Tolerability of Fosaprepitant and Bioequivalency to Aprepitant in Healthy Subjects

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Fosaprepitant is an intravenous formulation of aprepitant, an oral NK_1 antagonist used to prevent chemotherapy-induced nausea and vomiting. This randomized study was designed to evaluate fosaprepitant in polysorbate 80 vehicle for tolerability and bioequivalency to aprepitant. Tolerability was assessed by physical and laboratory examinations and adverse events. Plasma collected for 72 hours was assayed for aprepitant and fosaprepitant. Analysis of variance models were applied to natural log-transformed aprepitant area under the curve (AUC) data. Fosaprepitant up to 150 mg (1 mg/mL) was generally well tolerated. Fosaprepitant 115 mg was AUC bioequivalent to aprepitant 125 mg; the 90% confidence interval for the geometric mean ratio of aprepitant AUC for fosaprepitant 115 mg/aprepitant 125 mg fell within prespecified equivalence bounds of 0.80 to 1.25.

Keywords: *Fosaprepitant; aprepitant; bioequivalency; tolerability*

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The brain-penetrant, selective NK_1 receptor antagonist aprepitant was developed for use in combination with a $5HT_3$ receptor antagonist and a corticosteroid for the prevention of chemotherapy-induced nausea and vomiting (CINV).[1] The recommended doses of aprepitant in this regimen are a single 125-mg oral capsule on the day of chemotherapy (day 1), followed by an aprepitant 80-mg oral capsule on day 2 and day 3. The antiemetic efficacy of oral aprepitant in the setting of CINV is well documented.[2-4] Although the oral capsule is appropriate for many patients, the availability of an intravenous (IV) alternative would provide greater treatment flexibility and convenience when the oral route of administration is not feasible on day 1, such as in patients with impaired consciousness or those with disease-related nausea who cannot tolerate drugs by mouth.

Fosaprepitant (also known as L-758,298 and MK-0517) is the water-soluble prodrug of aprepitant currently under development as an IV formulation.[5-7] Because fosaprepitant is rapidly converted to the active form (aprepitant) by phosphatase enzymes,[5,6] it is expected to provide the same aprepitant exposure in terms of AUC and a correspondingly similar antiemetic effect.

Preclinical toxicology studies, in which fosaprepitant was administered as a bolus dose over a few seconds, showed that concentrations ≤1 mg/mL were generally well tolerated in rats and dogs. Higher concentrations (up to 25 mg/mL) at relatively low doses (2-4 mg/kg/day) were also generally well tolerated in dogs. However, an intermediate concentration (10 mg/mL) given at 32 mg/kg/day in dogs resulted in significant venous irritation after 1 to 4 doses. This irritation was postulated to be due to the infusate concentration, the absolute dose administered, or a combination of both.

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Table I Study Design and Allocation of Subjects to Treatments

Subjects	Treatments		
Part I (randomized double blind)	Period 1	Period 2	Period 3 (open label)
n = 10	Fos 100 mg	Fos 150 mg	Apr 125 mg
n = 2	Placebo	Fos 150 mg	Apr 125 mg
n = 2	Fos 100 mg	Placebo	Apr 125 mg
Part II (randomized, open label, crossover)	Period 1	Period 2	—
n = 14	Apr 125 mg	Fos 90 mg	—
n = 14	Fos 90 mg	Apr 125 mg	—
Part III (randomized, open label, crossover)	Period 1	Period 2	Period 3
n = 11	Apr 125 mg	Fos 100 mg	Fos 115 mg
n = 11	Fos 100 mg	Fos 115 mg	Apr 125 mg
n = 11	Fos 115 mg	Apr 125 mg	Fos 100 mg
n = 11	Apr 125 mg	Fos 115 mg	Fos 100 mg
n = 11	Fos 100 mg	Apr 125 mg	Fos 115 mg
n = 11	Fos 115 mg	Fos 100 mg	Apr 125 mg

Apr, aprepitant oral capsule; Fos, fosaprepitant intravenous infusion. All treatments were single doses.

The tolerability of fosaprepitant has also been evaluated in clinical trials with approximately 700 subjects/patients (data on file).[8,9] In most of these studies, fosaprepitant was given as single doses ranging from 0.2 to 200 mg, reconstituted in saline or a polysorbate 80 vehicle to a concentration of 1 mg/mL, and infused over 15 to 30 minutes. In 1 study, fosaprepitant was administered in single daily doses (25-100 mg) on 4 consecutive days (data on file). The studies showed acceptable venous tolerability at 1 mg/mL infused over 15 to 30 minutes, whereas a concentration of 25 mg/mL infused over 30 seconds was associated with venous irritation at doses of 50 mg and 100 mg (data on file). Based on these studies and the preclinical findings, the incidence of venous irritation with fosaprepitant appears to depend on both the total dose and concentration and possibly also the rate of infusion.

During development of aprepitant, several studies using the IV prodrug were conducted in patients receiving chemotherapy. A comparison of fosaprepitant versus ondansetron given as monotherapy prior to cisplatin showed that fosaprepitant was active against cisplatin-induced acute emesis.[9] A separate trial demonstrated the tolerability and efficacy of fosaprepitant as part of combination therapy with dexamethasone.[8] The overall preclinical and clinical profiles of fosaprepitant in these early studies suggested that fosaprepitant could be appropriate as an IV alternative to the aprepitant oral capsule.

The present study sought to establish the dose(s) at which IV fosaprepitant was bioequivalent, in terms of aprepitant AUC, to the oral 125-mg aprepitant capsules currently approved for the prevention of CINV and to determine the tolerability of these IV doses. Based on preliminary data, we expected that an IV fosaprepitant dose close to 100 mg would be bioequivalent to oral aprepitant 125 mg and would be well tolerated.

METHODS

Design

The study was approved by Southern Institutional Review Board (Miami, Florida), and all subjects gave written informed consent to participate in study protocol 012. The study was conducted at the Clinical Pharmacology Research Unit of Pharmanet Development Group, Inc (Miami, Florida), which enrolled subjects from January 31, 2005, to December 1, 2005. Details of the study design are shown in Table I. The study was conducted in 3 parts. Parts I and II investigated fosaprepitant doses ranging from 90 to 150 mg. Based on these findings, fosaprepitant doses of 100 and 115 mg were selected for the definitive investigation of bioequivalence in part III.

Subjects and Procedures

Eligible subjects were healthy, nonsmoking adult men and women between the ages of 18 and 45 years. Female subjects could not be pregnant or breastfeeding, and those of childbearing potential were required to use specified birth control measures. Subjects were excluded who had donated blood, received another investigational drug within 4 weeks prior to the study, or had any other illness or condition that the

investigator believed could place the subject at risk or confound the study results. Subjects were not permitted to take any prescription or over-the-counter medication or herbal remedy or to consume grapefruit or grapefruit juice for 2 weeks prior to and throughout the study. Allowable medications included study drug, up to 1300 mg acetaminophen, or medication required to treat an adverse event. Timing and dose of any nonstudy drugs were documented.

Subjects were randomized according to a computer-generated allocation schedule created by Merck Research Laboratories. A complete physical examination including height, weight, vital signs, and a 12-lead electrocardiogram (ECG) was performed prestudy and poststudy for all subjects. Vital signs were also measured at predose and 4 and 24 hours postdose. Hematology, 8-hour fasting serum chemistry, and urinalysis were obtained at prestudy, 24 hours postdose, and poststudy. Subjects were monitored throughout the study for adverse events.

Details of the treatments given in each part of the study are shown in Table I. Periods 1 and 2 of part I (IV fosaprepitant or IV placebo) were double blind, whereas period 3 of part I (oral aprepitant) was open label. All periods in parts II and III were open label. To maintain blinding for the IV study drug in part I, preparation of the IV solutions was performed by a pharmacist uninvolved with the study, and study drug was delivered to the study site as bottles/syringes labeled with the appropriate allocation number. Fosaprepitant in a polysorbate 80 vehicle was supplied in 10-mL capacity vials, for reconstitution in 0.9% normal saline to the appropriate concentration (1 mg/mL). Matching volumes of saline were used as IV placebo to maintain blinding in part I. In all study parts, IV infusions were administered over 15 minutes, and oral aprepitant (EMEND) was provided as oral capsules.

Blood Sampling/Pharmacokinetics Methods

Blood samples were collected for 72 hours following study drug administration for aprepitant assay. Additional samples at predose and 2, 5, 10, 15, 30, and 45 minutes postdose were taken for fosaprepitant assay following fosaprepitant administration. Plasma analyses were conducted by Merck Research Laboratories. The analytical method used for the analysis of fosaprepitant was based on high-performance liquid chromatography with atmospheric-pressure chemical ionization mass spectrometric (MS) detection using triple (MS/MS) quadrupole MS detection (Sciex API 4000). The drug and stable isotope-labeled internal standard were isolated from the plasma matrix buffered to pH 7.4 using a C-18 solid-phase extraction in a 96-well format. The analytes were separated on a Phenomenex polar RP 4-µm 50 × 2-mm analytical column, using a mobile phase of 52% methanol and 48% water containing 10 mM ammonium acetate and 0.1% EDTA delivered at a flow rate of 1 mL per minute. The heated nebulizer probe was used to thermally convert/cleave the phosphate group with >99.99% efficiency, allowing for analysis of the thermally stable product. The triple quadrupole mass spectrometer was operated in the multiple-reaction monitoring mode, monitoring the precursor → product ion combinations of *m/z* 535→277 and 539→281 for drug and internal standard, respectively. The linear calibration range was from 10 to 5000 ng per mL of plasma with coefficients of variation less then 6% at all concentrations (Table II).

For samples collected after dosing with aprepitant and fosaprepitant, the plasma concentration profile and pharmacokinetics of aprepitant were determined. The $t_{1/2}$ was estimated by regression of the terminal log-linear portion of the plasma concentration-time curve. The aprepitant $AUC_{0-\infty}$ was calculated using a linear up/log down trapezoidal method up to the last measured concentration at time t. The fosaprepitant $AUC_{0-\infty}$ was estimated by non-compartmental analysis using the commercially available software WinNonlin. Actual sampling times were used in these calculations, and actual IV doses were calculated from nominal doses by adjusting for the total volume of fosaprepitant infusate delivered. The actual volume of fosaprepitant delivered was estimated from the difference in mass of the filled syringe, before and after drug administration. The density of the fosaprepitant solution was assumed to be that of water and the nominal dose of the solution was used in this calculation.

Statistical Methods

Merck Research Laboratories managed the data and performed the analyses. The $AUC_{0-\infty}$ data were natural log-transformed before analysis. The primary pharmacokinetic measurement was $AUC_{0-\infty}$ of aprepitant following a single oral dose of aprepitant 125 mg and following single IV doses of fosaprepitant 90 mg, 100 mg, 115 mg, and 150 mg. The equivalence hypotheses in each study part were addressed with a linear mixed-effects analysis of variance (ANOVA) model. The geometric mean ratios (fosaprepitant/aprepitant) and confidence intervals (CIs) were then calculated. For part II, 90% CIs were calculated for the mean difference (fosaprepitant – aprepitant) in AUC. These limits were exponentiated to obtain the 90% CI for the AUC

Table II Intraday Precision and Accuracy Data for the Determination of Fosaprepitant in 5 Lots of Human Plasma Using Atmospheric-Pressure Chemical Ionization High-Performance Liquid Chromatography Mass Spectrometry

Nominal Concentration, ng/mL	Mean[a] Concentration, ng/mL	Precision,[b] CV, %	Accuracy,[c] %
10	10	5.9	100
25	26	3.8	104
50	52	4.9	104
100	98	2.0	98
500	502	3.4	100
1000	958	3.4	96
2500	2597	5.7	104
5000	4873	4.5	97

a. Mean concentrations calculated from the weighted linear least squares regression curve constructed using all 5 replicate values at each concentration.
b. Expressed as coefficient of variation (CV, %) of peak height areas (analyte area/internal standard area).
c. Expressed as [(mean calculated concentration)/(nominal concentration)] × 100%.

Table III Subject Disposition

	Number of Subjects		
	Part I	Part II	Part III
Randomized	16	34	76
Men	7	13	36
Age range, y	25-34	19-43	20-44
Women	9	21	40
Age range, y	23-44	19-43	19-45
Discontinued	2	6	12
Clinical adverse event	0	0	0
Laboratory adverse event	0	0	0
Withdrew consent	2	6	12
Completed	14	28	64

geometric mean ratio (fosaprepitant/aprepitant). A CI within the bounds of 0.8 to 1.25 supported the hypothesis. No multiplicity adjustments were required in part II. Because the equivalence hypotheses for part I and Part III were for 1 *or* the other of the 2 fosaprepitant doses, a stepwise testing procedure (Hochberg) was used to adjust for multiplicity.[10] If the 90% CI for the AUC geometric mean ratio (fosaprepitant/aprepitant) for each dose lay within the bounds 0.8 to 1.25, equivalence for both doses would be supported. Otherwise, testing would continue with calculation of 95% CIs. The respective probabilities that the AUC equivalence hypothesis would be supported were 96%, 97%, and >99% for part I, part II, and part III.

Tolerability was assessed by clinical and laboratory adverse experiences, vital signs, laboratory tests, and ECGs.

RESULTS

Table III shows the disposition of subjects. In total, 106 subjects completed the study parts involving fosaprepitant 90 to 150 mg. No subjects were discontinued because of an adverse experience. Those who did not complete the study were lost to follow-up.

In part I, the 150-mg fosaprepitant dose did not meet AUC bioequivalence criteria relative to aprepitant 125 mg based on the 90% CI criteria (Table IV). Therefore, per the testing strategy, both the 100-mg and 150-mg fosaprepitant doses were evaluated using 95% CIs. Neither dose had 95% CIs that fell within the prespecified boundaries (Table IV). When fosaprepitant 90 mg was evaluated in part II, AUC bioequivalence was likewise not demonstrated (Table IV). Part III evaluated 100 and 115 mg fosaprepitant, with results as described below.

Pharmacokinetics

The mean fosaprepitant pharmacokinetic parameters for the 100-mg and 115-mg doses are shown in Table V, and the mean fosaprepitant plasma concentration versus time profiles are shown in Figure 1a. Fosaprepitant plasma elimination half-life averaged

Table IV $AUC_{0-\infty}$ (ng·h/mL) of Aprepitant Following Administration of Oral Aprepitant 125 mg, IV Fosaprepitant 100 mg, IV Fosaprepitant 115, or IV Fosaprepitant 90 mg, in Parts I and II

	Geometric Mean $AUC_{0-\infty}$, ng·h/mL				
Fosaprepitant Dose	**Fosaprepitant**	**Aprepitant**	**Ratio (Fosaprepitant/ Aprepitant)**	**90% CI for Ratio**	**95% CI for Ratio**
Part I (n = 14)					
100 mg	29 269	27 759	1.054	0.914, 1.216	0.888, 1.252
150 mg	44 578	27 759	1.606	1.393, 1.852	1.352, 1.907
Part II (n = 28)					
90 mg	23 191	32 400	0.72	0.66, 0.78	—

IV, intravenous; CI, confidence interval.

Table V Pharmacokinetic Parameters of Fosaprepitant Following Administration of IV Fosaprepitant 100 mg or IV Fosaprepitant 115 mg in Part III

	Geometric Mean[a]	
Variable	**Fosaprepitant 100 mg**	**Fosaprepitant 115 mg**
$AUC_{0-\infty}$, ng·h/mL	1302	1452
$C_{15\ min}$, ng/mL	4848	5353
Cl_p, mL/min	1280	1320
V_{ss}, L	5.0	4.8
$t_{1/2}$, min[a]	2.2	2.3

$C_{15\ min}$, maximum observed concentration; Cl_p, plasma clearance; $t_{1/2}$, half-life; V_{ss}, volume of distribution; IV, intravenous.
a. Harmonic mean for $t_{1/2}$.

approximately 2.3 minutes, and the volume of distribution was approximately 5 L, indicating that fosaprepitant was not distributed meaningfully to tissues.

Following IV administration of fosaprepitant 100 and 115 mg over a 15-minute infusion period, fosaprepitant is rapidly converted to aprepitant. Aprepitant pharmacokinetics were compared in a crossover fashion in subjects who received IV fosaprepitant 100 mg, fosaprepitant 115 mg, and oral aprepitant 125 mg (Table VI). Mean aprepitant plasma concentration-time profiles are depicted in Figure 1b. For approximately 4 hours postdose, plasma aprepitant concentrations were somewhat higher following the fosaprepitant doses versus the oral aprepitant dose but were very similar between the 2 treatments thereafter. At ≥12 hours postdose, mean aprepitant concentrations after fosaprepitant 100 mg were slightly lower than those after oral aprepitant.

As shown in Table VI, plasma $C_{24\ h}$ was similar between fosaprepitant 115 mg and aprepitant 125 mg. However, $C_{24\ h}$ was somewhat lower for fosaprepitant 100 mg. Mean aprepitant apparent terminal $t_{1/2}$ was similar among all doses (13.0-13.6 hours). Plasma aprepitant C_{max} was approximately 2.5-fold higher for fosaprepitant 115 mg compared with aprepitant 125 mg.

AUC Bioequivalency

For both the 100-mg and 115-mg fosaprepitant doses, the 90% and 95% CIs fell within prespecified bounds based on data adjusted for actual IV dose received. In terms of plasma AUC, fosaprepitant 115 mg was bioequivalent to 125 mg aprepitant based on the AUC geometric mean ratio (1.13, 90% CI: 1.06, 1.20). Fosaprepitant 100 mg was also bioequivalent to 125 mg aprepitant, based on the AUC geometric mean ratio (0.87, 90% CI: 0.82, 0.93). Based on data unadjusted for actual dose received, 90% and 95% CIs for fosaprepitant/aprepitant AUC geometric mean ratios fell outside the prespecified bounds for the 100-mg dose (90% CI: 0.797, 0.904; 95% CI: 0.788, 0.915) but remained within bounds for the 115-mg dose (90% CI: 1.036, 1.174; 95% CI: 1.024, 1.188).

Tolerability

Fosaprepitant was well tolerated at all doses tested, and there were no reports of serious adverse events, laboratory adverse events, or discontinuations related to tolerability in any part of the study. Adverse events that did occur were mild or moderate in intensity, with headache and infusion site symptoms the most commonly reported. Table VII shows a summary of adverse events for fosaprepitant 100 mg and 115 mg in part III. No clinically meaningful relationships were observed for differences between vital signs, physical examinations, and ECGs as a function of treatment.

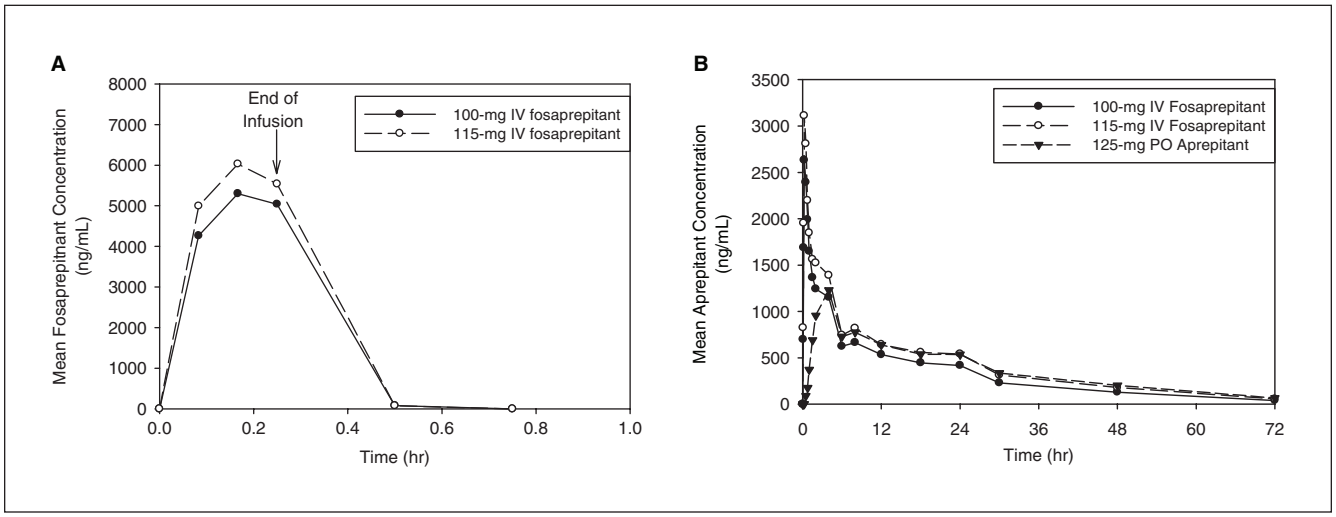

Figure 1. (a) Mean plasma concentrations of fosaprepitant after dosing with intravenous (IV) fosaprepitant 100 mg or IV fosaprepitant 115 mg in part III. (b) Mean plasma concentrations of aprepitant after dosing with IV fosaprepitant 100 mg, IV fosaprepitant 115 mg, or oral aprepitant 125 mg.

Table VI Pharmacokinetic Parameters of Aprepitant Following Administration of Oral Aprepitant 125 mg, IV Fosaprepitant 100 mg, or IV Fosaprepitant 115 mg in Part III

	Geometric Mean[a]		
Variable	**Aprepitant 125 mg**	**Fosaprepitant 100 mg**	**Fosaprepitant 115 mg**
$AUC_{0-\infty}$, ng·h/mL	27 759	22 889	29 611
$AUC_{0-\infty}$ ratio		0.87	1.13
(fosaprepitant/aprepitant)	—	90% CI: 0.82, 0.93	90% CI: 1.06, 1.20
C_{max}, ng/mL	1354	2607	3095
C_{max} ratio		2.08	2.47
(fosaprepitant/aprepitant)	—	95% CI: 1.98, 2.28	95% CI: 2.25, 2.71
$C_{24\ h}$, ng/mL	494	374	504
t_{max}, h[a]	4.0	0.25	0.25
$t_{1/2}$, h[a]	14.0	13.0	13.6

AUC, area under the concentration-time curve; C, concentration; t, time; CI, confidence interval; IV, intravenous.
a. Median for t_{max} and harmonic mean for $t_{1/2}$.

Table VII Summary of Adverse Events for Subjects Taking Oral Aprepitant 125 mg, IV Fosaprepitant 100 mg, or IV Fosaprepitant 115 mg in Part III

Number (%) of Subjects With:	**Aprepitant 125 mg (n = 72)**	**Fosaprepitant 100 mg (n = 67)**	**Fosaprepitant 115 mg (n = 66)**
≥1 adverse event	0 (0.0)	7 (10.4)	7 (10.6)
Infusion site conditions			
Erythema	0 (0.0)	1 (1.5)	0 (0.0)
Induration	0 (0.0)	0 (0.0)	1 (1.5)
Pain	0 (0.0)	7 (10.4)	5 (7.6)
Other			
Dizziness	0 (0.0)	1 (1.5)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	2 (3.0)

DISCUSSION

Fosaprepitant, the IV prodrug of aprepitant, is in development as an alternative formulation to oral aprepitant. This study examined the tolerability of fosaprepitant and defined the dose at which fosaprepitant was AUC bioequivalent to the 125-mg oral formulation currently approved for the prevention of chemotherapy-induced nausea and vomiting. Fosaprepitant was well tolerated at doses up to 150 mg.

When fosaprepitant 100 mg was assessed in part I, AUC bioequivalency criteria were narrowly missed, with the 100-mg dose yielding plasma aprepitant exposure similar enough to that of aprepitant 125 mg to warrant retesting. Accordingly, based on these findings and previous studies with fosaprepitant, part III of the study retested pharmacokinetic parameters for fosaprepitant 100 mg and also for fosaprepitant 115 mg. For both doses, the 90% CIs fell within prespecified bounds based on data adjusted for actual IV dose received. In a final assessment based on data unadjusted for actual dose received, the 100-mg dose failed to show AUC equivalence, but fosaprepitant 115 mg was AUC equivalent to the 125-mg oral capsule based on both adjusted and unadjusted analyses. Fosaprepitant is rapidly converted (complete conversion within 30 minutes; $t_{1/2}$ ~2.3 minutes) to aprepitant following an IV dose. Furthermore, the volume of distribution of fosaprepitant is small (~5 L), indicating that it is not extensively distributed to tissues. In establishing the dose at which fosaprepitant was AUC bioequivalent to the oral 125-mg oral capsule, demonstrating definitive AUC bioequivalence was not feasible as fosaprepitant resulted in a higher C_{max} than the aprepitant capsule due to the difference in route of administration. Although the aprepitant C_{max} was higher for the fosaprepitant doses (approximately 2- to 2.5-fold higher), it was less than that observed in large clinical trials with aprepitant 375 mg where aprepitant was well tolerated.[11,12] In addition, the concentration 24 hours postdose ($C_{24\ h}$), or trough concentrations, were comparable between fosaprepitant 115 mg (504 ng/mL) and aprepitant 125 mg (494 ng/mL). This similarity in trough concentrations would correlate with a similar NK_1 receptor occupancy, which is near maximal at ~500 ng/mL.[13] Therefore, the present findings suggest that fosaprepitant 115 mg administered IV can be used interchangeably with aprepitant 125 mg administered orally.

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