CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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STATISTICAL REVIEW(S)

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- ADDENDUM

Clinical Studies

NDA/Serial Number:	22445/0073
Drug Name:	SUSTOL® (granisetron extended release) Injection
Indication:	Chemotherapy-Induced Nausea and Vomiting (CINV)
Applicant:	Heron Therapeutics, Inc.
Dates:	Received: July 17, 2015 PDUFA: January 15, 2016
Review Priority:	Standard but 6 Months for Re-Submission
Biometrics Division:	DBIII
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewers:	Stephen Wilson, Dr.P.H.
Medical Division:	Division of Gastroenterology and Inborn Errors Products
Clinical Team:	Lauren Weintraub, M.D. and Stephanie Omokaro, M.D. (TL)
Project Manager:	James Carr

Keywords: Subgroup Analysis

I. Introduction

After the statistical review was completed and signed off on 1/4/2016, the clinical review team informed the statistical reviewer that they had observed some discrepancies in the applicant's re-classifications for Study C2006-01. In particular, the applicant included liposomal doxorubicin as HEC chemotherapy when combined with cyclophosphamide, but as MEC when not combined with cyclophosphamide. In other words, the applicant only considered liposomal doxorubicin mildly emetogenic. The clinical reviewers also noted that the sponsor had inconsistently applied the specifications for defining the per-protocol population. As a result, several Information Requests (IRs) were sent to the applicant asking for data and re-analyses.

The sponsor's response to the aforementioned IRs was submitted and stored in the following links: \\CDSESUB1\evsprod\NDA022445\0096, \\CDSESUB1\evsprod\NDA022445\0113, and \\CDSESUB1\evsprod\NDA022445\0115.

II. Statistical Reviewer's Re-Analyses and Comments

1. (***Sponsor's Re-analysis Results for MEC plus AC***) Using the applicant's re-submitted data in SN0096 submission, the statistical reviewer successfully confirmed the applicant's re-analysis results. As the sponsor only submitted their re-analysis results for MEC and MEC plus AC populations (see Tables 4.1 and 4.2 in Appedix), the clinical review team asked the statistical reviewer to perform the re-analysis for the AC only subpopulation for Study C2006-01 and results are displayed in Table 2.1. As shown in the table, none of the p-values are less than 0.05 even though all of the upper bounds of the 95% confidence intervals for the observed difference between Sustol-10 mg and Aloxi 0.25 mg (i.e., Palonosetron, abbreviated as Palo) are greater than zero and lower bounds are greater than -15 (the sponsor's pre-specified margin), which indicates the non-inferiority of Sustol 10 mg to Aloxi 0.25 mg.

Table 2.1: Statistical Reviewer's Analysis for AC-Only Subgroup for Study C2006-01

Acute	AC Only		
	Sustol-10 mg	Aloxi-0.25 mg	p-value*/95% CI
ITTA	70.1% (N=174)	63.4% (N=161)	0.19 (-3.3, 16.8)
MITTA	70.2% (N=171)	63.5% (N=156)	0.20 (-3.5, 16.9)
PPREV (ONLY PTS IN MITTA)	72.8% (N=162)	66.7% (N=144)	0.24 (-4.1, 16.5)
Delay			
ITTA	50% (N=174)	47.8% (N=161)	0.69 (-8.5, 12.9)
MITTA	49.7% (N=171)	47.4% (N=156)	0.68 (-8.6, 13.1)
PPREV (ONLY PTS IN MITTA)	51.9% (N=162)	47.9% (N=144)	0.49 (-7.3, 15.2)

*p-values were obtained by the CMH test

4. (***Age Subgroup Analyses for MEC plus AC in Study C2006-01***) To further examine the Sustol's efficacy in different age subgroups, the sponsor was asked to conduct subgroup analyses by age for the MEC plus AC patients for Study 2006-01. The sponsor's analysis results, confirmed by the statistical reviewer, are shown in the following Tables 2.6 and 2.7. Based on the results, it is noted that in all three treatment arms, the younger patients (i.e., those patients less than 65 years of age) had a much lower response rate than the older patients (i.e., those patients equal to or greater than 65 years). In addition, for the acute phase, in both age groups, the observed response rates in the Sustol arms were not much larger than those for the Aloxi (i.e., Palonosetron) patients, however, for the delayed phase, the CR response rate for the younger patients in the Sustol 500 mg arm was 5% higher than the rate observed for Aloxi.

Table 2.6 Sponsor's Age Subgroup Analysis Results for CR-Acute Phase for Study C2006-01 Based on MITT Population

Age Group	Statistic	APF530 250 mg	APF530 500 mg	Aloxi	Between Treatment P-Value (1)
<65 years	N	266	274	253	
	N (pct)	199 (74.8)	205 (74.8)	186 (73.5)	0.9264
	P-value vs. Aloxi (1)	0.7640	0.7655		
>=65 years	N	105	97	109	
	N (pct)	87 (82.9)	81 (83.5)	96 (88.1)	0.5077
	P-value vs. Aloxi (1)	0.3330	0.4233		
Age Group Comparison	P-value (<65 vs. >=65) (1)	0.1019	0.0920	0.0022	

Source: Sponsor's Revised Table 2.1.1.1 from SN0113

Table 2.7 Sponsor's Age Subgroup Analysis Results for CR-Delay Phase for Study C2006-01 Based on MITT Population

Age Group	Statistic	APF530 250 mg	APF530 500 mg	Aloxi	Between Treatment P-Value (1)
<65 years	N	266	274	253	
	N (pct)	135 (50.8)	160 (58.4)	135 (53.4)	0.1928
	P-value vs. Aloxi (1)	0.5981	0.2546		
>=65 years	N	105	97	109	
	N (pct)	75 (71.4)	62 (63.9)	83 (76.1)	0.1556
	P-value vs. Aloxi (1)	0.4418	0.0668		
Age Group Comparison	P-value (<65 vs. >=65) (1)	0.0003	0.3991	<0.0001	

Source: Sponsor's Revised Table 2.1.1.2 from SN0113

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6. (***Labeling Implication***) For Study C2006-01, even though both analysis results based on the older Hesketh or the newer ASCO 2011 emetogenic classification supported the Sustol's efficacy in treating patients with MEC plus AC, one question is that which set of results should be described in the label. Now that this reanalysis was requested by the FDA and whether patients would be determined as MEC or HEC was based on the specific rule defined in ASCO 2011 emetogenic classification, where results could not be altered or selected, the statistical reviewer determined that it is appropriate to describe the findings based on the currently adopted ASCO 2011 standard.

III. Appendix (Sponsor's Re-analysis Results for Study C2006-01)

The following Tables 4.1 and 4.2 display the sponsor's re-analysis results for MEC and MEC+AC populations separately, before and after correcting their misclassification for patients' emetogenicity status as well as the definition for the per-protocol population.

Table 4.1 Sponsor's Results for ASCO MEC Classification Before and After Correction in Liposomal Doxorubicin ASCO Classification for Study C2006-01

Endpoint/ Population	APF 500 mg (Sustol 10 mg) n/N (%)	Palonosetron n/N (%)	Difference (%) (APF-Palo)	95% CI	Fisher's p-value
ASCO MEC – Acute CR (Original, 0-24 hours post-chemotherapy)					
ITT	176/216 (81.5)	188/219 (85.8)	-4.3	(-11.5, 2.7)	0.2438
mITT	171/205 (83.4)	187/211 (88.6)	-5.2	(-12.1, 1.5)	0.1566
PP	153/180 (85.0)	177/193 (91.7)	-6.7	(-13.6, -0.2)	0.0514
ASCO MEC – Acute CR (New, 0-24 hours post-chemotherapy)					
ITT	171/210 (81.4)	184/214 (86.0)	-4.6	(-11.6, 2.5)	0.2367
mITT	166/200 (83.0)	183/206 (88.8)	-5.8	(-12.6, 0.9)	0.1155
PP	148/175 (84.6)	173/189 (91.5)	-6.9	(-13.6, -0.3)	0.0506
PP (IV Dex Revised)	148/175 (84.6)	171/187 (91.4)	-6.8	(-13.6, -0.2)	0.0512
ASCO MEC – Delayed CR (Original, 24-120 hours post-chemotherapy)					
ITT	147/216 (68.1)	148/219 (67.6)	0.5	(-8.3, 9.4)	0.9187
mITT	142/205 (69.3)	147/211 (69.7)	-0.4	(-9.4, 8.5)	1.0000
PP	126/180 (70.0)	139/193 (72.0)	-2.0	(-11.3, 7.2)	0.7320
ASCO MEC – Delayed CR (New, 24-120 hours post-chemotherapy)					
ITT	142/210 (67.6)	145/214 (67.8)	-0.2	(-9.0, 8.8)	1.0000
mITT	137/200 (68.5)	144/206 (69.9)	-1.4	(-10.4, 7.6)	0.8298
PP	121/175 (69.1)	136/189 (72.0)	-2.9	(-12.2, 6.6)	0.5669
PP (IV Dex Revised)	121/175 (69.1)	135/187 (72.2)	-3.1	(-12.4, 6.3)	0.5641
ASCO MEC – Overall CR (Original, 0-120 hours post-chemotherapy)					
ITT	139/216 (64.4)	143/219 (65.3)	-0.9	(-9.9, 8.0)	0.8416
mITT	134/205 (65.4)	142/211 (67.3)	-1.9	(-11.1, 7.2)	0.6797
PP	120/180 (66.7)	136/193 (70.5)	-3.8	(-13.3, 5.7)	0.4369
ASCO MEC – Overall CR (New, 0-120 hours post-chemotherapy)					
ITT	134/210 (63.8)	140/214 (65.4)	-1.6	(-10.7, 7.5)	0.7610
mITT	129/200 (64.5)	139/206 (67.5)	-3.0	(-12.2, 6.2)	0.5317
PP	115/175 (65.7)	133/189 (70.4)	-4.7	(-14.2, 4.9)	0.3687
PP (IV Dex Revised)	115/175 (65.7)	132/187 (70.6)	-4.9	(-14.5, 4.7)	0.3663

Source: Sponsor's Heron Table2 (Revised) in SN0096 IR Response Submission.

Table 4.2 Sponsor's Results for ASCO MEC Classification Before and After Correction Plus AC in Liposomal Doxorubicin ASCO Classification for Study C2006-01

Analysis Population[3]	CINV Phase	Combined MEC[1] and AC-treated patients[2]					
		Treatment Arm		Difference, %(Sustol-Palonosetron)	Statistics		
		Sustol 10 mg n/N (%)	Palonosetron n/N (%)		Confidence Intervals		p-value
					Size	Interval	
ITTA (N=759)	Acute	293/384 (76.3)	286/375 (76.3)	0.0	95% 97.5% 98.33% 98.75%	(-6.0, 6.1) (-6.9, 7.0) (-7.4, 7.4) (-7.7, 7.7)	1.0000
	Delayed	229/384 (59.6)	222/375 (59.2)	0.4	95% 97.5% 98.33% 98.75%	(-6.6, 7.4) (-7.6, 8.4) (-8.1, 9.0) (-8.5, 9.3)	0.9411
MITTA (N=733)	Acute	286/371 (77.1)	282/362 (77.9)	-0.8	95% 97.5% 98.33% 98.75%	(-6.9, 5.2) (-7.7, 6.1) (-8.2, 6.6) (-8.5, 6.9)	0.8596
	Delayed	222/371 (59.8)	218/362 (60.2)	-0.4	95% 97.5% 98.33% 98.75%	(-7.5, 6.7) (-8.5, 7.7) (-9.0, 8.3) (-9.4, 8.7)	0.9400
PERPROTA (N=670)	Acute	266/337 (78.9)	269/333 (80.8)	-1.9	95% 97.5% 98.33% 98.75%	(-7.9, 4.2) (-8.8, 5.1) (-9.3, 5.6) (-9.6, 5.9)	0.5646
	Delayed	205/337 (60.8)	205/333 (61.6)	-0.8	95% 97.5% 98.33% 98.75%	(-8.1, 6.6) (-9.2, 7.7) (-9.7, 8.3) (-10.1, 8.7)	0.8742

Abbreviations: AC, anthracycline-cyclophosphamide; CINV, chemotherapy-induced nausea and vomiting; CR, Complete Response; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy

[1] Chemotherapy regimens classified as moderately emetogenic by ASCO 2011 guidelines

[2] All AC chemotherapy regimens classified as HEC by ASCO 2011 guidelines. (Basch, Prestrud et al. 2011)

[3] Analysis populations for the C2006-01 Sustol 10 mg and Palonosetron treatment arms, per the ADEM dataset submitted in SN0096.

Source: Sponsor's Table 1.11.3-2 from SN0115 submission

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/s/

YEH FONG CHEN
05/27/2016

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06/02/2016

U.S. Department of Health and Human Services
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STATISTICAL REVIEW AND EVALUATION

Clinical Studies

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Applicant:	Heron Therapeutics, Inc.
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Biometrics Division:	DBIII
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewers:	Mike Welch, Ph.D.
Medical Division:	Division of Gastroenterology and Inborn Errors Products
Clinical Team:	Lauren Wientraub, M.D. and Anil Rajpal, M.D. (TL)
Project Manager:	James Carr

Keywords: NDA review, clinical studies, Cochran-Mantel-Haenszel

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1. EXECUTIVE SUMMARY

In order to demonstrate efficacy of SUSTOL for the prevention of chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy (HEC), the sponsor reclassified HEC patients in previously submitted, non-inferiority Study C2006-01 based on the 2011 American Society of Clinical Oncology (ASCO) guidelines and submitted a new analysis. The sponsor also conducted a new phase 3 Study C2013-01 which enrolled patients receiving only HEC as defined in the ASCO guidelines. However, the comparator the sponsor used in Study C2013-01 was ondansetron 0.15 mg/kg, not Aloxi 0.25 mg that was used in Study C2006-01. In addition, one should also note that in earlier clinical trials for assessing the efficacy of Aloxi 0.25 mg, the dose for ondansetron was 32 mg.

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2. INTRODUCTION

2.1 OVERVIEW

The sponsor developed APF530 (trade name SUSTOL®), a long-acting granisetron formulation for subcutaneous (SC) injection for prevention of acute- and delayed CINV in patients undergoing moderately and highly emetogenic chemotherapy (MEC and HEC, respectively). The polymer vehicle of SUSTOL was designed to maintain a sustained plasma concentration of granisetron for up to 120 hours following SC injection. In May 2009, the sponsor submitted their original NDA based on a single Study C2006-01 to support the APF530's efficacy under the 505 (b)(2) filing pathway.

Due to many issues including a problematic site and the inadequate use of patient populations in the non-inferiority study, the sponsor re-submitted their NDA in September 2012 in response to the Agency's complete response letter (CRL) dated March 2010.

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In March 2013, the Sponsor received a second CRL in which the Agency expressed concern that the American Society of Clinical Oncology (ASCO) guidelines for classification of anti-emetic status had been updated and that the labeling claims for APF530 were based on results using the Hesketh emetogenicity classification. Therefore, the Agency asked the Sponsor to provide the dataset for Study C2006-001 and identify the variables used to determine if a subject was in the "HEC" or "MEC" stratum for randomization. The

sponsor provided their algorithm and/or program for classification as well as the appropriate information to the Agency in October 2013 as a summary to facilitate their re-examination of the C2006-01 data based on the ASCO 2011 guidelines as part of a Type B FDA meeting in which responses to the CRL were discussed.

This NDA submission included the sponsor's two Phase 3 studies that explored treatment with SUSTOL for CINV experienced by subjects administered MEC and HEC. Study C2006-01 explored the efficacy of APF530 250 mg and 500 mg compared with Aloxi (palonosetron, 0.25 mg) in cancer patients receiving up to 4 cycles of chemotherapy while Study C2013-01 examined the efficacy of 500 mg of APF530 compared with Ondansetron 0.15 mg/kg in the delayed phase complete response (CR) rate in cancer patients receiving HEC for the first cycle.

Based on the results from C2006-01, only the 500 mg dose of APF530 (10 mg granisetron) has been selected for marketing (as SUSTOL [granisetron] Injection, extended release).With the positive findings shown in Study C2013-01 and with no new or unexpected safety findings since the 2012 resubmission, the sponsor concluded that SUSTOL has a favorable benefit-risk profile (b) (4).

2.2 DATA SOURCES

The NDA resubmission including clinical study reports and data sets for Study C2013-01 are stored in: \\CDSESUB1\evsprod\NDA022445\0073. The sponsor's re-submission including data of Study 2006-01 are stored in: \\CDSESUB1\evsprod\NDA022445\0033. The sponsor's variable for re-classification patients to MEC or HEC based on ASCO Guidelines are stored in: \\CDSESUB1\evsprod\NDA022445\0064.

3. STATISTICAL EVALUATION

(b) (4) The results for the reanalyis of data from Study C2006-01 are presented in the Appendix.

3.1 DATA AND ANALYSIS QUALITY

The statistical reviewer has successfully confirmed the sponsor's analysis results from the Individual event raw data submitted in this application. The efficacy data included in this application were carefully examined and the quality was determined to be acceptable.

3.2 EVALUATION OF EFFICACY

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6. Appendix

6.1 Introduction and Brief Study Description for Study C2006-01

(Extracted from Sponsor's Addendum to Clinical Study Report)

Study C2006-01 was a global, multicenter, randomized, observer-blind, double-dummy, parallel- group study conducted in subjects undergoing moderately or highly emetogenic chemotherapy (MEC and HEC, respectively). The study assessed the safety and effectiveness of 2 doses of an extended-release formulation of granisetron (APF530, 250 mg and 500 mg, corresponding to 5 mg and 10 mg granisetron, respectively) administered as a single subcutaneous (SC) injection versus a single intravenous (IV) injection of the active control, Aloxi (palonosetron, 0.25 mg), in the prevention of acute and delayed phase chemotherapy-induced nausea and vomiting (CINV). Subjects received study drug for up to 4 treatment cycles, each of which began the day of qualifying chemotherapy treatment (Day 1) and terminated at the conclusion of the antiemetic efficacy monitoring period (Day 5/120 hours after chemotherapy administration). Treatment cycles were separated by a period of at least 7 days and no more than 28 days.

The original report for this study (C2006-01 Clinical Study Report) was included in a New Drug Application (NDA) for APF530 (SUSTOL™) submitted by Heron Therapeutics, Inc. to the Food and Drug Administration (FDA) in May 2009 under the 505(b)(2) filing pathway. The NDA was resubmitted in September 2012 (Submission 033 Module 5 Section 5.3.5) in response to the Agency's complete response letter (CRL) dated 16 March 2010 (Complete Response Letter16 Mar 2010). In particular, the sponsor conducted the re-analyses using different types of patient population including ITT, modified ITT and Per-Protocol. In addition, due to the unexplained and non-verifiable irregularities in the data from Site 504, the sponsor also conducted two types of sensitivity analyses by including or excluding data of Site 504. The 2012 analyses handled the calculation of delayed-onset complete response (CR) differently than originally done for subjects with partial diary data on Days 2 through 5. Per advice of the FDA, the outcome for these subjects was imputed as failure. The 2012 resubmission also included a more substantial justification for the 15% non-inferiority margin used in the original filing and refiling and included better justification for the exclusion of Site 504 data from the efficacy analyses.

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The higher dose of APF530 (500 mg), but not the low dose (250 mg), was non-inferior to Aloxi following MEC in the delayed phase, with non-inferiority declared at the second stage of the Hochberg procedure. (b) (4)

. These findings were consistent across the analysis populations and whether or not data from Site 504 were excluded.

In March 2013, the Sponsor received a second CRL (Complete Response Letter 27 Mar 2013) in which the Agency expressed concern that the American Society of Clinical Oncology (ASCO) guidelines for classification of anti-emetic status had been updated (Antiemetics: ASCO ClinicalPractice Guideline Update; Basch et al., 2011) and that the labeling claims for APF530 were based on results using the Hesketh emetogenicity classification. The Agency asked the Sponsor to provide the dataset for Study C2006-01 and identify the variables used to determine if a subject was in the "HEC" or "MEC" stratum for randomization. The algorithm and/or program for classification was also requested. Moreover, the Sponsor was to reclassify subjects into the "HEC" and "MEC" categories using the modified ASCO 2011 guidelines.

The Sponsor was to provide the dataset with subject information, variables used for the classification, and category index for both the original and new classification. The Sponsor complied with this request and submitted the appropriate information to the Agency in October 2013 as a summary to facilitate their re-examination of the C2006-01 data based on the ASCO 2011 guidelines as part of a Type B FDA meeting in which responses to the CRL were discussed (Type B EOR Meeting Background Package 08 Oct 2013).

This addendum to the original C2006-01 clinical study report presents retrospectively analyzed efficacy results based on the considerations outlined above, including emetogenicity reclassification using the ASCO guidelines. Focus is placed on results from the first cycle of chemotherapy, the cycle used for analysis of the primary efficacy endpoints. The 2 doses of APF530 (APF530 250 mg and APF530 500 mg) represent the 2 doses of active ingredient, 5 mg and 10 mg granisetron, respectively.

6.2 Sponsor's Efficacy Endpoints and Results

To address the first 2 primary objectives of the study, the efficacy analyses tested 4 hypotheses for the moderately emetogenic stratum:

- 250 mg APF530 (5 mg granisetron) is non-inferior to Aloxi during the acute phase
- 250 mg APF530 (5 mg granisetron) is non-inferior to Aloxi during the delayed phase
- 500 mg APF530 (10 mg granisetron) is non-inferior to Aloxi during the acute phase
- 500 mg APF530 (10 mg granisetron) is non-inferior to Aloxi during the delayed phase

As in the original analysis, the Hochberg's sharper Bonferroni approach (Hochberg, 1988) was applied within each emetogenic stratum to control the overall Type I error rate at 5% for the 4 simultaneous comparisons (each of 2 APF530 doses for each of 2 endpoints). A stepwise approach with up to 4 stages was used, with an increased level of confidence at each successive stage. Confidence intervals (CIs) (95% CI, 97.5% CI, 98.33% CI, and 98.75% CI) were constructed for testing of the 4 hypotheses. Non-inferiority was demonstrated when the lower limit of the corresponding CI for the difference between APF530 and Aloxi (APF530 – Aloxi) was greater than -15%. Superiority was demonstrated when the lower limit of the corresponding CI was greater than 0%.

Within the moderately emetogenic stratum, non-inferiority was declared for both doses of APF530 for the acute and delayed phases if all 4 lower limits of the 95% CIs were greater than −15%. If this was not the case, the 97.5% CIs were reviewed. If 3 of the 4 lower limits of the 97.5% CIs were greater than −15%, non-inferiority was declared for each APF530 dose/phase combination which met the criterion and was not declared for the APF530 dose/phase combination which did not meet the criterion. If 3 of the 4 lower limits of the 97.5% CIs were not greater than −15%, the 98.33% CIs were reviewed. If 2 of the 4 lower limits of the 98.33% CIs were greater than −15%, non-inferiority was declared for the 2 APF530 dose/phase combinations which were met. The step-down procedure was to continue to the fourth stage as needed.

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Table 6.1 displays disposition of patients for Study C2006-01. Tables 6.2 to 6.4 display the sponsor's analysis results for CR for different study populations.

Tables 6.2 to 6.4 present the sponsor's primary efficacy results for the proportion of subjects with CR during the acute phase (0-24 hours) and delayed phase (>24-120 hours) after chemotherapy administration in Cycle 1 for the ITT population, mITT and PP by emetogenic stratum and treatment group.

Based on these results, the sponsor concluded that results from the current retrospective analysis of C2006-01 based on reclassification of subjects into the MEC and HEC strata using ASCO 2011 guidelines were consistent with the original prospective results based on the Hesketh randomized strata. In particular, their analyses demonstrated that both doses of APF530 were non-inferior to Aloxi with respect to the acute and delayed CR following MEC in the ITT, mITT, and PP populations. (b) (4)

Table 6.1 Subject Disposition for Cycle 1 for Study C2006-01

	MEC (ASCO)			HEC (ASCO)		
	APF530 250 mg	**APF530 500 mg**	**Aloxi 0.25 mg**	**APF30 250 mg**	**APF530 500 mg**	**Aloxi 0.25 mg**
Randomized (N)	199	216	219	256	235	225
Initiated Cycle 1: n (%)	199 (100)	216 (100)	219 (100)	256 (100)	235 (100)	225 (100)
Completed Cycle 1: n (%)	195 (98)	211 (97.7)	215 (98.2)	249 (97.3)	232 (98.7)	221 (98.2)
Discontinued During Cycle 1: n (%)	4 (2.0)	5 (2.3)	4 (1.8)	7 (2.7)	3 (1.3)	4 (1.8)
Adverse event	0	0	0	1 (0.4)	1 (0.4)	0
Lost to follow-up	2 (1.0)	2 (0.9)	3 (1.4)	2 (0.8)	1 (0.4)	2 (0.9)
Withdraw consent	1 (0.5)	1 (0.5)	0	1 (0.4)	1 (0.4)	0
Death	1 (0.5)	1 (0.5)	1 (0.5)	1 (0.4)	0	0
Other	0	1 (0.5)	0	2 (0.8)	0	2 (0.9)
Did Not Continue to Cycle 2: n (%)	50 (25.1)	65 (30.1)	54 (24.7)	47 (18.4)	48 (20.4)	50 (22.2)

Source: Sponsor's Table 8.1 from CSR Addendum

Table 6.2 Sponsor's Primary CR Results by Emetogenic Stratum for ITT Population

	APF530 250 mg	**APF530 500 mg**	**Aloxi 0.25 mg**
MEC (ASCO)			
Acute Phase CR			
CR, n/N (%)	161/199 (80.9)	176/216 (81.5)	188/219 (85.8)
P-value vs. Aloxi	0.19	0.24	
95% CI (diff w/Aloxi)	-12.3, 2.3	-11.5, 2.7	
97.5% CI (diff w/Aloxi)	-13.3, 3.3	-12.5, 3.9	
98.33% CI (diff w/Aloxi)	-14.0, 4.0	-13.0, 4.4	
98.75% CI (diff w/Aloxi)	-14.3, 4.6	-13.4, 4.9	
Delayed Phase CR			
CR, n/N (%)	130/199 (65.3)	147/216 (68.1)	148/219 (67.6)
P-value vs. Aloxi	0.68	0.92	
95% CI (diff w/Aloxi)	-11.4, 6.8	-8.3, 9.4	
97.5% CI (diff w/Aloxi)	-12.7, 8.1	-9.6, 10.6	
98.33% CI (diff w/Aloxi)	-13.4, 8.8	-10.3, 11.3	
98.75% CI (diff w/Aloxi)	-13.9, 9.3	-10.8, 11.7	

(b) (4)

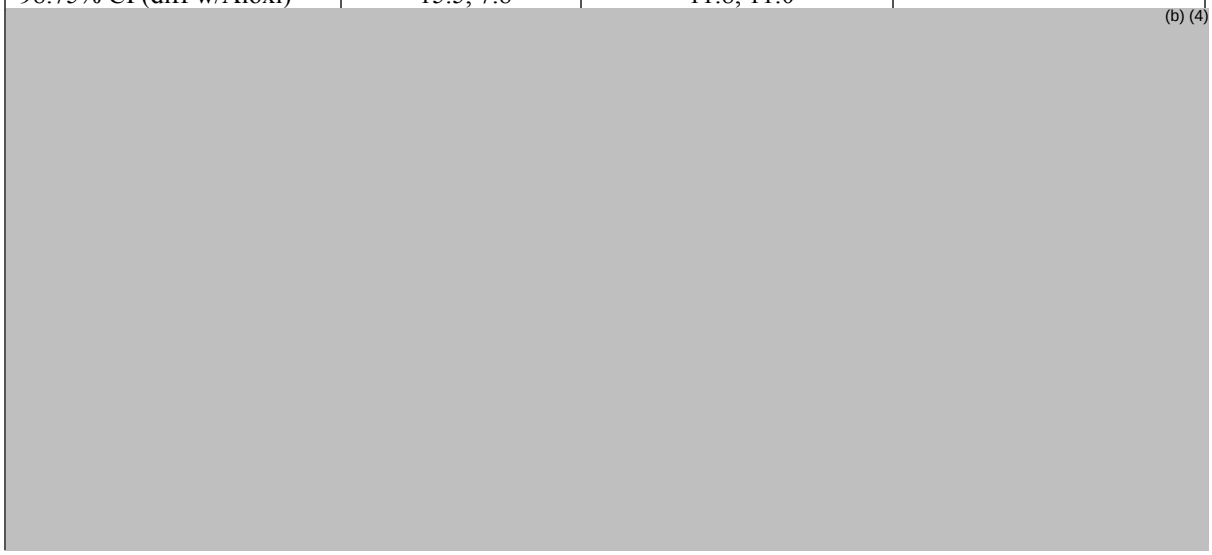
(b) (4)

Source: Sponsor's Table 9.8 of CSR Addendum

Table 6.3 Sponsor's Primary CR Results by Emetogenic Stratum for mITT Population

	APF530 250 mg	**APF530 500 mg**	**Aloxi 0.25 mg**
MEC (ASCO)			
Acute Phase CR			
CR, n/N (%)	158/193 (81.9)	171/205 (83.4)	187/211 (88.6)
P-value vs. Aloxi	0.07	0.16	
95% CI (diff w/Aloxi)	-14.0, 0.2	-12.1, 1.5	
97.5% CI (diff w/Aloxi)	-15.0, 1.2	-13.1, 2.9	
98.33% CI (diff w/Aloxi)	-15.6, 1.7	-13.7, 3.5	
98.75% CI (diff w/Aloxi)	-15.9, 2.1	-14.0, 3.7	
Delayed Phase CR			
CR, n/N (%)	127/193 (65.8)	142/205 (69.3)	147/211 (69.7)
P-value vs. Aloxi	0.46	1	
95% CI (diff w/Aloxi)	-13.1, 5.3	-9.4, 8.5	
97.5% CI (diff w/Aloxi)	-14.4, 6.6	-10.7, 9.8	
98.33% CI (diff w/Aloxi)	-15.1, 7.4	-11.3, 10.5	
98.75% CI (diff w/Aloxi)	-15.5, 7.8	-11.8, 11.0	

(b) (4)



Source: Sponsor's Table 9.9 of CSR Addendum

Table 6.4 Sponsor's Primary CR Results by Emetogenic Stratum for PP Population

	APF530 250 mg	APF530 500 mg	Aloxi 0.25 mg
MEC (ASCO)			
Acute Phase CR			
CR, n/N (%)	148/176 (84.1)	153/180 (85.0)	177/193 (91.7)
P-value vs. Aloxi	0.03	0.05	
95% CI (diff w/Aloxi)	-14.7, -0.9	-13.6, -0.2	
97.5% CI (diff w/Aloxi)	-15.7, 0.0	-14.6, 0.7	
98.33% CI (diff w/Aloxi)	-16.3, 0.5	-15.2, 1.2	
98.75% CI (diff w/Aloxi)	-16.7, 0.8	-15.6, 1.6	
Delayed Phase CR			
CR, n/N (%)	118/176 (67.0)	126/180 (70.0)	139/193 (72.0)
P-value vs. Aloxi	0.31	0.73	
95% CI (diff w/Aloxi)	-14.4, 4.5	-11.3, 7.2	
97.5% CI (diff w/Aloxi)	-15.8, 5.8	-12.6, 8.5	
98.33% CI (diff w/Aloxi)	-16.5, 6.5	-13.3, 9.2	
98.75% CI (diff w/Aloxi)	-17.0, 7.0	-13.9, 9.7	
[redacted]			(b) (4)

Source: Sponsor's Table 9.10 of CSR Addendum

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/s/

YEH FONG CHEN
01/04/2016

MICHAEL E WELCH
01/04/2016

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 #:	NDA 22-445
Supplement #:	EDR 0033 (Resubmission); SDN 37
Drug Name:	SUSTOL® (granisetron extend release) subcutaneous injection, 500 mg (contains 10 mg of granisetron)
Indication(s):	(1) Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses; (2) Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses
Applicant:	A.P. Pharma, Inc.
Date(s):	Stamp Date: 9/27/2012 PDUFA Date: 3/27/2013
Review Priority:	Priority
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Freda W. Cooner, Ph.D.
Concurring Reviewers:	Mike Welch, Ph.D.
Medical Division:	Division of Gastroenterology and Inborn Error Products (DGIEP)
Clinical Team:	Karyn Berry, M.D., Medical Reviewer Ruyi He, M.D., Team Leader
Project Manager:	Jagjit Grewal

Keywords:

Clinical studies, NDA review

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1 EXECUTIVE SUMMARY

This resubmission includes A.P. Pharma's responses to the deficiencies identified in the Complete Response (CR) Letter (dated March 16, 2010). The statistical CR issues were mainly regarding the analysis populations. The CR letter requested: 1) a new per protocol population analysis based on corrected protocol violation definitions; and 2) new analysis data sets with Site 504 data that was excluded from efficacy analysis and the datasets in the original submission. In addition, we requested a justification of the non-inferiority margin used in the trial. The sponsor provided the new analysis and datasets requested, and a justification of the non-inferiority margin; and so the responses to the CR issues are acceptable. The efficacy conclusion from the last review cycle still withholds.

2 INTRODUCTION

2.1 Overview

The current application is a resubmission of NDA 22445 (dated May 14, 2009). A.P. Pharma has provided a complete response to the deficiencies identified in the Complete Response Letter (dated March 16, 2010). This application has been filed under 505(b)(2), referencing KYTRIL® (granisetron hydrochloride) Injection, KYTRIL® Tablets, and KYTRIL® Oral Solution, marketed by Roche Laboratories, Inc., New Jersey. Granisetron is a member of a therapeutic class known as 5-hydroxytryptamine type 3 ($5\text{-}HT_3$) receptor antagonists, which are widely used antiemetic drugs for chemotherapy induced nausea and vomiting (CINV) and postoperative nausea and vomiting (PONV).

In the United States, KYTRIL® Injection is indicated for: 1) prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin; and 2) prevention and treatment of PONV in adults. The tablets and oral solution dosage forms of KYTRIL® are also approved for prevention of CINV.

The requested name for the drug product is SUSTOL® (b) (4) Injection. It is also referred to by the laboratory code APF530 within this application. SUSTOL® is a novel polymeric formulation of granisetron, designed to prolong the plasma concentration of granisetron. The prolongation is intended to provide long-lasting control of nausea and emesis for up to 120 hours after chemotherapy administration, during both the acute and delayed phases. The proposed indications for SUSTOL® are: 1) Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses; and 2) Highly emetogenic cancer therapy – prevention of acute nausea and vomiting associated with initial and repeat courses.

SUSTOL® contains 2% granisetron and a polymer vehicle. It is provided in a pre-filled glass syringe and is delivered by a single subcutaneous injection in the abdominal region

approximately 30 minutes prior to initiation of chemotherapy treatment. A single dose of SUSTOL® delivers 10 mg of granisetron over 120 hours.

One pivotal Study C2006-01 was submitted in support of SUSTOL® APF530 10 mg (granisetron injection, extended release, for subcutaneous use) for two indications: prevention of acute and delayed-onset phase of CINV following the administration of moderately emetogenic chemotherapy (MEC); and prevention of acute-onset phase of CINV following the administration of highly emetogenic chemotherapy (HEC).

During the first review cycle, it was found that the sponsor did not include data from Site 504 in their primary efficacy analysis. The sponsor's response to our Information Request was not received until late in that review cycle and was reviewed during this review cycle.

(b) (4)

A more thorough assessment of efficacy, including additional sensitivity analyses were investigated during this review cycle with newly provided additional information.

The sponsor claims that this NDA resubmission addresses all of the items identified in the Complete Response Letter dated March 16, 2010. Responses and information have been submitted to address facility inspection, container/closure system, device constituent parts, drug product quality, clinical/clinical pharmacology, clinical/statistical, patent certification, and labeling deficiencies outlined in the Complete Response Letter; and take into account clarifications, advice and agreements from the FDA Meeting Minutes dated March 25 and April 30, 2011.

For the resubmission, the sponsor has provided the requested re-analyses of the primary efficacy data for the phase 3 Study C2006-01. The sponsor also provided the requested justification for patient assignments to Per-Protocol (PP) or Intent-to-Treat (ITT) groups, the requested justification for exclusion of Site 504 patients from the PP analysis, and a justification for the non-inferiority margin. The sponsor also has provided additional secondary efficacy analyses. This reviewer will focus on these additional, exploratory efficacy assessments

2.2 Data Sources

The resubmission in electronic Common Technical Document (eCTD) format is located in the EDR at: \\CDSESUB1\EVSPROD\NDA022445\0033.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The newly submitted analysis datasets were all in a sponsor-defined format, which was similar to the ADaM format. It was possible to conduct all the statistical analyses needed with the datasets provided for this submission. However, the sponsor did not provide the exact algorithm and/or variables in the datasets used to classify patients as MEC or HEC subjects for the randomization. Furthermore, the recently modified ASCO 2011 Guideline, *Anti-emetic: American Society of Clinical Oncology Clinical Practice Guideline Update*, has reclassified some MEC regime to HEC, and it would be important to examine the sensitivity of efficacy results under the new classification criteria. An Information Request (IR) letter was sent to the sponsor and the sponsor's responses were received in March 2013. Additional analyses of the MEC and HEC subgroups may be warranted.

3.2 Evaluation of Efficacy

Study C2006-01 was a randomized, multicenter, observer-blind, double-dummy, parallel group study conducted in subjects with confirmed malignant disease who were scheduled to receive single-day administration of moderately or highly emetogenic chemotherapy (MEC or HEC) as classified according to the Hesketh algorithm. The sponsor defined observer-blind as both the subject and investigator not knowing what was being administered, however due to the differences in study drugs an unblinded pharmacist/nurse was assigned at all sites to administer all treatments. Subjects were to receive study drug in up to four treatment cycles (Cycles 1, 2, 3, and 4) and each of which began the day of qualifying chemotherapy treatment (Day 1) and terminated at the conclusion of the antiemetic efficacy monitoring at 120 hours (+72 hours) after chemotherapy administration.

A total enrollment of 1404 subjects was planned, 669 in the MEC stratum (223 subjects per treatment arm in Cycle 1) and 735 in the HEC stratum (245 subjects per treatment arm in Cycle 1). The planned enrollment was higher than the 1338 subjects (636; 212 per group in the MEC stratum and 702; 234 per group in the HEC stratum) specified in the protocol due to a calculation error in the protocol, which was discovered by the sponsor during preparation of the statistical analysis plan (SAP).

A double-dummy design was used to aid blinding in the first treatment cycle (Cycle 1) due to the difference in routes of administration between APF530 (SC: subcutaneous) and Aloxi® (IV: intravenous). The study subjects were assigned in two strata by a centralized process on the basis of the emetogenic potential of their chemotherapy (moderate or high) and a computer-generated randomization schedule was used to assign eligible subjects to one of the following three treatment groups in each stratum in a 1:1:1 ratio:

- Aloxi® 0.25 mg IV and placebo SC;
- 250 mg APF530 SC (5 mg granisetron) referred to as 5 mg APF530, and placebo IV;
- 500 mg APF530 SC (10 mg granisetron) referred to as 10 mg APF530, and placebo IV.

Following the first study cycle, re-randomization was applied so that subjects who received Aloxi® in Cycle 1 were assigned in a 1:1 ratio to receive SC injections of either 5 mg APF530 or 10 mg APF530 in each subsequent treatment cycle. Subjects who received APF530 in Cycle 1 continued to receive their assigned dose in each subsequent treatment cycle. The blind was to be maintained throughout the re-randomization. Thus, in Cycles 2, 3, and 4, subjects received either 5 mg or 10 mg APF530.

A diary was used to collect data for each 24-hour period from 0 hour, at the start of chemotherapy administration (Day 1), to 120 hours after chemotherapy administration (Day 5) for each treatment cycle. In the diary, subjects rated severity of nausea (classified as none, mild, moderate, or severe), number of vomiting and/or retching episodes, use of rescue medication, and information regarding global satisfaction with antiemetic therapy.

Based on diary entries, the following efficacy measures were evaluated daily during the first five days after administration of chemotherapy in each treatment cycle:

- Complete Response (CR): No emetic episodes and no use of rescue medication;
- Complete Control (CC): Complete response with no more than mild nausea;
- Total Response (TR): Complete response with no nausea.

The primary efficacy parameters were proportion of subjects with:

- CR during the acute phase (0-24 hours) following the administration of chemotherapy in Cycle 1;
- CR during the delayed-onset phase (24-120 hours) following the administration of chemotherapy in Cycle 1. CR was measured in 24-hour increments up to 120 hours.

Many secondary efficacy endpoints were identified; however, no multiplicity adjustment strategy was specified. Hence, the results for the other cycles as well as secondary endpoints are exploratory and may not be candidates for labeling purposes.

The primary hypothesis for the MEC stratum was that at least one APF530 dose was non-inferior to Aloxi® in either acute or delayed-onset CR rate using a non-inferiority margin of 15%. The primary hypothesis for the HEC stratum was that at least one APF530 dose was non-inferior by no more than 15% compared to Aloxi® in the acute-onset CR rate; or at least one APF530 dose was superior to Aloxi® in the delayed-onset CR rate. For superiority comparisons, the CI lower bounds would be compared with 0 instead of -15%.

CR issue:

24. Your single clinical trial did not provide substantial evidence of efficacy of Sustol for your proposed indications for the following reasons:

    a. The Per Protocol analysis is important for evaluating and establishing non-inferiority. We cannot accurately characterize your Per Protocol analysis population because we have identified discrepancies in how you applied the protocol violation definitions. The protocol violation definitions are key for determining whether a patient should be

included in the Per Protocol population. To address this deficiency, you will need to submit an electronic listing of all patients in the study identified by their Per Protocol or Intent-to-Treat status and provide justification for patient assignment to their respective groups. Per Protocol violations should be clearly explained.

b. We cannot accurately characterize your Intent–to-Treat (ITT) and Per Protocol analysis populations because there is insufficient information to determine whether the exclusion of all of the data from Site 504 was valid. To address this deficiency, you will need to provide clear justification as to why the Site 504 patients should be excluded from the Per Protocol analysis.

After correcting these analysis populations, including corrections defined in part a. and b. above, resubmit your primary efficacy analyses for the following populations: the full ITT population (all subjects randomized); the modified ITT population (all subjects randomized with at least one diary entry) and the Per-Protocol population. Your ITT and mITT analyses should assign treatment failure to patients with missing data (i.e. no imputation). Subjects from Site 504 should be included in the appropriate analysis populations. This resubmission of your primary analysis should also include the corrected analysis data sets, supporting data definition files, and SAS programs.

c. Your submission lacks clear justification for your non-inferiority margin of 15%. Ideally, non-inferiority margin selection is based on historical studies with similar design demonstrating the effect size of your current active control. For further discussion of margin selection criteria, we refer you to the following draft guidance: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf. To address this deficiency, you will need to submit an evidence based justification for your selection of a 15% non-inferiority margin.

Sponsor's Responses:

To address parts a. and b., the sponsor conducted a thorough review of each patient according to the violation rules assigned in the SAP, dated September 5, 2008. Adjustments were made for 62 patients according to the PP efficacy analysis exclusion rules. Another 10 patients had their previous diary imputations removed and were assigned as treatment failures. The sponsor also conducted a review of the Site 504 patients included and excluded from the PP and mITT populations for the phase 3 study C2006-01. Note that the mITT population was used as the primary analysis in the original submission. Additionally, an ITT analysis was performed, and the mITT and PP populations were reanalyzed for the primary efficacy analyses as well as the secondary analyses; overall treatment period complete response and the complete response over multiple treatment cycles. Some of the reanalysis was already conducted in the original review and the results concurred with those from this submission.

The primary efficacy results between the reanalyzed data and the data from the original submission closely match and the conclusions still withhold. Non-inferiority of 500 mg APF530 (10 mg granisetron) to Aloxi is demonstrated in all three efficacy analysis populations, regardless of whether Site 504 patients were included or excluded. Superiority

could not be declared for any treatment comparisons. As an example, the results from the true ITT population with Site 504 patients included are presented in the table below with the shaded part in the table contingent to the proposed indications.

Table 3.1. Primary Results of Complete Response in Cycle 1 (ITT Population)

Phase	Statistic	MEC			(b) (4)
		5 mg APF530	10 mg APF530	0.25 mg Aloxi®	
	N	222	221	216	
Acute	CR	161 (72.5%)	164 (74.2%)	157 (72.7%)	
	98.75% CI* (%)	(-11.0, 10.6)#	(-9.5, 12.5)#	–	
Delayed	CR	111 (50.0%)	125 (56.6%)	120 (55.6%)	
	98.75% CI* (%)	(-18.0, 6.8)	(-11.3, 13.3)#	–	

CI: Confidence Interval

* CIs are for the comparisons between each APF530 arm and Aloxi® arm.

Met the non-inferiority margin of 15%

(b) (4)

Source: Reviewer's Table (the results concur with those from the sponsor)

The sponsor explained that the main reason site 504 in Hyberdad, India, was excluded from the efficacy analyses in the original submission, was that all 19 patients received study drug reported 100% CR, 100% CC, and 100% TR with limited variations on other clinical assessments. This reviewer agrees with the sponsor's judgment that the data from this site is unreliable and should be omitted from the efficacy analyses.

For part c., the sponsor provided detailed justification on the non-inferiority margin of 15% based on the Aloxi registration studies and literature. The justification closely followed the reference guidance. This reviewer believes that the justification is acceptable.

4 SUMMARY AND CONCLUSIONS

Based on the newly provided data sets and sensitivity analyses within this resubmission, it can be concluded that SUSTOL® APF530 10 mg (granisetron injection, extended release, for subcutaneous use) is non-inferior to Aloxi® 0.25 mg (Intravenous) with respect to antiemetic response for prevention of acute and delayed-onset phase of chemotherapy-induced nausea and vomiting (CINV) following the administration of moderately emetogenic chemotherapy (MEC);

(b) (4)

However, the recently modified ASCO 2011 Guideline, *Anti-emetic: American Society of Clinical Oncology Clinical Practice Guideline Update*, has reclassified some MEC regime to HEC. Furthermore, the available data sets provided by the sponsor are not sufficient for this reviewer to conduct exploratory subgroup analyses regarding this MEC/HEC reclassification. An Information Request (IR) letter regarding this issue has been sent and the responses have been received; however, due to the late stage of this review cycle, the responses may be reviewed during the extension of this review cycle or the third review cycle.

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/s/

FREDA COONER
03/18/2013

MICHAEL E WELCH
03/18/2013
Concur with review.

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/Serial Number:	22-445 / 000; 012
Drug Name:	SUSTOL® APF530 (granisetron injection, extended release, for subcutaneous use, a serotonin subtype 3 antagonist ($5HT_3$)) 10 mg/ 0.4mL single use
Indication(s):	Moderately emetogenic cancer chemotherapy – prevention of acute and delayed nausea and vomiting associated with initial and repeat courses; Highly emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses
Applicant:	A.P. Pharma, Inc.
Date(s):	Stamp Date: 05/18/2009 PDUFA Date: 03/18/2010
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 3
Statistical Reviewer:	Freda W. Cooner, Ph.D.
Concurring Reviewers:	Mike Welch, Ph.D.
Medical Division:	Division of Gastroenterology Products
Clinical Team:	Karyn Berry, M.D., Medical Reviewer Nancy Snow, M.D., Team Leader
Project Manager:	Todd D. Phillips

Keywords: Clinical studies, NDA review, Non-inferiority, Per-Protocol population

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

One pivotal Study C2006-01 was submitted in support of SUSTOL® APF530 10 mg (granisetron injection, extended release, for subcutaneous use) for two indications: prevention of acute and delayed-onset phase of chemotherapy-induced nausea and vomiting following the administration of moderately emetogenic chemotherapy (MEC); and prevention of acute-onset phase of chemotherapy-induced nausea and vomiting following the administration of highly emetogenic chemotherapy (HEC).

During this review cycle, it was found that the sponsor did not include data from Site 504 in their primary efficacy analysis. The sponsor's reply to our Information Request was not received until Feb. 3, 2010 and will be reviewed during the second review cycle. Additionally, an Agency inspection has shown protocol violations inconsistent with the sponsor's reports, and these need to be clarified.

(b) (4)

A more thorough assessment of efficacy, including additional sensitivity analyses will be investigated by this reviewer after the sponsor addresses the inspection deficiencies and provides any required additional information.

1.2 Brief Overview of Clinical Studies

The clinical development program for APF530 comprised four completed studies, all of which were conducted under IND #68,213. In addition to the clinical data from these clinical studies, this application partly relies on published literature as permitted by section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act.

The efficacy of subcutaneous (SC) APF530 in the prevention of CINV (chemotherapy-induced nausea and vomiting) is primarily supported by the pivotal phase 3 study C2006-01, which was a randomized, multicenter, observer-blind, double-dummy, parallel group study conducted in cancer patients with confirmed malignant disease who were scheduled to receive single-day administrations of moderately or highly emetogenic chemotherapy (MEC or HEC). In this pivotal study patients who had previously received chemotherapy were eligible for enrollment irrespective of their emetogenic history. Patients were allowed to continue to subsequent cycles regardless of their performance in the previous treatment cycle. Supportive efficacy data are provided from the phase 2 dose-ranging study C2005-01, which included an exploratory endpoint to evaluate the efficacy of APF530 against CINV in cancer patients receiving moderately or highly emetogenic chemotherapy. This review will focus on the initial cycle data from the pivotal phase 3 study C2006-01.

Two doses of APF530, 250 mg and 500 mg (5 mg and 10 mg granisetron, respectively), were selected for evaluation in the phase 3 study (C2006-01) on the basis of prior clinical experience. The comparator for this study is Aloxi® IV (intravenous) 0.25 mg. The primary objectives were to establish non-inferiority of APF530 for the prevention of acute-onset (0-24 hours) and delayed-onset (24-120 hours) CINV MEC, and for the prevention of acute-onset CINV HEC, and to establish superiority of APF530 for the prevention of delayed-onset CINV HEC, in comparison to Aloxi®. (b) (4) A 15% non-inferiority margin (delta) was employed for the non-inferiority analyses.

1.3 Statistical Issues and Findings

The clinical study report and the efficacy analysis data sets excluded a site in India (Site 504) which randomized 19 subjects. Moreover, the Agency's inspection had shown different counts of protocol violations than reflected in the sponsor's report. Some sensitivity analyses will be investigated in this review cycle; however, additional information from the sponsor will be required, and a more thorough assessment of data sensitivity will be conducted in the next review cycle.

Approximately mid-way through the conduct of Study C2006-01, the sample size had been increased due to a planning error, and consequently additional sites outside of the U.S. were utilized. At the end of the study, the missing data handling strategy was amended in the final SAP (statistical analysis plan). It does not appear that these two late-study amendments will impact the efficacy conclusions.

The sponsor's submission did not include any justification for their 15% non-inferiority margin. Although this margin has been used in the past for antiemetic products, documentation supporting the sponsor's margin selection should be provided.

2. INTRODUCTION

2.1 Overview

Nausea and vomiting are considered serious side effects of chemotherapy. The severity of the nausea and vomiting has been reported to result in some patients refusing subsequent chemotherapy cycles. In addition, serious complications have been associated with CINV (chemotherapy-induced nausea and vomiting) including dehydration, electrolyte imbalance, and metabolic alkalosis. The causes of CINV appear to be multi-factorial, but a major mechanism appears to be mediated through the activation of serotonin receptors. The nausea and vomiting associated with chemotherapy can be acute or may have a delayed onset which can last for several days.

Granisetron is a widely used $5HT_3$ receptor antagonist antiemetic with a plasma half-life of approximately 8 hours following IV (intravenous) administration in humans. APF530, is a novel polymer formulation of granisetron, which is designed to maintain a sustained plasma

concentration of granisetron for up to 120 hours following SC injection. Prolongation of the plasma concentration of granisetron by means of the polymer formulation has the potential to provide long-lasting prevention of both acute and delayed CINV with a single administration.

Granisetron was first approved by the FDA for commercial use in 1994 (Kytril®, Roche). Kytril® contains granisetron hydrochloride, formulated as an aqueous solution for IV injection, or as tablets, or an aqueous solution for oral administration. Kytril® is indicated for chemotherapy-induced, radiation-induced, and postoperative nausea and vomiting (CINV, RINV, and PONV, respectively). In 2008, FDA approved a transdermal patch containing granisetron for the prevention of CINV (Sancuso®, ProStrakan).

Three other $5HT_3$ receptor antagonists are currently approved for marketing in the US: ondansetron (Zofran®, GlaxoSmithKline), dolasetron (Anzemet®, Sanofi-Aventis) and palonosetron (Aloxi®, MGI Pharma). Zofran® and Anzemet® have similar indications to Kytril®. Aloxi®, the most recently approved $5HT_3$ receptor antagonist, is the only $5HT_3$ receptor antagonist specifically indicated for delayed-onset CINV following the administration of moderately emetogenic chemotherapy (MEC). Two other $5HT_3$ receptor antagonists are available in other regions, but have not been approved in the US. Tropisetron (Navoban®, Novartis), is approved in several European, Asia-Pacific and Latin American counties for the treatment and prevention of CINV and PONV; and ramosetron (Nasea®, Yamanouchi) is approved in Japan and Thailand for the treatment and prevention of CINV.

Current practice guideline published by the American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network (NCCN) and the Multinational Association of Supportive Care in Cancer (MASCC) all recommend the use of a $5HT_3$ receptor antagonist in subjects undergoing moderately or highly emetogenic chemotherapy (HEC) regimens, in combination with other antiemetics. All three guidelines recommend that a $5HT_3$ receptor antagonist should be administered on the day of chemotherapy (Day 1), to prevent acute-onset CINV in patients undergoing either MEC or HEC. They also recommend the use of a corticosteroid in all patients undergoing MEC or HEC and dexamethasone is the preferred corticosteroid.

Aprepitant (Emend®, Merck & Co) is a neurokinin-1 receptor antagonist approved by the FDA in 2003 for prevention of acute and delayed nausea and vomiting associated with MEC and HEC in combination with other antiemetics. All three aforementioned clinical guidelines now recommend that aprepitant should be given in addition to a $5HT_3$ receptor antagonist and corticosteroid to prevent acute-onset CINV in patients undergoing HEC, and that the preferred regimen for delayed-onset CINV HEC should be aprepitant and a corticosteroid only.

The clinical development program for APF530 comprised four completed studies: one phase 1 study C2004-01, two phase 2 studies C2005-01 and C2007-01, and one phase 3 study C2006-01. For Studies C2006-01 and C2007-01, dose levels of APF530 were described in terms of granisetron content; while for Studies C2004-01 and C2005-01, dose levels were described in terms of the total quantity of the APF530 formulation administrated. As such, doses described as 250 mg, 500 mg, 750 mg, and 1 g APF530 in C2004-01 and C2005-01 CSRs (clinical study

reports) are described as 5 mg, 10 mg, 15 mg, and 20 mg APF530 in C2006-01 and C2007-01 CSRs. These four clinical studies are summarized in the table below.

Table 2.1. Clinical Studies Listing

Study Type	Study ID	Title	Objective(s)	Study Products	No. of Subjects	Treatment Duration
BA/PK and Safety	C2004-01	A Phase I, Double-Blind, Placebo Controlled, Ascending Single Subcutaneous Dose, Safety, Tolerability and Pharmacokinetic Study in Healthy Male Subjects Including an Assessment of Absolute Bioavailability	Primary: - Safety and tolerability of APF530 - PK of APF530 Secondary: - Absolute bioavailability of APF530 - Safety and tolerability of SC administration of APF530 compared to IV granisetron	Granisetron APF530, SC 125 mg APF530 (2.5 mg) 250 mg APF530 (5 mg) 500 mg APF530 (10 mg) 1 g APF530 (20 mg) vs. Kytril®, IV 100 µg/kg	26	14 days
PK and Safety	C2005-01	A Phase II, Open-Label, Ascending Single Subcutaneous Dose, Evaluation of Pharmacokinetics, Tolerability and Safety, of APF530 (Sustained-Release Granisetron) in Patients Undergoing Moderately Emetogenic Chemotherapy for Cancer	Primary: - PK of APF530 Secondary: - Safety and tolerability of APF530 Exploratory: - Efficacy of APF530	Granisetron APF530, SC 250 mg APF530 (5 mg) 500 mg APF530 (10 mg) 750 mg APF530 (15 mg)	45	14 days
Efficacy and Safety	C2006-01	A Pivotal Phase 3 Observer-Blind, Randomized Clinical Trial of the Efficacy and Safety of APF530 Compared to Aloxi® for the Prevention of Acute-Onset and Delayed-Onset Chemotherapy-Induced Nausea and Vomiting Following the Administration of Either Moderately or Highly Emetogenic Chemotherapy Regimens	Primary: - Efficacy of a single SC dose of a APF530 in comparison to Aloxi® Secondary: - Safety and tolerability of APF530 - Efficacy of APF530 over multiple treatment cycles - PK of APF530 - ECG data of APF530	Granisetron APF530, SC 250 mg APF530 (5 mg) 500 mg APF530 (10 mg) + Placebo Saline IV vs. Aloxi®, IV 0.25 mg + Placebo Saline SC	1428 randomized 1395 received study drug	Up to four doses of study drug
PK and Safety	C2007-01	An Open-Label, Uncontrolled, Randomized, Multicenter, Pharmacokinetic Study of Two Doses of APF530 in Patients Undergoing Moderately or Highly Emetogenic Chemotherapy Treatment	Primary: - PK of APF530 Secondary: - Safety of the route of administration for APF530 Exploratory: - Efficacy of APF530	Granisetron APF530, SC 250 mg APF530 (5 mg) 500 mg APF530 (10 mg)	35	1 week

BA: Bioavailability; PK: Pharmacokinetic; SC: Subcutaneous; IV: Intravenous; ECG:
Source: Table 2.5.1 (Module 2.5 Clinical Overview)

The efficacy of APF 530 against CINV is primarily supported by the pivotal phase 3 study C2006-01, which was a randomized, multicenter, observer-blind, double-dummy, parallel group study conducted in subjects with confirmed malignant disease who were scheduled to receive single-day administration of MEC or HEC. Supportive efficacy data is provided from the phase 2 dose-ranging study C2005-01, which included an exploratory endpoint to evaluate the efficacy of APF530 against CINV in subjects receiving MEC. This review will only evaluate the pivotal Study C2006-01.

2.2 Data Sources

Materials reviewed include clinical study report, protocols and SAPs (statistical analysis plans) for Study C2006-01. Supplement #012 amending the protocol violation subjects submitted on January 21, 2010 was also reviewed. This application was submitted in electronic Common Technical Document (eCTD) format, with SAS datasets and programs provided, to the Electronic Document Room (EDR) at \\Cdsesub1\evsprod\NDA022445.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Enrollment for Study C2006-01 began on June 7, 2006 and concluded on August 12, 2008. Two protocol amendments were issued to the original protocol (dated April 10, 2006, revised on April 26, 2006). Amendment 1 was issued on September 7, 2006 with changes broadly related to subject criteria, which were made less stringent to allow more eligibility, and administrative clarifications. Amendment 2 was issued on March 5, 2007 after the investigators' meeting held on February 23-25, 2007 to clarify enrollment criteria and clearly define pre-dosing conditions and study procedures. An addendum to Amendment 2 was issued on August 8, 2007 to include additional investigative sites outside of the U.S. to the study, planning to include approximately 25 sites in India and 10 sites in Poland in order to increase the enrollment rate. The sample size was eventually increased by 5% (66 subjects) because of a calculation error in the protocol.

A statistical analysis plan (SAP) dated June 19, 2008, amended on September 4, 2008, was finalized on September 5, 2008 before database lock. The SAP amendment included changes in definition of study population (per-protocol population), efficacy data imputation (delayed phase) strategy, other missing data handling approaches, and an added regional subgroup analysis. A SAP addendum was issued on April 7, 2009 to explain a disparity in the control of emesis categories within the document and identify the correct category used for the final clinical study report.

3.1.1 Study Design and Endpoints

Study C2006-01 was a randomized, multicenter, observer-blind, double-dummy, parallel group study conducted in subjects with confirmed malignant disease who were scheduled to receive

single-day administration of moderately or highly emetogenic chemotherapy (MEC or HEC) as classified according to the Hesketh algorithm. The sponsor defined observer-blind as both the subject and investigator not knowing what was being administered, however due to the differences in study drugs an unblinded pharmacist/nurse was assigned at all sites to administer all treatments. Subjects were to receive study drug in up to four treatment cycles (Cycles 1, 2, 3, and 4) and each of which began the day of qualifying chemotherapy treatment (Day 1) and terminated at the conclusion of the antiemetic efficacy monitoring at 120 hours (+72 hours) after chemotherapy administration.

A total enrollment of 1404 subjects was planned, 669 in the MEC stratum (223 subjects per treatment arm in Cycle 1) and 735 in the HEC stratum (245 subjects per treatment arm in Cycle 1). The planned enrollment was higher than the 1338 subjects (636; 212 per group in the MEC stratum and 702; 234 per group in the HEC stratum) specified in the protocol due to a calculation error in the protocol, which was discovered by the sponsor during preparation of the SAP. The sponsor claimed that the planned enrollment was increased before subject enrollment was completed; however, neither the exact information on the enrollment at the time of change nor related randomization and blinding information was provided. Sample size calculation details will be discussed further in Section 3.1.3 Statistical Methodologies. Blood for the analysis of plasma granisetron concentration was to be collected in a planned subset of 100 to 130 subjects during Cycle 1 and none of the Indian or Polish sites would participate this study.

A double-dummy design was used to aid blinding in the first treatment cycle (Cycle 1) due to the difference in routes of administration between APF530 (SC: subcutaneous) and Aloxi® (IV: intravenous). The study subjects were assigned in two strata by a centralized process on the basis of the emetogenic potential of their chemotherapy (moderate or high) and a computer-generated randomization schedule was used to assign eligible subjects to one of the following three treatment groups in each stratum in a 1:1:1 ratio:

- Aloxi® 0.25 mg IV and placebo SC;
- 250 mg APF530 SC (5 mg granisetron) referred to as 5 mg APF530, and placebo IV;
- 500 mg APF530 SC (10 mg granisetron) referred to as 10 mg APF530, and placebo IV.

Following the first study cycle, re-randomization was applied so that subjects who received Aloxi® in Cycle 1 were assigned in a 1:1 ratio to receive SC injections of either 5 mg APF530 or 10 mg APF530 in each subsequent treatment cycle. Subjects who received APF530 in Cycle 1 continued to receive their assigned dose in each subsequent treatment cycle. The blind was to be maintained throughout the re-randomization. Thus, in Cycles 2, 3, and 4, subjects received either 5 mg or 10 mg APF530.

Intravenous dexamethasone (8 mg and 20 mg for MEC and HEC, respectively) was administered to all subjects 30 to 90 minutes before the start of chemotherapy on Day 1 of each cycle and oral dexamethasone (8 mg twice a day) was prescribed on Days 2, 3, and 4 to all subjects treated with HEC. In addition, subjects were provided a prescription for rescue medication following each study drug administration for use only when they experienced nausea and/or vomiting. Treatment cycles were to be separated by a period of at least seven days, but no more than

28(+3) days and subjects were required to meet inclusion and exclusion criteria including additional criteria before receiving study drug in each treatment cycle.

A diary was used to collect data for each 24-hour period from 0 hours, at the start of chemotherapy administration (Day 1), to 120 hours after chemotherapy administration (Day 5) for each treatment cycle. In the diary, subjects rated severity of nausea (classified as none, mild, moderate, or severe), number of vomiting and/or retching episodes, use of rescue medication, and information regarding global satisfaction with antiemetic therapy. A follow-up visit was scheduled 30±3 days after the final study drug administration. Subject completion was defined as a subject that had completed at least one treatment cycle and the final follow-up visit.

Subjects were free to withdraw from the study at any time. In addition, the investigator could discontinue a subject from additional study drug administrations for reasons of medical prudence of lack of compliance with the protocol. Subjects were to be discontinued from further participation if they received study drug treatment and either received granisetron (Kytril®), palonosetron (Aloxi®) or aprepitant (Emend®) at any time prior to the conclusion of the final treatment cycle, or received prohibited or restricted medication within the specified washout periods, or if they had a QT_c interval greater than 500 msec or changes in QT_c interval greater than 60 msec from baseline.

Procedures scheduled at the follow-up visit were to be performed whenever possible for discontinued subjects. Subjects were not replaced in the event of withdrawal or discontinuation from the study. Subjects who discontinued due to an AE (adverse event), or who had an AE at the final study visit, were to be contacted for resolution/status within two weeks of discontinuation.

Based on diary entries, the following efficacy measures were evaluated daily during the first five days after administration of chemotherapy in each treatment cycle:

- Complete Response (CR): No emetic episodes and no use of rescue medication;
- Complete Control (CC): Complete response with no more than mild nausea;
- Total Response (TR): Complete response with no nausea.

For analysis, a single emetic episode was defined as a single vomit or retch separated by an interval of at least one minute. Continuous vomits or retches were defined as two or more vomits or retches with a gap of less than one minute between the individual vomits or retches.

The primary efficacy parameters were proportion of subjects with:

- CR during the acute phase (0-24 hours) following the administration of chemotherapy in Cycle 1;
- CR during the delayed-onset phase (24-120 hours) following the administration of chemotherapy in Cycle 1. CR was measured in 24-hour increments up to 120 hours.

Secondary efficacy variables included:

- Proportion of subjects, following the completion of Cycle 1, with CR during the overall treatment cycle (0-120 hours);
- Proportion of subjects, following the completion of Cycle 1, with CC during the acute phase, delayed-onset phase, and overall treatment cycle;

- Proportion of subjects, following the completion of Cycle 1, with TR during the acute phase, delayed-onset phase, and overall treatment cycle;
- Proportion of subjects, following the completion of Cycle 1, with major control of emesis, minor and failure; during the acute phase, delayed-onset phase, and overall treatment cycle;
- Number of emetic episodes during the acute and delayed-onset phase;
- Time to first emetic episode;
- Time to first use of rescue medication;
- Time to treatment failure (based on time to first emetic episode or time to rescue medication, whichever occurred first);
- Use of rescue medication;
- Severity of nausea measure daily and overall;
- Subject's global satisfaction with antiemetic therapy during the acute phase and overall study period, recorded in 24-hour increments;
- Quality of Life (QoL) assessment, the impact of nausea and vomiting on Day 5;
- Sustainability of antiemetic effect of APF530 during multiple chemotherapy cycles.

This review will focus on the two primary endpoints for cycle 1 data only. The results for the other cycles as well as secondary endpoints are exploratory and may not be candidates for labeling purposes. Due to the large number of secondary endpoints, this review will briefly discuss the first three listed.

3.1.2 Patient Disposition, Demographic and Baseline Characteristics

A total of 1428 subjects were randomized at 73 sites in the US, 19 sites in India (including Site 504), and 11 sites in Poland. Of the randomized subjects in Cycle 1, 659 were in the MEC stratum and 769 were in the HEC stratum. A total of 33 subjects were randomized but did not receive study drug. Overall, 29 subjects discontinued from the study during Cycle 1. The most frequent reason for discontinuation (13 subjects) was lost to follow-up. Four subjects died and two subjects discontinued due to AEs during Cycle 1. Other reasons for discontinuation during Cycle 1, in a total of 10 subjects, were withdrawn consent, protocol violation or deviation, and study termination.

Of the 1366 subjects who completed Cycle 1, 1043 subjects were re-randomized and initiated Cycle 2. A total of 75 subjects were ineligible to proceed to Cycle 2 because they had either completed chemotherapy, were no longer receiving qualifying chemotherapy, or did not meet dosing criteria. In addition, 248 subjects discontinued between Cycles 1 and 2. Seven subjects died and 22 subjects, 17 of whom were in the HEC stratum, had AEs that led to discontinuation between Cycles 1 and 2.

A total of 25 subjects discontinued from the study during Cycles 2 to 4 (9 in Cycle 2, 5 in Cycle 3, and 11 in Cycle 4). A total of 234 subjects out of 1034 subjects who completed Cycle 2 did not continue to Cycle 3, and 204 out of 795 subjects who completed Cycle 3 did not continue to Cycle 4. Out of these 438 (234+204) subjects 249 subjects discontinued from the study. Among these discontinued subjects, eight discontinued because they had AEs during Cycles 2, 3, or 4

and an additional 15 discontinued due to AEs between cycles. Fifteen (15) subjects died during or between Cycles 2, 3, and 4.

Subject disposition is summarized in the table below:

Table 3.1. Subject Disposition

	MEC			HEC		
	5 mg APF530	**10 mg APF530**	**0.25 mg Aloxi®**	**5 mg APF530**	**10 mg APF530**	**0.25 mg Aloxi®**
Cycle 1						
Randomized	222	221	215	253	260	256
Initiated	220	218	215	244	250	248
Completed	215	214	209	237	245	245
Discontinued	4	4	6	7	5	3
Did not continue to Cycle 2	45	52	46	52	66	62
Chemo completed	0	1	4	5	3	6
No additional chemo	2	7	11	3	6	4
Dosing criteria not met	3	7	4	5	2	2
Discontinued	40	37	27	39	55	50
Cycle 2						
Initiated	253	243		275	272	
Completed	250	242		271	271	
Discontinued	3	1		4	1	
Did not continue to Cycle 3	56	56	–	59	63	–
Chemo completed	5	10		8	10	
No additional chemo	7	4		11	15	
Dosing criteria not met	0	2		3	1	
Discontinued	44	40		37	37	
Cycle 3						
Initiated	194	186		212	208	
Completed	194	184		211	206	
Discontinued	0	2		1	2	
Did not continue to Cycle 4	57	48	–	47 (1 unknown)	52	–
Chemo completed	14	10		19	17	
No additional chemo	9	13		3	11	
Dosing criteria not met	4	4		5	3	
Discontinued	30	21		19	21	
Cycle 4						
Initiated	137	136		164	154	
Completed	136	134	–	160	150	–
Discontinued	1	2		4	4	

Source: Reviewer's Table

Four study populations were defined as follows:

- Safety: all subjects who were randomized and received any amount of study drug;
- Modified Intent-to-Treat (mITT): all subjects who were randomized and received study drug and had post-baseline efficacy data. Separate mITT sets were created for each of the four treatment cycles. The primary analysis was based on this population;
- Per-Protocol (PP; Cycle 1 only): all subjects in the mITT population who had evaluable assessments of emetic episodes and use of rescue medication during the first 24 hours after

administration of chemotherapy, and who did not have any protocol violations considered likely to interfere with the evaluation of therapeutic efficacy;

- ECG/PK population: all subjects who entered into the PK/Holter monitoring study who received study drug.

The numbers of subjects in the mITT population and the PP population in the original NDA submission are presented as follows:

Table 3.2. Summary of mITT and PP Populations

Population	MEC			HEC		
	5 mg APF530	10 mg APF530	0.25 mg Aloxi®	5 mg APF530	10 mg APF530	0.25 mg Aloxi®
Randomized	222 (100%)	221 (100%)	216 (100%)	253 (100%)	260 (100%)	256 (100%)
Cycle 1 mITT	214 (96.4%)	212 (95.9%)	208 (96.3%)	229 (90.5%)	240 (92.3%)	238 (93.0%)
Cycle 1 PP	201 (90.5%)	195 (88.2%)	192 (88.9%)	197 (77.9%)	192 (73.8%)	203 (79.3%)
Cycle 2 mITT	247	240		263	263	
Cycle 3 mITT	191	184	–	207	202	–
Cycle 4 mITT	134	134		158	148	

Source: Table 11.1 (Module 5 C2006-01 Clinical Study Report)
Both mITT and PP populations excluded Site 504.

The sponsor claimed that there were 54 of 1395 treated subjects had no diary or rescue medication data collected on the Case Report Form (CRF) and were not included in the analysis. The sponsor also stated that in addition to the subjects who were excluded from the mITT population because of missing post-baseline data, all 19 subjects from an Indian site (Site 504) were excluded by the sponsor from both the mITT and PP populations for the efficacy analyses, allegedly prior to unblinding because of unexplained and non-verifiable irregularities in the data. A request on more details and explanation for this site was issued by the Agency to the sponsor on December 15, 2009 and the response (Supplement #015) dated February 3, 2010 was officially received on February 19, 2010. Decision has been made that the additional information contained in the supplement will be reviewed during the next cycle. Without sufficient qualification of the data from this site, this reviewer will use the efficacy data with Site 504 excluded as provided by the sponsor.

For the PP population in Cycle 1, all protocol violations and deviations were defined in the SAP after the study conclusion, but allegedly prior to the database lock, and briefly included: missing informed consent; failure to meet enrollment criteria; improper administration of the study drugs; administration of prohibited medications during the participation period in violation of protocol provisions; administration of restricted CYP3A4 inhibitors during the pre-treatment and monitoring period in violation of protocol provisions; inappropriate stratification; administration of single day chemotherapy of duration longer than five hours; administration of multi-day chemotherapy of Hesketh level 3 or more; breaking of the blind; inappropriate administration of rescue medication on Day 1; incomplete diary for determination of acute CR. The analysis based on this population was considered supportive by the sponsor; however, for a non-inferiority design the PP principle may be more conservative than the ITT principle.

Although the sponsor submitted a supplement (#012) to correct incomplete protocol violation and deviation identification, specifically use of prohibited medication, the protocol violation and deviation listing still did not coincide with the Agency's inspection results. In particular, in S-013 the sponsor identified 10 subjects who were misclassified: two of them were 10 mg APF530 HEC subjects incorrectly categorized as protocol violations in the original submission and so were added into the PP population; and eight more subjects were found as protocol violations in this supplement and so were shifted out of the PP population. One newly identified subject was from an Indian site, nine were from US sites. In addition, two of the ten subjects were in the MEC stratum; eight subjects were in the HEC stratum. The inspection initiated by the FDA was conducted in two US sites. In one Ohio site (Site 003), the inspection revealed an important protocol violation in that the first 49 randomized subjects were found to have taken prohibited medication and should be excluded from the PP population. In the original NDA application, the sponsor excluded 14 out of 85 randomized subjects in that site from the PP population due to aforementioned protocol violations or deviations. Supplement #012 added two more subjects with protocol violations from that site. Altogether, the sponsor only provided a list of 16 subjects with either protocol violations or deviations who should not be included in the PP population. The discrepancy in numbers of protocol violators cannot be resolved during this review cycle, and differently defined PP populations will be used for the discussion in this review.

For the safety population, the majority of subjects in each treatment group were female. In particular, the percentage of females in the MEC stratum was 83.3 to 87.7% across treatment groups and 62.8 to 67.2% in the HEC stratum. The average age ranged from 54.8 to 58.1 years and average weight was between 156 and 159 pounds across the groups in both strata. Most of the study subjects were white/Caucasian (56.4 to 66.5% across strata and treatment groups) and were mainly enrolled at centers in the US and Poland. The remaining subjects primarily consisted of Asians (22.3 to 30.5% across groups) who were enrolled mainly at centers in India. The mean time since diagnosis of the current cancer ranged 0.6 to 1.0 year among MEC subjects and 0.5 to 0.7 year among HEC subjects. Breast cancer was the most common cancer in the MEC stratum (63.3 to 69.5% across treatment groups), while lung cancer (25.4 to 32.8%) and breast cancer (25.4 to 27.6%) occurred with similar frequencies among treatment groups in the HEC stratum. Approximately half of the MEC subjects had received prior chemotherapy (47.3 to 50.0% across treatment groups) while it was more prevalent in the HEC subjects (55.6 to 58.6% across treatment groups).

3.1.3 Statistical Methodologies

The primary analyses were conducted separately for the individually powered HEC and MEC strata, each with type I error controlled at a significance level of 5%. The primary hypothesis for the MEC stratum was that at least one APF530 dose was non-inferior to Aloxi® in either acute or delayed-onset CR rate using a non-inferiority margin of 15%. The sponsor did not appear to provide justification on this non-inferiority margin; however, this margin has been used for antiemetic products in the past. Two-sided confidence intervals (CIs) of the CR rate difference in each APF530 dose group minus Aloxi® were to be calculated and non-inferiority would be claimed if the lower confidence bound was above -15%. Using the sponsor's proposed Hochberg's sharper Bonferroni adjustment (called Hochberg's approach hereafter) for multiple

comparisons, starting with 95% CIs for the four tests (two doses and two endpoints) and if all comparisons met the non-inferiority criteria then successes would be declared for all tests. If not, failure would be declared for the one with the lowest CI lower bound and 97.5% (0.05/2) CIs were to be used for the remaining three with higher CI lower bounds. If these three comparisons met the non-inferiority criteria, i.e., the CI lower bounds were all above -15%, then successes would be declared accordingly. Otherwise, another failure would be declared for the one with the lowest CI lower bounds out of these three comparisons and 98.33% (0.05/3) CIs were to be used; and so forth, 98.75% (0.05/4) CIs were to be used at the final stage. However, a more conservative Bonferroni approach will be assessed in this review, i.e., two-sided 98.75% CIs will be used for all the comparisons.

The primary hypothesis for the HEC stratum was that at least one APF530 dose was non-inferior by no more than 15% compared to Aloxi® in the acute-onset CR rate; or at least one APF530 dose was superior to Aloxi® in the delayed-onset CR rate. For superiority comparisons, the CI lower bounds would be compared with 0 instead of -15%. The multiple comparisons adjustment was then the same to that for the MEC stratum.

For both chemotherapy regimens, the sponsor's protocol also proposed to use Fisher's exact test for an overall comparison of the three treatment groups and pair-wise comparisons between each APF530 dose and Aloxi®. The purpose of this test was not clearly stated; however, in the protocol the sponsor mentioned that in case of each successful non-inferiority comparison, an additional superiority test would be performed using the same statistical methodology and p-value as those for the non-inferiority assessments. Conceivably, the superiority claims were ultimately intended, but without appropriate analysis details, labeling usage of resultant p-values from the Fisher's exact tests would be problematic.

The protocol stated that all sample size calculations were based on the two-sided type I error rate of 0.0125 within each stratum, which was adjusted for two APF530 dosages and two primary endpoints using the proposed Hochberg's approach. Later the sponsor claimed that an error was discovered while preparing the SAP and that a one-sided significance level of 0.0125 was actually used for the sample size calculation. The sample size was hence increased by adjusting the significance level to two-sided alpha of 0.0167 (0.05/3), which was claimed to correspond to the third stage of Hochberg's approach.

For the MEC stratum, the protocol specified a sample size of 573 evaluable subjects in total (191 subjects per group) based on the assumptions of a CR rate of 65% in each APF530 and Aloxi® groups, a non-inferiority margin of 15%, and a power of 80%. Assuming a drop-out rate of no more than 10% in Cycle 1, 212 subjects per group (636 subjects in total) were planned to be enrolled. After adjusting the significance level in the SAP, a sample size of 624 evaluable subjects in total (208 subjects per group) was determined based on the same assumptions on CR rates and non-inferiority margin, but a smaller power of 76%. Moreover, a smaller drop-out rate of less than 7% was assumed and so an enrollment of 223 subjects per group (669 subjects in total) was planned in the SAP.

For the HEC stratum, the protocol specified a sample size of 633 evaluable subjects in total (211 subjects per group) based on the assumptions of a CR rate of 50% in each group, non-inferiority

margin of 15%, and a power of 80%. Assuming a drop-out rate of less than 10% in Cycle 1, 234 subjects per group (702 subjects in total) were originally planned. For the superiority comparison in delayed-onset CINV, the sponsor estimated the required number of subjects as 471 (157 subjects per group). This sample size was based on the assumption of a CR rate of 48% in the Aloxi® and 65% in the APF530 group, using a two-sided significance level of 0.0125, and a study power of 80%. Again, the sponsor estimated a drop-out rate of no more than 10% in Cycle 1, 173 subjects (519 subjects in total) must be enrolled. Since the sample size required for the non-inferiority section was larger than the superiority section, the SAP only recalculated the sample size for the non-inferiority comparison. In particular, a two-sided significance level of 0.0167 (0.05/3) was used to render a revised evaluable sample size of 674 subjects in total (228 subjects per group) and a less than 7% drop-out rate was assumed to determine the final planned enrollment of 245 subjects per group (735 subjects in total) in the SAP.

The sponsor indicated in the original SAP that no data imputation would be required for the efficacy data for Study C2006-01, though also being claimed was that for the efficacy analyses, in case of any efficacy assessments (including CR, CC, and TR) could not be determined for a patient because of missing data the according assessments would be set to "failure" for that patient. Moreover, the sponsor specified that separate assessments of missing data would be made for the acute and delayed-onset responses. However, later in the final SAP, the sponsor updated the data imputation and efficacy analyses sections to include some less stringent details. Particularly, the sponsor indicated that for the calculation of CR, CC, and TR an acute phase response still required complete data while for the delayed phase a response would be calculated from the available data provided that a rescue medication page was completed and there were at least two complete days of diary data among Days 2 to 5 relevant to the calculation. A response for the total 120 hour period would be calculated provided that the acute and delayed responses were calculable. Only for diaries with less than this minimum required data the relevant responses (acute, delayed, or overall) would be imputed as failures. It is difficult to predict for treatment comparisons which imputation strategy will be more conservative and hence a more thorough investigation on the missing data is guaranteed.

While no subgroup analysis were planned in the original SAP, the amended SAP added a subgroup summary of the CR rates (acute and delayed-onset phases) in Cycle 1 on country (US, Poland, and India). Although subgroup analyses (age, gender, and race) should be conducted, a regional efficacy review is encouraged. In the final clinical study report for Study C2006-01, the sponsor performed subgroup analyses for country, corticosteroid dosing, prior chemotherapy, success of prior antiemetic treatment in the most recent chemotherapy, age group (less than 65 years vs. no less than 65 years), gender, and chemotherapy regimen. However, the efficacy comparisons conducted by the sponsor were among the subgroups within each treatment arm. This reviewer will conduct comparisons between treatment arms within each subgroup of age group, gender, race, and country.

3.1.4 Results and Conclusions

The percentage of subjects with CR during the acute, delayed-onset, and overall phases following the administration of chemotherapy in Cycle 1 for the mITT population (excluding Site 504) using the sponsor's imputation technique is summarized in the table below. Currently,

the sponsor is seeking indications for acute and delayed MEC CINV and acute HEC CINV for the 10 mg APF530 dose only. (b) (4) For both MEC and HEC strata, one of the primary objectives of the study was to demonstrate the non-inferior efficacy of APF530 to Aloxi® with a margin of 15% for CR during the acute-onset phase based on the exact CIs for the difference in CR rates (APF530 - Aloxi®). Overall, 74.8% to 76.9% of the MEC subjects (b) (4) had CR during 0 to 24 hours after chemotherapy administration, with no significant differences between each APF530 dose and Aloxi®. For both chemotherapy groups, the 5 mg APF530 group showed lower CR rate estimates than the Aloxi® group while the 10 mg APF530 group had higher CR rate estimates. Based on these results, non-inferiority could be claimed for both APF530 doses (b) (4) strata for the acute phase using a non-inferiority margin of 15%.

Table 3.3. Primary Results of Complete Response in Cycle 1 (mITT Population)

Phase	Statistic	MEC			(b) (4)
		5 mg APF530	**10 mg APF530**	**0.25 mg Aloxi®**	
	N	214	212	208	
Acute	CR	160 (74.8%)	163 (76.9%)	156* (75.0%)	
	98.75% CI (%)	(-10.9, 10.4)#	(-8.6, 12.4)#	–	
Delayed	CR	110 (51.4%)	125 (59.0%)	120 (57.7%)	
	98.75% CI (%)	(-18.4, 5.8)	(-10.7, 13.3)#	–	
Overall	CR	104 (48.6%)	115 (54.2%)	109 (52.4%)	
	95% CI (%)	(-13.4, 5.7)	(-7.8%, 11.4)	–	

* The sponsor reported 160 but with percentage 75.0%, presumably was a typographic error.
# Met the non-inferiority margin of 15%.
Source: Reviewer's Table (the results concur with those from the sponsor except noted in *)
Site 504 excluded.

For the MEC regime, one of the primary objectives of the study was to demonstrate the non-inferior efficacy of APF530 to Aloxi® for CR during the delayed-onset phase (24 to 120 hours). (b) (4) (b) (4) Overall, the percentages of subjects with CR during the delayed-onset phase were similar among treatment groups in the MEC stratum (51.4% to 59.0%) (b) (4) with no significant difference between each dose of APF530 and Aloxi . (b) (4) The information submitted in supplement #015 regarding Site 504 will be reviewed during the next review cycle. The true mITT population should include the randomized subjects from this site and so the efficacy estimates will be affected.

Since this study was mainly a non-inferiority trial, efficacy should also be demonstrated in the PP population, since ITT principle may in favor of showing null by imputing missing data as failures. Due to the difficulties mentioned earlier on correctly defined PP subjects, multiple PP populations are used for this review. More analyses on this population will be performed during the second cycle. (b) (4)

(b) (4)

Table 3.4. Primary Results of Complete Response in Cycle 1 (PP Population)

(b) (4)

Phase	Statistic	MEC 5 mg APF530	MEC 10 mg APF530	MEC 0.25 mg Aloxi®
Original PP Population				
N		201	195	192
Acute	CR	150 (74.6%)	153 (78.5%)	146 (76.0%)
	98.75% CI (%)	(-12.3, 9.7)	(-8.4, 13.2)	–
Delayed	CR	101 (50.2%)	115 (59.0%)	109 (56.8%)
	98.75% CI (%)	(-19.0, 6.1)	(-10.3, 14.7)	–
Overall	CR	95 (47.3%)	107 (54.9%)	99 (51.6%)
	95% CI (%)	(-14.2, 5.6)	(-6.8, 13.3)	–
Original PP Population Excluding Site 003				
N		188	183	186
Acute	CR	139 (73.9%)	141 (77.0%)	140 (75.3%)
	98.75% CI (%)	(-12.6, 10.0)	(-9.4, 12.9)	–
Delayed	CR	92 (48.9%)	106 (57.9%)	103 (55.4%)
	98.75% CI (%)	(-19.3, 6.5)	(-10.3, 15.5)	–
Overall	CR	87 (46.3%)	98 (53.6%)	93 (50.0%)
	95% CI (%)	(-13.9, 6.5)	(-6.7, 13.9)	–
Updated PP Population				
N		200	195	191
Acute	CR	149 (74.5%)	153 (78.5%)	145 (75.9%)
	98.75% CI (%)	(-12.4, 9.7)	(-8.3, 13.4)	–
Delayed	CR	100 (50.0%)	115 (59.0%)	108 (56.5%)
	98.75% CI (%)	(-19.0, 6.1)	(-10.1, 14.9)	–
Overall	CR	94 (47.0%)	107 (54.9%)	98 (51.3%)
	95% CI (%)	(-14.2, 5.6)	(-6.5, 13.5)	–
Updated PP Population Excluding Site 003				
N		188	183	185
Acute	CR	139 (73.9%)	141 (77.0%)	139 (75.1%)
	98.75% CI (%)	(-12.5, 10.1)	(-9.3, 13.1)	–
Delayed	CR	92 (48.9%)	106 (57.9%)	102 (55.1%)
	98.75% CI (%)	(-19.1, 6.7)	(-10.1, 15.6)	–
Overall	CR	87 (46.3%)	98 (53.6%)	92 (49.7%)
	95% CI (%)	(-13.7, 6.8)	(-6.5, 14.1)	–

Source: Reviewer's Table
Site 504 excluded.

Patients with missing diary entries are summarized in the table below. The sponsor noted in the clinical study report that there were rare cases of patients with fewer than two days of complete diary data during the delayed-onset phase (three MEC subjects and five HEC subjects). Although this reviewer's assessment does not coincide with the sponsor's, the sensitivity analyses for the delayed-onset phase and overall CR rates of imputing CR as "failure" for any missing diary entries showed quite consistent results with those from the sponsor's primary analysis because most of the treatment failures were due to the subjects' taking rescue medicine during the treatment period. Note that acute-onset phase only contains one day and so the sponsor's primary analysis was already imputing any missing data as "failures".

Table 3.5. Summary of Missing Data in mITT Population

Phase	MEC			(b) (4)
	5 mg APF530	10 mg APF530	0.25 mg Aloxi®	
N (%)	214 (100%)	212 (100%)	208 (100%)	
Acute				
Rescue med	42 (19.6%)	37 (17.5%)	41 (19.7%)	
Complete	214 (100.0%)	212 (100.0%)	206 (99.0%)	
Missing	0 (0.0%)	0 (0.0%)	2 (1.0%)	
Delayed				
Rescue med	83 (38.8%)	69 (32.5%)	63 (30.3%)	
No diary	0 (0.0%)	0 (0.0%)	1 (0.5%)	
1 day diary	1 (0.5%)	0 (0.0%)	0 (0.0%)	
2 days diary	3 (1.4%)	2 (0.9%)	1 (0.5%)	
3 days diary	2 (0.9%)	2 (0.9%)	0 (0.0%)	
Complete	208 (97.2%)	208 (98.1%)	206 (99.0%)	

Source: Reviewer's Table
Site 504 excluded.

Table 3.6. Sensitivity Analysis Results of Complete Response in Cycle 1 (mITT Population)

Phase	Statistic	MEC			(b) (4)
		5 mg APF530	10 mg APF530	0.25 mg Aloxi®	
	N	214	212	208	
Delayed	CR	110 (51.4%)	124 (58.5%)	119 (57.2%)	
	98.75% CI (%)	(-17.9, 6.3)	(-10.7, 13.3)	–	
Overall	CR	104 (48.6%)	114 (53.8%)	108 (51.9%)	
	95% CI (%)	(-12.9, 6.2)	(-7.8, 11.5)	–	

Source: Reviewer's Table
Site 504 excluded.

All the secondary efficacy endpoints analyses were not adjusted for multiplicity and the results are only supportive and exploratory. The results on overall CR, CC, and TR are consistent with those on the primary endpoints of acute and delayed-onset phase CR. The overall CR results are presented above along with the primary endpoints. The CC and TR results are listed in the table below. The sponsor reported that the results for the later cycles show a trend of increasing CR rates from cycle to cycle. This review will not further elaborate on the secondary efficacy endpoints findings.

Table 3.7. Results of Complete Control and Total Response in Cycle 1 (mITT Population)

Phase	Statistic	MEC			(b) (4)
		5 mg APF530	10 mg APF530	0.25 mg Aloxi®	
	N	214	212	208	
Complete Control					
Acute	CC	154 (72.0%)	152 (71.7%)	147 (70.7%)	
	98.75% CI (%)	(-9.7, 12.4)	(-10.0, 12.1)	–	
Delayed	CC	100 (46.7%)	115 (54.2%)	107 (51.4%)	
	98.75% CI (%)	(-16.8, 7.7)	(-9.4, 15.0)	–	
Overall	CC	93 (43.5%)	107 (50.5%)	99 (47.6%)	
	95% CI (%)	(-13.7, 5.5)	(6.7, 12.5)	–	

Source: Reviewer's Table (the results concur with those from the sponsor)
Site 504 excluded.

Table 3.7. (Cont'd) Results of Complete Control and Total Response in Cycle 1 (mITT Population)

(b) (4)

Phase	Statistic	MEC		
		5 mg APF530	10 mg APF530	0.25 mg Aloxi®
	N	214	212	208
Total Response				
Acute	TR	135 (63.1%)	121 (57.1%)	113 (54.3%)
	98.75% CI (%)	(-3.3, 20.6)	(-9.4, 14.8)	–
Delayed	TR	76 (35.5%)	89 (42.0%)	73 (35.1%)
	98.75% CI (%)	(-11.2, 12.0)	(-5.0, 18.6)	–
Overall	TR	68 (31.8%)	79 (37.3%)	65 (31.3%)
	95% CI (%)	(-8.4, 9.4)	(-3.2, 15.1)	–

Source: Reviewer's Table (the results concur with those from the sponsor)
Site 504 excluded.

3.2 Overview of Safety

The safety database included data from all four clinical studies undertaken to date with APF530 (C2004-01, C2005-01, C2006-01, and C2007-01). More than 95% of all subjects came from C2006-01 and data from other studies were transformed as required to meet the specifications of C2006-01.

A total of 1534 subjects were randomized, 1501 of whom reportedly received study drug (1038 received APF530, 463 received Aloxi® [palonosetron]). Of the subjects who received APF530, the sponsor reported that the vast majority of subjects (more than 97%) in the APF530 development program received doses of 250 mg (5 mg granisetron) or 500 mg (10 mg granisetron) (48.7% and 48.8%, respectively), while the remaining subjects received doses of 125 mg (2.5 mg granisetron), 750 mg (15 mg granisetron) or 1 g (20 mg granisetron).

It is reported that 687 subjects scheduled to undergo MEC were randomized, 681 of whom received study drug (466 received APF530 and 215 received Aloxi®). Also reported is that 821 subjects scheduled to undergo HEC were randomized, 794 of whom received study drug (546 received APF530 and 248 received Aloxi®). The sponsor reported that the most common diagnosis among patients undergoing MEC was breast cancer (62.0-67.2%), followed by ovarian cancer (8.6-9.8%) and lung cancer (4.7-7.3%). The most common diagnosis reported among patients undergoing HEC was lung cancer (25.4-31.1%), followed by breast cancer (25.2-25.4%) and ovarian cancer (15.4-17.7%). No other type of cancer was reported in more than 5% of the subjects receiving either MEC or HEC. Overall, subjects received 54 different MEC agents and 62 different HEC agents.

In Cycle 1, 73.6-75.1% of APF530 subjects and 68.9% of Aloxi® subjects reported at least one treatment-emergent AE (adverse event), while in Cycles 2-4, 80.9%-81.7% of APF530 subjects reported at least one treatment-emergent AE. Overall, in both APF530 dose groups, treatment-emergent AEs were reported in a marginally higher proportion of subjects in the HEC stratum (85.3-86.0%) than in the MEC stratum (79.7-79.9%) except for injection site nodule and injection site pain. Collectively, administration site reactions were among the most common AEs reported across all treatment groups. Injection site bruising was the most common AE reported in both APF530 groups (16.4-18.4% in Cycle 1) and the second most common AE

reported in the Aloxi® group (8.9%). Other common reported (i.e., more than 5% in any treatment group) treatment-emergent AEs in Cycle 1 were: constipation, nausea, fatigue, diarrhea, headache, neutropenia, anemia, asthenia, alopecia, abdominal pain and vomiting.

A total of 34 subjects reportedly died during APF530 clinical studies. The sponsor stated that none of the deaths was considered by the investigator to be possibly, probably, or definitely related to study drug. Of these subjects, the sponsor reported that 14 had received 250 mg APF530 (5 mg granisetron) only, 9 had received 500 mg APF530 (10 mg granisetron) only, 2 had received Aloxi® only, 3 had received Aloxi® then 250 mg APF530 (5 mg granisetron), and 6 had received Aloxi® then 500 mg APF530 (10 mg granisetron). No death of subjects who received APF530 doses higher than 500 mg (10 mg granisetron) was reported.

In Cycle 1, 7.8-8.6% of the APF530 subjects and 5.8% of the Aloxi® subjects were reported having experienced at least one treatment-emergent SAE (serious adverse event). The only treatment-emergent SAE reportedly occurred in at least 1% of the subjects in any treatment group during Cycle 1 was febrile neutropenia (0.4-1.3% in the APF530 groups and 0.6% in the Aloxi® group). There was one treatment-emergent SAE reported as possibly related to the study drug in the APF530 clinical development program: a pulmonary embolism during Cycle 1 suffered by a subject who had received 250 mg APF530 (5 mg granisetron).

The sponsor's review of published literature revealed that the most common AE observed in clinical trials with Kytril® Injection was headache. So was reported in clinical trials with oral granisetron. Constipation was the most common AE reported in the pivotal safety study to support the recently authorized granisetron transdermal patch (Sancuso®). The sponsor concluded that APF530 in both dosage forms was safe and well tolerated over initial and subsequent cycles of chemotherapy. Moreover, the sponsor also stated that the AE profile of APF530 appeared to be broadly similar to that of other granisetron formulations currently approved for marketing.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The sponsor only provided subgroup summaries on age group, gender, country (US, Poland, and India), and some other subgroup analyses (such as for different types of chemotherapy). The comparisons performed by the sponsor, however, were among the subgroups within each treatment group. The results on the some subgroup analyses performed by this reviewer are summarized in the table below. The efficacy results were relatively consistent among the subgroups while the small sample sizes should be noted. Compared to Aloxi®, younger subjects and female subjects appeared to have better treatment reaction to APF530 than older and male patients, respectively. Caucasian and Asian seemed to react to APF530 more than the other races compared with Aloxi®. Geographically, patients in the US or Indian sites showed larger treatment effects (APF530 vs. Aloxi®) than those from Poland. All these observations did not seem to contradict the results from the primary analysis.

Table 4.1. Subgroup Results of Complete Response in Cycle 1 (mITT Population)

(b) (4)

Phase	Statistic	MEC 5 mg APF530	MEC 10 mg APF530	MEC 0.25 mg Aloxi®
Age (< 65 years)				
N		162	160	149
Acute	CR	117 (72.2%)	121 (75.6%)	107 (71.8%)
	98.75% CI (%)	(-12.5, 13.3)	(-8.8, 16.4)	–
Delayed	CR	75 (46.3%)	92 (57.5%)	76 (51.0%)
	98.75% CI (%)	(-18.7, 9.7)	(-7.7, 20.5)	–
Age (≥ 65 years)				
N		52	52	59
Acute	CR	43 (82.7%)	42 (80.8%)	49 (83.1%)
	98.75% CI (%)	(-19.5, 18.3)	(-22.0, 16.6)	–
Delayed	CR	35 (67.3%)	33 (63.5%)	44 (74.6%)
	98.75% CI (%)	(-28.9, 14.6)	(-32.8, 10.9)	–
Gender (Female)				
N		189	177	177
Acute	CR	138 (73.0%)	132 (74.6%)	130 (73.4%)
	98.75% CI (%)	(-12.0, 11.3)	(-10.6, 12.9)	–
Delayed	CR	91 (48.1%)	95 (53.7%)	97 (54.8%)
	98.75% CI (%)	(-19.0, 7.0)	(-14.3, 12.1)	–
Gender (Male)				
N		25	35	31
Acute	CR	22 (88.0%)	31 (88.6%)	26 (83.9%)
	98.75% CI (%)	(-23.2, 29.1)	(-18.1, 28.9)	–
Delayed	CR	19 (76.0%)	30 (85.7%)	23 (74.2%)
	98.75% CI (%)	(-28.8, 30.4)	(-14.0, 37.3)	–
Race (Caucasian/White)				
N		123	122	141
Acute	CR	101 (82.1%)	95 (77.9%)	104 (73.8%)
	98.75% CI (%)	(-5.3, 21.0)	(-9.6, 17.2)	–
Delayed	CR	66 (53.7%)	67 (54.9%)	83 (58.9%)
	98.75% CI (%)	(-20.4, 10.1)	(-19.1, 11.4)	–
Race (Asian)				
N		63	54	43
Acute	CR	42 (66.7%)	42 (77.8%)	33 (76.7%)
	98.75% CI (%)	(-31.1, 14.0)	(-20.4, 23.6)	–
Delayed	CR	29 (46.0%)	35 (64.8%)	24 (55.8%)
	98.75% CI (%)	(-33.2, 15.7)	(-15.7, 33.6)	–
Race (Other)				
N		28	36	24
Acute	CR	17 (60.7%)	26 (72.2%)	19 (79.2%)
	98.75% CI (%)	(-48.3, 14.6)	(-33.7, 23.7)	–
Delayed	CR	15 (53.6%)	23 (63.9%)	13 (54.2%)
	98.75% CI (%)	(-33.9, 33.3)	(-21.7, 40.4)	–
Country (US)				
N		130	135	136
Acute	CR	95 (73.1%)	101 (74.8%)	96 (70.6%)
	98.75% CI (%)	(-11.5, 16.4)	(-9.7, 17.9)	–
Delayed	CR	61 (46.9%)	76 (56.3%)	78 (57.4%)
	98.75% CI (%)	(-25.5, 4.9)	(-16.0, 14.0)	–

* The sponsor reported 91 and 98, respectively, but with the same percentage, presumably was a typographic error.
Source: Reviewer's Table
Site 504 excluded.

Table 4.1. (Cont'd) Subgroup Results of Complete Response in Cycle 1 (mITT Population)

(b) (4)

Phase	Statistic	MEC		
		5 mg APF530	10 mg APF530	0.25 mg Aloxi®
Country (India)				
N		53	52	39
Acute	CR	39 (73.6%)	41 (78.8%)	30 (76.9%)
	98.75% CI (%)	(-25.6, 21.4)	(-19.8, 25.7)	–
Delayed	CR	28 (52.8%)	35 (67.3%)	22 (56.4%)
	98.75% CI (%)	(-29.7, 23.3)	(-14.4, 35.7)	–
Country (Poland)				
N		31	25	33
Acute	CR	26 (83.9%)	21 (84.0%)	30 (90.9%)
	98.75% CI (%)	(-31.0, 16.2)	(-33.5, 16.2)	–
Delayed	CR	21 (67.7%)	14 (56.0%)	20 (60.6%)
	98.75% CI (%)	(-22.7, 36.1)	(-36.1, 26.7)	–

Source: Reviewer's Table
Site 504 excluded.

5. SUMMARY AND CONCLUSIONS

During the review cycle, it was found that the sponsor did not include data from Site 504 in their primary efficacy analysis. The sponsor's reply to our Information Request was not received until Feb. 3, 2010 and will be reviewed during the second review cycle. Additionally, an Agency inspection has shown protocol violations inconsistent with the sponsor's reports, and the affected subjects need to be identified so that the proper populations can be analyzed. Additional information to be requested includes justification of the non-inferiority margin. Until additional analyses are conducted in the next review cycle, this reviewer cannot conclude that SUSTOL® APF530 10 mg (granisetron injection, extended release, for subcutaneous use) is non-inferior to Aloxi® 0.25 mg (Intravenous) with respect to antiemetic response.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22445	ORIG-1	A. P. PHARMA, INC.	APF530

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/s/

FREDA COONER
03/08/2010

MICHAEL E WELCH
03/08/2010
Concur with review.