Pharmacokinetics of a Single 150-mg Intravenous Infusion of Fosaprepitant: Effects of Concentration and Infusion Time in Healthy Japanese Men

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Abstract

Purpose: Fosaprepitant dimeglumine (Proemend® for Injection; formerly ONO-7847) is a phosphorylated prodrug that is rapidly converted to aprepitant, an oral selective neurokinin-1 receptor antagonist approved for the prevention of chemotherapy-induced nausea and vomiting. This Phase I study evaluated the pharmacokinetics, safety, and tolerability of fosaprepitant after a single intravenous dose in healthy Japanese men.

Methods: All fosaprepitant- or placebo-treated subjects were assessed for the occurrence of adverse events.

Results: Ninety subjects were randomized into treatment and placebo groups. The plasma fosaprepitant concentrations generally reached steady state by 15 minutes after the start of infusion. Although the maximum concentration was proportional to the infusion time, no clinically important pharmacokinetic differences were noted in the cohorts examined. Most adverse events observed in this study were associated with infusion site reactions, which tended toward a higher incidence with shorter infusion times. These events were mild in severity.

Conclusions: These findings demonstrate that fosaprepitant at different concentrations and over different infusion times has a pharmacokinetic and safety profile that is comparable to the intravenous dose previously established as efficacious and well tolerated. The dosing flexibility afforded by the single-dose fosaprepitant formulation should lead to greater convenience for patients and health care providers.

Keywords

fosaprepitant, infusion, chemotherapy, nausea, emesis

Nausea and vomiting are common and distressing adverse events (AEs) associated with the administration of cytotoxic chemotherapeutic agents.¹ Aprepitant (Emend®; Merck Sharp & Dohme Corp., a subsidiary of Merck & Co. Inc., Whitehouse Station, NJ, USA) is an orally bioavailable and selective neurokinin-1 receptor antagonist, and was the first agent in this class approved for the prevention of chemotherapy-induced nausea and vomiting (CINV).² Antiemetic treatment guidelines recommend the use of aprepitant in combination with a 5-hydroxytryptamine-3 (5-HT₃) receptor antagonist plus dexamethasone for prevention of the acute and delayed nausea and vomiting that accompanies moderately and highly emetogenic chemotherapy, that is, that in which 30–90% and >90% of patients, respectively, experience nausea and vomiting.³⁻⁵

Fosaprepitant dimeglumine (Proemend® for Injection; Merck & Co. Inc., Whitehouse Station, NJ, USA; formerly ONO-7847) is a phosphorylated prodrug that is rapidly dephosphorylated and converted to aprepitant.⁶ A previous study demonstrated non-inferiority of a 150-mg fosaprepitant single-dose intravenous (IV) regimen compared with a standard aprepitant 3-day oral regimen (125 mg oral aprepitant on Day 1 and 80 mg on Days 2 and 3) in combination with ondansetron and dexamethasone for the prevention of CINV.⁷ It has not previously been determined whether the concentration of the infusion affects the

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pharmacokinetics (PK) and safety of the drug. The objective of the Phase 1 study described here was to investigate the PK, safety, and tolerability of a single IV dose of fosaprepitant given at different concentrations and over different infusion times in healthy Japanese men.

Subjects and Methods

Study Population

Healthy Japanese men aged 20–35 years with a body mass index between 18.5 and 25 kg/m² were enrolled in the study. Subjects were excluded if they had a history of respiratory, circulatory, neurologic, gastrointestinal, hepatic, renal, hematologic, or endocrine disorders. Subjects were also ineligible to enroll in the trial if they: (1) had received any medication within the 2 weeks before the study medication administration; (2) had received any other investigational product (including unapproved products) within the 4 months before the study medication administration; or (3) were expected to receive any drug during the study. Subjects who had donated ≥400 mL of blood within 3 months (or ≥200 mL within 1 month) or plasma/platelet components within 2 weeks before the study medication administration were also ineligible. Other exclusion criteria included excessive consumption of caffeine-containing beverages (equivalent to >4 cups of coffee per day), history of food or drug allergies, and hypersensitivity to polysorbate-80. The trial was conducted in compliance with the ethical principles stated in the Declaration of Helsinki, the provisions of the Pharmaceutical Affairs Law of Japan, and the Ministerial Order on Good Clinical Practice. The protocol was reviewed and approved by the CPC Clinic institutional review board. All subjects voluntarily signed an informed consent form before any study-related procedure was initiated.

Study Design

This was a Phase 1, randomized, double-blind, placebo-controlled, parallel-group, comparative study conducted at a single center (CPC Clinic, Medipolis Medical Research Institute). Subjects were admitted to the study center on the day before the study treatment administration and were discharged at 3 days after the end of the treatment. The subjects in each cohort were randomly assigned to receive either a solution containing 150 mg fosaprepitant (prepared at different concentrations and given over different infusion times) or placebo (i.e., study regimen). An active control group (n = 8) administered a single 30-minute IV infusion of 150 mg fosaprepitant at a concentration of 1.0 mg/mL in saline was also established in each cohort. This allowed investigation of the safety of a single 15- or 30-minute IV infusion of 150 mg fosaprepitant (1.5 mg/mL) (cohorts A and C, respectively) or a single 30-minute IV infusion of 150 mg fosaprepitant (0.6 mg/mL) (cohort B). Each cohort also included a placebo group (n = 6 per cohort). The subjects in cohort C began receiving infusions only after a Safety Monitoring Committee review of the safety information for cohort A. The subjects in each cohort received infusions independently and were observed under randomized double-blind conditions.

Pharmacokinetic Measurements and Statistical Analyses

Blood samples (7 mL) were collected on Day 1 before the study drug administration and at 5, 10, 15, 30, 45, and 60 minutes following the administration for measurements of the plasma concentrations of fosaprepitant and aprepitant. In addition, 2-mL blood samples were collected on Day 1 (1.5, 2, 4, 6, 8, and 12 hours after administration), Day 2 (24 hours after administration), Day 3 (48 hours after administration), and Day 4 (72 hours after administration) for measurements of the aprepitant plasma concentrations. The samples were collected into tubes containing ethylenediaminetetraacetic acid and centrifuged within 1 hour of collection to obtain the plasma. The plasma concentrations of fosaprepitant and aprepitant were determined using a liquid chromatography tandem mass spectrometry (LC–MS/MS) assay. The LC–MS/MS assay was performed with an Agilent 1200 system (Agilent Technologies, Santa Clara, CA, USA) and API 4000 (AB Sciex, Foster City, CA, USA). The respective lower limits of the quantification and the plasma sample volume were 10 ng/mL and 500 µL for fosaprepitant and 1 ng/mL and 100 µL for aprepitant.

The internal standards (ISs) used were a stable isotope labeled fosaprepitant and an analog of aprepitant. Fosaprepitant and the IS were extracted from plasma using Varian Ansys SPEC Plus (C18AR,15 mg) 96 well solid phase extraction plates (Varian, Palo Alto, CA, USA). After evaporation to dryness and reconstitution, the extracts were analyzed by LC–MS/MS. A Synergi Polar-RP, 2.0 mm I.D. × 50 mm, 4 µm (Phenomenex, Torrance, CA, USA) was used as the analytical column at a flow rate of 0.5 mL/min. The mobile phases consisted of A) methanol/10 mM ammonium acetate containing 0.1 mM EDTA (52:48, v/v) and B) methanol/10 mM ammonium acetate containing 0.1 mM EDTA (70:30, v/v). Aprepitant and the IS were extracted from plasma by liquid–liquid extraction using t-butyl methyl ether. After evaporation to dryness and reconstitution, the extracts were analyzed by LC–MS/MS. A SUPER-COSIL LC-8-DB, 4.6 mm I.D. × 33 mm, 3 µm (Supelco, Bellefonte, PA, USA) was used as the analytical column at a flow rate of 1.0 mL/min. The mobile phase consisted of a mixture (50:50, v/v) of 10 mM of ammonium acetate (containing 0.1% formic acid) and acetonitrile. The retention time for fosaprepitant was 1.8 minutes and for
the IS was 1.6 minutes. The retention time for both aprepitant and the IS was 2.1 minutes. All measurements were operated under the positive atmospheric pressure chemical ionization (APCI) mode. Multiple reaction monitoring (MRM)-mode was used for quantification at mass-to-charge ratio (m/z) 535 → 277 for fosaprepitant and aprepitant, m/z 539 → 281 for fosaprepitant-IS, and m/z 503 → 259 for aprepitant-IS. The range of the standard curve for fosaprepitant using a 0.5 mL sample of human plasma was 10–5,000 ng/mL and for aprepitant using a 0.1 mL sample of human plasma was 1–2,000 ng/mL. At the LLOQ (10 ng/mL) for the fosaprepitant assay, the intra-day and inter-day accuracy were −2.4 to 2.0% and −0.7%, respectively, and intra-day and inter-day precision were 3.7–5.9%, and 5.0%, respectively. At the LLOQ (1 ng/mL) for the aprepitant assay, the intra-day and inter-day accuracy were −14.4 to 7.0%, and −6.7%, respectively, and intra-day and inter-day precision were 4.6–9.8% and 12.2%, respectively. There were no interference peaks affecting quantification for either compound. WinNonlin Ver. 6.1 (Pharsight Corporation as part of Certara, St. Louis, MO, USA) was used for calculations of individual PK parameters, and SAS Ver. 9.1.3 (SAS Institute, Cary, NC, USA) was used for calculations of the summary statistics.

The peak plasma concentration (C_{max}) and time to maximum drug concentration (t_{max}) were obtained from the plasma concentration versus time profile for each subject. Each C_{max} was normalized for the dose and body weight (BW) in kilograms (C_{max}/[dose/BW]). The AUC values were also normalized for dose and body weight (AUC_{last}/[dose/BW]). Total clearance (CL) was calculated as follows: CL = dose/AUC_{∞}. The volume of distribution at steady state (V_{ss}) was calculated as follows: V_{ss} = MRT × CL, in which MRT is the mean residence time calculated using the equation MRT = AUMC_{∞}/AUC_{∞}–t_{ci}/2, where AUMC_{∞} is the area under the first moment curve from 0 to infinity and t_{ci} is the time of continuous infusion. The apparent terminal-phase elimination half-life (t_{1/2}) was calculated as ln(2)/λ. The plasma concentrations and PK parameter estimates were tabulated, and descriptive statistics were calculated.

The arithmetic mean value (mean) and standard deviation (SD) of plasma concentrations of fosaprepitant and aprepitant were calculated at each sampling point by treatment arm. When a measurement of plasma concentration was below the limit of quantification (BLQ), the value was treated as 0 in the calculation of mean and SD. When all of the measurements at a time point were BLQ, the mean at the time point was indicated as BLQ and SD was not calculated. When the actual sampling time was beyond ±10% from the scheduled sampling time (beyond ±20% on blood sampling within 15 minutes of the first infusion), or the sampling scheduled before administration was performed after administration, the plasma concentration at the timepoint was excluded from the calculation of the mean and SD. However, for the sampling time of 15 minutes after starting 15-minute continuous infusion, and the sampling time of 30 minutes after starting 30-minute continuous infusion, the plasma concentrations were included in the calculation of the mean and SD when the actual end time of infusion was within ±20% from the scheduled end time, and the actual sampling time was within −3 minutes of the actual end time of infusion, and when the actual end time of infusion was within ±10% from the scheduled end time, and the actual sampling time was within −3 minutes of the actual end time of infusion, respectively.

For C_{max}, AUC_{max}/(DOSE/BW), AUCinf, and AUCinf/(DOSE/BW) of plasma aprepitant, geometric mean ratios between treatment arm 2, 3, or 4 (study group) and treatment arm 1 (control group) and the 90% CIs of the geometric mean ratios were calculated. The geometric mean ratio and the 90% CI were obtained by exponential transformation of the difference of mean log transformed data and the 90% CI of each PK parameter. The residual mean square used in the calculation of the 90% CI was calculated using an analysis of variance with fixed effect (sequence) as a variation factor.

Safety Assessments
Safety was monitored through AE reporting, use of concomitant medication, physical examinations, vital sign assessments (including 12-lead electrocardiograms), and laboratory evaluations.

Results
Study Population
All 90 subjects randomized to receive fosaprepitant or placebo completed the treatment and were included in the safety analysis. Seventy-two subjects who received fosaprepitant were included in the PK analysis.

Pharmacokinetics
The mean plasma concentration versus time profiles of fosaprepitant following a single IV infusion of 150 mg
fosaprepitant are shown in Figure 1a. The plasma concentrations of fosaprepitant reached steady state at 15 minutes after the start of the infusion. The fosaprepitant C_{\text{max}} and C_{\text{max}}/(\text{dose/BW}) were proportional to the infusion rate, and were approximately twofold greater following the 15-minute infusion compared with the 30-minute infusion regimens (Table 1). In addition, the fosaprepitant AUC_{\text{last}} and AUC_{\text{last}}/(\text{dose/BW}) values were higher following the 15-minute infusion compared with the 30-minute infusion regimens. Fosaprepitant in the plasma was rapidly eliminated after the completion of infusion in each group.

The mean plasma concentration versus time profiles of aprepitant following a single IV infusion of 150 mg fosaprepitant are shown in Figure 1b. The distribution ranges for the aprepitant PK parameters (e.g., C_{\text{max}}, t_{\text{max}}, AUC_{\text{last}}, and t_{\frac{1}{2}}) were similar among the 1.0-mg/mL 30-minute infusion, 1.5-mg/mL 30-minute infusion, and 0.6-mg/mL 30-minute infusion groups (i.e., the 90% CIs of the geometric mean ratios of C_{\text{max}} and AUC include 1 or are close to 1). No clinically important PK differences were noted between the 1.0-mg/mL 30-minute infusion and 1.5-mg/mL 15-minute infusion groups (Table 2). In addition, the intergroup similarities in the bioavailability of aprepitant were retained after normalization of the PK parameters (i.e., C_{\text{max}}, AUC_{\text{last}}, and AUC_{\infty}) by the dose and BW.

Safety
No clinically important changes were noted in any of the safety parameters evaluated when 150 mg fosaprepitant was administered to healthy Japanese men in a single dose at different concentrations and over different infusion times. Among the 90 subjects enrolled in the study, 26 (28.9%) experienced at least one AE, of which most were considered to be treatment-related, including infusion site erythema (14.4% of subjects) and injection site pain (13.3%; Table S1). The combined frequency of infusion site reactions (injection site pain and infusion site erythema) following infusion was 5.6% for the placebo group, 18.8% for the 0.6-mg/mL 30-minute infusion group, 29.2% for the 1.0-mg/mL 30-minute infusion group, 43.8% for the 1.5-mg/mL 15-minute infusion group, and 31.3% for the 1.5-mg/mL 30-minute infusion group. Adverse events occurring less frequently included increased gamma-glutamyltransferase and upper respiratory tract inflammation (2% each), and abnormal sensations increased alanine aminotransferase, increased white blood cell count, increased percentage of eosinophils, and myalgia (one subject each). All AEs were mild in severity, and only one (upper respiratory tract inflammation) required treatment. No deaths or serious AEs were observed in the study.

Discussion
Oral administration of aprepitant on a multiple-day schedule (125 mg on Day 1 and 80 mg on Days 2 and 3) in combination with a 5-HT\textsubscript{3} receptor antagonist and dexamethasone has been shown to improve the control of CINV and is well tolerated in subjects receiving moderate to highly emetogenic chemotherapy. It therefore represents an important advance in the control of nausea and vomiting associated with cytotoxic chemotherapy.\textsuperscript{9–12} The subsequent development of its prodrug fosaprepitant has further improved the management of CINV by allowing a single IV administration without the need for extended oral dosing.\textsuperscript{7} In a study of 2,322 patients randomly assigned to 150 ml IV fosaprepitant or a 3-day regimen of oral aprepitant, both given concurrently with ondansetron and dexamethasone, the fosaprepitant was noninferior to aprepitant with respect to complete response in the overall phase of chemotherapy, demonstrating the benefits of a simplified regimen for the prevention of acute and delayed CINV.\textsuperscript{7} Moreover, IV fosaprepitant was generally safe and tolerable compared with oral aprepitant, with the exception of injection site reactions.\textsuperscript{7} Hence, evaluation of the safety of potential
dosing regimens and consequent PK profile was warranted.

In this study, we evaluated the PK and safety of a single IV infusion of 150 mg fosaprepitant administered at different concentrations and over different infusion times in healthy Japanese men. The plasma fosaprepitant concentrations generally reached steady state at 15 minutes after the start of the infusion. The fosaprepitant \( C_{\text{max}} \) was proportional to the infusion time, and was approximately twofold greater for the 15-minute infusion (1.5 mg/mL) than for the 30-minute infusions (1.0, 1.5, and 0.6 mg/mL). Although the fosaprepitant \( C_{\text{max}} \) was proportional to the infusion time, no clinically important PK differences in the plasma aprepitant concentrations were noted between the 1.0-mg/mL 30-minute infusion and 1.5-mg/mL 15-minute infusion groups. The distribution ranges for the plasma aprepitant PK parameters were similar between all three 30-minute infusion groups.

No deaths or serious AEs were associated with the administration of fosaprepitant to healthy Japanese men, regardless of the concentration or the infusion duration. The fosaprepitant group tended to show a higher incidence of infusion site reactions than the placebo group. However, all infusion site reaction events were mild in severity, and fosaprepitant was shown to have a good safety and tolerability profile. However, given that the incidence of infusion site reactions in the 1.5-mg/mL 15-minute infusion group tended to be higher than those in the other fosaprepitant regimen groups and the placebo group, we recommend that infusion of 150 mg fosaprepitant at a concentration of 1.5 mg/mL is performed over at least 30 minutes. No other clinically relevant changes in laboratory test values, physical examination data, and electrocardiographic findings were reported. These results are consistent with previously reported safety and tolerability results in patients receiving cisplatin, a highly-emergenic chemotherapy.

The results of this study show that IV administration of a single 150-mg dose of fosaprepitant at different concentrations and over different infusion times is safe and well tolerated in healthy Japanese men. The assessment of multiple additional concentrations in this study has demonstrated a PK and safety profile that is comparable to the IV dose previously shown to be efficacious and well tolerated.\(^7\) The dosing flexibility afforded by this single-dose fosaprepitant formulation should lead to greater convenience for patients and health care providers.

### Table 1. Pharmacokinetic Parameters of Fosaprepitant in Subjects Receiving a Single 150-mg Intravenous Infusion of Fosaprepitant

| Regimen            | N  | \( C_{\text{max}} \) (ng/mL) | \( t_{\text{max}} \) (h)\(^b\) | \( \text{AUC}_{\text{last}} \) (ng h/mL) | \( \text{AUC}_{\infty} \) (ng h/mL) | \( t_{\infty} \) (h) | CL (L/h) | \( V_{ss} \) (L) |
|--------------------|----|-----------------------------|---------------------------------|----------------------------------------|-------------------------------------|------------------|-----------|---------------|
| 1.0 mg/mL, 30 minutes | 24 | 3,280 ± 370                | 0.50 (0.50–0.40)                 | 51,900 ± 13,700                         | 54,800 ± 16,600                      | 15 ± 5           | 2.55 ± 0.62 | 51.9 ± 11.0 |
| 1.5 mg/mL, 30 minutes | 16 | 3,120 ± 490                | 0.50 (0.50–0.50)                 | 48,600 ± 10,500                         | 50,600 ± 11,700                      | 14 ± 3           | 2.69 ± 0.60 | 53.8 ± 11.8 |
| 0.6 mg/mL, 30 minutes | 16 | 3,240 ± 440                | 0.50 (0.50–0.50)                 | 53,300 ± 12,800                         | 54,400 ± 13,200                      | 16 ± 5           | 2.52 ± 0.59 | 54.0 ± 7.7   |
| 1.5 mg/mL, 15 minutes | 16 | 3,600 ± 480                | 0.25 (0.25–0.25)                 | 56,100 ± 21,100                         | 54,500 ± 15,000                      | 17 ± 9           | 2.59 ± 0.82 | 55.2 ± 10.2 |

\( \text{AUC}_{\infty} \), area under the plasma concentration versus time curve from time 0 to infinity; \( \text{AUC}_{\text{last}} \), area under the plasma concentration versus time curve from time 0 to the last measurable concentration; CL, total clearance; \( C_{\text{max}} \), peak plasma concentration; \( t_{\text{max}} \), time to maximum plasma concentration; \( t_{\infty} \), apparent terminal elimination-phase half-life; \( V_{ss} \), volume of distribution at steady state.

\(^{a}\)Mean ± SD, except where stated otherwise.

\(^{b}\)Median (range).

\(^{c}\)n = 15.
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Declaration of Conflicting Interests

Hiroyuki Fukase declared no conflicts of interest.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher’s web-site.

Table S1. Summary of Adverse Events