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APPLICATION NUMBER:

207865Orig1s000

MEDICAL REVIEW(S)

Application Type	NDA
Application Number(s)	207,865
Priority or Standard	Priority
Submit Date(s)	March 26, 2015
PDUFA Goal Date	December 26, 2015 (with 3-month extension due to a major amendment)
Division / Office	DGIEP/ODE III
Reviewer Name(s)	Aisha P. Johnson, MD, MPH, MBA
Review Completion Date	02 December 2015
Established Name	aprepitant
(Proposed) Trade Name	Emend
Therapeutic Class	NK-1 antagonist
Applicant	Merck Sharp & Dohme Corp.
Formulation(s)	Powder for oral suspension
Dosing Regimen	EMEND is given orally for 3 days, 1 hour prior to chemotherapy treatment on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, EMEND should be administered in the morning
Indication(s)	In combination with other antiemetic agents in patients 6 months of age and older for prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy HEC) including high-dose cisplatin • nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC
Intended Population(s)	Children 6 months to <12 years of age

NDA 207,865
Emend Oral Suspension Brief Clinical Review

I. Recommendation on Regulatory Action

In the opinion of this reviewer, EMEND FOR ORAL SUSPENSION should be approved for marketing in the United States for the prevention of chemotherapy induced nausea and vomiting (CINV). With the approval of the oral suspension, Emend for oral use (as tablets and oral suspension) can be used for the prevention of CINV in patients as young as 6 months of age.

Current EMEND CINV Indication (excerpt from 8/2015 version of label)

1 INDICATIONS AND USAGE
1.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

EMEND, in combination with other antiemetic agents, is indicated in patients 12 years of age and older and patients less than 12 years who weigh at least 30 kg 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 *[see Dosage and Administration (2.1)]*.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) *[see Dosage and Administration (2.1)]*.

Proposed EMEND CINV Indication

1 INDICATIONS AND USAGE

1.1 Prevention of Chemotherapy Induced Nausea and Vomiting (CINV)

EMEND®, in combination with other antiemetic agents, is indicated in 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.
- nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC).

II. Background

On July 28, 2014, the Applicant submitted a Prior Approval Supplement to NDA 21,549 (Supplement-025) providing non-clinical and clinical data to support the use of EMEND (aprepitant oral formulations) for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly and moderately emetogenic cancer chemotherapy in patients 6 months to 12 years of age (EMEND capsules are currently approved for use in patients 12 years of age and greater). Simultaneous to the prior approval supplement submission, the Applicant submitted an NDA (207,865) to support the use of a powder for suspension pediatric formulation of EMEND. The final necessary information to complete the submission of NDA 207,865 was received March 26, 2015 and the PDUFA clock for this NDA began on that date.

To support sNDA 21,549 and NDA 207,865 a single phase 3 efficacy and safety study was submitted. The clinical study and supporting information was reviewed and the supplemental NDA for the EMEND capsule was approved on 28 August 2015. See the full clinical review for sNDA 21,549/S-025 in DARRTS by Dr. Karyn Berry (17 August 2015) and subsequent clinical addendums in DARRTS (28 August 2015). Given that NDA 207,865 relied upon the same clinical information as sNDA 21,549/S-025, the clinical review and addendum are also in DARRTS under NDA 207,865 to provide details regarding the determination of efficacy and safety for Emend tablets and the powder for oral suspension for pediatric patients <12 years of age. The approval of sNDA 21,549/S-025 occurred on August 28, 2015.

The review clock for NDA 207,865 (EMEND for oral suspension) was extended in order to receive additional information to support appropriate labeling instructions for reconstitution and measurement of doses. The results of a Human Factors Study submitted with NDA 207,865 were found to be unacceptable by FDA's Division of Medication Error Prevention and Analysis (DMEPA). During the review cycle, the Applicant conducted an additional HF validation study using a revised protocol based on FDA recommendations. Sherly Abraham, R. PH, DMEPA reviewer, concluded the following:

> *The repeat human factors validation study was unable to show that the intended user population is able to use the product safely and effectively. Participants were only able to perform critical task functions safely and effectively 36/67 instances. Most of the task failures noted in the study would result in pediatric patients receiving either an under-dose, overdose or not receiving the medication at all.*

Given that two HF studies showed that lay caregivers were unable to reconstitute and measure accurate doses without an unacceptable rate of critical failures, FDA recommended that an additional HF study in HCP using revised instructions for use

(IFU) and incorporating redesigns recommended by DMEPA be conducted by the Applicant. These study results were submitted as a major amendment.

See the full HF Study Reviews in DARRTS (11 August 2015) by Sherly Abraham, R. Ph and section 4.5 of Dr. Karyn Berry's Clinical Review (17 August 2015).

The current review focuses on the additional information received to support the safe use and administration of EMEND powder for suspension.

III. Review Issues

a. Human Factor Study Results

Based on failed HF study results and discussion with FDA, the Applicant proposed revising their labeling to restrict reconstitution and preparation of Emend oral suspension to health care providers (HCPs) and administration of the pre-measured doses by lay patient caregivers. To support this proposed labeling change, the Applicant conducted two human factor studies with 21 oncology nurses and 16 patient caregivers.

Sherly Abraham DMEPA concluded the following:

> *The repeat human factors validation study results were generally acceptable since most of the intended user population was able to use the product safely and effectively. Participants were able to perform critical task functions safely and effectively in 64/76 instances. Most of the remaining use error tasks can be managed through improvements in the label and labeling.*

See the full HF Study Review by Sherly Abraham, R. Ph, in DARRTS (24 November 2015).

MO Comment:
This reviewer agrees that based on two failed HF studies in lay caregivers and an acceptable HF study in HCP, restricting reconstitution and preparation of EMEND for oral solution to health care professionals is appropriate. The first dose of EMEND oral suspension will be given by the HCP prior to chemotherapy. Syringes with subsequent pre-measured doses of Emend oral suspension will be prepared by the HCP and given to the lay caregiver for dosing on Days 2 and 3.

b. Contents of Emend for Oral Suspension Kit

In the human factor studies, the Applicant used an oral suspension kit that included the following:

- One pouch containing powder for suspension
- A 5-mL oral dispenser with a cap
- One mixing cup
- Instructions for Use (IFU) dosing instructions
- Prescribing Information (PI/PPI)
- Dosing of Emend for Oral Suspension

The FDA recommended that the Applicant add a 1 mL oral dispenser with cap to the EMEND for oral suspension kit. This recommendation was made in an effort to increase the accuracy of the doses can be measured by the oral dispenser. For example, the lowest dose is 0.6 mL which can best be measured using a 1 mL dispenser. In addition, other weight based doses can best be measured using a 5 mL dispenser (for the integer mL portion of the dose) in combination with a 1 mL oral dispenser (for the sub-mL portion of the dose).

The Applicant agreed to include a 1 mL oral dispenser with cap. To support the adequacy of this dispenser, the Applicant proposed to perform abbreviated in-use stability testing and only provide the data for assay and degradation products. The FDA agreed that the Applicant's proposal was acceptable.

MO Comment:
This reviewer agrees with the inclusion of both the 5 mL and 1 mL oral dispensers with caps in each Emend for oral suspension kit in an effort to increase dosing accuracy.

c. Weight-based Dosing

With the initial submission of NDA 207,865, the Applicant proposed to include a nomogram of weight bands in the label to assist lay caregivers in determining the correct dose. However, given the current plan to limit reconstitution of EMEND powder for suspension to HCP, the FDA recommended that the Applicant place mg/kg dosing in the label as was used in the clinical trial. The Sponsor agreed and submitted revised labeling on 01 December 2015.

MO Comment:
This reviewer agrees that the label should include weight-based dosing in lieu of a nomogram given that the labeling will restrict reconstitution and preparation of EMEND for oral solution to health care professionals.

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
12/14/2015

ANIL K RAJPAL
12/14/2015
I concur with Dr. Johnson.

Division of Gastroenterology and Inborn Error Products

Medical Officer Clinical Review Addendum: NDA 21549/S-025 and NDA 207865

NDA Number:	**21549/S-025 and NDA 207865**
Established name:	**aprepitant capsule and aprepitant oral suspension**
Trade Name:	**Emend**
Therapeutic Class:	**NK-1 Receptor Antagonist**
Applicant:	**Merck Sharp & Dohme Corp.**
Intended Population:	**Pediatric patients aged 6 months to 17 years**
Indication:	**Prevention of chemotherapy induced nausea and vomiting**
Clinical Reviewer:	**Karyn L. Berry, MD, MPH**

1. Explanation of Need for Clinical Review Amendment

This document is an addendum to a clinical review completed and finalized in DARRTS on August 17, 2015.

The original clinical review stated that the Applicant adequately demonstrated efficacy of aprepitant for the prevention of chemotherapy induced nausea and vomiting (CINV) associated with highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC) in pediatric patients aged 6 months to 17 years. However, outstanding issues related to aprepitant require clarification, including:

- Emetogenic classification scheme used in the key Phase 3 trials (Protocol 208)
- Capsule use in pediatric patients aged less than 12 years, but who weigh at least 30 kg
- Under and overdosing of aprepitant oral suspension in patients aged 6 months to 12 years

These updates to the original clinical review are summarized below with an updated recommendation on regulatory action.

2. Recommendation on Regulatory Action

This reviewer continues to recommend the approval of aprepitant capsules in

patients aged ≥ 12 to 17 years for the prevention of CINV associated with HEC and MEC. Based on pharmacokinetic (PK) data analyzed by the Clinical Pharmacology review team, this reviewer also recommends that aprepitant capsules be approved for use in pediatric patients who are aged <12 and weigh at least 30 kg.

3. Issues to be addressed

a. Emetogenic classification

A schema that appropriately classifies the emetogenic risk of chemotherapy regimens is important to provide a framework for treatment guidelines in the clinical setting and to define and standardize emetogenic potential in clinical trials. For adult CINV trials, a 4-level schema that classifies chemotherapeutic agents by emetogenicity (minimal risk is <10%; low risk is 10% - 30%; moderate risk is 31% - 90% and high risk is >90%) has been used by consensus groups in oncology, including the American Society of Clinical Oncology (ASCO) and Multinational Association of Supportive Care in Cancer (MASCC). See Table 1.

The Applicant stated that this system was developed based on adult experiences and cannot easily be extrapolated to the pediatric population due to potential differences in drug metabolism.

In the key, Phase 3 trial (Protocol 208), the Applicant used a 5-level system proposed by the Children's Oncology Group (COG), that classifies commonly used chemotherapeutic agents by emetogenicity. This classification ranks single chemotherapeutic agents as low risk, mild, moderate, high risk and very high risk, associated with <10%, 10-30%, 30-60%, 60-90% and >90% frequency of causing nausea and vomiting without antiemetic treatment. See Table 2

Table 1: Emesis Risk of Intravenous Antineoplastic Agents (ASCO)

Emetic Risk of Intravenous An ineoplastic Agents

Emetic Risk	Agent
High	Carmustine
	Cispla in
	Cyclophosphamide ≥1,500 mg/m^2
	Dacarbazine
	Dactinomycin
	Mechlorethamine
	Streptozotocin
Moderate	Azacitidine
	Alemtuzumab
	Bendamustine
	Carboplatin
	Clofarabine
	Cyclophosphamide < 1,500 mg/m^2
	Cytarabine > 1,000 mg/m^2
	Daunorubicin*
	Doxorubicin*
	Epirubicin*
	Idarubicin*
	Ifosfamide
	Irinotecan
	Oxaliplatin
Low	Fluorouracil
	Bortezomib
	Cabazitaxel
	Catumaxomab
	Cytarabine ::: 1,000 mg/m^2
	Docetaxel
	Doxorubicin HCL liposome injec ion
	Etoposide
	Gemcitabine
	Ixabepilone
	Methotrexate
	Mitomycin
	Mitoxantrone
	Paclitaxel
	Panitumumab
	Pemetrexed
	Temsirolimus
	Topotecan
	Trastuzumab
Minimal	2-Chlorodeoxyadenosine
	Bevacizumab
	Bleomycin
	Busulfan
	Cetuximab
	Fludarabine
	Pralatrexate
	Rituximab
	Vinblastine
	Vincristine
	Vinorelbine

NOTE. This list of agents is not exhaustive.
Abbreviation: HCL, hydrochloride.
*These anthracyclines, when combined with cyclophosphamide, are now designated as high emetic risk.

Table 2: Emetogenicity of Commonly Used Chemotherapeutic Agents

Adapted from [1] Altman, AJ, ed. *Supportive Care of Children with Cancer*. 3rd ed. Baltimore, MD: The Johns Hopkins University Press; 2004, and [7]Perry MC et al., ed. *Companion Handbook to Chemotherapy Source Book*. 2nd ed. Baltimore, MD: Lippinkott, Williams and Wilkins; 2004.
Added* or revised** from: Antiemetics. National Comprehensive Cancer Network (NCCN) Practice Guidelines in Oncology- V3.2008. http://www.nccn.org/professionals/physician_gls/PDF/antiemesis.pdf Accessed 5-14-08

Reviewer's comments: During a t-con between the Division of Gastroenterology and Inborn Errors Products (DGIEP) and the Applicant on March 16, 2011, the Applicant questioned the availability of consensus guidelines regarding chemo-therapy emetogenic potential in pediatric patients. Based on minutes from Mr. Jagjit Grewal, former DGIEP Regulatory Project Manager for this product, DGIEP and Pediatric and Maternal Health Staff (now called the Division of Pediatric and Maternal Health) had discussed the most appropriate emetogenic classification system for pediatric patients with the Division of Oncology Products. Reviewers in the oncology division recommended a classification of chemo-therapeutic agents by emetogenic potential for pediatric patients developed by the Children's Oncology Group. This was then conveyed to the Applicant during the above t-con.

In reviewing the two classification systems, there are a number of identified differences such as: dosing levels that qualify an agent for either very high or high emetogenic risk, such as cyclophosphamide > 1500 mg/m^2 (very high risk); ifosfamide ≥1.5 g/m^2 as a very high risk and ifosfamide < 1.5 g/ m^2 as moderate risk in the COG schema, while the ASCO consensus guidelines list cyclophosphamide ≥ 1500 mg/ m^2 as high risk and ifosfamide as moderate risk.

While there are differences between the two schemas, per the Division of Oncology recommendations, the COG emetogenic classification for pediatric patients used by the Applicant in Protocol 208 is acceptable.

b. Aprepitant capsules for patients less than 12 years of age who weigh at least 30 kg.

During the labeling negotiations and since no regulatory action would be taken for aprepitant oral suspension at this time, DGIEP requested that the Clinical Pharmacology Review Team assess whether PK data supported modifying the proposed pediatric dosing for the aprepitant capsule to include pediatric patients aged less than 12 years who weighed at least 30 kg, since the weight based dose for the suspension formulation in this specific pediatric population is equivalent to the adolescent dose.

The Applicant did not conduct a dedicated related bioavailability study comparing the oral suspension and approved oral capsule formulation. The Clinical Pharmacology Reviewer conducted a population PK analyses and found the available PK data supported extending the dosing capsule formulation in children less than 12 years of age who weigh at least 30 kg. See the Clinical Pharmacology Team review addendum in DARRTS.

Reviewer's comments: Use of aprepitant capsule in the patient population who are less than 12 years of age and weigh at least 30 kg and can swallow capsules would provide an additional drug to prevent CINV. This reviewer therefore agrees with including this population in the label for aprepitant capsules.

c. Under and overdosing of aprepitant oral suspension in patients aged 6 months to 12 years

An Information Request (IR) was sent to the Applicant to provide information on underdosing and overdosing of aprepitant oral suspension in patients aged 6 months to <12 years in Protocols 208 and 134. This IR was requested because of dosing administration errors observed in the Human Factor studies. It was expected that additional information from the clinical trials would further characterize these dosing errors.

The Applicant provided the following data on under and over dosing of aprepitant oral suspension in pediatric patients aged 6 months to < 12 years in Protocols 208 and 134.

Underdosed

In Protocol 208, the Applicant defined underdose as an administered dose < 90% of protocol specified dose. Underdosing occurred in two patients:

- AN070529, who was randomized to the control regimen, received 40 mg of placebo for aprepitant, which was less than the protocol specified dose of 65.2 on Day 3. Reported AEs included: nausea (moderate severity), abdominal pain (moderate severity) and headache (mild severity). The Applicant considered all AEs as unrelated to the study drug.
- AN070808, who was randomized to the aprepitant regimen, received 15.5 mg, which was less than the protocol specified dose of 31.2 mg on Day 3. Reported AEs included: back pain, cough, anemia, decreased appetite, febrile neutropenia, decreased platelet count and upper respiratory infection. All were considered by the Applicant as mild in severity and unrelated to the study drug.

In Protocol 134, subjects were administered either a single dose (Part II or a three day regimen (Part IV) of aprepitant oral suspension. Using a similar definition as in Protocol 208, the Applicant identified one subject who was underdosed in Protocol134 (Part II):

- AN10189 who was administered 74mg of aprepitant instead of 103.6 mg. Adverse events reported in this patient included vomiting (mild severity),

abdominal pain (mild severity), headache (mild severity) and neutropenia (moderate severity).

There were no identified cases of underdosing in the 20 subjects in Part IV.

Overdosed

In Protocols 208 and 134, all overdoses were required to be reported to the Sponsor. An overdose was defined in Protocol 208 as a single dose greater than the allocated dose of study medication. In Protocol 134, an overdose was defined as a single dose exceeding the permitted maximum daily dose for each dose level of either oral or IV study drug. If an AE resulted from the overdose, the AE was to be reported as a serious adverse event, even if no other criteria for serious are met. If the overdose was not associated with any clinical symptoms or abnormal laboratory results, the overdose was reported as a non-serious Event of Clinical Interest (ECI) using the terminology “accidental or intentional overdose without adverse event”.

Protocol 208

There were five subjects who experienced an accidental overdose in Cycle 1. Of these, one subject received an overdose of aprepitant and four subjects received an overdose of placebo for aprepitant. In the case of the subject who received an overdose of aprepitant (AN070412), the site used an incorrect subject weight to calculate the weight-based dose adjustment. Of the four subjects who received an overdose of placebo for aprepitant; two were due to incorrect subject weight or incorrectly calculated weight-based dose adjustment (AN070408 and AN070403) and two were due to nursing errors, in which one subject received the Day 1 dose of 3.0 mg/kg on Day 2 instead of 2.0 mg/kg (AN071301), and one subject received 0.19 mL more than prescribed (AN070936). Three of the five accidental overdoses in Cycle 1 occurred at the same site (Site 0045).

There were six subjects 6 months to <12 years of age who experienced an accidental overdose in Cycles 2-6, two of which also experienced an accidental overdose in Cycle 1 (AN070408 and AN070403). Of the accidental overdoses in Cycles 2-6, four were due to nursing errors, two were due to incorrect weight used to calculate the weight-based dose adjustment, and one was due to a parent error. Of the four nursing errors: one nurse followed the Day 1 instructions, rather than the Day 2 instructions resulting in administration of a Day 1 dose on Day 2 of Cycle 3 (AN070601) and one sub-investigator made an error in transcribing the dose adjustment, prescribing 3 mg/kg on Days 2 and 3 of Cycle 5, rather than 2 mg/kg (AN071314). One subject (AN070418) experienced two accidental overdoses: on Day 2 of Cycle 2, the nurse could not recall exactly how much of the aprepitant suspension was administered to the subject, but copied the same dose transcribed for Day 1 (site was not able to confirm the actual dose administered), and on Day 1 of Cycle 3, the nurse administered the full 5 mL dose of study medication rather than the 125 mg equivalent based on a weight of 60 mg (2.4 mL). In the case of the

parent error (AN070407), following administration of the Day 1 dose of Cycle 2, a parent was given the Day 2 and 3 doses to take home and administer on Days 2 and 3, but due to a misunderstanding the parent gave the Day 2 dose on Day 1.

Table 3: Protocol 208 Overdose Details

Allocation Number	Cycle/Day	Per Protocol Dose	Actual dose
070408	Cycle 1/Day 1	69 mg	72 mg
	Cycle 1/Day 2	46 mg	48 mg
	Cycle 1/Day 3	46 mg	48 mg
	Cycle 2/Day 1	70.8 mg	72 mg
	Cycle 2/Day 2	47.2 mg	48 mg
070403	Cycle 1/Day 1	93.6 mg	96 mg
	Cycle 2/Day 1	93.9 mg	96 mg
	Cycle 2/Day 2	62.4 mg	64 mg
	Cycle 2/Day 3	62.4 mg	64 mg
071301	Cycle 1/Day 2	20.8 mg	31.2 mg
070412	Cycle 1/Day 1	87.9 mg	92.5 mg
	Cycle 1/Day 2	58.6 mg	62.5 mg
	Cycle 1/Day 3	58.6 mg	62.5 mg
070936	Cycle 1/Day 1	1.05 ml/ 26.2 mg	1.2 ml/ 30 mg
070407	Cycle 2/Day 1	75 mg	125 mg
070418	Cycle 2 /Day 2	38.6 mg	57.9 mg
	Cycle 3/Day 1	60 mg	125 mg

070601	Cycle 3/Day 2	77.1 mg	115.6 mg
071314	Cycle 5/Day 2	15 mg	22 mg
	Cycle 5/Day 3	15 mg	22 mg

Applicant's table

Protocol 134

There were two subjects who experienced an overdose in Part II. At the time Part II was conducted, subjects were dosed based on body surface area (BSA). One subject (AN 10122) experienced an overdose as the BSA was calculated incorrectly leading to an error in the volume of aprepitant suspension administered. The other subject, AN10135 also had an error with the BSA that led to an overdose. There were no identified cases of overdose in the 20 randomized subjects 6 months to <12 years of age in Part IV of Protocol 134.

Table 4: Protocol 134 Overdose Details

Allocation Number	Day	Per Protocol Dose	Actual dose
10122	Day 1	91.76 mg	113.96 mg
10135	Day 1	18 mg	20 mg

Adverse Events Overdosing

Table 5: Listing of AEs Protocol 208 for Underdosing

Study ID	Subject ID	Preferred Term	Serious Event	AE Relative to Treatment Start in Cycle 1	AE Duration	Duration	Intensity	Action Taken with Study Medication	Relationship	AE Outcome	EPOCH
0869-208_003200014	070529	Nausea	N	1	5	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Treatment Cycle 1
		Abdominal pain upper	N	2	2	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Treatment Cycle 1
		Headache	N	3	12	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Treatment Cycle 1
0869-208_003500001	070808	Back pain	N	3	2	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Treatment Cycle 1
		Cough	N	3	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Treatment Cycle 1
		Anaemia	N	11	5	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Post Treatment Cycle 1
		Decreased appetite	N	11	1	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Post Treatment Cycle 1
		Febrile neutropenia	Y	12	6	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Post Treatment Cycle 1
		Platelet count decreased	N	12	6	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Post Treatment Cycle 1
		Upper respiratory	N	12	6	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED/ RESOLVED	Post Treatment cycle 1

Table 6: Listing of AEs Protocol 208 for Overdosing

Study ID	Subject ID	Preferred Term	Serious Event	AE Relative to Treatment	AE Duration	Duration	Intensity	Action Taken with Study Medication	Relationship	AE Outcome	EPOCH
0869-208_00450004	070403	Accidental overdose	N	1	1	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Accidental overdose	N	22	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Febrile neutropenia	Y	34	3	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Accidental overdose	N	43	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
0869-208_00250001	070407	Accidental overdose	N	41	23.9997	HOURS		DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Somnolence	N	41	2.1429	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Decreased appetite	N	42	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Pyrexia	Y	42	14.25	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Anaemia	N	63	40	MINUTE	MILD	DOSE NOT	NOT	RECOVERED	Cycle 2

		Vomiting	N	69	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Decreased appetite	N	76	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
0869-208_004500005	070408	Accidental overdose	N	1	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Febrile neutropenia	Y	12	5	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Allergic transfusion reaction	N	13	23	HOURS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Electrolyte imbalance	N	13	23	HOURS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Purulence	N	25	6	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Accidental overdose	N	37	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Renal tubular disorder	Y	44	1.2857	WEEKS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Thrombocytopenia	N	44	1.1429	WEEKS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Stomatitis	N	45	1.4286	WEEKS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2

0869-208_00450007	*070412 (received aprepitant)	Accidental overdose	N	1	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Febrile neutropenia	Y	8	4	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
0869-208_00350004	070418	Accidental overdose	N	49				DOSE NOT CHANGED	NOT RELATED		Cycle 2
		Vomiting	N	56	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Nausea	N	58	6	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Anaemia	N	60	3	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Febrile neutropenia	Y	60	1.4286	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Vomiting	N	60	4	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Abdominal pain	N	61	5	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Stomatitis	N	62	4	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
		Accidental overdose	N	78				DOSE NOT CHANGED	NOT RELATED		Cycle 2

		Anaemia	N	78	1.5714	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 2
0869-208_00450006	070601	Accidental overdose	N	80	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 3
0869-208_00270005	070936	Accidental overdose	N	1	3	DAYS		DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Pneumonia	Y	10	1.1429	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Pancytopenia	Y	11	6	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
0869-208_00360001	071301	Accidental overdose	N	2	5	MINUTES	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
		Febrile neutropenia	Y	5	2.7143	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 1
0869-208_00230005	071314	Accidental overdose	N	93	2	DAYS		DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Nausea	N	93	1.5714	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Hypotension	N	95	1	WEEKS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5

		Vomiting	N	95	3	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Blood creatinine increased	Y	97	5	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Acidosis	N	98	4	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Vomiting	N	99	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Hypophosphataemia	N	100	2	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Neutropenia	N	100	2.2857	WEEKS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Vomiting	N	101	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Febrile neutropenia	Y	103	1.8571	WEEKS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Hypophosphataemia	N	103	4	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Hypotension	N	103	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Melaena	N	103			MILD	DOSE NOT CHANGED	NOT RELATED	UNKNOWN	Cycle 5
		Thrombocytopenia	N	103	7.4669	HOURS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5

		Abdominal pain	N	104	4	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Vomiting	N	105	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Vomiting	N	106	2	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Thrombocytopenia	N	108	3	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Abdominal pain	N	113	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Anaemia	N	113	2	DAYS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Fall	N	113	1.0169	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Subcutaneous haematoma	N	113	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Thrombocytopenia	N	113	23.4669	HOURS	MODERATE	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Diarrhoea	N	114	2	DAYS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5
		Vomiting	N	115	23.9997	HOURS	MILD	DOSE NOT CHANGED	NOT RELATED	RECOVERED /RESOLVED	Cycle 5

Applicant's table
In cycles 2-6 all subjects received aprepitant oral suspension
*Only one subject in cycle 1 - 070412 received aprepitant oral suspension

Reviewer's comments: Per the Applicant's response, of the nine subjects who experienced an accidental overdose in Protocol 208 (cycle 1 and cycles 2 to 6), four were from the same site (site 0045). Two of the four subjects each experienced two accidental overdoses at site 0045, for a total of six accidental overdoses at that site. Of the six accidental overdoses at that particular site, five were due to an incorrect weight being used to calculate the adjusted dose of aprepitant to be administered.

Unlike in the HF studies which were not set up to actually calculate patient weight, weight calculation errors were the primary issue in the clinical trial, specifically at one particular site. Other nursing and parent errors related to dosing errors in the clinical trials, confirmed the errors that were observed in the HF studies.

Concerning the AEs observed in the underdosing of the subject who received aprepitant, the AE of nausea could possibly be related to decreased efficacy of the lower aprepitant dose. Of the nine subjects in P208 who received overdosing none of the reported AEs the Applicant stated that none were related to the study drug. The reported AEs, such as febrile neutropenia, thrombocytopenia and anemia, would not be unusual In this patient population with a malignancy diagnosis and receiving chemotherapeutic agents.

The issues of underdosing and overdosing with the aprepitant oral suspension will be further evaluated during the continued review of NDA 207865.

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/s/

KARYN L BERRY
08/28/2015

DONNA J GRIEBEL
08/28/2015

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	21549/S-025 207865
Priority or Standard	NDA 21549/S-025 (Standard with 3-month extension based on major amendment) NDA 207865 (Fast Track – Priority)
Submit Date(s)	NDA 21549/S-025 (July 28, 2014) NDA 207865 (March 26, 2015)
Received Date(s)	July 28, 2014 and March 26, 2015
PDUFA Goal Date	NDA 21549/S-025 (revised- August 28, 2015) NDA 207865 (revised - December 26, 2015)
Division / Office	ODE 3/DGIEP
Reviewer Name(s)	Karyn L. Berry, MD, MPH
Review Completion Date	August 7, 2015
Established Name	Aprepitant
(Proposed) Trade Name	Emend
Therapeutic Class	Neurokinin (NK)-1 receptor antagonist

Applicant	Merck Sharp & Dohme Corp.
Formulation(s)	Capsules (ages 12 (b) (4) NDA 21549/S-025) Oral suspension (ages 6 months to < 12 years NDA 207865)
Dosing Regimen	EMEND is given orally for 3 days, 1 hour prior to chemotherapy treatment on Days 1, 2 and 3. If no chemotherapy is given on Days 2 and 3, EMEND should be administered in the morning • Ages 12 (b) (4): Aprepitant capsules- 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3. • Ages 6 months to < 12 years: Aprepitant oral suspension is based on weight.
Indication(s)	In combination with other antiemetic agents in patients 6 months of age and older for prevention of: • acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy HEC) including high-dose cisplatin • nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC
Intended Population(s)	Ages 6 months to 17 years

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval of NDA 21549/S-025 Emend (aprepitant) capsules for ages 12 years to 17 years for the following indications:

In combination with other antiemetic agents for prevention of:

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

The recommended dose of aprepitant capsules for this population is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3.

This reviewer recommends a major amendment extension for NDA 207865 aprepitant for oral suspension for ages 6 month to < 12 years for the following indications:

In combination with other antiemetic agents for prevention of:

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

The major amendment would extend the PDUFA goal date for NDA 207865 by three months to December 26, 2015. The major amendment is related to additional data needed to support the safe use and administration of the oral suspension formulation.

During the review of NDA 207865, critical task failures were identified in the results of the Human Factor (HF) studies (conducted in lay caregivers and healthcare professionals) submitted by the Applicant. These failures which included measuring the reconstitution volume and dose volume of the product may result in pediatric patients receiving either an under-dose or over-dose of the medication. Based on the inability of the intended population to safely and effectively use the product as labeled, additional data has been requested from the Applicant.

Because the Applicant conducted one trial to evaluate the prevention of chemotherapy induced nausea and vomiting (CINV) with HEC and MEC in pediatric patients aged 6 months to 17 years, both applications NDA 21549/S-025 and NDA 207865 were initially

submitted for review on July 28, 2014. Due to filing deficiencies identified with NDA 207865, it was re-submitted on March 26, 2015 and therefore the applications have different PDUFA goal dates.

1.2 Risk Benefit Assessment

Aprepitant capsules have been prescribed in the United States since 2003 for the prevention of CINV in adults.

Nausea and vomiting, the most distressing side effects of adult cancer chemotherapy, are also a major problem in the treatment of childhood malignancies. Nausea and vomiting are potentially severe and debilitating side effects of chemotherapy. They can lead to increased patient morbidity, for example electrolyte imbalance, dehydration, poor nutrition and prolonged hospitalization.

CINV in both children and adults is classified as acute and delayed. The acute and delayed phase definitions of CINV are frequently used to describe the pattern of efficacy of antiemetic therapeutic agents or regimens. The acute phase occurs within the first 24 hours following chemotherapy administration and the delayed phase occurs after 24 hours until 120 hours.

The analysis of data in this submission demonstrated the superiority of the aprepitant regimens (capsules and oral suspension) over the control regimen in the prevention of acute and delayed CINV with HEC and MEC in pediatric patients aged ≥12 to 17 years (capsules) and 6 month to <12 years (oral suspension) receiving emetogenic chemotherapy for a documented malignancy.

Study Protocol 208 (P208) was a randomized, double-blind, active-comparator controlled, parallel-group study (with in-house blinding) designed to assess the efficacy and safety of aprepitant for the prevention of CINV in pediatric patients receiving emetogenic chemotherapy for a documented malignancy. Dosing regimen for the aprepitant capsule (patients aged ≥12 to 17 years) was 125 mg on Day 1 and 80 mg on Days 2 and 3. The dosing regimen for the oral suspension (patients aged 6 month to <12 years) was weight based, 3 mg/kg on Day 1 and 2 mg/kg on Days 2 and 3. The primary efficacy endpoint was Complete Response (CR) in the delayed phase, or the 25 to 120 hours following initiation of emetogenic chemotherapy in Cycle 1. Secondary efficacy endpoints were CR in the acute (0 to 24 hours) and overall (0 to 120 hours) phases in Cycle 1. CR was defined as “no vomiting, no retching and no use of rescue medication.” The proportion of pediatric subjects in the aprepitant regimen that demonstrated CR in the delayed phase was 50.7% as compared with 26% of pediatric subjects in the control regimen.

The safety analysis was based on a safety databased of 357 pediatric subjects. A potential issue with the safe use and administration of the oral suspension was

identified during this review. Otherwise, no other safety signals were identified in the clinical data submission.

The overall efficacy and safety results for NDA 21549/S-025 (aprepitant capsules) for use in pediatric patients ages ≥ 12 to 17 years for the prevention of CINV associated with HEC and MEC demonstrate an acceptable risk/benefit profile.

During the review of NDA 207865, critical task failures were identified in the results of the Human Factor (HF) studies (conducted in lay caregivers and healthcare professionals) submitted by the Applicant. These failures, which included measuring the reconstitution volume and dose volume of the product, would result in pediatric patients receiving either an under-dose or over-dose of the medication. Based on the inability of the intended population to safely and effectively use the product as labeled, additional data has been requested from the Applicant. The Applicant has agreed to submit the results of the following proposed actions by October 31, 2015:

1.) Conduct an additional Human Factor study in Oncology Nurses. As discussed in the teleconference Merck will conduct this study in nurses that are experienced in preparing chemotherapy drugs for administration.

2.) Conduct a study to evaluate the compatibility and in-use stability (microbial and chemical) of the EMEND PFS suspension in a container for 72 hours. This data will support a process for the health care provider to prepare the dose to be administered to the patient and transfer it to a container for administration by the caregiver at home with no further preparation or measurement required.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended for the NDA 21549/S-025.

1.4 Recommendations for Postmarket Requirements and Commitments

This medical officer recommends no postmarket requirements or commitments for the NDA 21549/S-025.

NDA 21549 Emend (aprepitant) has the following post-marketing requirements (PMRs) under the Pediatric Research Equity Act. Of note, only PMRs related to the CINV indications were submitted by the Applicant for this review.

- NDA 021549
  1395-7: Deferred pediatric studies in patients 2 years to 17 years of age for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

- NDA 021549/S-008
  331-1: Deferred pediatric study under PREA for the use of Emend (aprepitant) in the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in pediatric patients 6 months to less than 17 years of age.

- NDA 021549
  Deferred pediatric study under PREA for the treatment of post-operative nausea and vomiting in pediatric patients ages 0 to less than 17 years of age.

In this reviewer's assessment, with the approval of NDA 21549/S-025, the Applicant has not fulfilled the Pediatric Research Equity Act (PREA) postmarket requirements related to CINV. To completely fulfill the PMRs the Applicant will need to develop an age appropriate formulation.

These studies were also included as part of a Written Request (WR) issued on February 2, 2009 for Emend (aprepitant).

With this submission, the Applicant has stated that they are not requesting pediatric exclusivity under the "Best Pharmaceuticals for Children Act of 2007".

2 Introduction and Regulatory Background

NDA 21549/S-025 was submitted as an efficacy supplement because it proposes to significantly alter the patient population (e.g., proposes use in pediatric population). NDA 207865 was submitted under 505(b)(1) because it is a new dosage form.

Two PREA requirements were established with approval of NDA 21549 and NDA 21549/S-008. The Applicant submitted applications NDA 21549/S-025 (b) (4) 207865 as a response to PREA post market requirements to evaluate the PK, safety and efficacy of aprepitant in the prevention of CINV with HEC and MEC in pediatric patients 6 months to 17 year of age. The Applicant is seeking approval for aprepitant

oral capsules in pediatric patients aged 12 (b) (4) and aprepitant oral suspension for patients 6 months to less than 12 years for the prevention of CINV. The applicant submitted one pivotal trial (Protocol 208) which included all age groups. The product formulation for the adolescent population component of the trial was the capsule (NDA 21549/S-025) that is approved in adults. The applicant developed an age appropriate formulation (oral suspension) for use in patients aged 6 month to < 12 years (b) (4) 207865).

With the initial approval of NDA 21549 for aprepitant for the prevention of CINV associated with HEC, including high-dose cisplatin and supplemental NDA 21549/S-008 for the prevention of CINV associated with MEC, the applicant agreed to defer PREA pediatric studies. The PREA pediatric studies were conducted under Investigational New Drug Application (IND) 50283.

The following are the deferred pediatric studies required under PREA for the CINV indications:

NDA 021549

- 1395-7: Deferred pediatric studies in patients 2 years to 17 years of age for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

NDA 021549/S-008

- 331-1: Deferred pediatric study under PREA for the use of Emend (aprepitant) in the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy in pediatric patients 6 months to less than 17 years of age.

Aprepitant 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 regimens in adults. 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. Of note, on January 25, 2008, Emend (fosaprepitant dimeglumine) injection was approved under NDA 22023 for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of HEC, including high-dose cisplatin; and, the prevention of nausea and vomiting associated with initial and repeat courses of MEC.

Aprepitant is a highly selective substance P neurokinin-1 (NK1) receptor antagonist. Aprepitant crosses the blood-brain barrier and occupies NK1 receptors in the brain. It is theorized that NK1 receptor antagonists exert their main antiemetic action by

depressing the neural activity of the nucleus tractus solitarius lying ventrally to the area postrema. Aprepitant was the first in this therapeutic class of antiemetics to be approved.

Aprepitant is currently approved in adults for the following indications:

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

- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) and

- prevention of postoperative nausea and vomiting (PONV)

For the prevention of CINV, aprepitant is approved for use in combination with standard antiemetic regimens including a $5HT_3$ receptor antagonist and a corticosteroid.
The approved triple therapy regimen for orally administered aprepitant (for both HEC and MEC) includes a 3-day administration of aprepitant: 125 mg on Day 1, followed by 80 mg on Days 2 and 3.

CINV Background

Nausea and vomiting, the most distressing side effects of adult cancer chemotherapy, are also a major problem in the treatment of childhood malignancies. Nausea and vomiting are potentially severe and debilitating side effects of chemotherapy. They can lead to increased patient morbidity, for example electrolyte imbalance, dehydration, poor nutrition and prolonged hospitalization.[1]

It has been estimated that nausea and vomiting occur in up to 70% of children receiving chemotherapy. In addition, children above the age of 5 years are more prone to vomiting than adults.[2] Several risk factors for CINV in both adult and pediatric populations have been identified. They include: female sex, age, history of prior CINV and emetogenicity of planned chemotherapy, which is the most important risk factor.

Antineoplastic agents and their combinations can be categorized according to their emetogenic level, and this categorization is helpful for classifying the severity of CINV and treating it. Highly emetogenic chemotherapy (HEC) agents are those associated with CINV in >90% of treated patients; Moderately emetogenic chemotherapy (MEC) agents are those associated with CINV in 30 to 90% of patients; Low emetogenic chemotherapy agents are those associated with CINV in 10 to 30% of patients; and

1 Roila F, Optimal selection of antiemetics in children receiving cancer chemotherapy. Support Care Cancer (1998) 6:215:220
2 Jordan K., Antiemetics in children receiving chemotherapy. MASCC/ESMO guideline update 2009. Supportive Care Cancer 2011; 19:S37-S42

Minimally emetogenic chemotherapy agents are those associated with CINV in <10% of patients.

CINV in both children and adults is classified as acute and delayed. The acute and delayed phase definitions of CINV are frequently used to describe the pattern of efficacy of antiemetic therapeutic agents or regimens. The acute phase occurs within the first 24 hours following chemotherapy administration and the delayed phase occurs after 24 hours until 120 hours. The 5-HT3 receptor antagonists form the cornerstone of the prevention of CINV. However, studies have shown that the efficacy of this class is reduced during the delayed phase.

The pathophysiology of CINV in the pediatric cancer patients involves the same neurotransmitters and pathways that govern CINV in adult cancer patients.[3] As in adults, the acute phase of CINV is mediated largely by the release of serotonin (5-HT) via direct cytotoxic damage to enterochromaffin cells in the intestinal mucosa and activation of vagal afferent neurons in the gut. A 5-HT3 antagonist, such as ondansetron, in combination with dexamethasone is recommended in both adult and pediatric patients receiving highly emetogenic chemotherapy (HEC) or moderately emetogenic chemotherapy (MEC) for the control of acute CINV.[4]

NK-1 receptor antagonists have a role in mediating delayed CINV 2 to 5 days following chemotherapy. Delayed CINV appears to involve the release of neurokinin peptide substance P in the brainstem. In adults, when an NK-1 antagonist, 5-HT3 antagonist, and corticosteroid are given in combination, there is a significantly greater reduction in CINV that occurs during the delayed phase than that seen with the use of the combination of a 5-HT3 antagonist and corticosteroid alone.[5]

The Applicant proposes that the beneficial effect of NK-1 antagonist in the prevention of CINV can also be demonstrated in pediatric patients.

Aprepitant, as part of the triple-therapy regimen including a 5-HT3 antagonist and a corticosteroid, is recommended by Multinational Association of Supportive Cancer Care (MASCC), American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) for the prevention of nausea and vomiting associated with HEC and selected MEC regimens in adults.

3 Bayo J., Chemotherapy-induced nausea and vomiting: pathophysiology and therapeutic principles. Clin Transl Oncology 2012; 14:413-422
4 Basch E, Prestrud A, Hesketh P, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology 2011;29:4189-98
5 Rapoport B., Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Support Care Cancer 2010; 18:423-431

Current MASCC, ASCO and the Pediatric Oncology Group of Ontario guidelines for children undergoing chemotherapy recommend the use of a 5-HT3 antagonist, such as ondansetron, and a corticosteroid to alleviate nausea and vomiting associated with emetogenic chemotherapy. However, despite the widespread use of these agents, nausea and vomiting continue to occur and remain a major source of distress for children undergoing emetogenic chemotherapy. Thus, the Applicant states that there is an ongoing need to evaluate new anti-emetic agents, such as aprepitant, in alleviating CINV in children receiving emetogenic chemotherapy.

2.1 Product Information

Trade Name: Emend

Generic name: Aprepitant

Proposed Age Group: 6 months to 17 years

Proposed Indication: Aprepitant capsules (in patients 12 years of age and older) and Aprepitant for oral suspension (in patients 6 months to less than 12 years), are indicated in combination with other antiemetic agents for prevention of:

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

Pharmacologic Class: Neurokinin-1 receptor antagonist

Formulation: oral capsule (NDA 21549/S-025) and oral suspension (NDA 207865)

- Oral capsule: 40 mg, 80 mg, 125 mg
- Oral suspension: 125 mg as a pink to light pink powder in a single-use pouch with 5 mL oral dosing dispenser and mixing cup.

(b) (4)

Proposed Treatment Regimen:

NDA 21549/S-025 – Dosing for Prevention of CINV- HEC and MEC

Pediatric patients aged 12 (b) (4): The recommended dose of capsules of EMEND is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3 (see Tables 1 and 2 XX).

Table 1 : Dosing for Prevention of Nausea and Vomiting associated with HEC

	Population	Day 1	Day 2	Day 3	Day 4
EMEND capsules*	Pediatric Patients 12 Years and Older	125 mg orally	80 mg orally	80 mg orally	none
Dexamethasone†					
	Pediatric Patients 12 Years and Older	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4			
5-HT_3 antagonist	Pediatric Patients 12 Years and Older	See selected 5-HT_3 antagonist prescribing information for the recommended dosage	none	none	none

*Administer EMEND capsules 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND capsules in the morning on Days 2 and 3.
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1 and in the morning on Days 2 through 4. The dose of dexamethasone reflects a 50% dosage reduction to account for a drug interaction with EMEND
Applicant's table

Table 2: Dosing for Prevention of Nausea and Vomiting associated with MEC

	Population	Day 1	Day 2	Day 3
EMEND capsules*	Pediatric Patients 12 Years and Older	125 mg orally	80 mg orally	80 mg orally
Dexamethasone†				
	Pediatric Patients 12 Years and Older	If a corticosteroid, such as dexamethasone, is co-administered, administer 50% of the recommended corticosteroid dose on Days 1 through 4		
5-HT_3 antagonist	Pediatric Patients 12 Years and Older	See the selected 5-HT_3 antagonist prescribing information for recommended dosage	none	none

*Administer EMEND capsules 1 hour prior to chemotherapy treatment on Days 1, 2, and 3. If no chemotherapy is given on Days 2 and 3, administer EMEND capsules in the morning on Days 2 and 3.
†Administer dexamethasone 30 minutes prior to chemotherapy treatment on Day 1. The dose of dexamethasone reflects a 50% dosage reduction to account for a drug interaction with EMEND
Applicant's table

NDA 207865 –Dosing for Prevention of CINV HEC and MEC
Pediatric patients aged 6 months to less than 12 years: The recommended dose of EMEND for oral suspension is based on weight, as specified in the table below:

2.2 Table of Currently Available Treatments for Proposed Indications

Table 4: Currently Available Treatments for Prevention of CINV in Pediatric Patients

Drug Formulation	Labeled CINV Indication	Dosage and Administration in Pediatric Patients
5-HT3 Receptor Antagonist		

Ondansetron HCl I.V.	Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin	Patients aged ≥6 months: 3 x 0.15 mg/kg doses up to a maximum of 16 mg per dose. First dose is infused beginning 30 minutes before the start of chemotherapy
Ondansetron HCl Oral (tablet, disintegrating tablet, solution)	1. Prevention of nausea and vomiting associated with HEC, including cisplatin ≥50 mg/m^2 2. Prevention of nausea and vomiting associated with initial and repeat courses of MEC	Patients aged 4 through 11 years: 4 mg given 3 times a day. First dose should be given 30 minutes before the start of chemotherapy, with subsequent doses 4 and 8 hours after the first dose. 4 mg orally every 8 hours may be continued for 1 to 2 days after chemotherapy is complete. Pediatric patients aged ≥12 years: 8 mg given 2 times a day. First dose should be given 30 minutes before the start of chemotherapy, with subsequent dose 8 hours after the first dose. 8 mg orally every 12 hours may be continued for 1 to 2 days after chemotherapy is complete.
Granisetron HCl I.V.	Prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin	Pediatric patients aged ≥2 years: 10 mcg/kg given within 30 minutes before initiation of chemotherapy
Dolasetron mesylate Oral tablet	Prevention of nausea and vomiting associated with MEC, including initial and repeat courses	Pediatric patients aged ≥2 years: 1.8 mg/kg given within 1 hour before initiation of chemotherapy, up to a maximum of 100 mg
Palonosetron HCl I.V.	Prevention of acute nausea and vomiting with initial and repeat courses of emetogenic cancer chemotherapy, including highly emetogenic chemotherapy	Pediatric patients aged ≥1 month: 20 mcg/kg (maximum 1.5 mg) dose administered as a 15 minute intravenous infusion starting approximately 30 minutes before initatiation of chemotherapy

Abbreviations: HCl, hydrochloride; I.V., intravenous; HEC, highly emetogenic cancer chemotherapy; MEC, moderately emetogenic cancer chemotherapy
Source: Reviewer's table, with information obtained from current ondansetron, granisetron, dolasetron and palonosetron labeling.

There are currently no NK-1 inhibitors approved for use in pediatric patients.

2.3 Availability of Proposed Active Ingredient in the United States

Aprepitant capsules are currently approved and available for use in adults. Aprepitant oral suspension is a new formulation developed for pediatric use (ages 6 months to less than 12 years).

2.4 Important Safety Issues With Consideration to Related Drugs

There are currently two NK-1 products on the market in the U.S.—Emend and Akynzeo. Emend is available in two formulations- oral (aperepitant) and solution for injection (fosaprepitant). Akynzeo, available as an oral formulation, is a fixed

combination of netupitant, a substance P/neurokinin1 receptor antagonist, and palonosetron, a 5-HT3 receptor antagonist. Akynzeo was approved October 10, 2014 for use in adults for the following indication, "the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Oral palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting during both the acute and delayed phase after cancer chemotherapy."

Contraindications

Aprepitant (excerpt from 08/2014 label)

EMEND is contraindicated in patients who are hypersensitive to any component of the product. EMEND is a dose-dependent inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4). EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions [see Drug Interactions (7.1)]

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Fosaprepitant (excerpt from 10/2014 label)

4.1 Hypersensitivity

EMEND for Injection is contraindicated in patient s who are hypersensitive to EMEND for Injection, aprepitant, polysorbate 80 or any other components of the product. Known hypersensitivity reactions include: flushing, erythema, dyspnea, and anaphylactic reactions [see Adverse Reactions (6.2)].

4.2 Concomitant Use with Pimozide or Cisapride. Aprepitant, when administered orally, is a moderate cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor following the 3-day antiemetic dosing regimen for CINV. Since fosaprepitant is rapidly converted to aprepitant, do not use fosaprepitant concurrently with pimozide or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or lifethreatening reactions [see Drug Interactions (7.1)].

Warnings and Precautions

Aprepitant

- *5.1 CYP3A4 Interactions*
- *5.2 Coadministration with Warfarin (a CYP2C9 substrate)*
- *5.3 Coadministration with Hormonal Contraceptives*
- *5.4 Patients with Severe Hepatic Impairment*
- *5.5 Chronic Continuous Use*

Fosaprepitant

- *5.1 CYP3A4 Interactions*
- *5.2 Hypersensitivity Reactions*
- *5.3 Coadministration with Warfarin (a CYP2C9 substrate)*
- *5.4 Coadministration with Hormonal Contraceptives*
- *5.5 Chronic Continuous Use*

Drug Interactions

Akynzeo has no contraindications in the current version of the label (10/2014). The Akynzeo label has no Warnings and Precautions related to the netupitant component of the fixed dose combination product.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

February 24, 2014
Agency granted a deferral extension of Commitments 1395-7 and 331-1 until July 31, 2014.

November 26, 2013
Applicant submitted a requested for a deferral extension to the PREA commitment due dates.

November 6, 2013
PREA non-compliance letters sent to Applicant for NDA 21549 and NDA 21549/S-008 communicating that FDA had determined that Merck failed to submit the pediatric assessments by the required PREA target date which was deferred until October 31, 2013.

April 12, 2013
Agency granted deferral extension for commitments 1395-7 and 331-1 until October 31, 2013.

January 2, 2013
Applicant requested an extension to the PREA commitment due dates

March 15, 2012 (WR Amendment 2)
Agency amended the WR

September 30, 2011
Applicant requested changes to February 2, 2009 WR

April 8, 2011 (WR Amendment 1)
Agency amended the WR.

July 29, 2009
Applicant requested changes to FDA's WR

February 2, 2009 (Written Request [WR])
To obtain needed pediatric information on aprepitant and fosaprepitant dimeglumine, the FDA made a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that the Applicant submit information from studies that evaluate the prevention of CINV and PONV using age appropriate formulations.

Also, in this letter, the Applicant was informed that since fosaprepitant has EDTA (15.1 mg/vial) and since safety ramifications of this dose has not been established, an age appropriate formulation of fosaprepitant would need to be developed.

December 19, 2007
Agency agreed to grant Applicant requested deferral of Postmarketing pediatric studies.

August 20, 2007
Applicant request extension of to submit data from pediatric CINV prevention studies from December 31, 2007 to December 31, 2009.

January 31, 2006 (NDA 21549) & February 14, 2006 (IND 50, 283)
Applicant submitted revised PPSR for Emend capsules to both the NDA and IND in response to Agency comments dated April 26, 2005 to original PPSR submitted September 15, 2004.

October 28, 2005
Upon approval of efficacy supplement #8 for the prevention of nausea and vomiting associated with initial and repeat courses of MEC, one of the PMR's included deferred pediatric study under PREA for the use of Emend in pediatric patients 6 months to less than 17 years of age.

April 26, 2005 (Denied Inadequate Pediatric Study Request)
Letter sent to sponsor informing them of denial of Written Request and recommending that they resubmit proposed pediatric study to address the following:

- To be consistent with WR issued for other antiemetics used for the prevention of CINV they should evaluate patients as young as 6 months of age.
- In Study # 1, you propose to evaluate safety, tolerability, and efficacy of aprepitant in children 12 to < 17 years of age. To be consistent with recent Written Requests for other antiemetics used to prevent CINV, you should expand the age range. The studies should include at least 60 pediatric cancer patients between the ages of 6 months to < 17 years of age. These patients should be approximately and uniformly distributed according to age. You should also consider evaluating one or more dose levels of aprepitant.
- In Study # 2, you propose to evaluate the pharmacokinetics of aprepitant in the following four pediatric age groups: [6 patients in each age group (9 to < 12 years of age), (6 to < 9 years of age), (4 to < 6 years of age), and (2 to < 4 years of age)]. To be consistent with recent Written Requests, pharmacokinetic (PK) studies should include a sufficient number of patients to adequately characterize the PK of aprepitant in pediatric patients. If a traditional PK approach is used, at least 10 patients should be in the age range 6 to 12 months of age. Alternatively, if a population PK approach is used, you should attempt to include at least 20 patients in the age range of 6 to 12 months of age. Additionally, you will need to develop an age appropriate formulation for patients unable to swallow capsules.
- In general, pediatric PK studies should be conducted before the efficacy studies. A dose finding study may be conducted with doses of aprepitant less than the dose approved for adults.
- The dosing regimen of aprepitant and co-medications such as 5HT3- receptor antagonists should be proposed with dosage adjustment based on age or body weight.
- The dose of corticosteroid that should be co-administered may be determined considering the drug interaction with aprepitant.
- Apart from the proposed PK study, additional studies to determine the pharmacokinetics of aprepitant in children 12 to < 17 years of age, and 6 months to < 2 years of age should be proposed.
- An age-appropriate formulation of aprepitant suitable for pediatric patients, 6 months to < 6 years of age should be developed.
- Relative bioavailability of the age-appropriate formulation should be conducted in healthy adults.
- Either a traditional or population PK approach may be used to characterize the pharmacokinetics of aprepitant on days 1 and 3 of treatment.

January 21, 2005
Letter sent to sponsor informing them of denial of waiver for pediatric studies for patients less than 2 years of age for the prevention of nausea and vomiting associated with highly emetogenic chemotherapy. The Division agreed with and granted the sponsor's request for a deferral of pediatric studies in patients 2 years of age to 17 years of age for Emend capsules for the prevention of acute and delayed nausea and

vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin.

October 19, 2004 (Clinical review)
The sponsor was informed that the 2 studies proposed were not adequate to support a Written Request for aprepitant.

The request for a partial waiver in the age group of < 2 years was denied. The decision noted that to be consistent with recent Written Requests for other antiemetics used to treat CINV, the sponsor should evaluate patients as young as 6 months of age.

Study 1: To be consistent with recent Written Requests for other antiemetics used to prevent CINV, the sponsor should expand the age range. The studies should include at least 60 pediatric cancer patients between the ages of 6 months through 17 years. The Sponsor should also consider evaluating one or more dose levels of aprepitant.

Study 2: To be consistent with recent Written Requests, PK studies should include a sufficient number of patients to adequately characterize the PK of aprepitant in pediatric patients. If a traditional PK approach is used, at least 10 patients should be in the age range 6-12 months. Alternatively, if a population PK approach is used, the sponsor should attempt to include at least 20 patients in the age range of 6 -12 months. Additionally, the Sponsor will need to develop an age appropriate formulation for patients unable to swallow capsules.

September 29, 2004
The sponsor submitted an efficacy supplement for NDA 21549/S-008. In this submission, the sponsor requested a partial waiver in the age group < 2 years for the moderately emetogenic cancer chemotherapy (MEC) indication.

September 15, 2004
The sponsor submitted a “proposed pediatric study request” (PPSR) for Emend capsules to qualify for pediatric exclusivity as defined in the Best Pharmaceuticals for Children Act and section 505A of the Federal FD&C Act. The proposed studies were also intended to fulfill the Pediatric Research Equity Act of 2003. The sponsor proposed 2 pediatric studies (ages 2 to 17 years) as a basis for the Agency’s issuance of a Written Request for pediatric studies with Emend.

The sponsor requested a partial waiver for the age group <2 years because “necessary studies are impossible or highly impractical.”

Study 1 : A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of Aprepitant for the Prevention of Chemotherapy- Induced Nausea and Vomiting Associated with High Dose Cisplatin in Adolescent Patients (aged 12 to 17

years, with confirmed solid malignancies, naive to cisplatin chemotherapy, and who will be treated with cisplatin chemotherapy).

Study 2: An open-label two part study in pediatric patients receiving emetogenic chemotherapy primarily to evaluate aprepitant PK. Part I will include 12 patients age 6 to < 12 (six in each age group of age 6 to <9 and 9 to <12). Since children <6 years of age will likely have difficulty swallowing the currently marketed capsule formulation, an alternative formulation will be needed for this younger age group. If an appropriate non-capsule formulation can be developed, Part II of the study will enroll 12 patients age 2 to <6 (six in each age group of age 2 to <4 and age 4 to <6 years).

March 27, 2003
At the time of approval of NDA 21549, FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] had been challenged in court on October 17, 2002, the court ruled that the FDA did not have the authority to issue the Pediatric Rule. Since the initial approval date of oral aprepitant for the prevention of CINV in adults (March 27, 2003) preceded PREA, the March 27, 2003 approval letter did not stipulate any required pediatric studies. The sponsor was encouraged to submit a pediatric plan that described development of the product in the pediatric population.

2.6 Other Relevant Background Information

When initially submitted on July 25, 2014, NDA 207865 was found to be not fileable from the CMC perspective. The CMC reviewer at the time, Dr. Marie Kowblansky noted in her filing review dated September 16, 2014, that "the Office of Compliance has determined that this application should not be filed because the manufacturing facilities are not ready for inspection." The application was not sufficiently complete to permit a substantive review. Therefore, CMC refused to file the application under 21 CFR 314.101(d)(3).

Specifically, the application did not identify those facilities which would be responsible for commercial manufacturing of the API and critical API intermediates and the application form listed inactive facilities.

The Applicant was notified of data that would be needed to resubmit the NDA (e.g., clearly identified manufacturing facilities sufficient for commercial API and drug product manufacturing operations). See Dr. Kowblansky's filing review for additional information.

Multiple **c**linical Information requests were submitted for both NDA 21549/S-025 (b) (4) NDA 207865 to obtain safety and efficacy data and analyses for subset of patients aged 12 to 17 years and patients aged 6 months to less than 12 years.

NDA 21549/S-025 and NDA 207865

July 28, 2014

Applicant submitted requested clinical study data to fulfill the pediatric aprepitant PREA study commitments 1395-7 and 331-1 for NDA 21549 and NDA 21549/S-008. The Applicant stated in the application cover letter that they are not requesting pediatric exclusivity under the "Best Pharmaceuticals for Children Act of 2007" with this submission.

NDA 21549/S-025

February 6, 2015

The Agency informed the Applicant that the goal date for NDA 21549/S-025 would be extended by 3 months to provide time for a full review and re-analyses of additional safety and efficacy data, in the subset of patients aged 12 to 17 years, that was received on October 20, 2014. The new goal date for NDA 21549/S-025 is August 28, 2015.

NDA 207865

March 26, 2015

Applicant submitted final CMC data to complete application submission for NDA 207865.

October 29, 2014

FDA granted Applicant's request for rolling review, including timeline for submitting portions of the application.

September 29, 2014

Applicant submitted a request for Rolling Review.

September 23, 2014

Agency reviewed fast track request and concluded that it met the criteria for Fast Track designation- investigation of aprepitant for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic chemotherapy (HEC) including high-dose cisplatin; and the prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) in pediatric patients 6 months to 12 years of age.

September 19, 2014

Applicant submitted request for fast track designation for aprepitant oral suspension formulation program.

September 18, 2014 (telephone conference)

Applicant and Division discussed review of application, specifically CMC deficiencies that prevented filling of NDA 207865 (oral suspension formulation).

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The Sponsor submitted the application in electronic modular format. The application was generally well organized and navigable.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all trials were conducted in accordance with the Monitoring Plan and the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements of the countries in which they were conducted.

A request for an audit by the Office of Scientific Investigations (OSI) was submitted for both applications. The Office of Scientific Investigations (OSI) inspected three clinical investigator sites for these applications. All clinical sites had the classification of NAI. OSI reported that the studies appeared to have been conducted adequately, and the data generated by this study appeared acceptable in support of the respective indication. For further details regarding this application's site investigations, see the review in DARRTS by Dr. Susan Leibenhaut.

3.3 Financial Disclosures

The Sponsor provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangements with their clinical investigators, whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Sponsor also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Sponsor as defined by 21 CFR 54.2(b). As defined by 21 CFR 54.2(f), the Sponsor certified that no clinical investigator received any significant payments of any sorts.

See Appendix 1

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Regarding NDA 21549/S-025, the Applicant indicated that because the FDA-approved oral aprepitant capsule is proposed for commercial pediatric use, no new CMC information would be included in the supplemental NDA. Dr. Yong Wang, the CMC reviewer, recommended approval from a CMC perspective of NDA 21549/2-025. See Dr. Wang's full review in DARRTS.

In his review of NDA 207865, Dr. Hamid Shafiei, the CMC reviewer, found that the applicant had provided sufficient information to assure the identity, strength, purity and quality of the drug product. However, he states that label/labeling issues have not been completely resolved and will need to be addressed by the Applicant before a CMC regulatory action can be taken.

Aprepitant oral solution is a pink to light pink (b) (4) powder. It contains 125mg of (b) (4) aprepitant as the active ingredient and hydroxypropyl cellulose (b) (4) sodium lauryl sulfate, sucrose, lactose, (b) (4) red ferric oxide, sodium stearyl fumarate, (b) (4) as excipients (b) (4) .

Per Dr. Shafiei review, the drug product is packaged (b) (4) The to-be-marketed drug product packaging configuration is a cartoned kit consisting of the drug product (b) (4) a mixing cup, a 5-mL oral dispenser, instruction for use, and literature approved by the agency. The propose (b) (4) The appropriateness of the proposed packaging is further supported by the results from long-term and accelerated stability studies. Therefore, the proposed packaging configuration is deemed satisfactory.

CMC has recommended a Phase 4, Postmarket Commitment that the Applicant has agreed to perform.

> *To develop appropriate acceptance criteria for the particle size distribution (PSD) (b) (4) postapproval, update the drug product release and stability specification with a proposed acceptance criterion for D(b) (4) PSD (b) (4) and submit the updated drug product specification to the FDA in a postapproval supplement within a year after the approval of this application.*

See Dr. Shafiei's full CMC review in DARRTS.

4.2 Clinical Microbiology

Dr. Bryan Riley, OPS/New Drug Microbiology conducted a product quality microbiology assessment of Microbial Limits for EMEND (aprepitant) oral suspension. The Microbial Limits specification for EMEND were acceptable and he recommended approval from the product quality microbiology standpoint. See Dr. Riley's full review in DARRTS.

4.3 Preclinical Pharmacology/Toxicology

The pharmacology/toxicology data was reviewed and described by Dr. Sushanta Chakder. A juvenile animal study was conducted in young rats to evaluate the effects of aprepitant on growth and on neurobehavioral and sexual development. Slight changes in the onset of sexual maturation were observed in female and male rats (accelerated vaginal patency and delayed preputial separation up to 4 days compared to control); however, there were no effects on mating, fertility, embryonic-fetal survival, or histomorphology of the reproductive organs. There were no effects in neurobehavioral tests of sensory function, motor function, and learning and memory.
Per Dr. Chakder, this study provided an assessment of potential toxicities of aprepitant that supported the youngest pediatric age (6 months).

Dr. Chakder found both applications acceptable from a nonclinical perspective. See Dr. Chakder's full review in DARRTS.

4.4 Clinical Pharmacology

The pediatric aprepitant pharmacology program focused on two trials (Protocols 097 and 134). The pivotal trial, Protocol 208, did not have PK data. In addition, the Applicant also submitted a clinical study (Protocol 148; N=45 subjects) containing PK data in patients aged 12 to 17 years receiving the adult 40 mg capsule single dose and patients aged 2 to <12 years receiving single doses of aprepitant oral suspension (dose adjusted by body size) for post-operative nausea and vomiting (PONV). The PK data were used in population PK analysis.

The Office of Clinical Pharmacology reviewed both applications and found them acceptable from a clinical pharmacology perspective. Pharmacology reviews were conducted by Dr. Elizabeth Shang and Dr. Jian Wang. See their full reviews in DARRTS.

4.4.1 Mechanism of Action (per the package insert)

Aprepitant is a selective high-affinity antagonist of human substance P/neurokinin 1 (NK1) receptors. Aprepitant has little or no affinity for serotonin (5-HT3), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV).

Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK1 receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT3-receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis.

4.4.2 Pharmacodynamics

PK data was not collected in the phase 3 clinical trials in pediatrics and therefore the exposure-response analysis in pediatrics was not possible.

4.4.3 Pharmacokinetics

Summary of PK parameters – Protocol 097
A descriptive summary of PK parameters and a cross study comparison to parameters from healthy subjects who had the same three day regimen (Study P067 previously conducted to support the original NDA 21549) was performed by Dr. Elizabeth Shang, Clinical Pharmacology reviewer. The Cmax and AUC0-24hr in adolescents were 24% and 30% lower than those in healthy adult subjects. See table below.

Table 5: Summary of PK parameters

	AUC0-24hr (hr*ng/mL)	CMAX (ng/mL)	C24 (ng/mL)	C48 (ng/mL)	C72 (ng/mL)	TMAX (hour)
N	18	18	9	8	16	18
Mean	16648.5	1268.6	512.4	624.7	595.8	--
SD	7143.3	763.7	250.6	472.4	549.2	--
%CV	42.9	60.2	48.9	75.6	92.2	--
Median	17133.0	1251.1	448.2	499.8	499.2	**4**
Min	--	--	--	--	--	2
Max	--	--	--	--	--	24.05

Source: Clinical Pharmacology reviewer's analysis

Table 6: Cross study comparison to healthy adult subjects

Pharmacokinetic Parameter	N	Geometric Mean		Geometric Mean Ratio
		Adolescent Patients (N=18) (95% CI)	Healthy Adult Subjects (N=12) (95% CI)	Adolescent Patients / Healthy Adult Subjects (90% CI)†
$AUC_{(0\text{-}24hr)}$ (ng*hr/mL)	18	14318.4 (11106.7, 18458.9)	19455.8 (14254.1, 26553.1)	0.74 (0.53, 1.03)
C_{max} (ng/mL)	18	1070.1 (828.0, 1383.0)	1539.2 (1124.2, 2107.2)	0.70 (0.50, 0.97)
C_{24hr} (ng/mL)	9	449.7 (327.0, 618.6)	554.1 (420.4, 730.3)	0.81 (0.57, 1.15)
C_{48hr} (ng/mL)	8	460.5 (260.1, 815.4)	516.0 (323.6, 822.7)	0.89 (0.49, 1.64)
C_{72hr} (ng/mL)	16	367.0 (223.4, 602.9)	612.8 (345.4, 1087.1)	0.60 (0.32, 1.12)

† Based on least squares estimate from an ANOVA performed on natural log-transformed values.

Source: CSR P097

Summary of PK parameters – Protocol 134 Part II

Per Dr. Shang's review, "the geometric means of systemic exposures (Cmax and AUC0-24hr) in children 2 to 6 years old were 11% and 23% higher than that in healthy adults receiving 125 mg of dose (data from Study P067). While the geometric means of systemic exposure were 12% and 3.3% higher in children 2 to 6 years old. The systemic exposures in children 6 months to 2 years old were lower, presumably due to lower dose given (1.3 mg/kg)."

Summary of PK parameters – Protocol 134 Part IV

Patients received three day oral regimen of 3/2/2/ mg/kg in this part. Per Dr. Shang's review, "the geometric means of systemic exposure (Cmax and AUC0-24hr) in children 6 months to 12 years old were comparable (< 20% difference) to healthy adults receiving 125 mg of dose (data from Study P067)."

Reviewer's comments: The Pharmacology reviewers assessment found that the PopPK results support the use of weight-based dosing regimens in younger patients (<12 years of age). None of the other factors (sex, BMI and race) were found to have a significant association with the aprepitant PK parameters that would indicate a clinically relevant effect on aprepitant exposure.

Of note, the Applicant did not conduct a BA study (b) (4) *. Clinical pharmacology is reviewing PK data to determine if this is feasible. See Section 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.*

4.5 Division of Medication Error Prevention and Analysis (DMEPA)

4.5.1 Proprietary Name Review

The Applicant's proposed proprietary name of Emend was determined to be acceptable.

4.5.2 Human Factor Studies

DMEPA was consulted to review the human factor (HF) study submitted with NDA 207865 (oral suspension formulation). This HF study protocol was not submitted to the Agency for review prior to the start of the study.

This study was reviewed by Dr. Sherly Abraham, DMEPA reviewer. It was conducted in 35 participants (12 pharmacist; 12 nurses and 11 lay caregivers). There were two different testing sessions, first one was Instructions for Use (IFU)-optional and second one was IFU mandatory. The IFU had (b) (4) total steps and four subsections. The applicant tested six critical functions.

DMEPA found the results of the study unacceptable for the following reasons:
1) The participant numbers included in the study were inadequate because they did not include sufficient number of lay caregiver participants. Studies demonstrate that enrolling lower than 15 participants per arm could cause a percentage of the problems that they may experience with the proposed product go undetected.
2) Twenty-eight critical task failures occurred during the study
3) Omission of testing of some critical tasks (e.g. steps in the IFU involving reconstitution)

Table 7: Summary of Critical Task Failures

Critical Task	Subtask	Number of Participants	Total Critical Use Errors	
			IFU optional	IFU mandatory
Failure to determine correct dose/volume to administer using patient weight and PI *Pharmacists only	Determined incorrect dose	24	1	1
Failure to measure correct volume for reconstitution	Over-filling with water Under-filling with water	69	8	6
Failure to withdraw correct dose volume	Under-filling with medicine Over-filling with medicine Didn't administer the correct dose Administered all the contents of the pouch	69	5	7

DMEPA Reviewer's table

Per Dr. Abraham's review, the study was unable to show that the intended population was able to use the product safety and effectively. She stated in her review that most of the task failures noted (e.g., measuring the reconstitution volume and dose volume) would result in pediatric patients receiving either an under-dose, over-dose or not receiving the medication at all.

Reviewer's comments: This reviewer agrees with Dr. Abraham's assessment, that the results of the initial HF study demonstrated that neither lay caregivers nor healthcare professionals were able to use the product safely and effectively and that an additional HF study was warranted to implement corrective and preventive measures to address the identified failures.

On May 4, 2015, a teleconference was held between FDA and the Applicant. The Applicant agreed to conduct a supplemental human factors validation study with 15 lay patient caregivers, to test the home setting environment, focusing on evaluating the IFU changes. During the teleconference the FDA recommended changes to the product administration process and IFU based on results identified in the previous failed human factor study. The Agency also recommended including healthcare professionals (HCP) in the repeat study. On May 12, 2015, the Applicant submitted a revised protocol to repeat the human factor study.

The Applicant submitted the results of the 2nd HF study on July 1, 2015. The Applicant conducted the 2nd HF study in 17 lay caregivers. DMEPA found the results of the repeat HF unacceptable. Per Dr. Abraham's review, the errors observed in this study were very similar to the 1st failed HF study (e.g. measuring the reconstitution volume and measuring the dose volumes).

T-cons were held with the Applicant on July 20 and July 29, 2015 to discuss the failed results of the 2nd HF study. The discussion centered on potential options to correct identified failed critical task. Options discussed with the Applicant included 1) repeating the HF study with the revised IFU in HCPs, specifically pharmacist and nurses who are involved with chemotherapy infusion and 2) demonstrating stability of the drug so that HCPs could prepare and administer the drug for home use on Days 2 and 3 if a patient doesn't need to return to clinic on those days. This would eliminate the need for lay caregivers to mix and prepare the oral suspension for home use.

On July 31, 2015, the Applicant submitted follow-up correspondence that proposed the following:

1.) Conduct an additional Human Factor study in Oncology Nurses. As discussed in the Teleconference, Merck will conduct this study in nurses that are experienced in preparing chemotherapy drugs for administration.

2.) Conduct a study to evaluate the compatibility and in-use stability (microbial and chemical) of the EMEND PFS suspension in a container for 72 hours. This data will support a process for the health care provider to prepare the dose to be administered to the patient and transfer it to a container for administration by the caregiver at home with no further preparation or measurement required.

The Applicant agreed to submit the data by October 31, 2015.

Reviewer's comments: This reviewer again agrees with Dr. Abraham's assessment. The Applicant should re-design the product to improve usability and reduce difficulty in measuring an unrounded volume. Based on the failed HF studies, this reviewer has concerns about the safe and effective use of the oral suspension by HCP and especially lay caregivers. In the second HF study, the sponsor revised the IFU, but only included lay caregivers. A second HF study in HCP using the revised IFU and incorporating re-designs recommended by DMEPA may demonstrate success in safer use and administration of the oral suspension.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical data utilized in this review were based on the sponsor's electronic submission, and the Agency's amended Written Request was used as a reference. Table 8 summarizes key aspects of the submitted clinical trials.

Table 8: Clinical Trials

Trial (Country)	Trial Design & Objectives	Dosing Regimen	Patient exposure	Study population	Efficacy Endpoints
P208 (worldwide)	Ph 3, R, DB, AC-C Evaluate the efficacy & safety for the prevention of CINV	**Cycle 1** **Aprepitant Regimen** Patients 12-17 years of age: Day 1: aprepitant 125 capsule PO + ondansetron (Zofran™) Days 2 and 3: aprepitant 80 capsule PO Patients <12 years of age: Day 1: aprepitant powder-for-suspension (PFS): 3.0 mg/kg (up to 125 mg) + ondansetron (Zofran™) Days 2 and 3: aprepitant PFS: 2.0 mg/kg (up to 80 mg) **Control Regimen** Patients 12 – 17 years of age: Day 1: matching placebo for aprepitant 125 mg capsule PO + ondansetron (Zofran™) Days 2 and 3: matching placebo for aprepitant 80 mg capsule PO Patients <12 years of age: Day 1: matching placebo for aprepitant PFS: 3.0 mg/kg (up to 125 mg) + ondansetron (Zofran™) Days 2 and 3: matching placebo for aprepitant PFS: 2.0 mg/kg (up to 80 mg) **Optional Cycles 2-6** Patients 12-17 years of age: Day 1: aprepitant 125 mg capsule PO + ondansetron Days 2 and 3: aprepitant 80 capsule PO Patients < 12 years of age: Day 1: aprepitant PFS: 3.0 mg/kg (up	**Cycle 1** Aprepitant regimen:152 pts Control regimen: 150 pts	Males/females Age: 6 months to 17 years scheduled to receive emetogenic chemotherapy for documented malignancy.	**Cycle 1 only** Primary endpoint: Proportion of pts with Complete Response (no vomiting, no retching, and no use of rescue medication) in the 25 to 120 hrs following initiation of emetogenic chemotherapy Secondary endpoints: ---Proportion of pts with Complete Response (no vomiting, no retching, and no use of rescue medication) in: 1) 0-24 hrs (acute phase) following initiation of emetogenic chemotherapy and 2) 0-120 hrs (overall phase) following initiation of emetogenic chemotherapy ---Proportion of pts with no vomiting in the 120 hrs following initiation of emetogenic chemotherapy

Trial (Country)	Trial Design & Objectives	Dosing Regimen	Patient exposure	Study population	Efficacy Endpoints
		to 125 mg) + ondansetron Days 2 and 3: aprepitant PFS: 2.0 mg/kg (up to 80 mg)			
P097 (Australia, Brazil, US)	Ph 3, R, DB, PC, PG Evaluate the safety, tolerability, & efficacy for the prevention of CINV in adolescents	**Cycle 1 – Part I** Aprepitant Regimen Day 1: aprepitant 125 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 8 mg, PO Day 2: aprepitant 80 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 4 mg, PO Day 3: aprepitant 80 mg capsule PO + dexamethasone 4 mg PO Day 4: dexamethasone 4 mg PO Standard Therapy Day 1: dexamethasone 16 mg PO + ondansetron (0.15 mg/kg x 3 doses) IV Day 2: dexamethasone 8 mg PO + ondansetron (0.15 mg/kg x 3 doses) IV Days 3 and 4: dexamethasone 8mg PO **Cycle 1 – Part II** Open-label Aprepitant Regimen Day 1: aprepitant 125mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 8mg, PO Days 2: aprepitant 80 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 4 mg, PO Day 3: aprepitant 80 mg capsule PO + dexamethasone 4 mg PO Day 4: dexamethasone 4 mg PO	**Cycle 1** Aprepitant regimen: 32 pts Standard Regimen: 18 pts	Male and female adolescent patients aged 12 to 17 with confirmed malignancies being treated with an emetogenic chemotherapy regimen.	Proportion of pts with Complete Response (no vomiting with no rescue medication) in the overall phase (0-120hrs); acute phase (0-24 hrs); delayed phase (25-120 hrs)

Trial (Country)	Trial Design & Objectives	Dosing Regimen	Patient exposure	Study population	Efficacy Endpoints
		Optional Cycles 2-10 Day 1: aprepitant 125 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 8 mg, PO Day 2: aprepitant 80 mg capsule PO + ondansetron (0.15 mg/kg x 3 doses) IV + dexamethasone 4 mg, PO Day 3: aprepitant 80 mg capsule PO + dexamethasone 4 mg PO Day 4: dexamethasone 4 mg PO			
P 134 Worldwide	MC,OL,5 part study To evaluate PK, safety , tolerability and exploratory efficacy	**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	**Part IA** Three day regimen (fosaprepitant on Day 1 and aprepitant on Days 2 and 3, along with ondansetron): 12 subjects **Part IB** Single day regimen of fosaprepitant: 11 subjects **Part IIA** Single day regimen of aprepitant:19 subjects **Part IIB** Single day regimen of aprepitant:19 subjects **Part III** Three day regimen of ondansetron: 19 subjects **Part IV** Three day regimen of aprepitant: 20 subjects **Part V** Single day regimen of fosaprepitant: 23	Males/females Age:birth to 17 years of age scheduled to receive moderately or highly emetogenetic chemotherapy or a chemotherapy regimen not previously tolerated due to nausea and/or vomiting for a documented malignancy.	Efficacy was an exploratory endpoint No Vomiting, regardless of use of rescue medication, and Complete Response (no vomiting and no use of rescue meds) evaluated at 3 time periods: 0 to 24 (acute), 25 to 120 (delayed), and 0 to 120 (overall) hours post initiation of chemotherapy.

Trial (Country)	Trial Design & Objectives	Dosing Regimen	Patient exposure	Study population	Efficacy Endpoints
		equivalent to 150 mg in adults with IV ondansetron ± IV dexamethasone.	subjects		

5.2 Review Strategy

The Applicant conducted three clinical trials (Protocol 208, Protocol 097 and Protocol 134) to investigate the efficacy, safety and pharmacokinetics of oral aprepitant (capsules and oral suspension) in the prevention of CINV in pediatric cancer patients.

Based on the results from studies 097 and 134, Protocol 208 was subsequently conducted. Therefore, P208 is considered the key phase 3 study that provides substantial evidence for the efficacy and safety of oral aprepitant in the prevention of CINV in pediatric cancer patients aged ≥6 months. The efficacy findings from P208 are reviewed in detail in section 6 Review of Efficacy. Efficacy findings from the supportive trials Protocols 097 and 134 are also discussed in this review. The safety data from all three studies is reviewed in Section 7 Review of Safety.

5.3 Discussion of Individual Studies/Clinical Trials

Protocol Summaries

5.3.1 Protocol 208

This was a worldwide, multi-center, phase 3, randomized, double-blind, active comparator-controlled trial conducted in pediatric cancer patients aged 6 months to 17 years who were receiving emetogenic chemotherapy for a documented malignancy.

Of the 342 patients screened for inclusion in the trial, 307 patients were randomized to treatment (155 patients in the aprepitant regimen and 152 patients in the control regimen).

The trial was conducted in 51 centers. Of those, 49 centers randomized at least 1 subject: 2 in Republic of Korea, 4 in Israel, 2 in Russia, 4 in Turkey, 3 in Italy, 3 in Spain, 2 in United Kingdom, 1 in Croatia, 1 in Denmark, 2 in Greece, 2 in Hungary, 2 in Lithuania, 2 in Netherlands, 3 in Poland, 1 in Slovenia, 2 in Sweden, 1 in Argentina, 2 in Chile, 2 in Colombia, 1 in Dominican Republic, 2 in Ecuador, 2 in Mexico, 1 in Peru, and 2 in the United States.

Randomization was stratified based on the patient's age into one of four age groups (6 months to < 2 years; 2 to < 6 years; 6 to <12 years; or 12 to 17 years) on Day 1 of chemotherapy in Cycle 1, planned use of a chemotherapy agent associated with a Very High Risk of Emetogenicity in Cycle 1 (Yes or No), and planned use of dexamethasone as an antiemetic in Cycle 1 (Yes or No). The Applicant stated that the emetogenicity of chemotherapy agents was determined using the Children's Oncology Group (COG) Emetogenicity of Commonly Used Chemotherapeutic Agents.

During the post-treatment efficacy assessment period (the 120 hours following initiation of chemotherapy in Cycle 1), patients used a paper patient diary to record episodes of vomiting or retching, and/or use of rescue medication during the efficacy assessment period. The primary efficacy assessment period was the delayed phase, or the 25 to 120 hours following initiation of emetogenic chemotherapy. Secondary analysis included the acute (0 to 24 hours) and overall (0 to 120 hours) phases.

Objectives

The primary objective of the trial was to evaluate the efficacy and safety of Aprepitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) by comparing the three-day oral aprepitant regimen (aprepitant plus ondansetron), to ondansetron alone (the control regimen) with respect to the efficacy endpoint of Complete Response (no vomiting, no retching, and no use of rescue medication) in the 25 to 120 hours following the initiation of emetogenic chemotherapy in Cycle 1 (delayed phase).

Secondary objectives were:

- To compare the three-day oral aprepitant regimen, to the control regimen with respect to the efficacy endpoint of Complete Response in the 0 to 24 hours following the initiation of emetogenic chemotherapy in Cycle 1 (acute phase).

- To compare the three-day oral aprepitant regimen, to the control regimen with respect to the efficacy endpoint of Complete Response in the 0 to 120 hours following the initiation of emetogenic chemotherapy in Cycle 1 (overall phase).

- To compare the three-day oral aprepitant regimen, to the control regimen with respect to the efficacy endpoint of No Vomiting, regardless of rescue medication use, in the 120 hours following the initiation of emetogenic chemotherapy in Cycle 1 (overall phase).

- To assess the safety and tolerability of the three-day oral aprepitant regimen in patients from 6 months to 17 years of age who are receiving emetogenic chemotherapy in Cycle 1.

Inclusion/Exclusion criteria for cycle 1:

- Patient is 6 months to 17 years of age at time of study entry.
- Parent/guardian (legally authorized representative) agrees to the patient's participation as indicated by parent/legal guardian signature on the informed consent form. Patients 12 to 17 years of age, or as required by local regulation, assents and has the ability to understand the nature and intent of the study including the ability to comply with study procedures, complete study diary, and is willing to keep scheduled study visits.

- Patient is scheduled to receive chemotherapeutic agent(s) associated with moderate, high risk or very high risk of emetogenicity for a documented malignancy, or a chemotherapy regimen not previously tolerated due to vomiting.
- Patient is expected to receive ondansetron as part of their antiemetic regimen.
- Female patient who has begun menses has a negative urine pregnancy test prior to randomization. A female patient who is of reproductive potential agrees to remain abstinent or use a barrier form of contraception for at least 14 days prior to, throughout, and for at least one month following the last dose of study medication. Women taking oral contraception must agree to add a barrier form of contraception. For countries where abstinence is not considered an acceptable method of birth control, a locally acceptable birth control method must be used.
- Patient aged >10 years has a Karnofsky score ≥60; patient aged ≤10 years has a Lansky Play Performance score ≥60.
- Patient has a predicted life expectancy of ≥3 months.

Exclusion critieria:

- Patient has vomited in the 24 hours prior to Treatment Day 1.
- Patient is currently a user of any illicit drugs or has current evidence of alcohol abuse (defined using DSM-IV criteria) as determined by the investigator.
- Patient is scheduled to receive stem cell rescue therapy in conjunction with study related course(s) of emetogenic chemotherapy.
- Patient has received or will receive radiation therapy to the abdomen or pelvis in the week prior to Treatment Day 1 and/or during the course of the study.
- Patient is pregnant or breast feeding. (Females of child bearing potential are required to have a negative urine pregnancy test prior to entering the study.)
- Patient is allergic to aprepitant, ondansetron, or any other 5-HT3 antagonist.
- Patient has a symptomatic primary or metastatic CNS malignancy causing nausea and/or vomiting. Patient who is asymptomatic is allowed to participate.
- Patient has abnormal laboratory values as follows (deviations from these guidelines require discussion with the Merck Clinical Monitor):
    - a. Bone Marrow Function:
        - Peripheral absolute neutrophil count (ANC) <1000/mm3
        - Platelet count <100,000/ mm3
    - b. Liver Function
        - AST >5.0 x upper limit of normal (ULN) for age
        - ALT >5.0 x upper limit of normal (ULN) for age
        - Bilirubin > 1.5 x upper limit of normal (ULN) for age
    - c. Renal function
        - A serum creatinine > 1.5 x upper limit of normal (ULN) for age
- Patient has a known history of QT prolongation or is currently taking other medications that lead to QT prolongation.
- Patient has an active infection (e.g., pneumonia), congestive heart failure (CHF),

bradyarrythmia, or any uncontrolled disease (e.g., diabetic ketoacidosis, gastrointestinal obstruction) except for malignancy, or has a history of any illness which, in the opinion of the investigator, might confound the results of the study or pose unwarranted risk in administering study drug or concomitant therapy to the patient.

- Patient has had benzodiazepine or opioid therapy initiated within 48 hours of study drug administration, except for single daily doses of triazolam, temazepam, or midazolam.
    - Continuation of chronic benzodiazepine or opioid therapy is permitted provided it was initiated at least 48 hours prior to study drug administration.
- Patient has been started on systemic corticosteroid therapy within 72 hours prior to study drug administration or is planned to receive a corticosteroid as part of the chemotherapy regimen.
    - Exceptions:
    - Patients who are receiving chronic (>72 hours), daily steroid therapy can be enrolled provided the steroid dose is not >0.14 mg/kg (up to 10 mg) of prednisone daily or equivalent.
    - For supportive care, patients are permitted to receive a single dose of corticosteroid within 3 days prior (but not on the day of study drug administration) provided it is < the equivalent of 20 mg of prednisone.
- Patient is currently taking warfarin.
- Patient has ever participated in a study with aprepitant or fosaprepitant, or has taken a non-approved (investigational drug) within the last 4 weeks.
- Note: Patients in investigational studies with marketed chemotherapeutic agents (whether explicitly for children or only marketed for adults and usually administered to children with the appropriate dose adjustments) are allowed to enroll if they fulfill all other entry criteria.
- Other Excluded Medications: NOTE: The CYP3A4 and Anti-emetics

Treatment

Patients were assigned to one of two treatment regimens (aprepitant regimen or control regiment). Appropriate pediatric dosing for the capsule (patients > 12 years of age) and powder for suspension (patients aged ≥6 months to 12 years) was based on pharmacokinetic (PK) data from Protocol 097 and Protocol 134.

Cycle 1

Aprepitant Regimen

Subjects in the aprepitant regimen received the following:

Subjects 12-17 years of age:

Day 1: aprepitant 125 mg capsule PO + ondansetron (Zofran™)

Days 2 and 3: aprepitant 80 mg capsule PO

Subjects <12 years of age:
Day 1: aprepitant powder-for-suspension (PFS): 3.0 mg/kg (up to 125 mg) + ondansetron (Zofran™)
Days 2 and 3: aprepitant PFS: 2.0 mg/kg (up to 80 mg)

Control Regimen

Subjects in the control regimen received the following:

Subjects 12-17 years of age:
Day 1: matching placebo for aprepitant 125 mg capsule PO + ondansetron (Zofran™)
Days 2 and 3: matching placebo for aprepitant 80 mg capsule PO

Subjects <12 years of age:
Day 1: matching placebo for aprepitant PFS: 3.0 mg/kg (up to 125 mg) + ondansetron (Zofran™)
Days 2 and 3: matching placebo for aprepitant PFS: 2.0 mg/kg (up to 80 mg)

Zofran™ was required during Cycle 1. The dose of Zofran™ was selected at the discretion of the investigator according to the product label for pediatric usage or local standard of care. After Day 1, subjects receiving multi-day chemotherapy were permitted to receive prophylactic treatment with Zofran™, if clinically indicated and consistent with local standard of care. Once the chemotherapy regimen was complete, Zofran™ was no longer permitted as prophylactic treatment. If needed, ondansetron was permitted as rescue medication to alleviate established nausea or vomiting.

Intravenous dexamethasone was permitted for subjects in both treatment groups as an optional component of the antiemetic regimen, at the discretion of the investigator. If dexamethasone was administered as part of the standard antiemetic regimen for subjects in the aprepitant regimen, the dose of dexamethasone was reduced to 50% of the established dose in children. No dose reduction was necessary for patients in the control regimen.

Table 9: Dosing Regimen

Regimen (N)	Study Medication	Subject Age	Day 1 Dose	Day 2 Dose	Day 3 Dose
Aprepitant [A] (150)	Aprepitant	12 to 17 years	125 mg capsule PO 60 minutes prior to initiation of chemotherapy	80 mg capsule PO[B]	80 mg capsule PO[B]
		6 months to <12 years	3.0 mg/kg (up to 125 mg) powder for suspension (PFS) PO 60 minutes prior to initiation of chemotherapy	2.0 mg/kg (up to 80 mg) PFS PO[B]	2.0 mg/kg (up to 80 mg) PFS PO[B]
	Ondansetron[C]	6 months to 17 years	administered according to the product label for pediatric usage or local standard of care[D]		
Control [A] (150)	Placebo for aprepitant	12 to 17 years	125 mg placebo capsule PO 60 minutes prior to initiation of chemotherapy	80 mg Placebo capsule PO[B]	80 mg Placebo capsule PO[B]
		6 months to <12 years	3.0 mg/kg (up to 125 mg) placebo PFS PO 60 minutes prior to initiation of chemotherapy	2.0 mg/kg (up to 80 mg) placebo PFS PO[B]	2.0 mg/kg (up to 80 mg) placebo PFS PO[B]
	Ondansetron[C]	6 months to 17 years	administered according to the product label for pediatric usage or local standard of care[D]		

[A] Intravenous dexamethasone was permitted to be administered to both treatment arms as part of the anti-emetic regimen, at the discretion of the investigator. If dexamethasone was administered as part of the anti-emetic regimen for patients receiving aprepitant, dexamethasone was to be administered at 50% of the established dose in children.

[B] For patients receiving chemotherapy on Days 2 or 3, aprepitant was to be administered 60 minutes prior to initiation of chemotherapy.

[C] Branded ondansetron (Zofran™) was required for Cycle 1 of this study. Zofran™ was not be supplied by the SPONSOR, meaning Merck Headquarters or IVRS. Zofran™ was to be provided (b) (4). If procurement of Zofran™ was not feasible, discussion with the Merck Clinical Monitor and/or delegate was required. Generic ondansetron was permitted during the Optional Cycles 2-6.

[D] Preventative antiemetic treatment with ondansetron was permitted ONLY on days that chemotherapy is administered. Once the chemotherapy treatment regimen was complete, ondansetron was no longer permitted as prophylactic treatment.

Applicant's table

Subjects were permitted to take rescue medication throughout the study to alleviate symptoms of established nausea and vomiting. See Table 10 for list of excluded medications:

Table 10: Excluded Medications

	Patient is taking, or has taken within 30 days of Treatment Day 1	Patient is taking, or has taken within **7 days** of Treatment Day 1		Patient has taken an antiemetic within **48 hours** of Treatment Day 1.
CYP3A4 Inducers	Phenytoin or carbamazepine, barbiturates, rifampicin or rifabutin, St. John's Wort			
CYP3A4 Substrates		Terfenadine, cisapride, astemizole, pimozide, amifostine, marinol		
CYP3A4 Inhibitors[a]			Clarithromycin, erythromycin, telithromycin, ketoconazole, itraconazole, posaconazole, voriconazole, nefazodone, troleandomycin, ritonavir, nelfinavir	
Antiemetics				5HT3 antagonists (e.g., ondansetron), Phenothiazines (e.g., prochlorperazine), butyrophenones (e.g., haloperidol), Benzamides (e.g., metoclopramide), domperidone, herbal therapies with potential antiemetic properties,scopolamine, cyclizine

Applicant's table

As a cytochrome P-450 isoenzyme 3A4 (CYP3A4) substrate and inhibitor and an inhibitor of CYP2C9/8 and CYP2C19, aprepitant has the potential for increasing the dose intensity of other CYP3A4 substrates given concurrently. Potential interactions

between aprepitant and antineoplastic agents are of concern due to their potential impact on toxicity and long-term outcomes.[6]

Optional Cycles 2 to 6

Exclusion Criteria from Cycle 1 applied to patients entering Cycles 2-6, with the exception of Exclusion Criteria as it relates to vomiting in the 24 hours prior to Treatment Day 1 and Exclusion Criteria as it relates to aprepitant use in the last 4 weeks. Subjects who elected to participate in the optional cycles received open-label aprepitant on Days 1-3. Generic ondansetron was permitted in the optional cycles.
Subjects 12-17 years of age received:
Day 1: aprepitant 125 mg capsule PO + ondansetron
Days 2 and 3: aprepitant 80 mg capsule PO

Subjects <12 years of age received:
Day 1: aprepitant PFS: 3.0 mg/kg (up to 125 mg) + ondansetron
Days 2 and 3: aprepitant PFS: 2.0 mg/kg (up to 80 mg)

Efficacy Endpoints
The primary efficacy endpoint was the proportion of patients with Complete Response (no vomiting, no retching, and no use of rescue medication) in the 25 to 120 hours following initiation of emetogenic chemotherapy.

The secondary efficacy endpoints were (1) the proportion of patients with Complete Response in the 0 to 24 hours following initiation of emetogenic chemotherapy; (2) the proportion of patients with Complete Response in the 0 to 120 hours following initiation of emetogenic chemotherapy; and (3) the proportion of patients with No Vomiting, irrespective of use of rescue medication, in the 120 hours following initiation of emetogenic chemotherapy.

The exploratory endpoints were the number of emetic episodes, the time to first rescue medication, and the time to first vomiting in the 120 hours following initiation of emetogenic chemotherapy.

Efficacy data was not be collected during Cycles 2 to 6. Only safety data was evaluated in Cycles 2 to 6.

Statistical Analysis
The Intent-to-Treat (ITT) population which consisted of all patients (in the group they were) randomized and who received study drug served as the primary population for the

6 Dupuis L, Boodhan S, et al., Guideline for the prevention of acute nausea and vomiting due to antineoplastic medication in pediatric cancer patients. Pediatric Blood & Cancer 2013 Jul;60(7):1073-82

analysis of efficacy data in this study.

The primary efficacy analysis compared the aprepitant regimen to the control regimen with respect to the proportion of patients reporting Complete Response in the 25 to 120 hours (delayed) following initiation of emetogenic chemotherapy. The secondary efficacy analyses compared the aprepitant regimen to the control regimen with respect to the proportion of patients reporting Complete Response (acute and overall) and the proportion of patients reporting No Vomiting overall.

The treatment comparisons for Complete Response and No Vomiting was made using the Cochran-Mantel-Haenzel (CMH) test stratified by age (<2 years, 2 to 17 years), use of dexamethasone as an antiemetic in Cycle 1 (yes, no), and receipt of very high risk emetogenic chemotherapy agent in Cycle 1 (yes, no). The superiority hypothesis was evaluated by comparing the 1-tailed p-value to 0.025 and significance declared if the p-value was ≤0.025.

5.3.2 Protocol 097

Title: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions, to Examine the Safety, Tolerability, and Efficacy of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting Associated With Emetogenic Chemotherapy in Adolescent Patients.

General Design and Objectives
This was a Phase 3, multi-center (10), multi-national, randomized, double-blind parallel-group, placebo controlled trial with in-house blinding to assess the safety, tolerability, plasma concentration and efficacy of aprepitant in the prevention of CINV in adolescent patients with confirmed malignancies and who were treated with an emetogenic chemotherapy regimen. Approved aprepitant capsules were used.

The sponsor states that this is an estimation study: in adolescent patients, aged 12 to 17 years, with confirmed malignancies, and who will be treated with emetogenic chemotherapy, aprepitant triple therapy will be generally well tolerated as assessed by estimating the difference (aprepitant triple therapy minus standard therapy) in the proportion of patients (Part 1 data only) who have one or more clinical or laboratory drug-related adverse experience(s) during the Cycle 1 study-drug therapy period plus 14 days post-therapy.

The protocol had 2 parts. Part One of the protocol had 2 components with 2 dosing regimens: standard therapy regimen and aprepitant triple therapy regimen. The first component, which was blinded, focused on the first cycle (Cycle 1) of chemotherapy. The second component consisted of an optional open-label multiple-cycle extension for up to 9 subsequent cycles of chemotherapy (maximum of 10 cycles total). All patients received aprepitant during the multiple-cycle extension.

Part 2 of the protocol, which was not blinded had 2 components with 1 dosing regimen: aprepitant triple therapy in both Cycle 1 and in the multiple-cycle extension. As in Part One of the protocol, the first component focused on the first cycle (Cycle 1) of chemotherapy and the second component focused on the multiple-cycle extension for up to 9 subsequent cycles of chemotherapy (for a maximum of 10 cycles total).

The study had 2 treatment groups:

- Aprepitant triple therapy regimen = Aprepitant 125 mg P.O. on Day 1 and 80 mg once daily on Days 2 and 3 plus ondansetron (0.15 mg/kg x 3 doses) IV on Day 1 and 2 and dexamethasone 8 mg P.O. on Day 1 and 4 mg P.O. once daily on Days 2 to 4.
- Standard therapy regimen = Ondansetron (0.15 mg/kg x 3 doses) IV on Day 1 and 2 plus dexamethasone 16 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

The trial was conducted at a total of 10 sites in three countries (Australia, Brazil and US). The trial period was from 02 April 2004 to 14 September 2006. The case report cut-off date was 17 October 2006. A total of 50 patients were randomized to receive treatment with aprepitant triple therapy (n=32) or standard therapy (n=18).

The primary objective of the trial was to estimate the difference for the proportion of adolescent patients treated with aprepitant triple therapy or standard therapy who have one or more clinical or laboratory drug related adverse experience(s) during the Cycle 1 study-drug therapy period plus 14 days post-therapy.

The secondary objectives were to:

- Report the proportion of patients who have a clinical or laboratory serious, or serious drug-related adverse experience during the study-drug therapy period plus 14 days post therapy or who discontinue study therapy due to a drug-related adverse experience.
- Report the efficacy of aprepitant triple therapy in the control of CINV.
- Obtain aprepitant plasma drug concentration profiles and pharmacokinetics in adolescents with confirmed malignancies.

Key Inclusion Criteria/Exclusion Criteria
Inclusion Criteria
Inclusion Criteria for Cycle 1

- Patient is ≥12 and <18 years of age.
- Patient is to be treated with an emetogenic chemotherapy regimen that includes either cisplatin, cyclophosphamide, or carboplatin, for a documented malignancy OR Patient did not tolerate a previously administered chemotherapy regimen, for a documented malignancy, secondary to nausea and/or vomiting that is planned to be repeated

- Patient has Karnofsky score ≥60 (Appendix 2).

- Patient has a predicted life expectancy of ≥3 months.

Exclusion criteria
Exclusion Criteria for Cycle 1
a. Patient will receive stem cell rescue therapy in conjunction with course of chemotherapy.
b. Abnormal laboratory values:
1) Absolute Neutrophil Count <1000/ mm3
2) Platelet count <100,000/mm3
3) AST >5.0 x upper limit of normal
4) ALT >5.0 x upper limit of normal
5) Bilirubin >1.5 x upper limit of normal
6) Creatinine >1.5 x upper limit of normal

Evaluation Criteria
Safety was the primary evaluation criteria. It was evaluated by assessing the proportion of patients reporting one or more drug-related clinical or laboratory drug related adverse experience during the Cycle 1 study drug therapy period plus 14 days post-therapy. Patients were monitored for adverse experiences and tolerability at scheduled visits that occurred between Days 6 and 8 and Days 19 and 29 post emetogenic chemotherapy. All adverse experiences were analyzed using the Common Terminology Criteria for Adverse Events v3.0.

Secondary safety objectives reported the proportion of patients who had a clinical or laboratory serious, or serious drug-related adverse experience during the study therapy period plus 14 days post-therapy or who discontinued study therapy due to a drug-related adverse experience. In the optional open-label multiple cycle extension, only serious adverse experiences and non-serious adverse experiences evaluated by the investigator as drug related or resulting in discontinuation from the study were collected.

A secondary evaluation criteria of the study was to estimate the efficacy of aprepitant triple therapy in the control of CINV. The main efficacy evaluation was the proportion of patients with complete response (no vomiting and no use of rescue medication) from 0 to 120 hours post chemotherapy in Cycle 1. Patient diaries were completed daily for 5 days after administration of emetogenic chemotherapy (in Cycle 1 only). The diary captured all emetic episodes, and all use of rescue therapy (taken for treatment of established nausea or emesis). The effect of nausea on patient's normal daily activity was assessed by asking the patient a single question at the day 6-8 visit in Cycle 1. The main efficacy measure was complete response (no emesis and no use of rescue therapy) in the 120 hours following initiation of emetogenic chemotherapy. In the optional open-label multiple cycle extension, limited efficacy information was collected (no patient diaries collected after Cycle 1).

The primary pharmacokinetics objective of the trial was to assess the plasma pharmacokinetics (AUC (0-24hr), Cmax, C24 hr, C48 hr, C72 hr and T max) of aprepitant in adolescent patients. Plasma samples for determination of aprepitant concentrations were obtained at specific time points for 72 hours in patients with established venous access. Samples were collected at predose (-2 hours), 1 (prior to chemotherapy infusion) 2, 3, 4, 8, 12 and 24 hours post aprepitant dose on Day 1 and at 24 hours post aprepitant dose on Day 2 and Day 3.

Treatment

In Group I (Aprepitant Triple Therapy):

On Day 1 prior to administration of chemotherapy, patients received an oral dose of aprepitant 125 mg, oral dexamethasone 8 mg, oral dexamethasone placebo, and IV ondansetron 0.15 mg/kg 30 minutes prior to the chemotherapy infusion and then 4 and 8 hours after the first dose of ondansetron (maximum total daily dose 32 mg).

On Day 2 prior to the administration of chemotherapy, patients received a morning (between 8 and 10 AM) oral dose of aprepitant 80 mg, oral dexamethasone 4 mg, and IV ondansetron 0.15 mg/kg 30 minutes prior to the chemotherapy infusion and then 4 and 8 hours after the first dose of ondansetron (maximum total daily dose 32 mg). In the evening (between 5 and 10 PM) patients took oral dexamethasone placebo.

On Day 3 patients took a morning (between 8 and 10 AM) oral dose of aprepitant 80 mg and oral dexamethasone 4 mg. In the evening (between 5 and 10 PM) patients took oral dexamethasone placebo.

On Day 4 patients took oral dexamethasone 4 mg in the morning (between 8 and 10 AM) and oral dexamethasone placebo in the evening (between 5 and 10 PM).

In Group II (Standard Therapy):

On Day 1 prior to the administration of chemotherapy, patients received an oral dose of placebo aprepitant, oral dexamethasone 16 mg, and IV ondansetron 0.15 mg/kg 30 minutes prior to the chemotherapy infusion, and then 4 and 8 hours after the first dose of ondansetron (maximum total daily dose 32 mg).

On Day 2 prior to the administration chemotherapy, patients took a morning (between 8 and 10 AM) oral dose of placebo aprepitant, oral dexamethasone 4 mg, and IV ondansetron 0.15 mg/kg 30 minutes prior to the chemotherapy infusion, and then 4 and 8 hours after the first dose of ondansetron (maximum total daily dose 32 mg). In the evening between (between 5 and 10 PM) patients took oral dexamethasone 4 mg.

On Day 3, patients took oral placebo aprepitant and oral dexamethasone 4 mg in the morning (between 8 and 10 AM) and oral dexamethasone 4 mg in the evening (between 5 and 10 PM).

On Day 4 patients took oral dexamethasone 4 mg in the morning (between 8 and 10 AM) and oral dexamethasone 4 mg in the evening (between 5 and 10 PM).

Patients were allowed to take "rescue therapy" throughout for nausea or vomiting. Patients who required rescue therapy were considered treatment failures according to the efficacy endpoint of Complete Response.

Additionally, patients receiving multi-day chemotherapy regimens were permitted to receive preventative antiemetic treatment with a 5HT3 antagonist if clinically indicated; this treatment was not supplied by the sponsor.

Table 11: Cycle 1 Treatment Regimen

Treatment Group	Day 1	Day 2	Day 3	Day 4
I Aprepitant Triple Therapy	Aprepitant 125 mg PO Dexamethasone 8 mg, PO Placebo for dexamethasone 8 mg PO Ondansetron (0.15 mg/kg x 3 doses) IV‡	Aprepitant 80 mg PO Dexamethasone 4 mg PO Placebo for dexamethasone 4 mg PO Ondansetron (0.15 mg/kg x 3 doses) IV‡	Aprepitant 80 mg PO Dexamethasone 4 mg PO Placebo for dexamethasone 4mg PO	Dexamethasone 4 mg PO Placebo for dexamethasone 4 mg PO
II Standard Therapy	Placebo for aprepitant 125 mg PO Dexamethasone 16 mg PO Ondansetron (0.15 mg/kg x 3 doses) IV‡	Placebo for aprepitant 80 mg PO Dexamethasone 8 mg PO Ondansetron (0.15 mg/kg x 3 doses) IV‡	Placebo for aprepitant 80 mg PO Dexamethasone 8 mg PO	Dexamethasone 8 mg PO
‡Ondansetron 0.15 mg/kg was administered 30 minutes prior to the chemotherapy infusion, and then 4 and 8 hours after the first dose of ondansetron (maximum total daily dose 32 mg). PO: By Mouth; IV: Intravenously				

Applicant's table CSR P097

Safety Assessments

In addition to the reporting of subjective adverse experiences, the following standard pre-study and post-study screening measurements (Cycles 1-10) were collected: medical history, physical exam, 12-lead ECG, laboratory tests including hematology, chemistry, urinalysis and pregnancy test for females of child bearing potential.

Analysis Population

The modified intention-to-treat (MITT) population was used for all efficacy evaluations and included those patients who (1) received emetogenic chemotherapy, (2) received at least one regimen of study therapy, and (3) had at least 1 post-treatment efficacy

assessment. In addition, as supportive to the MITT population, a per-protocol population (PPP) was used for the complete response endpoint, only. The per protocol population was a subset of the MITT population and excluded those patients identified as protocol violators.

Changes in Conduct of Study

This study was initially designed as a randomized, double-blind study in which patients were randomized at a 2:1 ratio to either the aprepitant triple therapy regimen or standard therapy. The study protocol underwent 2 amendments, primarily because of slow study enrollment. In the 1st amendment, chemotherapeutic agent was expanded to include agents other than cisplatin. Also, patients no longer had to be naïve to chemotherapy.

Due to continued slow enrollment, the protocol was amended a second time, changing the design of the study to an uncontrolled, open-label study in which patients received open-label aprepitant triple therapy. The original (randomized) protocol is referred to as Part 1; the amended (open-label) protocol is referred to as Part 2. Each Part had its own allocation schedule. Part 1 enrolled 46 patients. Part 2 enrolled 4 patients.

Demographics

Table 12: Baseline Patient Characteristics by Treatment Group P097

		Aprepitant Triple Therapy (N = 32)		Standard Therapy (N = 18)		Total (N = 50)	
		n	(%)	n	(%)	n	(%)
Gender	Female	8	(25.0)	6	(33.3)	14	(28.0)
	Male	24	(75.0)	12	(66.7)	36	(72.0)
Age (years)	11 And Under	0	(0.0)	1	(5.6)	1	(2.0)
	12 to 14	13	(40.6)	8	(44.4)	21	(42.0)
	15 to 17	17	(53.1)	9	(50.0)	26	(52.0)
	Over 17	2	(6.3)	0	(0.0)	2	(4.0)
	MEAN	15.0		14.6		14.9	
	SD	1.73		1.91		1.79	
	MEDIAN	15.0		14.5		15.0	
	RANGE	12 - 19		11 - 17		11 - 19	
Race	Black	4	(12.5)	4	(22.2)	8	(16.0)
	Hispanic American	8	(25.0)	3	(16.7)	11	(22.0)
	Multi-Racial	5	(15.6)	3	(16.7)	8	(16.0)
	Native American	1	(3.1)	0	(0.0)	1	(2.0)
	White	14	(43.8)	8	(44.4)	22	(44.0)

Source: CSR P097

Efficacy Analysis

The main efficacy evaluation was the proportion of patients with a complete response from 0 to 120 hours post initiation of emetogenic chemotherapy. Complete response was defined as the absence of vomiting episodes, retching or dry heaves (no vomiting) and no use of rescue medication. No vomiting was another efficacy analysis conducted in this trial.

Table 13: Number (%) of Patients With Complete Response by Treatment and Phase (Modified-Intention-to-Treat Population) – P097 Cycle 1 Part 1

	Aprepitant Triple Therapy Regimen n/m (%) (95% CI)	Standard Therapy n/m (%) (95% CI)
Overall Phase	8/28 (28.6) (13.2, 48.7)	1/18 (5.6) (0.1, 27.3)
Acute Phase	17/28 (60.7) (40.6, 78.5)	7/18 (38.9) (17.3, 64.3)
Delayed Phase	10/28 (35.7) (18.6, 55.9)	1/18 (5.6) (0.1, 27.3)

Applicant's table

Table 14: Number (%) of Patients With No Vomiting by Treatment and Phase (Modified-Intention-to-Treat Population) – P097 Cycle 1 Part 1

	Aprepitant Triple Therapy Regimen n/m (%) (95% CI)	Standard Therapy n/m (%) (95% CI)
Overall Phase	9/28 (32.1) (15.9, 52.4)	1/18 (5.6) (0.1, 27.3)
Acute Phase	18/28 (64.3) (44.1, 81.4)	8/18 (44.4) (21.5, 69.2)
Delayed Phase	11/28 (39.3) (21.5, 59.4)	1/18 (5.6) (0.1, 27.3)

Applicant's table

Reviewer's comments: For all three phases, a higher percentage of patients on the aprepitant triple therapy regimen than on standard therapy had a complete response. For all three phases the percentage of subjects with no vomiting was higher in the aprepitant regimen than in the control regimen.

5.3.3 Protocol 134

Title: A Multi-center, Open-label, 5-Part Study to Evaluate the Pharmocokinetics, Safety, and Tolerability of Aprepitant and Fosaprepitant Dimeglumine in Pediatric Patients Receiving Emetogenic Chemotherapy

Trial Design and Objectives

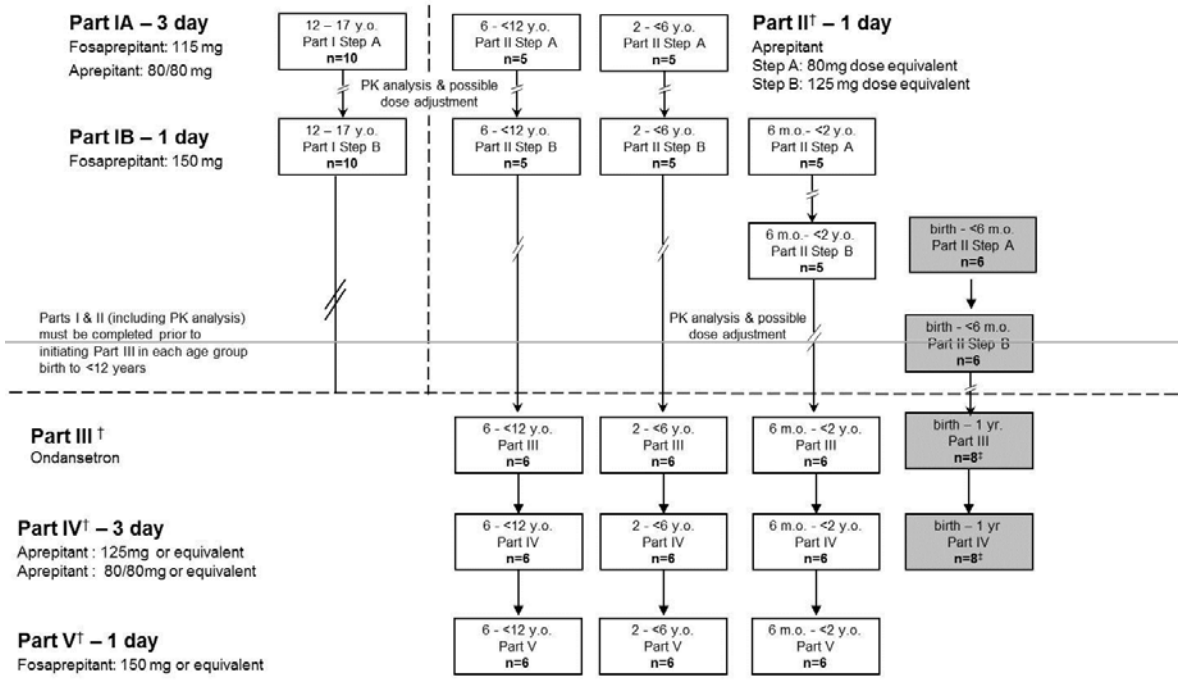
A multi-center, open-label, 5-part study to evaluate pharmacokinetics, safety, and tolerability of oral aprepitant and intravenous fosaprepitant dimeglumine. Eligible

patients were male and female, birth to 17 years of age and scheduled to receive moderately or highly emetogenic chemotherapy or a chemotherapy regimen not previously tolerated due to nausea and/or vomiting for a documented malignancy. Patients were entered at 21 study centers worldwide across the 5 Parts. Enrollment into one or more Parts at each study center ranged from 1 to 26 patients.The oral formulation used in this study was suspension (b) (4)

Patients were enrolled into 1 of 5 age groups as follows:

- 12 to 17 years,
- 6 years to <12 years,
- 2 years to <6 years,
- 6 months to <2 years,
- Birth to <6 months.

Figure 1: Study Schematic



† Patients in Part II Steps A and B >6 months old were expected to be unique patients. Patients in Parts III, IV, and V were expected to be the same patients undergoing subsequent rounds of chemotherapy.

‡ Enrollment in the birth to 1-year cohort into Parts III and IV for dexamethasone evaluation were expected to include approximately 2 patients each from the following age groups: birth to 2 months, 2 to 4 months, 4 to 8 months, and 8 to 12 months.

Note: Patients <1 year in the 6-month to 2-year cohort may have had dexamethasone PK samples obtained (asapplicable) but they were not required to do so; none were collected. Shaded cohorts were not enrolled.

The trial evaluated the PK, safety , tolerability and exploratory efficacy of oral aprepitant and IV fosaprepitant in the following Parts:

Part I, Step A — 3-day regimen that consisted of 115 mg IV fosaprepitant infused over 15 minutes via a central venous catheter approximately 75 minutes prior to the start of chemotherapy, along with IV ondansetron on Day 1, followed by 80 mg oral aprepitant and IV ondansetron on Days 2 and 3 in adolescent patients 12 to 17 years of age.

Part I, Step B — single-day regimen that consisted of 150 mg IV fosaprepitant infused over 30 minutes via a central venous catheter approximately 75 minutes prior to the start of chemotherapy, along with IV ondansetron on Day 1 in adolescent patients 12 to 17 years of age.

Part II, Step A — single-day oral aprepitant dose equivalent to 80 mg in adults administered approximately one hour prior to the start of chemotherapy, along with IV ondansetron on Day 1 in patients 6 months of age to <12 years of age.
Part II, Step B — single-day oral aprepitant dose equivalent to 125 mg in adults administered approximately one hour prior to the start of chemotherapy, along with IV ondansetron on Day 1 in patients 6 months to <12 years of age.

Part III — 3-day control regimen with IV ondansetron, administered prior to the start of chemotherapy in patients 6 months to <12 years of age.

Part IV — 3-day oral aprepitant regimen at a dose equivalent to 125 mg in adults administered approximately one hour prior to the start of chemotherapy, along with IV ondansetron on Day 1, followed by a dose equivalent to 80 mg in adults on Days 2 and 3, along with IV ondansetron in patients <12 years of age.

Part V — single-day IV fosaprepitant dose equivalent to 150 mg in adults infused over 60 minutes via a central venous catheter approximately 105 minutes prior to the start of chemotherapy, along with IV ondansetron on Day 1 in patients 6 months to <12 years of age.

The Applicant states that In Part IIA, a single-day oral aprepitant dose equivalent to 80 mg (Part A) and 125 mg (Part B) was planned to be evaluated in patients birth to 6 months of age. This was planned to support an evaluation of the PK of dexamethasone with and without aprepitant in patients birth to 1 year of age in Parts III and IV. Despite significant efforts, no patients < 6 months of age were enrolled over a two year recruitment period into Part II, so the evaluation of the effect of aprepitant on the PK of dexamethasone in Parts III and IV was not conducted.

Dosing with dexamethasone was at the discretion of the investigator in all Parts of the study. The use of IV dexamethasone was to be mandatory in patients birth to <1 year of age in Parts III and IV, however, since Part II did not enroll any patients <6 months of age, that cohort did not open.

Table 15: Treatment Groups

						Age range (yr)			
Part	**Step**	**Route**	**Dose on Day 1**	**Regimen**	**Dose on Days 2 and 3**	**12 to 17**	**6 to 12**	**2 to 6**	**0.5 to 2**
I	A	IV	115 mg	3-day	80	√			
I	B	IV	150 mg	1-day	--	√			
V	--	IV	3mg/kg	1-day	--		√	√	√
II	**A**	**PO**	**47 mg/m^2***	**1-day**	--		√	√	√
II	**B**	**PO**	**74 mg/m^2****	**1-day**	--		√	√	√
II	**B**	**PO**	**1.3 mg/kg**	**1-day**	--				√
IV	--	**PO**	**3mg/kg**	**3-day**	**2 mg/kg**		√	√	√
V	--	IV	3mg/kg	1-day	--		√	√	√
III	Ondansertron control group; no EMEND given					√: age group dosed			

* The dose was about 2 mg/kg for the age group.
** The dose was about 3 mg/kg for the age group.
Source: Table from Clinical Pharmacology reviewer

Reviewer's comments: Per Dr. Shang's review, only PK data from PO aprepitant regimens parts II and IV were reviewed by her since they were relevant to the approval of the oral suspension formulation.

Trial Population
Inclusion criteria

- Patients aged 0 (at least 37 weeks gestation) to 17 years of age
- Parent/guardian consent; patient assent depending on age
- Scheduled to receive MEC or HEC for a documented malignancy or patient did not tolerate a previously administered chemotherapy regimen due to nausea and/or vomiting that is planned to be repeated
- Expected to receive ondansetron as part of their antiemetic regimen
- Female patient who has begun menses has a negative urine pregnancy test prior to randomization.
- Patients age > 10 years has Karnofsky score ≥60; patients aged ≤10 years has Lansky Play Performance score ≥60.
- Patients weight
  - <6 months ≥3.0 kg
  - >6 months ≥6.0 kg
  - >2 years ≥7.6 kg
- Patient has a predicted life expectancy of ≥ 3 months.
- Patient has a preexisting functioning venous catheter prior to receiving aprepitant/fosaprepitant designated for pharmacokinetic sampling.

Inclusion criteria for Parts IV and V
Patients who successfully completed Part III and plan to continue onto Parts IV and V must continue to meet all inclusion criteria. Patients from Part III that do not continue into Part IV or V need to be replaced. Replacement patients do not have to enter the study at Part III, but will enter in the Part where replacement is necessary. Replacement patients in Part IV and/or V will need to meet all inclusion criteria.

Exclusion criteria

- Use of any illicit drug
- Scheduled to received stem cell rescue therapy
- Pregnant or breast feeding or sexually active without double barrier contraception
- Has ever participated in a study with aprepitant or fosaprepitant or is currently participating in a trial with casopitant
- Allergy to aprepitant, fosaprepitant, ondansetron or any other 5-HT3 antagonist
- Symptomatic primary or metastatic CNS malignancy
- Abnormal laboratory values:Bone Marrow function, Liver function, renal function
- Known history of QT prolongation
- Has an active infection or any uncontrolled disease, except for malignancy
- Treated with antiemetic agents within 48 hours prior to study day 1
- Has had benzodiazepine or opioid therapy within 48 hours of treatment day 1, except for single daily doses
- Started on systemic corticosteroid therapy within 72 hours prior to study drug administration
- Taking or has taken within 7 days of study drug administration CYP3A4 substrates
- Taking or has taken within 30 days of study day 1 CYP3A4 inducers
- Currently taking warfarin

Pharmacokinetic analysis:
Blood samples for PK following oral dosing were collected in Cycle 1 for 72 hours at: predose, 1.5, 3, 4, 6, 8, 24, 48 (Day 2), and 72 (Day 3) hours.

Demographics:

Table 16: Patient characteristics for Part II

	Aprepitant (80 mg eq.) Regimen (Step A)		Aprepitant (125 mg eq.) Regimen (Step B)	
	n	(%)	n	(%)
Subjects in population	19		19	
Gender				
Male	7	(36.8)	6	(31.6)
Female	12	(63.2)	13	(68.4)
Age (Months)				
6 months to <2 years	5	(26.3)	6	(31.6)
2 to <6 years	8	(42.1)	7	(36.8)
6 to <12 years	6	(31.6)	6	(31.6)
Mean	54.8		58.6	
SD	42.6		45.6	
Median	50.0		43.0	
Range	6 to 142		6 to 126	
Race				
Multi-Racial	0	(0.0)	2	(10.5)
White	19	(100.0)	17	(89.5)
Ethnicity				
Hispanic Or Latino	2	(10.5)	4	(21.1)
Not Hispanic Or Latino	17	(89.5)	15	(78.9)

Table 17: Patient characteristics Part IV

	Aprepitant Regimen (Part IV)	
	n	(%)
Subjects in population	20	
Gender		
Male	7	(35.0)
Female	13	(65.0)
Age (Months)		
6 months to <2 years	7	(35.0)
2 to <6 years	6	(30.0)
6 to <12 years	7	(35.0)
Mean	51.8	
SD	38.0	
Median	41.0	
Range	9 to 113	
Race		
Asian	1	(5.0)
Black Or African American	0	(0.0)
Multi-Racial	11	(55.0)
White	8	(40.0)
Ethnicity		
Hispanic Or Latino	10	(50.0)
Not Hispanic Or Latino	10	(50.0)

6 Review of Efficacy

Efficacy Summary

The efficacy data from Protocol 208 (P208), reviewed in detail in this section, provides substantial evidence of superiority of aprepitant regimens compared to control regimens for the proposed indications in pediatric cancer patients aged 6 months to 17 years (oral capsules for patients aged ≥ 12 (b) (4) and oral suspension for patients aged 6 months to <12 years

Study P208 was a randomized, double-blind, active-comparator controlled, parallel-group study (with in-house blinding) designed to assess the efficacy and safety of oral aprepitant for the prevention of CINV in pediatric patients, aged 6 months to 17 years, receiving emetogenic chemotherapy for a documented malignancy. For the primary

efficacy endpoint of Complete Response (CR) in the delayed phase, defined as no vomiting, no retching and no use of rescue medication in the 25 to 120 hours following the initiation of HEC or MEC in Cycle 1, the Applicant demonstrated that the aprepitant regimen was superior to that of the control regimen. The proportion of pediatric subjects on the aprepitant regimen that demonstrated CR in the delayed phase was 50.7% as compared with 26% of patients that received the active comparator (ondansetron). In addition, the Applicant also demonstrated that the aprepitant regimen was more effective in the prevention of CINV in the acute and overall phase. In the acute phase, the proportion of pediatric subjects on the aprepitant regimen that demonstrated CR was 66.4% as compared with 52% of patients that received the active comparator (control regimen).

6.1 Indication

In combination with other antiemetic agents in patients 6 months of age and older for prevention of:

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

6.1.1 Methods

The efficacy review focuses on Protocol 208 (P208). P208 is considered the key phase 3 study that provides substantial evidence for the efficacy and safety of oral aprepitant in the prevention of CINV in pediatric cancer patients aged ≥6 months who received HEC or MEC. The design, eligibility criteria and efficacy endpoints of P208 are summarized in Section 5.3.

Supportive evidence for efficacy of oral aprepitant is suggested by Protocols 097 and 134.

6.1.2 Demographics

Tables 18, 19 and 20 present key baseline demographic characteristics data for study Protocol 208.

Table 18: Demographic Characteristics Protocol 208

Variable	Aprepitant Regimen (N=152)	Control Regimen (N=150)	Total (N=302)
Sex, n (%)			
Female	68 (44.7)	71 (47.3)	139 (46)
Male	84 (55.3)	79 (52.7)	163 (54)
Age Groups, n (%)			
6 month to <2 years	19 (12.5)	16 (10.7)	35 (11.6)
2 years to < 6years	45 (29.6)	43 (28.7)	88 (29.1)
6 years to < 12 years	41 (27)	43 (28.7)	84 (27.8)
12 years to 17 years	47 (30.9)	48 (32)	95 (31.5)
Mean (months) ± SD	97.7 ±	99.4 ±	98.5 ±
Median (months) [Minimum, Maximum]	86.5 (6,213)	91.5 (6, 214)	89.45 (6, 214)
Race			
American Indian or Alaskan Native	2 (1.3)	0	2 (0.7)
Asian	11 (7.2)	16 (10.7)	27 (8.9)
Black or African American	0	2 (1.3)	2 (0.7)
Multiple	20 (13.2)	22 (14.7)	42 (13.9)
White	119 (78.3)	110 (73.3)	229 (75.8)
Ethnicity			
Hispanic or Latino	36 (23.7)	32 (21.3)	68 (22.5)
Not Hispanic or Latino	111 (73)	112 (74.7)	223 (73.8)
Not reported	2 (1.3)	4 (2.7)	6 (2.0)
Unknown	3 (2.0)	2 (1.3)	5 (1.7)
Use of Dexamethasone as part of the antiemetic regimen in Cycle 1			
Yes	44 (28.9)	42 (28)	86 (28.5)
No	108 (71.1)	108 (72)	216 (71.5)
Very High Risk Emetogenicity Chemotherapy			
Yes	99 (65.1)	101 (67.3)	200 (66.2)
No	53 (34.9)	49 (32.7)	102 (33.8)

Table 19: Most common malignancies – Protocol 208

Malignancy	Aprepitant Regimen n (%)	Control Regimen n (%)	Total n (%)
Ewing's sarcoma	17 (11.2)	16 (10.7)	33 (10.9)
Osteosarcoma	17 (11.2)	16 (10.7)	33 (10.9)
Rhabdomyosarcoma	12 (7.9)	13 (8.7)	25 (8.3)
Neuroblastoma	13 (8.6)	11 (7.3)	24 (7.9)
Acute lymphocytic leukemia	13 (8.6)	8 (5.3)	21 (7)
Medulloblastoma	9 (5.9)	12 (8)	21 (7)
Nephroblastoma	8 (5.3)	7 (4.7)	15 (5)

Modified applicant's table

Table 20: Subjects by Age and Gender

	Aprepitant Regimen			Control Regimen			Total		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**	**Male**	**Female**	**Total**
Subjects in population	**84**	**68**	**152**	**79**	**71**	**150**	**163**	**139**	**302**
Age (Months)									
6 months to <2 years	12	7	19	12	4	16	24	11	35
2 years to <6 years	29	16	45	18	25	43	47	41	88
6 years to <12 years	27	14	41	26	17	43	53	31	84
12 years to 17 years	16	31	47	23	25	48	39	56	95
Mean	84.4	114.1	97.7	96.8	102.2	99.4	90.4	108.0	98.5
SD	56.6	67.4	63.2	60.7	61.3	60.9	58.8	64.4	62.0
Median	73.5	122.5	86.5	91.0	101.0	91.5	83.0	107.0	89.5
Range	6 to 203	7 to 213	6 to 213	6 to 214	6 to 206	6 to 214	6 to 214	6 to 213	6 to 214

Applicant's table

Reviewer's comments: There were more males (54.0%) than females (46.0%) randomized, with a similar proportion of male and female subjects between the two treatment regimens. There was approximately an even distribution of patients in the 2<6 year, 6 to <12 year, and 12 to 17 year cohorts (29.1%, 27.8%, and 31.5%, respectively), with similar distribution of age in each age cohort between the two treatment regimens. Patients in the youngest cohort (6 months to <2 years of age) represented 11.6% of patients. The number of patients in the 6 months to <2 year cohort was evenly distributed between the two treatment groups.

Racially, the trial was not diverse. A majority, approximately 76% of the patients, were white, and approximately 24% of patients were representative of other races. Only 0.7% of the patients were Black or African American.

The most common primary malignancies were Ewing's sarcoma and osteosarcoma, followed by rhabdomyosarcoma and neuroblastoma, and then medullablastoma and acute lymphocytic leukemia. In general, the treatment groups were balanced with regard to primary malignancies.

Subjects were stratified by planned use of a VHEC agent in Cycle 1 at the time of randomization. The proportion of patients receiving a VHEC agent on Day 1 was similar in both treatment groups.

6.1.3 Subject Disposition

See Table 21 for the disposition of the 307 randomized patients. The disposition reflects that 96.8% of patients in the aprepitant regimen and 98% of patients in the control regimen completed the study.

Table 21: Disposition of Patients – Cycle 1

	Aprepitant Regimen		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	155		152		307	
Study Disposition						
Completed	150	(96.8)	149	(98.0)	299	(97.4)
Discontinued	5	(3.2)	3	(2.0)	8	(2.6)
Adverse Event	2	(1.3)	0	(0.0)	2	(0.7)
Physician Decision	0	(0.0)	1	(0.7)	1	(0.3)
Protocol Violation	2	(1.3)	0	(0.0)	2	(0.7)
Withdrawal By Subject	1	(0.6)	2	(1.3)	3	(1.0)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)

Following Cycle 1, 171 subjects elected to participate in the optional cycles (Cycles 2-6). Of those, all but one subject received study medication in Cycle 2. Of the 171 patients that entered the optional cycles, 46 patients (26.9%) completed all 6 cycles. The remaining 125 patients (73.1%) discontinued the study prior to the end of Cycle 6. Of those, 51 patients (29.8%) discontinued because they completed their chemotherapy treatment.

Table 22: Disposition of Patients – Cycles 2-6

	Aprepitant Regimen	
	n	(%)
Subjects in population	171	
Trial Disposition		
Completed	46	(26.9)
Discontinued	125	(73.1)
Adverse Event	2	(1.2)
Completed Chemotherapy Regimen	51	(29.8)
Did Not Meet Additional Criteria	25	(14.6)
Did Not Respond To Chemotherapy Regimen	4	(2.3)
Lack Of Efficacy Lost	1	(0.6)
To Follow-Up	1	(0.6)
Physician Decision	19	(11.1)
Protocol Violation	4	(2.3)
Withdrawal By Subject	18	(10.5)
Each subject is counted once for Trial Disposition based on the latest corresponding disposition record.		

Of the 47 patients who entered Cycle 6, all completed study medication.

Table 23: Number of Patients in each cycle

	Cycle 2	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**
Number of Patients	171	126	92	72	47

6.1.4 Analysis of Primary Endpoint(s)

The focus for the evaluation of efficacy is the Cycle 1 data. No efficacy evaluation was done for Cycles 2 through 6. The efficacy results presented are for the Intent- to-Treat population.

The primary endpoint of this trial was Complete Response in the delayed phase, defined as no vomiting, no retching and no use of rescue medication in the 25 to 120 hours following the initiation of emetogenic chemotherapy in Cycle 1.

In the delayed phase, significantly (p<0.0001) more patients on the aprepitant regimen had Complete Response compared to those on the control regimen.

Table 24: Number (%) of Patients with Complete Response by Phase and Treatment Group – P208 Cycle 1 (Intent to Treat Population)

	Aprepitant Regimen n/m (%)	**Control Regimen n/m (%)**
Acute Phase	101 / 152 (66.4) *	78 / 150 (52.0)
Delayed Phase	**77 / 152 (50.7) ****	**39 / 150 (26.0)**
Overall Phase	61 / 152 (40.1) **	30 / 150 (20.0)

* p<0.05 when compared with Control Regimen.
** p<0.01 when compared with Control Regimen.
† Complete Response = No vomiting or retching and no use of rescue medication.
Treatment comparison is made using the CMH test stratified by age group, use of dexamethasone as an antiemetic in Cycle 1, and receipt of a Very High Risk emetogenic chemotherapy agent in Cycle 1.
n/m = Number of patients with desired response/number of patients included in time point
Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: 25 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.

Applicant's table, CSR Protocol P208

Reviewer's comments: The Applicant was able to demonstrate superiority of aprepitant over control with respect to Complete Response in the delayed phase in pediatric subjects receiving emetogenic chemotherapy. See Dr. Wen Jen Chen's statistical review in DARRTS.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints for this trial were Complete Response in the acute phase (0 to 24 hours) and Complete Response in the overall phase (0 to 120 hours).

The aprepitant regimen was more effective than the control regimen in the acute phase (nominal p=0.0135) and the overall phase (nominal p=0.0002). See Table 24 in Section 6.1.4 Analysis of Primary Endpoint.

An additional secondary endpoint was No Vomiting overall, which was defined as no emesis or retching or dry heaves, regardless of whether or not the patient received

rescue medication, in the 120 hours following the initiation of emetogenic chemotherapy in Cycle 1. In the overall phase, more patients on the aprepitant regimen reported No Vomiting compared to those on the control regimen (nominal p=<0.0001). The aprepitant regimen was also more effective than the control regimen in the acute phase (nominal p=0.0023) and the delayed phase (nominal p=<0.0001). See Table 25:

Table 25: Number (%) of Patients with No Vomiting by Phase and Treatment Group - Cycle 1 (Intent to Treat Population)

	Aprepitant Regimen n/m (%)	**Control Regimen n/m (%)**
Acute Phase	108 / 152 (71.1) **	80 / 150 (53.3)
Delayed Phase	84 / 152 (55.3) **	42 / 150 (28.0)
Overall Phase	**71 / 152 (46.7) ** **	**32 / 150 (21.3)**

* p<0.05 when compared with Control Regimen.
** p<0.01 when compared with Control Regimen.
† No Vomiting = No emesis or retching or dry heaves.
Treatment comparison is made using the CMH test stratified by age group, use of dexamethasone as an antiemetic in Cycle 1, and receipt of a Very High Risk emetogenic chemotherapy agent in Cycle 1.
n/m = Number of patients with desired response/number of patients included in time point
Acute Phase: 0 to 24 hours following initiation of chemotherapy. Delayed Phase: 25 to 120 hours following initiation of chemotherapy. Overall Phase: 0 to 120 hours following initiation of chemotherapy.

6.1.6 Other Endpoints

Several exploratory endpoints were evaluated during this trial. These include: 1) the number of emetic episodes, 2) the time to first rescue medication, and 3) the time to first vomiting in the 120 hours following initiation of emetogenic chemotherapy.

The time to first vomiting was longer in patients in the aprepitant regimen group (estimated median time to first vomiting was 94.5 hours) compared with the control regimen group (estimated median time to first vomiting was 26.0 hours).

The time to first rescue was longer in patients in the aprepitant regimen group compared with the control group. At approximately 98 hours, 68% of the patients in the aprepitant group were free of rescue medication use compared to 52% of patients in the control group.

Table 26: Number (%) of Patients With Vomiting During the Delayed Phase by Frequency and Treatment Group - Cycle 1 (Intent to Treat Population)

	Aprepitant Regimen n/m (%)	**Control Regimen n/m**
No vomiting	84/152 (55.3)	42/150 (28.0)
1 episode of vomiting	18/152 (11.8)	17/150 (11.3)
2 episodes of vomiting	9/152 (5.9)	16/150 (10.7)
3 episodes of vomiting	11/152 (7.2)	12/150 (8.0)
>3 episodes of vomiting	30/152 (19.7)	62/150 (41.3)
† Delayed Phase: 25 to 120 hours following initiation of chemotherapy. n/m = Number of patients with desired response/number of patients included in time point.		

Applicant's table

6.1.7 Subpopulations

Subgroup summaries for age, gender, race, use of dexamethasone, receipt of very high risk chemotherapy in the delayed and overall phases demonstrated that the aprepitant group had better responses than the control group. See Tables 27 and 28

Table 27: Number (%) of Patients With Complete Response in the Delayed Phase by Subgroup and Treatment Group - Cycle 1 (Intent to Treat Population)

	Aprepitant Regimen n/N (%)	Control Regimen n/N (%)
Age Group		
6 months to <2 years	9/19 (47.4)	4/16 (25.0)
2 years to <6 years	25/45 (55.6)	16/43 (37.2)
6 years to <12 years	19/41 (46.3)	14/43 (32.6)
12 years to 17 years	24/47 (51.1)	5/48 (10.4)
Gender Group		
Male	47/84 (56.0)	19/79 (24.1)
Female	30/68 (44.1)	20/71 (28.2)
Race Group		
White	59/119 (49.6)	32/110 (29.1)
Black	0/0	0/2 (0.0)
Asian	2/11 (18.2)	2/16 (12.5)
Multi-Racial	14/20 (70.0)	5/22 (22.7)
Other	2/2 (100.0)	0/0
Use of Dexamethasone as an Antiemetic in Cycle 1		

Yes	16/44 (36.4)	9/42 (21.4)
No	61/108 (56.5)	30/108 (27.8)
Receipt of a Very High Risk Emetogenic Chemotherapy Agent in Cycle 1		
Yes	42/99 (42.4)	20/101 (19.8)
No	35/53 (66.0)	19/49 (38.8)
Chemotherapy Duration in Cycle 1		
One Day of Chemotherapy	21/26 (80.8)	5/16 (31.3)
More Than 1 Day of Chemotherapy	56/126 (44.4)	34/134 (25.4)

Applicant's table

Table 28: Number (%) of Patients With Complete Response in the Overall Phase by Subgroup and Treatment Group - Cycle 1 (Intent to Treat Population)

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Age Group		
6 months to <2 years	9/19 (47.4)	4/16 (25.0)
2 years to <6 years	22/45 (48.9)	13/43 (30.2)
6 years to <12 years	12/41 (29.3)	9/43 (20.9)
12 years to 17 years	18/47 (38.3)	4/48 (8.3)
Gender Group		
Male	39/84 (46.4)	15/79 (19.0)
Female	22/68 (32.4)	15/71 (21.1)
Race Group		
White	47/119 (39.5)	24/110 (21.8)
Black	0/0	0/2 (0.0)
Asian	1/11 (9.1)	2/16 (12.5)
Multi-Racial	12/20 (60.0)	4/22 (18.2)
Other	1/2 (50.0)	0/0
Use of Dexamethasone as an Antiemetic in Cycle 1		
Yes	15/44 (34.1)	7/42 (16.7)
No	46/108 (42.6)	23/108 (21.3)
Receipt of a Very High Risk Emetogenic Chemotherapy Agent in Cycle 1		
Yes	35/99 (35.4)	14/101 (13.9)
No	26/53 (49.1)	16/49 (32.7)
Chemotherapy Duration in Cycle 1		
One Day of Chemotherapy	15/26 (57.7)	2/16 (12.5)
More Than 1 Day of Chemotherapy	46/126 (36.5)	28/134 (20.9)

Applican'ts table

The statistical reviewer, Dr. Wen Jen Chen, conducted efficacy comparisons in subjects aged ≥12 to 17 years old and subjects aged 6 month to <12 years.

Table 29: Efficacy comparison by phase using patients with ages between 12 and 17 years old

Phase	Aprepitant Regimen (A) n/N (%)	Control regimen (C) n/N (%)	95% 2-sided C.I. for Diff. (A-C)	p-value
Delayed Phase	24/47 (51.1)	5/48 (10.4)	(0.23, 0.56)	P < 0.0001
Acute Phase	26/47 (55.3)	18/48 (37.5)	(-0.02, 0.37)	P = 0.099
Overall Phase	18/47 (38.3)	4/48 (8.33)	(0.14, 0.46)	P = 0.001

Statistical reviewer's table

Table 30: **Efficacy comparison by phase using patients with ages from 6 months to 12 years old**

Phase	Aprepitant Regimen (A) n/N (%)	Control regimen (C) n/N (%)	95% 2-sided C.I. for Diff. (A-C)	p-value
Delayed Phase	53/105 (50.5)	34/102 (33.3)	(0.04, 0.3)	P=0.013
Acute Phase	75/105 (71.4)	60/102 (58.8)	(-0.004, 0.25)	P =0.057
Overall Phase	43/105 (41.0)	26/102 (25.5)	(0.026, 0.28)	P=0.021

Statistical reviewer's table

Reviewer's comments: Per Dr. Chen's review, since the Applicant did not plan any type 1 error control for the analyses, the p-values in Tables 29 and 30 are included only for references. In both age group analyses, the results demonstrated that the CR rates of aprepitant regimens are numerically higher than those in the control regimen for the acute, delayed and overall phases.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

For patients aged 12 to 17 years the recommended dose is based on efficacy and safety results from the pivotal Phase 3 trial (P208). For patients aged ≥ 6 months and < 12 years, in the clinical trials, aprepitant oral suspension was dosed using a fixed dose, mg/kg, weight based dosing regimen (day 1- 3mg/kg and days 2 & 3- 2mg/kg).

For patients aged 6 months to less than 12 years the Applicant proposes a nomogram dosing by weight band which was not used in any of the clinical trials (see Table 31 for proposed marketing dosing regimen). The Applicant states that their proposed dose of aprepitant using the nomogram is will mimic the fixed weight based dosing regimen used in the Phase 3 trial for patients 6 months to less than 12 years of age and simplify calculation of the dose to improve ease of use in clinical practice.

Simulation analysis conducted by Dr. Jian Wang, the Pharmacometrics reviewer and Dr. Elizabeth Shang, the Clinical Pharmacology reviewer, indicated that the nomogram for pediatric patients from 6 months to 12 years of age results in slightly higher (~30%)

aprepitant exposures compared to the individualized weight-based regimen. Pharmacology reviewers note that the differences in PK values with the nomogram compared to strict weight based dosing are modest and unlikely to be clinically relevant. See the full Pharmacology review for further details.

Reviewer's comments: Per Pharmacology reviewers, these differences are not considered to be clinically relevant given aprepitant has generally been shown to be very well tolerated in clinical studies in adults even at higher (2- fold) exposures, coupled with the data demonstrating acceptable tolerance in the pediatric clinical trials.

Although, there are no apparent safety or efficacy issues related to the nomogram, this reviewer does not agree with the sponsor's statement that the nomogram dosing regimen will allow easier use compared to the fixed dose weight dosing regimen. Of note, the highest weight category in the nomogram (≥30 kg) would receive the full dose of aprepitant oral suspension, Day 1-125 mg and Days 2 and 3 – 80 mg. This is the same as the adolescent and adult dose. The Applicant though did not conduct a BA study (b) (4) (b) (4) (b) (4)

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The confirmatory study supports the efficacy of aprepitant capsule and aprepitant oral suspension (weight based) for the prevention of CINV in the acute (0 to 24 hours) and

the delayed phase (>24-120 hours post chemotherapy). This is the extent of persistence of effects described in the Applicant's submission.

Reviewer's comments: The Applicant did not assess efficacy in cycles 2 to 6 in P208.

6.1.10 Additional Efficacy Issues/Analyses

In P097, the efficacy of aprepitant was evaluated as a secondary objective. The main efficacy evaluation was the proportion of patients with CR overall (from 0 to 120 hours) following initiation of emetogenic chemotherapy. Additional secondary analyses were CR in the acute and delayed phases and No Vomiting in the acute, delayed and overall phases.

Table 32: Number (%) of Subjects with CR by Treatment and Phase (cycle 1- part 1) –Protocol 097

	Aprepitant Triple Therapy Regimen			Standard Therapy		
	n/m	(%)	(95% CI)	n/m	(%)	(95% CI)
Overall Phase	8/28	(28.6)	(13.2, 48.7)	1/18	(5.6)	(0.1, 27.3)
Acute Phase	17/28	(60.7)	(40.6, 78.5)	7/18	(38.9)	(17.3, 64.3)
Delayed Phase	10/28	(35.7)	(18.6, 55.9)	1/18	(5.6)	(0.1, 27.3)

Modified sponsor's table, IR

Reviewer's comments: For all three phases in P097, a supportive trial, a higher percentage of patients on the aprepitant regimen compared to the control regimen, experienced CR and No Vomiting.

Use of Corticosteroids

In Protocol 208, IV dexamethasone was permitted for subjects in both treatment groups as an optional component of the anti-emetic regimen at the discretion of the investigator, according to the product label for pediatric usage or local standard of care in a dose-adjusted and blinded manner. In cycle 1, 44 (29%) subjects in the aprepitant regimen received dexamethasone and 42 (28%) of subjects in the control regimen received dexamethasone.

Per the Emend (aprepitant) label for adults: Section 7 Drug Interactions:

(b) (4)

[redacted]

Dexamethasone, a corticosteroid, is an antiemetic used in the prevention of the delayed phase of CINV in adults and children. The 2011 American Society of Clinical Oncology Antiemetic Guidelines recommends the use of a corticosteroid with a 5-HT3 antagonist before chemotherapy in pediatric patients receiving HEC or MEC.[7] Unlike in adult CINV prevention regimens though, corticosteroids are not routinely used in pediatric patients. Many clinicians limit the use of dexamethasone due to concerns regarding increased risk of fungal infections or decreased penetration of chemotherapy into brain tumor tissue. Other pediatric patients do not receive dexamethasone as an antiemetic due to concerns of serious, but rare, adverse events such as avascular necrosis or neurocognitive disorders (e.g., behavioral disorders).[8]

7 Review of Safety

Safety Summary

Assessment of a possible association between adverse events (AEs) and study drug in the CINV studies of pediatric cancer subjects (i.e., Protocols 208, 097 and 134) is limited for a number of reasons. First, the study population is generally quite ill at baseline with underlying malignancies at various stages and of varying degrees of severity. Additionally, shortly after receiving the study drug, all study subjects received potentially toxic chemotherapeutic agents with extensive adverse reaction profiles. Finally, the pediatric studies were not safety studies and were thus not powered or designed to test safety-related hypotheses.

There was one death reported in Protocol 208 (aprepitant regimen) and two deaths reported in Protocol 097 (one aprepitant regimen and one control regimen). All deaths were reported after the follow-up period. No deaths were causally associated with the study drug.

In the CINV integrated safety population, which included subjects in Protocols 208 and 097, ninety-seven (27.6%) of the 352 subjects had one or more Serious Adverse Events (SAEs). Fifty-four subjects (29.3%) in the aprepitant regimen had one or more SAEs and 43 subjects (25.6%) in the control regimen had one or more SAEs. In combined P208 and P097 cycle 1, the most commonly reported SAEs occurred in the blood and lymphatic system organ class, with febrile neutropenia occurring most frequently (29 [15.8%] in the aprepitant regimen and 24 [14.3%] in the control regimen).

As expected in this pediatric cancer study population, treatment-emergent AEs (TEAEs) in the blood and lymphatic system disorders system organ class (SOC) were the most common overall (39%) and in both treatment groups (39% for aprepitant regimens and

7 Basch E, Prestrud AA, Hesketh P, et.al., Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update. Journal of Clinical Oncology 29:4189-4198, 2011
8 Discussions with FDA pediatric oncologist 06/23/2015

40% for control regimens). Anemia was the most commonly reported TEAE overall (19%) and in the aprepitant regimen (15%) and control regimen (23%) followed by febrile neutropenia (overall – 16%; aprepitant regimen- 16% and control regimen 16%). Other than the safe use and administration of aprepitant oral suspension, see Section 4.5.2 Human Factor Studies, no significant safety issues were identified in this review.

The three deaths reported in the combined Protocols 208 and 097 did not appear related to the study drug. While a significant number of Serious Adverse Events (SAEs) were reported by the Applicant, it is very likely that in this patient population, SAEs are related to the disease itself and/or complications of chemotherapeutic drugs.

7.1 Methods

The safety results of one Phase I (Protocol 134) and two Phase III studies (Protocol 097, Protocol 208) comprising the aprepitant pediatric clinical program are summarized. In all three studies, the safety analysis population included all subjects who received at least one dose of study medication. Subjects were counted in the treatment group for the treatment they actually received. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study medication was required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement was also required.

In the optional open-label multiple cycle extension (Cycles 2 to 10), only serious AEs and non-serious AEs evaluated by the investigator as drug-related or resulting in discontinuation from the study were collected.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data were reviewed from three (3) clinical trials, Protocols 208, 097 and 134, submitted by the Applicant.

Protocols 208, 097, and 134 (Part IV) randomized a total of 377 unique subjects (Protocol 208 N=307; Protocol 097 N=50; Protocol 134 Part IV N=20). Of those, 372 subjects received at least one dose of study medication (aprepitant or control) in Cycle 1.

Of the 372 subjects who received study medication in Protocols 208, 097 and 134 (Part IV), 308 subjects received aprepitant either in Cycle 1 and/or in an optional Cycle 2 to 10 (Protocols 208 and 097 only). Additionally, an additional 49 subjects were exposed to aprepitant either as single doses or as part of a combined regimen with intravenous fosaprepitant in Parts I (11 subjects) and II (38 subjects) of Protocol 134. Thus, 357 subjects were exposed to oral aprepitant within the three pediatric CINV studies included in this application. See Table 33

Table 33: Number of Subjects Exposed to Aprepitant By Age Category

Protocols 208, 097 Combined (Cycles 1 to 10), and 134 (Parts I, II, and IV)

		Aprepitant Exposure[T]			
Age Group	PN208 and PN097 Combined (Cycles 1-10)	PN134 (Part I)	PN134 (Part II)	PN134 (Part IV)	Total
6 months to < 2 years	31	0	11	7	49
2 years to < 6 years	63	0	15	6	84
6 years to < 12 years	72	0	12	7	91
12 years to < 18 years	120	11	0	0	131
18 years to 19 years	2	0	0	0	2
Total	288	11	38	20	357

[T] Number of subjects who received at least one dose of aprepitant.

7.1.2 Categorization of Adverse Events

Adverse events were classified by the Applicant using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant stated that safety data from the two blinded studies, Protocols 097 and 208, were pooled to support the ability to evaluate potential safety signals which may not be detectable within a single study. Safety data are also reported for each trial.

Since Protocol 134 was a small, 5-Part open-label Phase I study in which only Part IV (n= 20) included the 3-day oral aprepitant regimen, the applicant stated that this protocol was not integrated with the two Phase 3 studies (Protocols 208 and 097).

Reviewer's comments: The pooling of data as presented in the Sponsor's CINV clinical summary of safety and integrated safety population appears acceptable.

7.2 Adequacy of Safety Assessments

The database is adequate to allow for assessment of the safety profile of aprepitant capsule and oral suspension in the pediatric population. Although the assessment for these events has been adequate, there is limited data to allow for detection of adverse events that are rare. Adverse events that require a long duration exposure to occur are unlikely to be captured since both formulations are intended for limited use.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

In Protocol 208, subjects 12 to 17 years of age received the approved adult dose of 125 mg aprepitant (or matching-image placebo) on Day 1, followed by 80 mg aprepitant on Days 2 and 3. Subjects <12 years of age received an adjusted dose of 3.0 mg/kg aprepitant PFS (or matching-image placebo) on Day 1, followed by 2.0 mg/kg aprepitant PFS (or matching-image placebo) on Days 2 and 3 administered concomitantly with ondansetron, with or without dexamethasone.

In Protocol 097, adolescent subjects (aged 12 to17 years) received the approved adult regimen of 125 mg aprepitant (or matching-image placebo) on Day 1 followed by 80 mg aprepitant (or matching-image placebo) on Days 2 and 3, administered concomitantly with ondansetron and dexamethasone.

In Protocol 134 (Part IV), subjects 6 months to <12 years of age received an adjusted dose of open-label aprepitant 3.0 mg/kg oral suspension (up to 125 mg) on Day 1 and 2.0 mg/kg aprepitant oral suspension (up to 80 mg) administered concomitantly with ondansetron, with or without dexamethasone on Days 2 to 3.

In Protocols 208 and 097, eligible subjects had the opportunity to receive open-label aprepitant in subsequent cycles identical to the aprepitant treatment plan in Cycle 1 (up to 6 cycles in Protocol 208 and up to 10 cycles in Protocol 097).

Table 34 describes the extent to which subjects were exposed to assigned doses of aprepitant in Cycle 1 for the primary safety population for Protocol 208 and 097 combined. 184 of 187 randomized subjects in the aprepitant group received at least one dose of aprepitant.

Table 34: Extent of exposure to aprepitant by dose - Protocols 208 and 097 (cycle 1)

Aprepitant	1 Day	2 Days	3 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	2	1	181	184	1 to 3 days	3 days
10 to 20 mg	1	16	1	18	1 to 3 days	2 days
20.1 to 30 mg	16	25	0	41	1 to 2 days	1.6 days
30.1 to 40 mg	16	25	0	41	1 to 2 days	1.6 days
40.1 to 50 mg	27	10	0	32	1 to 2 days	1.3 days
50.1 to 65 mg	21	16	0	37	1 to 2 days	1.4 days
65.1 to 80 mg	10	87	0	97	1 to 2 days	1.9 days
80.1 to 125 mg	100	0	0	100	1 to 1 days	1 day

Applicant's table

In Cycles 2 to 10 all subjects were given open-label aprepitant (approved adult dosing regimen) for subjects 12 to 17 years of age in Protocols 097 and 208 and weight-

adjusted oral suspension for subjects 6 months to <12 years of age in Protocol 208. See Table 35

Table 35: Extent of exposure to aprepitant by dose -Protocols 208 and 097 (cycles 2-10)

Aprepitant	1-3 Days	4-6 Days	7-9 Days	10-12 Days	13-15 Days	>15 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	56	45	34	26	50	3	214	1-26 days	8.6 days
10 to 20 mg	4	10	2	1	0	0	17	2-10 days	4.8 days
20.1 to 30 mg	18	19	4	7	0	0	48	1-10 days	4.6 days
30.1 to 40 mg	24	16	0	6	0	0	46	1-10 days	3.9 days
40.1 to 50 mg	14	16	2	7	0	0	39	1-10 days	4.9 days
50.1 to 65 mg	23	13	5	3	0	0	44	1-10 days	3.8 days
65.1 to 80 mg	46	49	12	17	2	1	127	1-17 days	5.1 days
80.1 to 125 mg	94	35	3	0	0	0	132	1-9 days	2.7 days
>125 mg	1	0	0	0	0	0	1	1-1 days	1.0 days

Applicant's table

In Protocol 134 (Part IV), a 3-day regimen that included aprepitant (oral suspension) was administered to subjects 6 months to <12 years of age. All 20 subjects received the 3-day oral aprepitant regimen of aprepitant and were included in the safety analysis. See Table 36.

Table 36: Extent of exposure to aprepitant by dose –Protocol 134 (Part IV)

Aprepitant	1 Day	2 Days	3 Days	>3 Days	Total Subjects	Duration Range	Mean Duration
Any Dose	0	0	20	0	20	3-5 days	3 days
10 to 20 mg	0	4	0	0	4	2-2 days	2 days
20.1 to 30 mg	4	6	0	0	10	1-2 days	1.6 days
30.1 to 40 mg	4	5	0	0	9	1-2 days	1.6 days
40.1 to 50 mg	4	3	0	0	7	1-2 days	1.4 days
50.1 to 65 mg	4	2	0	0	6	1-2 days	1.3 days
65.1 to 80 mg	3	0	0	0	3	1-1 days	1 day
80.1 to 125 mg	1	0	0	0	1	1-1 days	1 day
>125 mg	0	0	0	0	0	0-0 days	0 days

Applicant's table

The demographic make-up of the submission was adequate. There were more male subjects than female subjects randomized. The youngest age cohort (6 months to <2 years of age) represented the smallest cohort, aprepitant regimen (10.3%) and the control regimen (9.5%). There was an approximately even distribution of subjects in the 2 to <6 year, 6 to <12 year, and 12 to 17 year cohorts. The most common primary malignancies overall were osteosarcoma (17.9%), followed by Ewing's sarcoma (10.5%), rhabdomyosarcoma (7.1%), medulloblastoma (6.8%), neuroblastoma (6.8%),

and acute lymphocytic leukemia (6%). There were slightly more subjects with acute lymphocytic leukemia in the aprepitant treatment group (7.1%) than in the control regimen (4.8%). See Table 37.

Part IV of Protocol 134 was similar to Protocols 208 and 097 with respect to baseline demographics and characteristics with the exception of gender. There were roughly twice as many females than males. Subjects were evenly distributed among the three age groups with approximately one-third of the subjects falling into each group (6 months to <2 years, 2 to <6 years, and 6 to <12 years). The mean age in months was just over 50 months. The most common primary malignancies, each reported in four subjects, were embryonal rhabdomyosarcoma, medulloblastoma, and neuroblastoma. See Table 38.

Table 37: Demographics Protocols 208 and 097 combined

	Aprepitant Regimen		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	184		168		352	
Gender						
Male	108	(58.7)	91	(54.2)	199	(56.5)
Female	76	(41.3)	77	(45.8)	153	(43.5)
Age (Months)						
6 months to < 2 years	19	(10.3)	16	(9.5)	35	(9.9)
2 years to < 6 years	45	(24.5)	43	(25.6)	88	(25.0)
6 years to < 12 years	41	(22.3)	44	(26.2)	85	(24.1)
12 years to < 18 years	77	(41.8)	65	(38.7)	142	(40.3)
18 years to 19 years	2	(1.1)	0	(0.0)	2	(0.6)
Mean	113.0		108.0		110.6	
SD	67.0		63.1		65.1	
Median	112.0		109.5		112.0	
Range	6 to 228		6 to 214		6 to 228	
Race						
American Indian Or Alaska Native	3	(1.6)	0	(0.0)	3	(0.9)
Asian	11	(6.0)	16	(9.5)	27	(7.7)
Black Or African American	4	(2.2)	6	(3.6)	10	(2.8)
Hispanic American	8	(4.3)	3	(1.8)	11	(3.1)
Multiple	25	(13.6)	25	(14.9)	50	(14.2)
White	133	(72.3)	118	(70 2)	251	(71.3)
Ethnicity						
Hispanic Or Latino	36	(19.6)	32	(19.0)	68	(19.3)
Not Hispanic Or Latino	111	(60.3)	112	(66.7)	223	(63.4)
Not Reported	2	(1.1)	4	(2.4)	6	(1.7)
Unknown	2	(1.1)	2	(1.2)	4	(1.1)
Missing	33	(17.9)	18	(10.7)	51	(14.5)

Applicant's table, CSS

Reviewer's comments: The two treatment groups in the combined Protocols 208 and 097 database were similar with respect to baseline demographics and characteristics. The enrollment of racial and ethnic minorities was low in all treatment groups. There were slightly more male subjects than female subjects randomized, with a similar proportion of male and female subjects between the two treatment regimens.

Table 38: Characteristics Protocol 134 (part IV)

	Aprepitant Regimen (Part IV)	
	n	(%)
Subjects in population	20	
Gender		
Male	7	(35.0)
Female	13	(65.0)
Age (Months)		
6 months to <2 years	7	(35.0)
2 to <6 years	6	(30.0)
6 to <12 years	7	(35.0)
Mean	51.8	
SD	38.0	
Median	41.0	
Range	9 to 113	
Race		
Asian	1	(5.0)
Multi-Racial	11	(55.0)
White	8	(40.0)
Ethnicity		
Hispanic Or Latino	10	(50.0)
Not Hispanic Or Latino	10	(50.0)

Applicant's table, CSS

Reviewer's comments: Part IV of Protocol 134 was similar to Protocols 208 and 097 with respect to baseline demographics and characteristics with the exception of gender. There were roughly twice as many females than males. Subjects were evenly distributed among the three age groups with approximately one-third of the subjects falling into each group (6 months to <2 years, 2 to <6 years, and 6 to <12 years).

7.2.2 Explorations for Dose Response

Assessment of dose response within each strata was adequate.

7.2.3 Special Animal and/or In Vitro Testing

The animal and/or in vitro testing data submitted by the Applicant as a part of the application was considered adequate by the Pharmacology/Toxicology Reviewer.

7.2.4 Routine Clinical Testing

The Applicant performed adequate monitoring of safety parameters including vital signs, physical exams, and laboratory testing.

7.2.5 Metabolic, Clearance, and Interaction Workup

The clinical pharmacology data submitted by the Applicant was considered adequate by the Clinical Pharmacology reviewer. No evaluation of drug interactions was performed in the pediatric population participating in these trials.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

None were conducted.

7.3 Major Safety Results

7.3.1 Deaths

Three deaths were reported in this submission. One death in Protocol 208 and two deaths in Protocol 097. None of the deaths were reported by the Applicant as related to the study medication. The Applicant reported no deaths in Protocol 208 in cycles 2-6 and no deaths in Protocol 134.

Deaths in Protocol 208

Patient AN 070712 who was randomized to the aprepitant regimen. He was a 6 year old male subject with a diagnosis of neuroblastoma. Patient weighed 15.2 kg. He experienced a seizure 4 days post initiation of study medication in Cycle 1 (Day 4), one day after the last dose of aprepitant, which resolved spontaneously within 30 seconds. The adverse event diagnosis was considered by the investigator as 'worsening neuroblastoma." The investigator did not consider this event related to study medication; no action was taken with study medication as the last dose of aprepitant was received on Day 3. The subject completed Cycle 1, then discontinued from the study. The subject did not participate in Cycles 2-6. The AE of "worsening neuroblastoma" was not resolved at the time the subject discontinued from the study.

Additional information was received by the Apprlicant that the neuroblastoma had worsened, which resulted in uncontrolled seizures and death. The subject died approximately 9 months after he was discontinued from the study (298 days after the last dose of study medication was administered).

Deaths in Protocol 097
Patient AN 10231, who was randomized to the aprepitant regimen, died due to AEs of metastases to the lung and respiratory failure which occurred > 6 months and > 12 months respectively, after entering the study (~300 days after the last dose of study medication). The patient had completed Treatment Cycle 3.

Patient AN 10221, who was randomized to the control regimen, died due to an AE of dyspnea which occurred 4 months after entering the study (~120 days after the last dose of study medication). The AE occurred after the subject completed Cycle 1 and the subject did not enter the multiple cycle extension,

Reviewer's comments: In this reviewer's assessment, the cause of these subjects' deaths does not appear to be related to the study drug.

7.3.2 Nonfatal Serious Adverse Events

Of the 352 subjects in cycle 1 in both trials, 97 subjects (27.6%) had one or more serious adverse events. In the aprepitant regimen 54 subjects (29.3%) had one or more SAEs and in the control regimen 43 subjects (25.6%) had one or more SAEs. In combined P208 and P097 cycle 1, the most commonly reported SAEs occurred in the blood and lymphatic system organ class, with febrile neutropenia occurring most frequently (29 [15.8%] in the aprepitant regimen and 24 [14.3%] in the control regimen.

In combined trials of P208 and P097 in Cycle 1, for patients aged 12 to 17 years, 23 subjects (29.8%) in the aprepitant group and 10 subjects (15.4%) in the control group reported a SAE. In Protocol 208 in subjects aged 6 months to <12 years, 31 subjects (29.5%) in the aprepitant regimen and 33 (32%) in the control regimen reported a SAE.

In Protocol 208 (cycle 1), Serious Adverse Events (SAEs) were reported in 87 patients (46 patients [30.3%]in the aprepitant regimen and 41 [27.3%]patients in the control regimen). The most commonly reported SAEs was febrile neutropenia (15% in the aprepitant regimen and 14.7% in the control regimen). Two subjects in the aprepitant regimen had SAEs that were determined by the investigator to be drug related. Per the Applicant, no subjects in the control regimen experienced a SAE that was considered drug related.

- AN071502, a 1.2 year old female subject with a diagnosis of Yolk Sac tumor had a serious drug-related adverse event of Clostridium Difficile infection that occurred on the 3rd day post initiation of study medication (Day 3). The subject

received 1.0 mL of aprepitant PFS on Day 1, then 0.68 mL on Days 2 and 3. The patient was hospitalized on Day 4 and treated with hydration only. On Day 5, a clostridium antibody test result was positive for Clostridium Difficile antigen but negative for the toxin, therefore, the patient was started on metronidazole (Flagyl). The intensity of this event was moderate, the NCI toxicity grade was 3, and the subject recovered without sequelae on Day 9. The investigator considered this event related to aprepitant and ondansetron. The subject completed Cycle 1 then discontinued from the study.

- AN070010, a 16 year old female subject with a diagnosis of osteosarcoma had a serious drug-related adverse event of electrocardiogram T wave inversion that occurred on the 8th day post initiation of study medication (Day 8), 5 days after the last dose of study medication. The subject received 125 mg aprepitant capsule on Day 1, then 80 mg on Days 2 and 3. No concomitant medication or treatment was given to the subject for this event. The adverse event of "T wave inversion" was considered an "other important medical event'; the intensity of this event was mild and the NCI toxicity grade was 1. On Day 20, the subject's ECG tracing spontaneously returned to baseline. The investigator considered this event possibly related to aprepitant and chemotherapy agents doxorubicin and cisplatin. The subject completed Cycle 1 then discontinued from the study.

In Protocol 097, SAEs were reported by 10 subjects (31.3%) on the aprepitant regimen and 3 subjects (16.7%) on the standard therapy regimen during Cycle 1. The most commonly reported serious adverse experience was febrile neutropenia (8 patients (25.0%) in the aprepitant triple therapy treatment group and 2 patients (11.1%) in the standard therapy treatment group).

Reviewer's comments: There was a discrepancy in the number of SAEs reported by the sponsor for Protocol 097. Three SAEs were not found in the combined Protocols 208 and 097 cycle 1 SAE report. An IR was submitted for clarification. The Applicant reported that these three subjects were not included in the combined SAE tables due to differences in the selection criteria used to produce the tables. In P097, the SAE had to occur in either the treatment phase (day 1 to subject's day 6 to 8 visit) or the follow-up phase (day 9 to the subject's last visit in cycle 1). The following are the subjects in P097 who were not included in the combined table:

- *AN10217 (febrile neutropenia on day 31)*
- *AN10233 (febrile neutropenia on day 21)*
- *AN10221 (poisoning on day 22)*

Table 39: Summary of Clinically Relevant Nonfatal Serious Adverse Events for Subjects that Received Aprepitant in P208 and P097 (Cycle 1)

Protocol/Subject ID/	Age (months)/ Gender	Cycle 1	Time to AE (days)	Preferred term	Relationship
Aprepitant Regimen					
P097/10211	195/F	Withdrawal	10	Febrile Neutropenia	Not related
P09710277	201/M	Withdrawal	10	Febrile Neutropenia	Not related
P097/10230	176/M	Treatment Withdrawal	1 8	Weight decreased Vomiting	Not related Not related
P097/10232	193/F	Withdrawal	13 14	Herpes zoster Febrile neutropenia	Not related Not related
P097/10235	196/M	Withdrawal	17	Febrile neutropenia	Not related
P097/10237	187/M	Withdrawal	14	Febrile neutropenia	Not related
P097/10218	210/M	Treatment	2	Overdose of dexamethasone	Not related
P907/10423	159/M	Withdrawal	9	Febrile neutropenia	Not related
P208/070140	163/F	Post treatment	11	Pancytopenia	Not related
P208/070305	210/F	Treatment	6 6	Mucosal inflammation Stomatitis	Not related Not related
P208/071106	55/M	Post Treatment	13	Febrile neutropenia	Not related
P208/071111	50/M	Treatment	8	Hepatotoxicity	Not related
P208/07010	203/M	Treatment	4 6	Neutropenia Pancytopenia	Not related Not related
P208/070817	51/F	Post Treatment	12	Febrile neutropenia	Not related
P208/070415	139/F	Treatment	2	Vomiting	Not related
P208/070812	50/M	Treatment	2	Vomiting	Not related
P208/070316	197/M	Post Treatment	16	Platelet count decreased	Not related
P208/071130	60/F	Treatment Post Treatment	8 11 11	Platelet count decreased Neutrophil count decreased White blood cell count decreased	Not related Not related Not related
P208/070919	43/F	Post Treatment	10	Neutropenia	Not related
P208/070510	90/F	Post Treatment	13	Febrile neutropenia	Not related
P208/070905	39/F	Treatment	7	Febrile neutropenia	Not related
P208/071502	14/F	Treatment	3	Clostridium difficile infection	Related
P208/070420	97/M	Treatment	1	Sepsis	Not related
P208/070417	118/M	Post Treatment	11	Febrile neutropenia	Not related
P208/070317	202/F	Post Treatment	10	Abdominal pain	Not related
P208/070925	36/F	Post	12	Anemia	Not related

Protocol/Subject ID/	Age (months)/ Gender	Cycle 1	Time to AE (days)	Preferred term	Relationship
		Treatment	12	Febrile neutropenia	
P208/071401	7/F	Treatment	8	Febrile neutropenia	Not related
P208/070814	25/F	Post treatment	15 15	Device related infection Febrile neutropenia	Not related Not related
P208/ 070815	31/F	Post treatment	7	Febrile neutropenia	Not related
P208/070501	126/M	Treatment	1	Hypersensitivity	Not related
P208/070104	144/F	Post treatment	12	Febrile neutropenia	Not related
P208/070133	167/M	Post treatment	12	Febrile neutropenia	Not related
P208/070528	133/F	Post treatment	14	Febrile neutropenia	Not related
P208/070808	30/M	Post treatment	12	Febrile neutropenia	Not related
P208/070138	155/F	Post treatment	10	Febrile neutropenia	Not related
P208/070931	32/M	Post treatment	13	Febrile neutropenia	Not related
P208/070915	62/F	Treatment	4	Varicella	Not related
P208/071508	18/M	Post treatment	13	Febrile neutropenia	Not related
P208/070301	198/M	Post treatment	15	Febrile neutropenia	Not related
P208/070412	112/F	Treatment	8	Febrile neutropenia	Not related
P208/070601	101/M	Treatment	3	Drug clearance decreased	Not related
P208/071002	67/M	Treatment	9	Neutropenia	Not related
P208/071104	38/F	Treatment	9 9	Otitis media acute Pancytopenia	Not related Not related
P208/071117	55/F	Treatment	4	Neutropenia	Not related
P208/071118	67/M	Treatment	1	Drug hypersensitivity	Not related
P208/070204	200/F	Post treatment	14 14	Febrile neutropenia Periorbital cellulitis	Not related Not related
P208/070917	61/M	Post treatment	16	Device related infection	Not related
P208/071316	7/M	Post treatment	12 12	Anemia Neutropenia	Not related Not related
P208/070010	200/F	Treatment	8	ECG T wave inversion	Related
P208/070115	185/F	Post treatment	10	Febrile neutropenia	Not related
P208/070132	196/F	Post treatment	10	Febrile neutropenia	Not related
P208/070120	179/F	Treatment	1	Anaphylactic shock	Not related
P208/070114	160/F	Post treatment	10 10	Febrile neutropenia Mucosal inflammation	Not related Not related
P208/070712	73/M	Treatment	4	Worsening of neuroblastoma	Not related
Control Regimen					

Protocol/Subject ID/	Age (months)/ Gender	Cycle 1	Time to AE (days)	Preferred term	Relationship
P097/10321	189/M	Withdrawal	9 13	Febrile neutropenia Catheter site infection	Not related Not related
P097/10238	195/F	Withdrawal	15 16	Cecal inflammation Febrile neutropenia	Not related Not related
P208/070503	97/F	Treatment	9	Pancytopenia	Not related
P208/071109	33/M	Treatment	4 9	Bronchitis Pancytopenia	Not related Not related
P208/070702	118/M	Treatment	9	Pancytopenia	Not related
P208/070416	119/M	Post treatment	15	Febrile neutropenia	Not related
P208/070801	61/F	Treatment	6	UTI	Not related
P208/070413	127/F	Post treatment	16	Febrile neutropenia	Not related
P208/070421	114/M	Treatment Post treatment	1 13	Vomiting Febrile neutropenia	Not related Not related
P208/070023	170/M	Treatment	1	Vomiting	Not related
P208/070708	105/F	Post Treatment	13	Febrile neutropenia	Not related
P208/070119	161/M	Treatment	7	Mucosal inflammation	Not related
P208/070918	39/F	Treatment Post Treatment	3 3 3 11	Hypokalemia Hyponatremia Pyrexia Febrile neutropenia	Not relate Not related Not related Not related
P208/071313	14/M	Post treatment	9	Febrile neutropenia	Not related
P208/070527	107/F	Post treatment	14	Dehydration	Not related
P208/070013	177/F	Treatment	5 5	Abdominal pain Vomiting	Not related Not related
P208/070914	29/F	Post treatment	10	Febrile neutropenia	Not related
P208/071507	20/M	Post treatment	11	Febrile neutropenia	Not related
P208/070936	35/F	Post treatment	10 11	Pneumonia Pancytopenia	Not related Not related
P208/070016	173/F	Post treatment	11	Febrile neutropenia	Not related
P208/070921	25/F	Post treatment	8	Bacillus infection	Not related
P208/070512	121/F	Treatment	6	Pyrexia	Not related
P208/070904	29/F	Post treatment	12	Febrile neutropenia	Not related
P208/071301	14/M	Treatment	5	Febrile neutropenia	Not related
P208/071306	24/F	Treatment	7	Febrile neutropenia	Not related
P208/070406	116/M	Post treatment	12	Febrile neutropenia	Not related
P208/071403	7/F	Treatment	8	Febrile neutropenia	Not related

Protocol/Subject ID/	Age (months)/ Gender	Cycle 1	Time to AE (days)	Preferred term	Relationship
P208/070401	116/F	Post treatment	10	Febrile neutropenia	Not related
P208/070408	91/M	Post treatment	12	Febrile neutropenia	Not related
P208/070125	206/F	Treatment Post treatment	8 10	Urinary tract infection Pancytopenia	Not related Not related
P208/070136	178/M	Post treatment	10 11 11	Bone marrow failure Anemia Thrombocytopenia	Not related Not related Not related
P208/070927	24/F	Post treatment	14 14	Anemia Thrombocytopenia	Not related Not related
P208/070932	30/F	Post treatment	13	Anemia	Not related
P208/070145	149/F	Post treatment	14	Pancytopenia	Not related
P208/070025	163/F	Treatment Post treatment	6 13	Hypotension Febrile neutropenia	Not related Not related
P208/070603	88/F	Treatment	5	Pre-syncope	Not related
P208/070719	89/F	Post treatment	10	Febrile neutropenia	Not related
P208/071207	21/F	Post treatment	16	Febrile neutropenia	Not related
P208/070524	134/F	Treatment	11	Neutrophil count decreased	Not related
P208/071319	12/F	Post treatment	14	Neutrophil count decreased	Not related
P208/071305	23/M	Treatment	7 7	Febrile neutropenia Mucosal inflammation	Not related Not related
P208/070923	62/M	Treatment	8	Febrile neutropenia	Not related
P208/070419	73/M	Treatment	7	Febrile neutropenia	Not related

Modified Applicant's table

In Cycles 2 to 10 combined from Protocols 208 and 097, the SAEs included all SAEs that occurred on-treatment during Cycles 2 to 10 and those that occurred within 14 days of the last dose of study medication. SAEs were reported in 104 subjects (48.6%). One subject experienced two SAEs, anaphylactic shock and toxicity to various agents, which were determined by the investigator to be drug-related.

In Cycles 2 to 10, as in cycle 1, the most commonly reported SAEs occurred in the blood and lymphatic system organ class, with febrile neutropenia occurring most frequently.

Reviewer's comments: *Overall in Cycle 1, the incidence of SAEs was similar between both treatment regimens. In Cycle 1 and Cycles 2 to 10 for combined Protocols 208 and*

097, the SAE profiles were typical of a patient population with cancer and/or receiving chemotherapeutic drugs.

Protocol 134 – Part IV
The SAEs included all SAEs that occurred on-treatment during Part IV of Protocol 134 and those that occurred within 14 days of the last dose of study medication. Two subjects in Part IV of Protocol 134 reported SAEs. Both subjects reported an SAE of febrile neutropenia. None of the SAEs were considered to be drug-related by the investigator.

Reviewer's comments: In general, the SAE profile was typical of a patient population with cancer and/or receiving chemotherapeutic drugs.

7.3.3 Dropouts and/or Discontinuations

The Applicant reported subject discontinuations separately for each study.

In Protocol 208 (cycle 1), two patients in the aprepitant regimen discontinued study medication due to an adverse event. No patients in the control regimen discontinued study medication due to an adverse event.

No patients in Protocol 097 (cycle 1) or Protocol 134 (Part IV) discontinued study medication due to an AE.

Protocol 208 (Cycle 1)

- AN071118, a 5 year old male subject with a diagnosis of astrocytoma experienced an allergic reaction on Day 1 after receiving carboplatin and 3.3 mL of aprepitant PFS. The adverse event of 'drug hypersensitivity' was considered by the Applicant as an 'other important medical event', severe in intensity, with a toxicity grade of 4. The investigator did not consider the event to be related to study medication, though the patient was discontinued from study medication on Day 1 and was discontinued from the study after the post-treatment visit on Day 8. The subject was treated with hydrocortisone sodium phosphate, dipyrone magnesium, dexchlorpheniramine, and ranitidine. The subject recovered from the event in 23 hours.

- AN070120, a 14 year old female subject with a diagnosis of ovarian cancer experienced anaphylactic shock on Day 1 after receiving etoposide and 125 mg capsule of aprepitant. The adverse event of 'anaphylactic shock' was considered a serious adverse event, severe in intensity, with a toxicity grade of 4. The investigator did not consider the event to be related to study medication, though the patient was discontinued from study medication on Day 1 and was discontinued from the study on Day 2. The subject was treated with adrenaline,

methylprednisolone, sodium, and chlorine. The subject recovered from the event in 10.5 minutes.

In Protocol 208 (cycle 2-6), four patients who participated in the open-labeled cycled discontinued study medication due to an adverse event. The investigators considered three of the four patients' adverse events related to the study medication.

- AN070909, a 4 year old male subject with a diagnosis of alveolar rhabdomyosarcoma experienced febrile neutropenia 11 days post initiation of study medication in Cycle 3 (Day 11). The subject received 1.8 mL of aprepitant PFS on Day 1, then 1.2 mL on Days 2 and 3. The adverse event of 'febrile neutropenia' was considered a serious adverse event, moderate in intensity, with a toxicity grade of 3. The investigator did not consider the event to be related to study medication. The study medication in Cycle 3 was completed 9 days prior to the onset of the event; no action was taken with the study medication. The subject completed Cycle 3, then discontinued from the study. The subject was treated with cefotaxime sodium, amikacin, platelets, red blood cells, and acetaminophen, The subject recovered from the event of febrile neutropenia in 5 days.

- AN070405, a 9 year old male subject with a diagnosis of osteosarcoma experienced four adverse events in Cycle 2, which led to discontinuation of study medication. On Day 1 of Cycle 2, the subject received open-label aprepitant (3.92 mL PFS) and methotrexate (13200.00 mg). On the same day, the subject experienced alanine aminotransferase increase (ALT; 2238.0 IU/L), aspartate aminotransferase increase (AST; 2738.0 IU/L), and lactate dehydrogenase increase. On the following day (Day 2 of Cycle 2), the patient experienced blood bilirubin increase (2.18 mg/dL). The adverse event of 'ALT increase' was considered moderate in intensity, with a toxicity grade of 4, and resolved in 21 days. The adverse event of 'AST increase' was considered moderate in intensity, with a toxicity grade of 4, and resolved in 15 days. The adverse event of 'lactate dehydrogenase increase' was considered moderate in intensity, with a toxicity grade of 3, and resolved in 21 days. The adverse event of 'blood bilirubin increase' was considered mild in intensity, with a toxicity grade of 1, and resolved in 8 days. Study medication was discontinued on Day 1 of Cycle 2. The subject discontinued from the study after the Cycle 2 follow-up visit. The investigator considered all four events related to study medication.

- AN070527, a 9 year old female subject with a diagnosis of osteogenic sarcoma experienced four adverse events in Cycle 2, which led to discontinuation of study medication. On Day 1 of Cycle 2, the subject received open-label aprepitant (3.48 mL PFS) and methotrexate (12000.0 mg). One the same day, the subject experienced ALT increase (1059.0 IU/L), AST increase (2031.0 IU/L), lactate dehydrogenase increase (1070.0 IU/L), and anaphylactic shock. The adverse

event of 'ALT increase' was considered moderate in intensity, with a toxicity grade of 4, and resolved in 16 days. The adverse event of 'AST increase' was considered moderate in intensity, with a toxicity grade of 4, and resolved in 11 days. The adverse event of 'lactate dehydrogenase increase' was considered moderate in intensity, with a toxicity grade of 1, and resolved in 10 days. The adverse event of 'anaphylactic shock' was considered severe in intensity, with a toxicity grade of 4, and resolved in 1 hour. Study medication was discontinued on Day 1 of Cycle 2. The subject discontinued from the study after the Cycle 2 follow-up visit. The investigator considered all four events related to study medication.

- AN070722, a 6 year old female subject with a diagnosis of gliosarcoma experienced a convulsion in Cycle 2, which led to discontinuation of study medication. The event of 'convulsion' was considered moderate in intensity, with a toxicity grade of 1. The study medication was discontinued on Day 2. The subject was treated with acetazolamide, carbamazepine, and topiramate. The subject discontinued from the study after the Cycle 2 follow-up visit. The event of convulsion resolved in 2 days. The investigator considered the event related to study medication.

See Tables 40 and 41 for patient disposition in Protocol 097

Table 40: Patient Disposition Protocol 097 (cycle 1)

Cycle 1	Aprepitant Triple Therapy Regimen N=32	Standard Therapy N=18
Pt. complete not contin. -	3	0
-ineligible	1	0
-withdrew consent	1	0
-refused chemo.	1	0
Pt. contin. trial[†]	1	0
Pt. discont.	1	0
Pt. discont. for other	1	0
Pt. extended	27	18

[†]One patient listed as continuing in Cycle 1 entered the multiple cycle extension and should be counted as extended.

Applicant's table

Table 41: Overall Patient Disposition Protocol 097 (cycles 2-10)

Time Frame	Aprepitant Therapy N=50
Cycles 2-10	n=45
pat. complete not contin.	25
completed chemo.	20
concomitant therapy	2
no response to chemo.	1
refused chemo.	2
pat. completed	11
pat. discont.	9
pat. discont. for other	5
pat. withdrew consent	2
protocol dev	2

Applicant's table

7.3.4 Significant Adverse Events

There were no significant adverse events reported in the aprepitant pediatric development program.

7.3.5 Submission Specific Primary Safety Concerns

There were no adverse events of special interest for this submission.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The most frequently reported AEs (combined protocols 208 and 097 in cycle 1) for all age groups were anemia, febrile neutropenia, vomiting, neutropenia, nausea, and neutrophil count decreased. These AEs occurred at a generally similar incidence in both treatment groups with the exception of anemia and neutrophil count decreased which occurred at a higher incidence in the control regimen. Dizziness and headache, although occurring less commonly, did occur more often in the aprepitant regimen. See Tables 42 and 43.

For patients aged 12 to 17 years in combined protocols 208 and 097, the most frequently reported AEs were nausea (aprepitant – 16.9%/control- 20%), decreased neutrophil count (aprepitant-10.4%/control-20%)), vomiting (aprepitant-11.7%/control-15.9%), febrile neutropenia (aprepitant-18.2%/control-6.2%), anemia (aprepitant-7.8%/control-15.4%), decreased platelet count (aprepitant-9.1%/control-13.8%) and headache (aprepitant-13%/control-7.7%). With the exception of febrile neutropenia,

which occurred at a higher incidence in the aprepitant regimen, these AEs occurred at a similar rate in both treatment groups.

In Protocol 208, of the 207 subjects aged 6 months to < 12 years, 162 (78.3%) had one or more AEs (84 [80%] in the aprepitant regimen and 78 [76.5] in the control regimen). The most frequently reported AEs were anemia (aprepitant regimen-20% and control regimen – 27.5%), febrile neutropenia (aprepitant – 15.2% and control – 21.6%), vomiting (aprepitant – 19% and control – 14.7%), neutropenia (aprepitant – 17.1% and control – 16.7%) and thrombocytopenia (aprepitant – 10.5% and control – 13.7%). These AEs occurred at a generally similar incidence in both treatment groups with the exception of anemia and febrile neutropenia which occurred at a higher incidence in the control regimen. Vomiting and neutropenia occurred more often in the aprepitant regimen.

In cycles 2 to 10, in the combined protocols 208 and 097, of the 215 subjects who received aprepitant, 170 (79.1%) had one or more AEs. The AE profile was similar to the AE profile observed in Cycle 1. The most common AEs were anemia 71 subjects (33%), febrile neutropenia 67 subjects (31.2%), neutropenia 43 subjects (20%), thrombocytopenia 41 subjects (19.1%), nausea 42 subjects (19.5%) and vomiting 62 subjects (28.8%).

Of the 20 subjects in Protocol 134 (part IV) who received oral aprepitant, 13 (65.5%) had one or more AEs. The most common AEs were thrombocytopenia (25%), anemia (15%), febrile neutropenia (15%) and neutropenia (15%).

Table 42: Analysis of AE Summary in Cycle 1 for all treated subjects in Protocols 208 and 097 combined

	Aprepitant Regimen		Control Regimen	
	n	(%)	n	(%)
Subjects in population	184		168	
with one or more adverse events	146	(79.3)	130	(77.4)
with no adverse events	38	(20.7)	38	(22.6)
with drug-related adverse events	12	(6.5)	4	(2.4)
with serious adverse events	54	(29.3)	43	(25.6)
with serious drug-related adverse events	2	(1.1)	0	(0.0)
who died	3	(1.6)	0	(0.0)
discontinued due to an adverse event	2	(1.1)	0	(0.0)
discontinued due to a drug-related adverse event	0	(0.0)	0	(0.0)
discontinued due to a serious adverse event	2	(1.1)	0	(0.0)
discontinued due to a serious drug-related adverse event	0	(0.0)	0	(0.0)

Modified Applicant's table 2.7.4 Summary of Clinical Safety

Table 43: Subjects With Adverse Events (Incidence ≥ 2% in One or More Treatment Groups) Cycle 1 - Protocols 208 and 097 Combined

System organ class Preferred term	Aprepitant Regimen N=184		Control Regimen N=168		Total N=352	
Number (%) of subjects with at least one AE	146 (79.3)		130 (77.4)		276 (78.4)	
Number (%) of subjects	n	%	n	%	n	%
Blood and lymphatic system disorders	**71**	**38.6**	**67**	**39.9**	**138**	**39.2**
Anemia	27	14.7	38	22.6	65	18.5
Febrile Neutropenia	30	16.3	26	15.5	56	15.9
Leukopenia	8	4.3	10	6	18	5.1
Neutropenia	24	13	18	10.7	42	11.9
Pancytopenia	4	2.2	6	3.6	10	2.8
Thrombocytopenia	15	8.2	16	9.5	31	8.8
Gastrointestinal disorders	**69**	**37.5**	**59**	**35.1**	**128**	**36.4**
Abdominal pain	12	6.5	11	6.5	23	6.5
Abdominal pain upper	5	2.7	1	0.6	6	1.7
Constipation	5	2.7	6	3.6	11	3.1
Diarrhea	11	6	9	5.4	20	5.7
Nausea	20	10.9	20	11.9	40	11.4
Stomatitis	6	3.3	5	3	11	3.1
Vomiting	30	16.3	26	15.5	56	15.9
General disorders and administration site conditions	**35**	**19**	**28**	**16.7**	**63**	**17.9**
Fatigue	9	4.9	3	1.8	12	3.4
Mucosal inflammation	7	3.8	7	4.2	14	4
Pyrexia	12	6.5	13	7.7	25	7.1
Infections and Infestations	**26**	**14.1**	**26**	**15.5**	**52**	**14.8**
Nasopharyngitis	3	1.6	4	2.4	7	2
Rhinitis	1	0.5	4	2.4	5	1.4
Urinary tract infection	5	2.7	5	3	10	2.8
Injury, poisoning and procedural complcations	**8**	**4.3**	**5**	**3**	**13**	**3.7**
Accidental overdose	1	0.5	4	2.4	5	1.4
Investigations	**49**	**26.6**	**45**	**26.8**	**94**	**26.7**
Alanine aminotransferase increase	6	3.3	8	4.8	14	4
Aspartate aminotransferase increased	5	2.7	6	3.6	11	3.1
Blood potassium decreased	4	2.2	2	1.2	6	1.7
Hemoglobin decreased	9	4.9	7	4.2	16	4.5
Neutrophil count decreased	16	8.7	23	13.7	39	11.1
Platelet count decreased	14	7.6	16	9.5	30	8.5
White blood cell count decreased	9	4.9	9	5.4	18	5.1

System organ class Preferred term	Aprepitant Regimen N=184		Control Regimen N=168		Total N=352	
Number (%) of subjects with at least one AE	146 (79.3)		130 (77.4)		276 (78.4)	
Number (%) of subjects	n	%	n	%	n	%
Metabolism and nutrition disorders	**20**	**10.9**	**21**	**12.5**	**41**	**11.6**
Decreased appetite	10	5.4	7	4.2	17	4.8
Dehydration	2	1.1	5	3	7	2
Hypokalemia	1	0.5	7	4.2	8	2.3
Hypomagnesemia	3	1.6	4	2.4	7	2
Hypophosphatemia	2	1.1	4	2.4	6	1.7
Nervous system disorders	**27**	**14.7**	**14**	**8.3**	**41**	**11.6**
Dizziness	9	4.9	1	0.6	10	2.8
Headache	17	9.2	8	4.8	25	7.1
Respiratory, thoracic, and mediastinal disorders	**27**	**14.7**	**13**	**7.7**	**40**	**11.4**
Cough	10	5.4	5	3	15	4.3
Hiccups	8	4.3	1	0.6	9	2.6

Reviewer's comments: The incidence of most observed AEs were similar among treatment groups. This reviewer agrees with the Applicant's assessment that many of these AEs are known to be associated with cancer and/or chemotherapy drugs.

7.4.2 Laboratory Findings

For selected laboratory tests (P208 and P097 combined), summary statistics including mean and standard deviation were calculated by the Applicant for baseline and post-treatment for Days 6 to 8.

Differences were observed from baseline for many of the laboratory safety tests. Changes for Days 6 to 8 included an increase in ALT and AST levels and a decrease in platelet count. Also, a difference in the mean change for ALT and AST is noted between the treatment groups, with the subjects in the aprepitant treatment regimen experiencing a greater change from baseline to post-treatment. See Table 44

Table 44: Mean changes from baseline for selected laboratory safety test cycle 1 (days 6 to 8); Protocols 208 and 097 combined

Laboratory test	Treatment	N[§]	Baseline[†]		Post Treatment[‡]		Change	
			Mean	SD	Mean	SD	Mean	SD
Alanine Transaminase (IU/L)	Aprepitant Regimen	149	32.7	26.7	74.0	116.7	41 3	112.5
	Control Regimen	143	35 5	49 5	52.4	59.6	17.0	41 3
Albumin (gm/dL)	Aprepitant Regimen	147	4.1	0.7	4.3	3.4	0.2	3.3
	Control Regimen	141	4.1	0.7	4.2	0.7	0.0	0.5
Alkaline phosphatase (IU/L)	Aprepitant Regimen	142	227.0	309.8	206.8	200.6	-20.1	134.8
	Control Regimen	133	190.7	107.9	178.8	95 3	-11.9	44.7
Aspartate Transaminase (IU/L)	Aprepitant Regimen	148	32.7	17.6	52.6	52 3	19 9	46 9
	Control Regimen	141	38 5	74 5	43.0	36.8	4.5	53 9
Total bilirubin (mg/dL)	Aprepitant Regimen	145	0.4	0.2	0.4	0.2	0.1	0.2
	Control Regimen	143	0.4	0.2	0.5	0.3	0.2	0.3
Serum creatinine (mg/dL)	Aprepitant Regimen	150	0.5	0.2	0.5	0.2	0.0	0.1
	Control Regimen	144	0.5	0.2	0.5	0.2	-0.0	0.1
Glucose (mg/dL)	Aprepitant Regimen	144	96 2	31 9	95.4	24 3	-0.8	38 3
	Control Regimen	134	90.4	13 2	93 5	17.0	3.1	20 1
Potassium (mEq/L)	Aprepitant Regimen	150	4.1	0.4	3.9	0.5	-0.1	0.5
	Control Regimen	144	4.1	0.4	4.0	0.5	-0.1	0.4
Sodium (mEq/L)	Aprepitant Regimen	150	138.9	3.0	137.3	3.4	-1.6	4.4
	Control Regimen	144	139.1	2.6	137.4	3.3	-1.7	3.3
Hemoglobin (gm/dL)	Aprepitant Regimen	148	10 9	1.6	10.4	1.8	-0.5	1.2
	Control Regimen	139	11.0	1.6	10 3	1.7	-0.6	1.2
Hematocrit (%)	Aprepitant Regimen	141	32 9	5.1	31.0	5.7	-1.9	3.7
	Control Regimen	132	32.4	4.6	30 3	5.2	-2.1	3.6

Laboratory test	Treatment	N[§]	Baseline[†]		Post Treatment[‡]		Change	
			Mean	SD	Mean	SD	Mean	SD
White blood cell count (10[3]/microL)	Aprepitant Regimen	147	6.7	5.4	4.5	4.6	-2.2	6.4
	Control Regimen	139	6.1	4.7	4.5	5.3	-1.6	5.7
Neutrophils (10[3]/microL)	Aprepitant Regimen	132	3.7	3.1	3.3	3.9	-0.4	4.3
	Control Regimen	130	3.7	4.0	3.3	5.1	-0.4	5.4
Lymphocytes (10[3]/microL)	Aprepitant Regimen	122	1.9	1.4	1.1	1.1	-0.8	1.4
	Control Regimen	110	1.7	1.3	1.0	1.2	-0.7	1.0
Platelet count (10[3]/microL)	Aprepitant Regimen	146	345.7	159.1	236.6	117.1	-109	159.2
	Control Regimen	137	317.2	153.0	229.1	120.3	-88.0	137.4

For selected laboratory tests (P134 Part 1V), summary statistics including mean and standard deviation the Applicant calculated for baseline and post-treatment for Days 5 to 9. See Table 45.

Table 45: Mean Changes From Baseline for Selected Laboratory Safety Tests All Subjects Part IV Protocol 134

Parameter	Units	Treatment	N§	Baseline†		Posttreatment‡		Change	
				Mean	SD	Mean	SD	Mean	SD
Alanine Aminotransferase	IU/L	Aprepitant Regimen (Part IV)	20	25.25	12.92	32.42	14.64	7.17	18.31
Albumin	gm/dL	Aprepitant Regimen (Part IV)	20	4.12	0.61	4.04	0.64	-0.08	0.43
Alkaline Phosphatase	IU/L	Aprepitant Regimen (Part IV)	20	160 35	46.02	156.65	58.12	-3.70	46.34
Aspartate Aminotransferase	IU/L	Aprepitant Regimen (Part IV)	20	33.50	12.09	35.57	15.72	2.07	14.84
Bilirubin	mg/dL	Aprepitant Regimen (Part IV)	20	0.36	0.14	0.46	0.21	0.09	0.12
Creatinine	mg/dL	Aprepitant Regimen (Part IV)	20	0.29	0.11	0.30	0.10	0.01	0.06
Glucose	mg/dL	Aprepitant Regimen (Part IV)	20	83.75	10.54	86.56	12.91	2.81	11.07
Parameter	Units	Treatment	N§	Baseline†		Posttreatment‡		Change	
				Mean	SD	Mean	SD	Mean	SD
Potassium	mEq/L	Aprepitant Regimen (Part IV)	20	4.38	0.44	4.07	0.44	-0.31	0.48
Sodium	mEq/L	Aprepitant Regimen (Part IV)	20	138 11	2.60	138.03	3.77	-0.09	2.92
Hemoglobin	gm/dL	Aprepitant Regimen (Part IV)	20	10.44	1.12	9.35	1 26	-1.09	1.02
Leukocytes	10[3]/microL	Aprepitant Regimen (Part IV)	20	7.88	5.93	3.04	1.75	-4.84	6.43
Neutrophils	10[3]/microL	Aprepitant Regimen (Part IV)	9	3.37	2.67	2.43	2.47	-0.94	2.92
Platelet	10[3]/microL	Aprepitant Regimen (Part IV)	20	414 31	229.01	219.85	159.31	-194.46	128.13

Part IV: Day1 – aprepitant 3 mg/kg + ondansetron; Days 2-3 – aprepitant 2 mg/kg + ondansetron.
†Within 1 month of treatment visit
‡Days 5 to 9

7.4.3 Vital Signs

Vital signs (blood pressure, pulse and respiratory rate) were assessed in Cycle 1 of Protocols 208 and 097 at baseline and days 6 to 8 and days 19 to 29. The Applicant noted no pronounced changes in the mean values of vital signs from baseline to days 6 to 8 and days 19 to 29.

In Protocol 134, vital signs (blood pressure, pulse rate and respiratory rate) were assessed at baseline and days 5 to 9. Mean changes were seen in systolic blood pressure in ages 6 years to < 12 years (101.29 to 96); pulse rate in ages 6 months to <2years (111.29 to 120.86) and ages 6 years to <12 years (95.43 to 100.86). Other than these changes, no pronounced changes were observed.

7.4.4 Electrocardiograms (ECGs)

ECGs were obtained in Protocol 208 (cycle 1) and Protocol 134 (part IV). Limited ECG data (PR interval and QTc interval at baseline and discontinuation) were the only

summary statistics provided by the Applicant. The Applicant noted that no significant findings were observed.

7.4.5 Special Safety Studies/Clinical Trials

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

Cases of potential drug-induced liver injury (DILI) were also monitored. The criteria for a potential DILI case was an elevated AST or ALT ≥3X the upper limit of normal (ULN) AND an elevated total bilirubin value ≥2 time the ULN AND, at the same time, an alkaline phosphatase <2X the ULN.

In Cycle 1, the incidences of subjects with ALT >10X and >20X the ULN were higher in the aprepitant group (8/181 [4.4%] and 3/181 [1.7%]) compared to the control group (4/166 [2.4%] and 1/166 [0.6%]). Of those with an elevation >20X the ULN, all 4 subjects were treated with methotrexate, a known hepatotoxic drug. No other hepatic parameter imbalances were noted. See Table 46

There were no subjects in Cycle 1 that met the DILI criteria.

In Cycles 2 to 10, the number of subjects with a liver function test that met predetermined criteria were similar to cycle 1. There were also no subjects that met the DILI criteria.

Table 46: **Subjects with liver function laboratory findings that met predetermined criteria – Protocols 208 and 097 (Cycle 1)**

	Aprepitant Regimen		Control Regimen		Total	
Criteria	n/m	(%)	n/m	(%)	n/m	(%)
Alanine Aminotransferase						
>5 x ULN	12/181	(6.6)	13/166	(7.8)	25/347	(7.2)
≥10 x ULN	8/181	(4.4)	4/166	(2.4)	12/347	(3.5)
≥20 x ULN	3/181	(1.7)	1/166	(0.6)	4/347	(1 2)
Aspartate Aminotransferase						
>5 x ULN	5/181	(2.8)	4/166	(2.4)	9/347	(2.6)
≥10 x ULN	2/181	(1.1)	2/166	(1.2)	4/347	(1 2)
≥20 x ULN	2/181	(1.1)	1/166	(0.6)	3/347	(0 9)
Aminotransferase (ALT or AST)						
>5 x ULN	12/181	(6.6)	13/166	(7.8)	25/347	(7.2)
≥10 x ULN	8/181	(4.4)	5/166	(3.0)	13/347	(3.7)
≥20 x ULN	3/181	(1.7)	1/166	(0.6)	4/347	(1 2)

Bilirubin						
≥2 x ULN	0/179	(0.0)	0/166	(0.0)	0/345	(0.0)
Alkaline Phosphatase						
≥1.5 x ULN	14/178	(7 9)	9/163	(5.5)	23/341	(6.7)
Aminotransferase (ALT or AST) and Bilirubin						
AT ≥3 x ULN and BILI ≥1.5 x ULN	1/181	(0.6)	0/166	(0.0)	1/347	(0 3)
AT ≥3 x ULN and BILI ≥2 x ULN	0/181	(0.0)	0/166	(0.0)	0/347	(0.0)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase						
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	0/181	(0.0)	0/166	(0.0)	0/347	(0.0)

Applicant's table

Table 47 shows the number of subjects in Protocol 134 (part IV) with a liver function test result that met predetermined criteria. The findings were similar to those observed in Protocols 208 and 097. As in Protocols 208 and 097, no subjects in P134 part IV met the DILI criteria.

Table 47: Subjects with liver function laboratory findings that met predetermined criteria – Protocol 134 Part IV

Criteria	Aprepitant Regimen (Part IV)	
	n/m	(%)
Alanine Aminotransferase		
>5 x ULN	1/20	(5.0)
≥10 x ULN	0/20	(0.0)
≥20 x ULN	0/20	(0.0)
Aspartate Aminotransferase		
>5 x ULN	1/20	(5.0)
≥10 x ULN	0/20	(0.0)
≥20 x ULN	0/20	(0.0)
Aminotransferase (ALT or AST)		
>5 x ULN	2/20	(10.0)
≥10 x ULN	0/20	(0.0)
≥20 x ULN	0/20	(0.0)
Bilirubin		
≥2 x ULN	0/20	(0.0)
Alkaline Phosphatase		
≥1.5 x ULN	6/20	(30.0)
Aminotransferase (ALT or AST) and Bilirubin		
AT ≥3 x ULN and BILI ≥1.5 x ULN	0/20	(0.0)
AT ≥3 x ULN and BILI ≥2 x ULN	0/20	(0.0)
Aminotransferase (ALT or AST) and Bilirubin and Alkaline Phosphatase		
AT ≥3 x ULN and BILI ≥2 x ULN and ALP <2 x ULN	0/20	(0.0)

7.4.6 Immunogenicity

Aprepitant is not a peptide or protein. Therefore, immunogenicity studies were not performed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no clear trend of increasing AEs for various aprepitant doses.

7.5.2 Time Dependency for Adverse Events

No explorations for time dependency of adverse events were conducted

7.5.3 Drug-Demographic Interactions

The Applicant reports that no dose adjustment of oral aprepitant is required based on gender.

7.5.4 Drug-Disease Interactions

The Applicant reports that no studies were conducted to specifically investigate the potential for aprepitant to cause or result in drug-disease interactions.

7.5.5 Drug-Drug Interactions

No studies were conducted to investigate drug-drug interactions. The current prescribing information contains extensive information on drug interactions for oral aprepitant in adults. The findings in adults are expected to be relevant to the pediatric population.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See the Pharmacology/Toxicology review for results of animal carcinogenicity studies.

7.6.2 Human Reproduction and Pregnancy Data

The Applicant states that there have not been any prospective studies evaluating aprepitant in pregnant or lactating women. Aprepitant may reduce the efficacy of

hormonal contraceptives; therefore, women of childbearing potential participating in aprepitant clinical studies were advised to avoid pregnancy and were required to use two adequate barrier methods of contraception while participating in clinical studies. There were no reports of pregnancy in Protocols 208, 097, or 134.

A consult was obtained from the DPMH for assistance with review of maternal health labeling subsections 8.1 and 8.2. Dr. Carrie Ceresa conducted a review of published literature on the use of Emend (aprepitant and fosaprepitant) during pregnancy and no information was found. Therefore, there is no safety information in humans to inform the drug associated risk with use during pregnancy. In animal reproduction studies, there is no evidence of fetal harm in rats at exposures 1.6 times the exposure at the recommended adult human dose and in rabbits at 1.4 times the exposure at the recommended adult human dose of 125 mg/day.

Also, no information was identified on the use of Emend and lactation. Therefore, because there is no current safety information to recommend against breastfeeding, the following regulatory statement has been added to subsection 8.2 Lactation as required by the PLLR: The development and health benefits of breastfeeding should be considered along with the mother's clinical need for EMEND and any potential adverse effects on the breastfed infant from EMEND or from the underlying maternal condition. In addition, Dr. Ceresa notes that there are no human data available regarding the effects of Emend on fertility.

The Pregnancy and Lactation subsections of labeling were structured to be consistent with the PLLR. See Dr. Ceresa's full review in DARRTS for further details.

7.6.3 Pediatrics and Assessment of Effects on Growth

Effects on growth were not assessed in Protocols 208 or 097.

Medical Reviewer's comments: Since aprepitant is not for chronic use, effects on growth would not be anticipated.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In the Clinical trials, an overdose was defined as ingestion of a dose of study medication (accidental or intentional) exceeding the specified dose to be administered in each protocol. A total of 11 subjects experienced accidental overdoses (Protocol 208 10 subjects; Protocol 097 one subject). In Protocol 208, five subjects experienced an accidental overdose in Cycle 1 (one subject in the aprepitant regimen; four subjects in the control regimen) and seven subjects experienced accidental overdoses of open-label aprepitant in the extension cycles. Three of the 10 subjects in Protocol 208 experienced more than one overdose in more than one cycle. The maximum reported overdose of aprepitant in Protocol 208 was 2.1-fold over the intended dose. In Protocol

097, one subject in the aprepitant regimen experienced an overdose. The subject overdosed with dexamethasone in Cycle 1. The Applicant states that no associated AEs occurred with any of the accidental overdoses.

There were no reports of overdose in Part IV of Protocol 134.

Aprepitant is intended for short term (3 days) use in the context of concomitant emetogenic chemotherapy. Even though the potential for withdrawal or rebound following chronic use of aprepitant has not been studied, the Applicant states that they are not expected.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

Aprepitant is approved for use in adolescent patients aged 12 to 17 years in Japan. Although aprepitant is only approved for use in adults in other countries, there have been reports of off-label use of aprepitant in the pediatric population.

The Applicant searched the Merck's Adverse Event Reporting and Review System (MARRS) database for postmarketing data on aprepitant use in pediatric patients. The Applicant searched for all postmarketing reports in patients less than 18 year of age from March 26, 2003 through March 25, 2014 with aprepitant as the primary suspect therapy.

A total of 2,555 spontaneous adverse experience reports for aprepitant were identified in the MARRS database from first market approval 26-Mar-2003 through 25-Mar-2014. Of these reports, 39 were pediatric reports; 37 were received from HCP and 2 were received from consumers. The 39 aprepitant reports in the pediatric population contained 73 adverse events. See Tables 48, 49 and 50 below.

Table 48: Aprepitant reports by Age & Gender (March 26, 2003 through March 25, 2014)

Age (years)	Total	Male	Female	Unknown
< 2	1	1	0	0
2 - < 6	7	3	1	3
6 - < 12	12	9	0	3
12 - < 18	19	8	6	5
Total	39	21	7	11

Applicant's table

Outcome was reported for 27 of the 73 adverse events: recovered or recovering in 23, not recovered in 3 and fatal in 1.

The fatal outcome (Case No. 1007USA00085) involved a 17 year old with Ewing's sarcoma with adverse events of constipation, disease progression and off label use. He was receiving unspecified "pain medicine" and developed constipation while receiving aprepitant. On an unspecified date, the patient died due to disease progression.

Reports on serious events are described below:

Case No. 0403USA01430 (tachycardia) - 17 year old male with testicular cancer who developed tachycardia at an unspecified time after administration of one dose of aprepitant (125 mg) and was hospitalized. Concomitant medications were dexamethasone, granisetron and "protonics". Aprepitant was discontinued. The outcome of tachycardia was reported as resolved. Nurse reporter

Case No. 0607GBR00126 (tachycardia, palpitations, sinus bradycardia) - 7 year old male with a history of an episode of "looking blue around the lips followed by facial flashing and palpitation" approximately 1 month prior to aprepitant administration who was prescribed aprepitant 80 mg orally twice daily for cyclic vomiting syndrome. He developed palpitations and tachycardia at an unspecified time after aprepitant administration and was hospitalized. The physician stated that on admission he had sinus bradycardia and the ECG was normal. Concomitant medications were propranolol, dexamethasone, ondansetron and chlorpromazine. Aprepitant therapy was continued. The outcome of tachycardia, palpitations and sinus bradycardia was recovered. The physician stated that he did not know if the patient's sinus bradycardia, tachycardia and palpitation were related to therapy with aprepitant

Case No. 0902USA04062 (drug ineffective) -14 year old female with cyclic vomiting syndrome who, on 21-Feb -2009, was placed on therapy with aprepitant 125 mg, for one day then 80 mg for two day ("tripak") for the treatment of nausea related to migraine headaches. Concomitant therapy included frovatriptan. On 23-Feb-2009, the patient still had nausea. Nurse reported considered the drug ineffective.

Case No. 0704USA00786 (neurotoxicity) - ~ 14-15 year old male with "NF1 gene", peripheral nerve sheath tumor who was prescribed with aprepitant for prophylaxis against CINV. Concomitant therapy included ifosfamide, doxorubicin, ondansetron, and dexamethasone. Two days after starting therapy with aprepitant, the patient experienced neurotoxicity. The patient's symptoms were somnolence and confusion. The patient sought medical attention. No diagnostic studies were performed. The patient was treated with methylene blue. Therapy with aprepitant was discontinued, subsequently the patient improved. Therapy with aprepitant was not reintroduced; no causality assessment was provided in the report.

Case No. 0506USA02386 (hypotension, dyspnea, pruritus) - 15 year old male with osteosarcoma who on 14-Jun-2005 was placed on aprepitant 125 mg one time dose (indication not reported and dose not specified). Concomitant therapy included methotrexate, dexamethasone, and ondansetron The patient was then given an infusion of methotrexate. While he was receiving the infusion of methotrexate, he developed shortness of breath, low blood pressure, and itching. The infusion of methotrexate was stopped. On 14-Jun-2005 therapy with aprepitant was discontinued. The patient was recovering from shortness of breath and low blood pressure and itching. Therapy with aprepitant was not reintroduced. In follow-up, the pharmacist reported that the patient's attending was attempting to rule out anaphylaxis. He stated that the methotrexate was discontinued. He stated that there was a 24 hour break and the patient was restarted on aprepitant. In follow-up, the pharmacist reported that he determined that the patient's experience was not related to aprepitant.

Table 49: Aprepitant – Pediatric Reports by System Organ Class (March 26, 2003 through March 25, 2014)

System Organ Class	Total No. Reports	% Total Reports	Total No. Serious Reports	% Total Serious Reports
Blood and lymphatic system disorders	1	2%	1	11%
Cardiac disorders	2	5%	2	22%
Eye disorders	1	2%	0	0%
Gastrointestinal disorders	4	10%	2	22%
General disorders and administration site conditions	11	27%	2	22%
Injury, poisoning and procedural complications	12	29%	0	0%
Metabolism and nutrition disorders	2	5%	0	0%
Nervous system disorders	3	7%	1	11%
Respiratory, thoracic and mediastinal disorders	4	10%	1	11%
Skin and subcutaneous tissue disorders	2	5%	2	22%
Surgical and medical procedures	21	51%	2	22%
Vascular disorders	1	2%	1	11%
Distinct No. of Reports*	**39**	---	**8**	---

Applicant's table

Table 50: Aprepitant–Most Frequently Reported Adverse Events in Pediatric Patients (March 26, 2003 through March 25, 2014)

Adverse event	No. of adverse events
Off label use	20
No adverse event	5
Drug administration error	4
Drug ineffective	3
Nausea	3
Drug prescribing error	2
Dyspnoea	2
Prescribed overdose	2
Tachycardia	2
Vomiting	2
Wrong technique in drug usage process	2

Applicant's table

Reviewer's comments: The majority of adverse events were reported in adolescents (patients aged 12 to < 18 years) receiving aprepitant for off label use. For the reported post marketing death and serious adverse events, the ability to determine causality is limited by insufficient data. In cancer patients, association between adverse events and aprepitant is also difficult to assess due to cancer and/or concomitant chemotherapy.

9 Appendices

Appendix 1

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 21549/S-025 and NDA 207865

Submission Date(s): NDA 21549 – July 28, 2014; NDA 207865 - March 26, 2015

Applicant: Merck Sharp & Dohme Corp.

Product: Emend (aprepitant)

Reviewer: Karyn L. Berry, MD, MPH

Date of Review: July 20, 2015

Covered Clinical Study (Name and/or Number): Protocol 208, Protocol 097, Protocol 134

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 408		
Number of investigators who are sponsor employees (including both full-time and part-time employees): unknown		
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: NA Significant payments of other sorts: NA Proprietary interest in the product tested held by investigator: NA Significant equity interest held by investigator in sponsor of covered study: NA		
Is an attachment provided with details of the disclosable financial interests/arrangements: NA	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: NA	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: NA	Yes ☐	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry. The applicant provided a list of all investigators/sub-investigators and reported no financial interest to disclose.

9.1 Literature Review/References

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9.2 Labeling Recommendations

Labeling discussions are ongoing at the time of this review. The label will provide information and data to support the use of aprepitant oral capsules in pediatric patients aged 12 (b) (4)

9.3 Advisory Committee Meeting

No Advisory Committee (AC) was held for this submission.

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/s/

KARYN L BERRY
08/17/2015

ANIL K RAJPAL
08/17/2015
I concur with Dr. Berry.