subjects were enrolled and each completed the study as planned. All 12 subjects in Part 3 received a single 250 mg oral dose of aprepitant in the fasted state in one of the 2 treatment periods and a single 250 mg oral dose of aprepitant in the fed state approximately 30 minutes after a standard light breakfast in the other treatment period.

Study P175

A total of 62 healthy young adult subjects (36 males and 26 females) were enrolled in this 2-part study, and their respective exposure to study drug(s) was determined by which part of the study they participated in, and whether or not they completed both treatment periods within that part of the study. All 62 subjects enrolled in the study were included in the assessment of safety and tolerability (32 in Part 1 and 30 in Part 2).

In Part 1 (dexamethasone interaction), 32 subjects were enrolled and 2 subjects discontinued prematurely (1 withdrew consent; 1 withdrew due to an adverse experience consisting of maculopapular rash, pruritus, fungal skin infection after completing Treatment A [dexamethasone alone] in Period 1). Both subjects were replaced and both replacement subjects completed the study. In this part of the study, all 32 subjects were exposed to dexamethasone and 31 of the 32 subjects were exposed to aprepitant (10 to 200 mg; 10 to 250 mg; and 11 to 375 mg)

In Part 2 (midazolam interaction), 32 subjects were enrolled and 1 subject was discontinued prematurely (withdrew consent) and was not replaced. In this part of the study, 30 subjects were exposed to midazolam and 30 subjects were exposed to aprepitant (10 to 200 mg; 10 to 250 mg; and 10 to 375 mg).

Study P183

A total of 16 healthy young adult male subjects were enrolled in this study: 8 were exposed to IV fosaprepitant 150 mg (Treatment A) and 8 were exposed to oral aprepitant 165 mg (Treatment B). In addition, all 16 subjects were also exposed to IV ondansetron 32 mg administered on Day 1 and oral dexamethasone 12/8/16/16 mg on Days 1/2/3/4, respectively. Three subjects had failed PET scans during the first dosing of study drug due to tracer synthesis problems and were required to repeat the dosing of the study drug in order to obtain post dose PET scans. Consequently, one subject had a repeated exposure to IV fosaprepitant 150 mg along with IV ondansetron and oral dexamethasone and two subjects had repeated exposure to oral aprepitant 165 mg along with IV ondansetron and oral dexamethasone. Of the 16 subjects, 14 (88%) completed the study as planned and 2 discontinued.

Adverse Experiences

Study P165

A total of 67 clinical adverse experiences (1 serious and 66 non-serious) were reported among 25 (59.5%) of the 42 subjects assessed for safety. Each of the clinical adverse experiences reported in the study was rated by the investigator as "mild". The investigator reported 40 of the 67 clinical adverse experiences as not related to study drug and 27 as related to study drug. The most commonly reported adverse experiences among the 66 non-serious clinical adverse experiences were headache (23 reports) and dizziness (7 reports).

The incidence of headache in subjects administered oral aprepitant 165 mg in the fasted and fed states was 22.0% (9/41) and 4.8% (1/21) respectively, compared with 14.6% (6/41) in subjects administered IV fosaprepitant 150 mg. The incidence of dizziness in subjects administered oral aprepitant 165 mg in the fasted and fed states was 7.3% (3/41) and 0%

(0/21), respectively, compared with 2.4% (1/41) in subjects administered IV fosaprepitant 150 mg.

Study P155

A total of 34 non-serious clinical adverse experiences were reported among 20 (40%) of the 50 subjects enrolled in the study. Of the 34 non-serious clinical adverse experiences, 24 were rated by the investigator as “mild”, 6 were rated as “moderate” and 4 were rated as “severe”. The investigator reported 30 of the 34 non-serious clinical adverse experiences as not related to study drug and 4 as related to study drug. The most commonly reported complaints among the 34 non-serious clinical adverse experiences were somnolence (10 reports) and headache (8 reports). Of the total 10 clinical adverse experiences of somnolence, 7 were reported in Part 2 of the study (midazolam interaction). Similarly, six of the total 8 clinical experiences of headache were also reported in Part 2.

Of the 34 non-serious clinical adverse experiences reported in the study, 3 were reported among 3 (25%) of the 12 subjects who were enrolled in Part 1 of the study. The 3 non-serious clinical adverse experiences were reported following administration of Treatment B [single 8 mg oral daily dose of dexamethasone on Days 1, 2 and 3 co-administered with single 250 mg oral dose of aprepitant on Day 1]. The 3 adverse experiences were somnolence (2 reports) and dizziness (1 report).

Of the 34 non-serious clinical adverse experiences reported in the study, 19 were reported among 11 (42%) of the 26 subjects who were enrolled in Part 2 of the study. Of these 19 non-serious clinical adverse experiences, 13 were reported for 9 (34.6%) of the 26 subjects who received Treatment C (single 2 mg oral daily dose of midazolam alone on Days 1 and 8) and 6 were reported among 4 (16.7%) of the 24 subjects who received Treatment D (single 2 mg oral daily dose of midazolam on Days 1 and 8 co-administered with a single 250 mg oral dose of aprepitant on Day 1). The most common adverse experiences reported in the 11 subjects was somnolence (8 reports) followed by headache (6 reports).

Of the 34 non-serious clinical adverse experiences reported in the study, 12 were reported among 6 (50%) of the 12 subjects who were enrolled in Part 3 of the study. Of these 12 non-serious clinical adverse experiences, 3 were reported among 3 (25%) of the 12 subjects who received Treatment E (single 250 mg oral dose of aprepitant on Day 1 in the fasted state) and 9 were reported among 5 (41.7%) of the 12 subjects who received Treatment F (single 250 mg oral dose of aprepitant on Day 1 in the fed state). The most commonly reported adverse experiences in the 12 subjects were dizziness (2 reports) and headache (2 reports), with all other experiences being reported once.

Study P175

A total of 197 non-serious clinical adverse experiences were reported among 54 (87%) of the 62 subjects who were enrolled in the study. Of the 197 non-serious clinical adverse experiences reported in the study, 103 were reported among 26 (81%) of the 32 subjects who were enrolled in Part 1 (dexamethasone interaction), and 94 were reported among 28 (93%) of the 30 subjects who were enrolled in Part 2 (midazolam interaction).

Of the 197 non-serious clinical adverse experiences reported, 196 were rated by the study investigator as "mild" and only 1 was rated as "moderate". The most commonly reported non-serious clinical adverse experiences were dyspepsia and hiccups in Part 1 (dexamethasone interaction) and somnolence in Part 2 (midazolam interaction). All subjects were reported to have fully recovered from the clinical adverse experiences.

The study investigator reported 189 (96%) of the 197 non-serious clinical adverse experiences as not related to study drug and 8 (4%) as related to study drug. The 8 drug-related non-serious clinical adverse experiences were reported among 7 subjects in Part 1 (dexamethasone

interaction) and 1 subject in Part 2 (midazolam Interaction): in Part 1; 1 x insomnia for 5 hrs following aprepitant 375 mg; 1 x constipation for 6 days following aprepitant 250 mg; 1 x pollakiuria for 3 days following aprepitant 250 mg; 1x pollakiuria for 3.75 hrs following aprepitant 200 mg; 1x pollakiuria for 3.5 hrs following aprepitant 200 mg; 1 x pollakiuria for 4 days following aprepitant 250 mg; and 1 x headache for 0.75 hrs following aprepitant 375 mg; and in Part 2; 1x headache for 2 days following aprepitant 200 mg. Each of the 8 drug-related non-serious clinical adverse experiences was rated by the study investigator as "mild".

Study P183

A total of 42 non-serious clinical adverse experiences were reported among 12 (75%) of the 16 subjects who were enrolled in the study. Of the total 42 non-serious clinical adverse experiences, 19 were reported among 5 of the 8 subjects who received IV fosaprepitant 150 mg and 23 were reported among 7 of the 8 subjects who received oral aprepitant 165 mg.

The most common clinical adverse experiences by System Organ Class (SOC) occurring in subjects in the oral aprepitant 165 mg group (versus fosaprepitant 150 mg) were Gastrointestinal disorders (5/8 [62.5%] versus 2/8 [25.0%]), Respiratory/Thoracic/Mediastinal disorders (5/8 [62.5%] versus 2/8 [25.0%]), Eye disorder (2/8 [25.0%] versus 1/8 [12.5%]) and General disorders/Administration site conditions (2/8 [25.0%] versus 0/8 [0%]). There were 3 SOC clinical adverse experiences which occurred more frequently in subjects in the IV fosaprepitant 150 mg group than in subjects in the oral aprepitant group: Nervous system disorders 5/8 (62.5%) versus 1/8 (12.5%); Psychiatric disorders 1/8 (12.5%) versus 0/8 (0%); and Vascular disorders 3/8 (37.5%) versus 1/8 (12.5%).

The most commonly reported events (reported in 2 or more subjects) among the 42 non-serious clinical adverse experiences were gastro-oesophageal reflux and hiccups and both of these experiences were considered by the study investigator to be likely related to dexamethasone. All subjects were reported to have recovered from the clinical adverse experiences.

Of the 42 reported non-serious clinical adverse experiences, 14 (9 reported among 5 subjects in Treatment A, and 5 reported among 3 subjects in Treatment B) were reported by the study investigator as “possibly” related to study drug. Of the 14 drug-related clinical adverse experiences, the study investigator rated 11 as “mild” and 3 as “moderate.

Serious Adverse Experiences

Study P165

There was one serious adverse experience consisting of an accidental overdose of 5 x 185 mg aprepitant capsules (a total dose of 925 mg). The subject reported a mild headache 4 hrs after his dose, which lasted about 27 hrs and for which he took 650 mg of paracetamol. The subject was discontinued from the study and was reported to have recovered fully from the serious adverse event. There were no deaths in the study.

Study P155

There were no serious adverse experiences or deaths reported in this study.

Study P175

There were no serious adverse experiences or deaths reported in this study.

Study P183

There were no serious adverse experiences or deaths reported in this study.

Discontinuations Due to Adverse Experiences

Study P165

One subject discontinued from the study due to a serious clinical adverse experience of accidental overdose.

Study P155

One subject discontinued from the study due to a “severe” clinical adverse experience of kidney stone not considered to be related to the study drug.

Study 175

One subject in Part 1 discontinued from the study due to clinical adverse experiences of maculopapular rash, pruritus, and fungal skin infection following Treatment A of Period 1 (dexamethasone 12/8/8/8 mg on Days 1/2/3/4, respectively). Each adverse experience was rated by the investigator as "mild" and "definitely not" related to study drug (aprepitant).

Study P183

There were no serious adverse experiences reported in this study.

Laboratory Adverse Experiences

Study P165

One subject experienced 1 laboratory adverse experience of increased blood creatinine concentration (1.88 mg/dL [normal range: 0.4 – 1.4]) at the post study visit considered to be unrelated to study drug treatment. The concentration was within the normal range 3 days later.

Study P155

One subject in Part 2 of the study experienced 2 laboratory adverse experiences on Day 8 of Treatment Period 2 that were discovered by an unscheduled urinalysis ordered in follow-up due to clinical symptoms (severe back/flank pain) that were confirmed to be from a kidney stone (1 x blood present in the urine and 1 x red blood cells urine positive). The study investigator reported the 2 laboratory adverse experiences as "definitely not" related to study drug.

Study P175

No laboratory adverse experiences were reported.

Study P183

One subject who received study oral aprepitant 165 mg with IV ondansetron 32 mg on Day 1 and oral dexamethasone 12/8/16/16 mg on Days 1/2/3/4, respectively, experienced 3 laboratory adverse experiences of neutropaenia noted at the post study assessment and at two follow-up assessments over the subsequent three weeks. The study investigator reported the 3 laboratory adverse experiences as non-serious and “possibly” related to the study drug.

Vital Signs, Other Physical Observations and Special Examinations

Study P165

No clinically meaningful relationships were observed between treatment and changes in vital signs, physical examinations or ECGs.

Of the 41 subjects who received IV fosaprepitant 150 mg, injection site pain, erythema or tenderness were reported at one or more protocol-specified time points for 19 (46.3%) of the 41 subjects/ Fourteen (34.1%) subjects experienced slight to moderate pain at the injection

site. The most common injection site finding was slight tenderness which was reported by 14 (34.1%) subjects. None of the injection site findings were reported as clinical adverse experiences.

Study P155

No clinically meaningful relationships were observed between treatment and changes in vital signs, physical examinations or ECGs.

Study P175

No clinically meaningful relationships were observed between treatment and changes in vital signs, physical examinations, or ECGs.

Study P183

No clinically meaningful relationships were observed between treatment and changes in vital signs, physical examinations or ECGs.

One subject had 3 "other" adverse experiences consisting of separate observations of "hotspot skull parieto-occipital right on PET" noticeable on the one pre study and two post dose PET scans. These 3 "other" adverse experiences were reported as non-serious and "definitely not" related to the study drug.

Postmarketing Experience

There were no postmarketing safety data in the submission for oral aprepitant 165 mg at the proposed dose for the proposed indication. At the date of the submission this regimen had not been approved in any country.

Evaluator's Comments on Safety

The submission did not include a combined analysis of adverse experiences by SOC or individual preferred events across the four clinical pharmacology studies in healthy adult subjects. Consequently, the safety data from each of the four studies was examined individually.

In the four clinical pharmacology studies, there was total of 440 clinical adverse experiences (339 non-serious and 1 serious) reported in 111 (65.3%) of 170 healthy young adult subjects of both sexes. Of the 339 non-serious reports, 52 were reported by the respective primary study investigator of each study to be related (possibly, probably or definitely) to study drug, and of the 52 drug-related clinical adverse experiences, 49 were rated as "mild" and 3 were rated as "moderate". The 1 serious clinical adverse experience was an accidental overdose of aprepitant (925 mg), resulting mainly in headache and from which the subject fully recovered.

The most common clinical adverse experiences (reported in 2 or more subjects) in Studies P165 and P183 following single dose administration of IV fosaprepitant 150 mg and single dose administration of oral aprepitant 165 mg were headache and dizziness. The most common clinical adverse experiences (reported in 2 or more subjects) in Studies P155 and P175 following single dose administration oral aprepitant (200 mg, 250 mg or 375 mg) with co-administration of oral dexamethasone in Part 1 of each study and oral midazolam in Part 2 of each study were somnolence and headache in Study P155 and dyspepsia, hiccups and somnolence in Study P175. The study investigators considered dyspepsia and hiccups to be commonly observed side effects of dexamethasone, while somnolence is an expected pharmacological effect of midazolam. In Study P183, which also included co-administration of oral dexamethasone and IV ondansetron, gastro-oesophageal reflux and hiccups were common complaints and reported as being most likely related to dexamethasone. There was only 1 serious clinical adverse experience reported in the four studies (accidental overdose in Study P165) and no deaths were reported in the studies.

Haematology, blood chemistry and urinalysis laboratory tests were obtained at pre and post study in each of the four Phase I clinical pharmacology studies. In addition, as Studies P155, P165 and P175 included women of childbearing potential, serum β-hCG tests were obtained at the pre and post study visits and urine β-hCG tests were obtained pre dose on Day 1 of each treatment period. No consistent changes in laboratory safety parameters related to treatment were reported in the studies.

In each of the four clinical pharmacology studies, complete vital signs including heart rate, blood pressure, respiratory rate, and temperature were measured pre and post study, in the sitting position for Studies P155, P165, and P175 and in the semi-recumbent position for Study P183. There were no consistent changes in vital signs, ECG safety parameters or physical examination findings related to treatment in the studies.

There was no formal safety comparison between oral aprepitant 165 mg administered in the fasting and fed state. The PK data from Study P165 showed that the aprepitant $AUC_{0-\infty}$ was 8% and 47% higher when oral aprepitant 165 mg was administered with a low-fat and a high-fat meal, respectively, relative to fasting administration. The safety data from this study showed that 12/41 (29.3%) of subjects treated with aprepitant 165 mg in the fasted state reported at least 1 adverse experience compared with 6/21 (28.6%) of subjects treated with aprepitant 165 mg in the fasted state. Furthermore, the safety data from this study showed that 13/42 (31.0%) of subjects treated with aprepitant 185 mg in the fasted state reported at least 1 adverse experience compared with 3/20 (15.0%) of subjects treated with aprepitant 185 mg in the fed state. The small subject numbers from this study indicate no significant difference in the safety profile of oral aprepitant administered in the fasting and fed states in healthy young adults.

A subgroup safety analysis (examining the effect of gender, age, race) of the safety/tolerability data obtained in the four clinical pharmacology studies was not conducted due to the relatively small number of subjects and the different designs of each study.

List of Questions

After an initial clinical evaluation, a List of Questions to the sponsor is generated by the evaluator.

A range of questions regarding the draft PI were raised by the clinical evaluator but these are beyond the scope of this AusPAR.

Clinical Summary and Conclusions

Preliminary Benefit-Risk Assessment and Recommendations

Benefits

The sponsor is proposing single dose oral aprepitant 165 mg regimens for the prevention of CINV associated with highly and moderately emetogenic chemotherapy treatment for cancer. These regimens include identical dexamethasone and ondansetron dosages as those for the approved IV infusion fosaprepitant 150 mg regimens for the same indications. The pivotal PK Study P165 has demonstrated that a single oral fasting dose of aprepitant 165 mg and an IV infusion of fosaprepitant 150 mg administered over 20 minutes are bioequivalent as regards the aprepitant $AUC_{0-\infty}$. However, the C_{max} after IV fosaprepitant 165 mg was approximately 2.4 fold higher than that after oral aprepitant 165 mg and the respective T_{max} values were 20 minutes and 4 hrs. Exposure to aprepitant over the first 4 hrs following initiation of treatment was

greater with IV fosaprepitant 150 mg than with oral aprepitant 165 mg but the plasma concentration–time curves for both treatments were similar from 4 through to 72 hrs.

The data from the previously evaluated clinical efficacy and safety Study PO17 suggest that the efficacy of a single oral fasting dose of aprepitant 165 mg will be similar to that of an IV infusion of fosaprepitant 150 mg in the first 24 hrs following initiation of treatment as regards the prevention of nausea and/or vomiting induced by chemotherapy. Consequently, the efficacy of the two aprepitant treatments is likely to be similar despite lower aprepitant plasma concentrations being observed with oral aprepitant 165 mg compared with IV fosaprepitant 150 mg over the first 4 hrs of treatment. In addition, the time-on-target PET pharmacodynamic study indicated that NK_1-receptor occupancy at 24 and 48 hrs was ≥ 97% following both oral aprepitant 165 mg in the fed state and IV fosaprepitant 150 mg [Study P183]. Furthermore, it was estimated that NK_1-receptor occupancy at T_{max} (~ 30 minutes and ~ 4 hrs after IV and oral administration, respectively) was ≥ 100% following IV fosaprepitant 150 mg and ≥ 99% following oral aprepitant 165 mg.

The PET results support the clinical efficacy findings from Study PO17 and suggest that the lower systemic exposure to aprepitant over the first 4 hrs of treatment following oral aprepitant 165 mg compared with IV fosaprepitant 150 mg is unlikely to be clinically significant. Overall, it is considered that the submitted data indicate similar clinical benefits relating to the prevention of CINV for the proposed single oral fasting dose of aprepitant 165 mg *administered in the fasting state* and the approved IV infusion dose of aprepitant 150 mg.

Risks

The Emend PI states that the drug may be taken with or without food and the sponsor has proposed no food related dosage modification for the proposed single oral aprepitant dose of 165 mg. There are no bioequivalence data comparing single dose oral aprepitant 165 mg in the fed state with IV fosaprepitant 150 mg. However, the pivotal PK Study P165 showed that the aprepitant $AUC_{0-\infty}$ following a single oral dose of aprepitant 165 mg was 8% and 47% higher when administered in the fed state (low-fat and high-fat meal, respectively) relative to the fasting state. The increased exposure to aprepitant when oral aprepitant 165 mg is administered with food is unlikely to result in increased adverse events relating to aprepitant alone. Furthermore, the bioequivalence data from Study P165 relating to the aprepitant $AUC_{0-\infty}$ and C_{max} suggest that the safety profile of IV fosaprepitant 150 mg can be extrapolated to oral aprepitant 165 mg when administered in the fasting state.

However, the major clinical safety issue associated with increased exposure to aprepitant when aprepitant 165 mg is administered in the fed compared with the fasting state relates to the increased inhibitory effect on CYP3A4. There are no data on the effect of the proposed oral single dose aprepitant 165 mg on CYP3A4 substrates in the fed (or fasting) state. The closest aprepitant dose with relevant PK interaction data involving CYP3A4 substrates to that being proposed is 200 mg in the fed state [Study P175].

The PK interaction data from Study P175 showed that a single oral 200 mg dose aprepitant in the fed state (standard light breakfast) on Day 1 with oral dexamethasone co-administered orally as 12 mg on Day 1 and 8 mg on Days 2 through 4, increased the AUC_{0-24h} of dexamethasone by 2.1 fold and 2.3 fold on Days 1 and 2 and 1.4-fold and 1.1 fold on Days 3 and 4. The draft PI (under *Precautions*) states that the daily dose of dexamethasone on Days 1 and 2 should be reduced by approximately 50% when co-administered with aprepitant 165 mg on Day 1 to achieve exposures of dexamethasone similar to those obtained when given without aprepitant 165. Presumably this means that the dose of dexamethasone should be 6 mg on Day 1 and 4 mg on Day 2 when administered with aprepitant 165 mg. However, the draft PI (under *Dosage and Administration*) indicates that the dose of dexamethasone on Days 1 and 2 should be 12 mg and 8 mg respectively (the doses used in Study P175) when co-administered with single dose aprepitant 165 mg. Furthermore, the 50% reduction in dexamethasone on Day 1 (6 mg)

and Day 2 (4 mg) appears to be indicated only when aprepitant 165 mg is administered in the fed state. The approved dose of dexamethasone on Days 1 and 2 is 12 mg and 8 mg, respectively, when co-administered with IV fosaprepitant 150 mg and this dose of fosaprepitant has been shown to be bioequivalent to oral aprepitant 165 mg in the fasted state as regards the aprepitant $AUC_{0-\infty}$. Therefore, it appears that the dose of dexamethasone on Days 1 and 2 should be 6 mg and 4 mg, respectively, when co-administered with single dose aprepitant 165 mg *in the fed state* and 12 mg and 8 mg, respectively, when co-administered with aprepitant 165 mg *in the fasted state*. There are no PK interaction data between the proposed single oral dose of aprepitant 165 mg in the fed state and dexamethasone at the doses proposed by the sponsor to prevent CINV associated with MEC and HEC agents. This is considered to be a significant deficiency in the submitted data and results in uncertainty relating to the safety of the proposed dexamethasone doses when co-administered with aprepitant 165 mg *in the fed state*.

The PK interaction data from Study P175 also showed that co-administration of a single oral dose of aprepitant 200 mg (taken with a standard light breakfast) and a single oral dose of midazolam 2 mg results in an approximately 3.2 fold increase in the midazolam AUC_{0-24h} compared with midazolam 2 mg alone. This result indicates that a 200 mg dose of aprepitant taken with a light meal is a moderate inhibitor of CYP3A4 (AUC ≥ 2 fold increase and < 5 fold increase). The PK interaction data from Study P175 also showed that a single dose of aprepitant 200 mg *in the fed state* on Day 1 had a weak effect on CYP3A4 inhibition on Day 4 (midazolam $AUC_{0-\infty}$ increased 1.2 fold), and a modest effect on CYP3A4 induction on Day 8 (midazolam $AUC_{0-\infty}$ decreased by 35%). The PK interaction data from Study P155 showed that co-administration of a single oral dose of aprepitant 250 mg *in the fasted state* and a single oral dose of midazolam 2 mg resulted in an approximate 1.6 fold increase in the midazolam $AUC_{0-\infty}$ compared with midazolam 2 mg alone (a weak inhibitory effect on CYP3A4 as the AUC increase was < 2-fold). Therefore, when considered together the data from Studies P175 and P155 showed that oral aprepitant administered *in the fed state* had a greater effect on CYP3A4 inhibition than oral aprepitant administered *in the fasting state*.

It is noted that the ACPM expressed concern at its 273rd meeting, when considering the application to approve IV fosaprepitant 150 mg for MEC and HEC, "that inhibition of CYP3A4 may result in increased toxicity when used with MEC agents, many of which were CYP3A4 substrates". This observation raises serious concerns about the safety of the proposed single oral aprepitant dose of 165 mg when administered *in the fed state* in a regimen to prevent CINV associated with MEC agents which are CYP3A4 substrates. The single oral dose of aprepitant 200 mg taken with a standard light breakfast and co-administered with midazolam 2 mg (a CYP3A4 probe) increased the midazolam AUC_{0-24h} by 3.2 fold on Day 1 [Study P175]. While this results indicates that a single oral dose of aprepitant 165 mg in the fed state is a moderate inhibitor of CYP3A4, increases in exposure of 3.2 fold with MEC agents known to be CYP3A4 substrates would raise serious concerns regarding increased toxicity of these agents. There are no PK interaction data between the proposed single oral dose of aprepitant 165 mg *in the fed state* and midazolam 2 mg (a CYP 3A4 probe). This is considered to be a significant deficiency in the submitted data and results in uncertainty relating to the safety of the proposed dose when administered *in the fed state* to prevent CINV associated with MEC agents known to be CYP3A4 substrates.

Benefit-Risk Balance

The benefit-risk balance of oral aprepitant 165 mg *in the fed state (light meal)*, given the proposed usage, is unfavourable.

The benefit-risk balance of oral aprepitant 165 mg *in the fasted state*, given the proposed usage, is favourable.

Preliminary Recommendation Regarding Authorisation

It was recommended that that application to approve single dose oral aprepitant 165 mg for the proposed usage should be rejected for the following reasons:

a) There are no PK interaction data between the proposed single oral dose of aprepitant 165 mg *in the fed state* and dexamethasone at the proposed doses. This is considered to be a significant deficiency in the submitted data and results in uncertainty relating to the safety of the proposed dexamethasone doses when co-administered with aprepitant 165 mg *in the fed state.*

b) There are no PK interaction data between the proposed single oral dose of aprepitant 165 mg *in the fed state* and midazolam 2 mg (a CYP 3A4 probe). This is considered to be a significant deficiency in the submitted data and results in uncertainty relating to the safety of the proposed aprepitant dose when administered *in the fed state* to prevent CINV associated with MEC agents known to be CYP3A4 substrates.

c) The benefit-risk balance of oral aprepitant 165 mg *in the fasted state* is favourable, given the proposed usage. However, administration of oral aprepitant 165 mg in the fasted stated is considered not to represent best clinical practice for the prevention of CINV associated with MEC and HEC. The submission states that standard practice for patients receiving MEC and HEC involves administration of a light meal prior to chemotherapy.

Preliminary Recommendations Regarding the Product Documentation

The clinical aspects of the draft Product Information are not entirely satisfactory and should be revised, having regard to comments raised by this evaluator. All of the provided comments are considered to be relevant in the event that the TGA approves Emend 165 mg at the proposed dosage for the proposed indication. However, in the event that the submission to register the single dose Emend 165 mg regimen for the proposed indication is not approved it is recommended that the proposed PI amendments not directly relating to this aspect the submission be approved.

Additional clinical evaluation

An additional clinical evaluation report (CER) provided a *Final Benefit-Risk Assessment and Recommendations* (see below) and comments on the sponsor's response to the clinical questions regarding the draft PI but the latter are beyond the scope of this AusPAR.

Final Benefit-Risk Assessment and Recommendations

Benefits

After consideration of the sponsor's responses to the clinical questions, the benefits of single oral dose aprepitant 165 mg for the proposed usage are unchanged from those identified in the initial CER.

Risks

After consideration of the sponsor's responses to the clinical questions, the risks associated with co-administration of single dose aprepitant 165 mg in *the fed state* and emetogenic chemotherapeutic agents known to be metabolised by CYP3A4 are unchanged from those identified in the initial CER.

Benefit-Risk Balance

The benefit-risk balance of oral aprepitant 165 mg *in the fed state (light meal)*, given the proposed usage, is unfavourable.

The benefit-risk balance of oral aprepitant 165 mg *in the fasted state*, given the proposed usage, is favourable. However, standard clinical practice for the administration of oral aprepitant 165 mg for the proposed usage would be to administer the medicine in the fed state (light meal) rather than the fasted state.

Recommendation Regarding Authorisation

It is recommended that that application to approve single dose oral aprepitant 165 mg for the proposed usage should be rejected for the following reasons:

1) There are no PK interaction data between the proposed single oral dose of aprepitant 165 mg *in the fed state* and midazolam 2 mg (that is, CYP 3A4 probe). This is considered to be a significant deficiency in the submitted data and results in uncertainty relating to the safety of the proposed aprepitant dose when administered *in the fed state* to prevent CINV associated with MEC agents known to be CYP3A4 substrates.

2) The benefit-risk balance of oral aprepitant 165 mg *in the fasted state* is favourable, given the proposed usage. However, administration of oral aprepitant 165 mg in the fasted stated is considered not to represent best clinical practice for the prevention of CINV associated with MEC and HEC. The submission states that standard practice for patients receiving MEC and HEC involves administration of a light meal prior to chemotherapy.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The sponsor provided a summary of Ongoing Safety Concerns which are shown at Table 18.

Table 18: Summary of Ongoing Safety Concerns

Important identified risks	Hypersensitivity Drug Interaction: hormonal contraceptives
Important potential risks	Potential for medication errors
Important missing information	Use in pregnancy Use in patients < 18 years of age Use in patients with moderate or severe hepatic impairment

OPR reviewer comment

The RMP currently lists drug interactions with oral contraceptives in the Ongoing Safety Concerns, Pharmacovigilance plan and Routine risk minimisation activities. However, aprepitant is an inhibitor and inducer of CYP3A4 and an inducer of CYP2C9, for which multiple drug interactions are listed in the Australian PI but not specifically addressed in the Ongoing Safety Concerns, Pharmacovigilance plan and Routine risk minimisation activities in the RMP.

As part of the TGA's request for information, the sponsor was asked to clarify why these drug interactions are omitted.

In response, which was accepted, the sponsor states:

*"...that all drug-drug (*interactions*) have been recognised and well described in the relevant RMP section (RMP Section 1.6 Identified and potential interactions with other medicinal products, food, and other substances). The drug interaction with oral contraceptives was the only one included in the RMP as a safety concern in view of the additional risk minimisation activity involving the need of alternative or back-up contraceptive methods during treatment through two months following the treatment with emend.*

No drug-drug interactions with clinically significant outcomes have been observed during the several years of product safety surveillance. Merck will continue to closely monitor the reports of drug-drug interactions and ensure the adequacy of the product label as the cornerstone risk minimisation system for the product risks.

While not all drug-drug interactions have been listed in the Pharmacovigilance plan of the RMP all of them are well described in the product labelling as routine risk minimisation. Additionally, the drug-drug interactions are part of routine pharmacovigilance along with all other product risks. Reviews of the drug-drug interactions data are presented as a standard section in each PSUR for the product."

Therefore, the above summary of the Ongoing Safety Concerns, including the sponsor's response, is considered acceptable.

Pharmacovigilance Plan

Routine and additional (ongoing clinical trials) are proposed to monitor all safety concerns.

OPR reviewer's comments in regard to the pharmacovigilance plan (PP) and the appropriateness of milestones

The routine activities that the sponsor has outlined are consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices. Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)* and are considered sufficient to monitor the Ongoing Safety Concerns associated with Emend (aprepitant).

Risk Minimisation Activities

The sponsor did not provide a conclusion in regards to the needs for risk minimisation activities as such. However, a summary table of planned actions in the RMP is provided. Routine risk minimisation activities are considered sufficient by the sponsor to mitigate all risks associated with Emend (aprepitant).

OPR reviewer comment

Routine risk minimisation activities are considered sufficient to monitor ongoing safety concerns associated with Emend (aprepitant).

It was recommended to the Delegate that the draft Product Information and Consumer Medicine Information documents are considered satisfactory. However, the Australian PI contraindicates the co-administration of pimozide, terfenadine, astemizole, or cisapride with aprepritant. These drugs are no longer listed on the Australian Register of Therapeutic Goods (ARTG). If the Delegate considers interactions with these drugs to not be of any future importance it is recommended that these drugs are removed from the Australian PI.

In the sponsor's response to a request for information and the RMP the sponsor states that alternative or back-up contraceptive methods should be used during and for *two months*

following treatment with Emend. However, it is stated that alternative or back-up contraceptive methods should be used during and for *one month* following treatment with Emend in the Australian PI and CMI. It was recommended that the sponsor correct this discrepancy.

Summary of Recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application;

It is recommended to the Delegate that the sponsor:

- Implement RMP Version 3.1, dated 10 December 2010, including the sponsor's response to the TGA's request for information/documents and any future updates be imposed as a condition of registration.
- Remove the contraindication of the co-administration of pimozide, terfenadine, astemizole, or cisapride with aprepritant in the Australian PI if they consider these drug interactions to not be of any significant importance.
- Correct the discrepancy between the RMP and the Australian PI/CMI for the number of months alternative or back-up contraceptive methods should be used for following Emend treatment (RMP states 2 months and Australian PI/CMI states 1 month).

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no quality objections to the new 165 mg presentation on chemistry, manufacturing, quality control or bioavailability grounds. As the application only involves a new strength of a registered product, the application has not been referred to the Pharmaceutical SubCommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM).

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended rejection of the application. The sponsor has provided a response to the clinical evaluation.

The application seeks to establish equivalence between the approved fosaprepitant 150 mg IV single dose regimen and the proposed aprepitant 165 mg PO single dose regimen. The clinical data submitted with the application consisted of pharmacokinetic and pharmacodynamic studies conducted in healthy volunteers. No new clinical efficacy data were submitted.

Bioequivalence / Food effects

Study P165 was a randomised, open trial with a cross-over design which examined PK bioequivalence between the IV fosaprepitant and PO aprepitant regimens. Three treatments were compared; aprepitant 165 and 185 mg orally and fosaprepitant 150 mg IV. Results are shown in the clinical evaluation report (CER). Both the 165 and 185 mg aprepitant oral doses were found to be bioequivalent with the 150 mg fosaprepitant IV dose with respect to

aprepitant $AUC_{0-\infty}$. As would be expected, C_{max} values were significantly lower with the oral regimens.

The study also examined the effect of food on the new 165 mg oral presentation. Results are shown in the CER. Administration of aprepitant with a high fat meal resulted in a 47% increase in aprepitant $AUC_{0-\infty}$. Administration with a low fat meal did not result in any significant alteration in absorption.

Interactions

Aprepitant is known to be an inhibitor of CYP3A4. *Study P155* examined the effects of the drug on two CYP3A4 substrates; dexamethasone and midazolam.

- In Part 1 of the study, dexamethasone 8 mg PO was given on Days 1, 2 and 3 with or without a *250 mg* dose of aprepitant given fasted on Day 1. Dexamethasone AUC was increased up to **2.29 fold** by aprepitant.
- In Part 2 of the study, midazolam 2 mg PO was given on Days 1 and 8 with or without a *250 mg* dose of aprepitant given fasted on Day 1. Midazolam AUC was increased **1.63 fold** by aprepitant.

Study P175 also examined the effects of aprepitant on the PK of dexamethasone and midazolam.

- In Part 1 of the study, dexamethasone (12 mg PO on Day 1, and 8 mg PO on Days 2, 3 and 4) was given with or without a *200, 250 or 375 mg* dose of aprepitant given fed on Day 1. Results for the 200 mg aprepitant dose (the closest to the proposed 165 mg dose) are shown under *Clinical findings* above. Dexamethasone AUC was increased up to **2.33 fold** by aprepitant.
- In Part 2 of the study, midazolam 2 mg PO was given on Days 1, 4 and 8 with or without a *200, 250 or 375 mg* dose of aprepitant given fed on Day 1. Results for the 200 mg aprepitant dose are shown under *Clinical findings* above. Midazolam $AUC_{0-\infty}$ was increased up to **3.15 fold** by aprepitant.

The effects of aprepitant on the AUC of dexamethasone and midazolam are shown in studies P155 and P175 are summarised in Table 19 below.

Pharmacodynamics

Study 183 compared the aprepitant 165 mg PO regimen with the fosaprepitant 150 IV regimen with respect to brain NK1 receptor occupancy, as assessed by displacement of a NK-1 receptor binding ligand. Results are shown under *Clinical findings* above. The two regimens produced comparable receptor occupancy at time points up to 120 hrs (5 days).

Safety

The submitted studies included a total of 170 healthy volunteers. No new safety issues were raised. Two of the studies (P165 and P183) directly compared the aprepitant 165 mg PO and fosaprepitant 150 mg IV regimens. There were no notable differences in adverse events seen with the two regimens (see *Clinical findings* above).

Risk Management Plan

The Risk Management Plan submitted with the application has been found to be acceptable by the TGA's Office of Product Review.

Risk-Benefit Analysis

Delegate Considerations

1. *Potential for interactions with CYP3A4 substrates*

   The sponsor has demonstrated bioequivalence between the oral and IV single dose regimens, where the oral regimen is given in the fasted state. It could therefore be concluded that the new oral regimen, if given in the fasted state, would have equivalent efficacy and safety to the approved IV regimen. However, the safety of the oral regimen may be affected by co-administration of food and the sponsor has stated that the standard of care in antiemetic administration for the prevention of CINV is to advise the patient to eat a light meal prior to the administration of chemotherapy.

   The food effects study (P165) showed that co-administration of the 165 mg capsule with a low fat meal resulted in an increase in aprepitant AUC of approximately 8%, and administration with a high fat meal increased aprepitant exposure by 47%. The concern raised by the clinical evaluator was that any increased aprepitant exposure may result in increased inhibition of CYP3A4. Several cytotoxic agents are substrates for CYP3A4 and systemic concentrations of these agents could be increased. As these agents are typically administered at their maximum tolerated dose (MTD), any increase in systemic concentrations could result in significant toxicity.

   As shown in Table 19, the increase in midazolam AUC on Day 1 appeared to be greater in Study P175 (following aprepitant 200 mg in the *fed* state) than in Study P155 (with aprepitant 250 mg in the *fasted* state); 3.15 fold versus 1.63 fold. In Study P175 subjects had a standard light breakfast, not a high fat breakfast.

   The basis for this application is that the oral aprepitant 165 mg single dose regimen should have the same efficacy and safety as the approved IV fosaprepitant 150 mg single dose regimen. The above interaction findings suggest that comparable safety cannot be concluded for the IV regimen and the PO regimen, if the PO regimen were to be administered according to the usual standard of care (that is, in the fed state). The Delegate was therefore inclined to agree with the clinical evaluator that the application should be rejected.

   In its response to the clinical evaluation, the sponsor has argued that the magnitude of the CYP3A4 inhibition produced by the fed single oral dose regimen is likely to be comparable to that produced by the approved 3 day regimen. However, the effects of these two regimens on CYP3A4 have not been directly compared and hence it is not possible to conclude comparable safety.

2. *Product Information*

   If the Committee considers that the application should be approved, changes to the PI were also recommended but these are beyond the scope of this AusPAR.

The Delegate proposed to reject the application on the grounds that safety has not been satisfactorily established, due to concerns regarding an increased risk of interactions due to CYP3A4 inhibition, compared to the registered IV single dose regimen.

The advice of the ACPM was requested.

Table 19: Effects of single dose aprepitant on AUC of CYP3A4 substrates

	Fold increase in AUC						
Substrate	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 8**	**Aprepitant single dose (Day 1)**	**Study**
Dexamethasone 8 mg Days 1, 2, 3	1.96	2.29	1.61	-	-	250 mg fasted	P155
Dexamethasone 12 mg Day 1, 8 mg Days 2, 3, 4	2.09	2.33	1.42	1.06	-	200 mg fed*	P175
Midazolam 2 mg Day 1	1.63	-	-	-	0.69	250 mg fasted	P155
Midazolam 2 mg Days 1, 4, 8	3.15	-	-	1.24	0.65	200 mg fed*	P175

* standard light breakfast

Response from Sponsor

Sponsor response to the Clinical Evaluation

Merck Sharp & Dohme (Australia) Pty Ltd refers to the Clinical Evaluation Report (CER) for the application to support registration of a single oral 165 mg dose of Emend (aprepitant). In the report, the preliminary recommendation regarding authorisation it was stated:

> *"It is recommended that the application to approve single dose oral aprepitant 165 mg for the proposed usage should be rejected for the following reasons:*
>
> *a.) There are no PK interaction data between the proposed single oral dose of aprepitant 165 mg in the fed state and dexamethasone at the proposed doses. This is considered to be a significant deficiency in the submitted data and results in uncertainty relating to the safety of the proposed dexamethasone doses when co-administered with aprepitant 165 mg in the fed state.*
>
> *b.) There are no PK interaction data between the proposed single oral dose of aprepitant 165 mg in the fed state and midazolam 2 mg (CYP 3A4 probe). This is considered to be a significant deficiency in the submitted data and results in uncertainty relating to the safety of the proposed aprepitant dose when administered in the fed state to prevent CINV associated with MEC agents known to be CYP3A4 substrates.*
>
> *c.) The benefit-risk balance of oral aprepitant 165 mg in the fasted state is favourable, given the proposed usage. However, administration of oral aprepitant 165 mg in the fasted stated is considered not to represent best clinical practice for the prevention of CINV associated with MEC and HEC. The submission states that standard practice for patients receiving MEC and HEC involves administration of a light meal prior to chemotherapy."*

The sponsor addressed the specific concerns raised by the clinical evaluator in CER in their response.

Summary of Sponsor's Response to the Clinical Evaluation

Aprepitant is a substrate, a weak-to-moderate (dose dependent) inhibitor and an inducer of CYP3A4. To support the use of the 3 day oral regimen of Emend (125/80/80 mg) for the prevention of acute and delayed nausea and vomiting due to highly emetogenic and moderately emetogenic chemotherapy the sponsor conducted a series of drug-drug interaction studies which included both midazolam and dexamethasone to characterise the effect that aprepitant has on these CYP3A4 substrates. This data is presented in the draft PI under the *Interactions* section. Although it is acknowledged that no additional studies have been conducted specifically with the 165 mg dose, the sponsor believed that prior data in the aprepitant program can be used to characterise the profile of this dose in chemotherapy patients, along with drug interactions data using higher oral doses. Additionally, considering the drug-drug interaction profile, the sponsor believed that the safety data collected in the program supports the administration of aprepitant 165 mg with a favourable risk benefit.

A similar application has been approved by the European Medicines Agency (EMA) in 2011. The EMA acknowledged that the risk/benefit of aprepitant 165 mg single oral dose is positive and appropriate studies to evaluate the effect of food on the new capsule, and the interaction potential of the new higher single dose have been performed. Approval of the 165 mg dose was granted on 28 November 2011.

Sponsor's Conclusion

Bioequivalence studies conducted with single doses of IV fosaprepitant (150 mg) and oral aprepitant (165 mg and 185 mg) assessed the plasma $AUC_{0-\infty}$ equivalence. The studies

were conducted in the fasted state, in order to eliminate the potential variability due to the effect of food on the estimate of relative bioavailability. It is not considered necessary to conduct the bioequivalence studies in both the presence and absence of food. The single doses of aprepitant 165 mg or 185 mg and fosaprepitant 150 mg were shown to be bioequivalent.

A standard light breakfast and a standard high-fat breakfast caused minimal to moderate increase in aprepitant plasma $AUC_{0-\infty}$, following single oral doses of 165 mg and/or 185 mg aprepitant. The difference in the fed/fasted state showed minimal impact on single dose aprepitant 165 mg.

The interaction with dexamethasone has been investigated at aprepitant doses of 125 mg and 200 mg and the effect of aprepitant on the pharmacokinetics of dexamethasone is similar. As these doses cover the intended 165 mg oral dose and it has been shown that the exposure of aprepitant in both the fed and fasted state is within the exposure produced by 125 mg and 200 mg, the proposed dosing regimen in the presence of dexamethasone is justified by the available data.

The assessment of drug interactions with midazolam as a model CYP3A4 substrate showed a 3.15 fold increase in midazolam $AUC_{0-\infty}$ when taken with a 200 mg dose of aprepitant and following a light breakfast. This interaction demonstrated that regardless of food the 165 mg oral aprepitant dose is not likely to pose a greater risk of interactions than shown with a higher dose of 200 mg in the fed state.

The data supports that administration of 165 mg oral aprepitant with/without food, including a high fat meal, would result in no higher than a 3.15 fold increase in midazolam $AUC_{0-\infty}$ and is classified as a moderate CYP3A inhibitor similar to the previously registered 3 day oral regimen of aprepitant. Therefore, the sponsor believed that a single oral dose of 165 mg aprepitant carries the same potential to cause drug-drug interactions as the currently registered 3 day oral aprepitant regimen.

Dose studies with significantly higher daily doses of aprepitant (375 mg) when taken for up to 8 weeks showed no safety concerns despite steady-state exposures up to 5 fold higher when compared to exposures following a single 165 mg dose in the fed state.

As discussed above, the sponsor felt that there is sufficient data characterising the drug interaction potential of 165 mg oral aprepitant which has been reflected in the PI.

However, the sponsor acknowledged the clinical evaluator's concern that co-administration of oral aprepitant, either the 165 mg single dose regimen or the 3 day regimen, with oral or IV compounds which are primarily metabolised by CYP3A should be used with caution. The sponsor proposed to maintain this precaution in the PI as previously submitted. Additionally, the sponsor updated the PI as requested, to provide further details on the pharmacokinetic profile of the 165 mg dose.

Sponsor's Response to the Delegate's Overview

The sponsor disagreed with the Delegate's proposed action to reject this application on the basis that the safety has not been satisfactorily established compared to the registered 150 mg IV single dose regimen and the greater risk of interactions due to CYP3A4 inhibition. MSD maintains that the development of Emend 165 mg single oral dose as a line extension of the currently registered oral and IV presentations has been demonstrated via a bioequivalence study (P165), a study that demonstrates similar NK_1 receptor occupancy following administration of the 165 mg oral and 150 mg IV single doses (P183) and is supported by the known efficacy and safety data. The drug interaction potential with concomitant administration of products that are substrates for CYP3A4 has been investigated (P155, P175) and the potential for interactions, including chemotherapy agents that are CYP3A4 substrates, is documented in the Product Information document.

The data presented supports the registration of Emend 165 mg single oral dose for the current indication of:

> *Prevention of nausea and vomiting associated with cancer chemotherapy (in combination with other antiemetic agents.*
>
> *Establishing the efficacy and safety of Emend 165 mg single oral dose*

The sponsor understood the Delegate's concern that the safety of the 165 mg oral dose has not been compared directly to the 150 mg IV dose in a clinical trial. The efficacy of the single 165 mg oral dose has been established by measuring bioequivalence to the 150 mg IV dose ($AUC_{0-\infty}$) under fasting conditions (a bioequivalence study with an IV presentation in the fed state is not meaningful due to a lack of food interaction on the IV dose). The sponsor also demonstrated a similar level and duration of NK_1 receptor occupancy that is required to mediate the antiemetic effect of aprepitant. Previously the equivalence of the 150 mg IV dose was established compared to the 3 day oral regimen.

The sponsor also acknowledged that the Delegate and clinical evaluator have raised a major concern that the potential for a drug-drug interaction (DDI) via CYP3A4 is greater for the 165 mg oral dose compared with the 150 mg IV dose and this can be expected simply due to the different mode of administration. However as shown below, the 165 mg single oral dose has a similar profile to the registered 3 day oral regimen (125 mg/80 mg/80 mg) when considering the potential interaction with other CYP3A4 substrates. The DDI potential of the 165 mg dose was investigated following co-administration of aprepitant in the presence of dexamethasone (co-administered drug that is a substrate and inducer of CYP3A4) and midazolam (a sensitive probe substrate for CYP3A4 interactions).

The evidence presented on the safety of the 165 mg oral dose is limited to that included in the bioequivalence study and the drug interactions studies where oral doses up to 375 mg were administered resulting in exposure greater than the 150 mg IV dose, along with the established safety profile of the currently registered IV and oral doses. The clinical evaluator raised the safety concern about the drug interaction potential in the fed state compared to the fasted state (due to the higher exposures when given with a high-fat meal), yet a common adverse event such as headache was seen numerically more frequently when aprepitant is given in the fasted state (numbers consider too small to show statistical difference, CER p52) suggesting that increased aprepitant exposure may not always correlate to an increase in adverse event frequency. There is little evidence that the safety profile is different than for the currently registered Emend presentations.

Drug interaction potential

To address the concerns raised by the Delegate and clinical evaluator regarding the potential interactions with other substrates of CYP3A4 and the lack of a drug interaction study with the single oral 165 mg dose of aprepitant, the sponsor presented data in Table 20 that outlines the inhibitory effect of aprepitant on midazolam pharmacokinetics over a wide range of aprepitant doses and conditions along with the aprepitant exposures ($AUC_{0-\infty}$ and C_{max} values). As shown, increasing doses of aprepitant translate to a greater CYP3A4 interaction potential as assessed by the sensitive oral probe midazolam. However, the increase in CYP3A4 inhibition potential between the 125 mg oral aprepitant dose (2.3 fold on Day 1; 3.3 fold on Day 5) and the 200 mg aprepitant dose (3.15 fold on Day 1) is similar and both fall under the classification of "moderate" CYP3A4 inhibition (between 2 and 4.9 fold inhibition). Even at higher doses of aprepitant (375 mg oral dose) the inhibition is 3.5 fold (C. upper limit 4.00 fold) and hence the extent of CYP3A4 inhibition remains in the moderate range.

Table 20: Summary of aprepitant drug interaction studies with midazolam.

Aprepitant Single Oral Dose, Dosing Condition (fed or fasted), and Clinical Study[#]	Aprepitant Exposure		Fold-Change in Oral Midazolam $AUC_{0-\infty}$	
	Geometric Mean $AUC_{0-\infty}$ (ng·hr/mL)	Geometric Mean C_{max} (ng/mL)	GMR	90% CI
40 mg day 1/25 mg days 2-5 in fed state in P041	7999[↔]	522[↔]	Day 1: 1.22 Day 5: 1.02	0.93, 1.61 0.77, 1.35
125 mg day 1/80 mg day 2-5 in fed state in P041 (Application No. 99.4626.4)	25897.9[↑]	1254.7[↑]	Day 1: 2.27 Day 5: 3.3	1.64, 3.14 2.39, 4.56
165 mg fasted state in P165	32520	1666		
165 mg fed state (lb) in P165	35149	1728		
165 mg fed state (hfb) in P165	47785	2210		
250 mg fasted state in P155 (administered simultaneously)	47383	1973	Day 1: 1.63 Day 8: 0.69	1.50, 1.77 0.63, 0.75
200 mg fed state (lb) in P175	64955[‡]	2897[‡]	Day 1: 3.15 Day 4: 1.24 Day 8: 0.65	2.76, 3.58 1.09, 1.41 0.57, 0.74
250 mg fed state (lb) in P175	95012[‡]	3564[‡]	Day 1: 3.31 Day 4: 1.49 Day 8: 0.67	2.91, 3.77 1.30, 1.70 0.58, 0.76
375 mg fed state (lb) in P175	141529[‡]	4205[‡]	Day 1: 3.51 Day 4: 2.02 Day 8: 0.58	3.08, 4.00 1.77, 2.30 0.51, 0.66

lb=light breakfast: hfb=high fat breakfast
GMR = Geometric Mean Ratio (midazolam + aprepitant / midazolam alone).
CI = Confidence interval.
[#] All midazolam doses administered 1 hour following administration of aprepitant unless otherwise noted
[↔] Study conducted with multiple days of dosing; C_{max} and $AUC_{0-\infty}$ for single dose obtained from single dose study P107 (Application No. 2005-2513-1)
[↑] Study conducted with multiple days of dosing; C_{max} and $AUC_{0-\infty}$ for single dose obtained from single dose study P049 (Application No. 99.4626.4)
[‡] Arithmetic Mean

The drug interaction potential of a single oral dose of 165 mg is also limited to only the first few days, while the interaction potential for 3 day oral regimen (125/80/80 mg) can be more prolonged. As demonstrated in Study P041, the drug interaction potential for multiday dosing of aprepitant 125/80/80/80/80 mg on Day 5 was 3.3 fold, which is greater than the drug interaction potential observed for 200 mg aprepitant on Day 1. The observation that the multiday regimen provides comparable net CYP3A4 inhibition supports our claim that, relative to the approved 3 day oral regimen, a single oral dose of 165 mg aprepitant is not anticipated to provide significantly greater drug interaction risk. The 3.15 fold increase in midazolam AUC after administration of 200 mg aprepitant in the fed state represents an upper bound of the possible drug interaction potential as assessed with oral midazolam. Therefore, the inhibitory effect of aprepitant on the sensitive model CYP3A4 substrate midazolam has been characterised over a wide range of oral aprepitant doses. Based on this characterisation further DDI studies specifically with the 165 mg oral dose will not provide more information than is currently available.

Food Effect on Drug Interaction Potential

The Delegate has noted that food intake has an impact on the drug interaction potential of aprepitant. The results in Study P155 are for simultaneous co administration of 250 mg oral aprepitant in the fasted state with oral midazolam and these results demonstrate that the effect on midazolam exposure is considered weak (1.63 fold inhibition). This difference is a result of not having the 1 h interval of aprepitant administration prior to midazolam administration, which presumably results in both reduced first pass (gut level) effect as well as reduced system CYP3A4 metabolism inhibition. From Table 20 above the aprepitant exposure ($AUC_{0-\infty}$) in this study for 250 mg dose in the fasted state is lower than for the aprepitant 200 mg dose in the fed state in Study P175. In Study P175 the oral midazolam was administered 1 h after aprepitant hence the exposure to aprepitant was greater at the time of midazolam administration and hence the inhibition was 3.15 fold.

As demonstrated earlier, exposure to aprepitant has an impact on the CYP3A4 mediated inhibition of midazolam and the magnitude of the inhibitory effect reaches a maximum of approximately 3 fold at a 250 mg aprepitant dose. Therefore, despite increases in exposure to aprepitant when administered in the fed state this will not translate into a differential DDI potential for 165 mg single oral dose.

To further explore the relationship between aprepitant exposure and drug interaction potential with midazolam (and in particular the potential effect of food), a linear regression model was developed relating the ratio of midazolam $AUC_{0-\infty}$ with/without co administration with aprepitant 1 h prior to midazolam dosing. Individual subject data for this analysis were obtained from P175 and P041 (mean values shown in Table 21). As shown in Figure 12, the relationship appears to be linear, with an intercept of 1 (no DDI when no aprepitant AUC =0) and 1 fold increase in the midazolam GMR for every 18,298 ng.hr/mL (standard error =1,262) AUC_{0-24h} of aprepitant. The predicted fold change in midazolam for various doses of aprepitant based on this linear regression model are shown in Table 21. This model predicts the drug interaction potential for 165 mg aprepitant administered either fasted, with a low fat meal or with a high fat meal would produce a 2.1, 2.3, and 2.6 fold increase in midazolam $AUC_{0-\infty}$. The predictions suggest that the degree of CYP3A4 interaction potential for 165 mg oral dose administered with or without food is between the observations with 125 mg oral aprepitant and 200 mg oral aprepitant administered with a low fat meal. As demonstrated in Study P175, the 3.15 GMR observed from co administration with 200 mg oral aprepitant is the upper bound and the 165 mg oral dose would fall within this boundary.

Figure 12: Plot of observed midazolam $AUC_{0-¥}$ ratio versus corresponding observed aprepitant AUC_{0-24h}, with linear regression model

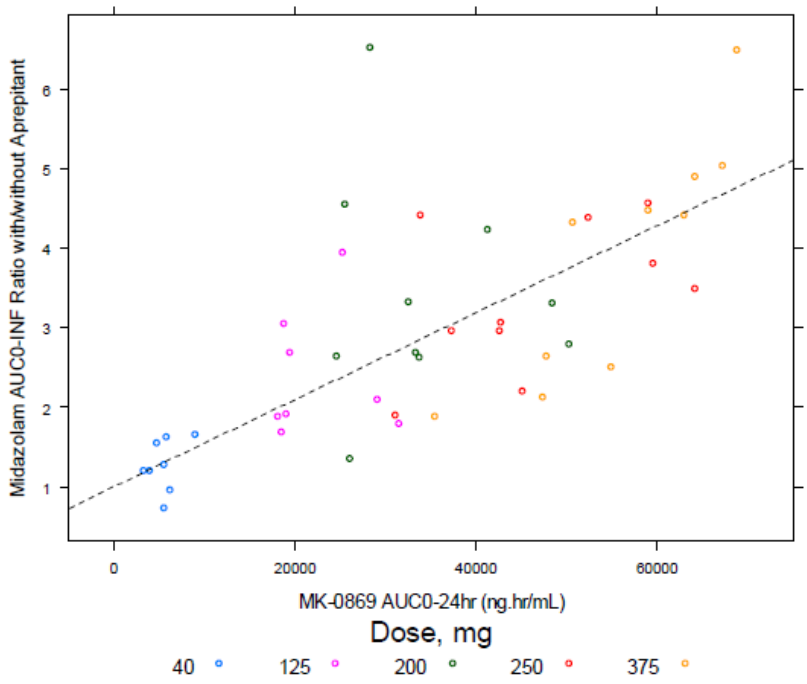


Table 21: Observed Day 1 midazolam $AUC_{0-¥}$ GMR (without aprepitant) and linear regression model-based predictions for midazolam $AUC_{0-¥}$ ratio (without aprepitant).

MSD Protocol	Dose	Day 1 Aprepitant AUC_{0-24hr}[#]	Day 1 Observed Midazolam GMR	Day 1 Predicted Midazolam Ratio
041	40 mg low fat meal	5500	1.22	1.3
041	125 mg low fat meal	22500	2.27	2.2
165	165 mg fasted	21336	-	2.2
165	165 mg low fat meal	24520	-	2.3
165	165 mg high fat meal	29480	-	2.6
175	200 mg low fat meal	34409	3.15	2.9
175	250 mg low fat meal	46801	3.31	3.6
175	375 mg low fat meal	55831	3.51	4.1

[#] Arithmetic Mean

Drug interaction potential with other chemotherapeutic agents and use of Product Information (PI) to address the CYP3A4 drug interaction potential

MSD acknowledged the Delegate's comment that the potential CYP3A4 inhibition caused by aprepitant when co administered with other CYP3A4 substrates (including chemotherapeutic agents in both HEC and MEC regimens) needs to be considered given that the effect of CYP3A4 inhibition on the metabolism of co-administered CYP3A4 substrates, if substantial enough, could lead to increased drug exposure that could cause toxicity. This topic has also been considered in recent reviews[3, 4] and clinicians need to be aware of potential interactions that could impact on the treatment of patients. As

[3] Ruhlmann C.H. and Herrstedt J. (2011). Safety evaluation of aprepitant for the prevention of chemotherapy-induced nausea and vomiting. Expert Opin. Drug Saf. 10(3):449-462

[4] Aapro M.S. and Walko C.M. (2010). Aprepitant: drug–drug interactions in perspective. Annals of Oncology 21: 2316–2323, 2010

elucidated in the table of aprepitant exposures and fold changes in midazolam $AUC_{0-\infty}$, the CYP3A4 interaction potential of oral aprepitant in both the fasted and fed states has been characterised. In particular, from a drug-drug interaction perspective single dose aprepitant 165 mg is anticipated to have a similar drug interaction profile compared with the 3 day oral aprepitant (125/80/80 mg) regimen.

During the development program for the 3 day oral aprepitant regimen, studies were conducted with chemotherapy agents docetaxel and vinorelbine, which are substrates of CYP3A4. In these pharmacokinetic studies, the oral aprepitant 3 day regimen (125/80/80-mg) did not influence the pharmacokinetics of either docetaxel or vinorelbine to a clinically significant degree. In recognition of the potential risk associated with the CYP3A4 drug interaction profile the following precautionary text is already included in the current Australian PI section *Precautions*:

> *Emend, a dose-dependent inhibitor of CYP3A4, should be used with caution in patients receiving concomitant orally administered medicinal products that are primarily metabolised through CYP3A4; some chemotherapy agents are metabolised by CYP3A4 (see Interactions With Other Medicines).*

Along with this text under *Interactions with other medicines, Chemotherapeutic agents*:

> *"Chemotherapy agents that are known to be metabolised by the CYP3A4 include docetaxel, paclitaxel, etoposide, irinotecan, ifosfamide, imatinib, vinorelbine, vinblastine and vincristine. In clinical studies, Emend (125 mg/80 mg regimen) was administered commonly with etoposide, vinorelbine, and paclitaxel. The doses of these agents were not adjusted to account for potential drug interactions. Adequate data are not available on interactions between Emend and other chemotherapy agents primarily metabolised by CYP3A4, and particular caution and careful monitoring are advised in patients receiving these agents (see Precautions).*
>
> *Docetaxel: In an interaction study, Emend (125 mg/80 mg regimen) did not influence the pharmacokinetics of docetaxel.*
>
> *Vinorelbine: In a separate pharmacokinetic study, Emend (125 mg/80 mg regimen) did not influence the pharmacokinetics of vinorelbine.*

As such, the sponsor believed that the current PI appropriately addresses the potential concerns and is consistent with the available data and literature on the potential for interaction of aprepitant and other CYP3A4 substrates.

The PI has been updated to include a summary of plasma aprepitant pharmacokinetic parameters and a recommendation that the 165 mg dose of Emend should be administered in the fasted state or with a light (low fat) meal.

Finally, the safety profile of aprepitant is closely monitored through routine pharmacovigilance and reviewed in Periodic Safety Update Reports, including drug interactions. Drug interactions have been reported with Emend and these events can be explained on the basis of the known interaction with cytochrome P450 enzymes. The Product Information is regularly reviewed and amended accordingly on the availability of new safety information.

Sponsor's Conclusion

Emend 165 mg single oral dose has been developed as an extension of the 150 mg IV single dose and is also a single dose alternative to the current 3 day regimen for Emend allowing shorter, more convenient dosing while maintaining efficacy and overall therapeutic benefit.

The equivalence of Emend 165 mg single oral dose has been shown with the 150 mg IV dose and previously the equivalence of the 150 mg IV dose was established compared to the current 3 day oral regimen. The potential for drug interactions with other CYP3A4

substrates has been characterised and is similar to the approved 3 day oral regimen. The Product Information contains multiple references to the potential for drug-drug interactions, particularly with CYP3A4 substrates such as chemotherapeutic agents, to alert and inform the clinician.

Therefore, the sponsor considered that the concerns raised by the Delegate and clinical evaluator (and also previously highlighted by the Committee on drug interaction potential) have been addressed and that Emend 165 mg single oral dose could be recommended for registration.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following;

The application seeks to register a major variation, a new dosage regimen, for a currently registered product.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, considered this product to have an overall *positive benefit–risk profile* for the current indication for the new dosage regimen.

In making this recommendation the ACPM noted the significant issue of the safety risks of drug interactions with agents and substrates that require the CYP3A4 system for metabolism. The drug interaction data provided from normal populations was noted but may not accurately reflect the risks in the cancer patient group. However, in considering this risk the ACPM advised that the risk of the oral preparation is comparable to the intravenous presentation, and the risks could be managed through a strong referencing in the Product Information.

Further, the ACPM advised that the product should not be used in children due to the absence of data for this patient group and the safety issues associated with the size of the dosage form.

The ACPM agreed with the delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and in particularly acknowledged the reference to the significant CYP3A4 drug interactions and specifically advised on inclusion of the following:

- Specific information on the impact of the fed versus fasting state on absorption in the *Dosage and Administration* section of the PI and CMI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Emend aprepitant 165 mg capsule blister pack; the proposed alternative single dose regimen specific to Emend aprepitant 165 mg for the indication:

> *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.*
> - *moderately emetogenic cancer chemotherapy*

Emend is indicated for the prevention of postoperative nausea and vomiting.

Specific conditions of registration applying to these therapeutic goods:

1. It is a condition of registration that the sponsor implement in Australia the aprepitant Risk Management Plan (RMP), dated 10 December 2010, Version 3.1, included with this submission and any subsequent revisions, as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

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Reference/Publication #