CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207865Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

ONDP BIOPHARMACEUTICS REVIEW ADDENDUM

NDA#:	207865/N000
Submission Date:	07/25/14, 09/12/14, 06/05/15, 06/26/15 (T-con) 07/01/15, and 07/07/15(T-con)
Brand Name:	Emend
Generic Name:	Aprepitant
Formulation:	Oral powder for suspension
Strength:	125 mg/ (b) (4)
Applicant:	Merck
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SYNOPSIS

Biopharmaceutics Review

During the review process, several Biopharmaceutics information requests were conveyed to the Applicant and the Applicant responded on 09/12/14, 06/05/15, 07/01/15, and 07/07/15. T-cons were also held on 06/26/15 and 07/07/15 for the discussions on the proposed dissolution method.

It is concluded that the Applicant:

1. Agreed to explore the Agency's proposed dissolution method with the proposed acceptance criterion (shown in point No. 2 below) as a PMC.

2. Committed within one year post NDA approval to implement the new dissolution test method as shown below to generate new dissolution data to evaluate the feasibility of proposed acceptance criterion of Q = (b) (4)% at 10 minutes.

   Apparatus: **USP Paddle (II) with 50rpm**

   Medium: **Water (with 1.2% Tween80), 900ml at 37± 0.5°C.**

   Acceptance Criterion: **Q= (b) (4)% at 10 minutes.**

3. The expiration dating of the stability batches will need to be reassessed based on data using the new dissolution method from the new stability batches up to 1 year post approval.

4. Will update Section M32P51 Specifications and other related sections to support the new dissolution test method and proposed specification within one year following approval.

5. Agreed to employ their dissolution method (**USP Apparatus 2 (Paddle) x 50 rpm in 900 mL water with 2.4% Tween 80, at 37°C**) with acceptance criterion of Q= (b)(4)% at 20 min for interim analysis for the release and shelf-life testing up to one year post NDA approval.

RECOMMENDATION

From the Biopharmaceutics perspectives, this NDA is acceptable to support the approval of Emend (Aprepitant) oral powder for suspension (125mg/(b)(4)). The Division of Biopharmaceutics is looking forward to reviewing the new dissolution data and to reassess the dissolution acceptance criterion. No further comments are to be sent to the Applicant.

Tienmien Chen -S

Digitally signed by Tienmien Chen -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tienmien Chen -S, 0.9.2342.19200300.100.1.1=13000 73135
Date: 2015.12.03 09:00:43 -05'00'

11/30/15

Tien-Mien Chen, Ph.D.
ONDP/DB Acting Biopharmaceutics Team Leader

Date

Tapash K. Ghosh -S

Digitally signed by Tapash K. Ghosh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13001482 62, cn=Tapash K. Ghosh -S
Date: 2015.12.07 12:32:13 -05'00'

12/01/15

Tapash Ghosh, Ph.D.
ONDP/DB Acting Branch Chief

Date

CC: DARRTS/NDA No.207865/N000/PSeo

Clinical Pharmacology Review Addendum

NDA	21549/S-025; 207865
Submission Date	03/04/2014
Drug	Emend (aprepitant)
Submission Type; Code	Pediatric Supplement
Indication	Prevention of CINV in children 6 months to 12 years (NDA 21549/S-025 Emend Capsules for children 12-17 years/ NDA 207865 Emend Powder for Suspension for children 6 months to 12 years)
Applicant	Merck Sharp & Dohme
OCP-Pharmacometrics Review Team	Jian Wang, Ph.D., Nitin Mehrotra, Ph.D.

The clinical pharmacology review team provides the following summary in support of the approval of weight based dosing for oral suspension formulation in pediatric patients 6 month – 12 years old. The dose of 3 mg/kg on day 1 and 2 mg/kg on day 2 & 3 (3/2/2 mg/kg) in 6 month to 12 year old pediatric patients is acceptable. This was the dosing regimen utilized the registration trial. Please refer to the clinical pharmacology review by Dr. Elizabeth Shang in DAARTS dated 07/20/2015 for more details.

- The sponsor proposed a nomogram based on different weight tiers for ease of dosing in clinical practice to reduce potential dosing errors. In the clinical pharmacology review dated 07/20/2015, the OCP review team concluded that the nomogram based dosing is acceptable. However, since the clinical team considers that the weight based dosing with 3/2/2 mg/kg can be administered accurately in clinical practice, the OCP review team agrees to go without a nomogram.

- The nomogram as developed by the sponsor was based on the 3/2/2 mg/kg regimen applied to the highest weight in each weight tier. It should be pointed out that this was done to avoid underdosing in any patient because efficacy of doses lower than 3/2/2 mg/kg has not been determined. Based on the proposed weight tiered nomogram, the mean simulated systemic exposure was 30% higher that the weight based dosing (3/2/2 mg/kg), which the sponsor considers acceptable based on the overall safety data for aprepitant in adults. There appears to be significant overlap in the distribution of exposures between nomogram-based dosing compared to weight-based dosing. In addition, the mean exposure in adult cancer patients is ~2- fold higher than pediatric exposures.

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

/s/

JIAN WANG
12/02/2015

NITIN MEHROTRA
12/02/2015

Clinical Pharmacology Review Addendum

NDA	21549/S-025; 207865
Submission Date	03/04/2014
Drug	Emend (aprepitant)
Submission Type; Code	Pediatric Supplement
Indication	Prevention of CINV in children 6 months to 12 years(NDA 21549/S-025 Emend Capsules (b) (4) children 12 (b) (4) NDA 207865 Emend Powder for Suspension for children 6 months to 12 years)
Applicant	Merck Sharp & Dohme
OCP PM Review Team	Jian Wang, Ph.D., Nitin Mehrotra, Ph.D.
OCP CP Review Team	Elizabeth Shang, Ph.D. Sue-Chih Lee, Ph.D.

Summary

When review issues related to human factor studies for the aprepitant suspension precluded approval of the suspension formulation in pediatrics less than 12 years, the Clinical Pharmacology review team was asked to evaluate whether pharmacokinetic (PK) data supported modifying the proposed pediatric dosing for the aprepitant capsule to include pediatric patients less than 12 years who weighed at least 30 kg since their weight based dose for the suspension formulation is equivalent to the adolescent (and adult) dose.

In the phase 3 efficacy trial, pediatric patients less than 12 years who weighed at least 30 kg received oral suspension. However, the oral suspension formulation failed the human factor studies, which precluded approval of the suspension. The review team raised the question whether the capsule formulation could be used in patients less than 12 years who weighed at least 30 kg and can swallow oral capsules.

There was no dedicated relative bioavailability study comparing the oral suspension and approved oral capsule formulation. Furthermore, the PK sampling schedule in the efficacy trial also limited the ability to assess the relative bioavailability of the two formulations using non-compartmental analysis approach. Therefore, population PK analysis was conducted to address this question. Please refer to the clinical pharmacology review by Dr. Elizabeth Shang for other details of the NDA review.

The population pharmacokinetics analysis indicated that body weight, age and dose are significant covariates for apparent clearance, and body weight is a significant covariate for apparent volume of distribution. The type of formulation was not found to be a significant covariate on bioavailability. The clearance for patients aged 12 through 17 years was similar to 16 patients aged less than 12 years who weighed at least 30 kg. The median clearance was 4.4 L/h in 48 patients aged 12 through 17 years, and 4.8 L/h in 16 patients aged less than 12 years who weighed at least 30 kg. As a result, no significant difference of aprepitant AUC is anticipated between the two formulations. In addition, when pediatrics less than 12 years who weighed at least 30 kg were included with pediatrics age 12-17 years for the efficacy analysis (see Table 1 provided by Clinical Review), the EMEND arm had better efficacy compared to placebo for the primary and secondary endpoints.

Overall, it was recommended that the available PK data supported extending the dosing using capsule formulation in children less than 12 years who weighed at least 30 kg.

Table 1: Efficacy Endpoint Responses for Patients Aged 12 to 17 Years and Patients less than 12 Years Who Weighed at least 30 kg

	EMEND Regimen n/m (%)	Control Regimen n/m (%)
Patients Aged 12 to 17 Years or Body Weight ≥ 30 kg		
PRIMARY ENDPOINT		
Complete Response* - Delayed phase	31/63 (49.2)	13/69 (18.8)
OTHER PRESPECIFIED ENDPOINTS		
Complete Response* – Acute phase	35/63 (55.6)	26/69 (37.7)
Complete Response* – Overall phase	22/63 (34.9)	9/69 (13.0)

*Complete Response = No vomiting or retching and no use of rescue medication.
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.

Note: Included in this table are 47 subjects 12 to 17 years of age (weight range 28 to 104 kg) and 16 subjects 6 to <12 years of age (weight range 30 to 63 kg) in the EMEND regimen group. The control regimen group includes 48 subjects 12 to 17 years of age (weight range 33 to 135 kg) and 21 subjects 6 to <12 years of age (weight range 30 to 66 kg). The subset of 37 subjects aged 6 to <12 years and weighing ≥30 kg represents 44% of the total number (84) of subjects aged 6 to <12 years included in the efficacy analysis. All subjects aged 12 to 17 years are included here.

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

/s/

JIAN WANG
08/27/2015

ELIZABETH Y SHANG
08/27/2015

SUE CHIH H LEE
08/27/2015

NITIN MEHROTRA
08/27/2015

CLINICAL PHARMACOLOGY REVIEW

NDA	21549/S-025 (Efficacy Supplement)	207865
Submission Dates	7/28/2014, 4/9/2015, 5/20/2015, 6/30/2015	3/26/2015, 4/9/2015, 5/20/2015, 6/30/2015
Brand Name	Emend	Emend
Generic Name	Aprepitant	Aprepitant
Indication	Prevention of acute and delayed CINV MEC and CINV HEC in pediatric patients 12 (b) (4)	Prevention of acute and delayed CINV MEC and CINV HEC in pediatric patients 6 months to less than 12 years
Formulation	Oral capsule	Powder forsuspension
Strengh	80 and 125 mg (already marketed)	125 mg powder for suspension to be reconstituted with 4.6 mL water to a concentration of 25 mg/mL
Proposed Dosing	(b) (4)	(b) (4)
Review Prioity	Standard with Major Amendment	Fast track, priority
Applicant	Merck	
OCP Division	Clinical Pharmacology 3	
Clinical Division	DGIEP (OND-180)	
Reviewer:	Elizabeth Shang, Ph.D., R.Ph.	
Team Leader	Sue-Chih Lee, Ph.D.	
Pharmacometrics Reviewer	Jian Wang, Ph.D.	
Pharmacometrics Team Leader	Nitin Mehtroa, Ph.D.	

TABLE OF CONTENTS

1 Executive Summary

1.1 Background

These two NDAs were submitted to fulfill PREA PMRs. The sponsor is seeking the marketing approval for Emend oral capsules in pediatric patients 12 (b) (4) and oral suspension for 6 months to 12 years old with chemotherapy induced nausea and vomiting (CINV). Supporting studies in patients < 12 years were conducted with a new age appropriate formulation which is an oral suspension (b) (4).

1.2 Recommendation

The Office of Clinical Pharmacology has reviewed both applications and found them acceptable from a clinical pharmacology perspective.

1.3 Summary of Clinical Pharmacology Findings

1.3.1 Age-appropriate pediatric formulation

EMEND™ capsule formulation, which is already approved for adults, involves (b) (4)

(b) (4)

1.3.2 Pediatric Dosing Recommendation

The proposed dosing regimens as shown below are acceptable from a clinical pharmacology perspective.

Adolescents (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.

Children (aged 6 months to less than 12 years): The recommended dose of EMEND for oral suspension (b) (4)

For adolescents, the dose is recommended based upon the acceptable efficacy and safety results from the pivotal Phase 3 study P208 even though the systemic exposures (Cmax and AUC) are lower in adolescents receiving the same dosing regimen as the healthy adults (Study P067) and adult cancer patients (Study P051). The complete response rate in the delayed phase defined as no vomiting or retching and no use of rescue medication, the primary efficacy endpoint, was 51.1% in the aprepitant treatment group comparing to 10.4% in the control group.

For children aged 6 months to less than 12 years, the proposed nomogram dosing per each weight band was not used in any of the clinical studies where a mg/kg weight based dosing regimen was implemented. However, the simulated systemic exposure from nomogram dosing is only 30% higher than the observed exposure from the weight based dosing regimen while the range of exposure between the two regimens were overlapping due to the variability. Thus, the 30% difference was not considered clinically relevant. Furthermore, the range of exposures largely overlapped with exposures achieved in adults with higher variability observed in the pediatric exposures. In addition, the mg/kg weight-based dosing used in Phase 3 study P208 resulted in acceptable efficacy and safety. The overall complete response rate in the delayed phase was 50.5% in the aprepitant treatment group comparing to 33.3% in the control group. Subgroup analysis showed that the complete response rate in the delayed phase was similar across the three different age groups ranging from 46.3% to 55.6% (6 months to < 2 years old, 2 years to < 6 years, and 6 years to < 12 years) in aprepitant treatment group. In all three age groups, the response rates were better than those in control group. For details, refer to Dr. Karyn Berry's Clinical Review.

2 Question Based Review

2.1 General Attributes/Background

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of Emend® in pediatric patients?

This submission is to fulfill PREA PMRs (PMR#1395-7 and 331-1) for Emend oral dosing regimen. The sponsor does not seek pediatric exclusivity for oral Emend, and this submission is not intended to fulfill the Written Request.

The original NDA (021549) for Emend oral capsules was approved on March 27, 2003. Two PREA PMRs were issued:

- PMR 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.

- 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.

2.1.2 What is the formulation of the drug product as it relates to clinical pharmacology and biopharmaceutics review?

To support the use of aprepitant in pediatric patients younger than 12 years of age, an age appropriate formulation i.e. oral suspension, was developed. Each pouch of EMEND for oral suspension contains 125 mg of aprepitant which is to be suspended in 4.6 mL of water giving a final concentration of 25 mg/mL. In clinical trials in patients younger than 12 years old, the oral suspension was administered.

To support the use of aprepitant in pediatric patients 12 to 17 years old, approved oral capsules were studied for its efficacy and safety in this age range.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Adolescents (aged (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.

Children (aged 6 months to less than 12 years): The recommended dose of EMEND for oral suspension (b) (4)

(b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Clinical studies conducted in pediatric patients with CINV are shown in Table 1.
Study P134 and P097 contain PK data. Pivotal phase 3 study P208 does not have PK data.

Table 1. List of the clinical trials conducted in pediatric patients with CINV

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2006-005515-10 [Ref. 5.3.3.2: P134]	I	Australia, Brazil, Canada, Colombia, France, Germany, Hungary, Israel, Mexico, Norway, Peru, Poland, Spain, Sweden, Switzerland, USA	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	Multi-center, open-label, 5-part study	**Part IA:** Subjects 12-17 years of age. Day 1: 115 mg IV fosaprepitant with IV ondansetron ±IV dexamethasone. Days 2 and 3: 80 mg oral aprepitant and IV ondansetron ±IV dexamethasone. **Part IB:** Subjects 12-17 years of age. Day 1: 150 mg IV fosaprepitant with IV ondansetron ±IV dexamethasone. **Part IIA:** Subjects <12 years of age. Day 1: Oral aprepitant dose equivalent to 80 mg in adults with IV ondansetron ±IV dexamethasone. **Part IIB:** Subjects <12 years of age. Day 1: Oral aprepitant dose equivalent to 125 mg in adults with IV ondansetron ±IV dexamethasone. **Part III**: Subjects <12 years of age. Days 1-3: IV ondansetron ±IV dexamethasone. **Part IV:** Subjects <12 years of age. Day 1: Oral aprepitant at a dose equivalent to 125 mg in adults with IV ondansetron ± IV dexamethasone. Days 2 and 3: Oral aprepitant at a dose equivalent to 80 mg in adults with IV ondansetron ± IV dexamethasone. **Part V:** Subjects 6 months to <12 years of age. Day 1: IV fosaprepitant at a dose equivalent to 150 mg in adults with IV ondansetron ±IV dexamethasone.	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.	**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 subjects

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
0869-097 [Ref. 5.3.5.1: P097]	III	Australia, Brazil, United States	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 nausea and vomiting associated with emetogenic chemotherapy in adolescent patients.	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study, Conducted Under In-House Blinding Conditions	**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 **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	Male and female adolescent patients aged 12 to 17 with confirmed malignancies being treated with an emetogenic chemotherapy regimen.	**Cycle 1** Aprepitant regimen: 32 pts Standard Regimen: 18 pts

Trial ID	Phase	Country	Trial Title	Trial design	Dosing regimen	Trial population	Subject exposure
2011-000651-16 [Ref. 5.3.5.1: P208]	III	Worldwide	A Phase III, Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, Conducted Under In-House Blinding Conditions, to Examine the Efficacy and Safety of Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Pediatric Patients	Randomized, Double-Blind, Active Comparator-Controlled Clinical Trial, Conducted Under In-House Blinding Conditions	**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 to 125 mg) + ondansetron Days 2 and 3: aprepitant PFS: 2.0 mg/kg (up to 80 mg)	Males/females Age: 6 months to 17 years scheduled to receive emetogenic chemotherapy for documented malignancy.	**Cycle 1** Aprepitant regimen: 152 pts Control regimen: 150 pts

In addition, the sponsor also submitted a clinical study (P148) containing PK data in patients less than 12 years with post-operative nausea and vomiting (PONV) given oral suspension (b) (4). The PK data were used in population PK analysis. (b) (4)

Table 2. Composition of EMEND™ Capsules and EMEND™ for Oral Suspension Formulations

Component	Function	mg/ 40 mg capsule	mg/ 80 mg capsule	mg/ 125 mg capsule	(b) (4)
Aprepitant	(b) (4)				
Aprepitant	Active Ingredient	40.00	80.00	125.0	
Hydroxypropyl Cellulose (b) (4)					(b) (4)
Sodium Lauryl Sulfate					
[Sucrose (b) (4)					
Microcrystalline Cellulose (b) (4)					
Lactose, (b) (4)					(b) (4)
Gelatin Capsule (b) (4)					(b) (4)
					(b) (4)

Source data: Table 2.7.1:1, Summary of biopharmaceutic studies/associated analytical methods

As the sponsor is not seeking indication of PONV in this submission, individual study review of this study is not conducted in this review cycle.

2.2.2 Exposure-Response Evaluation

2.2.2.1 What are the characteristics of the exposure-response (E-R) relationships (dose-response, concentration-response) for efficacy and safety?

E-R analysis was not performed no systemic exposure data were evaluated in the pivotal phase study P208. The E-R relationship for efficacy and safety are not assessed in adult in the original NDA 21549.

2.2.2.2 Is the proposed fixed dose in 12-17 year pediatrics and body weight based dosing for pediatrics 6 month to 12 years appropriate?

Yes, for adolescents, the proposed dose is appropriate and is recommended based upon the acceptable efficacy and safety results from the pivotal Phase 3 study P208 even though the systemic exposures (Cmax and AUC) are lower in adolescents receiving the same dosing regimen as the healthy adults (Study P067) and adult cancer patients (Study P051). See

Figure 1 in *Appendix 2 – Pharmacometrics Review*. The complete response rate in the delayed phase defined as no vomiting or retching and no use of rescue medication, the primary efficacy endpoint, was 51.1% in the aprepitant treatment group comparing to 10.4% in the control group.

For children aged 6 months to less than 12 years , the proposed nomogram dosing per each weight band was not used in any of the clinical studies where a mg/kg weight based dosing regimen was implemented. However, the simulated systemic exposure from nomogram dosing is only 30% higher than the observed exposure from the weight based dosing regimen while the range of exposure between the two regimens were overlapping due to the variability. Thus, the 30% difference was not considered clinically relevant. In addition, the mg/kg weight-based dosing used in Phase 3 study P208 resulted in acceptable efficacy and safety across various age groups (Table 3).

Table 3. Number (%) of Patients With Complete Response in the Delayed 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	25/45 (55.6)	16/43 (37.2)
6 years to <12 years	19/41 (46.3)	14/43 (32.6)

The systemic exposures obtained with the weight-based dosing regimen in patients 6 months to 12 years and the fixed dosing regimen in adolescents are on the plateau of the established exposure-response relationship for striatal NK-1 receptor occupancy in healthy adults. This observation provides supportive evidence for the adequacy of the proposed dosing regimen from a receptor occupancy perspective. However, it is worth noting that the relationship between NK-1 receptor occupancy and the primary efficacy endpoint of complete response in the delayed phase is unknown.

2.2.3 What are the pharmacokinetic characteristics of aprepitant in pediatric patients with CINV?

The systemic exposures (Cmax and AUC0-24) on Day 1 following the treatment with a three-day regimen were presented in Table 4 below. The adolescents received 125, 80, and 80 mg on Days 1, 2 and 3, respectively. Children 6 months to less than 12 years old received 3, 2, and 2 mg/kg on Days 1, 2, and 3, respectively. Refer to Individual Study Review (*Appendix 1*) for other parameters such as concentrations at 24 hours after 2nd and 3rd day doses.

Table 4. Mean (%CV) Cmax and AUC in Pediatric Patients with CINV following administration of oral aprepitant on Day 1

Age Group (years) (N)	Study ID	Dose Day 1	Formulation	Cmax (ng/mL) (CV%)	AUC0-24hr (hr*ng/mL) (CV%)
0.5 – 2 (N=6)	P134 Part IV	3 mg/kg	Suspension	1810 (51)	21000 (56)
2 – 6 (N=6)				1840 (51)	17300 (29)
6 – 12 (N=7)				1800 (89)	24400[§] (65)
12 – 17 (N=18)	P097	125 mg	Capsule	1269 (60)	16649 (43)
[§] N=6					

2.3 Intrinsic factors

2.3.1 Effect of Age, weight, Sex, Race

Body weight and age are significant covariates for apparent clearance and apparent volume of distribution. Therefore, proposed nomogram dosing per each weight band is reasonable. None of the other factors (sex and BMI) was found to have a significant association with the aprepitant PK parameters that would indicate a clinically relevant effect on aprepitant exposure. About 73 of the patients were Caucasians in the study while 17% patients were of multi-ethnic region making assessment of race as a covariate not feasible.

2.4 General Biopharmaceutics

2.4.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

No dedicated study was conducted to assess the relative bioavailability (b) (4) (b) (4). No capsule was given to patients aged 6 months to 12 years. The capsules were administered to 12 to 17 year olds (Study P097) (b) (4) mg) was also used in the 12 to 17 year olds in a different part of Study P134, however, it was given on Day 2 and Day 3 following Day 1 fosaprepitant IV administration. (b) (4)

2.4.2 What is the food effect?

Approved EMEND™ oral capsules may be administered with or without food. No food effect study was conducted using the oral suspension. Study P208 was conducted without providing specific meal instructions yet achieved satisfactory clinical efficacy and safety. Thus, the food effect, if it exists on oral suspension, is not clinically important.

2.4.3 Did the sponsor use the to-be-marketed formulation in the pivotal clinical trials? Is there any change in formulation during product development?

Yes, to-be-marketed oral suspension formulation (125 mg (b) (4)) was used in the pivotal phase 3 clinical trial (P208). No formulation change has occurred during the drug development for this product.

3 Labeling Recommendations

Labeling revisions are ongoing. Please refer to the final approved labeling when available. Detailed recommendations will be sent to the sponsor regarding the correct formatting and organization as well as the content related to Highlights, Dosage and Administration, Drug Interactions, Specific Populations as well as Clinical Pharmacology sections of the PLR labeling. The following labeling language different from sponsor's original proposals is recommended by OCP (b) (4)

- 12.3 Pharmacokinetics
  Age: Pediatric Population
  The results will be limited to adolescents 12 to 17 years old only because only capsules will be approved during this review cycle..

4 Appendices

4.1 Appendix 1 – Individual Study Review

4.1.1 Study P097

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.

Study Design: This is a randomized, double-blind, controlled with parallel design study in adolescent patients aged 12 to 17 years old. Approved aprepitant capsules were used. The protocol had 2 parts:

- Part One had 2 components with 2 dosing regimens: standard therapy regimen and aprepitant three-day regimen. The first component 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, which was not blinded, had 2 components with 1 dosing regimen: aprepitant three-day regimen 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).

Reviewer's comment: All the patients in the study were administered either aprepitant or ondansetron as well as dexamethasone. See treatment group below. Apprepitant placebo was given to maintain blinding.

Treatment groups:

- Aprepitant three-day 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 Days 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 Days 1 and 2 plus dexamethasone 16 mg P.O. on Day 1 and 8 mg P.O. once daily on Days 2 to 4.

Pharmacokinetic analysis:
Blood samples for PK were collected in Cycle 1 for 72 hours at: predose (-2 hours), 1 (immediately prior to chemotherapy infusion), 2, 3, 4, 8, 12, 24, 48 (Day 2), and 72 (Day 3) hours.

Bioanalytical method: The method used in this study (DM-359O) was previously used to support the original NDA for aprepitant oral capsules. Refer to original NDA review.

Pharmacokinetic Results:
Demographics

Baseline Patient Characteristics by Treatment Group

		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 data: Table 10-5, Clinical study report of P097.

Summary of PK parameters

Descriptive Summary of the PK parameters estimated by non-compartmental analysis is shown below:

	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 data: Reviewer's analysis based upon individual parameters submitted.

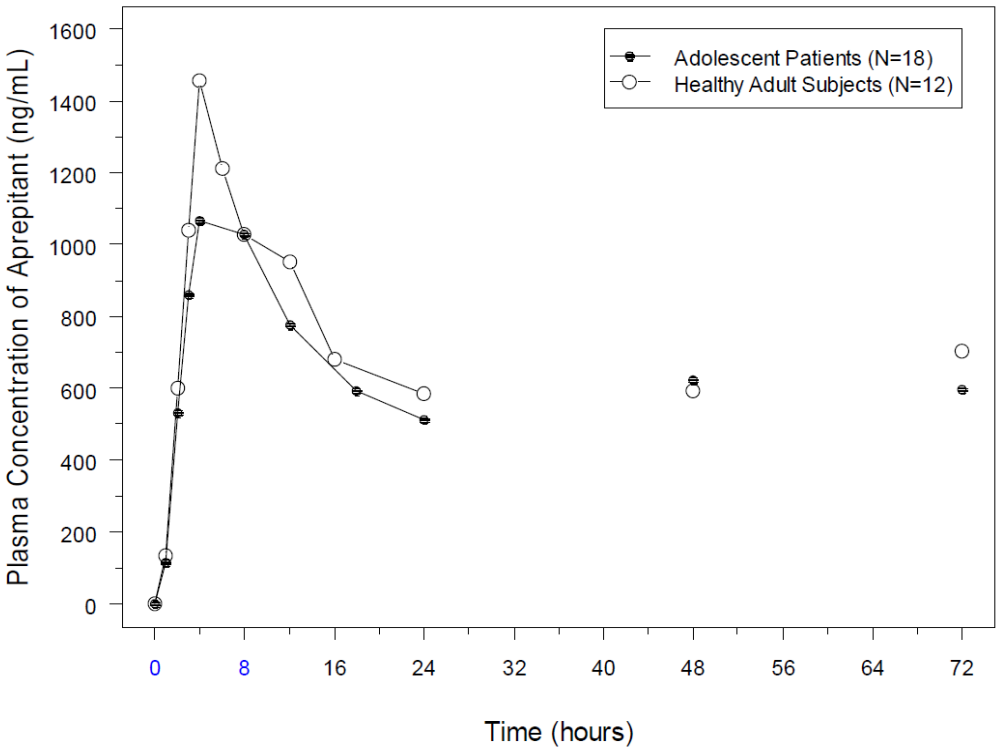
A cross study comparison to those from healthy adult subjects who had same three-day regimen (Study P067 previously conducted to support the original NDA) was performed. The Cmax and AUC0-24hr in adolescents were 24% and 30% lower than those in healthy adult subjects. See the table and figure below.

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 data: Table 11-1, Clinical Study Report of P097.

Mean Plasma Concentrations of Aprepitant in Adolescent Patients
And Healthy Adult Subjects Following a 3-day Aprepitant Regimen



Source data: Figure 11-1, Clinical Study Report of P097

Reviewer's comments: The systemic exposures (Cmax and AUC0-24hr) in adolescent patients with CINV were lower than that in healthy adults following same three-day regimen with oral capsules. However, this is a cross study comparison between two different

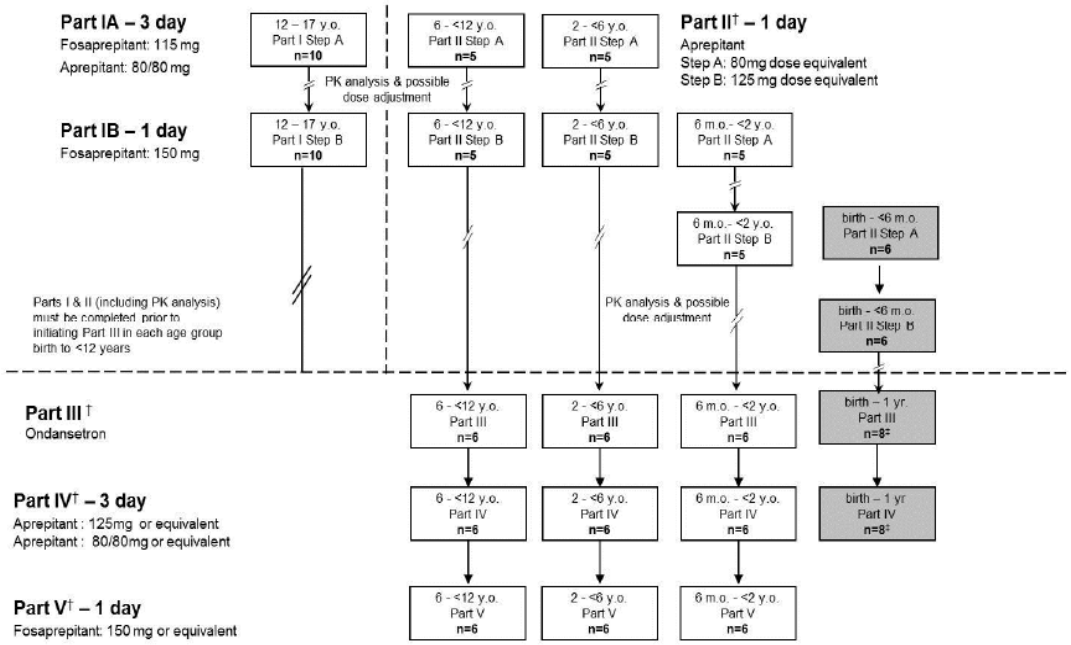
populations with different ages and health status. A more comprehensive exposure comparison was made via population PK analysis on pooled data including this study. Refer to Population PK review in Appendix 2.

4.1.2 Study P134

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

Study Design: 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. The oral formulation used in this study was suspension (b) (4).

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 (as applicable) but they were not required to do so; none were collected. Shaded cohorts were not enrolled.

Treatment groups summarized by the reviewer:

						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.

Reviewer's comment: Only PK data from PO aprepitant regimens (Part II and IV) are reviewed here as they are relevant to the approval of oral suspension in this NDA.

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.

Bioanalytical method and results: Aprepitant (MK-0869) was measured by an adequately validated high performance liquid chromatography with tandem mass spectrometric detection (HPLC-MS/MS) with acceptable accuracy and precision. The lowest limit of quantification (LLOQ) was 10.000 ng/mL. The detection ranged from 10.000 to 2500.000 ng/mL. [Triazolone-$^{13}C_2$,$^{15}N_3$] MK-0869 is used as an internal standard.

The method (09BASM032V2) used in this study was modified based upon a previous (DM-359O) method used to support the original NDA for aprepitant oral capsules. The assay procedures have the same LLOQ of 10.000 ng/mL. There were minor differences in sample volume, sample extraction, internal standard, linear range and detection conditions.

The major analytical characteristics of this modified method are presented below.

	N	Mean (%)
Intra-day Accuracy with Quality Control Samples[a]	5	99.6 – 103.7
Intra-day Precision (CV) with Quality Control Samples[a]	5	1.2 – 2.0
Inter-day Percent Difference with Calibration Standards[b]	9	-3.0 – 2.3
Inter-day Precision (CV) with Calibration Standards[b]	9	1.3 – 3.9
Inter-day Accuracy with Quality Control Samples[b]	18	92.6 – 95.9
Inter-day Precision (CV) with Quality Control Samples[b]	18	4.2 – 5.2
Absolute Matrix Effect[a]	6	99.4 – 103.0
Accuracy of Dilution Integrity (25,000 ng/mL, 20X)[a]	5	97.5
Precision (CV) of Dilution Integrity[a]	5	1.2
Percent of Nominal of Reinjection Integrity of Quality Controls after 3 Days Stored at 8 °C[a]	5	-2.8 – 2.2
Precision (CV) of Reinjection Integrity of Quality Controls after 3 Days Stored at 8 °C[a]	5	1.0 – 2.6
Difference from Control for Quality Control Samples after 3 Freeze (at -20°C)/Thaw Cycles[a]	5	-0.7 – 2.3
Precision (CV) of Quality Control Samples after 3 Freeze (at -20°C)/Thaw Cycles[a]	5	1.0 – 2.9
Difference from Control for Quality Control Samples after Room Temperature Storage for 19 Hours[a]	3	-1.5 – 1.1
Precision (CV) of Quality Control Samples after Room Temperature Storage for 19 Hours[a]	3	0.2 – 2.3
Difference from Nominal for Processed Samples Assayed after 3 Days Stored in the Autosampler[a]	5	2.7 – 6.9
Precision (CV) of Processed Samples after 3 Days Stored in the Autosampler[a]	5	1.0 – 2.6
Difference from Initial of Long-Term Storage Stability Quality Control Samples (106 Days): -20°C	5	5.5 – 7.6

a Data from assay validation report 09BAS0015 (b) (4) [appended to the bioanalytical report for Protocol 148]

b Representative data from the bioanalytical report for Protocol 148 (Approximately 450 samples analyzed in 9 runs, (b) (4) Study No. 09BAS0075)

Pharmacokinetic Results:

Demographics:

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)

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)

Summary of PK parameters – Part II

Patients received single oral dose of either 47 mg/m^2 or 74 mg/m^2.

The descriptive statistics of the PK parameters estimated by non-compartmental analysis in different age bands (6mon - 2yr, 2-6 years, 6 to 12 years) receiving 47 mg/m^2 dose were provided in the table below.

	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL/F (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	AUC_{0-48hr} (hr*ng/ml)	AUC_{0-72hr} (hr*ng/ml)	$AUC_{0-\infty}$ (hr*ng/ml)
6-Month- to <2-Year-Olds											
N	5	5	5	5	5	5	5	5	5	5	5
AM	1930	2.33	480	52.3	--↓	7.28	1200	20000	24500	25000	25100
SD	1000	1.16	253	63.8	--↓	1.47	1080	7890	9930	10200	10400
Min	731	1.50	41.0	BLQ	BLQ	5.22	590	6460	6950	6950	6770
Median	1840	1.58	533	38.3	BLQ	7.79	725	23400	28500	29400	29500
Max	3320	4.07	659	162	15.3	8.84	3120	26100	31200	31400	31700
"CV%	51.9	49.9	52.6	122	--↓	20.2	90.4	39.4	40.5	40.8	41.3
HM	1480	1.97	160	--	--	7.02	828	15300	17700	17900	17700
Pseudo SD	1120	0.76	803	--	--	1.65	341	16300	22700	23500	24200
GM	1710	2.13	345	--	--	7.16	952	18000	21700	22100	22000
*CV%	63.7	49.27	178	--	--	21.7	76.8	63.5	71.0	72.2	74.2
2- to <6-Year-Olds											
N	8	8	7	7	6	6	6	8	8	7	6
AM	1300	3.78	262	70.7	--↓	8.27	2040	16400	18900	20000	19200
SD	609	1.92	200	108	--↓	2.67	1050	8080	9650	11400	12700
Min	803	1.50	78.0	BLQ	BLQ	5.65	885	8080	9220	9220	8990
Median	948	3.58	215	14.3	BLQ	7.34	1820	13000	17300	15200	15100
Max	2280	8.00	678	262	246	13.0	3340	29700	39100	41800	42800
"CV%	46.7	50.8	76.5	153	--↓	32.3	51.5	49.1	51.0	57.3	66.3
HM	1100	3.09	169	--	--	7.68	1600	13500	15500	15600	14500
Pseudo SD	416	1.68	131	--	--	2.06	909	6120	7400	8000	7310
GM	1190	3.41	209	--	--	7.95	1810	14800	17000	17600	16400
*CV%	46.5	50.66	83.0	--	--	30.4	58.8	51.1	51.2	58.6	63.9
6- to <12-Year-Olds											
N	6	6	6	6	6	5	5	6	6	6	5
AM	1300	5.17	365	56.6	--↓	9.17	2890	16000	20200	21000	21700
SD	275	1.83	477	108	--↓	4.00	1160	4810	10200	11500	13200
Min	853	3.00	81.4	BLQ	BLQ	5.83	1430	8820	9790	9790	9520
Median	1310	5.00	171	13.3	BLQ	7.84	2710	15900	17800	17800	18100
Max	1700	8.00	1330	274	62.2	15.3	4310	23900	39900	43400	44300
"CV%	21.1	35.5	131	190	--↓	43.7	40.2	30.1	50.5	54.8	60.9
HM	1250	4.65	171	--	--	8.01	2480	14700	17100	17400	17100
Pseudo SD	327	1.71	126	--	--	2.98	1280	5610	7800	8230	9620
GM	1280	4.90	226	--	--	8.54	2690	15300	18500	18900	19100
*CV%	23.0	37.12	123	--	--	43.2	46.1	32.8	47.3	50.5	59.4

Pseudo SD = Jackknife estimate of the standard deviation of the harmonic mean.

N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation.

BLQ = Below limit of quantitation (<10.0 ng/mL); BLQ values have been considered as zero for calculation of descriptive statistics.

Min: Minimum; Max: Maximum; GM: Geometric Mean; HM: Harmonic Mean.

"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.

*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

#: (Apparent) terminal half-life.

↓ Not reportable since <50% of the concentration results ≥ Lower Limit of Quantitation (LLOQ).

The descriptive statistics of the PK parameters estimated by non-compartmental analysis in different age bands receiving 74 mg/m^2 dose (2-6 years, 6 to 12 years) or 1.3 mg/kg (6 mon to 2 years) dose were provided in the tables below.

	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL/F (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	AUC_{0-48hr} (hr*ng/ml)	AUC_{0-72hr} (hr*ng/ml)	$AUC_{0-\infty}$ (hr*ng/ml)
6-Month- to <2-Year-Olds dose=1.3 mg/kg											
N	5	5	5	5	5	3	3	5	5	4	3
AM	659	3.45	89.2	--↓	BLQ	8.09	1680	6310	7270	8030	7770
SD	107	2.89	93.8	--↓	--↓	2.54	405	2040	3010	3310	4180
Min	508	1.50	BLQ	BLQ	BLQ	5.94	1220	4660	4820	5280	5210
Median	665	1.57	52.1	BLQ	BLQ	7.42	1870	5170	5630	7230	5500
Max	795	8.00	240	41.7	BLQ	10.9	1960	9240	11900	12400	12600
"CV%	16.2	83.8	105	--↓	--↓	31.5	24.1	32.3	41.4	41.3	53.9
HM	644	2.16	--	--	--	7.60	1610	5850	6470	7130	6620
Pseudo SD	114	1.21	--	--	--	2.23	492	1620	2150	2630	2510
GM	651	2.65	--	--	--	7.83	1650	6070	6830	7550	7120
*CV%	16.8	92.30	--	--	--	31.4	26.7	31.6	39.9	41.8	52.7
2- to <6-Year-Olds dose=74mg/m2											
N	7	7	7	7	7	4	4	7	7	6	4
AM	2100	5.28	400	--↓	BLQ	6.06	1870	23000	26800	28600	29100
SD	1170	1.97	287	--↓	--↓	3.03	1150	8390	9070	8800	11100
Min	1350	2.98	56.5	BLQ	BLQ	3.60	1140	12200	12900	12900	12600
Median	1450	6.00	499	BLQ	BLQ	5.16	1380	25300	31100	32000	33500
Max	4360	7.95	822	114	BLQ	10.3	3580	33000	36700	36900	36900
"CV%	55.4	37.3	71.9	--↓	--↓	50.0	61.3	36.5	33.9	30.8	38.3
HM	1740	4.60	171	--	--	5.15	1530	20200	23400	25200	24000
Pseudo SD	624	1.95	243	--	--	2.13	576	8530	11200	14200	19100
GM	1890	4.94	279	--	--	5.56	1670	21600	25200	27100	26900
*CV%	49.7	41.91	140	--	--	49.5	55.8	40.9	41.3	40.7	54.2
6- to <12-Year-Olds dose=74mg/m2											
N	6	6	6	6	6	6	6	6	6	6	6
AM	1930	3.08	460	22.7	BLQ	6.89	4080	22000	25500	25700	25800
SD	873	0.95	301	15.5	--↓	1.35	1730	9440	11200	11300	11400
Min	640	1.42	57.1	BLQ	BLQ	4.54	2750	10800	11500	11500	11100
Median	2050	3.03	480	23.2	BLQ	6.96	3250	23600	27700	28000	28200
Max	3030	4.00	970	47.4	BLQ	8.73	6910	34400	40700	41000	41100
"CV%	45.3	30.7	65.4	68.4	--↓	19.6	42.5	42.9	44.0	44.0	44.4
HM	1480	2.73	213	--	--	6.63	3600	18100	20700	20800	20700
Pseudo SD	1250	1.48	561	--	--	1.69	1180	9980	12100	12300	12600
GM	1720	2.92	349	--	--	6.77	3810	20100	23100	23300	23300
*CV%	61.8	39.49	124	--	--	21.8	40.4	52.1	54.2	54.4	55.5

Pseudo SD = Jackknife estimate of the standard deviation of the harmonic mean.

N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation.

BLQ = Below limit of quantitation (<10.0 ng/mL); BLQ values have been considered as zero for calculation of descriptive statistics.

Min: Minimum; Max: Maximum; GM: Geometric Mean; HM: Harmonic Mean.

"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.

*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

#: (Apparent) terminal half-life.

↓ Not reportable since <50% of the concentration results ≥ Lower Limit of Quantitation (LLOQ).

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). See the comparison table made by the reviewer below.

Table 5. Geometric mean of Cmax and AUC (Day1) in children and adults following oral administration of aprepitant oral suspension and 125 mg capsules, respectively

Age range (years)	Dose	Median Dose (Min, Max) converted to mg/kg	Cmax (ng/mL)	AUC0-24hr (hr*ng/mL)
0.5 – 2 (N=5)	1.3 mg/kg	1.3	651	6070
2 – 6 (N=7)	74 mg/m^2	3.3 (3.1, 3.4)	1890	21600
6 - 12 (N=6)	74 mg/m^2	2.4 (1.6, 3.0)	1720	20100
Adults (N=12)[ǂ]	125 mg	N/A	1539	19455
ǂ Study P067				

Reviewer's comments: The comparison to adults is a cross study comparison between two different populations with different ages and health status. A more comprehensive exposure comparison was made via population PK analysis on pooled data including this study. Refer to Population PK review in Appendix 2

Summary of PK parameters – Part IV

Patients received three-day oral regimen of 3/2/2 mg/kg in the study.

The descriptive statistics of the PK parameters estimated by non-compartmental analysis in different age bands (6mon - 2yr, 2-6 years, 6 to 12 years) were provided in the table below.

	Cmax (ng/ml)	Tmax (hr)	C_{24hr} (ng/mL)	$t_{½}^{\#}$ (hr)	CL/F (ml/hr)	AUC_{0-24hr} (hr*ng/ml)	C_{48hr} (ng/mL)	C_{72hr} (ng/mL)
6-Month- to 2-Year-Olds								
N	6	6	6	3	2	6	6	6
AM	1810	7.34	538	6.18	1910	21100	376	476
SD	925	8.28	490	4.12	962	11800	476	748
Min	550	2.52	53.7	3.09	1230	8170	BLQ	BLQ
Median	1700	4.50	465	4.59	1910	19500	158	73.2
Max	3230	24.00	1280	10.9	2600	40800	1180	1840
"CV%	51.0	113	91.1	66.7	50.2	56.0	126	157
HM	1330	4.13	145	4.73	1670	16100	--	--
Pseudo SD	1260	2.40	216	2.77	962	10200	--	--
GM	1590	5.13	301	5.36	1790	18400	--	--
*CV%	67.2	100.33	233	71.4	56.4	63.1	--	--
2- to <6-Year-Olds								
N	6	6	6	5	4	6	6	6
AM	1840	4.92	279	9.21	2930	17300	124	120
SD	933	2.20	152	5.57	1390	5060	134	78.1
Min	1130	2.52	75.8	5.24	1760	10500	17.7	51.3
Median	1510	4.50	275	6.76	2660	17300	53.2	83.3
Max	3670	9.00	464	18.5	4620	24100	332	261
"CV%	50.7	44.6	54.4	60.4	47.5	29.3	108	65.1
HM	1590	4.26	191	7.39	2470	16000	45.0	90.9
Pseudo SD	517	1.83	198	3.12	1110	5380	49.8	47.3
GM	1690	4.57	237	8.15	2690	16600	71.5	103
*CV%	43.3	43.46	77.3	56.8	51.1	31.7	171	63.7
6- to <12-Year-Olds								
N	7	7	6	4	2	6	6	7
AM	1800	6.42	711	10.8	3870	24400	673	768
SD	1610	7.84	636	4.27	553	15800	755	1110
Min	988	1.50	94.0	5.45	3480	11200	46.8	22.3
Median	1150	4.00	552	11.5	3870	18100	402	229
Max	5410	24.00	1700	14.7	4260	50900	2020	2730
"CV%	89.4	122	89.6	39.6	14.3	64.6	112	144
HM	1310	3.39	270	9.26	3830	18100	163	64.5
Pseudo SD	461	2.55	388	5.34	553	9330	362	91.8
GM	1470	4.32	451	10.1	3850	20800	342	201
*CV%	66.0	104.04	163	48.0	14.4	66.7	246	673

Pseudo SD = Jackknife estimate of the standard deviation of the harmonic mean.

N: Number of observations; AM: Arithmetic Mean; SD: Standard Deviation; HM: Harmonic Mean.

Min: Minimum; Max: Maximum; GM: Geometric Mean.

"CV%: Arithmetic Coefficient of Variation, where "CV% = SD/AM*100.

*CV%: Geometric Coefficient of Variation, where *CV% = 100xsqrt(exp(S^2)-1) and S^2 is the observed variance on the natural log-scale.

#: (Apparent) terminal half-life.

C24 refers to concentration 24hr after start chemotherapy (i.e. 25hr post aprepitant administration).

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). See the comparison table made by the reviewer below.

Table 6. Geometric mean of Cmax and AUC (Day1) in children and adults following oral administration of 3 mg/kg and 125 mg aprepitant, respectively

Age range (years)	Dose	Cmax (ng/mL)	AUC24 (hr*ng/mL)
0.5 – 2	3 mg/kg	1590	18400
2 - 6	3 mg/kg	1690	16600
6 - 12	3 mg/kg	1470	20800
Adults‡	125 mg	1539	19455
‡ Study P067			

Reviewer's comments: The comparison to adults is a cross study comparison between two different populations with different ages and health status. A more comprehensive exposure comparison was made via population PK analysis on pooled data including this study. Refer to Population PK review in Appendix 2.

4.2 Appendix 2 – Pharmacometrics Review

Table of contents

List of Tables

List of Figures

Summary of Findings

1.1 Key Review Questions

The purpose of this review is to address the following key question.

1.1.1 Is the proposed fixed dose in 12-17 year pediatrics and body weight dosing for pediatrics 6 month to 12 years appropriate?

Yes, the proposed dosing regimen is reasonable based on the following three rationales:

- PK rationale

The results of PopPK model simulation support the dosing recommendations provided in the original application.

Adolescents (aged 12 (b) (4) The Applicant proposed dose of capsules of EMEND is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3, which is the same as implemented in clinical trials for this age group.

Children (aged 6 months to less than 12 years): The Applicant proposed dose of EMEND for oral suspension (b) (4) A nomogram is proposed to mimic the weight-based dosing regimen implemented in Phase 3 (3.0 mg/kg on Day 1 followed by 2.0 mg/kg on Days 2 and 3) for patients 6 months to 12 years of age, which would simplify calculation of the dose to improve ease of use in in clinical practice. It is expected to reduce the potential for dosing errors and dispensing complexities, when delivered with a single oral dispenser, while maintaining the excellent efficacy and safety profiles established in the pediatric clinical trials.

Simulation results indicated that the differences in PK values with the nomogram compared to strict weight-based dosing are modest and unlikely to be clinically relevant. 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. 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 considerable data demonstrating acceptable tolerated in the pediatric clinical trials. In general, the variability in pediatric patients are higher than in adults and the range of exposure in pediatric are highly overlapped between the proposed nomogram regimen and individual body weight based regimen studied in clinical trials.

Table 1. The Applicant proposed dose of EMEND for oral suspension for pediatric patients aged 6 months to less than 12 years

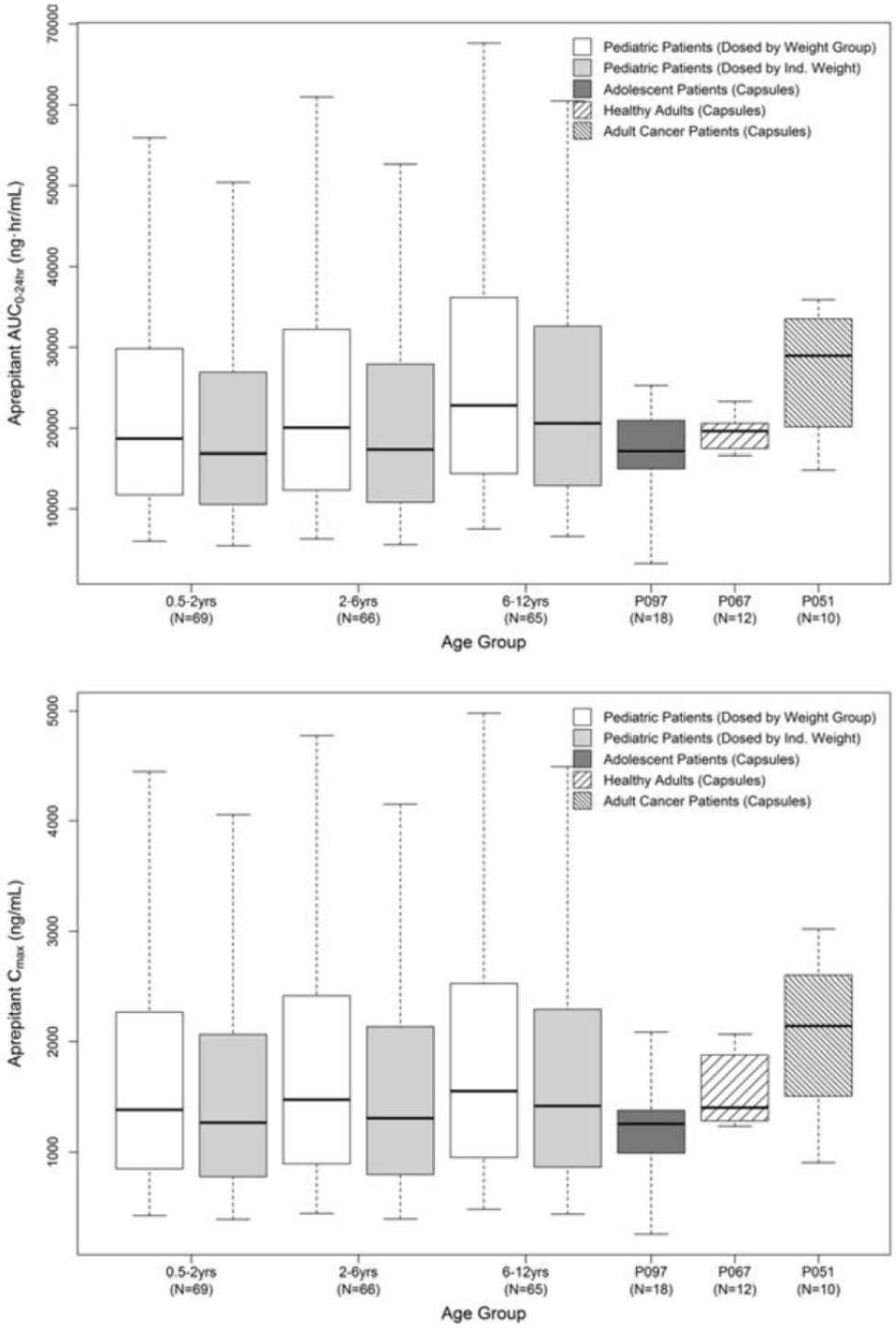


Figure 1. Simulated Aprepitant $AUC_{0\text{-}24hr}$ (Top Panel) and C_{max} (Bottom Panel) on Day 1 in Different Age Groups Using Individualized Dosing and Nomogram Dosing Table Compared With Observed Aprepitant Exposures in Adolescents, Healthy Adults and Adult Patients

- PKPD relationship:
  Based upon the PKPD relationship (refer to Pharmacometrics review Section 4) for NK-1 receptor occupancy, the pharmacokinetic profile obtained with the weight-based regimen in patients 6 months to 12 years (3.0 mg/kg on Day 1 followed by 2.0 mg/kg on Days 2 and 3) and the fixed dose regimen in adolescents (125 mg on Day 1 followed by 80 mg on Days 2 and 3) result in aprepitant exposures, across the 3-day treatment period, that are on the plateau of the exposure-response relationship NK-1 receptor occupancy. This relationship provides supportive evidence for the adequacy of dose. It is important to note however that the relationship between NK-1 receptor occupancy and primary end point in not known.

- Observed efficacy and safety in the phase 3 trial:
  The mg/kg weight-based dosing evaluated in the phase 3 study P208 resulted in acceptable efficacy and safety. The overall complete response rate in the delayed phase was 50.5% in the aprepitant treatment group comparing to 33.3% in the control group. Subgroup analysis by age showed that the complete response rate in the delayed phase was similar across the three different age groups ranging from 46.3% to 55.6% (6 months to < 2 years old, 2 years to < 6 years, and 6 years to < 12 years) in aprepitant treatment group. In all three age groups, the response rates were better than those in control group. For details, refer to Dr. Karyn Berry's Clinical Review.

1.2 Label Statements

Refer to Section 3 of Question Based Review for details.

2 Pertinent regulatory background

EMEND™ (aprepitant) is an antagonist of human substance P neurokinin 1 (NK1) receptors that, in combination with other antiemetic agents including a 5-HT3 receptor antagonist and a corticosteroid, is approved for the prevention of acute and delayed nausea and vomiting due to highly emetogenic and moderately emetogenic cancer chemotherapy in adults . To support the use of aprepitant (EMEND) in pediatric patients 6 months to 17 years of age, an efficacy supplement is being submitted to NDA 21549 (EMEND capsules) (b) (4) (b) (4) 207865). The proposed update to the EMEND product label is supported by a single pivotal Phase 3 efficacy/safety study conducted in patients 6 months to 17 years of age in which both capsule and powder for suspension formulations were evaluated. Based on this study, the Applicant is proposing an indication for use of EMEND in the prevention of acute and delayed nausea and vomiting due to highly and moderately emetogenic cancer chemotherapy in patients 6 months to 17 years.

3 Population pharmacokinetics Analysis

3.1 Sponsor's Analysis

3.1.1 Objectives

- Update the existing population PK model of MK-869/MK-517 using final clinical data from protocols P097, P134 and P148 and assess the impact of key covariates in CINV / PONV patients;
- Evaluate the updated population PK model to insure its accuracy, precision and robustness;
- Perform a model-based simulation to predict exposure of aprepitant in two targeted age groups of pediatric patients, 0.5 – 12 years (oral suspension 3/2/2 mg/kg QD on Days 1/2/3) and 12-17 years (capsules 125/80/80 mg QD on Days 1/2/3).

3.1.2 Data Sets

The final data from 3 pediatric studies were used in this analysis:

- Protocol P097 CINV, a PK/PD study in adolescents aged 12 – 17 years receiving the adult 3-day oral dosing regimen (final market capsules, 125 mg on Day 1, 80 mg on Days 2-3);
- Protocol P134 CINV, a study in adolescents aged 12 – 17 years receiving the adult 3-day
  IV EMEND regimen (115 mg IV EMEND on Day 1, 80 mg oral suspension EMEND on Days 2-3), and single doses of aprepitant as oral suspension to pediatric patients aged 6 months – 12 years (doses adjusted by body size);

- Protocol P148 PONV, a study in adolescents aged 12 – 17 years receiving the adult 40 mg capsule single dose, and pediatrics aged 2 – 12 years receiving single doses of aprepitant as oral suspension (doses adjusted by body size).

A total of 148 subjects completed study procedures in the 3 clinical studies (P097 N=18, P134 N=85, P148 N=45). Descriptive statistics of continuous and categorical covariates in pediatric subjects are summarized by age group in the following tables. A total of 1326 plasma measurable concentrations were included in the analysis.

Table 2. Descriptive Statistics of Continuous Covariates in Pediatric Subjects by Age Group Included in the Population PK Analysis

Covariate	Number of Subjects Mean (CV%) Median [Min – Max]				
	0.5-2 yrs	2-6 yrs	6-12 yrs	12-19 yrs	Overall
Age (years)	n = 30 1.2 (40.5%) 1.2 [0.5-1.9]	n = 35 3.8 (34.2%) 3.7 [2-5.9]	n = 32 9.1 (19.0%) 9.3 [6-11.9]	n = 50 14.7 (11.8%) 14.7 [12–19]	n = 147 8.1 (69.0%) 7.9 [0.5–19]
Weight (kg)	n = 30 10.1 (17.9%) 10.1 [7-14.3]	n = 35 15.3 (20.7%) 14.8 [10.5-23.4]	n = 32 31.1 (29.2%) 30 [15.9-48.3]	n = 50 55.8 (26.3%) 54.2 [32–104]	n = 147 31.4 (67.6%) 25 [7–104]

Source: Sponsor's Population PK Report, Page 19

Table 3. Descriptive Statistics of Categorical Covariates of Pediatric Subjects by Age Group Included in the Population PK Analysis

Covariate		Count (%) of Subjects in Sub-Populations				
		0.5-2 yrs	2-6 yrs	6-12 yrs	12-19 yrs	Overall
Sex	Male	17(56.7%)	12(34.3%)	16(50.0%)	30(60.0%)	75(51.0%)
	Female	13(43.3%)	23(65.7%)	16(50.0%)	20(40.0%)	72(49.0%)
Race	White	22(73.3%)	29(82.9%)	28(87.5%)	33(66.0%)	112(76.2%)
	Black	1(3.3%)	0(0.0%)	2(6.3%)	5(10.0%)	8(5.4%)
	Asian	1(3.3%)	0(0.0%)	0(0.0%)	1(2.0%)	2(1.4%)
	Native American	1(3.3%)	0(0.0%)	0(0.0%)	1(2.0%)	2(1.4%)
	Multi-Ethic	5(16.7%)	6(17.1%)	2(6.3%)	10(20.0%)	23(15.6%)
Population	CINV	18(60%)	24(68.6%)	20(62.5%)	41(82.0%)	103(70.1%)
	PONV	12(40%)	11(31.4%)	12(37.5%)	9(18.0%)	44(29.9%)
Formulation	IV Solution	2(6.7%)	3(8.6%)	1(3.1%)	23(46.0%)	29(19.7%)
	Oral Capsules	0(0.0%)	0(0.0%)	0(0.0%)	18(36.0%)	18(12.2%)
	Oral Suspension	28(93.3%)	32(91.4%)	31(96.9%)	9(18.0%)	100(68.0%)

Source: Sponsor's Population PK Report, Page 19

3.1.3 Model

The final population PK model included the following covariate effects:

• effect of age (CYP3A4 maturation) on systemic clearance (CL):

$\times(0.639 \times Age / (2.4+Age)+0.42)$

• effect of body weight on clearance (CL and Q) normalized to 70 kg to a power of 0.75:

$\times(\text{Weight}/70)^{0.75}$

• effect of body weight on volumes (V2 and V3) normalized to 70 kg:

$\times(\text{Weight}/70)$

• effect of dose on systemic clearances (CL) normalized to 80 mg to a power of -0.394:

$\times(\text{Dose}/80)^{-0.394}$

Based on these equations, the typical value of systemic clearance (CL) derived from the final population PK model of aprepitant represents an individual of 23.5 years old with body weight of 70 kg who received oral aprepitant dose of 80 mg. The clinical relevance of the dose effect on systemic clearance can be illustrated by the following example. For a typical adolescent patient receiving oral capsule administration of aprepitant (P097, median weight = 54.6 kg and median age = 15 yrs), the predicted CL will be 16% lower after 125 mg dose (4.27 L/hr) than after 80 mg dose (5.09 L/hr).

Table 4. Typical Population PK Parameters of Aprepitant in Pediatric Population – Final Population Pharmacokinetic Model

Parameter	Units	Estimate	SE	RSE	Shrink	Equation
OFV		-2352.21				
CL	L/hr	6.32	0.523	8.3%		$CL = tvCL \times (0.639 \times Age/(2.4+Age)+0.42) \times (Weight/70)^{0.75} \times \exp(\eta_{CL})$
V2	L	42.9	6.90	16.1%		$V2 = tvV2 \times (Weight/70) \times \exp(\eta_{V2})$
Q	L/hr	44.4	8.25	18.6%		$Q = tvQ \times (Weight/70)^{0.75} \times \exp(\eta_{Q})$
V3	L	56.5	6.66	11.8%		$V3 = tvV3 \times (Weight/70) \times \exp(\eta_{V3})$
Ka	1/hr	0.447	0.0688	15.4%		$Ka = tvKa \times \exp(\eta_{Ka})$
Susp_Tlag	hr	0	fixed			$Tlag = 0$
Caps_Tlag	hr	0.946	0.022	2.3%		$Tlag = Caps\_Tlag \times \exp(\eta_{Tlag})$
F1		0.990	0.100	10.1%		$F1 = tvF1 \times \exp(\eta_{F1})$
Dose_CL		-0.394	0.0763	19.4%		$CL = CL \times (Dose/80)^{Dose\_CL}$
iivCL		0.324(56.9%)*	0.0738	22.8%	17.0%	ω^2_{CL}
iivV2		0.480(69.3%)*	0.168	34.9%	35.6%	ω^2_{V2}
iivQ		0.652(80.7%)*	0.345	52.9%	51.3%	ω^2_{Q}
iivV3		0.272(52.1%)*	0.0806	29.6%	33.3%	ω^2_{V3}
iivKa		0.907(95.2%)*	0.229	25.3%	28.6%	ω^2_{Ka}
iivTlag		0	fixed			ω^2_{Tlag}
iivF1		0.275(52.5%)*	0.0893	32.4%	28.7%	ω^2_{F1}
Log10ResErr		0.168	0.00816	4.90%	16.2%	$\log_{10}(C_{obs}) = \log_{10}(C_{pred})+Log10ResErr$

Abbreviations: OFV = objective function value; tv = typical value; CL = systemic clearance; V2 = central volume of distribution; Q = inter-compartmental clearance; V3 = peripheral volume of distribution; Ka = absorption rate constant; Tlag = lag-time (delay in absorption); F1 = relative bioavailability; Susp = oral suspension; Caps = oral capsules; Dose_CL = dose effect on systemic clearance; SE = Standard Error; RSE = Relative Standard Error (RSE = 100% × SE/Estimate); Log10ResErr = Log-Additive Residual Error; C_{obs} = observed concentration; C_{pred} = predicted concentration.

* iiv CV% were calculated as $100\% \times (\omega^2)^{0.5}$

Source: Sponsor's Population PK Report, Page 26

Model evaluation:

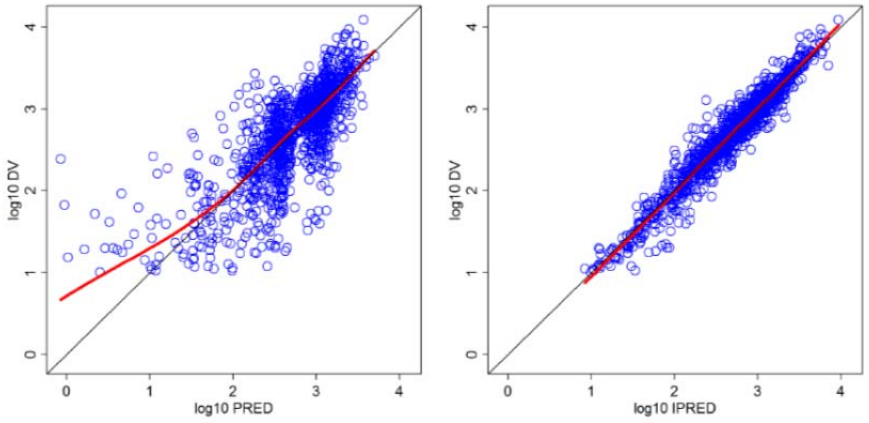


Figure 2. Diagnostic Plots for Final Population Pharmacokinetic Model (run019) of Aprepitant in Pediatric Population: Goodness-of-Fit

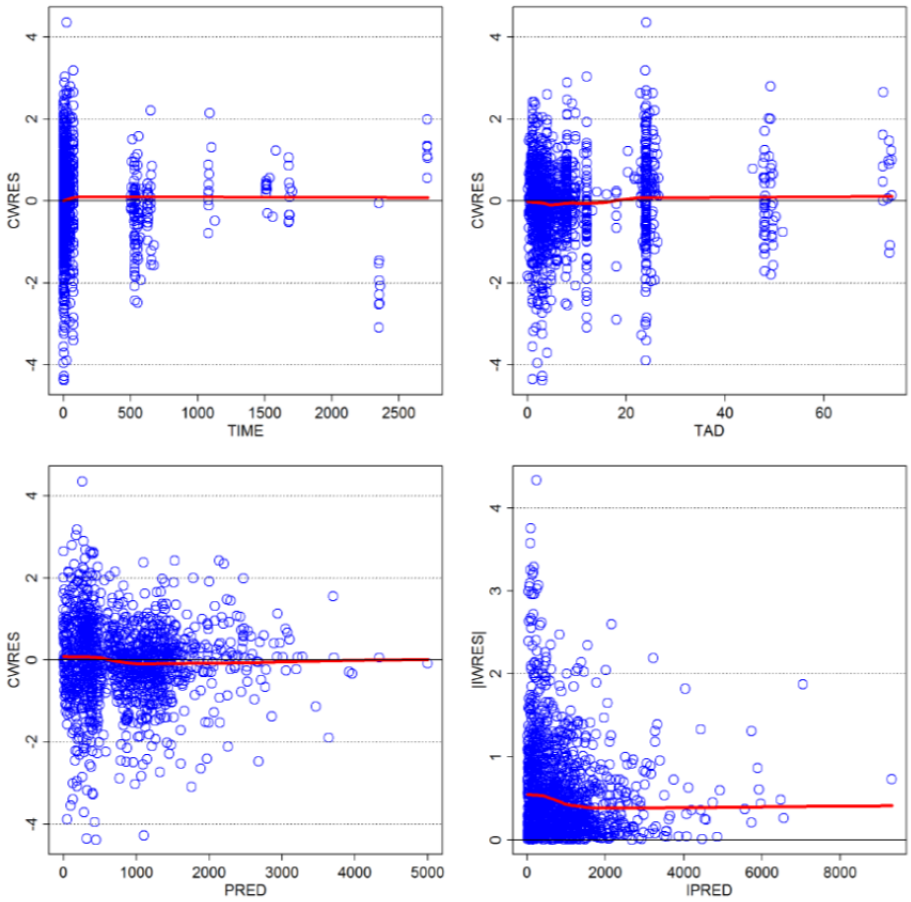


Figure 3.Diagnostic Plots for Final Population Pharmacokinetic Model of Aprepitant in Pediatric Population: Residual Plots
Source: Sponsor's Population PK Report, Page 26

Model evaluation using a simulation-based VPC showed that the model tracked the central tendency of the observed data and that an appropriate distribution of observed data fell within the 5th and 95th percentiles of model simulated data, indicating that the model reasonably describes aprepitant concentration data with fixed effects of weight and age. Median, 90% PI and 95% PI for model-based predicted concentration profiles of aprepitant with superimposed actual observed concentrations of aprepitant obtained in the targeted age groups (i.e., P134 Part IV < 12 years dosed with oral suspension QD 3/2/2 mg/kg, and P097 ≥ 12 years dosed with capsules QD 125/80/80 mg) are presented in Figure below.

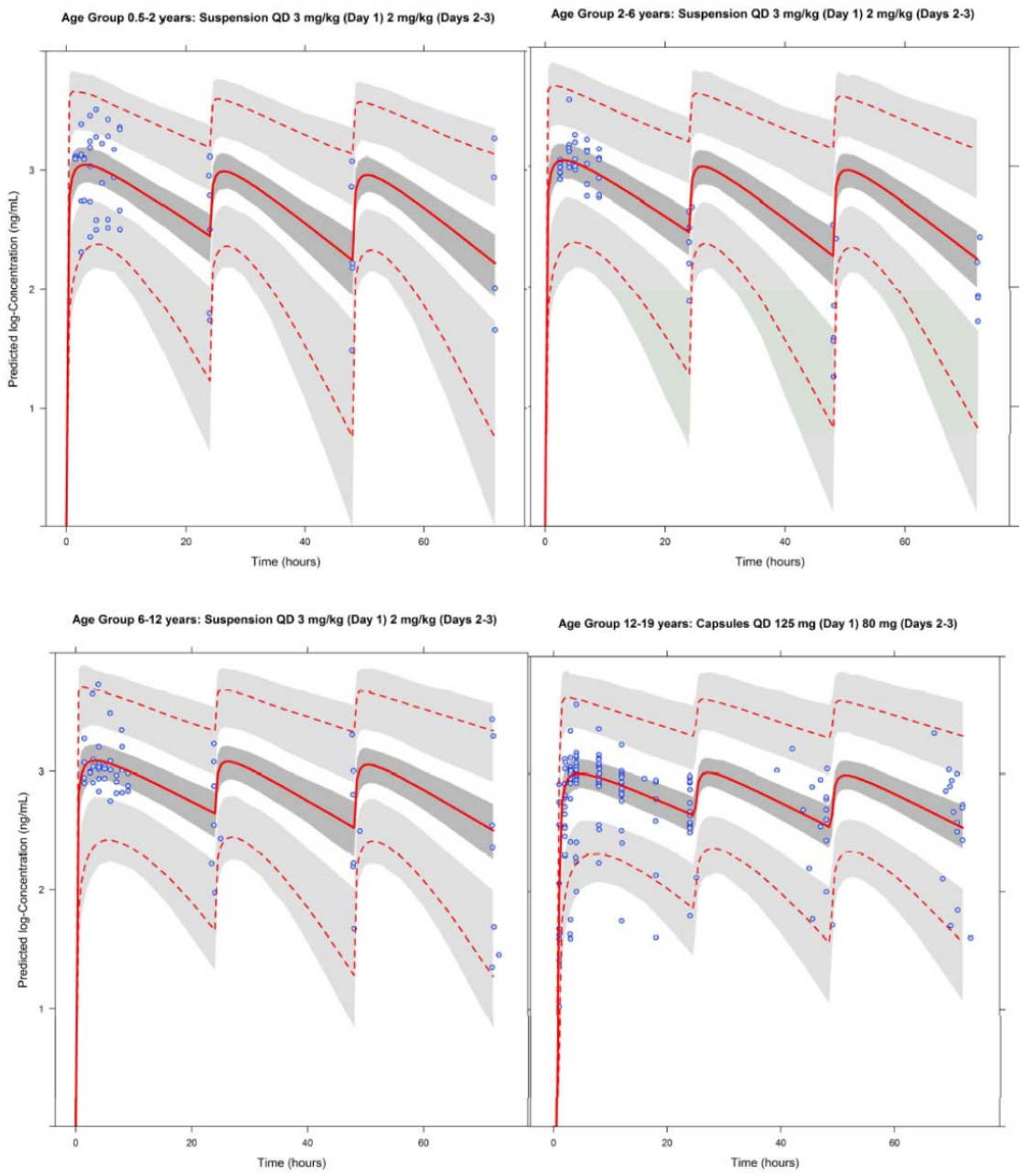


Figure 4. Median, 90%PI and 95%PI for Simulated Concentrations of Aprepitant in Pediatric Patients Stratified by Age Groups

Of note: Capsules (125 mg on Day 1 and 80 mg on Days 2 and 3) were administered to adolescents, 12-19 years old in P097 while power-for suspension (3mg/kg on Day 1 and 2 mg/kg on Days 2 and 3) were given to pediatric patients0.5 - < 12 years old.

Covariates

Body weight and age are significant covariates for apparent clearance and apparent volume of distribution, with the inter-subject variability for clearance decreased from 64% to 56.9%

under the final population pharmacokinetics (PopPK) model. The PopPK results support the use of weight-based dosing regimens in younger patients (<12 years of age). None of other factors (sex, BMI and race) was found to have a significant association with the aprepitant PK parameters that would indicate a clinically relevant effect on aprepitant exposure. One caveat is that majority of patients in the dataset are Caucasians (76.2%, **Table 3**).

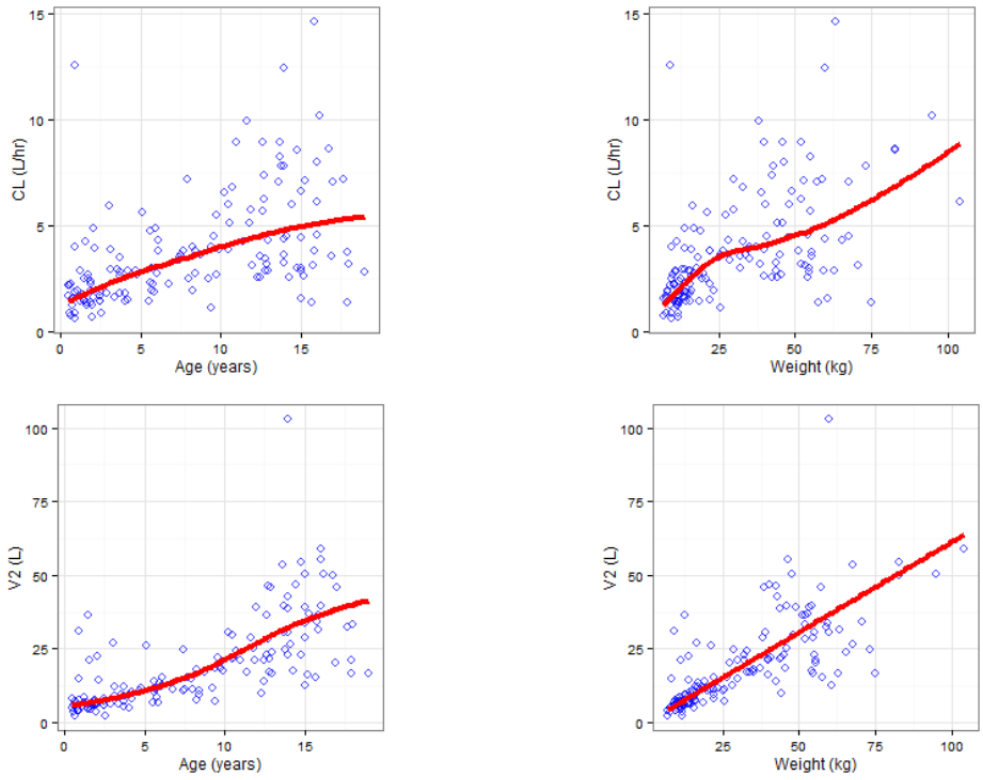


Figure 5. Relationships of Age and Body Weight on Population PK Model Parameters, Clearance and Central Volume of Distribution, Supported Application of a Weight-Based Dosing Regimen in Patients <12 years of age

Reviewer's comment: *In Applicant's base and final population PK model, the effect of age on drug clearance was modeled with fixed values adapted from the publication by Johnson et al, 2006. It should be noted that the adapted formula refers to the maturation of intestinal/gut CYP3A only. However, aprepitant is primarily metabolized by CYP3A4 in the liver.*

3.2 Information Request and Reviewer's Analyses

3.2.1 Information Request

The reviewer sent the Information Request to the Applicant to justify and clarify the

physiological rationale of your final model on age effect, and consider re-evaluating the final popPK model in this regard. The review team suggested that one way to account for age effect on clearance is to use the hepatic maturation factor (see the review at Drugs at FDA, page 42, for more details, *http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources /UCM177428.pdf*).

The population PK model was re-run by the Applicant with the hepatic CYP3A4 maturation function cited in the reference provided in the Agency's comment as well as the CYP3A4 hepatic maturation function described by Johnson et al (2006). The model results are partially discussed below shown as Model 2 and Model 3, respectively.

3.2.2 Reviewer's Analyses and Applicant's re-analyses

Objectives:

- Evaluate the ontogeny functions developed by different models and data
- Sensitivity analyses on different PopPK models for their estimates on PK parameters in each age group

Methods

The population PK model was re-run by the Reviewer. The structure model is based on the Applicant's final PopPK model. The relationship between CL and age was explored using the following different models:

Model 1: F_{age} =0.639 × Age / (2.4 + Age) + 0.42

Model 2: $F_{age} = \frac{Age}{Age + MATCL_{50}}$

Model 3: $F_{age} = \frac{Age^{0.83}}{Age^{0.83}+0.31}$

Model 4: F_{age} =1-(1- β_{CL}) ×exp(- Age × (0.693/Tcl)

Where, Fage = fraction of mature CL, β = fractional CL at birth, TCL or $\mathrm{MATCL}_{50}^{\mathrm{HillCL}}$ is the age at which clearance is 50% of the typical CL value. The above mentioned parameters are estimated by the available data using the NONMEM software program (Version 7.2, (b) (4)) by the reviewer. *Age* is postnatal age in

years Model 1 and 3 are modeled with fixed values adapted from the publication by Johnson *et al*, 2006.

Results

Ontogeny function/Age effect

Based on the final model estimates, the reviewer compared different age functions on clearance. β , *TCL and* $\mathrm{MATCL}_{50}^{\mathrm{HillCL}}$ are estimated to be 0.4, 3.6, and 0.6 respectively. The plots of fraction to adult level versus age are shown below.

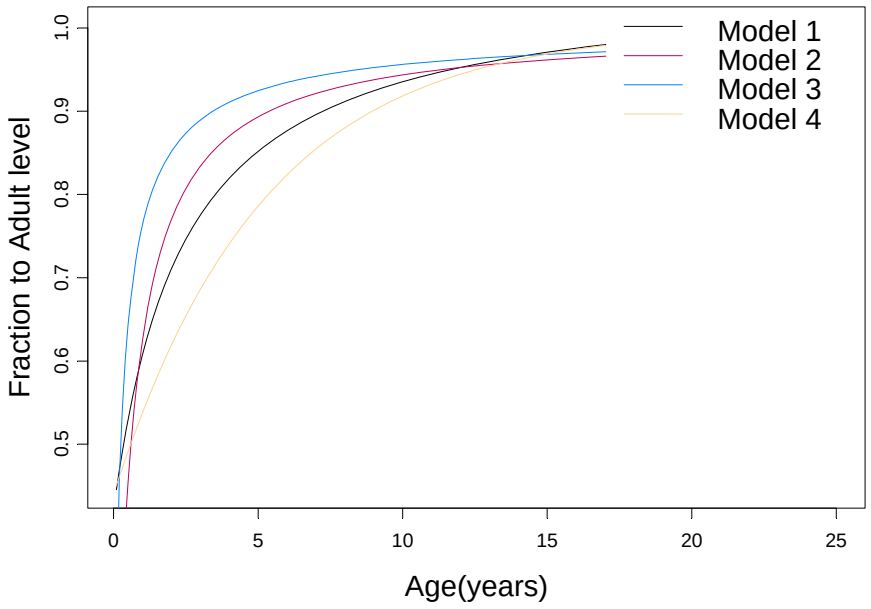


Figure 6. Ontogeny function derived from different PopPK models

Of note, the effect of age on drug clearance under Model 1 and 3 was modeled with fixed values adapted from the publication by Johnson et al, 2006, which refers to the maturation of intestinal/gut CYP3A, liver CYP3A, respectively. For Model 2 and 4, the maturation half-life was estimated by the observed data, at 0.598 and 3.8 years of age, respectively. The literature reports suggest that maturation half-life for CYP3A is in the range of 2.4-3.6 months. This indicates that the available data is limited and insensitive to estimate a true age effect on clearance.

PK comparisons on different ontogeny models

PK parameters and exposure metrics derived from the Model1-3 are compared. Model 4 is not considered in this comparison as the maturation half-life estimate is highly deviated from the reported value. In general, the results are not different from the original model estimated intrinsic clearance provided in the NDA application. Specifically,

- Comparing results from Model 1 and Model 2: model point-estimates using the suggested CYP3A4 maturation function differences between 0.03 to 0.1 L/hr in CL across all age groups. The smallest difference, a 0.03 L/hr decrease, occurs in the 6-12 year-old age group, while a difference of a 0.05 L/hr increase is estimated in the 0.5 – 2 year-old group.
- Comparing results from Model 1 and Model 3: the smallest difference in CL reflects a 0.05 L/hr increase estimated in the 2-6 year-old age group with a difference of a 0.15 L/hr increase found in the 0.5 – 2 year-old group.
- The model-predicted exposures are also compared across all three models (**Table 4**). The results between each model are similar to each other, with the majority of parameters with < 1% differences,
- There is no consistent or monotonic trend in the new estimates of CL based upon the re-evaluations and a clear bias was not identified.

In summary, model-predicted PK parameters and exposure metrics are comparable across the models, indicating that data used in the population PK model is relatively insensitive to various maturation functions used to describe intrinsic clearance of the population. As the original model by the Applicant was evaluated using Goodness-of-Fit plots, visual predictive check and nonparametric bootstrap, the reviewer agrees to use it as the final model for the purpose of comparison of the Applicant proposed dosing nomogram versus weight-based dosing regimen in clinical trials.

It should be noted that a definitive approach has yet to be identified for this drug describing the ontogeny/maturation of drug metabolizing enzymes enabling translation into younger pediatric patients. Keeping this caveat in mind; the Applicant's proposed population PK model should not be used to extrapolate the PK outside the age range studied (See Section for Rationale of Dose Selection).

4 PKPD relationship

The exposure-response for efficacy or safety are not described in the original NDA 21549 review. The PK was not collected in the phase 3 clinical trials in pediatrics and therefore the exposure-response analysis in pediatrics was not possible. The PKPD relationship assessed by the Applicant is as follows:

In the original NDA submission, the Applicant assessed the correlation of plasma aprepitant levels with the binding of aprepitant to brain NK_1 receptors in 2 Phase 1 studies (Protocol 027) and (Protocol 045) in healthy young men. The data from both of these studies combined in an exploratory post-hoc analysis showed the relationship between plasma aprepitant concentration and NK_1 receptor occupancy as in the figure below. Based on this curve, aprepitant plasma concentrations of ~10 ng/mL and ~100 ng/mL produce brain NK_1 receptor occupancies of ~50 and 90%, respectively. In adults, the 3-day CINV aprepitant dose regimen (125 mg on Day 1 followed by 80 mg on Days 2 and 3) results in mean plasma concentrations of >500 ng/mL that are expected to achieve greater than 95% striatal NK1-receptor occupancy on each day of dosing. Generally, these concentrations are associated with an $AUC_{0\text{-}24hr}$ on Day 1 of ~20,000 ng*hr/mL.

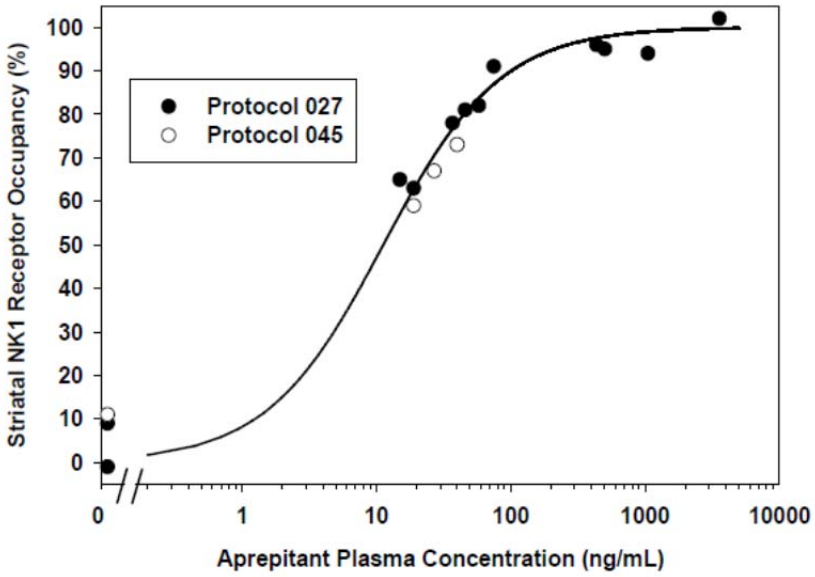


Figure 7. Correlation of Plasma Aprepitant Concentration with Binding of Aprepitant to Striatal NK_1 Receptors

Based upon the PKPD relationship for NK-1 receptor occupancy, the pharmacokinetic profile obtained with the weight-based regimen in patients 6 months to 12 years (3.0 mg/kg on Day 1 followed by 2.0 mg/kg on Days 2 and 3) and the fixed dose regimen in adolescents (125 mg on Day 1 followed by 80 mg on Days 2 and 3) result in aprepitant exposures, across the 3-day treatment period, that are on the plateau of the exposure-response relationship.

5 Rationale of Dose Selection

The results of PopPK model simulation support the dosing recommendations provided in the original application.

Adolescents (aged 12 (b) (4) The Applicant proposed dose of capsules of EMEND is 125 mg orally on Day 1 and 80 mg orally on Days 2 and 3, which is the same as implemented in clinical trials for this age group.

Children (aged 6 months to less than 12 years): The Applicant proposed dose of EMEND for oral suspension (b) (4)

Table 1. A nomogram is proposed to mimic the weight-based dosing regimen implemented in Phase 3 (3.0 mg/kg on Day 1 followed by 2.0 mg/kg on Days 2 and 3) for patients 6 months to 12 years of age, which would simplify calculation of the dose to improve ease of use in in clinical practice. It is expected to reduce the potential for dosing errors and dispensing complexities, when delivered with a single oral dispenser, while maintaining the excellent efficacy and safety profiles established in the pediatric clinical trials.

Simulation results indicated that the differences in PK values with the nomogram compared to strict weight-based dosing are modest and unlikely to be clinically relevant (**Figure 1**). 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. 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 considerable data demonstrating acceptable tolerated in the pediatric clinical trials. In general, the variability in pediatric patients are higher than in adults and the range of exposure in pediatric are highly overlapped between the proposed nomogram regimen and individual body weight based regimen studied in clinical trials.

Table 4. Comparisons of Exposure Estimates from Three Different PopPK Models

Parameter	Age Group*	Nsubj	Model 1			Model 2			Model 3		
			Median	Q5%	Q95%	Median	Q5%	Q95%	Median	Q5%	Q95%
$AUC_{0\text{-}24hr}$ ng·hr/mL	0.5-2 yrs	6	14126	8062	42097	14136	8037	42023	14159	8010	41793
	2-6 yrs	6	18247	11503	23611	18220	11498	23567	18105	11470	23398
	6-12 yrs	7	13287	11486	49769	13267	11450	49685	13185	11370	49428
	>12 yrs	18	16258	3051	26254	16263	3043	26202	16323	3059	26136
$AUC_{48\text{-}72hr}$ ng·hr/mL	0.5-2 yrs	6	8557	6397	34369	8611	6426	34419	8744	6526	34465
	2-6 yrs	6	11125	7077	15951	11164	7109	15992	11286	7208	16123
	6-12 yrs	7	9288	7039	48501	9312	7057	48633	9399	7129	48956
	>12 yrs	18	16554	2562	30474	16621	2570	30598	16728	2602	30811
C_{max} ng/mL	0.5-2 yrs	6	1248	438	2364	1250	438	2363	1260	436	2364
	2-6 yrs	6	1294	980	1675	1295	981	1675	1296	988	1677
	6-12 yrs	7	1064	902	2781	1064	901	2779	1066	904	2778
	>12 yrs	18	1001	282	2032	999	282	2034	997	289	2007
C_{24hr} ng/mL	0.5-2 yrs	6	216	61.9	902	215	61.8	899	212	61.8	891
	2-6 yrs	6	177	98.2	381	175	97.0	378	170	93.8	371
	6-12 yrs	7	224	113	1432	222	111	1427	219	108	1412
	>12 yrs	18	519	81.6	798	521	81 2	796	523	80.1	789
C_{48hr} ng/mL	0.5-2 yrs	6	151	28.9	900	152	29.4	901	153	31.2	899
	2-6 yrs	6	82.3	45.9	248	82.6	46.1	248	83.9	46.9	250
	6-12 yrs	7	160	53.1	1262	161	53.4	1265	163	54.3	1272
	>12 yrs	18	443	55.2	869	444	55.4	872	448	56.1	876
C_{72hr} ng/mL	0.5-2 yrs	6	142	27.7	960	143	28 2	962	144	29.9	961
	2-6 yrs	6	80.4	44.3	242	80.7	44.6	243	82.1	45.5	246
	6-12 yrs	7	144	46.2	1215	145	46.4	1220	148	47.4	1231
	>12 yrs	18	379	41.6	817	381	41.8	822	387	42.6	841

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

/s/

ELIZABETH Y SHANG
07/20/2015

JIAN WANG
07/20/2015

NITIN MEHROTRA
07/20/2015

SUE CHIH H LEE
07/20/2015

ONDP BIOPHARMACEUTICS REVIEW

NDA#:	207865/N000
Submission Dates:	07/25/14, 09/12/14, 06/05/15, 06/26/15 (T-con) 07/01/15, 07/07/15(T-con), and 07/10/15
Brand Name:	Emend
Generic Name:	Aprepitant
Formulation:	Powder for Oral Suspension
Strength:	125mg (b) (4)
Applicant:	Merck
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SYNOPSIS

Background

Merck's NDA 21549 for Emend (Aprepitant) oral capsules was approved on 03/27/03 for three strengths, 125, 80, and 40 mg for a three-day treatment regimen. Emend (aprepitant), in combination with other antiemetic agents including a 5-HT3 receptor antagonist and a corticosteroid, is indicated for the prevention of acute and delayed nausea and vomiting due to highly emetogenic and moderately emetogenic cancer chemotherapy in adults (CINV-HEC, CINV-MEC). The Aprepitant drug substance (DS) in Emend capsules was manufactured as (b) (4) DS.

Merck developed Aprepitant oral powder for suspension (PFS) formulation for pediatric patients, 6 months to 17 years old. Emend for Oral Suspension is proposed as an alternative to the 125 mg capsule formulation for use in pediatric patients. The pediatric plan for Emend included trials in chemotherapy induced nausea and vomiting (CINV).

Current Submission

On 07/25/14, Merck submitted NDA207865 for Emend (Aprepitant) powder for suspension (PFS) seeking approval for 125 mg/ (b) (4) for pediatric use. The same PFS information for pediatric patients, 6 months to 17 years old, is also submitted to update sNDA 21549/S-25. The review clock for this NDA was not started until the last portion of CMC was submitted on 03/30/15. However, an early action/decision will be taken and the PDUFA goal date is 08/28/15.

The proposed update to the Emend product label is supported by a single pivotal Phase III efficacy/safety study conducted in patients 6 months to 17 years of age. Both capsule and PSF were evaluated in pediatric patients, 12-17 years old. Subjects < 12 years of age were dosed with the PFS formulation based on body weight (3 mg/kg on Day 1 and 2 mg/kg on Days 2 and 3 of a three-day Aprepitant regimen).

Aprepitant is poorly soluble in water and is reported as a BCS Class (b) (4) drug. The Aprepitant DS for powder for oral suspension was manufactured using (b) (4). A phase-III dissolution method was developed, tested, and employed for release and stability testing. However, upon NDA submission, the Applicant proposed a test method, (b) (4) and sought for NDA approval.

Several Biopharmaceutics information requests were conveyed to the Applicant and the Applicant responded on 09/12/14, 06/05/15, 07/01/15, and 07/07/15. T-cons were also held on 06/26/15 and 07/07/15 for the discussions on the proposed dissolution method.

Biopharmaceutics Review

The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution method development report and supportive dissolution profile data.

Reviewer's Comments:

1. The Applicant proposed a test method, (b) (4) for Release and Shelf-Life, and it was reviewed and found not acceptable.
2. Instead, a regulatory dissolution method with a specification for product quality control (b) (4) was proposed by the Agency.
3. The Applicant accepted the Agency's proposed dissolution method with a specification which will be proposed and reviewed as part of the next cycle submission (b) (4).

RECOMMENDATION

From the ONDP/Division of Biopharmaceutics perspective, this NDA is recommended for a CR. The following comments need to be communicated to the Applicant.

COMMENTS: (Need to be conveyed to the Applicant)

1. Your proposed test method, (b) (4) for Release and Shelf-Life, and it was reviewed and found not acceptable.
2. Your previous dissolution test method, USP Apparatus 2 (Paddle) x 50 rpm in 900 mL water at 37°C with 2.4% Tween 80, is not acceptable.
3. Implement new dissolution test method and acceptance criterion as you agreed with and shown below for your NDA:

Apparatus:	**USP Paddle (II) with 50rpm**
Medium:	**Water (with 1.2% Tween80), 900ml at 37± 0.5°C.**
Acceptance Criterion:	**Q= (b) (4)% at 10 minutes.**

Tienmien Chen -A

Digitally signed by Tienmien Chen -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Tienmien Chen -A, 0.9.2342.19200300.100.1.1=1300073135
Date: 2015.07.17 12:29:29 -04'00'

Tapash K. Ghosh -S

Digitally signed by Tapash K. Ghosh -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300148262, cn=Tapash K. Ghosh -S
Date: 2015.07.17 12:44:44 -04'00'

Tien-Mien Chen, Ph.D.
ONDQA Biopharmaceutics Acting Lead

07/15/15
Date

Tapash Ghosh, Ph.D.
ONDQA Biopharmaceutics Acting Branch Chief

07/15/15
Date

CC: NDA No.207865/PSeo

PRODUCT QUALITY - BIOPHARMACEUTICS ASSESSMENT

BACKGROUND

Merck's Emend (aprepitant) is an antagonist of human substance P neurokinin 1 (NK1) receptors that, in combination with other antiemetic agents including a 5-HT3 receptor antagonist and a corticosteroid, is approved for the prevention of acute and delayed nausea and vomiting due to highly emetogenic and moderately emetogenic cancer chemotherapy in adults (CINV-HEC, CINV-MEC).

NDA 21549 for Emend (Aprepitant) oral capsules was approved on 03/27/03 for three strengths, 125, 80, and 40 mg for a three-day treatment regimen. The Aprepitant drug substance (DS) in Emend capsules was manufactured as (b) (4) DS.

Merck developed Aprepitant oral powder for suspension (PFS) formulation for pediatric patients, 6 months to 17 years old. Emend for Oral Suspension is proposed as an alternative to the 125 mg capsule formulation for use in pediatric patients. The pediatric plan is for Emend included trials in chemotherapy induced nausea and vomiting (CINV).

The general approach to dose selection for the pediatric trials was to match pharmacokinetic exposures to those previously demonstrated to be safe and efficacious in adults. Merck reported that pharmacokinetic (PK) data were collected in the program; subjects, 12 to 17 years of age, were administered for the same dose/regimen of capsules as currently approved in adults, while subjects < 12 years of age were dosed with the PFS formulation based on body weight.

CURRENT SUBMISSION

On 07/25/14, Merck submitted NDA207865 for Emend (Aprepitant) powder for suspension seeking approval for 125 mg/ (b) (4) for pediatric use. The same PFS information for pediatric patients, 6 months to 17 years old, is also submitted to update sNDA 21549/S-25. The review clock for this NDA was not started until the last portion of CMC was submitted on 03/30/15. However, an early action/decision will be taken and the PDUFA goal date is 08/28/15.

The proposed update to the Emend product label is supported by a single pivotal Phase III efficacy/safety study conducted in patients 6 months to 17 years of age. Both capsule and PSF were evaluated in pediatric patients, 12-17 years old. Subjects < 12 years of age were dosed with the PFS formulation based on body weight (3 mg/kg on Day 1 and 2 mg/kg on Days 2 and 3 of a three-day Aprepitant regimen).

Aprepitant is poorly soluble in water and is reported as a BCS Class (b) (4) drug. The Aprepitant DS for powder for oral suspension was manufactured using (b) (4). A finalized phase III dissolution method was developed, tested, and employed for release and stability testing prior to NDA submission. However, the Applicant proposed a test method, (b) (4) and sought for NDA approval.

Several Biopharmaceutics information requests were conveyed to the Applicant and the Applicant responded dated 09/12/14, 06/05/15, 07/01/15, and 07/07/15. T-cons were also held on 06/26/15 and 07/07/15.

BIOPHARMACEUTICS REVIEW

The Biopharmaceutics review is focused on the evaluation and acceptability of the proposed dissolution method and acceptance criterion of Emend PFS with supportive dissolution profile data, responses to Biopharmaceutics information request.

COMPOSITION AND FORMULATION

The proposed composition/formulation of Emend PFS 125 mg/ (b) (4) is shown below.

Table 1. Emend for PFS Product Composition (125 mg/ (b) (4)

Components	Function	Theoretical Quantity per (b) (4) (mg)
(b) (4)		
Aprepitant	Active Ingredient	125.0
Hydroxypropyl Cellulose (b) (4		(b) (4)
(b) (4) Sodium Lauryl Sulfate		
Sucrose		
(b) (4		
(b) (4 Lactose,		
Red Ferric Oxide		
Sodium Stearyl Fumarate		
(b) (4)		
(b) (4)		

Emend PFS is to be dissolved in 4.6 mL of water for administration (with a dosing cup) as an oral suspension as depicted in Figure 1 below.

Figure 1. Suggested Dosing Protocol for EMEND® for Oral Suspension

DISSOLUTION METHODOLOGY AND ACCEPTANCE CRITERION

I. Aprepitant Physical/Chemical Properties:

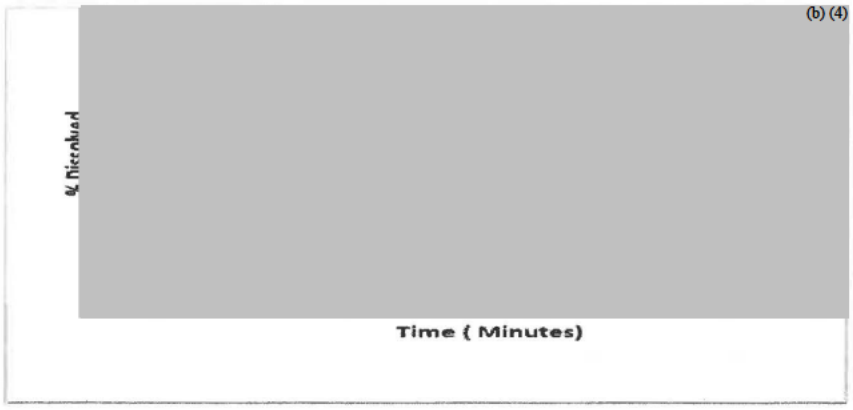
Aprepitant is poorly soluble in water which is classified as a BCS class (b) (4) compound. The equilibrium solubility of Apripitant (b) (4) DS at ambient temperature is shown below.

Table 2. Equilibrium Solubility of Aprepitant (b) (4) DS at Ambient Temperature

Medium	Solubility of Aprepitant (mg/mL)
Water, pH = 6.5	0.001
0.01N HCl, pH = 2	0.005
0.1N HCl, pH = 1	0.030

For the approved Emend capsules (NDA 21549), Aprepitant was manufactured as (b) (4) DS. The preliminary mean dissolution profile of Emend for oral suspension formulated with (b) (4) DS is shown below.

Figure 2. Typical Mean Dissolution Profile of Emend for Oral Suspension Formulated with (b) (4) DS at 37°C



II. Dissolution Method Development Report:

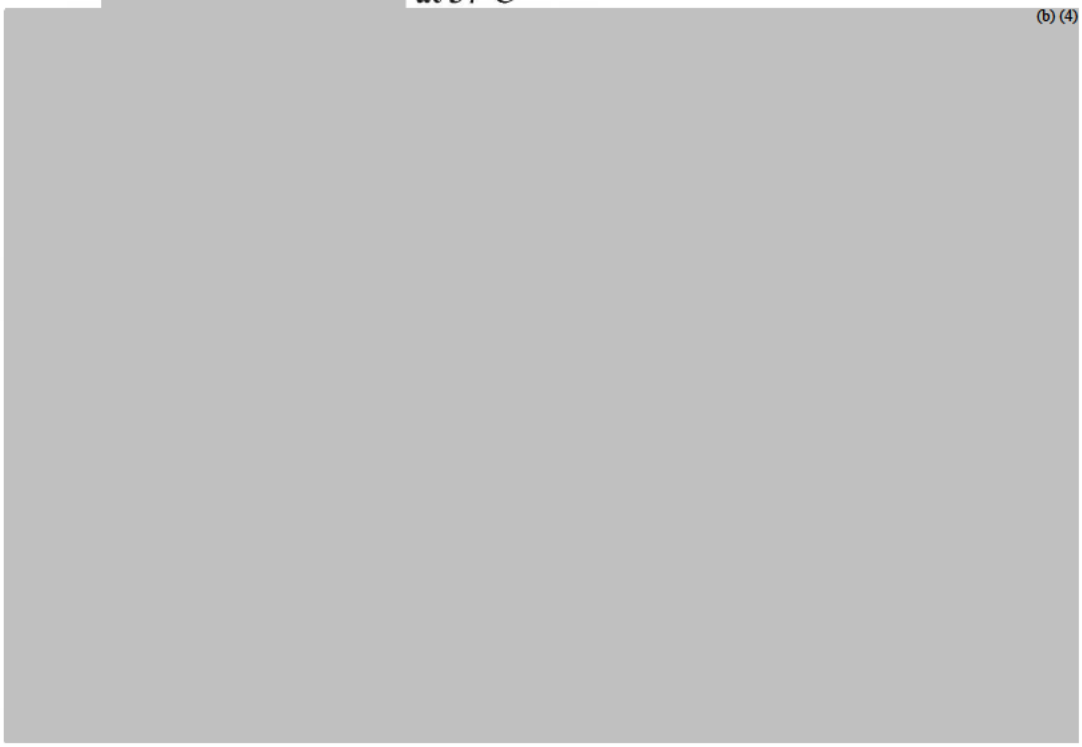
For the approved NDA 21549, the Applicant reported that the surfactant (b) (4) % was utilized in the approved dissolution method for Emend capsule (Aprepitant (b) (4) DS) as it was necessary for capsule rupture. Merck determined that (b) (4) is not necessary for Aprepitant (b) (4) DS. However, due to its poor water solubility, a surfactant is needed for dissolution testing. During dissolution development, the Applicant selected Tween 80. The equilibrium solubility of Aprepitant "(b) (4)" DS in various Tween 80 solutions (0.5% - 3.0%) under ambient temperature is shown below.

Table 3. Equilibrium Solubility of Aprepitant (b) (4) DS in Tween 80 solutions at Ambient Temperature

Aqueous Medium	Solubility of Aprepitant (mg/mL)
Water	< 550 ng/mL
0.5% Tween 80	0.07
0.6% Tween 80	0.09
1.2% Tween 80	0.17
1.5% Tween 80	0.22
2.0% Tween 80	0.30
2.4% Tween 80	0.34
2.5% Tween 80	0.35
3.0% Tween 80	0.43

The Applicant reported that a 2.4% of Tween 80 was determined as a solubility of 0.34 mg/mL which is required to dissolve 125 mg Aprepitant ((b) (4) DS) in 900 mL water dissolution medium and to maintain sink conditions ((b) (4) times of solubility). Upon information requests, the Applicant submitted dissolution profiles of Aprepitant (b) (4) DS using various concentrations for Tween 80 as shown below.

Figure 3. Dissolution Profiles of Emend (Aprepitant (b) (4) DS) for Oral Suspension in Various Media (% of Tween 80) (b) (4) at 37°C



The Applicant reported that Aprepitant dissolved in water medium almost instantaneously due to (b) (4) Aprepitant DS (Figure 3). However, it should be noted that 1). The selected surfactant, 2.4% of Tween 80 was based on the equilibrium solubility of "(b) (4)" Aprepitant DS at ambient temperature (Table 3) and 2). The dissolution testing for "(b) (4)" Aprepitant DS was conducted at 37°C (Figure 3).

Reviewer's Comments:

1. The dissolution results of "(b) (4)" Aprepitant DS at 37°C (Figure 3) showed that a 2.4% of Tween 80 is more than what was needed/selected.
2. A (b) (4)% of Tween80 may be inadequate to provide sufficient solubility for Aprepitant "(b) (4)" DS as it reached only around (b) (4)% dissolution at 37°C.
3. A 1.2% of Tween80 is adequate to maintain (b) (4)% complete dissolution for (b) (4) Aprepitant DS at 37°C. Therefore, it is expected that at 37°C, the % of Tween 80 needed is probably at 1.2% of Tween 80 (according to Figure 3).

III. Dissolution Method and Acceptance Criterion for Aprepitant PFS:

For this NDA 207865, Aprepitant is manufactured as a (b) (4) DS. The finalized phase III dissolution method was tested as shown below and employed for release and stability testing prior to NDA submission.

Apparatus: **USP Paddle (II) with 50rpm**

Medium: **Water (with 2.4% Tween80), 900ml at 37± 0.5°C.**

Acceptance Criterion: **Q= (b) (4)% at 20 minutes.**

The above Phase III dissolution method, however, was not to be proposed for approval. The mean dissolution profile of Emend PFS ((b) (4)" DS) is as shown below.

Figure 4. Typical Mean Dissolution Profile of Emend Powder (b) (4) DS) for Oral Suspension at 37°C

The Applicant reported that

1). The critical quality attributes (CQA) for bioavailability is particle size distribution and not API solubility; therefore, a specification for dissolution of the finished product is not required for release or shelf-life.

2). Instead, from a patient-use perspective, the Emend's PFS product dispersion in water is evaluated by time for constitution testing at release and shelf life which is considered important.

Reviewer's Comments:

1. The Applicant's intention not to propose a dissolution method and acceptance criterion for Emend PFS formulation is considered not acceptable.
2. A dissolution method with an appropriate acceptance criterion needs to be set for PFS formulation for quality control and future biowaiver purposes.

The following Agency's information request for proposing a dissolution method and setting dissolution acceptance criterion for PFS formulation was sent to the Applicant on 06/22/15 as stated below.

> "For quality control purpose, propose a regulatory specification of NLT (b)(4)% at 10 min using (b)(4) 1.2% Tween 80 when the drug powder product is poured directly to the dissolution medium."

On 06/26/15, a T-con was held between the Applicant and The Agency and the following was discussed 1). The minimum % of Tween 80 needed for dissolution, 2). The need for development of a regulatory specification for quality control and future biowaiver purposes, and 3) Clarification of the detailed dissolution testing process.

On 07/01/15, the Applicant responded and accepted Agency's recommendation to propose a regulatory specification as shown below.

Apparatus:	**USP Paddle (II) with 50rpm**
Medium:	**Water (with 1.2% Tween80), 900ml at 37± 0.5°C.**
Acceptance Criterion:	**Q= (b)(4)% at 10 minutes**

It should be note that as reported by the Applicant, "the dissolution sample preparation was updated to specify using the dosing cup to suspend the powder prior to addition into the dissolution vessel instead of any suitable container." (according to the sample constitution procedure from dissolution method 001863D05.003)

The Applicant stated in the 06/26/15 T-con that the constituted Aprepitant samples should be used as dissolution samples to achieve appropriate sample preparation robustness. Upon request, the Applicant further provided the justification in the 07/01/15 responses as stated below.

- Emend powder for oral suspension is (b)(4)

Reviewer's Comment:
The Applicant's justification is reviewed and found acceptable.

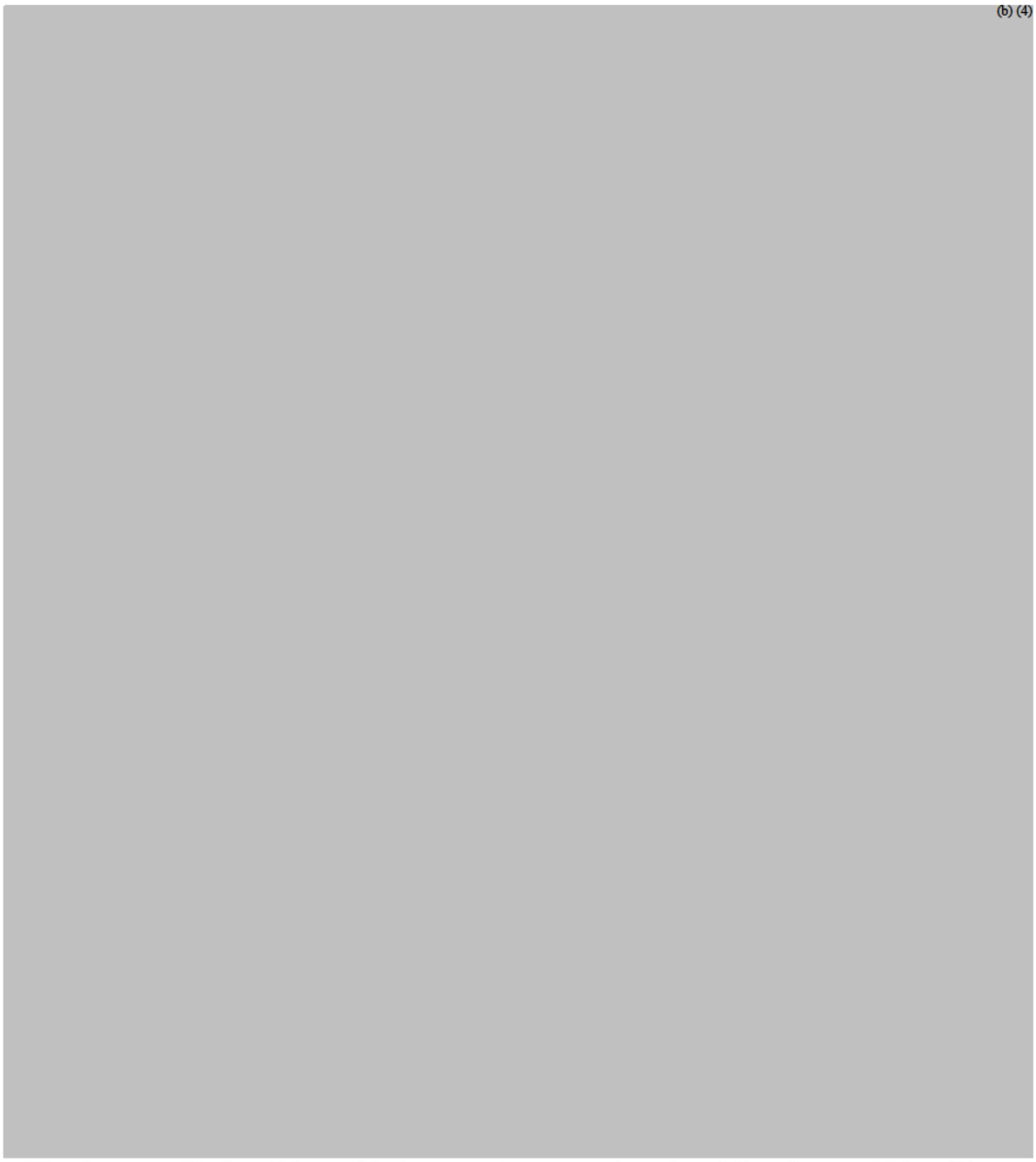
On 07/02/15 another Biopharmaceutics was conveyed to the Applicant requesting the Applicant to

- Clarify if the dissolution testing for Lots WL00029923, WL00046426, WL00051680, WL00051678, and WL00051679 Emend for Oral Suspension (M32P54; Tables 2 and 3 in the Batch Analyses section) employed the dissolution test method using USP Apparatus 2 (Paddle) x 50 rpm in water (with 2.4% Tween 80) of 900 mL water at 37°.
- Submit an update to M32P51 Specification section to reflect the newly accepted dissolution method and acceptance criterion.
- Accept a post marketing commitment (PMC) and the previous dissolution test method employing USP Apparatus 2 (Paddle) x 50 rpm in 900 mL water at 37°C with 2.4% Tween 80 will be used for interim analysis up to 1 year upon approval.
- Reassess the drug product proposed expiration dating period based on the new stability results from the first three commercial batches of drug product.

On 07/07/15 was held between the Applicant and the Agency regarding PMC and on 07/08/15, the Applicant updated the M32P51 Specification section.

Reviewer's Comment:
On 07/08/15, the Applicant accepted the Agency's recommendation as stated above. Therefore, the Applicant's responses are acceptable.

IV. Assay Method Validation:
The method was reportedly validated per ICH guideline to support late phase drug development. The evaluated validation elements are specificity, accuracy, linearity and range, measurement precision, method precision, intermediate precision, reproducibility, solution stability, filter qualification, and robustness. The results of validation report are summarized below.



The Assay method and its validation report were reviewed and found acceptable. The validated dissolution method has been utilized to release biobatch and to monitor the stability performance of the product on formal stability studies. Their profiles are presented below.

V. **Mean Dissolution Profiles at Release and Stability Initial Using 900mL Water Medium with 2.4% Tween 80 (Note: Batch No. WL00051678 is a biobatch)**

Mean Dissolution Profiles on Stability Using 900mL Water Medium with 2.4% Tween 80

The detailed information on batch analyses of these batches is presented in Appendix 2.

Overall Comments:

1. For quality control and future biowaiver purposes, the Applicant accepted on 07/01/15 a regulatory specification of **NLT (b) (4)% at 10 min** using USP Apparatus II Paddle with 50 rpm in water (with 1.2% Tween 80) 900 mL at 37°C.

2. The dissolution method and acceptance criterion tested during the Phase III stage are considered not acceptable since 2.4% Tween 80 used is considered excess. This method will be accepted for interim analysis and a PMC will be issued.
3. The Applicant's justification is acceptable to constitute the Emend powder (b) (4) .
4. The Applicant accepted on 07/08/15 the Agency's recommendation to update the M32P51 specification section, for a PMC and
5. From the Biopharmaceutics perspective, this NDA is reviewed and found acceptable. Therefore, NDA207865 is recommended for approval with a PMC.

5 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

07/10/15 updated M32P51 Specifications to include Dissolution and Acceptance Criterion

Table 1. Specification Established for EMEND® for Oral Suspension

Tests	Acceptance Criteria	Test Methods
Description	**Release and Shelf-Life** Pink to light pink (b) (4) powder	Visual observation.
Identity by HPLC-DAD	**Release** The wavelengths of maximum absorbance in the UV spectrum taken at the apex of the Aprepitant peak in the sample chromatogram are within (b) (4) of the wavelengths of maximum absorbance in the corresponding UV spectrum taken for the standard.	Assay, Degradation Products, Uniformity of Dosage Units & Identity by HPLC Sec 3.2.P.5.2.1
Identity by HPLC*	The retention times of the Aprepitant peak in the sample and standard chromatograms are essentially the same (within ± 2.5%)	Assay, Degradation Products, Uniformity of Dosage Units & Identity by HPLC Sec 3.2.P.5.2.1
Assay	**Release and Shelf-Life** 90.0 – 110.0% of Label Claim (b) (4)	Assay, Degradation Products, Uniformity of Dosage Units & Identity by HPLC Sec 3.2.P.5.2.1
Degradation Products	**Release and Shelf-Life** Any Unspecified: NMT (b) (4)% Total Degradation Products: NMT (b) (4)%	Assay, Degradation Products, Uniformity of Dosage Units & Identity by HPLC Sec 3.2.P.5.2.1
Uniformity of Dosage Units	**Release** Complies with the requirements of the USP <905>	Assay, Degradation Products, Uniformity of Dosage Units & Identity by HPLC Sec 3.2.P.5.2.1
Time for Constitution	**Release and Shelf-Life** Average Constitution Time (b) (4) seconds	Time for Constitution Sec 3.2.P.5.2.2
Dissolution	**Release and Shelf-Life**** Conforms to USP <711> Q= (b) (4)% at 10 minutes	Dissolution Sec 3.2.P.5.2.5
Dispersion Fineness	**Release and Shelf-Life**** Conforms to USP	As per USP <2>
Particle Size Distribution: Drug Substance Particle Size in In-Use Suspension	**Release*** and Shelf-Life** D (b) (4)	Particle Size Sec 3.2.P.3.4