MEMORANDUM OF STATISTICAL REVIEW

NDA #:	022-023
Supplement #:	017 (SDN 0139 & SN 0532) pediatric supplement efficacy
Related IND #:	48,924
Product Name:	Emend (fosaprepitant 150-mg) I.V.
Indication(s):	prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatric patients 6 months and older
Applicant:	Merck Sharp & Dohme (Merck & Co.)
Dates:	Stamp date: 10/03/2017 Primary review due date: 3/5/2018 PDUFA date: 4/3/2018
Review Priority:	standard
Biometrics Division:	III
Statistical Reviewer:	Ling Lan, PhD
Concurring Reviewers:	George Kordzakhia, PhD
Medical Division:	DGIEP
Clinical Team:	Aisha Johnson, M.D., Anil Rajpal, M.D. (Team Leader)
Project Manager:	Mary Chung

Oral aprepitant (EMEND™) is a potent and selective NK1 receptor antagonist. It is approved for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC) in oncology patients 6 months and older under NDA 21-549 in 2014. Fosaprepitant is a water-soluble prodrug that is completely converted to aprepitant within the 30- to 60-minute duration of IV administration. Fosaprepitant is approved for the prevention of HEC and MEC in adults under NDA 22023/S-004 (HEC) in 2010 and NDA 22023/S-006 (MEC) in 2016, respectively.

This submission intends to fulfill the Written Request for pediatric exclusivity. The sponsor proposes to extrapolate the efficacy of the proposed pediatric 1-day fosaprepitant regimen from the adult fosaprepitant program and bridge the efficacy of the pediatric 3-day fosaprepitant regimen from that demonstrated with the pediatric 3-day oral aprepitant regimen.

This submission also included clinical data from a pre-maturely terminated phase 3 study, Study 044, and cited two studies in the ISE: a Phase IIb Study 029 and an open-label PK Study 134 (no CSRs or data sets were included for the two Phase II studies). For a summary

of the three pediatric studies, please refer to the Appendix. The dataset for Study 044 located at the link below:
\\CDSESUB1\evsprod\NDA022023\0139\m5\datasets\p044mk0517\analysis\legacy\datasets

The sponsor terminated Study 044 pre-maturely due to the approval of the oral aprepitant in a similar pediatric population. The study design did not pre-specify or assume an option for early stopping. By the time of study termination, there were 71 subjects who completed the trial out of the planned 180 subjects. The efficacy analyses were not performed by the sponsor, and no efficacy results were included in Section 14 of the proposed draft label. The sponsor stated that the dataset from Study 044 is not intended to support the applied indication. Since the efficacy relies on the extrapolation, statistical review team did not conduct further statistical assessment on the data of Study 044.

Appendix

Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID Design*	Treatment/ Sample Size	Endpoint/Analysis	Preliminary Findings (Sponsor)
Study 044 MC, R, DB, PG, about 15 days main phase after maximum 28 days of screening phase and followed by maximum 6-month extension PC trial	Fosaprepitant + Ondansetron Versus Ondansetron alone N(1:1) = 37:34 Randomization stratified by age (<2 years, 2 to <6 years, 6 to <12 years and 12 to 17 years), HEC in Cycle 1 and use of dexamethasone in Cycle 1	Complete Response (CR) at the delayed phase, defined as no vomiting, no retching and no use of rescue medication in the >24 to 120 hours following initiation of emetogenic chemotherapy in Cycle 1. No formal hypothesis testing was performed.	Due to early termination of the trial, data from this study were decided not to be used to support the current marketing, i.e. not included in the proposed label, by the sponsor. Descriptive summaries were calculated for each treatment group and their difference on primary and key secondary endpoints.
Study 029 MC, open-label Phase 2b PK study	n=153 pediatric subjects from birth to <12 years old with no control arm	PK and safety endpoints	No study report
Study 303 MC, open-label, 6-month	Birth to 17 years old No control arm	PK and safety endpoints	No study report

* MC: multi-center, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, AC: active controlled

Table 11-1

Number (%) of Subjects with Complete Response or No Vomiting
by Phase and Treatment in Cycle 1
Intent to Treat (ITT) Population

	Fosaprepitant Regimen	Control Regimen	Difference[b]
Endpoint and phase	n/m[a] (%)	n/m (%)	%
Complete Response in Acute Phase	26 / 37 (70.3)	20 / 34 (58.8)	11.4
Complete Response in Delayed Phase	18 / 37 (48.6)	14 / 34 (41.2)	7.5
Complete Response in Overall Phase	15 / 37 (40.5)	11 / 34 (32.4)	8.2
No Vomiting in Overall Phase	15 / 37 (40.5)	11 / 34 (32.4)	8.2

[a]n/m = Number of Subjects with desired response/number of Subjects included in time point
[b]Difference: Fosaprepitant Regimen - Control Regimen
Complete Response = No vomiting, no retching and no use of rescue medication.
Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: >24 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.

Source: [P044MK0517: analysis-adsl; adeff]

Source: Page 115 on Study 044 CSR

Table 11-3

Number (%) of Subjects with Complete Response in the Delayed Phase
by Subgroup and Treatment in Cycle 1
Intent to Treat (ITT) Population

	Fosaprepitant Regimen n/m (%)	Control Regimen n/m (%)	Difference[b] %
Age			
2 years to <6 years	2/6 (33.3)	5/7 (71.4)	-38.1
6 years to <12 years	9/13 (69.2)	3/11 (27.3)	42.0
12 years to 17 years	7/18 (38.9)	6/16 (37.5)	1.4
Gender			
Male	11/24 (45.8)	8/20 (40.0)	5.8
Female	7/13 (53.8)	6/14 (42.9)	11.0
Race			
Asian	2/8 (25.0)	1/5 (20.0)	5.0
Multiple	1/1 (100.0)	1/2 (50.0)	50.0
White	14/27 (51.9)	12/27 (44.4)	7.4
Other	1/1 (100.0)	0/0	100.0
Receipt of High Risk Emetogenic Chemotherapy in Cycle 1			
Yes	16/34 (47.1)	13/32 (40.6)	6.4
No	2/3 (66.7)	1/2 (50.0)	16.7
Use of Dexamethasone as Part of the Antiemetic Regimen in Cycle 1			
Yes	5/14 (35.7)	4/11 (36.4)	-0.6
No	13/23 (56.5)	10/23 (43.5)	13.0
Single versus multiple day chemotherapy			
Single day	6/7 (85.7)	6/12 (50.0)	35.7
Multiple day	12/30 (40.0)	8/22 (36.4)	3.6

Complete Response: No vomiting, no retching and no use of rescue medication.
[a]n/m = Number of Subjects with desired response/number of Subjects included in time point
[b]Difference: Fosaprepitant Regimen - Control Regimen
Delayed Phase: >24 to 120 hours following initiation of chemotherapy.

Source: [P044MK0517: analysis-adsl; adeff]

Source: Page 117 on Study 044 CSR

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

/s/

LING LAN
02/28/2018

GEORGE KORDZAKHIA
03/02/2018