U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Supplement Number:	207865 and 21549 / 25
Drug Name:	EMEND™ (Aprepitant) 25 mg Capsule & Powder for Suspension
Indication:	Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy in pediatrics.
Applicant:	Merck Sharp & Dohme Corp.
Dates:	Received: July 28 2014; PDUFA: August 28, 2015
Review Priority:	Standard
Biometrics Division:	DBIII
Statistical Reviewer:	Wen-Jen Chen, Ph.D.
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Medical Division:	Division of Gastroenterology and Inborn Errors Products
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Keywords: NDA review, clinical studies, Cochran-Mantel-Haenszel test

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1. EXECUTIVE SUMMARY

The applicant submitted NDAs 21549 and 207865 to fulfill the PREA PMRs associated with Emend (aprepitant) Capsules. To fulfill the PREA PMR, the applicant was required to study the safety and efficacy of Emend (capsules) in patients 6 months to 17 years. However, in order to study the drug product in younger children, the applicant developed a pediatric dosage form (oral suspension) for younger children. The primary objectives for NDA 21549 is to evaluate the efficacy of EMEND capsules for use in adolescents, ages 12 to 17 while NDA 207865 is to support the use of emend powder in pediatric patients 6 months to less than 12 years old.

For the two NDA submissions (NDAs 207865 and 21549), the applicant conducted only one phase-3 trial (Study P208) to support the use of aprepitant regimen for prevention of nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy in pediatric patients (6 months to 17 years) receiving emetogenic chemotherapy for a documented malignancy.

Study P208 was a randomized, double-blind, active-comparator controlled, parallel-group study (with in-house blinding) designed to assess the efficacy and safety of oral aprepitant for the prevention of CINV in pediatric patients receiving emetogenic chemotherapy for a documented malignancy. Assignment to one of two treatment regimens (aprepitant regimen or control regimen) was done via an Interactive Voice Response System (IVRS).

The primary efficacy assessment period was the delayed phase, or the 25 to 120 hours following initiation of emetogenic chemotherapy. Secondary assessments were the acute (0 to 24 hours) and overall (0 to 120 hours) phases. Patients who elected to participate in this study were required to participate in Cycle 1, which is the only cycle that the data were based on. Following Cycle 1, at the discretion of the investigator, subjects were invited to receive open label aprepitant in subsequent cycles (Cycles 2-6).

The statistical reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints along with the efficacy comparisons by site and country and agrees that the superiority of aprepitant regimen to control regimen claimed by the applicant for the proposed indication was demonstrated. In other words, data of Study 208 support aprepitant's use for the prevention of CINV in pediatric patients receiving emetogenic chemotherapy for a documented malignancy.

2. INTRODUCTION

For the two NDA submissions (NDAs 207865 and 21549), the applicant mainly conducted one phase-3 trial (Study P208) to support the use of aprepitant regimen for prevention of nausea and vomiting associated with initial and repeat courses of emetogenic chemotherapy in pediatric patients receiving emetogenic chemotherapy for a documented malignancy. The primary objectives for NDA 21549 is to evaluate the efficacy of EMEND capsules for use in adolescents, ages 12 to 17, while NDA (207865) is to support the use of emend power in pediatrics with ages from 6 months to 12 years old.

2.1 OVERVIEW FOR STUDY P208

The primary objective for Study P208 was to compare the three-day oral aprepitant regimen (aprepitant plus ondansetron) to ondansetron alone (hereafter referred to as the control regimen) with respect to the efficacy endpoint of Complete Response (no vomiting, no retching, and no use of rescue medication) in the 25 to 120 hours following the initiation of emetogenic chemotherapy in Cycle 1 (delayed phase).

There were 51 trial centers that participated in this study. Of those, 49 centers randomized at least one subject: two in Republic of Korea, four in Israel, two in Russia, four in Turkey, three in Italy, three in Spain, two in United Kingdom, one in Croatia, one in Denmark, two in Greece, two in Hungary, two in Lithuania, two in Netherlands, three in Poland, one in Slovenia, two in Sweden, one in Argentina, two in Chile, two in Colombia, one in Dominican Republic, two in Ecuador, two in Mexico, one in Peru, and two in the United States.

Protocol 208 was a randomized, double-blind, active-comparator controlled, parallel-group study (with in-house blinding) designed to assess the efficacy and safety of oral aprepitant for the prevention of CINV in pediatric patients receiving emetogenic chemotherapy for a documented malignancy. Assignment to one of two treatment regimens (aprepitant regimen or control regimen) was done via an Interactive Voice Response System (IVRS).

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

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

Total 307 subjects met inclusion criteria and were randomized to treatment groups (155 for aprepitant regimen versus 152 for control regimen) based on a computer generated allocation schedule. Randomization occurred centrally via the Interactive Voice Response System (IVRS).

2.2 DATA SOURCE

To assess the clinical efficacy of Study P208 used in support of the proposed indication, this reviewer reviewed the original electronic NDA supplement submission, dated 07/28/2014 located at "\\CDSESUB1\evsprod\NDA021549\021549.enx".

3. STATISTICAL EVALUATION

3.1 DATA AND ANALYSIS QUALITY

The statistical reviewer has successfully confirmed the sponsor's analysis results from the analysis datasets submitted in this application. The efficacy data for the phase 3 Study P208 included in this application were carefully examined and the quality was determined to be acceptable.

3.2 EVALUATION OF EFFICACY FOR STUDY P208

3.2.1 Description of Studies

The applicant submitted single study (P208) to support the emend regimen in the prevention of chemotherapy-induced nausea and vomiting (CINV) in pediatrics patients. Study P208 was titled as "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". Trial initiation date was 22-Sep-2011 while completion date was 16-Aug-2013

There were 51 trial centers that participated in this study. Of those, 49 centers randomized at least one subject: two in Republic of Korea, four in Israel, two in Russia, four in Turkey, three in Italy, three in Spain, two in United Kingdom, one in Croatia, one in Denmark, two in Greece, two in Hungary, two in Lithuania, two in Netherlands, three in Poland, one in Slovenia, two in Sweden, one in Argentina, two in Chile, two in Colombia, one in Dominican Republic, two in Ecuador, two in Mexico, one in Peru, and two in the United States.

3.2.1.1 Study Design and Objectives

Protocol 208 was a randomized, double-blind, active-comparator controlled, parallel-group study (with in-house blinding) designed to assess the efficacy and safety of oral aprepitant for the prevention of CINV in pediatric patients receiving emetogenic chemotherapy for a documented malignancy.

Randomization was stratified based on the patient's age into one of four age groups (6 months to < 2 years; 2 to < 6 years; 6 to <12 years; or 12 to 17 years) on Day 1 of chemotherapy in Cycle 1, planned use of a chemotherapy agent associated with a Very High Risk of Emetogenicity in Cycle 1 (Yes or No), and planned use of dexamethasone as an antiemetic in Cycle 1 (Yes or No). Patients who satisfied all study entry criteria were randomized (1:1) centrally to receive aprepitant plus ondansetron, with or without dexamethasone (aprepitant regimen), or ondansetron alone, with or without dexamethasone (control regimen) concomitantly with emetogenic chemotherapy for treatment of a documented malignancy. Assignment to one of two treatment regimens (aprepitant regimen or control regimen) was made via an Interactive Voice Response System (IVRS).

The treatment regimens are outlined in Table 3.2.1.1.1

Table 3.2.1.1.1 (Applicant's) Treatment plans

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

[A] Intravenous dexamethasone was permitted to be administered to both treatment arms as part of the anti-emetic regimen, at the discretion of the investigator. If dexamethasone was administered as part of the anti-emetic regimen for patients receiving aprepitant, dexamethasone was to be administered at 50% of the established dose in children.
[B] For patients receiving chemotherapy on Days 2 or 3, aprepitant was to be administered 60 minutes prior to initiation of chemotherapy.
[C] Branded ondansetron (Zofran™) was required for Cycle 1 of this study. Zofran™ was not be supplied by the SPONSOR, meaning Merck Headquarters or IVRS. Zofran™ was to be provided (b) (4). If procurement of Zofran™ was not feasible, discussion with the Merck Clinical Monitor and/or delegate was required. Generic ondansetron was permitted during the Optional Cycles 2-6.
[D] Preventative antiemetic treatment with ondansetron was permitted ONLY on days that chemotherapy is administered. Once the chemotherapy treatment regimen was complete, ondansetron was no longer permitted as prophylactic treatment.

As noted by this reviewer from the study reports, the primary data were confined to cycle 1 only.

The primary efficacy assessment period was the delayed phase, or the 25 to 120 hours following initiation of emetogenic chemotherapy. Secondary analysis included the acute (0 to 24 hours) and overall (0 to 120 hours) phases. Patients who elected to participate in this study were required to participate in Cycle 1. Following Cycle 1, at the discretion of the investigator, subjects were invited to receive open label aprepitant in subsequent cycles (Cycles 2-6).

A subject could have withdrawn from the trial at any time or could have been dropped from the trial at the discretion of the investigator should any untoward effects have occurred. In addition, the investigator or the applicant may have withdrawn a subject for violating the trial plan or for administrative and/or other safety reasons. The investigator or trial coordinator was required to notify the applicant immediately (by telephone or FAX) when a subject was discontinued/withdrawn due to an adverse experience. When a subject discontinued/withdrew prior to trial completion, all applicable activities scheduled for the final visit were to be performed at the time of discontinuation.

3.2.1.2 Efficacy Endpoints and Analyses

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

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

In addition to the above mentioned efficacy endpoints, the exploratory endpoints included the number of emetic episodes, the time to first rescue medication, and the time to first vomiting in the 120 hours following initiation of emetogenic chemotherapy .

Analysis Populations and Methods

The applicant indicated that there were three types of patient populations analyzed in the study: intent-to-treat (ITT) population, full analysis set (FAS), and per-protocol population.

The intent-to-treat (ITT) population which consists of all patients (in the group they were) randomized and who received study drug will serve as the primary population for the analysis of efficacy data in this study.

A supportive analysis will be performed for the primary and secondary efficacy endpoints using the full analysis set (FAS) population. The FAS population is a subset of all randomized patients including all patients who have received chemotherapy, received a dose of study drug and have at least one post-treatment efficacy assessment. Patients excluded from the FAS will be considered as having an unfavorable response in the ITT analysis.

An additional supportive analysis using the per-protocol (PP) population will be performed for the primary efficacy endpoint. The per-protocol population excludes patients due to important deviations from the protocol that may substantially affect the results of the primary efficacy endpoint.

Nominal p-values were computed for other efficacy analyses as a measure of strength of association between the endpoint and the treatment effect rather than formal tests of hypotheses. Unless otherwise stated, all statistical tests were conducted at significant level of 0.05 (two-sided).

The primary efficacy analysis compared the aprepitant regimen to the control regimen with respect to the proportion of patients reporting Complete Response in the delayed phase.

The secondary efficacy analyses compared the aprepitant regimen to the control regimen with respect to the proportion of patients reporting Complete Response in the acute and overall phases along with the proportion of patients reporting No Vomiting in the overall phase.

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

A supportive analysis was made using a logistic regression model that includes terms for treatment (aprepitant regimen, control regimen), use of dexamethasone as an antiemetic in Cycle 1 (yes, no), receipt of a very high risk emetogenic chemotherapy agent in Cycle 1 (yes, no), and age (<2 years, 2 to 17 years). The final model did not include treatment interaction terms

Any vomiting, retching, dry heaves, or use of rescue therapy within a phase (acute or delayed) defined a patient as having an unfavorable response for that phase and for the overall analysis (regardless of missing data at other time points) for all three efficacy patient populations (ITT, FAS, and PP). In the ITT and FAS, response to therapy in a particular phase was assessed based on the observed data in that phase. Patients with missing binary data for the primary and secondary endpoints were classified as non-responder/failure in both the ITT and FAS efficacy analyses. In the PP population, patients with any missing data (in the absence of vomiting or use of rescue therapy at another time point) were excluded from the analysis for that phase and for the overall phase analysis.

For the exploratory analysis of time to first use of rescue medication, Kaplan-Meier curves depicting the percentage of patients who did not use rescue medication (since the initiation of emetogenic chemotherapy) were presented. Kaplan-Meier curves depicting the percentage of patients who are vomiting-free (ignoring rescue) since the initiation of emetogenic chemotherapy were also presented for the time to first vomiting. The Log-Rank test will be used for the treatment comparison.

As to the multiplicity adjustments, the applicant indicated that no multiplicity adjustments were planned since for the primary hypothesis, there was a single comparison of two treatments using one endpoint. However, the applicant provided an analysis strategy for the primary and secondary endpoints. Table 3.2.1.2.1 summarizes the hierarchical order of the analyses for the primary and secondary endpoints.

Table 3.2.1.2.1 (Applicant's) Analysis Strategy for primary and secondary endpoints

Endpoint/Variable (Description, Time Point)	Primary vs. Supportive Approach†	Statistical Method	Analysis Population	Missing Data Approach
Primary Hypothesis				
Proportion of patients with complete response from 25 to 120 hours following initiation of emetogenic chemotherapy	P	Stratified Cochran-Mantel-Haenzel test‡	Intent-to-treat	Observed Data
Proportion of patients with complete response from 25 to 120 hours following initiation of emetogenic chemotherapy	S	Stratified Cochran-Mantel-Haenzel test	FAS	Observed Data
Secondary Objectives				
Proportion of patients with complete response from 0 to 24 hours following initiation of emetogenic chemotherapy	P	Stratified Cochran-Mantel-Haenzel test	Intent-to-treat	Observed Data
Proportion of patients with complete response from 0 to 120 hours following initiation of emetogenic chemotherapy	P	Stratified Cochran-Mantel-Haenzel test	Intent-to-treat	Observed Data
Proportion of patients with no vomiting from 0 to 120 hours following initiation of emetogenic chemotherapy	P	Stratified Cochran-Mantel-Haenzel test	Intent-to-treat	Observed Data

† P=Primary approach; S=Secondary approach.
‡ Stratified by age (<2 years, 2 to 17 years), use of dexamethasone as an antiemetic in Cycle 1 (yes, no), and receipt of Very High Risk emetogenic chemotherapy agent in Cycle 1 (yes, no).
Source: Table 9-6 at page 56 of Study P208 report.

Sample size

For sample size calculation, the applicant indicated that this study randomized approximately 150 patients into the aprepitant regimen group and 150 patients into the control regimen group and has 80% power to demonstrate the superiority of the aprepitant regimen over the control regimen at an overall one-sided 2.5% alpha-level if the underlying treatment difference in Complete Response is 15 percentage points. The power and sample size are based on the following assumptions: 1) an approximately 3% (overall) dropout rate, and 2) an underlying response rate of 60% for the control regimen.

Missing Data

Patients with missing binary data for the primary and secondary endpoints were classified as non-responder/failure in the ITT efficacy analyses.

3.2.2 Patient Disposition and Demographic and Baseline Characteristics

Of the 342 subjects screened for inclusion in the study, 35 subjects were excluded during screening and not randomized: 2 for physician decision, 27 for screen failure, and 6 for withdrawal by subjects. The remaining 307 subjects met inclusion criteria and were randomized to treatment based on a computer generated allocation schedule. As previously stated, randomization occurred centrally via the Interactive Voice Response System (IVRS). Subjects were randomized at 49 sites worldwide. Enrollment at study sites ranged from 1 to 16 subjects. The disposition of the 307 subjects who met the inclusion criteria and were randomized is in Table 3.2.2.1.

Table 3.2.2.1 (Applicant's) Disposition of patients for cycle 1 – Study P208

	Aprepitant Regimen		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	155		152		307	
Study Disposition						
Completed	150	(96.8)	149	(98.0)	299	(97.4)
Discontinued	5	(3.2)	3	(2.0)	8	(2.6)
Adverse Event	2	(1.3)	0	(0.0)	2	(0.7)
Physician Decision	0	(0.0)	1	(0.7)	1	(0.3)
Protocol Violation	2	(1.3)	0	(0.0)	2	(0.7)
Withdrawal By Subject	1	(0.6)	2	(1.3)	3	(1.0)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)
Study Medication Disposition						
Completed	149	(96.1)	149	(98.0)	298	(97.1)
Did Not Take Study Medication	3	(1.9)	2	(1.3)	5	(1.6)
Discontinued	3	(1.9)	1	(0.7)	4	(1.3)
Adverse Event	2	(1.3)	0	(0.0)	2	(0.7)
Non-Compliance With Study Drug	1	(0.6)	0	(0.0)	1	(0.3)
Withdrawal By Subject	0	(0.0)	1	(0.7)	1	(0.3)
Unknown	0	(0.0)	0	(0.0)	0	(0.0)
Each subject is counted once for Study Disposition, Study Medication Disposition based on the latest corresponding disposition record.						
Unknown: A disposition record did not exist at the time of reporting.						

Source: Table 10-4 at page 69 in Study P208 Report.

Based upon Table 3.2.2.1, the applicant indicated that 96.8% of subjects in the aprepitant regimen and 98% of subjects in the control regimen completed Cycle 1. There were no clinically significant differences between treatment regimens in the percentage of subjects who completed the study. In addition, the study medication disposition reflects that 96.1% of subjects in the aprepitant regimen and 98.0% of subjects in the control regimen completed study medication.

Of the 307 subjects randomized, 302 subjects were included in the ITT population. Five subjects were excluded from the ITT population because they did not receive study medication. A supportive analysis using the Full Analysis Set (FAS) patient population included all randomized patients who (1) received chemotherapy, (2) received at least one dose of study medication, and (3) had at least one post-treatment efficacy assessment. The five subjects excluded from the ITT population were also excluded from the FAS because

they did not receive study medication. An additional subject was excluded from the FAS population because this subject did not complete the post-treatment efficacy assessment; this subject was considered as having an unfavorable response in the ITT analysis.

An additional supportive analysis using the Per-Protocol (PP) population excludes patients due to important deviations from the protocol that may substantially affect the result of the primary efficacy endpoint. Patients excluded from the PP analysis may be excluded from all phases of the analysis (acute, delayed, and overall), or by overall phase plus acute or delayed phases. Exclusion from analysis by phase was determined by when the violation occurred. Any patient excluded from the acute or delayed phase was also excluded from the overall phase. A total of 63 subjects were excluded from the PP population due to protocol violations.

Table 3.2.2.2 displays the baseline demographic and characteristics of all randomized subjects.

Table 3.2.2.2 (Applicant's) Baseline demographic and characteristics – Study P208

	Aprepitant Regimen		Control Regimen		Total	
	n	(%)	n	(%)	n	(%)
Subjects in population	152		150		302	
Gender						
Male	84	(55.3)	79	(52.7)	163	(54.0)
Female	68	(44.7)	71	(47.3)	139	(46.0)
Age (Months)						
6 months to <2 years	19	(12.5)	16	(10.7)	35	(11.6)
2 years to <6 years	45	(29.6)	43	(28.7)	88	(29.1)
6 years to <12 years	41	(27.0)	43	(28.7)	84	(27.8)
12 years to 17 years	47	(30.9)	48	(32.0)	95	(31.5)
Mean	97.7		99.4		98.5	
SD	63.2		60.9		62.0	
Median	86.5		91.5		89.5	
Range	6 to 213		6 to 214		6 to 214	
Race						
American Indian Or Alaska Native	2	(1.3)	0	(0.0)	2	(0.7)
Asian	11	(7.2)	16	(10.7)	27	(8.9)
Black Or African American	0	(0.0)	2	(1.3)	2	(0.7)
Multiple	20	(13.2)	22	(14.7)	42	(13.9)
White	119	(78.3)	110	(73.3)	229	(75.8)
Ethnicity						
Hispanic Or Latino	36	(23.7)	32	(21.3)	68	(22.5)
Not Hispanic Or Latino	111	(73.0)	112	(74.7)	223	(73.8)
Not Reported	2	(1.3)	4	(2.7)	6	(2.0)
Unknown	3	(2.0)	2	(1.3)	5	(1.7)
Use of Dexamethasone as Part of the Antiemetic Regimen in Cycle 1						
Yes	44	(28.9)	42	(28.0)	86	(28.5)
No	108	(71.1)	108	(72.0)	216	(71.5)
Very High Risk Emetogenicity Chemotherapy						
Yes	99	(65.1)	101	(67.3)	200	(66.2)
No	53	(34.9)	49	(32.7)	102	(33.8)

Source: Table 10-7 at page 73 in Study P208 Report.

Based upon Table 3.2.2.2, the applicant indicated that there were more males (54.0%) than females (46.0%) randomized, with a similar proportion of male and female subjects between the two treatment regimens. There was an approximately even distribution of subjects in the 2 to <6 year, 6 to <12 year, and 12 to 17 year cohorts (29.1%, 27.8%, and 31.5%, respectively),

with similar distribution of age in each age cohorts between the two treatment regimens. Subjects in the youngest cohort (6 months to <2 years of age) represented 11.6% of subjects.

The applicant indicated that enrollment of subjects into the youngest cohort was challenging. Efforts were made to increase the focus on enrollment of the subjects in this cohort, including selection of participating sites with access to young patients and closing enrollment of subjects in the older age cohorts. The number of subjects in the 6 months to <2 year cohort was evenly distributed between the two treatment groups.

A majority of the subjects were of the white race, and approximately 25% of subjects were representative of other races. The proportions of subjects of specific ethic origin were similar between the two treatment groups. The most common primary malignancies were Ewing's sarcoma and osteosarcoma (~11%), followed by rhabdomyosarcoma and neuroblastoma, representing approximately 8% of the population and medullablastoma and acute lymphocytic leukaemia, which represented 7% of the population. In general, the treatment groups were balanced with regard to primary malignancies.

Receipt of a chemotherapy agent associated with a very high risk of emetogenicity (VHEC) is considered a risk factor for experiencing CINV. Subjects were stratified by planned use of a VHEC agent in Cycle 1 at the time of randomization. The proportion of patients receiving a VHEC agent on Day 1 was similar in both treatment groups.

Because of the prophylactic benefit of intravenous dexamethasone in the prevention of CINV, subjects were also stratified by the planned use of dexamethasone as part of the antiemetic regimen in Cycle 1 at the time of randomization. A majority of patients did not receive dexamethasone as part of the antiemetic regimen in Cycle 1 (71.5%). Of those subjects that did receive prophylactic dexamethasone in Cycle 1 (28.5%), their use was approximately even between the two treatment groups.

3.2.3 Sponsor's Efficacy Results and Conclusions

The applicant indicated that the focus for the evaluation of efficacy is the Cycle 1 data and thus no efficacy evaluation was performed for Cycles 2 through 6. Of note, the p-values reported from the primary CMH analysis using ITT population in the following table were one-sided. Therefore, the differences between Aprpitant regimen and the control regimen was declared if $p \leq 0.025$.

Recall that the Complete Response in the delayed phase (i.e., 25 to 120 hours) was the primary endpoint of this study and Complete Response in the acute phase (0 to 24 hours), Complete Response and No Vomiting in the overall phase (0 to 120 hours) were secondary endpoints.

Complete Response: Delayed (Primary), Acute and Overall (Secondary)

The proportion of patients with Complete Response in the delayed, acute, and overall phases, using the CMH test and ITT patient population, is displayed in Table 3.2.3.1.

Table 3.2.3.1 (Applicant's) Number (%) of Patients with Complete Response† by Phase and Treatment Group - Cycle 1 using ITT Population – Study P208

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

* $p<0.05$ when compared with Control Regimen.
** $p<0.01$ when compared with Control Regimen.
† Complete Response = No vomiting or retching and no use of rescue medication.
Treatment comparison is made using the CMH test stratified by age group, use of dexamethasone as an antiemetic in Cycle 1, and receipt of a Very High Risk emetogenic chemotherapy agent in Cycle 1.
n/m = Number of patients with desired response/number of patients included in time point
Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: 25 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.
Source: Table 11-1 at page 138 in Study P208 Report.

Based upon Table 3.2.3.1, the applicant indicated that in the delayed phase, significantly ($p<0.0001$) more patients on the aprepitant regimen had Complete Response compared to those on the control regimen. The aprepitant regimen was also more effective than the control regimen in the acute phase (nominal $p=0.0135$) and the overall phase (nominal $p=0.0002$). Similar results were seen using the logistic regression model.

In support of the ITT population, an analysis based on the FAS population was performed. Only one subject (control regimen) was excluded from the FAS population because the subject did not complete the post-treatment efficacy assessment. The results analyzed by the FAS population were nearly identical to those of the ITT population analysis. The results support the finding that the aprepitant regimen is more effective than the control regimen with regard to the Complete Response endpoint.

Finally, the applicant indicated that the results analyzed using the per-protocol population further support the finding that the aprepitant regimen is more effective than the control regimen with regard to the Complete Response endpoint in the delayed, acute, and overall phases.

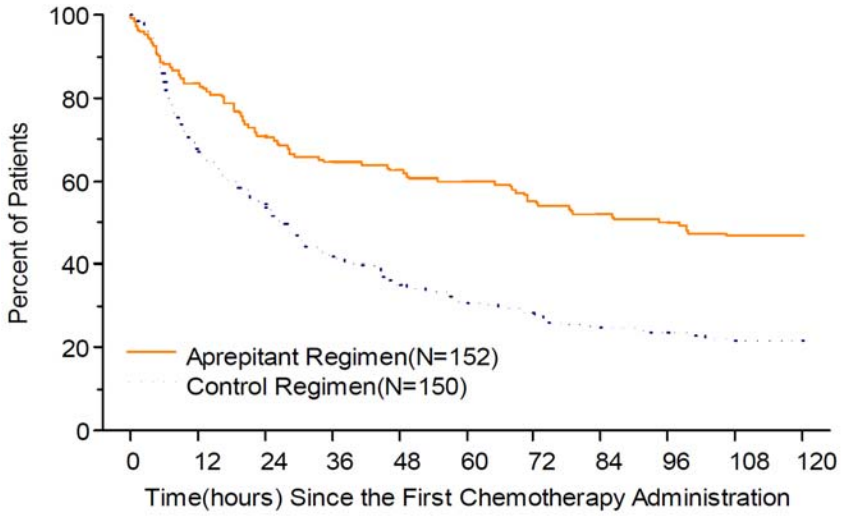
No Vomiting: Overall (Secondary), Acute and Delayed

No Vomiting in the overall phase was a secondary endpoint and defined as no emesis or retching or dry heaves, regardless of whether or not the patient received rescue medication, in the 120 hours following the initiation of emetogenic chemotherapy in Cycle 1. In the overall phase, the percent of patients with no vomiting on the aprepitant regimen (46.7%: 71/152) were significantly greater than that of the control regimen (21.3%: 32/150; $p<0.0001$). The percent of patients in the aprepitant regimen was also numerically higher than that of the control regimen in the acute phase (71.1% versus 53.3%) and in the delayed phase (55.3% versus 28.0%).

Time to First Vomiting in overall phase (Exploratory)

Kaplan-Meier curves for the exploratory endpoint, time to first vomiting, regardless of use of rescue medication, in the overall phase for the Cycle 1 ITT population, are displayed in Figure 3.2.3.2. The Kaplan-Meier curves depict the cumulative percentage of patients who remained vomiting free since the initiation of chemotherapy. The estimated median time is the 50th percentile.

Figure 3.2.3.2 (Applicant's) Kaplan-Meier Curves for Time to First Vomiting Episode from initiation of Chemotherapy in the Overall Phase-Cycle 1 using intent to treat population



The applicant indicated that the Kaplan-Meier curves show that the time to first vomiting was numerically longer in patients in the aprepitant regimen group (estimated median time to first vomiting was 94.5 hours) compared with the control regimen group (estimated median time to first vomiting was 26.0 hours).

Number of Patients with No Use of Rescue Medication Overall, Acute, and Delayed Phases (Exploratory)

Patients were allowed to take rescue medication if needed for treatment of established nausea or vomiting. No rescue is defined as no use of rescue medication. Table 3.2.3.3 displays the proportion of patients who did not use rescue medication by phase and treatment group.

Table 3.2.3.3 (Applicant's) Number (%) of Patients with No Use of Rescue Therapy by Phase and Treatment Group - Cycle 1 using intent to treat Population

	Aprepitant Regimen n/m (%)	Control Regimen n/m (%)
Acute Phase	133 / 152 (87.5)	115 / 150 (76.7)
Delayed Phase	110 / 152 (72.4)	81 / 150 (54.0)
Overall Phase	101 / 152 (66.4)	73 / 150 (48.7)

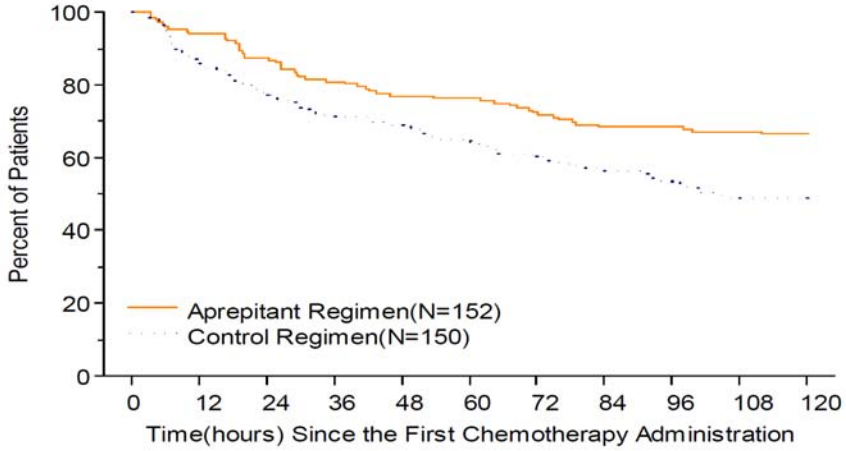
n/m = Number of patients with desired response/number of patients included in time point
Acute Phase: 0 to 24 hours following initiation of chemotherapy.
Delayed Phase: 25 to 120 hours following initiation of chemotherapy.
Overall Phase: 0 to 120 hours following initiation of chemotherapy.

The applicant indicated that in all three phases, the aprepitant regimen showed numerically higher percentage of patients with no use of rescue medication compared to the control regimen.

Time to First Rescue in overall phase (Exploratory)

Kaplan-Meier curves for time to first use of rescue medication in the overall phase for the Cycle 1 using ITT population are displayed in Figure 3.2.3.4.

Figure 3.2.3.4 (Applicant's) Kaplan-Meier Curves for Time to First Rescue Medication from Start of Chemotherapy in the Overall Phase - Cycle 1 using Intent to Treat population



The applicant indicated that the Kaplan-Meier curves show that the time to first rescue was numerically longer in patients in the aprepitant regimen group compared with the control regimen group.

3.2.4 Sponsor's Conclusion

Based on the applicant's results on the CINV study, they concluded that in pediatric cancer subjects 6 months to 17 years of age treated with emetogenic chemotherapy, the 3-day oral aprepitant regimen is more effective than the control regimen for the prevention of chemotherapy induced nausea and vomiting, as measured by the proportion of patients who achieved Complete Response in all phases.

In addition, aprepitant regimen is more effective than the control regimen for the prevention of chemotherapy induced nausea and vomiting, as measured by the proportion of patients who achieved No Vomiting in the 0 to 120 hours following initiation of emetogenic chemotherapy of Cycle 1 (Overall Phase).

3.2.5 Statistical Reviewer's Findings and Comments

In order to validate the applicant's claim on the efficacy of aprepitant regimen superior to that of control regimen assessed by the proportion of complete response in the delayed phase, in this section, this reviewer has performed the following four analyses based upon the complete response in the delayed phase

1) efficacy comparison by investigator site,
2) efficacy comparison by country,
3) sensitivity analysis using all randomized patients,
4) efficacy comparison using patients with ages in the range of 12 to 17 years old, and
5) efficacy comparison using patients with ages from 6 months to less than 12 years old.

Following the efficacy analyses, this reviewer makes comments on the efficacy strength of the single study.

Statistical Reviewer's Statistical Analysis

1) Efficacy comparison by investigator-site

In order to explore whether the superiority of aprepitant regimen to control regimen assessed by the complete response in the delayed phase was dominated by certain investigator-sites, this reviewer compares the efficacy of aprepitant regimen versus control regimen by investigator-site based upon the complete response in the delayed phase using the ITT population.

Since a small site has no capability to dominate the superiority of aprepitant regimen to control regimen, the numbers of patients for sites with no less than eight patients are explored and presented in Table 3.2.5.1.

Table 3.2.5.1 (Reviewer's) proportions of complete response in the delayed phase by site using ITT population

SITE NUMBER	APREPITANT (A) % (n/N)	CONTROL (C) % (n/N)	DIF. A –C	SITE NUMBER	APREPITANT (A) % (n/N)	CONTROL (C) % (n/N)	DIF. A –C
Site 100936	88.3 (5/6)	33.3 (1/3)	50.0%	**Site 118873**	40.0 (2/5)	0.0 (0/4)	40.0%
Site 188845	37.5 (3/8)	0.0 (0/5)	37.5%	**Site 118875**	60.0 (3/5)	16.7 (1/6)	43.4%
Site 188846	100.0 (5/5)	75.0 (3/4)	25.0%	**Site 79164**	0.0 (0/4)	16.7 (2/12)	-16.7%
Site 110269	25.0 (1/4)	60.0 (3/5)	-35.0%	**Site 94241**	100.0 (7/7)	71.4 (5/7)	28.6%
Site 110274	0.0 (0/3)	0.0 (0/5)	0.0%	**Site 94467**	85.7 (6/7)	33.3 (2/6)	52.4%
Site 112404	40.0 (2/5)	25.0 (1/4)	15.0%	**Site 94621**	100.0 (3/3)	42.9 (3/7)	57.1%
Site 115796	33.3 (1/3)	33.3 (2/6)	0.0%	**Site 97431**	16.7 (1/6)	0.0 (0/3)	16.7%
Site 118868	66.7 (2/3)	20.0 (1/5)	46.7%	**Total**	50.7 (77/152)	26.0 (39/150)	24.7 %

Based upon the results from Table 3.2.5.1, for most sites, the proportions of complete response of aprepitant regimen were 25% higher than that of control regimen. However, since numbers of patients enrolled in most sites were small, no larger than ten, it appears that no site is identified to have abnormally large effect to dominate the superiority of aprepitant regimen to control regimen.

2) Treatment difference analysis by country

In order to explore whether the therapeutic gains (defined as the complete response rate of aprepitant regimen minus that of control regimen) for aprepitant regimen versus control regimen were affected by country, this reviewer tabulates the proportions on the complete response in the delayed phase by country using the ITT population. As the rationale for site comparisons, the numbers of patients for country with no less than eight patients are explored.

The complete responses in the delayed phase by country using ITT population are presented in Table 3.2.5.2.

Table 3.2.5.2 (Reviewer's) Complete response rate in the overall phase by country using ITT population

COUNTRY	APREPITANT (A) % (n/N)	CONTROL (C) % (n/N)	THERAPEUTIC GAIN† % (A - C)
Chile	40.0 (4/10)	12.5 (1/8)	27.5%
Ecuador	75.0 (6/8)	40.0 (2/5)	25.0%
Greece	87.5 (7/8)	44.4 (4/9)	43.1%
Hungary	62.5 (5/8)	12.5 (1/8)	50.0%
Israel	36.4 (4/11)	37.5 (3/8)	-1.1%
Italy	57.1 (4/7)	33.3 (3/9)	23.8%
Korea	10.0 (1/10)	13.3 (2/15)	-3.3%
Lithuania	25.0 (1/4)	14.3 1/7)	10.7%
Netherlands	30.0 (3/10)	0.0 (0/7)	-30.0%
Peru	100.0 (3/3)	42.9 (3/7)	57.1%
Poland	80.0 (8/10)	25.0 (2/8)	55%
Russian Federation	100.0 (7/7)	75.0 (6/8)	25.0%
Spain	45.5 (5/11)	25.0 (2/8)	20.5%
Sweden	20.0 (1/5)	33.3 (1/3)	-13.3%
Turkey	37.5 (3/8)	0.0 (0/10)	37.5%
United Kingdom	25.0 (1/4)	33.3 (3/9)	-8.3%
United States	33.3 (2/6)	0.0 (0/1)	33.3%%
Overall	50.7 (77/152)	26.0 (39/150)	24.7%

†: defined as proportion of complete response of Fosaprepitant regimen minus that of Aprepitant regimen.

Based upon the results from Table 3.2.5.2, the therapeutic gains assessed by complete response rates in the delayed phase for aprepitant regimen versus control regimen for three countries (Hungary, Peru, and Poland) are greater than or equal to 50.0%. However, the therapeutic gains for aprepitant regimen versus control regimen seem to be evenly distributed in the range of -30% to 57.1%. Accordingly, no country is deemed to have abnormally large therapeutic gain to dominate the superiority of aprepitant regimen to control regimen.

3) Sensitivity analysis using all randomized patients

This reviewer noted that five subjects (three subjects in aprepitant regimen and two in control regimen) were excluded from the ITT population because they did not receive study medication. In order to assess the impact of these five subjects on the efficacy comparisons, this reviewer performs proportion difference analysis to compare the effect of aprepitant regimen to that of control regimen using ITT population including these five patients treated as non-responders.

The analysis results are presented by Table 3.2.5.3.

Table 3.2.5.3 (Reviewer's) Efficacy comparisons† assessed based upon complete response by phase

Phase	Aprepitant Regimen n/N (%)	Control regimen n/N (%)	p-value
Delayed Phase	77/155 (49.7)	39/152 (25.7)	P < 0.0001
Acute Phase	101/155 (65.2)	78/152 (51.3)	P = 0.0139
Overall Phase	61/155 (39.4)	30/152 (19.7)	P = 0.00017

†: Efficacy comparison using ITT population including five patients without taking medication and treated as non-responders.

Based upon Table 3.2.5.3, after including the five patients without taking medication but treated as non-responders, the complete response rates of aprepitant regimen are significantly higher than that of control regimen for delayed, acute, and overall phases.

4) Efficacy comparison using patients with ages in the range of 12 to 17 years old.

The Medical Division requested this reviewer to explore the effect of aprepitatnt on the pediatric patients with ages between 12 and 17 years old (i.e., $12 \leq$ years ≤ 17) for NDA 21549. In order to accomplish this requirement, this reviewer applies the applicant's CMH method to compare the effects of aprepitant versus control assessed by complete responses in the delayed, acute, and overall phases using subjects with ages from 12 to 17 years old. The results are presented in Table 3.2.5.4.

Table 3.2.5.4 (Reviewer's) Efficacy comparison by phase using patients with ages between 12 and 17 years old

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

Since type I error rate for the analyses using subjects with ages from 12 to 17 years old was not pre-specified in the protocol, p-values in the above table are included only for references.

Based upon Table 3.2.5.4, the analysis results show that the complete response rates of aprepitant regimen are numerically higher than that of control regimen assessed in the delayed, acute, and overall phases.

5) Efficacy comparison using patients with ages from 6 months to less than 12 years old.

Again, requested by the Medical Division, the statistical reviewer explored the effect of aprepitatnt on the pediatric patients with ages from 6 months to 12 years old for NDA 207865. In order to fulfil the request, this reviewer applies the applicant's CMH method to compare the effects of aprepitant versus control assessed by complete responses in the delayed, acute, and overall phases using subjects with ages under 12 years old. The results are presented in Table 3.2.5.5.

Table 3.2.5.5 (Reviewer's) Efficacy comparison by phase using patients with ages from 6 months to 12 years old

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

Again, the sponsor did not plan any type I error control for the analyses using subjects with ages from 6 months to less than 12 years old, thus p-values in the above table are included only for references.

Based upon Table 3.2.5.5, the analysis results show that the complete response rates of aprepitant regimen are numerically higher than that of control regimen assessed in the delayed, acute, and overall phases.

Summary of Reviewer's Comments on the efficacy strength for Study P208

- Based upon the applicant's statistical analysis results for the primary endpoint, i.e., the complete response rate in the delayed phase, the aprepitant regimen was superior to that of control regimen.

- The reviewer's efficacy comparisons for the CR in the delay phase by site and by country showed that the superiority of the aprepitant regimen versus the control regimen is not dominated by certain sites and countries.

- The reviewer's sensitivity analysis based on the ITT population, including five patients without taking medication and treated as non-responders, showed the CR rates of aprepitant regimen are still significantly higher than that of control regimen for all of the delayed, acute, and overall phases.

- The applicant's results of the secondary endpoint analysis for the complete response rates in the acute and delayed phases along with the no vomiting rate in the overall phase all showed positive in favor of aprepitant regimen. In addition, no vomiting rates of aprepitant regimen were numerically higher than that of control regimen in the acute and delayed phases.

- Finally, the exploratory analyses performed by this reviewer using patients with ages between 12 and 17 years old and ages from months to 12 years old both show that the complete response rates of aprepitant regimen are numerically higher than that of control regimen assessed in the delayed, acute, and overall phases.

- Accordingly, the superiority of aprepitant regimen to control regimen claimed by the applicant for the proposed indication is supported by the submitted data with substantial evidence.

3.3 EVALUATION OF SAFETY

The evaluation of safety of rolapitant is not performed in this statistical review. Please refer to the medical review for this evaluation.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE FOR STUDY P208

The goal of the subgroup analysis is to assess the consistency of the treatment effect for the Aprepitant regimen versus control regimen across subgroups (identified by gender, age group, and race group) assessed by the primary endpoint (complete response for the delayed phase) using the ITT population. Since for age subgroup analysis, pediatric patients with ages from 6 months to less than 12 years old and ages between 12 and 17 years old are already performed in section 3.2.5, age subgroup analysis is not performed in this section. In addition, these subgroup efficacy results (gender and race) should be considered exploratory only and not intended to imply confirmatory hypothesis testing.

For subgroup analysis, this reviewer applies Cochran-Mantel-Haenszel (CMH) test procedure to analyze data since this method was proposed by the applicant for the efficacy comparisons assessed by the primary endpoint.

Gender group (Females versus Males)

Table 4.1.1 presents the results of treatment efficacy comparisons by gender group (Females versus Males).

Table 4.1.1 (Reviewer's) Efficacy comparison assessed by the complete response in the delayed phase using the ITT population - Study P208

Females	n	Number (%) of Patients Responding	Aprepitant versus Control[a] % Difference	P-value
Control Regimen	68	30 (44.1%)		
Aprepitant Regimen	71	20 (28.2%)	15.9	0.049*

Males	n	Number (%) of Patients Responding	Aprepitant versus Control[a] % Difference	P-value
Control Regimen	84	47 (56.0%)		
Aprepitant Regimen	79	19 (24.1%)	31.9	<0.0001*

[a]: Analysis via Cochran Mantel-Haenszel test stratified by gender.
*: Significant at two-sided significance level of 0.05

Table 4.1.1 shows that for both females and males, the responder rates of subjects in the aprepitant regimen are significantly higher than that of control regimen.

Race group (White versus Non-White)

Table 4.1.2 presents the results of treatment efficacy comparisons by race group.

Table 4.1.2 (Reviewer's) Efficacy comparison assessed by the complete response in the delayed phase using the ITT population - Study P208

White	n	Number (%) of Patients Responding	Rolapitant versus Control[a] % Difference	P-value
Control Regimen	119	59 (49.6%)		
Aprepitant Regimen	110	32 (29.1%)	20.5	0.0008*

Non-White	n	Number (%) of Patients Responding	Rolapitant versus Control[a] % Difference	P-value
Control Regimen	33	18 (54.6%)		
Aprepitant Regimen	40	7 (17.5%)	37.1	0.0015*

Analysis via Cochran Mantel-Haenszel test stratified by gender.*: Significant at two-sided significance level of 0.05

Table 4.1.2 shows that for both White and Non-White subgroups, the responder rates of subjects in the aprepitant regimen are significantly higher than that of control regimen.

4.2 Other Special/Subgroup Populations- Not applicable

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

- Based upon the statistical analysis results for the primary endpoint performed by the applicant showed that the complete response rate in the delayed phase of aprepitant regimen was superior to that of control regimen.

- The efficacy comparisons by site and by country performed by this reviewer showed that the superiority of aprepitant regimen versus control regimen assessed by the complete response in the delayed phase is not dominated by certain sites and countries.

- The sensitivity analysis performed by this reviewer using ITT population including five patients without taking medication and treated as non-responders showed the complete response rates of aprepitant regimen are still significantly higher than that of control regimen for delayed, acute, and overall phases.

- The results of the secondary endpoint analyses for the complete response rates in the acute and delayed phases along with the no vomiting rate in the overall phase performed by the applicant all showed positive in favor of aprepitant regimen. In addition, no vomiting rates of aprepitant regimen were numerically higher than that of control regimen in the acute and delayed phases.

- Finally, the exploratory analyses performed by this reviewer using patients with ages between 12 and 17 years old and ages from 6 months to 12 years old both show that the complete response rates of aprepitant regimen are numerically higher than that of control regimen assessed in the delayed, acute, and overall phases.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Based upon the comments given in section 5.1, the superiority of aprepitant regimen to control regimen claimed by the applicant for the proposed indication is supported by the submitted data.

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

/s/

WEN JEN CHEN
07/29/2015

YEH FONG CHEN
07/29/2015

MICHAEL E WELCH
07/30/2015