CLINICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	22,023/S-017, IND 48924
Priority or Standard	Priority
Submit Date(s)	02 October 2017
Received Date(s)	02 October 2017
PDUFA Goal Date	03 April 2018
Division/Office	DGIEP/ODE3
Reviewer Name(s)	Aisha Peterson Johnson, MD, MPH, MBA
Review Completion Date	March 2, 2018
Established/Proper Name	fosaprepitant dimeglumine
(Proposed) Trade Name	Emend for Injection
Applicant	Merck Sharp & Dohme Corp.
Dosage Form(s)	Solution for injection
Applicant Proposed Dosing Regimen(s)	• In pediatric patients (6 months to 17 years of age) receiving single or multi-day chemotherapy regimens of HEC or MEC, a 3-day intravenous regimen of EMEND for injection is recommended. ○ EMEND capsules or EMEND for oral suspension may also be used on Days 2 and 3 instead of EMEND for injection. • In pediatric patients (6 months to 17 years of age) receiving a single-day chemotherapy regimen, an alternative 1-day intravenous regimen of EMEND for Injection may be administered. EMEND for Injection is administered as an intravenous infusion through a central venous catheter over 30 minutes (12 years of age to 17 years) or over 60 minutes (6 months of age to less than 12 years) completing the infusion approximately 30 minutes prior to chemotherapy.
Applicant Proposed Indication(s)/Population(s)	EMEND for injection, in combination with other antiemetic agents, is indicated in adults and pediatric patients 6 months of age and older for the prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin. • delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).
Recommendation on Regulatory Action	Approval with modification to proposed dosing regimens to exclude fosaprepitant on Days 2 and 3 of the proposed 3-day regimen due to lack of safety data to support proposed 3-day fosaprepitant/fosaprepitant/fosaprepitant regimen

Recommended Indication(s)/Population(s) (if applicable)	Same as Applicant's proposed

Table of Contents

Table of Tables

Executive Summary

1.1. Product Introduction

Trade Name: EMEND® for Injection
Generic Name: Fosaprepitant dimeglumine
Pharmacological Class: Neurokinin type 1 receptor antagonist
Fosaprepitant is a prodrug of aprepitant that can be administered intravenously (IV).
Fosaprepitant is converted to aprepitant (within 30 minutes) after IV administration via the action of ubiquitous phosphatases, and the pharmacological effect of fosaprepitant is attributed to aprepitant.

Proposed Dosing Regimen

Table 1. Proposed 3-Day IV/PO Fosaprepitant/Aprepitant Dosing Regimen and 1-Day Fosaprepitant Regimens by Age Group

(b) (4)

Electronically copied and reproduced from Summary of Clinical Pharmacology, Table 2.7.2: 13

MO Comment:
Due to lack of safety data to support fosaprepitant dosing on Days 2 and 3 of the proposed 3-Day regimen, only regimens with fosaprepitant on Day 1 are recommended for approval. This issue will be discussed in detail in Section 8 of this review.

Currently approved indications

EMEND® for injection is a substance P/neurokinin-1 (NK1) receptor antagonist, indicated in adults, in combination with other antiemetic agents, for the prevention of:

- acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy (HEC) including high-dose cisplatin.
- delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Emend for Injection was found to be effective for prevention of CINV in pediatric patients receiving MEC and HEC. The efficacy of a 1-day fosaprepitant regimen in pediatric patients receiving one day of chemotherapy can be extrapolated from adult patients with similar exposures and receiving chemotherapy for a single day. The efficacy of a 3-day fosaprepitant regimen in pediatric patients receiving multi-day chemotherapy can be bridged from the approved pediatric 3-day oral aprepitant regimen based on matching aprepitant exposure for the fosaprepitant dose on Day 1 and using the same approved aprepitant oral dose for Day 2 and Day 3.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The benefit of fosaprepitant for the prevention of CINV in pediatric patients outweigh the known risks. Chemotherapy-induced nausea and vomiting (CINV) is a potentially severe and debilitating side effect of chemotherapy.

The safety profile observed in Protocols 134, 029, and 044 submitted in support of the current Application is consistent with the labeled safety profile of fosaprepitant. During these studies, pediatric patients were treated with fosaprepitant for no longer than one day. Exposure matching produced modeling and simulation results for Cmax values for the Day 2 and 3 fosaprepitant regimens that were 1.5- to 2-fold higher than observed with oral aprepitant. Although the Day 1 fosaprepitant Cmax is higher than the Day 2 and Day 3 Cmax simulated values, the lack of safety data in patients who had received 3 consecutive days of fosaprepitant recludes a clinical recommendation to approve any regimen including fosaprepitant on Day 2 and/or Day 3.. Therefore, the safety of the Applicant's proposed 3-Day fosaprepitant/fosaprepitant/fosaprepitant regimen is not supported by the safety information reviewed for this application. However, the safety information does support a 1-day fosaprepitant regimen for pediatric patients receiving 1-day chemotherapy and a 3-day fosaprepitant/aprepitant/aprepitant dosing regimen. The safety of aprepitant for Days 2 and 3 is supported

by pediatric studies and post-marketing experience of oral aprepitant for the prevention of CINV.

Fosaprepitant labeling adequately describes the known risks associated with the use of fosaprepitant in adults. The labeled Warnings and Precautions include Clinically Significant CYP3A4 Drug Interactions, Hypersensitivity Reactions, Decrease in INR with Concomitant Warfarin, and Risk of Reduced Efficacy of Hormonal Contraceptives. Of these, only hypersensitivity reactions were observed in the safety population of pediatric patients reviewed for the current Application.

Hypersensitivity reactions including anaphylaxis were observed at an incidence rate of 2% in the 199 patients of the primary safety population for the current Application. These reactions are of concern. The administration of fosaprepitant in a clinical setting by professionals trained to recognize these events can help to mitigate some of the risk of adverse outcome associated with these reactions. Current EMEND for Injection labeling instructs health care professionals (HCPs) to monitor patients during and after infusion. Labeling also instructs HCPs todiscontinue the fosaprepitant infusion and administer appropriate medical therapy if hypersensitivity reactions are observed. Further labeling warns HCPs not to reinitiate EMEND in patients who experience these symptoms with first-time use.

The efficacy of a 1-day fosaprepitant regimen in pediatric patients can be extrapolated from adult patients with similar exposures and receiving chemotherapy for a single day. The efficacy of a 3-day fosaprepitant regimen in pediatric patients can be bridged from the 3-day oral aprepitant regimen based on matching exposure for the Day 1 fosaprepitant dose and using the same oral aprepitant dose for Days 2 and 3.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Nausea and vomiting is a known adverse reaction associated with the use of chemotherapy agents • Highly emetogenic chemotherapy (HEC) agents are those associated with CINV in >90% of treated patients. Moderately emetogenic	Chemotherapy-induced nausea and vomiting (CINV) is a potentially severe and debilitating side effect of chemotherapy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	chemotherapy (MEC) agents are those associated with CINV in 31% to 90% of patients.	
Current Treatment Options	• NK-1 receptor antagonists are a class of drug approved in adults for the prevention of CINV. The class is known to have a good safety profile and work in the delayed phase of CINV. • Aprepitant, the active metabolite of fosaprepitant, is approved as a 3-day regimen in pediatric patients • 5HT3 receptor antagonists (known to work for prevention of CINV in the acute phase) are approved for pediatric patients	• There is currently no intravenous NK-1 receptor antagonist approved in pediatric patients for the prevention of CINV.
Benefit	• EMEND for Injection is known to be effective for the prevention of CINV in adults. • Aprepitant, the active metabolite of fosaprepitant, is approved as 3-day regimen in pediatric patients for the prevention of CINV • CINV pathophysiology and response to NK1 receptor blockade is similar in adult and pediatric patients	It is appropriate to extrapolate efficacy from adults to pediatric patients for both 1-day fosaprepitant and 3-day fosaprepitant/aprepitant/aprepitant regimens.
Risk and Risk Management	• Labeled Warnings and Precautions include Clinically Significant CYP3A4 Drug Interactions, Hypersensitivity Reactions, Decrease in INR with Concomitant Warfarin, and Risk of Reduced Efficacy of Hormonal Contraceptives • The safety profile was similar in the 199 pediatric patients who received fosapepitant as part of Protocols 134, 029, and 044	The risks associated with the use of fosaprepitant is adequately described in current labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Although multi-day chemotherapy was infrequently administered in the adult single dose IV fosaprepitant program, multi-day chemotherapy was commonly administered in the oral aprepitant pediatric development program. Protocol 208, the pivotal pediatric aprepitant safety and efficacy study, compared the 3-day oral aprepitant regimen versus the control regimen for the prevention of CINV in pediatric cancer patients. Eighty-six percent (86%) of the children enrolled in P208 (260 of 302 total subjects) received multi-day emetogenic chemotherapy; thus, there are considerable data available to justify the development of a multiday fosaprepitant regimen using model-based approaches. More importantly, the clinical benefit of aprepitant was demonstrated in children receiving either single or multiday chemotherapy.

2.2. Analysis of Current Treatment Options

Table 2. Summary of Prevention of CINV Products Approved for Pediatric Patients

Drug/Class	Indication	Pediatric Age Group
Ondansetron (Zofran) IV/ 5-HT3 receptor Antagonist	Prevention of CINV-HEC	6 months to 17 years
Palonosetron (Aloxi) IV/ 5-HT3 receptor antagonist	Prevention of CINV-HEC and CINV-MEC	1 month to 17 years
Aprepitant (Emend) oral	Prevention of CINV-HEC and CINV—MEC	6 months to 17 years

Reviewer's Table,

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

EMEND (oral capsules and oral suspension) Regulatory History

- Aprepitant (EMEND oral capsules) was approved on March 27, 2003 as part of a three day regimen for the prevention of acute and delayed chemotherapy induced nausea and vomiting (CINV) with initial and repeat courses of highly emetogenic chemotherapy (CINV-HEC) regimens in adults (NDA 21549/S-01).
- Efficacy supplement NDA 21549/S-008 was approved on October 28, 2005, for the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC) in adults (NDA 21549/S-008).

- On August 23, 2015, aprepitant capsules were approved for use in pediatric patients ages ≥ 12 to 17 years (and patients less than 12 years who weight at least 30 kg) for the prevention of CINV associated with HEC and MEC (NDA 21549/S-025).
- Aprepitant oral suspension was approved on 17 December 2015 for prevention of chemotherapy induced nausea and vomiting in patients ages 6 months of age and older.

EMEND for Injection Brief Regulatory History

- On January 25, 2008, EMEND for Injection 115 mg (fosaprepitant dimeglumine) was approved in adults as an alternative administration route for Day 1 of the aprepitant oral 3-day regimen (EMEND for Injection 115 mg on Day 1 followed by EMEND oral capsules 80 mg on Days 2 and 3):
    - the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin (CINV-HEC).
    - the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (CINV-MEC).

MO Comment:
The approval of EMEND for Injection 115 mg relied upon the demonstration of bioequivalence between fosaprepitant 115 mg and aprepitant 125 mg. The safety of the higher Cmax observed with fosaprepitant 115 mg was based upon previous clinical data for oral aprepitant 375 mg. The Sponsor did not pursue (b) (4) .

- On 12 November 2010, EMEND for Injection 150 mg was approved in adults as a single-day dosing regimen for CINV-HEC.

MO Comment:
The approval of the EMEND for injection 150 mg single day regimen for CINV-HEC in adults was based upon the results of a clinical trial showing fosaprepitant 150 mg single dose regimen was non-inferior to the approved aprepitant 3-day regimen (125 mg Day 1 and 80 mg on Days 2 and 3). The study did not include an adequate number of patients receiving MEC. Following the approval of the fosaprepitant 150 mg single dose, the Sponsor announced that beginning on 30 December 2010, sales of EMEND for Injection 115 mg would be discontinued. This action was not done as a result of safety or efficacy.

- On 10 February 2016, EMEND for Injection 150 mg was approved in adults as single -day dosing regimen for CINV-MEC, delayed phase only.

MO Comment:

The approval of the EMEND for injection 150 mg single day regimen for CINV-MEC in adults was based upon the results of a single adequate and well-controlled study showing fosaprepitant 150 mg single dose regimen was efficacious for the prevention of CINV-MEC for the delayed phase (>24-120 hours after chemotherapy). Efficacy was not shown during the acute phase.

3.2. Summary of Presubmission/Submission Regulatory Activity

Date	Relevant Regulatory History, pediatric fosaprepitant development program
02 Feb 2009	FDA Issued a single Written Request for aprepitant and fosaprepitant
8 April 2011	FDA issued Amendment #1 to the Written Request. Changes included eliminating apreptitant from current WR.
15 March 2012	FDA issued Amendment #2 to the WR
26 March 2012	FDA found the Sponsor's proposal to develop a pediatric fosaprepitant formulation with 5.4 mg of EDTA per vial acceptable (compared with 15.1 g EDTA per vial in the product marketed at that time)
22 March 2016	Type C, Teleconference • Sponsor proposed to extrapolate the efficacy of a single-day regimen of intravenous (IV) fosaprepitant from adults to pediatric patients based upon pharmacokinetic (PK) data showing similar aprepitant exposure observed in pediatrics in comparison to that of adults • FDA expressed concerns with the potential limitations of full extrapolation in the setting of multi-day chemotherapy given the differences in PK between one day IV dose regimen and 3- day oral dosing • FDA agreed that sponsor's revised proposal to obtain a 3-day IV fosaprepitant regimen in pediatrics based upon matching exposures observed with the approved multi-day oral aprepitant regimen in pediatrics appears reasonable • FDA stated that the amount of available safety data collected across the oral and IV pediatric programs *may be* sufficient to characterize the safety profile of a single -day regimen of fosaprepitant in the pediatric population (based on the age distribution of the observed data). • FDA agreed that diligent and reasonable efforts have been made to collect dexamethasone PK data in patients < 1 year of age as required as part of the WR.

14 June 2016	Sponsor requested release from the following Pediatric Research Equity Act (PREA) PMRs: <u>1450-1</u> A study in adolescents and younger pediatric patients receiving emetogenic chemotherapy (HEC or MEC) to evaluate fosaprepitant PK, safety, and tolerability. Final Report Submission: December 31, 2017 <u>1663-1</u> A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation. Final Protocol Submission: August 2012 Study/Trial Completion: March 2017 Final Report Submission: August 2017 <u>1663-2</u> An adequate, placebo-controlled, double-blind, randomized, add-on design, superiority study to evaluate the safety and efficacy of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist, as compared to standard therapy (a 5HT3 antagonist) in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation. Final Protocol Submission: August 2014 Study/Trial Completion: August 2017 Final Report Submission: December 2017
13 July 2016	Type C, Meeting Canceled after preliminary comments deemed sufficient by Sponsor • FDA found Sponsor's proposal to extrapolate the efficacy of single dose IV fosaprepitant from adults to pediatric patients receiving single day chemotherapy regimens reasonable

	• FDA disagreed with the Sponsor's proposed (b) (4) [redacted]. • FDA confirmed that the planned size and nature of the proposed safety data base (including available data collected across the oral and IV pediatric programs) appears reasonable to characterize the proposed fosaprepitant single-day and 3-day regimens in pediatric patients. FDA qualified this confirmation by stating that the "adequacy of the safety data will be determined when the application is reviewed". • FDA recommended that the Sponsor conduct label comprehension studies to better define appropriate approach to labeling given the challenges seen in writing the Dosage and Administration section of the label
13 October 2016	FDA issued Amendment # 3 to the WR FDA granted the Sponsor's request for release of PMRs 1450-1, 1663-1,and 1663-2 and issued a new deferred PREA PMR described below: 1663-3 A PK/PD study to characterize aprepitant PK parameters following administration of a single dose of intravenous fosaprepitant, in combination with a 5HT3 antagonist and dexamethasone, in pediatric cancer patients ages 0 to 17 years undergoing treatment with highly emetogenic chemotherapy. You must conduct this study with an age appropriate formulation. Use modeling and simulation including the results of the above study to identify 1-Day and 3-Day intravenous fosaprepitant doses in pediatric patients 0 to 17 years of age that provide similar aprepitant PK exposures to pediatric aprepitant doses and exposures which have demonstrated acceptable safety and efficacy profiles in patients receiving single and multi-day chemotherapy regimens, respectively. Final Report Submission: December 2017
18 Jan 2017	Type C FDA confirmed that diligent and reasonable efforts appear to have been made by the Sponsor to enroll patients less than 6 months of age. however, FDA declined to change the WR language of the youngest cohort (0-2 years of age) to document the importance of obtaining information in this age group.
27 Feb 2017	FDA issued Amendment # 4 to the WR

MO Comment: As described above, the current submission is being submitted to fulfill a PREA PMR and also a Written Request. The review team concluded that the Applicant fairly

responded to the written request (and any other relevant conclusions from the Ped Exclusivity Determination Checklist and/or the Ped Exclusivity Template). This Application was discussed at the FDA CDER OND Pediatric Exclusivity Board on 28 February 2018 and the Board agreed that the terms of the Written Request had been met and exclusivity will be granted.

3.3. Foreign Regulatory Actions and Marketing History

As of 10 May 2017, fosaprepitant 150 mg (single dose regimen) is registered and approved in more than 75 countries for prevention of CINV in adults. Although initially approved for use, most countries have deleted registration of the 115 mg dose of fosaprepitant, given the availability of the more convenient single day, 150 mg regimen. There are no records of any registration being revoked or withdrawn for safety reasons.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The OSI reviewer and OND review team concluded that OSI inspections are not indicated for the current supplement. This decision was based on the fact that no clinical efficacy study is being relied upon for the determination of efficacy combined with the lack of any other issues that need to be resolved on inspection.

4.2. Product Quality

No change in the currently marketed fosaprepitant dimeglumine (EMEND for Injection) formulation are proposed in the current Application.

4.3. Clinical Microbiology

No change in the currently marketed fosaprepitant dimeglumine (EMEND for Injection) formulation are proposed in the current Application.

4.4. Nonclinical Pharmacology/Toxicology

No change in the currently marketed fosaprepitant dimeglumine (EMEND for Injection) formulation are proposed in the current Application.

4.5. Clinical Pharmacology

Fosaprepitant is a neurokinin type 1 receptor antagonist. Fosaprepitant is a prodrug of aprepitant that can be administered intravenously (IV). Fosaprepitant is converted to aprepitant (within 30 minutes) after IV administration via the action of ubiquitous phosphatases, and the pharmacological effect of fosaprepitant is attributed to aprepitant. During each of the pharmacokinetic studies (Protocols 134, 029, and 044) submitted in support of the current Application, patients received fosaprepitant only once per cycle. For patients receiving multi-day chemotherapy in Study 134, patients were given oral aprepitant on Days 2 and 3. Study 029 was designed only to study single dose fosaprepitant. And the only phase 3 study, Study 044, was designed to study only single dose fosaprepitant. Study 044 was terminated early after consultation with FDA confirmed that the available PK, efficacy and safety data in the fosaprepitant and aprepitant programs were sufficient to support the approval of the proposed 1-day and 3-day IV fosaprepitant regimens.

Section 5.1 contains a table of the pharmacokinetic studies submitted in support of the current Application. Section 5.2 contains a discussion regarding the appropriateness of relying on simulation and modeling and extrapolation.

Section 7 contains additional details regarding the PK/PD studies submitted along with a review of the safety results of the pharmacokinetic studies. For a more detailed description of the pharmacokinetic studies and their results used to support bridging and extrapolation see the clinical pharmacology reviews in DARRTS.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Sample Table. Listing of Clinical Trials Relevant to this NDA/BLA

Trial ID	Protocol	Trial Design	Regimen/ schedule/ route	Location of Trial Centers
2006-005515-10	Protocol 134	Phase 1, Multicenter, open-label, 5-part study to Evaluate the Pharmocokinetics, Safety, and Tolerability of Aprepitant and Fosaprepitant Dimeglumine in Pediatric Patients Receiving Emetogenic Chemotherapy	**Part IA:** Subjects 12-17 years of age. Day 1: 115 mg IV fosaprepitant with IV ondansetron ±IV dexamethasone. Days 2 and 3: 80 mg oral aprepitant and IV ondansetron ±IV dexamethasone. **Part IB:** Subjects 12-17 years of age. Day 1: 150 mg IV fosaprepitant with IV ondansetron ±IV dexamethasone. **Part IIA:** Subjects <12 years of age. Day 1: Oral aprepitant dose equivalent to 80 mg in adults with IV ondansetron ±IV dexamethasone. **Part IIB:** Subjects <12 years of age. Day 1: Oral aprepitant dose equivalent to 125 mg in adults with IV ondansetron ±IV dexamethasone. **Part III**: Subjects <12 years of age. Days 1-3: IV ondansetron ±IV dexamethasone. **Part IV:** Subjects <12 years of age. Day 1: Oral aprepitant at a dose equivalent to 125 mg in adults with IV ondansetron ± IV dexamethasone. Days 2 and 3: Oral aprepitant at a dose equivalent to 80 mg in adults with IV ondansetron ± IV dexamethasone. **Part V:** Subjects 6 months to <12 years of age. Day 1: IV fosaprepitant at a dose equivalent to 150 mg in adults with IV ondansetron ±IV dexamethasone.	Australia, Brazil, Canada, Colombia, France, Germany, Hungary, Israel, Mexico, Norway, Peru, Poland, Spain, Sweden, Switzerland, USA
2012-002340-	Protocol 029	A Phase 2b, Partially-Blinded, Randomized, Active Comparator-Controlled Study to Evaluate the Pharmacokinetics/Pharmacodynamics,	**Dose 1**: Fosaprepitant 150 mg (*43 randomized*) • Subjects 12 to 17 years old administered 150 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 3 mg/kg (not to exceed 150 mg)	Argentina, Austria, Brazil, Canada, Chile, Colombia,

24		Safety, and Tolerability of Fosaprepitant in Pediatric Subjects for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) Associated with Emetogenic Chemotherapy	**Dose 2**: Fosaprepitant 60 mg (44 randomized) • Subjects 12 to 17 years old administered 60 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 1.2 mg/kg (not to exceed 60 mg) **Dose 3**: Fosaprepitant 20 mg (*41 randomized*) • Subjects 12 to 17 years old administered 20 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 0.4 mg/kg (not to exceed 20 mg) **Dose 4**: Fosaprepitant 5 mg/kg (*74 randomized*) • Subjects 4 months to <12 years old administered a weight-adjusted dose of 5 mg/kg (not to exceed 150 mg) • Subjects 1 to <4 months old administered a weight-adjusted dose of 2.5 mg/kg • Subjects 0 to <1 month old administered a weight-adjusted dose of 1.25 mg/kg	Estonia, Germany, Greece, Hungary, Italy, Lithuania, Mexico, Peru, Portugal, Romania, Russia, South Africa, South Korea, Spain, Switzerland, Turkey, United Kingdom, Ukraine, United States
2014-001783-34	Protocol 44 (P044MK0517)	A Phase 3, Randomized, Placebo-Controlled Clinical Trial to Study the Efficacy and Safety of MK-0517/Fosaprepitant and Ondansetron Versus Ondansetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Subjects Receiving Emetogenic Chemotherapy.	Cycle 1 and Optional Cycles 2 to 6 Age 0 to < 12 years: **Day 1**: Fosaprepitant 5 mg/kg (or age-specific adjustment not to exceed 150 mg), 90 minutes prior to initiation of the first emetogenic chemotherapy, via a central venous catheter, over a period of approximately 60 minutes + ondansetron (Cycle 1) or any 5-HT3 antagonist (Cycles 2 to 6), no later than 30 minutes prior to initiation of chemotherapy. Age 12 to 17 years: **Day** 1: Fosaprepitant 150 mg, 60 minutes prior to initiation of the first emetogenic chemotherapy, via a central venous catheter, over a period of	Chile, Colombia, Estonia, Finland, Greece, Hungary, Lithuania, Mexico, Netherlands, Norway, Poland, Russia, South Korea, Spain, Sweden, United Kingdom

			approximately 30 minutes + ondansetron (Cycle 1) or any 5-HT3 antagonist (Cycles 2 to 6), no later than 30 minutes prior to initiation of chemotherapy.	

5.2. Review Strategy

The Applicant did not submit the efficacy results of any well-controlled trials in support of the current Application. Instead, the Applicant is relying upon bridging and extrapolation. The Applicant uses the term "bridging" to refer to the inference that the efficacy of the proposed pediatric 3-day fosaprepitant regimen can be predicted from that demonstrated with the pediatric 3-day oral aprepitant regimen. This inference is possible given that the activity of fosaprepitant is attributable to aprepitant. For efficacy of the 1-day fosaprepitant regimen in children, the Applicant is relying upon extrapolation from efficacy demonstrated in adults. This extrapolation from adults to pediatric patients is only applicable to pediatric patients receiving a single day of chemotherapy.

Recently, similarities between adult and pediatric CINV pathophysiology and response to NK1 receptor antagonists were confirmed with the demonstration of aprepitant efficacy in children at exposures similar to those associated with safety and efficacy in adults. Based on these results, the efficacy of a 1-day fosaprepitant regimen in children can be extrapolated from that demonstrated in adults, given similar aprepitant exposures and comparable clinical circumstances (i.e., receipt of single-day emetogenic chemotherapy).

- Data suggest that the basic pathophysiology of CINV and CNS NK1 receptor distribution, affinity and density remain relatively stable throughout life.
- The substantial overlap of chemotherapeutic agents that cause CINV in adults and children suggests a common pathophysiology for CINV, regardless of age.
- Similarities in the prophylaxis and treatment of pediatric and adult CINV exist in established clinical practice and are reflected in published adult and pediatric oncology guidelines

The safety results from Studies 029, 033, and 129 were reviewed and are discussed in Section 6 of this review.

MO Comment:
The Sponsor's rationale for bridging and extrapolation are acceptable.

For the proposed 3-day pediatric regimen, bridging the pediatric 3-day fosaprepitant regimen to the approved pediatric 3-day oral aprepitant regimen is a scientifically rational approach suggested to the Sponsor by the FDA. The efficacy of the single day fosaprepitant pediatric dose was extrapolated from the efficacy of single dose fosaprepitant observed in adults.

While the AUCs of the bridged aprepitant and fosaprepitant doses (based on modeling and simulation) were relatively close, the Cmax (aprepitant) of the proposed fosaprepitant doses on each day are predicted to be 1.5-2x higher than those observed with oral aprepitant. The higher

Cmax was anticipated due to the differences in the route of administration (oral vs. intravenous). Safety information for the higher Day 1 Cmax is adequate from the PK studies used to support bridging and extrapolation. Given that no pediatric patients were given fosaprepitant on Days 2 or 3, there is inadequate safety data to support the higher Cmax predicted through simulation and modeling.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Protocol 044

Protocol 044 was planned as a phase 3 safety and efficacy study of single-dose fosaprepitant in pediatric patients for the prevention of chemotherapy-induced nausea and vomiting. However, the study was terminated early when the Applicant and the FDA reached agreement that no further studies were necessary and additional information to support approval could be obtained through modeling and simulation. Therefore, no efficacy information will be reviewed for this application.

Efficacy for the proposed 1-day fosaprepitant regimen will be extrapolated from the fosaprepitant 1-day regimen in adults. Efficacy for the proposed 3-day fosaprepitant regimen will be obtained by bridging to the 3-day aprepitant pediatric program by matching exposures.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

No efficacy trial data were reviewed as part of the current Application

7.2. Additional Efficacy Considerations

n/a

7.3. Integrated Assessment of Effectiveness

n/a

8. Review of Safety

8.1. Safety Review Approach

The safety results for the PK/PD Studies 134, 029, and the phase 3 efficacy and safety Study 044 will be discussed as part of the safety review. The primary safety population includes all patients who were exposed to fosaprepitant (any dose) in Protocols 134, 029, and 044 during Cycle 1. The supplemental safety population includes patients exposed during cycles 2 through 6.

PROTOCOL 134
Protocol 134 was a phase 1, multicenter, open-label, 5-part study to evaluate the pharmocokinetics, safety, and tolerability of aprepitant and fosaprepitant in pediatric patients receiving emetogenic chemotherapy. In Part I of the Study, 12-17 year old patients were treated with fosaprepitant. During Part IA, patients were treated with a 3-Day regimen of fosaprepitant on Day 1 and oral aprepitant on Days 2 and 3. During Part IB, patients were treated with 1-Day regimen of single dose fosaprepitant on Day 1 only.

Table 3. Protocol 134, Treatment Regimen Details

Study Part	Age Group Studied	Number of Patients Randomized	Treatment Regimen Day 1	Treatment Regimen Days 2 & 3
Part IA	12-17 years	43	115 mg IV fosaprepitant	80 mg oral aprepitant
Part IB	12-17 years	44	150 mg IV fosaprepitant	n/a
Part IIA	<12 years	n/a	Oral aprepitant dose equivalent to 80 mg in adults	n/a
Part IIB	<12 years	n/a	Oral aprepitant equivalent to 125 mg in adults	n/a
Part III	<12 years	n/a	n/a	n/a
Part IV	<12 years	n/a	Oral aprepitant at a dose equivalent to 125 mg in adults	Oral aprepitant at a dose equivalent to 80 mg
Part V	6 months to <12 years	23	IV fosaprepitant at a dose equivalent to 150 mg in adults	n/a

All aprepitant and fosaprepitant doses were accompanied by IV ondansetron ± dexamethasone
*During part III, patients were treated with ondansetron ± dexamethasone, only

PROTOCOL 029

Protocol 029 was a phase 2b, partially-blinded, randomized, active comparator-controlled study to evaluate the pharmacokinetics/pharmacodynamics, safety, and tolerability of single-dose fosaprepitant in pediatric subjects for the prevention of chemotherapy-induced nausea and vomiting (CINV). Protocol 029 was initially planned to include four treatment groups (administered with ondansetron ± dexamethasone):

- Control (placebo to fosaprepitant)
- Fosaprepitant 3 mg/kg (to a maximum of 150 mg),
- Fosaprepitant 1.2 mg/kg (to a maximum of 60 mg),
- Fosaprepitant 0.4 mg/kg (to a maximum of 20 mg).

The aim of the fosaprepitant dosing regimens was to achieve aprepitant PK exposures to match those seen in adults receiving 150 mg, 60, and 20 mg of single-day fosaprepitant IV. However, the interim analysis results revealed that while the plasma aprepitant concentrations in adolescents matched the adult targets, the plasma concentrations observed in patients <12

years of age were lower than seen in adults. Therefore, the protocol was amended to include an open-label treatment arm of fosaprepitant 5 mg/kg in pediatric patients <12 years of age in an effort to reach adult aprepitant targets.

Table 4. Protocol 029, Treatment Regimen Details

Adult Fosaprepitant Dose	Pediatric Dose Studied	Number of Patients Randomized
Fosaprepitant 150 mg	• Subjects 12 to 17 years old administered 150 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 3 mg/kg (not to exceed 150 mg)	43
Fosaprepitant 60 mg	• Subjects 12 to 17 years old administered 60 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 1.2 mg/kg (not to exceed 60 mg)	44
Fosaprepitant 20 mg	• Subjects 12 to 17 years old administered 20 mg • Subjects 2 to <12 years old administered a weight-adjusted dose of 0.4 mg/kg (not to exceed 20 mg)	41
Fosaprepitant 5 mg/kg*	• Subjects 4 months to <12 years old administered a weight-adjusted dose of 5 mg/kg (not to exceed 150 mg) • Subjects 1 to <4 months old administered a weight-adjusted dose of 2.5 mg/kg • Subjects 0 to <1 month old administered a weight-adjusted dose of 1.25 mg/kg	74

***** Fosaprepitant 5 mg/kg dose added after interim analysis

Protocol 044

Protocol 044 was initiated as a phase 3, randomized, placebo-controlled clinical trial comparing the combination of a single dose of fosaprepitant with ondansetron to ondansetron alone for the prevention of CINV in pediatric subjects receiving emetogenic chemotherapy. Dose selection was supported by PK/PD data from Protocol 134 and 029 (described above) along with data from the aprepitant pediatric development program.

Enrollment in Protocol 044 was closed early after the Applicant met with the FDA and it was

agreed that available PK, efficacy and safety data in the fosaprepitant and aprepitant programs were sufficient to support the approval of the proposed 1-day and 3-day fosaprepitant regimens. See regulatory history in Section 3.2 above.

Safety data from these three studies are reviewed. In general, the safety data are discussed as the 1-Day Supportive Pool and the 3-Day supportive Pool. The 1-Day Supportive Pool consists of pooled AE safety data from pediatric subjects who received fosaprepitant at or above the proposed 1-day fosaprepitant dose.

Safety Pooling Groups

The 1-Day Supportive Pool includes 139 pediatric subjects who received single-dose fosaprepitant 150 mg or 5 mg/kg in Protocol 134, and Cycle 1 of Protocols 029 and 044. The 3-Day Supportive Pool includes 199 patients from Protocols 029 and 044 who received a single IV fosaprepitant dose of 3 mg/kg, 5mg/kg or 150 mg or a 115 mg fosaprepitant dose as part of a 3-day IV/PO/PO regimen with oral aprepitant. It should be noted that these safety pooling groups are not discrete. All the patients in the 1-day Supportive Pool are also included in the 3-Day Supportive Pool. See Table 5 below.

Supportive safety data is also available from Cycles 2 through 6 of the Protocols 029 and 044. Due to differences in safety reporting for these optional cycles, these data are not integrated with Cycle 1 data. See Table 6 below.

Table 5. Pooled Dataset for Primary Safety Analysis, Protocols 134 Parts I and V, Protocol 029 (Cycle 1) and Protocol 044 (Cycle 1)

Integrated Dataset Treatment Groups	Age Subgroup and Protocol Numbers		Total
	12 to 17 years of age	<12 years of age	
1-Day Supportive Pool Includes: Fosaprepitant 150 mg + 5mg/kg doses to support 1-day dosing regimen	**150 mg** Includes data from Protocols: 134 Part IB (N=11) 029 (N=17) 044 (N=18)	**5mg/kg** Includes data from Protocols: 029 (N=74) 044 (N=19)	**N= 139**
3-Day Supportive Pool Includes: Fosaprepitant 150 mg + 5mg/kg + 3 mg/kg and a 3-day regimen of fosaprepitant 115 mg on Day 1 and aprepitant 80 mg on Days 2 and 3 to support 3-day dosing regimen	**150 mg** Includes data from Protocols: 134 Part IB (N=11) 029 (N=17) 044 (N=18) **115mg** Includes data from Protocol 134 Part IA (N=12)	**5mg/kg** Includes data from Protocols: 029 (N=74) 044 (N=19) **3mg/kg** Includes data from Protocols: 134 Part V (N=23) 029 (N=25)	**N=199**
Control Regimen	Includes subjects from the control regimen of Protocol 029 (N=35) and Protocol 044 (N=34)		**N=69**
Total	Includes subjects who received fosaprepitant (***3-Day Supportive Pool,*** N=199) and subjects in the control regimen (N=69).		**N=268**

Electronically copied and reproduced from Applicant's Summary of Clinical Safety p 24/224

Table 6. Integrated Dataset for Supplemental Safety Analysis, Protocols 029 and 044

Integrated Dataset Treatment Groups	Age Subgroup and Protocol Numbers		Total
	12 to 17 years of age	<12 years of age	
1-Day Supportive Pool Includes: Fosaprepitant 150 mg + 5mg/kg doses to support 1-day dosing regimen	**150 mg** Includes data from Protocols: 029 (N=46) 044 (N=26)	**5mg/kg** Includes data from Protocols: 029 (N=47) 044 (N=29)	**N=148**
3-Day Supportive Pool Includes: Fosaprepitant 150 mg + 5mg/kg + 3 mg/kg to support 3-day dosing regimen	**150 mg** Includes data from Protocols: 029 (N=46) 044 (N=26)	**5mg/kg** Includes data from Protocols: 029 (N=47) 044 (N=29) **3mg/kg** Includes data from Protocols: 029 (N=60)	**N=208**

Electronically copied and reproduced from Applicant's Summary of Clinical Safety p 26/224

MO Comment:
The Applicant's 1-Day Supportive and 3-Day Supportive safety pools are appropriate. It should be noted that while the 3-Day safety Pool supports the proposed doses for the 3-day fosaprepitant pediatric regimen, no patients in the development program received fosaprepitant on Day 2 or Day 3. Therefore, proposed regimens with fosaprepitant dosing on Days 2 or 3 are not supported by safety data submitted as part of the current Application.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In total, 199 patients are included in the primary safety population and received at least a partial dose of fosaprepitant during Cycle 1. See

Table 7 below.

Table 7. Extent of Exposure to Fosaprepitant by Dose in Cycle 1, All Subjects Treated, Protocols 134, 019, and 044 Combined

	12 to 17 years	6 to <12 years	2 to <6 years	birth to <2 years	Total
Any Dose	58	63	48	30	199
0-10 mg	1	1	1	0	3
20-30 mg	0	0	0	2	2
30-40 mg	0	0	3	12	15
40-50 mg	0	1	8	7	16
50-75 mg	0	9	17	9	35
75-100 mg	0	12	14	0	26
100-125 mg	14	9	4	0	27
125-150 mg	43	30	1	0	74
>150 mg	0	1	0	0	1
Each subject could be counted for different dosage categories row.					

Electronically copied and reproduced from Applicant's Summary of Clinical Safety p 27/224

8.2.2. **Relevant characteristics of the safety population:**

Most patients in the safety population were white and slightly more than half were male. There were no patients less than 2 years of age. The most common primary malignancies represented were sarcoma, CNS malignancy, bone-osteosarcoma, and neuroblastoma.

Table 8. Subject Characteristics, All Subjects as Treated, Protocols 134, 029, and 044 Combined

	1-Day Supportive Pool		3-Day Supportive Pool		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	139		199		69		268	
Gender								
Male	80	(57.6)	106	(53.3)	38	(55.1)	144	(53.7)
Female	59	(42.4)	93	(46.7)	31	(44.9)	124	(46.3)
Age (Months)								
birth to <2 years	23	(16.5)	30	(15.1)	0	(0.0)	30	(11.2)
2 to <6 years	32	(23.0)	48	(24.1)	16	(23.2)	64	(23.9)
6 to <12 years	38	(27.3)	63	(31.7)	20	(29.0)	83	(31.0)
12 to 17 years	46	(33.1)	58	(29.1)	33	(47.8)	91	(34.0)
Mean	104.0		100.5		128.9		106.5	
SD	64.5		60.9		54.5		61.8	
Median	104.0		101.0		138.0		108.0	
Range	4 to 215		4 to 215		28 to 206		4 to 215	
Race								
American Indian Or Alaska Native	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Asian	24	(17.3)	26	(13.1)	8	(11.6)	34	(12.7)
Black Or African American	2	(1.4)	5	(2.5)	2	(2.9)	7	(2.6)
Multiple	12	(8.6)	24	(12.1)	4	(5.8)	28	(10.4)
White	100	(71.9)	143	(71.9)	55	(79.7)	198	(73.9)
Ethnicity								
Hispanic Or Latino	38	(27.3)	56	(28.1)	11	(15.9)	67	(25.0)
Not Hispanic Or Latino	92	(66.2)	129	(64.8)	50	(72.5)	179	(66.8)
Not Reported	3	(2.2)	4	(2.0)	5	(7.2)	9	(3.4)
Unknown	6	(4.3)	10	(5.0)	3	(4.3)	13	(4.9)
Type of Malignancy								
Acute Lymphoblastic Leukemia	1	(0.7)	4	(2.0)	1	(1.4)	5	(1.9)
Acute Myeloid Leukemia	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
Bone	9	(6.5)	9	(4.5)	12	(17.4)	21	(7.8)
CNS	26	(18.7)	31	(15.6)	11	(15.9)	42	(15.7)
Colorectal	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
Ewing Sarcoma	5	(3.6)	10	(5.0)	2	(2.9)	12	(4.5)
Gastrointestinal	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Germ Cell	1	(0.7)	5	(2.5)	1	(1.4)	6	(2.2)
Head and Neck	3	(2.2)	4	(2.0)	1	(1.4)	5	(1.9)
Hematopoietic Malignancy	3	(2.2)	3	(1.5)	1	(1.4)	4	(1.5)

Table 8 Continued

	1-Day Supportive Pool		3-Day Supportive Pool		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Type of Malignancy								
Hepatic	2	(1.4)	4	(2.0)	1	(1.4)	5	(1.9)
Hepatobiliary	5	(3.6)	5	(2.5)	0	(0.0)	5	(1.9)
Histiocytosis	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Hodgkin's lymphoma	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Kidney	2	(1.4)	2	(1.0)	4	(5.8)	6	(2.2)
Lung	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Lymphoblastic Lymphoma T	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Lymphoproliferative	1	(0.7)	1	(0.5)	2	(2.9)	3	(1.1)
Male Reproductive System Cancer	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
Malignant Eye Cancer	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Medulloblastoma	0	(0.0)	5	(2.5)	0	(0.0)	5	(1.9)
Muscular	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Nasopharyngeal Carcinoma	0	(0.0)	0	(0.0)	2	(2.9)	2	(0.7)
Nephroblastoma	1	(0.7)	2	(1.0)	0	(0.0)	2	(0.7)
Neuroblastoma	9	(6.5)	15	(7.5)	2	(2.9)	17	(6.3)
Neuroendocrine	3	(2.2)	3	(1.5)	1	(1.4)	4	(1.5)
Non-Hodgkin Lymphoma	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)
Osteosarcoma	10	(7.2)	17	(8.5)	3	(4.3)	20	(7.5)
PNET	2	(1.4)	3	(1.5)	1	(1.4)	4	(1.5)
Retinoblastoma	2	(1.4)	4	(2.0)	0	(0.0)	4	(1.5)
Rhabdomyosarcoma	3	(2.2)	9	(4.5)	2	(2.9)	11	(4.1)
Sarcoma	28	(20.1)	38	(19.1)	15	(21.7)	53	(19.8)
Skin Cancer	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Soft Tissue Neoplasm	7	(5.0)	7	(3.5)	3	(4.3)	10	(3.7)
Teratoma	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)
Urogenital	7	(5.0)	7	(3.5)	0	(0.0)	7	(2.6)
Wilms Tumor	1	(0.7)	1	(0.5)	1	(1.4)	2	(0.7)

The column "1-Day Supportive Pool" includes subjects receiving fosaprepitant in single-day doses of 150mg and 5mg/kg.
The column "3-Day Supportive Pool" includes subjects receiving fosaprepitant in single-day doses of 150mg, 5mg/kg and 3mg/kg and a 3-day regimen of fosaprepitant 115 mg on Day 1 and aprepitant 80 mg on Days 2 and 3.
The column "Total" includes subjects receiving fosaprepitant in single-day doses of 150mg, 5mg/kg and 3mg/kg and a 3-day regimen of fosaprepitant 115 mg on Day 1 and aprepitant 80 mg on Days 2 and 3, and control regimen.

Electronically copied and reproduced from Applicant's Summary of Clinical Safety p 37-38/224

8.2.3. **Adequacy of the safety database:**

The safety database was not adequate to support approval of fosaprepitant on Days 2 and 3 of the proposed 3-day regimen as none of the patients received fosaprepitant on Days 2 or 3. The Sponsor's 3-Day supportive safety pool included patients who received fosaprepitant doses similar to or higher than proposed for Days 2 and 3 and not patients who actually received fosaprepitant on Days 2 and/or 3.

MO comments:
Fosaprepitant is rapidly (<30 minutes) and completely converted to aprepitant. However, the lack of safety data from patients who have received three consecutive days of fosaprepitant given the higher Cmax predicted through modeling and simulation is a concern.

The database was adequate to support the approval of the single dose (single day) fosaprepitant regimen for pediatric patients receiving one-day chemotherapy and to support the approval of a 3-day regimen of fosaprepitant on Day 1 and aprepitant on Days 2 and 3. The safety of multiple days of aprepitant in pediatric patients is supported by pre-marketing data and postmarketing experience of aprepitant (EMEND oral) which is currently approved as a 3-day regimen for pediatric CINV.[1]

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no significant concerns with data integrity or submission quality. The electronic submission was easily navigable and well organized.

8.3.2. Categorization of Adverse Events

The All Subjects as Treated (ASaT) population was used for the analysis of safety and includes all randomized patients who received at least one dose of fosaprepitant. Events related to the efficacy endpoint (vomiting and dry heaves/retching) were not defined as AEs during the period of diary data collection (120 hours post-dose, cycle 1) unless Serious adverse event (SAE) criteria were met. In the optional cycles (2 through 6) of protocols 029 and 044, only SAEs and non-serious AEs determined by the investigator to be drug-related or led to study discontinuation were required to be reported.

MO Comment:
The difference in adverse event reporting requirements between Cycle 1 and Cycles 2 through 6 is the reason that these data are not pooled for the safety evaluation.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA, versions 16.1 and 19.0). All AEs were also categorized categorized by the investigator using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).

8.3.3. Routine Clinical Tests

The safety variables assessed in Protocols 134, 044, and 029 included adverse events, vital signs, height, weight, physical examination, 12-lead ECG, laboratory safety assessments, and pregnancy testing. Laboratory safety tests included hematology, chemistry, and urinalysis.

[1] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=696f9e80-9cae-403b-de9e-078343ce4713

These safety assessments were conducted as outlined in Table 9,

Table 10, and Table 11 for Protocols 134, 044, and 029, respectively. See below.

MO Comment:
The frequency of assessing vital signs, height, weight, physical examination, 12-lead ECG, and laboratory measures was reasonable for Protocols 134, 044, and 029. The laboratory tests assessed were also appropriate given the known safety profile of fosaprepitant.

Table 9. Study Flow Chart, Protocol 134 (Parts I through V)

Procedure	Pre-study Visit[†]	Treatment Visit Day 1 minutes -150	-60	-50	-30	-15	0	hours 1.5	3	4	6	8	24	Treatment Visit Days 2-5 Day 2	Day 3	Day 4	Day 5	Post-treatment Visit Days 6-8	Telephone Contact Days 15-17[‡‡‡]
Obtain informed consent and/or assent[‡]	X																		
Review inclusion and exclusion criteria[§]	X	X																	
Collect medical history	X	X																	
Perform physical exam	X	X																X	
Collect vital signs, weight, height[‖]	X	X												X	X			X	
12-lead Electrocardiogram	X																		
Review prior/concomitant medications	X	X																X	X
Laboratory safety tests[¶]	X																	X	
Urine pregnancy testing[#]	X																		
Pre-hydration		X																	
Fosaprepitant dosing (I.V. administration)			X[††]																
Aprepitant dosing (oral administration)			X[‡‡]											X[§§]	X[§§]				
Ondansetron administration[‖‖]					X									X[‖‖]	X[‖‖]				
Rescue therapy if required (Part 1, III, IV, and V)							X---X												

Procedure	Pre-study Visit[†]	Treatment Visit Day 1 minutes -150	-60	-50	-30	-15	0	hours 1.5	3	4	6	8	24	Treatment Visit Days 2-5 Day 2	Day 3	Day 4	Day 5	Post-treatment Visit Days 6-8	Telephone Contact Days 15-17[‡‡‡]
Rescue therapy if required (Part II)							X---X												
Initiation of emetogenic chemotherapy infusion							X												
Blood –plasma for aprepitant/fosaprepitant assay		X	X[¶¶]	X[¶¶]	X[¶¶]	X[¶¶]	X[¶¶]	X	X	X	X	X	X	X[###]	X[###]				
Review adverse experiences	X---X																		
Provide diary card					X														
Patient telephone contact																X	X	X[†††]	X
Diary recording of emetic events and use of rescue medication [§§§]					X---X														
Obtain and review patient diary														X[‖‖‖]				X[####]	

Table 9 cont'd

†	Within 1 month of treatment with emetogenic therapy.
‡	Informed consent and/or assent approval will be obtained prior to study initiation.
§	Includes Karnofsky/Lansky performance scale evaluation.
‖	Height will be obtained only at the Prestudy Visit.
¶	Should be reviewed prior to study drug administration. If labs were not drawn within the preceding 7 days of Visit 2, they will be repeated. Urinalysis should only be obtained at the prestudy visit.
#	Only for menstruating females; within 7 days prior to treatment including repeated testing in subsequent cycles of chemotherapy (Parts IV and V)†† Part II and IV only
††	Part 1 and Part V only
‡‡	Part II and Part IV only,
§§	Part I, IV and Part V only.
‖‖	Ondansetron will be administered i.v. at dose and schedule according to local standard of care.
¶¶	**Parts I and V ONLY** will also include PK samples to evaluate aprepitant and fosaprepitant at 10, 30, 45 and 60 minutes post the start of the IV fosaprepitant dosing.
##	24 hours following aprepitant dosing on Days 2 and 3
†††	Telephone contact will only be made on Day 6 if the Day 6 to 8 Visit is not occurring on that day.
‡‡‡	14 days after the last dose of study drug administration.
§§§	Part II Diary is complete after Day 2
‖‖‖	Part II Only
###	Part I, III, IV, and V

Electronically copied and reproduced from Applicant's Protocol 134, pages 16-18

Table 10. Study Flow Chart, Protocol 044, Cycle 1

Cycle 1 Study Day and Time are relative to initiation of the first emetogenic chemotherapy infusion (T_{zero}).					
Trial Period	Screening	Treatment		Post-Treatment	
Visit Number/Title:	1 Screening	2 Randomization	Telephone/ Direct Contact	3 Post-Treatment	4 Follow-Up/ Discontinuation
Study Day	-28 to 1 [A]	1	2 to 5 [B]	6 to 9 [C]	15 to 20 [C]
Administrative Procedures					
Informed Consent and Assent (if applicable)	X [D]				
Informed Consent and Assent (if applicable) for Future Biomedical Research	X [E]				
Inclusion/Exclusion Criteria	X	X			
Subject Identification Card	X (dispense)				X (collect) [F]
Medical History	X	X			
Prior Medication Review	X	X			
Concomitant Medication Review		X		X	X
Register Study Visit/Assignment of Screening & Randomization Numbers and/or Dispense Study Therapy via IVRS/IWRS	X	X			X [G]
Patient Diary Education for Subject/Parent/Caregiver and dispense diary		X [H]			
Laboratory and/or ECG Safety Test Review	X	X			X
Rescue Medication Prescription		X			
Subject/Parent/Caregiver Diary Completion		X----------		----------X	
Telephone/Direct Contact (scripted questions)			X [B]	X [B]	
Patient Diary Review/Collection (with Subject/Parent/Caregiver)				X	
Clinical Procedures/Assessments					
Full Physical Examination	X [I]				
Directed Physical Examination					X
Height		X			
Weight		X			
Vital Signs (blood pressure, heart rate, respiratory rate, axillary/oral/ rectal/temporal/tympanic temperature)	X	X [J]		X	X
12-Lead Electrocardiogram (ECG)	X [K]	X [L]			X
Lansky or Karnofsky Performance Status Evaluation	X				
Fosaprepitant or Matching Placebo Administration		X [M]			
IV Ondansetron Administration		X [N]			
Optional Dexamethasone Administration		X [O]			
Chemotherapy Infusion		X [P]			
Adverse Event Monitoring	X----------				----------X

Table 10 cont'd

Cycle 1 Study Day and Time are relative to initiation of the first emetogenic chemotherapy infusion (T_{zero}).					
Trial Period	Screening	Treatment		Post-Treatment	
Visit Number/Title:	1 Screening	2 Randomization	Telephone/ Direct Contact	3 Post-Treatment	4 Follow-Up/ Discontinuation
Study Day	-28 to 1 [A]	1	2 to 5 [B]	6 to 9 [C]	15 to 20 [C]
Laboratory Procedures/Assessments					
Laboratory Safety Evaluations (Hematology, Chemistry)	X [K]				X
Ionized Calcium evaluation	X [Q]	X [Q]			
Urine Pregnancy Test – if applicable	X [KK]				
Buccal swab samples for Future Biomedical Research		X [S]			

[A] The Screening and Randomization visits can occur on the same day as long as all study procedures are completed and subject eligibility is confirmed.

[B] Telephone or direct contact must be made daily on Days 2, 3, 4, and 5. Telephone/direct contact must also be made on Day 6 if the Post Treatment visit is not on Day 6.

[C] One visit occurs during the designated period of study days. The Follow-Up Visit can be scheduled to coincide with the start of the next study cycle provided that the next round of chemotherapy is 14-19 days after Treatment Day 1 (study days 15 to 20).

[D] Informed consent/assent MUST be obtained prior to any Visit 1 procedures.

[E] Subject participation in Future Biomedical Research is optional.

[F] A reasonable attempt should be made to collect the Subject Identification Card if subject discontinues during Cycle 1 or if subject is not participating in optional cycle(s).

[G] Register study discontinuation visit in IVRS/IWRS if subject discontinues during Cycle 1 or if subject is not participating in optional cycle(s).

[H] The Subject/Parent/Caregiver should be educated on the use of the Patient Diary prior to the start of emetogenic chemotherapy.

[I] Full physical exam (excluding breast, rectal, and urogenital, unless clinically indicated).

[J] All vital sign measurements will be obtained prior to fosaprepitant infusion. Blood pressure and heart rate will be measured again ~ 15 minutes after completion of fosaprepitant infusion, prior to the start of chemotherapy.

[K] ECG, Laboratory Safety Evaluations and Urine Pregnancy Test must be completed within 7 days prior to initiation of study medication. See Section 7.1.3.1 – Local Laboratory Safety Evaluations for the list of Laboratory Tests.

[L] This ECG is obtained ~2 (no later than 3) hours after initial administration of IV ondansetron in those subjects with a baseline potassium and/or magnesium level below the normal range for the subject's age.

[M] Fosaprepitant or matching placebo dose is initiated at ~90 minutes prior to initiation of the first emetogenic chemotherapy and administered via a central venous catheter over a period of ~60 minutes for subjects <12 years old and ~60 minutes prior to initiation of the first emetogenic chemotherapy and administered over a period of ~30 minutes for subjects 12 to 17 years old. The infusion will be complete ~30 minutes prior to chemotherapy initiation.

[N] IV ondansetron is required for Cycle 1 and will be supplied for prophylaxis use only by the Sponsor to be used on days of chemotherapy administration and up to 24 hours after chemotherapy. For subjects 6 months to 17 years old, the first dose on Day 1 should be no later than 30 minutes prior to initiation of the first emetogenic chemotherapy. The timing of the first dose of ondansetron administration for subjects <6 months old should be scheduled according to local standard of care. Additional doses of IV ondansetron on Day 1 should be administered according to local standard of care. For multi-dose chemotherapy regimens, IV ondansetron can be administered on subsequent days if clinically warranted and per local standard of care; however, it should only be administered on the day(s) of chemotherapy administration and up to 24 hours after chemotherapy administration.

Electronically copied and reproduced from Applicant's Protocol 044, pages 16-18

Table 11. Study Flow Chart, Protocol 029, Cycle 1

Trial Period	Screening	Treatment											Post-Treatment	Follow-Up/ Discontinuation
Visit Number	1	2 (Randomization)							3	4	5	6	7	8
		Time and Study Day are relative to initiation of emetogenic chemotherapy infusion												
Study Day	-28 to 1	Day 1							2	3	4	5	6 to 8[A]	15 to 17[A]
Time		- 2.5 hr	-1.5/ -1.0 hr	- 0.5 hr	0 hr	2 hr	4 hr	10 hr						
Procedures														
Informed Consent and Assent (where applicable)	X													
Informed Consent for Future Biomedical Research[B]	X													
Screening Number from IVRS	X													
Patient Identification Card	X													
Medical history	X	X												
Prior medications	X	X												
Inclusion/exclusion criteria[C]	X	X												
Physical exam	X													X[D]
Weight and height[E]	X	X												X
Vital signs	X	X							X[Q]				X	X
Twelve-lead ECG	X[F]					X[G]							X	
Laboratory safety tests[H,I]	X[F]												X	X
Review of laboratory safety tests results	X	X												X
Urine pregnancy test[J]	X[F]													X
Randomization Number and Component ID from IVRS		X												
Concomitant medications			X						X[Q]				X	X
Buccal swab samples for Future Biomedical Research[K]		X												
Pre-hydration, if indicated		X												
Dispense diary to patient/parent/guardian		X												
Fosaprepitant or matching placebo dosing[L]			X[L]											
IV Ondansetron dosing				X----------X[M]										
Optional Dexamethasone dosing[N]				X										
Pharmacokinetic blood sample collection[I]				X[O]----------X[O]					X[O]					
Chemotherapy infusion					X									
Rescue medication, if indicated					X----------X									
Patient/parent/guardian diary completion					X----------X									

Trial Period	Screening	Treatment											Post-Treatment	Follow-Up/ Discontinuation
Visit Number	1	2 (Randomization)							3	4	5	6	7	8
		Time and Study Day are relative to initiation of emetogenic chemotherapy infusion												
Study Day	-28 to 1	Day 1							2	3	4	5	6 to 8[A]	15 to 17[A]
Time		- 2.5 hr	-1.5/ -1.0 hr	- 0.5 hr	0 hr	2 hr	4 hr	10 hr						
Telephone Contact (scripted questions)[P]									X[P]	X	X	X	X[P]	
Review diary with patient/parent/guardian													X	
Adverse Event Monitoring	X----------X													

[A] One visit occurs during the designated period of study days. The Follow-Up Visit can be scheduled to coincide with the start of the next chemotherapy cycle provided that the next round of chemotherapy is 15 to 17 days after Treatment Day 1.
[B] Patient participation in Future Biomedical Research is optional for the patient/parent.
[C] Includes Karnofsky-Lansky Performance Status Scale Evaluation.
[D] Physical exam at Follow-Up Visit may be a directed physical exam.
[E] Height will be obtained only at Screening Visit.
[F] ECG, lab tests, and urine pregnancy test must be completed within 7 days prior to initiation of study medication.
[G] This ECG is obtained 2 hours after initial administration of IV ondansetron in those patients with a baseline potassium and/or magnesium level below the normal range for the patient's age.
[H] Blood draws shall not exceed 3% of total blood volume in a 24-hour period and 10% of total blood volume in a month period (Appendix 6.2).
[I] PK sampling for selected patients only (chosen randomly via IVRS). In patients who have a multi-lumen central venous catheter, one line will be designated strictly for the infusion of fosaprepitant and another line designated for the collection of PK and safety blood samples. To avoid the potential of cross contamination, a patient that has fosaprepitant administered through a single lumen central venous catheter cannot have PK samples drawn from that same line, but instead should have a peripheral line inserted or perform blood draws at the specified time points.
[J] Urine pregnancy test for female patients of reproductive potential only. Results must be obtained prior to study drug administration.
[K] Informed consent for future biomedical research must be obtained before the buccal swab DNA samples are collected. The buccal swab DNA samples should be obtained predose on Day 1, on randomized subjects only, or at a later date as soon as the informed consent is obtained.
[L] Fosaprepitant or matching placebo dose initiated at -1.0 hr (or 60 minutes prior to initiation of chemotherapy) and administered over a period of 30 minutes for patients 12 to 17 years old and at -1.5 hr (or 90 minutes prior to initiation of chemotherapy) and administered over a period of 60 minutes for patients <12 years old.
[M] Branded IV ondansetron (Zofran™) is required for Cycle 1 and will be supplied by the SPONSOR to be used only on days of chemotherapy administration during the diary reporting period. The timing of IV ondansetron administration for patients 6 months to 17 years old on Day 1 should be no later than 30 minutes prior to chemotherapy initiation for the first dose; the second and third doses of IV ondansetron should be administered approximately 4 and 8 hours after the first dose, respectively. The timing of IV ondansetron administration for patients <6 months old on Day 1 should be scheduled according to local standard of care. For multi-dose chemotherapy regimens, IV ondansetron can be administered on subsequent days if clinically warranted and per local standard of care; however, it should only be administered on the day(s) of chemotherapy administration.
[N] IV dexamethasone may be administered as part of an anti-emetic regimen based on local standard of care, but no later than 30 minutes prior to chemotherapy initiation. For patients receiving fosaprepitant 150 mg, IV dexamethasone should be administered at 50% of the established dose in children when administered within 2 days following administration of IV fosaprepitant 150 mg; no dose adjustment to dexamethasone will be made for patients receiving fosaprepitant 60 mg, fosaprepitant 20 mg, or placebo for fosaprepitant.
[O] Pharmacokinetic samples to be collected at five time points: (1) end of fosaprepitant infusion; (2) 2 to 4 hours after (completion of) fosaprepitant dosing; (3) 5 to 7 hours after fosaprepitant dosing; (4) 8 to 10 hours after fosaprepitant dosing; (5) and 23 to 25 hours after fosaprepitant dosing.
[P] Telephone contact should be made daily on Days 2, 3, 4, and 5. Note: Day 2 telephone contact only if no clinic visit for the 23- to 25-hour PK sample. Telephone contact is only made on Day 6 if the Day 6 to 8 visit is not on Day 6.
[Q] Vital signs and concomitant medications on Day 2 only if visit occurs for the 23- to 25-hour PK sample.
DNA = deoxyribonucleic acid; ECG = electrocardiogram; ID = identification; IV = intravenous; IVRS = interactive voice response system; PK = pharmacokinetic.

Electronically copied and reproduced from Applicant's Protocol 029, pages 20-21

8.4. Safety Results

8.4.1. Deaths

Primary Safety Population
No subjects included in the primary safety population (Cycle 1 integrated dataset of Protocols 134, 044, and 029) died.

Secondary Safety Population
During and following the optional cycles of Protocols 029 and 044, three deaths occurred. Of these, one death occurred during the follow-up period. None of the adverse events leading to these deaths was determined by the investigator to be related to the study drug. See Table 12 below.

Table 12. Deaths, Cycles 2-6, Protocols 044 and 029

Study	Age (years)	Gender	Cycle of Onset	Adverse Event
044	14.6	Female	4	Sepsis
029	13.6	Female	4	Neutropenia
029	12.8	Male	Follow-up period	Metastases to lung

Reviewer's Table. Source, Summary of Clinical Safety Table 2.7.4:32

8.4.2. Serious Adverse Events

Primary Safety Population
In the primary safety population (both 3-Day and 1-Day Supportive Pools), 30.7 % of patients had a serious adverse event (SAE). The most commonly reported SAE was febrile neutropenia. The incidence of febrile neutropenia was similar across fosaprepitant and control regimens. This SAE is a known adverse reaction associated with chemotherapy.

No safety signals were observed in review of the SAE data. There did not appear to be any SAE with a substantial difference in incidence between the fosaprepitant and control regimen groups. See

Table 13 below.

Secondary Safety Population

Consistent with what was observed in Cycle 1, the most commonly reported SAEs in the optional Cycles 2 through 6 of Protocols 044 and 029 were in the Blood and lymphatic system disorders SOC, with febrile neutropenia occurring most frequently.

Table 13. Primary Safety Population, SAEs, Protocols 134, 044, and 029

	1-Day Supportive Pool		3-Day Supportive Pool		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)	n	(%)
Subjects in population	139		199		69		268	
with one or more serious adverse events	40	(28.8)	61	(30.7)	20	(29.0)	81	(30.2)
with no serious adverse events	99	(71.2)	138	(69.3)	49	(71.0)	187	(69.8)
Blood and lymphatic system disorders	**22**	**(15.8)**	**38**	**(19.1)**	**13**	**(18.8)**	**51**	**(19.0)**
Anaemia	0	(0.0)	0	(0.0)	2	(2.9)	2	(0.7)
Bone marrow failure	1	(0.7)	1	(0.5)	1	(1.4)	2	(0.7)
Febrile neutropenia	19	(13.7)	30	(15.1)	9	(13.0)	39	(14.6)
Leukopenia	1	(0.7)	2	(1.0)	1	(1.4)	3	(1.1)
Neutropenia	0	(0.0)	3	(1.5)	2	(2.9)	5	(1.9)
Pancytopenia	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Thrombocytopenia	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)
Cardiac disorders	**1**	**(0.7)**	**1**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.4)**
Tachycardia	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Gastrointestinal disorders	**2**	**(1.4)**	**3**	**(1.5)**	**1**	**(1.4)**	**4**	**(1.5)**
Stomatitis	0	(0.0)	1	(0.5)	1	(1.4)	2	(0.7)
Vomiting	2	(1.4)	2	(1.0)	0	(0.0)	2	(0.7)
General disorders and administration site conditions	**4**	**(2.9)**	**5**	**(2.5)**	**1**	**(1.4)**	**6**	**(2.2)**
General physical health deterioration	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Mucosal inflammation	2	(1.4)	3	(1.5)	0	(0.0)	3	(1.1)
General disorders and administration site conditions	**4**	**(2.9)**	**5**	**(2.5)**	**1**	**(1.4)**	**6**	**(2.2)**
Pyrexia	1	(0.7)	1	(0.5)	1	(1.4)	2	(0.7)
Immune system disorders	**2**	**(1.4)**	**2**	**(1.0)**	**0**	**(0.0)**	**2**	**(0.7)**
Anaphylactic reaction	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Hypersensitivity	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Infections and infestations	**4**	**(2.9)**	**7**	**(3.5)**	**3**	**(4.3)**	**10**	**(3.7)**
Enterobacter bacteraemia	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Fungal sepsis	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)
Gastroenteritis norovirus	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Herpes virus infection	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Infection	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
Neutropenic sepsis	0	(0.0)	2	(1.0)	0	(0.0)	2	(0.7)
Otitis media chronic	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
Septic shock	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)
Skin infection	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
Tooth infection	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Injury, poisoning and procedural complications	**0**	**(0.0)**	**1**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.4)**
Wound dehiscence	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)
Investigations	**4**	**(2.9)**	**4**	**(2.0)**	**2**	**(2.9)**	**6**	**(2.2)**
Amylase increased	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
C-reactive protein increased	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Neutrophil count decreased	2	(1.4)	2	(1.0)	2	(2.9)	4	(1.5)
White blood cell count decreased	0	(0.0)	0	(0.0)	1	(1.4)	1	(0.4)
Metabolism and nutrition disorders	**2**	**(1.4)**	**4**	**(2.0)**	**0**	**(0.0)**	**4**	**(1.5)**
Decreased appetite	2	(1.4)	2	(1.0)	0	(0.0)	2	(0.7)
Dehydration	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)
Hyponatraemia	0	(0.0)	1	(0.5)	0	(0.0)	1	(0.4)
Nervous system disorders	**3**	**(2.2)**	**3**	**(1.5)**	**1**	**(1.4)**	**4**	**(1.5)**
Hydrocephalus	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Seizure	2	(1.4)	2	(1.0)	1	(1.4)	3	(1.1)
Product issues	**1**	**(0.7)**	**1**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.4)**
Thrombosis in device	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)
Respiratory, thoracic and mediastinal disorders	**1**	**(0.7)**	**1**	**(0.5)**	**0**	**(0.0)**	**1**	**(0.4)**
Asthma	1	(0.7)	1	(0.5)	0	(0.0)	1	(0.4)

Every subject is counted a single time for each applicable row and column.
A system organ class or specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.
The column "1-Day Supportive Pool" includes subjects receiving fosaprepitant in single-day doses of 150mg and 5mg/kg.
The column "3-Day Supportive Pool" includes subjects receiving fosaprepitant in single-day doses of 150mg, 5mg/kg and 3mg/kg and a 3-day regimen of fosaprepitant 115 mg on Day 1 and aprepitant 80 mg on Days 2 and 3.
The column "Total" includes subjects receiving fosaprepitant in single-day doses of 150mg, 5mg/kg and 3mg/kg and a 3-day regimen of fosaprepitant 115 mg on Day 1 and aprepitant 80 mg on Days 2 and 3, and control regimen.

Electronically copied and reproduced from the Applicant's Summary of Clinical Safety, p 100-104

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Primary Safety Population (Cycle 1)
In the primary safety population (both 3-Day and 1-Day Supportive Pools), four patients (4/199) discontinued from a trial due to an adverse effect of the drug. It should be noted that all AEs resulting in discontinuation resolved.

Table 14. Adverse Events Resulting in Discontinuation in Cycle 1, Protocols 134, 029 and 044

Study	Age (years)	Gender	Study Day of Onset	Adverse Event	Duration
029	2.8	Female	1	Anaphylactic Reaction	10 minutes
044	7.3	Female	1	Discomfort, flushing	20 minutes
044	13.4	Male	1	Hypersensitivity	1 Hour
134 (Part 5)	2.6	Female	158	Pyrexia	4 hours

Reviewer's Table. Source, Summary of Clinical Safety Table 2.7.4:35

Patient narratives of Adverse Discontinuations
A 3-year-old girl (Study 134) with a diagnosis of medulloblastoma, experienced an SAE of pyrexia on Day 1 of Part V (Day 158 from entry into the study in Part III) post initiation of fosaprepitant and IV dexamethasone. She was treated with dipyrone, and the event resolved within 4 hours. The investigator assessed the event as moderate in intensity, with a toxicity grade of 1, and not related to study medication. Chemotherapy was cancelled and the rest of study medication regimen (ondansetron) was discontinued. The subject was discontinued from the study due to the AE of pyrexia.

A 13-year old white male (Study 044) with a diagnosis of soft tissue neoplasm NOS experienced an SAE of hypersensitivity reaction on Study Day 1 immediate after starting infusion of fosaprepitant 10 mg. The event was severe in intensity. The patient experienced shortness of breath, choking, red flushing of the head, cramping of the jaw and arms, and chest pain. The infusion was immediately stopped. Treatment of the event included hydrocortisone and clemastine fumarate. The event was considered resolved after 1 hour. Chemotherapy was continued according to the schedule. The subject was discontinued due to the AE of hypersensitivity reaction.

A 7-year old white male (Study 044) with a diagnosis of hematopoietic malignancy NOS experienced flushing and discomfort (Grade 2) on Study Day 1 during an infusion of fosaprepitant 100 mg. The event of flushing and discomfort reportedly lasted 20 minutes. No treatment was administered. Vital signs were normal.

A 2-year old white female (Study 029) with a diagnosis of bilateral congential retinoblastoma experienced an anaphylactic reaction with the symptoms of facial swelling, tachycardia, tachypnea, lower oxygen saturations, lip swelling, tongue edges swollen, erythema, red rash on chest, head and face. The event occurred three minutes into a 60-minute infusion. At this point, the patient had received approximately 7 mg of the fosaprepitant dose. The patient was randomized to the 5 mg/kg treatment arm. Study medication was discontinued and the patient began to improve 10 minutes after receiving treatment for anaphylactic reaction. Treatments included chlorpheniramine (administered approximately 4 minutes after the onset of the event) and hydrocortisone (administered approximately 2 hours and 20 minutes after the onset of the event). The event was considered resolved on Day 1. Fosaprepitant was permanently discontinued due to this event anaphylactic reaction.

Secondary Safety Population (Cycles 2 through 6)
No subjects in the optional Cycles 2 to 6 of Protocols 029 and 044 had an AE that resulted in discontinuation of study medication. Study 134 did not include optional Cycles 2 through 6.

MO Comment:
The 13-year old patient (Study 044) whose adverse discontinuation event was categorized as a hypersensitivity reaction should have been more specifically categorized as anaphylaxis, per World Allergy Organization guidelines.[2] The narrative for the adverse event of flushing and discomfort may also have been an event of hypersensitivity. The narrative did not contain adequate information to determine if the event should have been described as anaphylaxis. If we conservatively categorize each of these 3 events as hypersensitivity reactions, the incidence rate for hypersensitivity would be 1.5% (3/199). These events are already described in the Warnings and Precautions Section of the EMEND for Injection label. Therefore, no labeling changes based on these events is recommended.

> *Excerpt from Current EMEND for IV labeling*
>
> ***5.2 Hypersensitivity Reactions***
>
> *Serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion of fosaprepitant have occurred. Symptoms including flushing, erythema, dyspnea, hypotension and syncope have been reported [see Adverse Reactions (6.2)]. Monitor patients during and after infusion. If hypersensitivity reactions occur, discontinue the infusion and these symptoms with first-time use [see Contraindications (4)].[3]*

[2] http://www.bsaci.org/Guidelines/WAO_anaphylaxis_guideline_2012.pdf
[3] https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/022023s014lbl.pdf

8.4.4. Significant Adverse Events

The NCI CTCAE Grades and their associated assignments of severity are listed below:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living (ADL)*.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

Primary Safety Population (Cycle 1)

The most commonly reported Grade 3 AEs were febrile neutropenia and anemia. The incidence of anemia was greater in the control group than in the fosaprepitant group and is therefore not represented in **Table 15**, below. These events are consistent with a population of patients with cancer receiving chemotherapy. In general, the incidence of severe and life-threatening AEs was relatively similar between the fosaprepitant and control regimens.

Table 15. Subjects With Adverse Events by Maximum Toxicity Grade (Incidence ≥5% in One or More Treatment Groups), in Cycle 1, All Subjects as Treated, Protocols 134, 029 and 044 Combined, Incidence Greater than Control Group

Adverse Event	NCI CTAE Severity Grade	3-Day Supportive Pool n=199	Control Group n=69
Febrile neutropenia	3	29 (14.6)	9 (13.0)
	4	4 (2.0)	2 (2.9)
Leukopenia	3	6 (3.0)	2 (2.9)
	4	9 (4.5)	1 (1.4)
Neutropenia	3	15 (7.5)	3 (4.3)
	4	17 (8.5)	7 (10.1)
Nausea	3	1 (0.5)	0
	4	n/a	
Vomiting	3	4 (2.0)	0
	4	n/a	
Mucosal Inflammation	3	3 (1.5)	0
	4	n/a	
Pyrexia	3	1 (0.5)	0
	4	n/a	
AST increased	3	1 (0.5)	0
	4	n/a	
Neutrophil count decreased	3	8 (4.0)	1 (1.4)
	4	11 (5.5)	5 (7.2)
Platelet count decreased	3	6 (3.0)	2 (2.9)
	4	8 (4.0)	3 (4.3)
White blood cell count decreased	3	5 (2.5)	1 (1.4)
	4	3 (1.5)	4 (5.8)
Decreased appetite	3	4 (2.0)	1 (1.4)
	4	n/a	

Reviewer's Table. Source Table 2.7.4: 28, Summary of Clinical safety.

Secondary Safety Population (Cycles 2 through 6)

During Cycles 2 through 6, the most commonly reported Grade 3 AEs were febrile neutropenia and anemia, similar to what was seen in Cycle 1. Overall, the incidence of severe and life-threatening AEs was higher than was seen during Cycle 1. For example, the incidence of grade 3 febrile neutropenia was 23.6% during Cycles 2 through 6 compared with 13.0% in the 3-Day Supportive Group.

MO Comment:
The general trend of increased incidence of certain severe AEs is not unexpected given that many of the severe AEs were known to be associated with chemotherapy. The increased rate of severe AEs likely represents the cumulative effect of multiple rounds of chemotherapy.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Current EMEND for Injection labeling includes adverse reactions from clinical trials and from post-marketing reporting. See current EMEND labeling.

MO Comment:
The Adverse Reactions section of the current EMEND for Injection labeling is adequate. The Application does not contain any new safety information that is not currently reflected in EMEND for Injection labeling.

8.4.6. Laboratory Findings

Primary Safety Population (Cycle 1)
The treatment arms were generally balanced with respect to the number of subjects with a laboratory value outside of pre-specified limits. See Section 8.4.4 for a discussion of SAEs of laboratory abnormalities. The most notable laboratory abnormalities in both the fosaprepitant and control treatment arms were decreases in hematological measurements (WBCs, neutrophil count, platelet count, and hemoglobin,) and an increase in serum alanine transaminase (ALT).

Secondary Safety Population (Cycles 2 through 6)
Laboratory measurements were not required during Cycles 2 through 6.

Hepatic safety was monitored during the studies. Subjects with a liver function test result during the treatment and/or follow-up period that met predetermined criteria were reviewed. The normal range was defined at a site level by the site's local laboratory.

The criteria for a potential DILI case was an elevated aspartate transaminase (AST) or ALT ≥3X the upper limit of normal (ULN) AND an elevated total bilirubin value ≥2X the ULN AND, at the same time, an alkaline phosphatase <2X the ULN.

During Protocols 134, 029, and 044, a single case of DILI was reported. The case was reported during optional cycle 3 of Protocol 029. The patient was in the fosaprepitant 3 mg/kg treatment group. An AE of hepatoxicity was reported with an onset of Day 109. The investigator assessed this event as non-serious. The event resolved within 2 months.

Fosaprepitant has not been studied in patients with known severe hepatic impairment (Child-Pugh score greater than 9).

8.4.7. Vital Signs

No clinically significant changes in vital signs were reported in Protocols 134, 029, and 044.

8.4.8. Electrocardiograms (ECGs)

During Protocol 134, electrocardiograms were required only at baseline for subjects in Part I Step A. Subjects in Part I Step B and Part V received ECGs at baseline and post-treatment (Days 6 to 8).
During Protocol 029 (Cycle 1), ECGs were performed at baseline and on Days 6 to 8.
ECGs were not required in Cycles 2 to 6.

During Protocol 044, electrocardiograms were collected at baseline and at the follow-up/discontinuation visit (Day 15-17). ECGs were not required in Cycles 2 to 6.

No notable ECG findings were reported during Protocol l134, 029, and 044.

8.4.9. QT

The QT prolongation potential for fosaprepitant IV was evaluated in a previous study and no QT prolongation was detected for fosaprepitant 200 mg infused over 15 minutes. See current EMEND for Injection labeling.

8.4.10. Immunogenicity

N/a

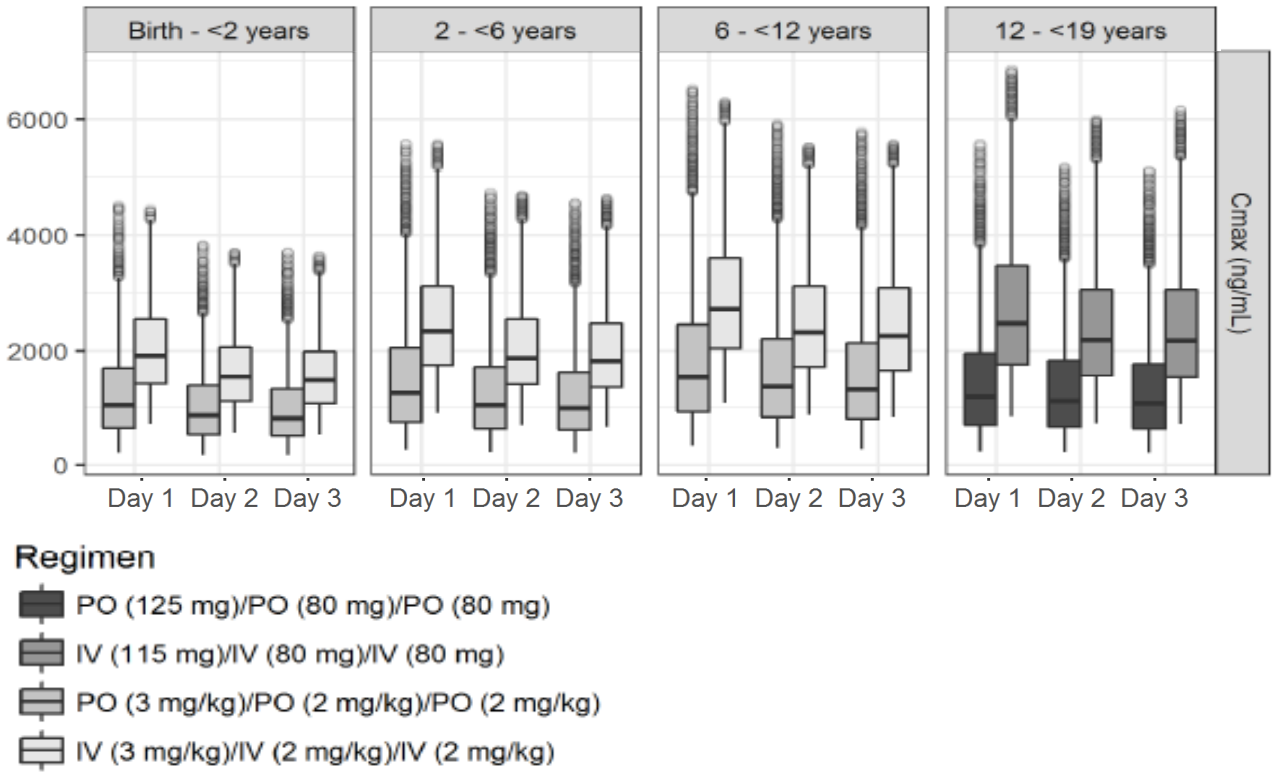
8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Increased Aprepitant C_{max} on Days 2 and 3

The Applicant used modeling and simulation to predict the fosaprepitant doses for Days 2 and 3 based on matching the aprepitant exposures of the approved 3-day EMEND oral regimen. The

aprepitant mean Cmax for the predicted fosaprepitant doses for each age group were 1.5 to 2-fold higher than the oral aprepitant mean Cmax for Days 2 and 3.

Figure 1. Predicted 3-Day IV PK Aprepitant Cmax vs Measured 3-Day oral Aprepitant Cmax



Source: clinical pharmacology Midcycle presentation by Dr. Elizabeth Shang

MO Comment:
The available safety data for the predicted higher Cmax values is limited to Day 1 of the proposed 3-Day (IV/IV/IV) regimen given that none of the fosaprepitant PK/PD or efficacy studies dosed patients with fosaprepitant past Day 1. While the Day 2 and Day 3 predicted Cmax values are less than what is seen for Day 1, this lack of patient safety data for fosaprepitant dosing on Days 2 and 3 cannot be overcome without an additional safety study.

The lack of safety data for patients receiving fosaprepitant on Days 2 and 3 of the proposed 3-day IV regimen was discussed with the Applicant during a teleconference on 13 February 2018. During the discussion, the Applicant decided to no longer pursue approval for any 3-day regimens involving dosing of fosaprepitant on days 2 or 3 given the lack of safety data. With this change, all proposed 3-day regimens would include only oral aprepitant on Days 2 and 3.

8.5.2. Safety Analyses by Demographic Subgroups

No demographic safety analyses by demographic subgroups were conducted given the small size of the safety data pool. Further subdividing this group would yield numbers too small to make inferences regarding safety.

8.6. Specific Safety Studies/Clinical Trials

N/A

8.7. Additional Safety Explorations

8.7.1. Human Carcinogenicity or Tumor Development

N/A

8.7.2. Human Reproduction and Pregnancy

No pregnancies were reported during trials submitted in support of this Application.

8.7.3. Pediatrics and Assessment of Effects on Growth

The current Application is a pediatric supplement. All sections of this review pertain to the pediatric population.

8.7.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

N/A

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

As of 10 May 2017, fosaprepitant 150 mg (single dose regimen) is registered and approved in more than 75 countries for prevention of CINV in adults. Although initially approved for use, most countries have deleted registration of the 115 mg dose of fosaprepitant, given the availability of the more convenient single day, 150 mg regimen. There are no records of any registration being revoked or withdrawn for safety reasons.

The only country in which fosaprepitant has been approved for pediatric patients is Japan. In Japan, EMEND for Injection is approved as a single dose of 150 mg in patients 12 to 17 years of age and 3 mg/kg dose in patients 6 months to <12 years of age.

Since its licensure through 10 May 2017, post-marketing experience with fosaprepitant has

been reviewed based on an estimated exposure of (b) (4) patient courses (b) (4) of the 115 mg dose and (b) (4) of the 150 mg dose). The Applicant searched their own safety database for postmarketing reports, including spontaneous, literature and non-interventional study reports from market launch (14-Aug-2007) through 10 May 2017. A total of 4,983 (1,328 [27%] serious) spontaneous and non-interventional study reports for fosaprepitant received from HCPs and consumers were identified. Of these, 69 reports (12 serious [17%]) involved AEs in pediatric patients (17 years of age and younger); 67 cases were received from HCPs.

Most of the pediatric postmarketing cases were reported form Japan (25/69) where fosaprepitant is approved for pediatric patients. Of the 69 cases, most were nonserious and no safety signal was observed. Off-label use (41/69) and events related to hypersensitivity/anaphylaxis (7/69) were the most frequently reported AEs. See

Table **16** below.

Table 16 . Fosaprepitant Postmarketing Adverse Events in Pediatric Patients 20-Aug-2007 to 10-May-2017

SOC	Preferred Term	Total # Serious Events	Total # Non-serious Events	Total # Events
Blood and lymphatic system disorders	Febrile neutropenia*	2	0	2
Cardiac disorders	Tachycardia	1	0	1
Eye disorders	Eyelid thickening	0	1	1
Gastrointestinal disorders	Diarrhoea	0	2	2
	Dysphagia	0	1	1
	Lip swelling*	0	1	1
	Nausea*	2	5	7
	Vomiting*	1	3	4
General disorders and administration site conditions	Adverse drug reaction	0	1	1
	Chills	0	1	1
	Drug ineffective	0	2	2
	Infusion site erythema*	0	1	1
	Infusion site pain*	0	1	1
	Infusion site phlebitis*	0	1	1
	Infusion site reaction*	0	1	1
	Injection site erythema*	0	2	2
	Injection site pain*	0	2	2
	Injection site urticaria*	0	1	1
	No adverse event*	0	3	3
	Pain	0	2	2
Immune system disorders	Anaphylactic reaction*	1	0	1
	Anaphylactic shock*	3	0	3
	Anaphylactoid reaction*	1	0	1
	Drug hypersensitivity*	0	2	2
	Hypersensitivity*	0	2	2
Injury, poisoning and procedural complications	Drug administered to patient of inappropriate age	0	8	8
	Inappropriate schedule of drug administration	1	1	2
	Incorrect drug administration rate	0	1	1
	Incorrect product storage	0	1	1
	Medication error	0	1	1
	Off label use	0	33	33
	Overdose	1	0	1
	Prescribed overdose	1	0	1
	Product use issue	0	3	3

Table 15, cont'd

SOC	Preferred Term	Total # Serious Events	Total # Non-serious Events	Total # Events
Investigations	Alanine aminotransferase increased*	1	0	1
	Aspartate aminotransferase increased*	1	0	1
	pH urine decreased	0	1	1
	pH urine increased	0	1	1
	Weight decreased*	0	1	1
	White blood cell count decreased	1	0	1
Metabolism and nutrition disorders	Hypoalbuminaemia	0	1	1
Respiratory, thoracic and mediastinal disorders	Bronchospasm*	1	0	1
	Cough*	1	0	1
	Dyspnoea*	0	2	2
	Hiccups*	0	2	2
	Laryngeal oedema*	0	1	1
Skin and subcutaneous tissue disorders	Papule	0	1	1
	Petechiae	0	1	1
	Pruritus*	0	2	2
	Rash*	0	4	4
	Rash erythematous*	1	0	1
Social circumstances	Refusal of treatment by patient	0	1	1
Vascular disorders	Flushing*	1	0	1
Grand Total		21	103	124

*Indicates event listed in the CCDS for fosaprepitant.

Electronically copied and reproduced from the Summary of clinical safety, Table 2.7.4: 72

See current EMEND for Injection labeling.

8.8.2. Expectations on Safety in the Postmarket Setting

It is expected that the postmarketing safety profile of fosaprepitant in pediatric patients will be consistent with the safety profile outlined in the current EMEND for Injection labeling.

8.8.3. Additional Safety Issues From Other Disciplines

No other safety issues are known that are not discussed in other areas of the review.

8.9. Integrated Assessment of Safety

The primary safety issue of this Application is the absence of safety data in patients receiving fosaprepitant on Days 2 or 3 of the proposed 3-day regimen. The doses for Days 2 and 3 were obtained using modeling and simulation. However, the doses should have been administered in

some patients so that the safety of repeat fosaprepitant dosing could be confirmed. The lack of a theoretical safety concern does not preclude the need to collect safety information.

9. Advisory Committee Meeting and Other External Consultations

N/A

10. Labeling Recommendations

10.1. Prescription Drug Labeling

See Approved labeling for details.

10.2. Nonprescription Drug Labeling

N/A

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary based on information obtained in review of the current Application.

12. Postmarketing Requirements and Commitments

The current Application was submitted to fulfill PMRs. No additional PMRs are recommended in conjunction with approval of the current Application.

13. Appendices

13.1. References

See footnotes.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Protocol 134, 029, and 044

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: _____		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

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

/s/

AISHA P JOHNSON
03/02/2018

ANIL K RAJPAL
03/02/2018