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APPLICATION NUMBER:

022445Orig1s000

CLINICAL REVIEW(S)

FINANCIAL DISCLOSURE REVIEW
NDA Resubmission Class 2

Application Type	NDA
Application Number(s)	22445
Priority or Standard	Standard
Date of Submission	Current submission: July 17, 2015 Original submission: May 18, 2009
Division/Office	Division of Gastroenterology and Inborn Errors Products
Reviewer Name(s)	Lauren Weintraub
Review Completion Date	August 9, 2016
Established Name	Granisetron
(Proposed) Trade Name	Sustol
Applicant	Heron Therapeutics, Inc.
Dosage Form/Strength	10 mg/0.4 mL single use syringe for subcutaneous injection
Indication(s)/Population(s)	Chemotherapy induced nausea and vomiting associated with moderately emetogenic chemotherapy or anthracycline-cyclophosphamide combination chemotherapy regimens

Summary: The Applicant states that no disclosable financial arrangements were made with any Clinical Investigators who participated in Sustol clinical trials.

In the current submission, data from 4 clinical trials were submitted: Study C2013-01, C2013-02, C2013-03, and C2014-01. The individual Clinical Investigator Financial Disclosure Forms for each of these studies are provided below.

Clinical Investigator Financial Disclosure (Study 1 of 4)
Study C2013-01

Application Number: NDA 22445

Submission Date(s): July 17, 2015

Applicant: Heron Therapeutics

Product: SUSTOL (granisetron) Injection, extended release

Reviewer: Lauren Weintraub

Date of Review: August 9, 2016

Covered Clinical Study (Name and/or Number): **C2013-01**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 823 total clinical investigators—84 principal investigators and 739 sub-investigators <i>[note: the tally of sub-investigators includes some duplicates (at least 11) who were listed under more than 1 site; all principal investigators were only listed under a single site]</i>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements: N/A	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: N/A	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.¹ Also discuss whether these interests/arrangements, investigators who

¹ See [web address].

are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

None of the clinical investigators for Study C2013-01 were reported to have entered into a disclosable financial arrangement with the Applicant.

Clinical Investigator Financial Disclosure (Study 2 of 4)
Study C2013-012

Application Number: NDA 22445

Submission Date(s): July 17, 2015

Applicant: Heron Therapeutics

Product: SUSTOL (granisetron) Injection, extended release

Reviewer: Lauren Weintraub

Date of Review: August 9, 2016

Covered Clinical Study (Name and/or Number): **C2013-02**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>2</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements: <u>N/A</u>	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: <u>N/A</u>	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: <u>N/A</u>	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.² Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

² See [web address].

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

None of the clinical investigators for Study C2013-02 were reported to have entered into a disclosable financial arrangement with the Applicant.

Clinical Investigator Financial Disclosure (Study 3 of 4)
Study C2013-03

Application Number: NDA 22445

Submission Date(s): July 17, 2015

Applicant: Heron Therapeutics

Product: SUSTOL (granisetron) Injection, extended release

Reviewer: Lauren Weintraub

Date of Review: August 9, 2016

Covered Clinical Study (Name and/or Number): **C2013-03**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>6</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements: <u>N/A</u>	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: <u>N/A</u>	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: <u>N/A</u>	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.³ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

³ See [web address].

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

None of the clinical investigators for Study C2013-03 were reported to have entered into a disclosable financial arrangement with the Applicant.

Clinical Investigator Financial Disclosure (Study 4 of 4)
Study C2014-01

Application Number: NDA 22445

Submission Date(s): July 17, 2015

Applicant: Heron Therapeutics

Product: SUSTOL (granisetron) Injection, extended release

Reviewer: Lauren Weintraub

Date of Review: August 9, 2016

Covered Clinical Study (Name and/or Number): **C2014-01**

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: <u>6</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>N/A</u> Significant payments of other sorts: <u>N/A</u> Proprietary interest in the product tested held by investigator: <u>N/A</u> Significant equity interest held by investigator in sponsor of covered study: <u>N/A</u>		
Is an attachment provided with details of the disclosable financial interests/arrangements: <u>N/A</u>	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided: <u>N/A</u>	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason: <u>N/A</u>	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.⁴ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

⁴ See [web address].

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

None of the clinical investigators for Study C2014-01 were reported to have entered into a disclosable financial arrangement with the Applicant.

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/s/

LAUREN A WEINTRAUB
08/09/2016

STEPHANIE O OMOKARO
08/09/2016

**Medical Officer Review of Inter-office Consult
Division of Oncology Products-1**

NDA #	22445
Drug(s)	Sustol
Drug Class	5-HT3 antagonist, extended-release granisetron formulation
NDA Sponsor	Heron Therapeutics
Consulting Division	DGIEP
Primary Reviewer	Gwynn Ison, MD
Team Leader	Julia Beaver, MD
Consult due date	6/28/16

Background:

DGIEP requests input from OHOP/ DOP1 on prescribing information for Sustol (NDA 22445), which is an extended release formulation of the 5-HT3 receptor antagonist, granisetron. The extended release properties of Sustol are due to a novel polymer-based drug delivery system. Sustol is delivered by SQ injection, creating a depot in the tissues, a process which, according to the PK study in the phase 3 trial can exceed 7 days. Since chemotherapy regimens can be administered for 6 months or longer, this may result in utilization of Sustol, intermittently, for durations greater than 6 months. Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of the polymer vehicle of Sustol, but will be a post-marketing requirement. The Sustol NDA has been submitted under the 505(b)(2) pathway, with Kytril as the listed drug. For the listed drug, there was a statistically significant increased incidence of hepatocellular carcinoma and adenomas in male rats treated with ≥ 5 mg/kg/d and female rats treated with 25 mg/kg/d. Granisetron hydrochloride was also positive on the mouse lymphoma assay with metabolic activation and increase in UDS HeLa cells in vitro and increased incidence of cells with polyploidy in the in vitro human lymphocyte chromosomal aberration test. Granisetron was not mutagenic on an in vitro Ames test and mouse lymphoma cell forward mutation assay.

Input is requested regarding potential carcinogenicity risk associated with Sustol. Sustol is proposed for prevention of acute and delayed chemotherapy-induced nausea and vomiting and is being considered for use with moderately emetogenic chemotherapy, including anthracycline and cyclophosphamide combination chemotherapy. The following questions have been posed:

- 1) How should the product labeling of Sustol address the positive genotoxicity and carcinogenicity studies with granisetron (conducted with Sustol's reference drug), and the lack of carcinogenicity study data with the Sustol polymer? Is a limitation of use recommended based on the granisetron exposure of Sustol, and if so, what population should be included in the limitation of use?

- 2) Does this impact other antiemetics with indications for CINV with positive carcinogenicity and/or genotoxicity studies, currently marketed without limitations of use in their labels?

DOP1 Response to Questions 1 and 2:

Subsequent to the consult request the Pharm/Tox supervisor, Sushanta Chakder, PhD, in the DGIEP provided a detailed assessment of the genotoxic and carcinogenic risk of Sustol. His memo states that based on the available information on the polymer vehicle (b)(4) and its putative breakdown products, the polymer vehicle does not appear to be a carcinogenic risk in subjects receiving Sustol. The API, granisetron, also does not pose a carcinogenic risk to humans. The hepatocellular tumors observed in the 2-year daily oral dosing carcinogenicity study of granisetron in rats were likely due to a mode of action /pathway not relevant to humans and just as important, the tumors were observed only at extremely high multiples of human exposure.

John Leighton, PhD, Supervisory Pharmacologist and Director, DHOT, agrees with the above assessment and that the carcinogenic findings would not likely make it into the label today.

Recommendation:

Based on the above assessments, DOP1 does not recommend modification of the relevant aspects of the granisetron label and of other antiemetics to address potential carcinogenic risk, when administered as approved.

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/s/

GWYNN ISON
07/25/2016

JULIA A BEAVER
07/25/2016

JOHN K LEIGHTON
07/26/2016

CLINICAL REVIEW

Application Type NDA
Application Number(s) 22-445
Complete Response Class 2 Resubmission

Submit Date(s) September 29, 2012
Received Date(s) September 29, 2012
PDUFA Goal Date March 27, 2013
Division / Office ODE 3/DGIEP

Reviewer Name(s) Karyn L. Berry, MD, MPH
Review Completion Date March 22, 2013

Established Name Granisetron
(Proposed) Trade Name Sustol injection, extended
release
Therapeutic Class 5-HT3 receptor antagonist
Applicant A.P. Pharma, Inc.

Formulation(s) Subcutaneous (S.C.) injection
Dosing Regimen A single subcutaneous (SC)
injection administered
approximately 30 minutes
before the initiation of
chemotherapy. SUSTOL has
been administered as
frequently as once every 7
days and in up to 4

Proposed Indication(s)	consecutive cycles of chemotherapy. Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
Intended Population(s)	Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy. Adults

Template Version: [March 6, 2009](#)

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1 Recommendations/Risk Benefit Assessment

The Applicant, A. P. Pharma, Inc., resubmitted this 505(b)(2) application for Sustol (subcutaneous granisetron) in response to the Complete Response (CR) letter dated March 16, 2010. In this re-submission, the Sponsor provided responses to the deficiencies listed in the CR letter. The deficiencies cited in the CR letter were numerous and crossed multiple discipline reviews (i.e. Clinical, Chemistry, Microbiology, Biostatistical and Clinical Pharmacology, Center for Devices and Radiological Health).

The deficiencies included: manufacturing facilities deficiencies, container/closure system (i.e. use of two syringe design), terminal sterilization process, lack of information to assess the safety of device constituent parts, drug product quality, inadequate IVR specification proposed time points, thorough QT study requirement, inadequate identification and characterization of breakdown products of (b) (4) discrepancies in efficacy evaluation and administration site reactions.

1.1 Recommendation on Regulatory Action

From a clinical standpoint, the submitted data are not adequate to support the recommendation of US marketing approval for Sustol for the following proposed indications:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

It is the recommendation of this reviewer that a complete response (CR) action be taken for this re-submitted application.

This recommendation is based on safety issues and deficiencies identified during this review cycle by this reviewer and other discipline reviewers, such as the Division of Medication Error Prevention and Analysis (DMEPA), Center for Devices and Radiological Health (CDRH) and Chemistry, Manufacturing and Control (CMC).

The identified deficiencies include 1) drug administration technique, 2) withhold recommendations at manufacturing facilities and 3) revision of proposed indications to reflect the population that the product was effective in both acute and delayed phases.

1.2 Risk Benefit Assessment

Though the sponsor has addressed many of the deficiencies listed in the CR letter, the responses to the drug administration, drug delivery device and manufacturing facilities are not adequate to ensure safe administration of this drug product. Sustol injection, extended release is a new formulation of granisetron, a 5-HT₃ receptor antagonist. The previously approved granisetron formulations (intravenous, oral tablets, oral solution and transdermal) are indicated for the prevention of chemotherapy induced nausea and vomiting (CINV). The only 5-HT₃ receptor antagonist that is approved for prevention of delayed onset of CINV in MEC is intravenous palonosetron, the active comparator in the pivotal trial of this application.

Drug administration technique

The Applicant proposes that this product is to be administered subcutaneously by a healthcare provider (i.e. oncology nurse). Although most health care providers are trained to administer sc injections, the extreme viscosity of Sustol requires a different technique and device than what is usual with sc injections. SC injections are generally administered using a 25 to 31 gauge 5/8 inch needle. Because of Sustol's viscosity, the Applicant proposes to use an 18 gauge, 5/8 inch needle.

The Human Factors study conducted by the Applicant to assess use, identified safety issues related to the administration of Sustol. This includes the force required to safely extrude the drug, which may result in either failed injections, possible drug administration errors and/or incomplete injection of drug.

Review of the Applicant's most recently submitted Formative Study results identified Issues that will need to be addressed in the validated human factors study. The Applicant will need to demonstrate that the proposed product modifications (i.e. administration technique and administration instructions) are effective in reducing and minimizing patient harm.

Manufacturing Facilities

The Office of Compliance issued a withhold recommendation for three facilities (AP Pharma, (b) (4)). At the both the AP Pharma site and (b) (4) sites observations from previous inspection in early 2010 had not been fully resolved in addition to new observations this review cycle. AP Pharma deficiencies included: 1) not following standard operating procedures, 2) preventive maintenance programs not performed to a written program, 3) failure to establish scientifically sound and appropriate specifications, 4) accuracy of test methods had not been established and 5) release of drug product for distribution did not include appropriate laboratory determination of satisfactory conformance to final specifications prior to release.

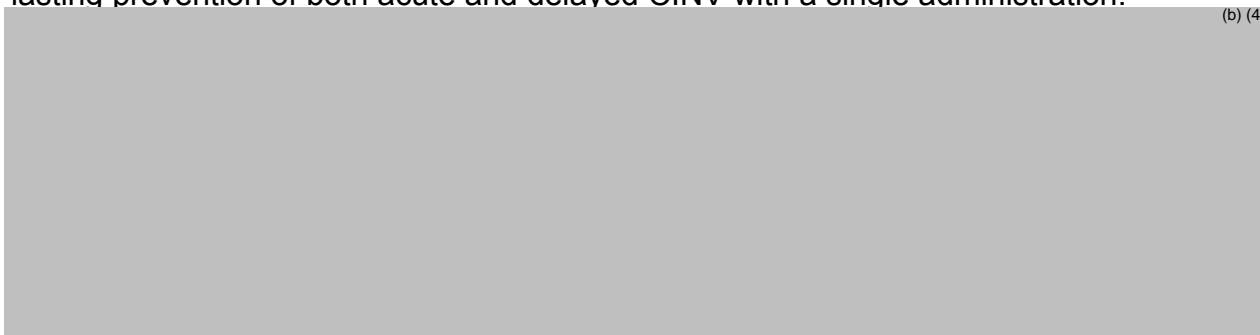
Deficiencies at the (b) (4) site included: 1) firm continues to document inadequate investigations to deviations, 2) inadequate batch and production records, 3) failure to limit and control system access to analytical data and 4) inadequate record retention of analytical data.

At the (b) (4) site observations identified this cycle inspection included issues with dosimeters used during sterilization.

All other manufacturing sites listed in this application have an OC acceptable recommendation (or the requests were previously cancelled). Per statements made on March 8, 2013, by Steven Hertz, from the Office of Compliance, at this time there are no plans to re-inspect these sites. Satisfactory resolution of these deficiencies is required prior to approval.

Revision of proposed indications to reflect appropriate population

As a novel polymer formulation of granisetron, Sustol (APF530), is designed to maintain a sustained plasma concentration of granisetron for up to 120 hours following S.C. injection. The Applicant rationalizes that 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.



this reviewer recommends that the indication be revised to reflect the population that will most benefit from Sustol in both the acute and delayed phase. This reviewer recommends that the indication for Sustol be revised to read *“For prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.”*

To support this revision, the Applicant should provide the dataset and identify the variables used to determine if a patient was in the “HEC” or “MEC” stratum for randomization in trial 2006-01, provide the algorithm and/or program for this classification. Moreover, please reclassify the patients into “HEC” and “MEC” categories according to the recently modified ASCO 2011 Guideline, Anti-emetic: American Society of Clinical Oncology Clinical Practice Guideline Update, and provide the dataset with patient information, variables used for the classification, and the category index for both original and new classification.

In conclusion, given the availability of alternative products, such as other 5-HT₃ receptor antagonist, for the prevention of CINV and the above listed issues, at this time the safety risks of treatment with Sustol (APF530) outweighs the benefits.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None this review cycle

1.4 Recommendations for Postmarket Requirements and Commitments

Because the metabolic fate study (C2011-02) only accounted for 1/3 of the polymer and the proposed dosing instructions allow for administration of Sustol every 7 days, additional data is needed to assess cumulative dosing. Although, the pivotal trial included patients who received up to 4 cycle of Sustol, only the first cycle had a comparator. In addition, no laboratory values, i.e. chemistries, were reported for cycles 2 to 4, which would be useful to assess effects of cumulative dosing.

Therefore, should this application be approved in the next review cycle, it is recommended that the Applicant conduct a postmarketing randomized, controlled safety trial that evaluates patients who receive multiple doses of Sustol..

2 Introduction and Regulatory Background

The Sponsor, A. P. Pharma, Inc., resubmitted this 505(b)(2) application for Sustol (subcutaneous granisetron) in response to the Complete Response (CR) letter dated March 16, 2010 (See appendix A). The applicant references the Agency's previous findings of safety and efficacy of approved and marketed formulations of the drug product Kytril. Kytril has three different formulations that contain information that support this application. They are: 1) Kytril I.V. (NDA 20239/S8), 2) Kytril oral solutions (NDA 21238) and 3) Kytril tablets (NDA 20305/S-004).

The sponsor of the referenced Kytril products, Hoffman-LaRoche, Inc. voluntarily submitted a request to withdraw approval of NDAs 20239, 21238 and 20305 on April 30, 2012. None of the NDA's were withdrawn due to reasons of safety or efficacy.

This review is an addendum to the 1st cycle Clinical Review and will only present information that is either new in this 2nd review cycle, is interpreted differently or is necessary for context so that this review may be use as a stand-alone document.

The proposed drug substance is granisetron free base. Currently there are four granisetron drug products on the US market. Three of them contain granisetron HCl and one contains granisetron base. Granisetron is a widely used 5-HT₃ receptor antagonist

antiemetic with a plasma half-life of approximately 8 hours following I.V. administration in humans. Sustol (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 S.C. injection. The Applicant believes that 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.

In the 1st cycle review, the Applicant proposed a dual syringe container-closure system. The Applicant now proposes to use a single syringe system to eliminate the product preparation and manipulation needed with the two syringe system. The Applicant now proposes to market Sustol in a 1.0 mL glass syringe, co-packaged with a (b) (4) 18 gauge 5/8 inch thin walled needle. The Applicant proposes that Sustol will be primarily administered by oncology nurses in inpatient or outpatient facilities.

Sustol (APF530) is a viscous tri(ethylene glycol) poly(ortho ester) (TEG-POE) based formulation that is intended to provide a sustained release of granisetron, present as the free base form. The final drug product contains 2% w/w granisetron base (10 mg) in 78.4% AP135, the TEG-POE polymer and 19.6% methoxy poly(ethylene glycol) (MPEG (b) (4) AP135 is a novel biodegradable excipient and is primarily responsible for the extended release of the granisetron from the drug product formulation. MPEG (b) (4) is used as an excipient (b) (6).

Table 1: Proposed formulation of APF530

Component	Concentration (% w/w)	To deliver Concentration (mg/unit)	To fill Concentration (mg/unit)	Function
AP135	78.4	392	(b) (6)	Excipient
MPEG (b) (4)	19.6	98	(b) (6)	Excipient
Granisetron ⁴	2	10	(b) (6)	Active
Totals	100	500	(b) (6)	

2.1 Product Information

Proposed Trade Name: Sustol (b) (4) granisetron)

Compositional Code/Name: APF530

Proposed Indications:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
- Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy

Proposed Age Group: Adults

Pharmacologic Class: 5-HT3 receptor antagonist

Route of Administration, Description, and Formulation: Subcutaneous (S.C.) injection; Sterile, semisolid injectable formulation is provided in a 1.0 mL pre-filled (b) (4) glass syringe with a 18 Gauge 5/8" thin wall needle for subcutaneous, abdominal administration; single use syringe.

Current Proposed Treatment Regimen:

(b) (4)

1st Review Cycle Proposed Regimen:

(b) (4)

Chemical name of the main ingredient in Sustol (granisetron):

1-Methyl-N-[(1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1H-indazole-3-carboxamide

or

endo-1-methyl-N-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1H-indazole-3-carboxamide.

Molecular formula: C₁₈H₂₄N₄O

Medical Reviewer's comments: The Applicant has made changes to the previous proposed regimen that was submitted during the 1st review cycle. These changes will need to be reviewed during the next review cycle labeling negotiations.

2.2 Table of Currently Available Treatments for Proposed Indications

Table 2: Currently Available Prescription Products for the Proposed Indications

DRUG NAME Formulations (Sponsor)	Approval Date	Indications and Dosages*
5-HT3 Receptor Antagonists		
ZOFRAN® (ondansetron) Oral tablets Orally disintegrating tablets Oral solution Intravenous injection (GlaxoSmithKline)	1991	Adults CINV – 16mg IV x 1 or 0.15mg/kg IV q4 hrs. x 3 CINV-HEC -- 24mg oral x 1 day CINV-MEC – 8mg oral BID x 2-3 days PONV— 4mg IV; 16mg oral 1 hr prior to induction RINV – 8mg oral TID x 1-3 days Pediatrics CINV – for ≥6 mo., 0.15-mg/kg IV q4 hrs. x 3 CINV-MEC – for 6mo. to 18yrs, 0.15mg/kg IV q4 hrs x 3; for ≥12 y.o., same oral as adult; 4-11y.o., 4mg oral TID x 2-3 days PONV—IV only, 1 month to 12 y.o. – a single 0.1-mg/kg dose for patients weighing ≤ 40 kg, or a single 4-mg dose for patients weighing > 40 kg RINV – N/A
KYTRIL (granisetron) Oral tablet Oral solution Intravenous injection (Roche Pharmaceuticals)	1993	Adults CINV- 10mcg/kg IV on the days chemotherapy is given; 2mg oral on the days chemotherapy is given PONV – 1mg IV x 1 RINV– 2mg oral x 1 Pediatrics CINV – IV same as adults for 2 y.o. and older PONV– N/A RINV– N/A

DRUG NAME Formulations (Sponsor)	Approval Date	Indications and Dosages*
ANZEMET (dolasetron mesylate) Oral tablet Oral solution Intravenous injection (Aventis Pharmaceuticals)	1997	Adults CINV--100mg oral x 1 PONV – 12.5mg IV x 1; 100mg oral x 1 RINV– N/A Pediatrics CINV – for 2 y.o. and older, 1.8mg/kg oral x 1 PONV– for 2 y.o. and older, 0.35mg/kg IV x 1; 1.2mg/kg oral x1 RINV – N/A
ALOXI (palonosetron HCl) Oral capsule Intravenous injection (MGI Pharma)	2003	Adults CINV-HEC (acute)– 0.25mg IV x 1 CINV-MEC (acute & delayed) – 0.25mg IV x 1; 0.5mg oral x 1 capsule PONV – 0.075mg IV x 1 <u>No Approved Pediatric Indications</u>
SANCUSO (transdermal granisetron) (ProStrakan)	2008	Adults CINV-HEC CINV-MEC Single patch is applied to upper outer arm 24 hrs before chemo; patch is removed 24 hrs after chemo; patch can be worn for up to 7 days <u>No Approved Pediatric Indications</u>
H1 Receptor Antagonists		
Hydroxyzine hydrochloride oral capsule oral suspension intramuscular injection (Generic) <i>Note: oral syrups and tablets are available but approved for indications other than antiemesis.</i>	1957	Adults NV -- 25–100 mg IM Pre- and Postoperative adjunctive medication -- 25–100 mg IM RINV – N/A Pediatrics NV-- 0.5 mg/lb body weight IM Pre- and Postoperative adjunctive medication -- 0.5 mg/lb body weight IM RINV – N/A
NK1 Receptor Antagonists		

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 Karyn L. Berry, MD, MPH
 NDA 22-445
 Sustol (granisetron) injection, extended release

DRUG NAME Formulations (Sponsor)	Approval Date	Indications and Dosages*
EMEND (aprepitant/fosaprepitant dimeglumine) Oral capsule Intravenous injection (Merck)	2003	Adults CINV-HEC – 125mg PO or 115mg IV on Day 1; 80mg PO on Days 2 & 3 CINV-MEC – 125mg PO or 115mg IV on Day 1; 80mg PO on Days 2 & 3 PONV – 40mg IV x 1 <i>No Approved Pediatric Indications</i>

2.3 Availability of Proposed Active Ingredient in the United States

See 1st cycle Clinical Review

2.4 Important Safety Issues With Consideration to Related Drugs

Granisetron has widespread distribution and a generally good safety profile. However, there exists the serious risk of cardiac arrhythmia with the class of 5HT₃ receptor antagonists. These events are primarily documented with intravenous use. All drugs in the class are noted to cause cardiac ion channel blockade, however, individual drug effect on QT prolongation varies. The effect of QT prolongation has been documented with ondansetron and dolasetron. No significant QT prolongation was found for palonosetron or transdermal granisetron. No thorough QT trial has been conducted for I.V. granisetron.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

See the 1st cycle Clinical Review for detail regarding pre-submission regulatory activity related to the 1st cycle submission. Below is a synopsis of regulatory guidance and advice provided by the Agency related to the pre-submission of the 2nd review cycle.

- February 15, 2011 Advice/Information Request to provide comments/recommendations regarding the Applicant's proposed thorough QT trial protocol (C2010-01- submitted under IND 68,213).

- February 25, 2011 End of Review meeting to discuss product presentation, clinical pharmacology and clinical/statistical deficiencies outlined in CR letter.

- March 31, 2011 End of Review meeting to discuss drug product quality, facility inspection, and container/closure system deficiencies.

- June 22, 2011 Advice/Information Request to provide comments/recommendations regarding the Applicant's revised QT trial protocol.
- August 24, 2011 Advice/Information Request to provide comments/recommendations on protocol to evaluate the metabolic fate of the novel AP135 polymer and the method development summary for the hydrolytic metabolites of the AP135 polymer (submitted under IND 68,213).
- August 25, 2011 Advice/Information Request to notify applicant that revised QT trial protocol was found acceptable.
- November 30, 2011 Advice/Information Request to notify applicant that the revised protocol to evaluate the metabolic fate of the polymer was found acceptable.
- June 1, 2012 Advice/Information Request to provide comments/recommendations regarding proposed human factors validation test protocol to address deficiency #2d in the CR letter (submitted under IND 68,213).

2.6 Other Relevant Background Information

During this review cycle multiple t-cons were held with the Applicant and multiple information requests (IRs) were sent to the Applicant.

November 14, 2012	IR (Microbiology) sent to request product quality microbiology information
November 19, 2012	T-con (CMC)
December 14, 2012	IR (CDRH) to obtain additional data regarding 1) usability testing (i.e. 12 of 15 subjects adequately performed, but sponsor concluded that this test was acceptable), 2) provide literature to support that force needed for injection can be sustained to expel drug from syringe over time, and 3) demonstrate that user is able to maintain SC injection technique while keeping needle in correct tissue plane.

December 14, 2012	IR (CMC) to provide additional data related to 1) analyzing Molar Mass Distribution in the AP135 excipient, 2) drug product stability data to include potential AP135 related degradation products, TEG, DEG and EG, 3) drug product post approval stability protocols.
December 18, 2012	T-con (Microbiology) with Applicant to discuss 1) issues related to validation of the terminal sterilization (b) (6) and 2) samples must represent the complete validated process
January 4, 2013	IR (Clin Pharm) sent to clarify on whether polymer metabolic fate study (C2011-02) monitored for ethylene glycol (EG) and diethylene glycol (DEG) levels, provide literature to address the likelihood of eventual breakdown of TEG to EG and DEG, as well as metabolites implicated in toxicity.
January 23, 2013	IR (CMC) sent to clarify the discrepancies in the filling temperatures for multiple batches.
January 24, 2013	IR (CMC) sent to request Certificate of Analysis with 590 mg fill weight
February 6, 2013	T-con (Clinical) with Applicant to discuss discrepancies in safety population databases
February 15, 2013	IR (CMC) sent to request revised proposed IVR specifications (time point and range)
February 13, 2013	T-con with Applicant to discuss Agency's concerns regarding drug administration and risks of administration errors, product presentation, educational material.
February 26, 2013	IR (Clinical) sent to request clarification of clinical labs collection in Phase 3 trial
February 28, 2013	IR (Pharm/Tox) sent to request additional information on nonclinical polymer studies

March 1, 2013

Face to Face meeting with Applicant to discuss drug administration concerns

The specific Clinical deficiencies outlined in the CR letter were:

Clinical/Clinical Pharmacology

Item #22

Your justification for your request to waive the thorough QT study is not acceptable because APF530 has demonstrated a higher pattern of granisetron exposure than other granisetron formulations.

Item #23

You have not adequately identified, characterized and quantified the specific breakdown products of (b) (4) in humans and have not adequately addressed the safety implications in humans. To address this deficiency you should identify, characterize, and quantify specific breakdown products of (b) (4) in the plasma, urine, and injection site in humans and the time course of their elimination using validated assay methods (non-radiometric). We recommend that you submit the protocol, including the validated assay methods, for the above study for review and evaluation prior to initiating the study.

Clinical/Statistical

Item #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.

Item #25

You have not provided sufficient information to describe the safety of Sustol because your administration site reaction data, as presented in the NDA, are inadequate to assess duration of these reactions and time to resolution of these reactions. You should provide the following additional information, by subject ID line listing, for administration site reactions: trial number, study drug and dose, emetogenic strata, type of administration site reaction (i.e. bruising, nodule, etc.), the date of onset of the adverse reaction, the date the adverse reaction resolved, the cycle when the adverse reaction occurred, information on whether the adverse reaction persisted into the subsequent cycle or cycles, and the time elapsed between injection and onset of the adverse reaction.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No new concerns

3.2 Compliance with Good Clinical Practices

The Applicant stated that all studies were conducted in compliance with Good Clinical Practice (GCP). The trial protocols and amendments were reviewed and approved by Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). Written consents were obtained from all subjects prior to any trial-related procedure. The clinical trials were conducted in accordance with the Declaration of Helsinki and with ICH Good Clinical Practice guidelines.

3.3 Financial Disclosures

The applicant submitted financial certification and disclosures for the two new trials conducted for this submission, C2011-01 and C2011-02. The Applicant certified that they have not entered into any financial arrangements with their investigators whereby the value of compensation to the investigator could be affected by the outcome of the trial as defined in 21 CFR 54.2(a). The Applicant also certified that each clinical investigator had no proprietary interest in this product or significant equity in the Applicant as defined by 21 CFE 54.2(b). As defined by 21 CFR 54.2(f), the Applicant certified that no clinical investigator was the recipient of any significant payments of any other sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The CMC reviewer, Dr. Zhengfang Ge, recommends not approving this Application based on deficiencies identified by the Office of Compliance at several manufacturing facilities. She also notes that the Applicant will need to complete resolution of In-Vitro release testing. Dr. Ge also recommends label/labeling changes which will be addressed during the next review cycle.

In the Agency's complete response for the original submission, the applicant was requested to include testing for low molecular weight impurities, unreacted monomers, and average molecular weight (Mn) or polydispersity ratio (PDI) in addition to weight average molecular weigh (Mw) in the novel excipient AP 135 specification and the drug product specification. The CMC Reviewer, Dr. Zhengfang Ge has determined that the specifications for AP135 and the drug product submitted in the resubmission have adequately addressed these issues.

In her review, Dr. Ge also notes that the manufacturing process of the drug product has been changed to terminal sterilization using gamma irradiation after filling the product into syringes (b) (4). The manufacturing process and process controls were revised accordingly and were found by Dr. Ge to be adequate.

Up to 24 months stability data are provided for the drug product using (b) (4) when stored at (2-8)°C. The applicant was also requested to submit 3 months stability data for the drug product using terminal irradiation. The drug products are stable for 18 months based on the stability data for the (b) (4) batches. Out of specification is observed for In-Vitro release testing for the drug product using (b) (4) at month 24. Since the manufacturing process for the drug product using terminal irradiation and

(b) (4) is similar (b) (4), 18 months expiration dating period should be granted based on the stability data for the batches (b) (4).

The applicant proposed to use (b) (4) for established name. “granisetron” should be the established name. The name of the drug product should be expressed as Sustol(granisetron) Injection, extended release has been communicated to the applicant. See Dr. Ge’s full review dated March 5, 2013.

ONDQA –Biopharmaceutics

The ONDQA reviewer, Dr. Tapash Ghosh did not recommend this application for approval based on the sponsor’s inadequate response to the *in vitro* drug release (IVR) test. Dr. Ghosh notes that the acceptance criteria for the IVR test will be used as a major attribute to control the quality of the drug product. He was concerned about the high level of variability for the different lots. The Applicant will need to set the acceptance criteria for the IVR of their product based on newly generated data. See Dr. Ghosh’s full review dated March 19, 2013 and March 13, 2013.

Office of Compliance

The Office of Compliance issued a withhold recommendation for three facilities (AP Pharma, (b) (4)). At the AP Pharma site, two observations from the previous inspection in early 2010 had not been fully resolved and additional observations this review cycle were observed. Some of the issues include: 1) not following standard operating procedures, 2) preventive maintenance programs not performed to a written program, 3) failure to establish scientifically sound and appropriate specifications, 4) accuracy of test methods had not been established and 5) release of drug product for distribution did not include appropriate laboratory determination of satisfactory conformance to final specifications prior to release. At the (b) (4) site one observation from an inspection in early (b) (4) had not been fully resolved and additional observations were identified this review cycle. These include: 1) firm continues to document inadequate investigations to deviations, 2) inadequate batch and production records, 3) failure to limit and control system access to analytical data and 4) inadequate record retention of analytical data. At the (b) (4) site observations were identified this cycle inspection. These included issues with (b) (4).

4.2 Clinical Microbiology

The Microbiology reviewer, Dr. Steven Donald, noted that the applicant did not address each of the microbiology deficiencies separately, but provided new validation data and information that does address the previous deficiencies. The microbiology reviewer did not identify product quality microbiology deficiencies and based on his review he recommends approval of this Application. See Dr. Donald’s full review dated January 30, 2013.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer, Dr. Tamal Chakraborti, noted that the applicant did not submit any new nonclinical study reports with this submission. Dr. Chakraborti reviewed the specification for the final drug product (FDP). The Applicant included three APF135 (TEG-POE polymer)-related impurities, i.e. (b) (4) NMT (b) (4) %, (b) (4) combined NMT (b) (4) %. He found that the Applicant's proposed specification of the final drug product (FDP) is acceptable from the nonclinical standpoint. Specification for (b) (4) at NMT (b) (4) % in the FDP appears to be acceptable based on the available toxicology information. In addition, combined specification for (b) (4) of NMT (b) (4) % in the FDP also appears to be acceptable based on the PDE. Dr. Chakraborti recommends approval of this application.

See Dr. Chakraborti's full review dated February 20, 2013.

4.4 Clinical Pharmacology

The Clinical Pharmacology reviewer, Dr. Sandhya Apparaju, found the Applicant's evaluation of the metabolic fate of the novel polymer and the additional assessment of literature pertaining to the potential for the formation of lower order glycols, their metabolites and the overall safety implications to be acceptable. She notes that even though there was incomplete recovery, $\sim 1/3^{\text{rd}}$, of the injected polymer load in the subjects, the study findings improve the Agency's understanding of the polymer's in vivo fate and confirm qualitatively the metabolites previously noted in the exploratory and non clinical investigations.

Dr. Apparaju reviewed the potential for further in vivo degradation of the Sustol excipients, particularly of MPEG (b) (4) to EG, DEG and their toxic metabolites. With the exception of glycolic acid (GA) that was adequately assayed in the completed study, EG, DEG and their other metabolites have not been directly assessed. In her review, she notes that the literature strongly supports that GA is primarily responsible for the clinical consequences of EG toxicity in cases of accidental or intentional poisoning due to its accumulation and rate limited conversion. The concentration of GA is well correlated to the incidence of anion gap. Using a well validated assay, GA was not detectable in the plasma of the polymer fate study subjects who were administered twice the clinical dose of Sustol.

In her review, Dr. Apparaju states that "it doesn't appear plausible that the systemic levels of GA would rise from virtually undetectable levels to toxic concentrations (≥ 980 $\mu\text{g/mL}$), even with a complete (100%) recovery of the polymer dose." Due to lack of knowledge for systemic levels associated with toxicity of other potential metabolites of EG and DEG, no additional in vivo study is recommended to evaluate these metabolites at this time.

See Dr. Apparaju's full review dated March 14, 2013.

The Applicant conducted a Phase 1, single blinded, randomized, single site, single dose study in 14 healthy male and female subjects, entitled, "A Randomized, Placebo-Controlled, Single-Dose Study to Examine the Fate of the Polymer of APF530 in Healthy Subjects" to address CR deficiency #23 (you should identify, characterize, and quantify specific breakdown products of (b) (4) in the plasma, urine, and injection site in humans and the time course of their elimination using validated assay methods (non-radiometric).

The primary objective of the study was to evaluate the rate and extent of the metabolism and urinary elimination of the TEG-POE polymer in normal volunteers. Subjects were randomized to receive either 1000 mg of APF530 or placebo (0.9% normal saline). Eligible subjects participated in a screening phase (within 28 days of dosing), a treatment phase, and a final visit conducted at discharge from the study. Subjects were required to remain in the study unit from the morning of Day -2 through the morning of Day 11 for a total of approximately 12 days of confinement. Study drug was administered in the morning on Day 1.

Blood and urine samples were collected throughout the 12-day period and analyzed using validated bioanalytical methods to determine the fate of potential TEG-POE hydrolytic products as well as evaluate the pharmacokinetics of granisetron and the potential further metabolism of the TEG-POE hydrolysis products. Sampling at the injection site was not done in this study due to the difficulty associated with this over an extended period.

For the experimental analysis for intermediate hydrolysis products or potential metabolites of hydrolysis products, organic urine or plasma extracts were pooled separately for APF530-dosed subjects and placebo-dosed subjects on a daily basis to encompass 24-hour sampling from predose through 240 hours postdose.

The following criteria were evaluated: Blood samples for PK analysis of the potential hydrolytic products of the TEG-POE polymer, (pentaerythritol [PE], triethylene glycol [TEG], glycolic acid [GA]), and propionic acid [PA]), Blood samples were collected for PK analysis of granisetron. Urine samples were collected for measurements of PE, TEG, PA, and GA

After a single S.C. administration of 1000 mg of APF530 (containing 20 mg granisetron), the drug was slowly absorbed and eliminated, with a median Tmax of 11.0 hours and a mean t 1/2 of 32.7 hours. The mean Cmax was 37.1 ng/mL. The mean AUC(0-24), AUC(0-120), and AUC(0-inf) values were 651, 1514, and 1684 ng•hr/mL, respectively.

Results:

For the polymeric metabolites PE, TEG, PA and GA the plasma concentration were all below the limit of detection. Detectable concentrations of PE, TEG and GA were noted in the urine samples. PA could not be detected in urine possibly due to lack of adequate assay sensitivity. PE and TEG levels were absent during baseline urine collection. GA levels noted at baseline and the post dose levels for the drug versus placebo group were comparable. The Applicant noted that GA levels appearing in placebo patients and at baseline are from endogenous or exogenous sources.

Safety:

There were no reported deaths, serious TEAEs, or TEAEs that led to study drug discontinuation.

Administration site reactions were the most common AEs. The most common injection site reaction after APF530 administration was induration (9 subjects [90.0%]), which lasted from 1 to 9 days (mean of 5 days). The S.C. reaction of nodule was reported by 8 subjects (80.0%) after receiving APF530. Overall, nodules lasted from 2 to 29 days (median of approximately 25 days). All skin reactions resolved completely. After placebo administration, no subjects reported the SC reaction of nodule and 1 subject (25.0%) reported the skin reaction of induration that lasted approximately 4 days. All SC injection site AEs resolved over time with a mean and median duration of 10 and 6 days, respectively.

After administration site reactions, constipation was the most common TEAE reported in the APF530 treatment arm (6 subjects; 60.0%), while no placebo-treated subjects reported constipation. The majority of TEAEs were considered mild in severity. Other than administration site reactions, the TEAEs considered possibly related to study drug were abdominal tenderness, constipation, headache, pruritis, and abdominal discomfort.

4.4.1 Mechanism of Action

See 1st cycle review

4.4.2 Pharmacodynamics

See 1st cycle review

4.4.3 Pharmacokinetics

See 1st cycle review

4.5 Office of Medication Error Prevention and Risk Management

Label, Labeling, Packaging and Human Factors Study Review (see section 4.7 for study review and results)

Dr. Teresa McMillan conducted a review of the Human Factors Study and concluded that *“the proposed label and labeling can be improved to increase readability and prominence of important information on the label to promote the safe use of the product. Additionally, the Human Factors Study confirmed that users may encounter difficulties while administering this product due to the amount of pressure needed.”* The Office has concerns regarding the potential difficulty in administration of this viscous product. In her review of the Human Factors Study, Dr. McMillan notes that participants in the study had the following concerns: 1) difficulty pushing the plunger due to the viscosity of the product and 2) attempting a SC injection with an 18 gauge needle and potential discomfort it may cause patients. The Office also had concerns that due to the amount of force required to expel the product, both the healthcare professional and the patient may move during the administration making it difficult to maintain the injection in the correct tissue plane.

Dr. McMillan also recommended multiple label revisions, under Prescribing Information and Instructions for Use, syringe label and carton labeling.

Proprietary Name Review

The Office conducted a proprietary name review and determined that the proposed proprietary name is acceptable from both a promotional and safety perspective.

4.6 Centers for Device and Radiological Health

QuynhNhu Nguyen, CDRH/Biomedical Engineer/Human Factors Reviewer, was consulted to review the Human Factors study submitted by the Applicant. Dr. Nguyen also noted that the Human Factors study suggested that there are issues with safe and effective use of Sustol. She stated that the performance data indicated the following problems: 1) incomplete injection of the drug product, and 2) difficulty by users in generating the required force to perform injection, which could result in administering the drug product in unintended areas, such as intramuscularly, that may lead to adverse reactions.

Dr. Jacquelyn Ryan, CDRH, was consulted to provide an assessment of the device performance. Dr. Ryan also identified safety issues related to the Applicant's Human Factors Study. These included: inability of 12 of the 15 subjects unable to expel all of the medication from all of the syringes during their attempted injections; high average initial peak force (breakloose) for injection was very high, especially when the drug was

delivered faster than the 1mm/sec recommended rate. Since the breakloose and glide forces are at the maximum achievable force for 50% of the population, Dr. Ryan was also concerned that users may not be able to achieve adequate control of the device to allow injection into the correct tissue plane.

Dr. Ryan noted that for the Sustol syringe, the average initial peak force (breakloose) for injection was 114.4 N and glide force was 98 N. An information request was sent to the Applicant requesting them to cite the literature, to justify if 95% percent of the US population could generate the required breakloose force using the thumb or hand, and can sustain the force needed to expel the drug from the syringe over the time needed to extrude the drug. The Applicant responded that the peak force and glide force required to expel the recommended Sustol dose within 30 seconds, as specified in the Instructions for Use, is calculated to be 76 N and 65 N, respectively. They also stated that Sustol is administered by positioning the index and middle finger underneath either side of the finger flange and pressing the plunger rod with the thumb or palm of the hand. Based on the literature, the Applicant responded that the force for females and males in the 95th percentile was determined to be 65 N and 94 N, respectively and that these values meet or exceed the force calculated for expelling Sustol.

Dr. Ryan notes that CDRH is still concerned that the breakloose and injection forces are close to maximum achievable force for about half the population and is above maximum achievable pinch force for 5% of the population. She states that this may result either in failed injections or possible drug administration errors.

4.7 Human Factors Study

Human Factors Validation Report for Sustol (APF530) Administration Kit (XP-1179-045)

15 nurses participated in the validation study. No prior training on the administration of Sustol was provided. A patient mannequin in a seated position with an injection pad was used for the administration of the study drug. The study included all steps associated with the use of the study drug. While most of the steps were considered essential (i.e. use errors/failures do not result in patient harm), three steps were considered critical (i.e. use errors/failures can result in patient harm). Those steps were: 1) choosing administration route, 2) discarding used needle and syringe and 3) handling syringe to avoid needlestick injuries and possible infection. Since Sustol is an extremely viscous product, the Agency requested that “warming to room temperature” be evaluated during validation testing. The Applicant evaluated warming at least 60 minutes prior to use (b) (4)

Warming may reduce the force required to inject the drug product.

Per the review of QuynhNhu Nguyen (Human Factors Reviewer), the study results showed that in examining the completion of injection, three participants did not appear to have expelled all of the medication from the syringe and had one or two droplets remaining. The Applicant provided additional response indicating that an independent observer visually inspected all of the syringes after injection, and of the 45 syringes (15 participants, 3 injections), 44 of the syringes were judged to have the plunger stopper flush with the bottom of the syringe barrel, and one syringe had two droplets remaining. In addition, some participants reported use difficulties during the study: one participant in unscrewing the tip cap from the end of the prefilled syringe; one participant in removing the hub cover from the needle; and two participants removing the white finger flange from the syringe prior to injecting. In addition, five participants indicated that on their first trial, the syringe was much harder to push than expected, and four other participants indicated that they were expecting the harder pressure because of the drug viscosity. In examining the warming of the syringe to room temperature, all 15 participants acknowledged the need for warming the syringe before use, and they rolled the syringe in the palm of their hands before injection.

Medical Reviewer's comments: Identified concerns from this study, such as incomplete injection of the drug product and user reported difficulty in generating the required force to perform the injection, could result in injecting Sustol in an unintended area, such as intramuscularly, which could lead to adverse reactions. The CDRH reviewer acknowledges that warming this viscous product may improve delivery. [REDACTED] (b) (4)

[REDACTED] **This will need to reviewed by the CMC reviewer to ensure that this does not alter the drug's properties.**

The CDRH Human Factors reviewer recommends that additional modifications either in the product labeling and/or product design are necessary. Additional human factors study should then be conducted to demonstrate that the product modifications are effective in reducing/minimizing patient harm. This reviewer concurs with CDRH reviewer's recommendations.

Both CDRH Human Factors and DMEPA determined that the original Human Factors study submitted by the Applicant was not adequate due to administration difficulties which the subjects experienced that were not classified as administration failures. After the face to face meeting held with the Applicant on March 01, 2013, the Applicant agreed to perform new Human Factors testing to demonstrate ease of use of the syringe and that the drug can be safely administered by users with variable levels of experience.

CDRH and DMEPA reviewed the results of a formative human factors validation study submitted by the Applicant on March 23, 2013. The sponsor included testing which demonstrated that the breakloose (expulsion force) for the syringe measured on the

(b) (4) Device

(b) (4)

which is below the maximum achievable pinch force for 95% of the population by normative data. CDRH ODE therefore believes that the device is appropriate for its intended use. However, the CDRH reviewer states that the safe and effective use of the device is dependent on several critical steps in the instructions for use, including removing the syringe from refrigeration, warming of the syringe with the hands, expelling the drug at the rate recommended by the sponsor, and not removing the finger flange prior to injection. Stabilization of the syringe with the non-dominant hand may also help to mitigate movement of the needle out of the tissue plane during injection.

Per the joint review by DMEPA and CDRH the following issues were identified with comments to be relayed to the Applicant:

The formative study results and follow-up comments:

1) Issue: The products used during the testing did not represent the finalized commercial products, which generated issues related to device performance such as disengagement of the finger flanges and malfunctions of the plunger.

Comments: In the Human Factors/Usability validation study, the Applicant should use products that have been assembled using a validated process and released under the Quality Management System.

2) Issue: While four of the 20 users did not follow the specific technique stated in the Instructions for Use, they were able to administer the product. No discuss was provided by the Applicant as to whether any of the techniques applied by these test participants had any potential negative consequences to the patient or the user.

Comments: If any of the techniques applied could result in patient harm, the Instructions for Use/labeling should be modified to warn users of those potential consequences, and the modified Instructions for Use/labeling should be used for the Human Factors/usability validation study.

3) Issue: An additional cautionary statement may need to be added to the Instructions for Use for not removing the white finger flanges.

Comments: Ensure that the data collected from the Human Factors/usability validation study demonstrate that this mitigation is effective.

5 Sources of Clinical Data

The Applicant submitted four clinical trials to support the initial application. Two of these studies were in healthy volunteers and two were in patients receiving chemotherapy. The Applicant submitted data from three new trials for this submission: 1) a thorough QT study (C2011-01), 2) an assessment of breakdown products of the polymer (C2011-

02) and 3) a Human Factors Validation Report for Sustol (APF530) Administration Kit (XP-1179-045), to assess the use of the administration device.

The Applicant submitted the requested re-analysis of the primary efficacy data from the pivotal Phase 3 trial, C2006-1, justification for patient assignments to Per-Protocol or Intent-to-Treatment groups, justification for exclusion of Site 504 patients from the Per-Protocol analysis, justification for the non-inferiority margin and additional secondary efficacy analysis. The Applicant also submitted additional pooled safety data analysis of administration site reactions (duration and incidence).

5.1 Tables of Studies/Clinical Trials

Table 3: Studies/Clinical Trials

Clinical Review
 Karyn L. Berry, MD, MPH
 NDA 22-445
 Sustol (granisetron) injection, extended release

Trial Code	Trial design	Trial Objective(s)	Treatment	Number of patients	Treatment Duration	Gender F/M	Primary Endpoint(s)
Number of trial centers							
Location(s)							
2 New Trials Submitted for 2 nd Review Cycle							
C2011-01 Phase I PK/PD and Safety US	Randomized Placebo controlled Positive (Moxifloxacin) controlled 4 period crossover	Primary Effects on QTcF Obtain Cmax & AUC values of granisetron equivalent to those seen in patients given APF530 500mg	APF530 SC 1000 mg APF530 (20 mg granisetron) Granisetron (IV) 50 µg/kg Moxifloxacin (oral) 400 mg Placebo (SC, IV, or oral)	56 Healthy subjects	Single doses in the am on Days 1, 11, 21 & 31	32 – M 24 - F	Difference between postdose time-matched baseline-adjusted mean QTcF (APF530) & post-dose time-matched baseline-adjusted mean QTcF (placebo) = [dQTcF (APF530) – dQTcF (placebo)] = ddQTcF.
C2011-02 Phase I PK & Safety US	Randomized Placebo-controlled	Primary Metabolism & urinary elimination of TEG-POE polymer vehicle (b) (4)	APF530 SC 1000 mg APF530 (20 mg granisetron) Placebo SC	14 (10 APF530; 4 placebo) Healthy Subjects	Single dose	7 – M 7 - F	PK assessments: plasma /urine concentrations of granisetron, PE, TEG, PA, GA
Efficacy & Safety in Cancer Patients							
C2006-01 (Phase 3 Pivotal trial) 72 US sites 19 India sites 11 Poland sites	Randomized, multicenter, observer-blind, double dummy, parallel group	Assess the safety & effectiveness of a single SC injections of APF530 (5 mg & 10 mg) versus a single IV injection of Aloxi (palonosetron, 0.25 mg) for both prevention of acute and delayed CINV in patients undergoing MEC or HEC	Test article- APF530 5 mg & APF530 10 mg SC injection Active Comparator- Aloxi 0.25 mg IV (placebo – isotonic saline for IV or SC injection) Injections were given 30 – 60 minutes before the start of chemo	1428 randomized 1395 received drugs	4 Cycles (up to 4 doses of study drug)	1040- F 355 - M	Proportion of patients with CR during the acute phase (0 to 24 hours) following the administration of chemotherapy in Cycle 1. Proportion of patients with CR during the delayed-onset phase (24 to 120 hours) following the administration of chemotherapy in Cycle 1.

Clinical Review
 Karyn L. Berry, MD, MPH
 NDA 22-445
 Sustol (granisetron) injection, extended release

Trial Code	Trial design	Trial Objective(s)	Treatment	Number of patients	Treatment Duration	Gender F/M	Primary Endpoint(s)
Number of trial centers							
Location(s)							
PK & Safety in Cancer Patients							
C2005-01 (Phase 2 Open Label trial) 6 US sites	Open-label, multicenter, ascending, single SC dose, sequential group trial	Assess the PK, tolerability and safety of a single SC injection of APF530 (5 mg, 10 mg and 15 mg) in patients undergoing MEC	Test article – APF530 5 mg APF530 10 mg APF530 15 mg - SC injection Injections were given ~30 ± 5 min before the start of chemo	45 enrolled & received study drug (17 – APF530 5 mg; 15 – APF530 10 mg; 13- APF530 15 mg)	14 ± 3 days after a single SC injection dose on the 1 st day of trial	27 – F 18 - M	Efficacy assessment was exploratory
C2007-01 3 Poland sites	Randomized, multicenter, uncontrolled, open-label, PK trial	Determine the PK parameters of 2 doses of APF530 (5 mg & 10 mg) in patients undergoing MEC or HEC	Test article – APF530 5 mg APF530 10 mg SC injection	35 enrolled (17 - 5mg APF530 & 18 – 10 mg APF530)	Single SC injection dose; 7 day washout period & 7 day treatment & blood sample collection period	All Females Mean Age – 55.7 yrs Age Range – 28 – 75 yrs	Efficacy assessment was exploratory
BA/PK & Safety in Healthy Subjects							
C2004-01 (Phase 1) 1 UK site	Single, ascending SC dose, sequential group trial, using a 2 period crossover to assess BA	Determine the PK, safety & tolerability of ascending SC doses of APF530 in healthy male subjects	Test article – APF530 5 mg APF530 10 mg APF530 15 mg - SC injection Kytril IV 100 mcg/kg	26 enrolled	14 days	All males Age Range – 21– 49 yrs	

5.2 Review Strategy

This review is an addendum to the first clinical review cycle and will only present information that is either new in this 2nd review cycle, is interpreted differently or is necessary for context so that this review may be use as a stand-alone document.

5.3 Discussion of Individual Studies/Clinical Trials

In the first review cycle, the Applicant submitted one pivotal Phase 3 study, C2006-1 in support of the efficacy of Sustol (APF530 10mg) 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 that review it was found that the sponsor did not include data from Site 504 in their primary efficacy analysis. Additionally, an Agency inspection showed protocol violations inconsistent with the sponsor's reports. For this 2nd review cycle, the Applicant submitted data to address the inspection deficiencies and provided a reanalysis of the efficacy data.

The sponsor conducted a review of the Site 504 patients included and excluded from the Per Protocol (PP) and modified Intent to Treat (mITT) populations for study C2006-1. An ITT analysis was performed and the mITT and PP populations were reanalyzed for the primary efficacy analyses as well as the secondary analyses.

C2006-01, Pivotal Phase 3 Trial (Protocol synopsis)

See 1st cycle review for additional details

This was a randomized, multicenter, observer-blind, double-dummy, parallel group study conducted in patients with confirmed malignant disease who were scheduled to receive single-day administrations of moderately or highly emetogenic chemotherapy regimens. Patients received study drug in up to four cycles, each of which began the day of qualifying chemotherapy treatment (Day 1) and terminated at the end of the antiemetic efficacy monitoring Day 5/120 hours (+72 hours) after chemotherapy administration. Treatment cycles were separated by a period of at least 7 days and no more than 28 (+3) days.

Treatment groups:

Cycle 1 (3 treatment groups)

- a single intravenous (I.V.) injection of 0.25 mg Aloxi and placebo SC.
- a single SC injection of 250 mg APF530 (5 mg granisetron), referred to as 5 mg APF530, and placebo I.V.
- a single SC injection of 500 mg APF530 (10 mg granisetron), referred to as 10 mg APF530, and placebo I.V.

After Cycle 1, patients were re-randomized to receive one of two treatments in up to three cycles

- a single SC injection of 5 mg APF530.
- a single SC injection of 10 mg APF530

Patients who received Aloxi in Cycle 1 were assigned in a 1:1 ratio to either dose of APF530, patients who received APF530 in Cycle 1 continued to receive the same dose of APF530 in subsequent cycles. All injections were to be given 30 to 60 minutes before the patient's scheduled chemotherapy. Patients received dexamethasone according to the standard guidelines provided for their emetogenicity stratum. Rescue medication was only to be used when patients experienced signs and symptoms of nausea and vomiting. Granisetron, palonosetron, and aprepitant were not to be used until Day 5 of the final treatment cycle.

The following efficacy measures were evaluated daily during the first 5 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 the purposes of analysis, a single emetic episode was defined as a single vomit or retch separated by an interval ≥ 1 minute. Continuous vomits or retches were defined as two or more vomits or retches with a gap of less than 1 minute between the individual vomits or retches. In addition to assessment of emesis, an assessment of Quality of Life using the FLIE, was made on Day 5 of Cycle 1.

The primary efficacy endpoints of this trial were:

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

The secondary efficacy endpoints were:

- 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 during the overall treatment cycle (0-120 hours).
- Proportion of subjects, following the completion of Cycle 1, with TR during the acute phase, delayed-onset phase, and overall treatment cycle (0-120 hours).
- Proportion of subjects, following the completion of Cycle 1, with major control of emesis (<2 emetic episodes), minor (3-5 emetic episodes) and failure (>5 emetic episodes); during the acute phase, delayed-onset phase, and overall treatment cycle (0-120 hours).
- 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 occurs first).
- Use of rescue medication.
- Severity of nausea measured daily and overall (0-120 hours).
- Subject's global satisfaction with antiemetic therapy during the acute phase and overall trial period, recorded in 24-hour increments.
- QoL assessment, the impact of nausea and vomiting on Day 5.
- Sustainability of antiemetic effect of APF530 during multiple chemotherapy Cycles.

Primary Efficacy Analysis

For moderately emetogenic chemotherapy regimens the objective of the trial was to demonstrate the non-inferior efficacy of APF530 for acute-onset and delayed-onset CR in comparison to Aloxi. For highly emetogenic chemotherapy regimens the objective of the trial was to demonstrate the non-inferior efficacy of APF530 for acute-onset and the superiority for delayed-onset CR in comparison to Aloxi.

Non-inferiority was declared if the lower bound of the Confidence Interval (CI) was above -15%. Superiority was declared if the lower bound of the CI was above 0%.

6 Review of Efficacy

Efficacy Summary

The CR letter requested the following statistical data: 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 and 3) a justification of the non-inferiority margin used in the trial. Per Dr. Freda Cooner, the Statistical Reviewer, the Applicant provided the new analysis and datasets requested, and a justification of the non-inferiority margin. Dr. Cooner found the Applicant's responses to the CR issues to be acceptable.

A re-analysis of each of the three efficacy populations (ITT, mITT, and PP) demonstrated the non-inferiority of 500 mg APF530 (10 mg granisetron) to Aloxi, regardless of whether Site 504 patients were included or excluded. (b) (4)

[REDACTED]

[REDACTED]

(b) (4)
Therefore, this reviewer recommends that the indication be revised to reflect the population that will benefit from this drug in both the acute and delayed phase, *“For prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.”*

6.1 Indication

The Applicant proposes the following indications:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

6.1.1 Methods

The Applicant conducted a review of each patient according to the violation rules assigned in the Statistical Analysis Plan (SAP) dated September 5, 2008. 62 patient adjustments were made according to the Per Protocol (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 Site 504 patients included and excluded from the PP and mITT populations. The Applicant stated that Site 504 was omitted from the mITT and PP analysis because the veracity of the data was questioned. During the Quality Control Review, the Site reported very similar patterns in the case report forms and this is what led the Applicant to question the truthfulness of the data.

The Applicant noted the following patterns in data from Site 504: all 19 patients that received study drug reported 100% CR; 100% CC and 100% TR. In addition to the identical response rates for all patients, minimal changes were observed in the blood pressure values pre and post chemotherapy for any patient. All systolic blood pressure measurements at that study site for all patients at all times are 110 mm Hg, 120 mm Hg, or 130 mm Hg. There are no values between these three values, above the 130 value or below the 110 value. Similar implausible values were observed for the diastolic blood pressure measurements, the respiratory rates, temperatures, and the pulse rates. All pulse rate values were between 76 and 88 bpm, except for a single value of 70 bpm and a single value of 89 bpm (the only odd number in the entire pulse database for the site).

The majority of the patients at Site 504 did not report any adverse events throughout the study. Also, the FLIE response markings and values were nearly identical for all patients

without any mistakes or line outs recorded on any of the 18 questions for each patient. Based on the assessment of this information, the decision was made by the Applicant to exclude the patient data from Site 504 in both the mITT and the PP analyses in the final clinical study report.

The Applicant also provided a response for justification of the use of a non-inferiority margin of 15%. Per the statistical reviewer, Dr. Freda Cooner, the Applicant provided detailed justification for the use of the NI margin of 15% based on the Aloxi registration studies and literature. She noted that the justification closely followed the reference guidance. Dr. Cooner found the Applicant's justification acceptable.

The primary efficacy analysis in the moderately emetogenic stratum was a test of the following four hypotheses:

- 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

(b) (4)

6.1.2 Demographics

See 1st cycle review

6.1.3 Subject Disposition

See 1st cycle review

6.1.4 Analysis of Primary Endpoint(s)

For those analyses with Site 504, 3 patients were included in the moderate emetogenic chemotherapy (MEC) (1 in each, 250 mg APF530 (5 mg granisetron), 500 mg APF530 (10 mg granisetron) and ALOXI groups, respectively) and 16 in the highly emetogenic chemotherapy (HEC) (6, 6, and 4 in the 250 mg APF530 (5 mg granisetron), 500 mg

APF530 (10 mg granisetron) and ALOXI groups, respectively). The Applicant notes that the inclusion of all three groups (250 mg APF530 (5 mg granisetron), 500 mg APF530 (10 mg granisetron) and ALOXI) of Site 504 patients (b) (4) classifications had the effect of slightly improving the results in both the acute and delayed phases of each of the analyses (ITT, mITT, and PP).

Table 4: Primary Results of Complete Response in Cycle 1 (mITT Population)

Phase	Statistic	MEC		
		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)#	-

Met the non-inferiority margin of 15%.
 Source: Dr. F. Cooner, Statistical Reviewer's, table

Medical Reviewer's comments: Re-analysis of each of the three efficacy populations (ITT, mITT, and PP) demonstrated the non-inferiority of 500 mg APF530 (10 mg granisetron) to Aloxi, regardless of whether Site 504 patients were included or excluded. (b) (4)

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant conducted a re-analysis of the following secondary endpoints: 1) CR for the period 0 to 120 hours during Cycle 1 and 2) Sustainability of antiemetic effect of APF530 during multiple chemotherapy cycles as measured by CR.

The Applicant stated that the analysis of secondary variables was considered supportive of the primary results and therefore statistical testing was not controlled for in the multiple tests performed.

CR for the period 0 to 120 hours during Cycle 1

The Applicant reports clinical equivalence between the two APF530 dose groups and ALOXI in the overall phase for patients receiving both moderately and highly emetogenic chemotherapy. The re-analysis is very similar to the analysis done in the 1st cycle review.

Table 5: Summary of CR in Subjects in the MEC (b) (4) Strata During 0 – 120 hours in Cycle 1

	MEC		
	APF530 5 mg (N=214)	APF530 10 mg (N=212)	Aloxi 0.25 mg (N=208)
CR (%)	104 (48.6)	114 (53.8)	108 (51.9) (b) (4)

Source: Modified Applicant's table: Main trial report, C2006-01

6.1.6 Other Endpoints

See review from 1st cycle

6.1.7 Subpopulations

Chemotherapy regimens

For subjects in the moderately emetogenic stratum the most common chemotherapy regimen in Cycle 1 for the mITT population was a cyclophosphamide/doxorubicin combination.

Table 6: Summary of Current Chemotherapy Regimens in Cycle 1 Among Subjects in the Moderately Emetogenic Stratum (mITT Population)

Chemotherapeutic Regimen	Moderately Emetogenic		
	APF530 5 mg	APF530 10 mg	Aloxi 0.25 mg
n	214	212	208
Cyclophosphamide/doxorubicin, n (%)	125 (58.4)	116 (54.7)	108 (51.9)
All other regimens, n (%)	89 (41.6)	96 (45.3)	100 (48.1)

Source: Applicant's table; Originally submitted C2006-01 final study report, p.82 (excludes site 504)

(b) (4)

Table 7: Summary of Current Chemotherapy Regimens in Cycle 1 Among Subjects in the Highly Emetogenic Stratum (mITT Population)

Chemotherapeutic Regimen	n	Highly Emetogenic		
		APF530 5 mg	APF530 10 mg	Aloxi 0.25 mg
		229	240	238
Carboplatin/taxol, n (%)		91 (39.7)	96 (40.0)	98 (41.2)
Carboplatin/no taxol, n (%)		23 (10.0)	22 (9.2)	19 (8.0)
Cisplatin regimens, n (%)		51 (22.3)	53 (22.1)	53 (22.3)
All other regimens, n (%)		64 (27.9)	69 (28.8)	68 (28.6)

Source: Applicant's table; Originally submitted C2006-01 final study report, p.83 (excludes site 504)

Table 8: Summary of Complete Response in Subjects in the MEC (b) (4) Strata by Chemotherapeutic Regimen During the Acute-onset and Delayed-onset Phases in Cycle 1 (mITT Population)

Emetogenicity Level	Chemotherapeutic Regimen		Treatment		
			APF530 5 mg	APF530 10 mg	Aloxi 0.25 mg
Moderate	CR during acute-onset phase				
	Cyclophosphamide/doxorubicin	n	125	116	108
		n (%)	88 (70.4)	82 (70.7)	71 (65.7)
	All other regimens	n	89	96	100
		n (%)	72 (80.9)	81 (84.4)	85 (85.0)
	<i>P</i> -value D/C vs all other regimens ^a		0.1099	0.0220	0.0014
	CR during delayed-onset phase				
	Cyclophosphamide/doxorubicin	n	125	116	108
		n (%)	54 (43.2)	55 (47.4)	50 (46.3)
	All other regimens	n	89	96	100
	n (%)	56 (62.9)	70 (72.9)	70 (70.0)	
<i>P</i> -value D/C vs all other regimens ^a		0.0055	0.0002	0.0007	

(b) (4)

Source: Applicant's table; Originally submitted C2006-01 final study report, p.82 (excludes site 504)

Medical Reviewer's comments: In the MEC stratum "all other regimens" showed greater CR than the cyclophosphamide/doxorubicin regimen in the APF530 5 mg, APF530 10 mg and ALOXI groups during both the acute phase and the delayed phase. (b) (4)



The applicant's Phase 3 trial, which was conducted from 2006 through 2008, used the Hesketh criteria for emetogenicity. Per the Hesketh criteria anthracycline/cyclophosphamide combinations were considered MEC. Since that time, the American Society of Clinical Oncology (ASCO) published updated antiemetic guidelines in 2011 which re-classified anthracyclines when combined with cyclophosphamide as high emetic risk.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See 1st cycle review

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

See 1st cycle review

6.1.10 Additional Efficacy Issues/Analyses

See 1st cycle review

7 Review of Safety

In the first Clinical review cycle, it was determined that the safety of Sustol, as related to QTc prolongation and administration site reactions, such as bruising, nodules, erythema, pain and hemorrhage, had not been adequately demonstrated. The safety evaluation in this 2nd review cycle addressed the duration and time to resolution of administration site reactions and the results of the thorough QTc (TQT) trial. Refer to the 1st cycle clinical review for additional safety details.

Safety Summary

The Applicant's TQT trial was reviewed by the Interdisciplinary Review Team for QT Studies Consultation and no significant QTc prolongation effect of APF530 or granisetron was detected in this TQT study.

Based on the mean duration of injection site reactions, i.e. 22.7 days for nodules, 18.5 days for erythema and 15.9 days for bruising, in the APF530 >500 mg group, injection site reactions generally carried over into multiple cycles (APF530 was allowed to be dosed every 7 days). The mean duration in days of injection site reactions was longer in the APF530 $\geq$ 500 mg dose than in the APF530 $\leq$ 250 mg group. The prolonged duration of injection site reactions is likely due to AP135, the novel polymer, which is responsible for the extended release of the granisetron from the drug product formulation.

In light of the Clinical Pharmacology reviewer's reliance on the clinical safety database to assess the potential toxicity that may be attributed to accumulation of ethylene glycol (EG), diethylene glycol (DEG) and their metabolites following the use of Sustol, death narratives were re-evaluated. This patient population had underlying malignancy and received chemotherapy that can have significant systemic toxicity and complications. These deaths could therefore be explained based on progression of malignancies and/or chemotherapy treatments. It is unlikely that the deaths were secondary to EG/DEG toxicity. Although, the pivotal trial included patients who received up to 4 cycle of Sustol, only the first cycle had a comparator. In addition, no laboratory values, i.e. chemistries, were reported for cycles 2 to 4, which would be useful to assess for safety issues related to cumulative dosing.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Safety data of administration site reactions were reviewed from six (6) clinical trials, C2004-01 (phase 1 healthy subjects), C2005-01 (phase 2 ascending dose and PK trial), C2006-01 (phase 3 pivotal trial), C2007-01 (phase 2 PK trial), C2011-01 (a thorough Qt study) and C2011-02 (an assessment of breakdown products of the polymer) submitted by the Applicant.

Of the 1450 subjects who received APF530, 94% received the dosage strengths used in the Phase 3 study C2006-01 (250 mg or 500 mg). The remaining subjects received doses of 125 mg, 750 mg, or 1000 mg.

Table 9: Safety database

Study	Comments	Total Patients	Total at ≥ 500 mg
C2004-01	24 planned + 2 replacements (one replacement subject received incomplete dose, not included in safety database, but actually received an estimated 50% of 250 mg of APF530, another received 75% of 250 mg dose) 6 – 125 6 – 250 6 – 500 6 – 1000 2 < 250	26	12
C2005-01	4 patients in the 250 mg dose group did not receive full injection amount 17 – 250 mg 15 – 500 mg 13 – 750 mg	45	28
C2006-01	Cycle 1: 464 received 250 mg dose 468 received 500 mg dose Cycles 2 – 4: 528 subjects received up to 3 single doses of 250 mg APF530 515 subjects received up to 3 single doses of 500 mg APF530 A total of 1043 initiated cycle 2 Over Cycles 1-4, 636 received 250 mg 642 received 500 mg	1278	642
C2007-01	17 – 250mg 18 – 500 mg	35	18
C2011-01	56 – 1000 mg	56	56
C2011-02	10 – 1000 mg	10	10
Total overall		1450	766

Sponsor's table: IR - Sequence #053

7.1.2 Categorization of Adverse Events

See 1st cycle review

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

Safety data for administration site reactions was pooled from all 6 clinical trials. Trial C2006-01 was the only trial to use multiple doses of APF530 up to 4 cycles of chemotherapy and therefore it is the only data source for the Cycle 2 to 4 analysis.

7.2 Adequacy of Safety Assessments

There is limited data to allow for detection of adverse events that are rare. Adverse events that require a long duration exposure to occur are unlikely to be captured since the subcutaneous formulation is intended for limited use. The Applicant reports that all patients who received a dose of the study medication were included in the safety analysis population.

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

See 1st cycle review

7.2.2 Explorations for Dose Response

See 1st cycle review

7.2.3 Special Animal and/or In Vitro Testing

See 1st cycle review

7.2.4 Routine Clinical Testing

See 1st cycle review

7.2.5 Metabolic, Clearance, and Interaction Workup

See 1st cycle review

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

Other than the administration site reaction concerns, which are inherent to the new formulation, the adverse event profile of granisetron S.C. is similar to other granisetron formulations as found in the package inserts.

7.3 Major Safety Results

7.3.1 Deaths

The Applicant reported a total of 34 deaths during the four APF530 clinical trials. No deaths occurred in trial C2004-01 (healthy subjects) or trial C2007-01. The Applicant did not consider any of the deaths as possibly, probably or definitely related to the study drug. The Applicant considered that there was no relationship with the study drug in 30 cases and that “a relationship with the study drug was improbable in the remaining 4 cases.” The Applicant reported that a total of 13 subjects died during Cycle 1, while 7, 8 and 6 subjects died during Cycles 2, 3, and 4 respectively. All deaths were reported related to progression of underlying cancer diagnosis, complications from underlying cancer or complications from cancer treatment.

In light of the Clinical Pharmacology reviewer’s reliance on the clinical safety database to assess the potential toxicity that may be attributed to accumulation of ethylene glycol (EG), diethylene glycol (DEG) and their metabolites following the use of Sustol, death narratives were re-evaluated. The deaths that had clinical signs of systemic toxicity related to EG, such as cardiopulmonary manifestations and central nervous system effects, were identified and the case report forms re-evaluated.

Thirteen deaths, related to respiratory failure, dyspnea, sudden death, cardio-pulmonary arrest and multi-organ failure, were reviewed. Seven deaths occurred in patients in the APF530 5 mg group, 3 deaths were in the APF530 10 mg group, one death occurred in the Aloxi to APF530 5 mg group and 2 deaths occurred in the Aloxi to APF530 10 mg group. Five (5) deaths occurred after cycle 1; two (2) deaths occurred after cycle 2; three (3) deaths occurred after cycle 3 and three (3) deaths occurred after cycle 4.

This patient population had underlying malignancy and received chemotherapy that can have significant systemic toxicity and complications. These deaths could therefore be explained based on progression of malignancies and/or chemotherapy treatment. It is unlikely that the deaths were secondary to EG/DEG toxicity.

See the 1st cycle review for additional details.

No deaths were reported in trials C2011-01 or C2011-02.

7.3.2 Nonfatal Serious Adverse Events

See 1st cycle review

7.3.3 Dropouts and/or Discontinuations

See 1st cycle review

7.3.4 Significant Adverse Events

See 1st cycle review

7.3.5 Submission Specific Primary Safety Concerns

Collectively, administration site reactions were among the most common AEs reported across all treatment groups, and the incidence of administration site reactions was higher in the APF530 groups than in the ALOXI group. Injection site bruising was the most common AE reported in both APF530 groups (16.4% of subjects in each group in Cycle 1), and the the Aloxi group (8.9% of subjects). Injection site erythema was commonly reported in both APF530 groups (9.2% to 11.1% of subjects) in Cycle 1 but not in the ALOXI group (3.0% of subjects). Injection site nodule (15.0% of subjects) and injection site pain (9.1% of subjects) were commonly reported in the ≥ 500 mg APF530 group. Injection site nodule was reported in 4.5% and 0.6% of ≤ 250 mg APF530 and Aloxi subjects, respectively, while injection site pain was reported in 4.5% and 1.1% of ≤ 250 mg APF530 and ALOXI subjects, respectively. The pattern was similar in Cycles 2 through 4 and across all cycles combined.

A total of 1501 patients (Studies C2004, C2005, C2006 and C2007) received at least one SC dose of either APF530 250mg (5 mg granisetron), APF530 500mg (10 mg granisetron) or Saline during cycle 1. Of these 1501 patients, 29.5% (APF530 ≤ 250 mg), 37.6% (≥ 500 mg APF500) and 15.6% (Aloxi), experienced at least one administration site reaction. In the APF530 250mg (5 mg granisetron), APF530 500mg (10 mg granisetron) and Saline groups, approximately 1.4%, 3.6% and 1.3%, respectively, of the patients still had administration site reactions continuing and not resolved at the end of the study.

A total of 1384 (Studies C2004, C2005, C2006 and C2007) patients received at least one SC dose of either APF530 250mg (5 mg granisetron) or APF530 500mg (10 mg granisetron) across all cycles. Of the 1384 patients, 39.9% and 45.3% in each treatment group, respectively, experienced at least one administration site reaction. In the APF530 250mg (5 mg granisetron) and APF530 500mg (10 mg granisetron), 3.4% and 6.6%, respectively, of patients still had administration site reactions continuing and not resolved at the end of study.

Table 10: Incidence of Injection Site AEs Safety Population – Cycle 1 (Studies C2004, C2005, C2006 and C2007, C2011-01, C2011-2)

	APF530 ≤ 250 mg (N = 512)	APF530 ≥ 500 mg (N = 592)	Aloxi (N=463)
% of subjects			
Injection site bruising	16.4%	16.4%	8.9%
Injection site nodule	4.5%	15.0%	0.6%
Injection site erythema	9.2%	11.1%	3%
Injection site pain	4.5%	9.1%	1.1%
Injection site induration	0.8%	7.8%	0
Injection site hemorrhage	4.3%	3.2%	2.2%
Injection site hematoma	0.4%	4.4%	0.2%
Injection site pruritis	0.8%	0.8%	0.2%
Injection site edema	0	1.4%	0

For those patients who received Aloxi in study C2006-01, a SC saline injection was administered as well in order to preserve the blind. These SC saline injection reactions that occurred during cycle 1 are included in the listing, but reactions at the IV administration site of Aloxi are not included.

Table 11: Incidence of Injection Site AEs Reported During All Cycles of APF530 (Studies C2004, C2005, C2006 and C2007, C2011-01, C2011-2)

	APF530 ≤ 250 mg (N = 684)	APF530 ≥ 500 mg (N = 766)
% of subjects		
Injection site bruising	26.3%	27.2%
Injection site nodule	10.1%	20.6%
Injection site erythema	14%	14.1%
Injection site pain	7.9%	9.9%
Injection site induration	0.9%	7.2%
Injection site hemorrhage	7.5%	5.9%
Injection site hematoma	0.4%	3.8%
Injection site pruritis	1%	1%
Injection site edema	0	1%

Source: sponsor's table 2.7.4.3, Summary of Clinical Safety, p21

In Cycle 1, 122 subjects (23.8%) who received ≤ 250 mg APF530, 208 (35.1%) who received ≥ 500 mg APF530, and 57 (12.3%) who received ALOXI experienced related AEs in this system organ class, while across all cycles combined, 236 subjects (34.5%)

who received ≤ 250 mg APF530 and 311 (40.6%) who received ≥ 500 mg APF530 experienced related AEs in this system organ class. Injection site reactions were more commonly assessed as being related to study drug than other types of AEs.

Duration of Administration site reactions

The protocols stated that for all AEs that were present at the Final Study Visit, contact for resolution/status (via telephone or visit) was to be made within 2 weeks. However, the applicant notes that this was not done for the observation around the injection site.

Of the 44 reported ongoing treatment-emergent administration site reactions in the ≤ 250 mg APF530 group, the most common were bruising, nodule, erythema, and hemorrhage, which occurred at 36.4% (16/44), 27.3% (12/44), 13.6% (6/44), and 13.6% (6/44), respectively. Of the 99 ongoing treatment-emergent administration site reactions in the ≥ 500 mg APF530 group, the most common were nodule, bruising, and erythema, which occurred at 41.4% (41/99), 31.3% (31/99), and 14.1% (14/99), respectively.

In the ≤ 250 mg APF530 groups, ongoing bruising occurred three times more frequently in the HEC stratum compared to the MEC stratum (75% (12/16) versus 25% (4/16)), while in the ≥ 500 mg group ongoing bruising was more frequent in the HEC stratum (18/32 (56%) HEC versus 14/32 (44%) MEC). Ongoing nodules occurred two times more frequently in the MEC stratum compared to the HEC stratum (66.6% (8/12) compared with 33.3% (4/12)) in the ≤ 250 mg group and three times more frequently in the MEC stratum (75.6% (31/41)) than in the HEC stratum (24.4% (10/41)) in the ≥ 500 mg group. In both dose groups, the numbers of ongoing nodules associated with the MEC stratum sequentially increased with cycle: Cycle 1: 0 and 4 ongoing; cycle 2: 1 and 7 ongoing; cycle 3: 2 and ongoing; cycle 4: 5 and 11 ongoing for the ≤ 250 mg and ≥ 500 mg APF530 dose groups, respectively. There was no apparent pattern of association with cycle for any other ongoing treatment emergent injection site reaction. Resolution of nodules could take up to 8 weeks from recorded data of onset in the MEC stratum as opposed to 3 weeks in the HEC stratum.

Time to injection site reaction resolution was generally collected at a patient visit and/or as the subject's self-assessment in telephone follow-up calls.

Table 12: Incidence & Duration of Administration Site Reactions in Cycle 1 (Studies C2004, C2005, C2006 and C2007)

	APF530 ≤ 250 mg N=512		APF530 ≥ 500 mg N=526	
	% of patients with AE	Mean (duration days)	% of patients with AE	Mean (duration days)
Bruising	16.8	15	18.6	15.9
Erythema	9	12.8	11.2	18.5
Nodule	5.3	21.4	11.2	22.7
Pain	4.7	8.3	8.2	11.7
Hemorrhage	4.7	10	3.8	11.5
Induration	0.8	8.5	1	7
Pruritus	0.8	3.8	1	9.6
Edema	0		1.3	7.6
Discoloration	0		1	24.4
Mass	0.8	8.8	0	
Hematoma	0.4	22	0.2	14

Source: Sponsor's revised table 0056 (60)

Table 13: Incidence & Duration of Administration Site Reactions in cycle 2 (Study C2006-01)

	APF530 ≤ 250 mg N=528		APF530 ≥ 500 mg N=515	
	% of patients with AE	Mean (duration days)	% of patients with AE	Mean (duration days)
Bruising	16.5	16.7	20	20.7
Erythema	37	16.7	8.2	18.8
Nodule	6.8	19.3	11.8	23.3
Pain	4.2	10.6	5.2	15.5
Hemorrhage	2.8	11.6	3.5	9.1
Induration	0.4	8.5	1	23.2
Discoloration	0.6	25	1.2	10.5
Pruritus	0.4	11.5	0.4	13
Hematoma	0	-	0.6	19.7
Edema	0	-	0.2	29

Medical Reviewer's comments: The Applicant did not provide similar injection site duration data for the saline s.c. injections. Just as incidence rates for injection site reactions were much lower in the saline group, the duration of injection site reaction would most likely also be much lower in the saline group

compared to the APF530 group. Based on the mean duration of injection site reactions in the APF530 >500 mg group, injection site reactions carried over into multiple cycles (APF530 was allowed to be dosed every 7 days). The mean duration in days of injection site reactions was longer in the APF530 $\geq$ 500 mg dose. The prolonged duration of injection site reactions is likely due to AP135, the novel polymer, which is responsible for the extended release of the granisetron from the drug product formulation.

Regarding the incidence of injection site reactions, the non-clinical data supports that these reactions are related to APF530. The non-clinical studies demonstrated that in rats, the major target organ appeared to be the injection site (injection site reactions characterized by edema, hemorrhage, fibrosis, epidermal hyperplasia, erosion/ulceration, and suppurative inflammation; skeletal muscle degeneration/necrosis; and inflammation).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Commonly reported AEs in Cycle 1, other than administration site reactions, were: constipation, nausea, fatigue, diarrhea, headache, neutropenia, anemia, asthenia, alopecia, abdominal pain and vomiting. In Cycles 2 to 4 and across all cycles combined, additional common treatment emergent AEs observed included: thrombocytopenia, leukopenia, dyspepsia, dysgeusia, stomatitis, edema peripheral, pyrexia, and pain. The incidence of common AEs, other than administration site reactions, was similar across treatment groups. The most common AE in any treatment group, other than administration site reactions, was constipation.

See 1st cycle review for additional details.

7.4.2 Laboratory Findings

During this review cycle, electrolyte data were re-evaluated to assess for changes that may be consistent with metabolic acidosis.

Mean changes from baseline were noted for following parameters across all treatment groups: increases in serum bicarbonate and urea nitrogen and decreases in serum chloride, serum sodium.

Table 13 shows the number of subjects who had low (L), normal (N), high (H) or missing (M) clinical chemistry values at Day 5 of Cycle 1, and the number of subjects who shifted between these levels from baseline to Day 5. Significant shifts were observed across all treatment groups in, serum chloride (N to L and N to H), serum sodium (N to L) and urea nitrogen (N to H). Significant shifts were observed in serum bicarbonate (N to L) and serum creatinine (N to L) in the ≤ 250 mg APF530 group only; serum bicarbonate (N to H) and serum potassium (N to L) in the ≥ 500 mg APF530 group only.

Table 14: Shifts from Baseline to Day 5 – Cycle 1

Parameter	Baseline	APF530 < 250 mg N=512				APF530 >500 mg N=526				Aloxi N=463			
		Day 5				Day 5				Day 5			
		L	N	H	M	L	N	H	M	L	N	H	M
Bicarbonate (mmol/L)	Low (L)	4	21	0	0	7	18	2	4	9	12	0	1
	Normal (N)	3	377	7	25	14	356	11	26	9	379	6	19
	High (H)	0	2	2	0	0	1	2	0	0	7	1	1
	Missing (M)	1	17	0	0	1	22	0	0	0	13	0	0
Chloride (mmol/L)	Low (L)	5	4	0	1	5	5	0	3	4	4	0	1
	Normal (N)	21	363	2	22	19	348	6	22	12	372	5	19
	High (H)	1	31	7	1	2	35	12	4	1	22	8	1
	Missing (M)	0	14	1	0	3	11	1	0	0	10	0	0
Creatinine (umol/L)	Low (L)	7	3	0	1	9	7	0	2	5	6	0	2
	Normal (N)	11	387	7	20	5	380	12	25	11	377	8	15
	High (H)	0	5	14	3	0	7	12	3	0	4	17	4
	Missing (M)	1	13	1	0	1	12	2	0	1	8	1	0
Potassium (mmol/L)	Low (L)	4	7	0	2	6	15	0	2	5	8	1	2
	Normal (N)	14	379	10	22	5	368	10	27	15	369	7	19
	High (H)	0	7	1	0	1	8	3	0	0	5	1	0
	Missing (M)	1	25	1	0	1	25	3	0	0	23	1	0
Sodium (mmol/L)	Low (L)	17	4	0	4	15	5	0	5	17	10	0	5
	Normal (N)	43	367	1	20	53	355	1	24	39	353	4	16
	High (H)	1	0	0	0	0	1	0	0	0	3	0	0
	Missing (M)	1	14	0	0	4	11	0	0	1	11	0	0
Urea Nitrogen (mmol/L)	Low (L)	1	7	0	0	1	7	0	0	0	1	0	1
	Normal (N)	1	353	45	22	2	346	46	27	1	352	52	17
	High (H)	0	10	17	2	0	12	18	3	0	8	14	3
	Missing (M)	0	12	3	0	0	11	4	0	0	7	3	0

Source: Applicant's table

Medical Reviewer's comments: The data is similar across all treatment groups. The Applicant did not collect data for Cycles 2 to 4, so it is unknown what cumulative effects APF530 may have on laboratory values. From the current data there does not appear to be a safety signal, though it is difficult to rule out potential safety concerns based on the following: patients underlying conditions and concomitant chemotherapy treatments; number of patients too small to identify minor differences and as previously noted, the data only includes Cycle 1. It does not look at cumulative effects (drug proposed to be given every 7 days) over multiple cycles.

7.4.3 Vital Signs

See 1st review

7.4.4 Electrocardiograms (ECGs)

See QTc trial data section 7.4.5

7.4.5 Special Safety Studies/Clinical Trials

Thorough QT (tQT) trial

The sponsor requested a waiver to conduct a thorough QT trial. The waiver request was denied because APF530 demonstrated a higher pattern of granisetron exposure than other granisetron formulations.

The sponsor therefore conducted protocol C2011-01 entitled, "A Randomized, Placebo-Controlled, Four-Period Crossover, Definitive QT Study of the Effects of APF530 Exposure, High-Dose IV Granisetron, and Moxifloxacin on QTc Prolongation." 56 healthy male and female subjects enrolled in this Phase 1, single site trial.

The study report for the TQT trial, protocol C2011-01, was reviewed by Dr. Janice Brodsky of the Interdisciplinary Review Team for QT Studies Consultation. The overall summary of findings by Dr. Brodsky and the QT-IRT was *"No significant QTc prolongation effect of APF530 or granisetron was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between APF530 or granisetron and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the $\Delta\Delta\text{QTcF}$ for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that assay sensitivity was established."*

Table 15: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for APF530 and Granisetron and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
APF530	3	3.5	(0.8, 6.1)
Granisetron	48	2.4	(-0.6, 5.4)
Moxifloxacin 400 mg*	2	11.3	(8.9, 13.7)
Moxifloxacin 400 mg*	3	11.6	(8.9, 14.2)

Multiple endpoint adjustment was not applied. The largest lower bounds after Bonferroni adjustment for 4 timepoints are 14.6 and 15.2 ms.
 Source: QT-IRT reviewer

The trial's primary objectives were:

1. To evaluate the effect of APF530, 1 g (20 mg granisetron) given S.C. in normal volunteers on the placebo-subtracted change of QTc by Fridericia method (QTcF) from Baseline over 48 hours.
2. To achieve a mean Cmax of granisetron and AUC exposure in normal volunteers equivalent to that achieved by APF530 500 mg (10 mg granisetron) given SC in patients.

This trial had four treatment arms. Subjects received the following 4 treatments in random order: APF530 (SC), granisetron (IV), moxifloxacin (oral), and placebo (SC, IV, or oral).

1. The primary active regimen (administered at time 0) consisted of APF530, 1 g (20 mg granisetron) administered as SC abdominal injections, placebo (0.9% normal saline) administered as an IV infusion, and a moxifloxacin placebo capsule administered orally.
2. The secondary active regimen (administered at time 0) consisted of granisetron 50 µg/kg in 0.9% normal saline administered as an IV infusion, placebo (0.9% normal saline) administered as SC abdominal injections, and a moxifloxacin placebo capsule administered orally.
3. The placebo control regimen (administered at time 0) consisted of placebo (0.9% normal saline) administered as SC abdominal injections, placebo (0.9% normal saline) administered as an IV infusion, and a moxifloxacin placebo capsule administered orally.
4. The positive control regimen (administered at time 0) consisted of moxifloxacin

(Avelox) administered orally, 400 mg tablet, placebo (0.9% normal saline) administered as an IV infusion, and placebo (0.9% normal saline) administered as SC abdominal injections.

The sponsor reported none of the following clinical events in the TQT trial: syncope, seizure, significant ventricular arrhythmias or sudden death. There were no clinically relevant changes in PR or QRS.

Table 16: Summary of PK Parameters

PK Parameter		APF530 SC 1 g	Granisetron IV 50µg/kg	Moxifloxacin PO 400 mg
AUC _{0-inf} (ng*hr/mL)	N	30	49	49
	Mean	1254	353	31528
	SD	578	153	6321
C _{max} (ng/mL)	N	56	52	53
	Mean	35.8	34.6	2123
	SD	13.3	15.3	502
T _{max} (hr)	N	56	52	53
	Median	11.1	0.183	2.08
	Range	4.08-23.1	0.167-4.15	0.583-4.08
T _{1/2} (hr)	N	31	49	49
	Mean	18.6	9.69	13.8
	SD	4.02	3.53	1.65

Medical Reviewer’s comments: This reviewer concurs with the conclusion of the QT team reviewer, Dr. Janice Brodsky, that “no significant QTc prolongation effect of APF530 or granisetron was detected in this TQT study.”

7.4.6 Immunogenicity

See 1st cycle review

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

See 1st cycle review

7.5.2 Time Dependency for Adverse Events

See 1st cycle review

7.5.3 Drug-Demographic Interactions

See 1st cycle review

7.5.4 Drug-Disease Interactions

See 1st cycle review

7.5.5 Drug-Drug Interactions

See 1st cycle review

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

7.6.2 Human Reproduction and Pregnancy Data

See 1st cycle review

7.6.3 Pediatrics and Assessment of Effects on Growth

(b) (4)



(b) (4)

The Applicant requested a deferral of studies in the pediatric age group of (b) (4) years. The Applicant proposed to conduct a pediatric trial under PREA for the prevention of nausea and vomiting in pediatric patients receiving moderately (b) (4) emetogenic chemotherapy. The primary objective of the trial is to evaluate the pharmacokinetics, safety and tolerability of (b) (4) SUSTOL in (b) (4) pediatric patients.

Although this application will not be approved this review cycle, the 505(b)(2) committee has requested the Division's input on whether Sustol can be approved and used safely if the labeling does not include Kytril injection.

(b) (4)

The pediatric section of the label will need to reflect that the safety and efficacy of Sustol have not been studied (b) (4)

(b) (4)

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

See 1st cycle review

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

Sustol (APF530) has not been approved for marketing in any country worldwide.

9 Appendices

9.1 Literature Review/References

9.2 Labeling Recommendations

Several meetings were held with the Applicant to discuss product administration concerns and modifying the package insert to address these concerns (see section 2.6). In response to these discussions, the Applicant submitted proposals to modify the instructions for use and provide administration technique educational materials. The Agency found the proposals unacceptable since they did not address all the issues of concern, such as the force required to administer the product and ensuring that the drug product is administered in the correct plane. The Agency has recommended that the Applicant submit a protocol to evaluate their new administration instructions and then conduct a new Human Factors Study.

Labeling negotiations with the Applicant will resume during the next review cycle.

9.3 Advisory Committee Meeting

None

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/s/

KARYN L BERRY
03/27/2013

RUYI HE
03/27/2013

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-445
Priority or Standard	Standard
Submit Date(s)	18 May 2009
Received Date(s)	29 May 2009
PDUFA Goal Date	18 March 2010
Division / Office	ODE III/DGP (HFD-180)
Reviewer Name(s)	Karyn L. Berry, MD, MPH
Review Completion Date	02 March 2010
Established Name	Granisetron
(Proposed) Trade Name	Sustol
Therapeutic Class	5-HT3 Receptor Antagonist
Applicant	A.P. Pharma, Inc.
Formulation(s)	Subcutaneous (S.C.) injection
Dosing Regimen	A single 10 mg S.C. dose administered approximately 30 minutes before the start of single-day chemotherapy. It may be given once every 7 days, and only on the day chemotherapy is given.
Indication(s)	Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy Prevention of acute nausea and vomiting associated with initial and

Intended Population(s) repeat courses of highly
emetogenic cancer chemotherapy
Adults

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

According to my review of the clinical data, I recommend a complete response for APF530 (granisetron subcutaneous [Sustol]) for the proposed indications:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

This recommendation is based on clinical safety issues associated with the drug product APF530 (Sustol) and deficiencies identified by reviewers in other disciplines including: Microbiology, Chemistry, Manufacturing and Control (CMC), and the Division of Medication Error Prevention and Analysis (DMEPA). Safety issues identified are: 1) drug administration and site reactions, 2) drug container closure system, 3) drug administration technique, 4) drug sterilization/irradiation process and 5) drug identification, strength and purity, 6) quality of the drug product and 7) manufacturing facilities.

The Applicant submitted a single pivotal trial to assess efficacy. The results of this trial demonstrated that APF530 5 mg and APF530 10 mg (granisetron S.C.) were both effective in preventing acute chemotherapy induced nausea and vomiting (CINV) in moderately emetogenic chemotherapy (MEC) and highly emetogenic chemotherapy (HEC); and APF530 10 mg was effective in preventing delayed CINV in MEC.

Safety analysis was based on a safety database of 1038 subjects (>97% were cancer patients) who received the study drug APF530 (Sustol). The database included all 4 trials submitted with this application.

The proposed drug label states that it is to be administered as a subcutaneous injection in the lower abdomen. (b) (4)

The drug is designed to be subcutaneously injected using a prepackaged (b) (4) inch needle.

Administration site reactions were among the most common AEs reported across all treatment groups, and the incidence of administration site reactions was higher in the APF530 groups than in the Aloxi group. The injection site reactions were generally considered by the investigator to be related to the study drug. The most common administration site reactions were: bruising, nodules, erythema, pain and hemorrhage.

1.2 Risk Benefit Assessment

This drug product is a new formulation of granisetron, a 5-HT₃ receptor antagonist. The previously approved granisetron formulations (intravenous, oral tablets, oral solution and transdermal) are indicated for the prevention of acute onset CINV in MEC and HEC. Intravenous palonosetron, the active comparator in the pivotal trial, is the only 5-HT₃ receptor antagonist that is approved for prevention of delayed onset of CINV in MEC. No 5-HT₃ is approved for the prevention of delayed onset of CINV in HEC. If approved, granisetron S.C. would be the second 5-HT₃ receptor antagonist approved for the prevention of delayed onset CINV in MEC. Although a single administration of Sustol for the prevention of CINV would be a convenience, at this time, the potential safety risks of the drug product outweigh any benefits.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Postmarket risk evaluation and marketing will be evaluated during the second review cycle.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarket requirements and commitments will be evaluated during the second review cycle.

2 Introduction and Regulatory Background

This application is submitted as part of a 505(b)(2) using safety and efficacy data from approved and marketed drug products, Kytril, which the Applicant states are supportive of APF530. Kytril has three different formulations that contain information that support this application. They are: 1) Kytril I.V. (NDA 20-239/S8), 2) Kytril oral solutions (NDA 21-238) and 3) Kytril tablets (NDA 20305/S-004).

Granisetron is a widely used 5-HT₃ receptor antagonist antiemetic with a plasma half-life of approximately 8 hours following I.V. 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 S.C. injection. The Applicant believes that 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.

APF530 is a viscous tri(ethylene glycol) poly(ortho ester) (TEG-POE) based formulation that is intended to provide a sustained release of granisetron, present as the free base

form. The vehicle formulation is comprised of two components: the TEG-POE polymer, AP135, and methoxy poly(ethylene glycol) (MPEG (b) (4)). MPEG (b) (4) is used as an excipient (b) (4). The final drug product contains 2% granisetron.

2.1 Product Information

Proposed Trade Name: Sustol ((b) (4) granisetron)

Compositional Code/Name: APF530

Proposed Indication:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy
- Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy

Proposed Age Group: Adults

Pharmacologic Class: 5-HT3 receptor antagonist

Route of Administration, Description, and Formulation: Subcutaneous (S.C.) injection; (b) (4) injectable, sustained-release formulation. A single use (b) (4) mL glass syringe that provides 10 mg granisetron/0.4 mL. (b) (4)

Proposed Treatment Regimen: A (b) (4)

Chemical name of the main ingredient in Sustol (granisetron):

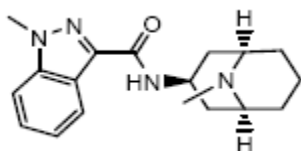
1-Methyl-N-[(1R,3r,5S)-9-methyl-9-azabicyclo[3.3.1]non-3-yl]-1H-indazole-3-carboxamide

or

endo-1-methyl-N-(9-methyl-9-azabicyclo[3.3.1]non-3-yl)-1H-indazole-3-carboxamide.

Molecular formula: C₁₈H₂₄N₄O

Structural formula:



2.2 Tables of Currently Available Treatments for Proposed Indications

The American Society of Clinical Oncology's (ASCO) 2006 guidelines for antiemetics in oncology recommend the use of a 3-drug combination consisting of 1) a 5-HT₃ serotonin receptor antagonist, 2) dexamethasone, and 3) a NK-1 antagonist. This 3-drug regimen is to be administered before chemotherapy of high emetic risk. The 3-drug combination of a 5-HT₃ serotonin receptor antagonist, dexamethasone, and NK-1 antagonist is also recommended for patients receiving an anthracycline and cyclophosphamide "AC" regimen. For patients receiving chemotherapy of moderate emetic risk other than "AC," the ASCO recommends the 2-drug combination of a 5-HT₃ serotonin receptor antagonist and dexamethasone.

There are currently four 5-HT₃ antagonist drugs that are FDA approved for the prevention of nausea and vomiting in patients receiving moderately and/or highly emetogenic chemotherapy. These are: Ondansetron, Granisetron, Dolasetron and Palonosetron. All four of these 5-HT₃ receptor antagonists are available in injectable (Intravenous) and oral formulations.

Ondansetron hydrochloride (Zofran) was approved in January 1991. Its label states that efficacy of the single dose beyond 24 hours in these patients has not been established. Granisetron hydrochloride (Kytril) was approved in December 1993. It is indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy. Dolasetron mesylate monohydrate (Anzemet) was approved in September 1997. It is currently indicated for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin. Palonosetron (Aloxi) was approved in July 2003. It is indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy and prevention of acute nausea and vomiting associated with highly emetogenic chemotherapy. Palonosetron is the only 5-HT₃ receptor antagonist that is indicated for the prevention of delayed onset CINV.

Table 1: FDA Approved 5-HT3 Receptor Antagonist

5-HT3 Receptor Antagonist			
Drug	Formulation	Indication	FDA approval of first formulation
Ondansetron	Injectable Oral	• Prevention of acute N/V assoc with MEC & HEC • Prevention of PONV	1991
Granisetron	Injectable Oral Transdermal	• Prevention of acute N/V assoc with MEC & HEC • Prevention of PONV • Prevention of RIND	1993
Dolasetron	Injectable Oral	• Prevention of acute N/V assoc with MEC & HEC • Prevention of PONV • Treatment of PONV	1997
Palonosetron	Injectable Oral	• Prevention of acute and delayed N/V assoc with MEC • Prevention of acute N/V assoc with HEC • Prevention of PONV	2003

Source: Reviewer's table

2.3 Availability of Proposed Active Ingredient in the United States

Granisetron is available in injectable, oral tablets, oral solution and transdermal formulations. It is indicated for the prevention of chemotherapy induced nausea and vomiting (CINV), radiation induced nausea and vomiting (RINV) and post operative nausea and vomiting (PONV).

Granisetron Injection (10 µg/kg) was approved for use in the United States for the prevention of CINV in pediatric and adult patients in December 1993. Granisetron Tablets were approved in March 1995 to treat adult patients with CINV, and in July 1999 it was approved for the prevention of adult radiation-induced nausea and vomiting (RINV). In June 2001, Granisetron Oral Solution was approved for the treatment of adult patients with CINV or RINV. In August 2002, Granisetron Injection was approved for the prevention and treatment of post operative nausea and vomiting in adult patients. Transdermal granisetron was approved in September 2008 for prevention of acute onset CINV in adults receiving MEC & HEC.

2.4 Important Safety Issues With Consideration to Related Drugs

As previously discussed, there are currently four 5-HT3 receptor antagonist that are FDA approved for the prevention of CINV. Although 5-HT3 receptor antagonists are generally perceived as safe, the class of drugs has been associated with cardiovascular adverse events: mainly hypertension, QT prolongation and rarely arrhythmias, such as atrial fibrillation.

The European Medicines Agency (EMA) has contraindicated the use of dolasetron in pediatric patients because of serious cardiovascular events associated with its use.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Drug development occurred under IND 68,213. Below is a summary of regulatory guidance and advice provided by the Agency.

- On 08 February 2004- A pre-IND meeting was held to discuss drug development plans.
- On 13 December 2005 - An End of Phase 2 meeting was held to discuss the Phase 3 protocol. Clinical issues discussed included: 1) Recommendation from Agency to either evaluate the safety and efficacy of the study drug in 2 clinical trials, one evaluating MEC regimens and the other evaluating HEC regimens. Alternatively, a single randomized, phase 3 trial stratified based on chemotherapy regimen could be used to demonstrate safety and efficacy of the study drug, 2) Recommendation from Agency on statistical plan – a.) justification for selecting a 15% non-inferiority margin and since the sponsor' plan for testing adjusted for 2 primary endpoints, the adjustment for multiplicity should also take into account the multiple doses of the study drug that are being compared to Aloxi.
- On 5 April 2006 - An advice letter, which included comments and recommendations of the revised Phase 3 protocol, was sent to the Applicant.
- On 13 December 2006 - A pre-NDA meeting was held to discuss and obtain consultation on the Applicant's preclinical and clinical development to support a 505(b)(2) application. The Applicant requested: 1) a waiver of segment I and II reproductive toxicity studies, 2) a waiver of carcinogenicity studies and 3) a waiver of a thorough QT/QTc trial. The Pharmacology/Toxicology Review Team did not agree with the waiver request and the Clinical Review Team recommended that the Applicant submit a waiver request, along with supportive data and it would be reviewed.
- On 13 May 2009 - A telephone conference was held with the Applicant to discuss the Applicant's eCTD application organization (specifically the Integrated Summary of Efficacy and Integrated Summary of Safety).

2.6 Other Relevant Background Information

APF530 has its development origins in other poly(ortho ester)-based products

(b) (4)



3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the clinical information contained in this submission is acceptable.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all clinical trials were conducted in accordance with the US Code of Federal Regulations (CFR) governing the protection of human subjects (21 CFR 50), IRBs (21 CFR 56) and the obligations of clinical investigators (21 CFR 312). These trials were also conducted in accordance with US Title 21 CFR on Good Clinical Practices (GCPs) which is consistent with the ethical principles set forth in the Declaration of Helsinki, the International Conference on Harmonization and the Food and Drug Administration.

The Division of Scientific Investigations (DSI) conducted inspections of two (2) clinical sites from the pivotal trial (Protocol C2006-01). These were: Site 007 (V. Charu, MD, Anaheim, CA) and Site 003 (N. Gabrail, MD, Canton, OH). These sites were selected by the Division based on the number of patients enrolled. The results of this inspection were:

- 1) No deviations from regulations at Site 007 and
- 2) Deviations from regulations at Site 003.

At Site 003, 86 subjects were randomized and 75 subjects completed the trial. The first 49 subjects were given a prohibited drug – Solumedrol. Two other subjects received a prohibited anti-emetic and one subject received lorazepam, also a prohibited medication. The DSI Investigator recommended that “apart from the subject who received protocol unapproved medications mentioned above at Dr. Gabrail’s site, the data from Dr. Charu’s site and the remaining subjects at Dr. Gabrail’s site can be used in support of the NDA indication.” See the DSI - Clinical Inspection Summary for additional information.

3.3 Financial Disclosures

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

defined by 21 CFE 54.2(b). As defined by 21 CFR 54.2(f), the Applicant certified that no clinical investigator was the recipient of any significant payments of any other sorts.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls (CMC)

The drug product, APF530, is a Tri(ethylene glycol) poly(ortho ester) polymer-based formulation containing Granisetron base. APF530 is the A.P. Pharma compositional code number assigned to this Tri(ethylene glycol) poly(ortho ester) polymer-based formulation containing 2% Granisetron base. Tri(ethylene glycol) poly(ortho ester) is known by the acronym TEG-POE. The APF530 drug product dosage form is (b) (4) injectable.

APF 530 is a viscous formulation designed to deliver granisetron in a controlled sustained release. APF530 contains three (3) materials: Granisetron (API), MPEG (b) (4) (compendial excipient) and AP135 (novel excipient, first regulatory review). The specific TEG-POE in APF530 is APF135. APF135 is the component primarily responsible for the sustained release of the granisetron from the APF530 drug product formulation. MPEG (b) (4) is used (b) (4)

The manufacturing process of the drug product consists of (b) (4)

The drug product is filled in (b) (4) glass syringe containing a (b) (4) Tip Cap, a (b) (4) Stopper and (b) (4) plunger rod. (b) (4)

Per the CMC reviewer, “the Applicant has not provided sufficient information to assure identity, strength, purity, quality of the drug product and manufacturing facilities approval.” The CMC reviewer has identified deficiencies that must be addressed. In summary these are:

- 1) Drug substance – acceptance criteria for impurities in the drug substance specifications

2) APF135 (novel polymeric excipient) - data on the structure, biodegradation pathway, drug specification, impurity testing

3) Drug product – drug specification, validation for gel permeation chromatography for molecular weight distribution, identification of devices to be co-packaged in the final product (identify suppliers of devices and if devices are approved for medical use, stability data.

A complete list of deficiencies can be found in the CMC review.

4.2 Clinical Microbiology

The Clinical Microbiology Division reviewed the manufacturing process of APF530 as it related to product quality microbiology. The Microbiology reviewer has listed deficiencies in this Application primarily related to the sterilization irradiation process of the drug product and the drug container closure system (which requires the transfer of the drug product to a second dosing syringe prior to administration). The reviewer states that “if these deficiencies are not addressed they could result in increased risk of product contamination.” Per the Microbiology reviewer, the deficiencies to be addressed are:

- 1) Product filled into [REDACTED] (b) (4) syringes must be transferred to 1 mL tuberculin syringes prior to dosing. Inadequate justification is provided for why the product cannot be filled into a syringe that permits direct product administration. Dosing and microbiology quality control studies should be performed with a syringe that allows for direct administration.
- 2) Dose determinations based on ISO 11137-2 Method 1 utilized [REDACTED] (b) (4). The determination should be based on a higher bioburden estimate that allows for a margin of error.
- 3) Inadequate information is provided regarding the location and description of the irradiation facility intended for commercial production, and the terminal sterilization irradiation process. Dosing determination and dose mapping studies should be performed at the facility intended for commercial irradiation.
- 4) Inadequate information was provided regarding the most valid dilution and routine dilution to be used for product endotoxin determination.

A complete list of deficiencies can be found in the Microbiology review.

4.3 Preclinical Pharmacology/Toxicology

The Pharmacology Toxicology Division reviewed several new toxicology studies that were conducted to address the safety of the new subcutaneous formulation.

Pharmacology Toxicology reviewed the following studies: 3 month (90-day) toxicology studies in a rodent and a non-rodent species by S.C. injection, absorption, distribution, metabolism and excretion (ADME), acute, subacute/subchronic (28 and 90 day) toxicology, genotoxicity and reproductive toxicology studies with (b) (4) a novel excipient vehicle.

Per the Pharmacology/Toxicology reviewer, in toxicology studies, the injection site (inflammatory reactions) appeared to be the major target organ. This appeared more pronounced in the rat compared to the dog. Lymphoid hyperplasia in the draining lymph nodes, splenic hematopoiesis and bone marrow myeloid hyperplasia were observed in the 3 month toxicology study (administered once every 24 hours). Similar doses administered S.C. (once every 72 hours) in the 28 day toxicology study in rats did not produce the same histopathological changes.

Both (b) (4) and APF530 were considered nongenotoxic. In reproductive toxicology studies, per the Pharmacology/Toxicology reviewer, (b) (4) did not appear to have adverse effects on fertility and early embryonic development in male and female rats and were not teratogenic in rats and rabbits.

In his review, the Pharmacology/Toxicology reviewer stated that in the acute S.C. toxicity studies in rats, drug related effects were observed at the injection site and included erythema, edema associated with inflammatory infiltrate, degeneration, and necrosis of cutaneous muscle. In dogs, drug related effects were also at the injection site and included, hemorrhage, subacute inflammation, degeneration and necrosis of cutaneous muscle and edema.

In the 28 day S.C. toxicity study in rats, the Pharmacology/Toxicology reviewer noted abnormal findings at the injection site (edema, hemorrhage, fibrosis, epidermal hyperplasia, erosion/ulceration and suppurative inflammation, skeletal muscle degeneration/necrosis and inflammation). In dogs, abnormal findings were also observed at the injection sites (edema, thickening, and inflammatory changes which included hemorrhage).

In the 90 S.C. toxicity study in rats, the target organs of toxicity were the injections site, lymph nodes, bone marrow, and spleen. In dogs, the target organ of toxicity could not be determined and per the Pharmacology/Toxicology reviewer, “the dose selection does not appear to be appropriate.”

The Pharmacology Toxicology reviewer concluded that the constituents of APF530 and (b) (4) were adequately characterized in general toxicology, genetic toxicology and reproductive toxicology studies to support approval of APF530.

Pharmacology Toxicology has recommended the following related to APF530:

- 1) A 2 year carcinogenicity study in the rat and an *in vitro* Syrian Hamster Embryo (SHE) cell transformation assay with (b) (4).
- 2) The Applicant should qualify the proposed total impurity specification level of $\leq$ (b) (4) % or reduce the specification level to $\leq$ (b) (4) %.
- 3) The Applicant should also provide information regarding the genotoxic potential of impurities.

Refer to the Pharmacology Toxicology review for a complete non clinical assessment of APF530.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Granisetron is a selective 5-hydroxytryptamine₃ (5-HT₃) receptor antagonist with little or no affinity for other serotonin receptors, including 5-HT₁; 5-HT_{1A}; 5-HT_{1B/C}; 5-HT₂; for alpha₁-, alpha₂- or beta-adrenoreceptors; for dopamine-D₂; or for histamine-H₁; benzodiazepine; picrotoxin or opioid receptors. Serotonin receptors of the 5-HT₃ type are located peripherally on vagal nerve terminals and centrally in the chemoreceptor trigger zone of the area postrema. During chemotherapy-induced vomiting, mucosal enterochromaffin cells release serotonin, which stimulates 5-HT₃ receptors. This evokes vagal afferent discharge and may induce vomiting. Animal studies demonstrate that, in binding to 5-HT₃ receptors, granisetron blocks serotonin stimulation and subsequent vomiting after emetogenic stimuli such as cisplatin. (from Kytril label)

The proposed product, APF530 – granisetron S.C., (Sustol) is a long-acting polymer (triethylene glycol based poly-ortho-ester polymer or TEG-POE polymer) formulation of granisetron that is anticipated to maintain a steady blood concentration of granisetron for 24 to 36 hours following subcutaneous (S.C.) injection. The Applicant believes that prolongation of the half-life of granisetron will provide long-lasting prevention and control of CINV with a single administration. Please refer to the Pharmacology/Toxicology review for a complete assessment.

4.4.2 Pharmacokinetics

Granisetron has a well defined pharmacokinetic (PK) profile. The pharmacokinetics of APF530 (granisetron S.C.) were studied in four clinical trials: one Phase 1 (healthy volunteers), two Phase 2 (cancer patients undergoing emetogenic chemotherapy) and one Phase 3 (a subset of cancer patients undergoing emetogenic chemotherapy). PK data for I.V. granisetron (Kytril) at a dose of 100 micrograms/kg were obtained in the Phase 1 trial in healthy volunteers.

Per the Applicant, granisetron was slowly absorbed from the APF530 formulation in all four PK studies, at a rate apparently independent of the dose administered. In cancer patients, the median T_{max} values across studies were 22.8-23.8 hours, 22.9-24.5 hours and 29.7 hours, for the 250 mg (5 mg granisetron), 500 mg (10 mg granisetron) and 750 mg (15 mg granisetron) dose levels, respectively. The absorption rate in healthy volunteers appeared to be markedly faster than in cancer patients at all dose levels, but there was little variation between dose levels within trial C2004-01: the median T_{max} value was identical (8 hours) for each of the three lower dose levels (125 mg (2.5 mg granisetron), 250 mg (5 mg granisetron) and 500 mg (10 mg granisetron), while the median T_{max} for the 1 g (20 mg granisetron) dose level was 10 hours. In some healthy volunteers, secondary peaks in plasma levels of granisetron were observed between 24 and 96 hours post-dose, but this was not observed in any of the studies involving cancer patients. As would be expected, T_{max} was reached very rapidly after administration of I.V. granisetron (median 35 minutes). See Table 2

Based on the AUC and C_{max} , the Clinical Pharmacology reviewer recommends that the Applicant conduct a thorough QT trial to assess the effects of APF530.

Refer to the Clinical Pharmacology review for a complete pharmacology assessment of APF530.

Table 2: Mean (SD) Pharmacokinetic Parameters for APF530 - Trial C2005-01

Dose group	C_{max} (ng/ml)	AUC(0-168 hr) (ng*hr/ml)	T_{max}^* (hr)	$T_{1/2}$ (hr)
5 mg (N=17)	10.3 (6.5)	645 (653)	23.1 (6-48)	31.7 (10.9)
10 mg (N=15)	22.5 (23.6)	1348 (1253)	23.3 (6-49.4)	28.4 (14.2)
25 mg (N=13)	29.8 (17.5)	2155 (1201)	24 (6-47.6)	32.1 (11.4)

Source: From Clinical Pharmacology Review

4.5 Other

Division of Medication Error Prevention and Analysis (DMEPA)

The DMEPA was consulted and identified potential safety sources of medication error, specifically with respect to preparation, wrong route of administration and overdose errors. They have identified deficiencies which must be addressed to mitigate the potential for medication errors. These include:

- 1) Product design may lead to route of administration and overdose errors. Most 5-HT₃ receptor antagonists are administered orally or I.V., healthcare practitioners who are accustomed to these routes of administration and may in error not administer APF530 the correct way. Also, features of the product design may contribute to wrong route of administration and overdose.
- 2) Proposed needle [REDACTED] (b) (4) is inconsistent with normal clinical practice for a S. injection. This may lead to route of administration errors if the medication is injected directly into the abdominal muscle, rather than subcutaneously.
- 3) Data from usability studies must be submitted. This includes: protocol, raw data, summary findings, and revisions made to product design, packaging, labels, and labeling based on the trial results.
- 4) There are no markings on the vial to indicate the fill volume. Without this marking, it is difficult to know the total fill volume in the syringe and users cannot tell if product tampering has occurred.

A complete list of deficiencies can be found in the DMEPA review.

Center for Devices and Radiological Health (CDRH)

The CDRH was consulted to assess the primary container closure system for the drug product APF530. The CDRH has requested additional information regarding the [REDACTED] (b) (4) syringe and other devices within the drug container closure system.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 below summarizes the primary studies used in the review of this NDA to evaluate the efficacy and safety of APF530 (granisetron S.C.). Trial C-2006-01 was the only pivotal efficacy trial submitted in support of this NDA for the indication of 1) prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of MEC and 2) prevention of acute nausea and vomiting associated with initial and repeat courses of HEC.

Table 3: Summary of Clinical Trials

Clinical Review
Karyn L. Berry, MD, MPH
NDA 22-445
Sustol (granisetron)

Trial Code	Trial design	Trial Objective(s)	Treatment	Number of patients	Treatment Duration	Gender F/M	Primary Endpoint(s)
Number of trial centers							
Location(s)							
Efficacy & Safety in Cancer Patients							
C2006-01 (Phase 3 Pivotal trial) 72 US sites 19 India sites 11 Poland sites	Randomized, multicenter, observer-blind, double dummy, parallel group	Assess the safety & effectiveness of a single SC injections of APF530 (5 mg & 10 mg) versus a single IV injection of Aloxi (palonosetron, 0.25 mg) for both prevention of acute and delayed CINV in patients undergoing MEC or HEC	Test article- APF530 5 mg & APF530 10 mg SC injection Active Comparator- Aloxi 0.25 mg IV (placebo – isotonic saline for IV or SC injection) Injections were given 30 – 60 minutes before the start of chemo	1428 randomized 1395 received drugs	4 Cycles (up to 4 doses of study drug)	1040- F 355 - M	Proportion of patients with CR during the acute phase (0 to 24 hours) following the administration of chemotherapy in Cycle 1. Proportion of patients with CR during the delayed-onset phase (24 to 120 hours) following the administration of chemotherapy in Cycle 1.
PK & Safety in Cancer Patients							
C2005-01 (Phase 2 Open Label trial) 6 US sites	Open-label, multicenter, ascending, single SC dose, sequential group trial	Assess the PK, tolerability and safety of a single SC injection of APF530 (5 mg, 10 mg and 15 mg) in patients undergoing MEC	Test article – APF530 5 mg APF530 10 mg APF530 15 mg - SC injection Injections were given ~30 ± 5 min before the start of chemo	45 enrolled & received study drug (17 – APF530 5 mg; 15 – APF530 10 mg; 13- APF530 15 mg)	14 ± 3 days after a single SC injection dose on the 1 st day of trial	27 – F 18 - M	Efficacy assessment was exploratory
C2007-01 3 Poland sites	Randomized, multicenter, uncontrolled, open-label, PK trial	Determine the PK parameters of 2 doses of APF530 (5 mg & 10 mg) in patients undergoing MEC or HEC	Test article – APF530 5 mg APF530 10 mg SC injection	35 enrolled (17 - 5mg APF530 & 18 – 10 mg APF530)	Single SC injection dose; 7 day washout period & 7 day treatment & blood sample collection period	All Females Mean Age – 55.7 yrs Age Range – 28 – 75 yrs	Efficacy assessment was exploratory
BA/PK & Safety in Healthy Subjects							
C2004-01 (Phase 1) 1 UK site	Single, ascending SC dose, sequential group trial, using a 2 period crossover to assess BA	Determine the PK, safety & tolerability of ascending SC doses of APF530 in healthy male subjects	Test article – APF530 5 mg APF530 10 mg APF530 15 mg - SC injection Kytril IV 100 mcg/kg	26 enrolled	14 days	All males Age Range – 21– 49 yrs	

Source: Modified table from Applicant's 5.2 Tabular Listing of Clinical Studies

BA= Bioavailability, PK=Pharmacokinetics, n=number of subjects, CINV=Chemotherapy induced nausea and vomiting, CR= Complete Response (no emetic episodes and no use of rescue medication), CC=Complete control (no emetic episodes, no use of rescue medication and no more than mild nausea), TR = Total Response (no emetic episodes, no use of rescue medication and no nausea), ME= Moderately emetogenic, HE=Highly emetogenic, M=Male, F=Female, APF530 250 = 5 mg of granisetron, APF530 500 = 10 mg of granisetron, APF530 750 = 15 mg of granisetron
CR was measured in 24-hour increments up to 120 hours

5.2 Review Strategy

A review of the pivotal trial C2006-01 and the other studies, C2004-01, C2005-01 and C2007-01 was performed using the sponsor's submitted data. Each trial was reviewed individually by the medical reviewer and compared to the results reported in the sponsor's safety and efficacy reports and with the drug's established safety profile.

The sources of clinical data used in this review are the results of the submitted clinical trials, with emphasis on the protocols and clinical trial reports, supporting granisetron sustained release S.C. injection as indicated for the 1) Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy and 2) Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

Other sources of clinical data consulted in this review include:

- Electronic submission of the medical section of the NDA (including narratives and case report forms)
- Electronic submitted data sets
- Physicians Desk Reference
- Electronic orange book
- Literature review

5.3 Discussion of Individual Studies/Clinical Trials

The only trial submitted by the Applicant that evaluated primary efficacy endpoints was C2006-01. Trials C2005-01 and C2007-01, which were conducted in patients undergoing chemotherapy, conducted efficacy assessments as exploratory.

5.3.1 Protocol Synopsis – Protocol Number: C2006-01 (Pivotal trial)

Title

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.

Trial Period

07 June 2006 (trial initiation date) to 12 August 2008 (trial completion date)

Trial Centers

The trial was conducted by 72 investigators in the United States, 19 investigators in India and 11 investigators in Poland. A total of 1428 patients were randomized. Of the randomized patients in Cycle 1, 659 were in the moderately emetogenic stratum and 769 were in the highly emetogenic stratum.

Trial Objectives

The primary objective of the trial was to evaluate in the first qualifying chemotherapy treatment the efficacy of a single S.C dose of a sustained-release formulation of granisetron (APF530) in comparison to Aloxi, for the prevention of acute-onset and delayed-onset CINV in patients currently undergoing moderately or highly emetogenic chemotherapy.

The secondary objectives were to evaluate the safety and tolerability, sustained efficacy and PK and ECG data (cycle 1 only) of APF530 in patients undergoing moderately or highly emetogenic chemotherapy over multiple chemotherapy treatments.

Trial Design

This was a Phase 3, randomized, multicenter, observer-blind, double dummy, parallel group trial conducted in patients with confirmed malignant disease who were scheduled to receive single-day administration of moderately or highly emetogenic chemotherapy as classified according to the Hesketh algorithm. Both the patient and investigator did not know what was being administered, but because of the differences in study drugs an unblinded pharmacist/nurse was assigned at all sites to administer all treatments. Patients were to receive study drug in up to four treatment cycles (cycles 1, 2, 3, and 4), each of which began the day of qualifying chemotherapy treatment (day 1) and ended at the conclusion of the antiemetic efficacy monitoring at 120 hours (+72 hours) after chemotherapy administration.

Trial Population

Male or female subjects $\geq$ 18 years old, with histologically or cytologically confirmed malignant disease who were scheduled to receive single-day administrations of moderately or highly emetogenic chemotherapy regimens (as defined by Hesketh algorithm), could be enrolled in this trial. Planned chemotherapy administration, was not to extend beyond 4 hours, excluding administration of monoclonal antibodies, and administrations were to be separated by at least 7 days but by no more than 28 (+3) days. Patients could receive up to four doses of study drug in conjunction with a qualifying chemotherapy administration (i.e., one assigned a Hesketh Score of 3, 4, or 5).

Treatment

The investigational product was APF530, a TEG-POE polymer based formulation containing 2% granisetron as a free base. The active comparator was Aloxi (palonosetron hydrochloride). See Figure 1

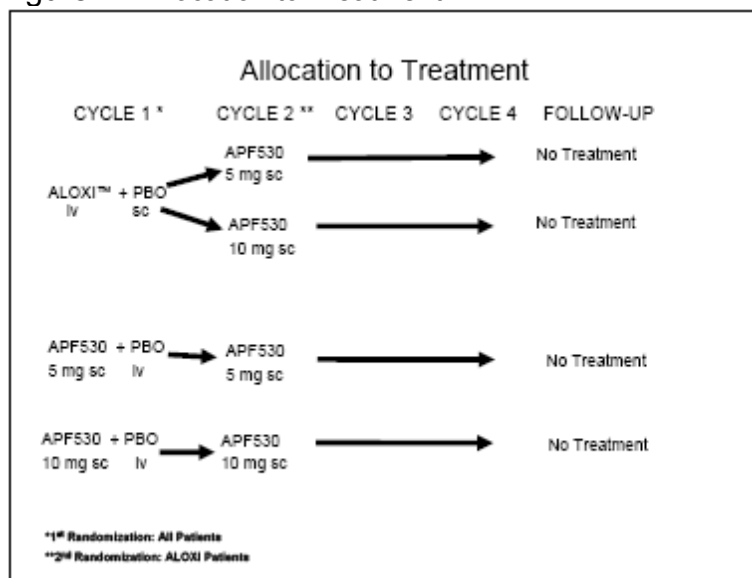
Patients received one of the following treatments in Cycle 1. The placebo was isotonic saline for both the I.V. and S.C. injections:

- A single dose of 0.25 mg Aloxi I.V. and placebo S.C.
- A single dose of 250 mg APF530 S.C. (containing 5 mg granisetron), referred to as 5 mg APF530 hereafter.
- A single dose of 500 mg APF530 S.C. (containing 10 mg granisetron), referred to as 10 mg APF530 hereafter.

Patients received one of the following treatments in each subsequent treatment cycle (Cycles 2, 3, and 4):

- A single S.C. dose of 5 mg APF530.
- A single S.C. dose of 10 mg APF530.

Figure 1: Allocation to Treatment



Source: Applicant's figure, Trial C2006-01

Method of Assigning Patients to Treatment Groups

Patients were stratified according to emetogenicity (Hesketh Score) of the chemotherapeutic agent(s) they were scheduled to receive: Emetogenic Level 3 and 4 in one stratum (moderately emetogenic) and Level 5 in another stratum (highly emetogenic) as defined by the Hesketh algorithm.

Following stratification of chemotherapy as either moderately or highly emetogenic, a computer-generated randomization schedule, created by a statistician was used to assign eligible subjects to one of the three treatment groups in Cycle 1. Following Cycle 1, all subjects were re-randomized, with a new randomization number being given to each subject in order to maintain the blind. Subjects who received APF530 in Cycle 1 continued to receive APF530 at the same dose in the subsequent treatment cycles. Subjects who received Aloxi in Cycle 1 were re-randomized to receive either 5 mg or 10 mg APF530 in a 1:1 ratio in subsequent cycles.

Prior and Concomitant Medications

All medications and supplements taken in the 4 weeks prior to trial enrollment and throughout the trial were documented in the CRF.

The study drug was to be administered on the same day as qualifying chemotherapy. The total time of chemotherapy administration including any hydration time (if hydration was given between administration of any chemotherapeutic agents) excluding monoclonal antibodies was not to exceed 4 hours. The previous two administrations of chemotherapy and any radiotherapy received in the two weeks prior to first study drug administration, as well as current cancer chemotherapy, were to be recorded on the CRF.

Dexamethasone was used as follows: on Day 1 of each cycle, I.V. dexamethasone was administered 30 to 90 minutes before the start of chemotherapy. For subjects in the moderately emetogenic chemotherapy stratum, the dexamethasone dose was 8 mg I.V., and for those in the highly emetogenic chemotherapy stratum, the dexamethasone dose was 20 mg I.V.. Additionally, dexamethasone was given orally at a dose of 8 mg twice-a-day on Days 2, 3, and 4 to all subjects treated with highly emetogenic chemotherapy.

Trial Procedure

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 (S.C.) and Aloxi (I.V.). The trial 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 three treatment groups in each stratum:

- Aloxi 0.25 mg I.V. and placebo S.C.
- 5 mg APF530 and placebo I.V.
- 10 mg APF530 and placebo I.V.

The I.V. and S.C. injections were given concomitantly 30 to 60 minutes before the subject's scheduled chemotherapy. Placebo was isotonic saline for both the I.V. and S.C. injections. Following the first trial cycle, re-randomization was applied so that

subjects who received Aloxi in Cycle 1 were assigned in a 1:1 ratio to receive S.C. 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 maintained throughout the re-randomization. Thus, in Cycles 2, 3, and 4, subjects received one of two treatments:

- 5 mg APF530.
- 10 mg APF530.

In all treatment cycles, the abdominal injection site area was cleaned and in most cases a local anesthetic was applied before S.C. injections. The time and site of all injections were noted in the CRF. There was no specific timing of dosing in relation to meals. Intravenous dexamethasone (8 mg and 20 mg for moderately and highly emetogenic chemotherapy, 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 highly emetogenic chemotherapy. 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. The choice of rescue medication was at the discretion of the investigator, but was not to include granisetron (Kytrel), palonosetron (Aloxi), or aprepitant (Emend). Treatment cycles were to be separated by a period of at least 7 days, but by no more than 28 (+3) days.

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. Additionally, each subject completed the Functional Living Index of Emesis (FLIE) a nausea- and vomiting-specific Quality of Life (QoL) assessment on Day 5 of Cycle 1. The FLIE is a subject reported outcome instrument comprising two domains (nausea and vomiting) with nine identical items in each domain.

Blood for the analysis of plasma granisetron concentration was to be collected in a planned subset of 100 to 130 subjects during Cycle 1, as follows: before study drug administration and just before being released from the clinic on Day 1, and at 22 to 28 hours, 48 ± 4 hours, 72 ± 4 hours, 96 ± 4 hours, and 120 ± 4 hours after study drug administration.

Safety measurements included vital signs, physical examinations, clinical laboratory parameters (hematology, blood chemistries, urinalysis), 12-lead ECG (including 24-hour Holter monitoring in a planned subset of 100 to 130 subjects during Cycle 1), and AEs, including injection site reactions. A follow-up visit was scheduled 30 ± 3 days after the final study drug administration.

All data were to be recorded in the case report form (CRF). No interim analysis was planned or performed.

Medical Reviewer's comments: The trial procedures were adequate.

Endpoints:

The following efficacy measures were evaluated daily during the first 5 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 the purposes of analysis, a single emetic episode was defined as a single vomit or retch separated by an interval ≥ 1 minute. Continuous vomits or retches were defined as two or more vomits or retches with a gap of less than 1 minute between the individual vomits or retches.

As previously noted, in addition to assessment of emesis, an assessment of QoL, using the FLIE, was made on Day 5 of Cycle 1.

The primary efficacy endpoints of this trial were:

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

The secondary efficacy endpoints were:

- 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 during the overall treatment cycle (0-120 hours).
- Proportion of subjects, following the completion of Cycle 1, with TR during the acute phase, delayed-onset phase, and overall treatment cycle (0-120 hours).
- Proportion of subjects, following the completion of Cycle 1, with major control of emesis (<2 emetic episodes), minor (3-5 emetic episodes) and failure (>5 emetic episodes).

episodes); during the acute phase, delayed-onset phase, and overall treatment cycle (0-120 hours).

- 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 occurs first).
- Use of rescue medication.
- Severity of nausea measured daily and overall (0-120 hours).
- Subject's global satisfaction with antiemetic therapy during the acute phase and overall trial period, recorded in 24-hour increments.
- QoL assessment, the impact of nausea and vomiting on Day 5.
- Sustainability of antiemetic effect of APF530 during multiple chemotherapy Cycles.

Medical Reviewer's comments: The primary and secondary endpoints are acceptable.

Statistical Plans

Four trial populations were defined, including:

- Safety: all subjects who were randomized and received any amount of study drug.
- Modified Intent-to-Treat (mITT): all subjects who were randomized, received study drug and had post-baseline efficacy data. Separate mITT sets were created for each of the four treatment cycles. As such, it was possible for a subject to be included in this population for one cycle and not included in the population for another cycle. The primary analysis of the trial's objectives 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. Protocol violations 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 > 5 hours; administration of multiday 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 of the trial's primary objective based on this population was considered supportive.

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

Primary Efficacy Analysis

For moderately emetogenic chemotherapy regimens the objective of the trial was to demonstrate the non-inferior efficacy of APF530 for acute-onset and delayed-onset CR in comparison to Aloxi. For highly emetogenic chemotherapy regimens the objective of the trial was to demonstrate the non-inferior efficacy of APF530 for acute-onset and the superiority for delayed-onset CR in comparison to Aloxi.

Non-inferiority was declared if the lower bound of the Confidence Interval (CI) was above -15%. Superiority was declared if the lower bound of the CI was above 0%.

5.3.2 Other Trials – Protocol Numbers: C2004-01, C2005-01, C2007-01

Trial C2004-01

Title

APF530 - 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

Trial C2004-01 was a Phase 1 double-blind, placebo controlled, single ascending subcutaneous dose, sequential group which incorporated a two period cross-over to assess safety, tolerability, and pharmacokinetics of APF530 in healthy male subjects.

The trial was planned for 24 subjects (healthy males between the ages of 18 and 55 years) to receive a S.C. dose of APF530 and sterile saline (placebo). 18 of these subjects were also to receive an I.V. dose of granisetron. Subjects were studied in four groups (Group A to Group D) with six subjects in each group.

Treatment Groups

Group A: 125 mg APF530 S.C.

Group B: 250 mg APF530 S.C.

Group C: 500 mg APF530 S.C.

Group D: 1 gm APF530 S.C.

Groups B, C and D: 100 mcg/kg of Granisetron 100 mcg/kg I.V. in a separate treatment period, prior to receiving the sc dose

Patients received the S.C. injection in one side of the abdomen and the placebo (sterile saline) in the opposite side of the abdomen. There was an interval of at least 7 days

between the I.V. and S.C. doses within each group and between the last dose of each group and the first dose of the following group to allow for a review of the safety and PK data prior to progression to the next higher dose level.

26 subjects were enrolled, which included 2 replacement subjects in Group B due to S.C. dosing problems. All subjects were Caucasian males between the ages of 21 and 49 years. The mean (SD) ages for 125 mg, 250 mg, 500 mg and 1 gm were 29 (10.7), 38 (9.0), 40 (8.6), and 28 (9.). Data for 20 subjects who received the I.V. doses of granisetron and for the 25 subjects who received the full S.C. dose of APF530 were included in the safety, tolerability and PK summaries and statistical analysis.

Safety and tolerability

Almost all subject experienced AEs, with the majority occurring at the site of the SC injection of APF530. There were only a small number of injection site reactions following the S.C. dose of sterile saline. The most frequently reported APF530 SC injection site reactions were pain and erythema which occurred across all dose levels and mass/edema which occurred following all S.C. doses of APF530 except the 250 mg dose. Injection site bruising occurred in at least one subject at all dose levels of APF530, most marked at the 250 mg dose level.

There were no deaths, serious adverse events or significant adverse events reported. There were no reported dose related trends in the serum biochemistry, hematology or urinalysis during the trial. There were no reported dose related trends in systolic and diastolic blood pressure and pulse during this trial.

Pharmacokinetics

Following SC doses of APF530 there was a slow absorption of granisetron with median Tmax occurring at 8 to 10 hours post dose. In some subjects, secondary peaks in plasma levels of granisetron occurred between 24 to 96 hours post dose. The terminal elimination phase could not be defined in most subjects. AUC and Cmax for granisetron generally increased in a dose proportion across the S.C. doses of 125 mg to 1 gm APF530. Both parameters showed high between subject variability. The PK parameters of I.V. granisetron showed high variability and were comparable to those published by Kytril.

Trial C2007-01

Title

An Open-Label, Uncontrolled, Randomized, Multi-Center, Pharmacokinetic Study of Two Doses of APF530 in Patients Undergoing Moderately or Highly Emetogenic Chemotherapy Treatment.

Trial 2007-01 was a Phase 2, open-label, uncontrolled, randomized, multi-center PK trial of two doses of APF530. It was conducted at three sites in Poland from 27 May 2008 to 04 August 2008. A total number of 35 subjects were planned to yield 30 subjects (15 per dose) for PK analysis.

The primary objective of the study was to assess PK parameters of APF530 in subjects undergoing MEC or HEC. The secondary objective was to assess the safety of the route of administration by monitoring vital signs prior to and following study drug administration, by recording AEs and evaluating the injection site.

Study Drug Treatment

Subjects were randomized to one of two treatment groups:

A single S.C. injection of 250 mg APF530

A single S.C. injection of 500 mg APF530

Injections were given in the abdominal area 30 to 60 minutes before the subject's scheduled chemotherapy. A local anesthetic may have been applied to the abdominal injection site area before S.C. injections.

In accordance with protocol, IV dexamethasone was administered to all subjects 30 to 90 minutes before the start of chemotherapy (8 mg for subjects scheduled to receive moderately emetogenic chemotherapy and 20 mg for those scheduled to receive HEC). Oral dexamethasone (8 mg twice a day) was given for the next 3 days (Days 1, 2, and 3) to all subjects treated with HEC. No oral dexamethasone was given for MEC.

Subjects were prescribed rescue medication (not to include granisetron) for nausea and vomiting.

PK

Blood samples for the analysis of plasma granisetron concentration were to be collected before study drug administration and at 2, 4, 6, 12, 18, 24, 48, 72, 96, 120, 144 and 168 hours after study drug administration. Area-under-the-concentration curve (AUC), maximal concentration (C_{max}), time of maximal concentration (T_{max}), apparent elimination half-life (t_{1/2}), apparent total clearance (Cl_{tot}/F), apparent volume of distribution (V_d/F), and mean residence time (MRT) were determined for each subject and for each dose of APF530.

Efficacy

Efficacy assessments were not specified in the protocol, but subjects were questioned about the occurrence of nausea and emesis, as well as the use of rescue medication during the 7-day monitoring period after chemotherapy for exploratory purposes. The efficacy parameters included complete response (CR) (no emetic episodes and no use of rescue medication); complete control (CC) (CR with no more than mild nausea); and total response (TR) (CR with no nausea).

Safety

Safety measurements included AEs, injection site reactions, concomitant medications, review of medical history, vital signs, physical examinations, pregnancy test, weight, and 12-lead electrocardiograms (ECGs). Clinical laboratory parameters (hematology, blood chemistries, urinalysis) were evaluated at screening.

Results

A total of 35 subjects enrolled, 17 in the 250 mg APF530 group and 18 in the 500 mg APF530 group. All 35 subjects were White/Caucasian and female. The mean age was 55.7 years (range: 28 to 75 years). Twenty-nine of thirty-five (82.8%) received HEC and 29 of 35 (82.8%) had ovarian cancer.

PK

Granisetron was slowly absorbed and eliminated following administration of APF530. Exposure to granisetron generally increased with dose level of APF530 (5 mg and 10 mg). Median Tmax values were 22.8 and 22.9 hours, respectively, for the 5 and 10 mg doses of APF530. After reaching Cmax (mean of 11.8 and 17.8 ng/mL, respectively) plasma concentrations of granisetron declined with mean t1/2 values of 31.6 and 28.8 hours, respectively. The 2-fold increases in dose level of APF530 resulted in 1.51-fold and 1.53-fold increases in mean granisetron Cmax and AUC0-168, respectively. Mean values for Cl_{tot}/F were 8496 and 27499 mL/hr, values for V_d/F were 367608 and 943758 mL, and values for MRT were 51.7 and 48.3 hours, respectively.

Efficacy

Efficacy was an exploratory endpoint.

Complete Response

[REDACTED] (b) (4)

All 6 subjects (100%) who received MEC achieved CR during the delayed-onset phase (>24 to 168 hours). Among these 6 subjects, 3 of the 4 subjects (75.0%) who received 10 mg APF530 also achieved CR during the acute-onset phase (0 to 24 hours) and during the overall risk period (0 to 168 hours) and 2 of 2 subjects (100%) who received 5 mg APF530 achieved CR during the acute-onset phase and during the overall risk period.

Complete Control

[REDACTED] (b) (4)

Total Response

[REDACTED] (b) (4)

Five of the 6 subjects who received MEC achieved TR during the delayed phase, including all 4 subjects (100%) who received 10 mg APF530 and 1 of 2 subjects (50.0%) who received 5 mg APF530. Among these 6 subjects, 3 of the 4 subjects (75.0%) who received 10 mg APF530 also achieved TR during the acute phase and during the overall risk period and 1 of 2 subjects (50.0%) who received 5 mg APF530 achieved CR during the acute phase and during the overall risk period.

Safety

No subjects discontinued from the study due to AEs. No subjects died and none had treatment-related SAEs. A total of 18 subjects (51.4%) experienced AEs, including 10 (58.8%) in the 5 mg APF530 dose group and 8 (44.4%) in the 10 mg APF530 dose group. AEs were treatment related in 10 subjects (28.6%): 6 (35.3%) in the 5 mg APF530 dose group and 4 (22.2%) in the 10 mg APF530 dose group.

Among all the AEs reported, 6 of 10 in the 5 mg dose group were mild and 4 of 10 were moderate; 5 of 10 in the 10-mg dose group were mild and 4 of 10 were moderate. One subject had severe AEs (Subject [REDACTED] (b) (6)).

Three subjects had Serious Adverse Events (SAEs). All were considered by the investigator to be unrelated to treatment. In the 5 mg APF530 dose group, Subject [REDACTED] (b) (6) had moderate anemia and, in the 10 mg APF530 dose group, Subject [REDACTED] (b) (6) had moderate thrombocytopenia and moderate anemia and Subject [REDACTED] (b) (6) had severe thrombocytopenia and severe abdominal pain.

Adverse Events (excluding injection site reactions)

The most frequently reported AE was constipation, which occurred in 4 subjects (23.5%) in the 5 mg dose group and 1 in the 10 mg dose group (5.6%). Constipation was considered by the investigator to be related to treatment in 4 subjects overall (11.6%), including 3 subjects in the 5 mg group (17.6%) and 1 subject in the 10 mg dose group (5.6%). Two occurrences of constipation were mild and 3 were moderate. The only other AEs to occur in a total of 2 or more subjects were abdominal pain (2 subjects in the 10 mg dose group), anemia (1 subject in each dose group), and thrombocytopenia (2 subjects in the 10 mg dose group). None of these were reported as related to treatment. Each occurrence of anemia was moderate. Thrombocytopenia

was mild in one subject and severe in the other, and abdominal pain was mild in one subject and severe in the other.

Injection site reactions

The most frequently reported injection site reaction was nodule, which occurred in 1 subject (5.9%) in the 5 mg dose group and 2 subjects (11.1%) in the 10 mg dose group. Injection site nodule was considered by the investigator to be related to treatment in 1 subject in the 5 mg group and 1 subject in the 10 mg dose group. All occurrences of injection site nodule were mild.

All other injection site reactions were considered by the investigator to be related to treatment and included bruising, erythema, and pain, each AE occurring in < 6% of subjects in either dose group. Injection site bruising occurred in 1 subject in each dose group and was mild and moderate in the 5 mg and 10 mg groups, respectively. Injection site erythema also occurred in 1 subject in each dose group, and was mild in both cases. Injection site pain occurred in 1 subject in the 10 mg dose group only and was of moderate severity.

All injection site reactions resolved except for injection site erythema in 1 subject who received 10 mg APF530 (Subject (b) (6)) and injection site bruising in 1 subject who received 5 mg APF530 (Subject (b) (6)). These reactions were first noted at the final visit and characterized as ongoing.

Trial C2005-01

See section 6.1.6 (Other Endpoints)

6 Review of Efficacy

Efficacy Summary

In conclusion, using a non-inferiority margin of 15%, the Applicant demonstrated non-inferiority of APF530 5 mg and APF530 10 mg (granisetron S.C.) compared with Aloxi in the prevention of acute CINV (b) (4). Non-inferiority was also demonstrated in the prevention of delayed CINV in MEC with APF530 10 mg. (b) (4)

There is concern with the significant protocol violations identified by the DSI Investigation (giving an excluded drug, methylprednisolone at the beginning of chemotherapy treatment) in 49 subjects out of a total of 86 subjects at site 003 (trial-C2006-01-Phase 3) in the US. The Applicant should re-analyze the primary efficacy endpoints: 1) excluding those 49 subjects and 2) excluding the entire site to determine if efficacy is impacted by this data. The Statistical Reviewer has requested additional

information and data regarding site 504 (India). The Applicant noted that this site was excluded from the efficacy evaluation because of “unexplained and non-verifiable irregularities in the data.” Based on identified protocol violations, there may be a need for additional site investigations to include all countries where the trial was conducted.

6.1 Indication

The Applicant proposes that APF530 (Sustol) receive the following indications:

- Prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
- Prevention of acute nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy.

6.1.1 Methods

The clinical data from trial C2006-01 was reviewed to determine whether a clinical benefit was demonstrated in patients receiving MEC and/or HEC. For each emetogenic group and for each treatment cycle, the Applicant conducted primary and secondary efficacy analysis on the mITT population (all subjects who were randomized, received study drug in the respective cycle, and had at least the minimum required post-baseline efficacy data for analysis for that cycle). The Applicant excluded subjects from the mITT population because of missing post baseline efficacy data and excluded subjects from Site 504 (excluded prior to the unblinding) because of “unexplained and non-verifiable irregularities in the data.”

The Applicant conducted supportive analysis of the trial’s primary objective on the PP population (Cycle 1 only).

Table 4: Summary of mITT and PP Populations

Population	MEC			HEC		
	APF530 5 mg N (%)	APF530 10 mg N (%)	Aloxi 0.25 mg N (%)	APF530 5 mg N (%)	APF530 10 mg N (%)	Aloxi 0.25 mg N (%)
Randomized	222 (100)	221 (100)	216 (100)	235 (100)	260 (100)	256 (100)
mITT Cycle 1	214 (96.4)	212 (95.9)	208 (96.3)	229 (90.5)	240 (92.3)	238 (93.0)
PP Cycle 1	201 (90.5)	195 (88.2)	192 (88.9)	197 (77.9)	192 (73.8)	203 (79.3)
mITT Cycle 2	247	240	-	263	263	-
mITT Cycle 3	191	184	-	207	202	-
mITT Cycle 4	134	134	-	158	148	-

Source: Applicant’s table, Main Trial Report C2006-01

6.1.2 Demographics

Populations across treatment and strata were balanced with respect to age, sex and race. The average age of the subjects was between 54.8 to 58.1 years across all

treatment groups. Most subjects were females (75% overall) and most subjects were White/Caucasian (56.4% to 66.5% across treatment and strata groups).

Table 5: Trial C2006-01-Demographics (Cycle 1) Safety Population

Variable		Moderately Emetogenic			Highly Emetogenic		
		APF530 5 mg (N=220)	APF530 10 mg (N=218)	Aloxi 0.25 mg (N=215)	APF530 5 mg (N=244)	APF530 10 mg (N=250)	Aloxi 0.25 mg (N=248)
Age (years)	Mean	54.8	55.1	57.3	57.4	56.7	58.1
	Sex %						
	Male	12.3	16.5	16.7	32.8	37.2	33.5
	Female	87.7	83.5	83.3	67.2	62.8	66.5
Race %	White	56.8	56.4	66.5	57.8	62.4	60.5
	Asian	30.5	27.1	22.3	25.4	27.2	23.8
	Black/African Am	5.0	10.1	6.5	8.2	4.8	8.1
	Hispanic/Latino	5.9	5.0	4.2	7.0	4.4	6.9
	Native Hawaiian	0.9	0.5	0.5	0.8	1.2	0.8
	Am Indian/Alaska Nat	0.5	0	0	0	0	0
	Other	0.5	0.9	0	0.8	0	0
Weight (lbs)	n	218	216	215	244	244	247
	Mean	158.9	158.3	159.3	159	156.6	155.5
Country %	USA	60.5	62.4	64.2	68.9	67.6	68.1
	India	25.5	25.7	20.5	22.5	24.8	21.4
	Poland	14.1	11.9	15.3	8.6	7.6	10.5

Source: Modified Applicant's table, Main Trial Report

Medical Reviewer's comments: The treatment and control populations were balanced with respect to baseline demographics.

6.1.3 Subject Disposition

Cycle 1

A total of 1428 subjects were randomized at 72 sites in the US, 19 sites in India, and 11 sites in Poland. Of the randomized subjects in Cycle 1, 659 were in the moderately emetogenic stratum and 769 were in the highly emetogenic stratum. A total of 33 subjects were randomized but did not receive study drug and were not discussed any further in the Applicant's report.

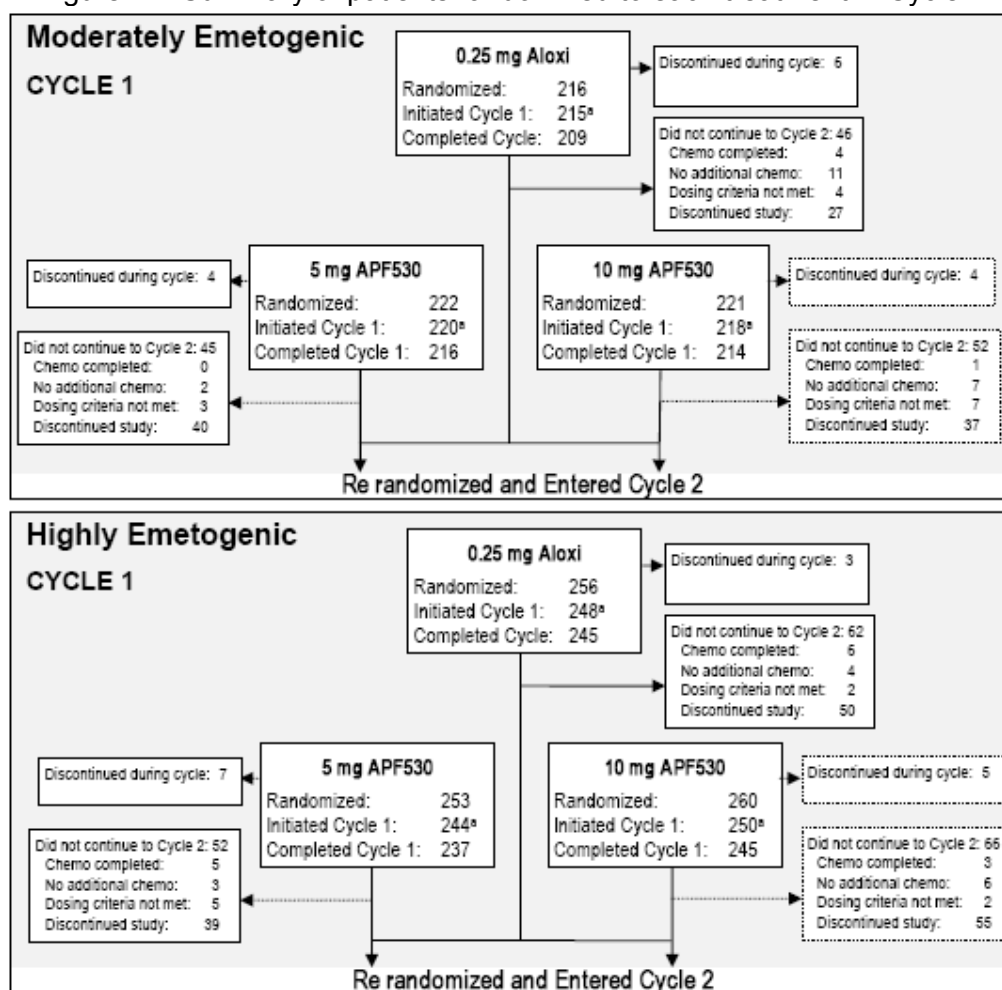
Overall, 29 subjects discontinued from the trial during Cycle 1. The most frequent reason for discontinuation (13 subjects) was that the subject was lost to follow up. Four subjects died and 2 subjects discontinued due to AEs during Cycle 1. None of the deaths while on treatment were considered by the Applicant as possibly, probably, or definitely related to study drug. The AEs (dyspnea in Subject (b) (6) and drug

hypersensitivity in Subject (b) (6) were considered by the investigator to be possibly related to treatment (5 mg and 10 mg APF530, respectively). Other reasons for discontinuation during Cycle 1, in a total of 10 subjects, were withdrawn consent, protocol violation or deviation, and trial termination.

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. A total of 248 subjects (12.5% to 21.2% of subjects across treatment groups and emetogenicity strata) discontinued between Cycle 1 and Cycle 2. Seven subjects died and 22 subjects, 17 of whom were in the highly emetogenic stratum, had AEs that led to discontinuation between Cycles 1 and 2. Lack of efficacy was cause for discontinuation in 13 subjects, including 6 subjects in the 5 mg APF530 dose group, 3 in the 10 mg APF530 dose group, and 4 in the Aloxi group. Other reasons for discontinuation, in 1 to 13 subjects (0.4% to 6.6%) across treatment groups and emetogenicity strata included protocol violations, lost to follow up, withdrawn consent, and noncompliance. Among the 14 subjects who withdrew consent, none returned for the 30-day follow-up visit. Investigator decision, subject decision, and trial termination were among the other reasons cited for discontinuation among the remaining 111 subjects (5.1% to 11.8% of subjects across treatment groups and emetogenicity strata) who discontinued between Cycles 1 and 2.

Of the 1366 subjects who completed Cycle 1, 1043 subjects were re-randomized and initiated Cycle 2. Reasons for not completing each treatment cycle included discontinuation from the trial or ineligibility to proceed from one cycle to the next because the subject had completed chemotherapy, was no longer receiving qualifying chemotherapy, or did not meet dosing criteria.

Figure 2 : Summary of patients randomized to each treatment in Cycle 1



Source: Applicant's Figure: Main Trial Report C2006-01, p. 66

Table 6: Reasons for Discontinuation From Trial C2006-01 During Cycle 1

Reason for Discontinuation	Moderately Emetogenic			Highly Emetogenic		
	APF530 5 mg n (%) ^a	APF530 10 mg n (%) ^a	Aloxi 0.25 mg n (%) ^a	APF530 5 mg n (%) ^a	APF530 10 mg n (%) ^a	Aloxi 0.25 mg n (%) ^a
Any reason	4 (1.8)	4 (1.8)	6 (2.8)	7 (2.8)	5 (1.9)	3 (1.2)
Adverse event	0	0	0	1 (0.4)	1 (0.4)	0
Lost to follow up	3 (1.4)	3 (1.4)	4 (1.9)	1 (0.4)	1 (0.4)	1 (0.4)
Withdrawn consent	1 (0.5)	1 (0.5)	0	1 (0.4)	1 (0.4)	0
Death	0	0	1 (0.5) ^b	2 (0.8)	1 (0.4)	0
Other	0	0	1 (0.5)	2 (0.8)	1 (0.4)	2 (0.8)

^a Percentage based on number of subjects randomized in Cycle 1

^b Subject was in the PK and ECG monitoring sub-trial

Source: Applicant's table, Main Trial Report C2006-01

Protocol Violations

The Applicant reported that a total of 367 subjects across treatment groups and emetogenicity strata, had protocol violations. These included 194 subjects (61 in the moderately emetogenic stratum and 133 in the highly emetogenic stratum) who had at least one protocol violation during Cycle 1 and 173 subjects (60 in the moderately emetogenic stratum and 113 in the highly emetogenic stratum) who had at least one protocol violation during Cycles 2 to 4. The most common protocol violation noted in all cycles was administration of non-protocol specified doses of oral dexamethasone, which occurred only among subjects in the highly emetogenic stratum. These subjects either took less than the protocol required or did not take any dexamethasone at all. There was no particular violation that occurred more frequently in the moderate emetogenic stratum.

Additional protocol violations for Cycles 2 to 4 included administration of prohibited medications during the participation period less than 6 days prior to study drug administration, administration of multi-day chemotherapy of Hesketh level >2, and administration of non-protocol specified doses of APF530 or Aloxi.

6.1.4 Analysis of Primary Endpoint(s)

1) Proportion of subjects with CR (no emetic episodes and no use of rescue medication) During the Acute-onset Phase (0 to 24 Hours) following the administration of chemotherapy in Cycle 1

For (b) (4) moderately emetogenic strata, one of the primary objectives of the trial was to demonstrate the non-inferior efficacy of APF530 to Aloxi for CR (no emetic episodes and no use of rescue medication) during the acute-onset phase (0 to 24 hours). Non-inferiority would be declared if the lower bound of the CI was above -15%.

Table 7: Summary of Complete Response in Subjects in the Moderately (b) (4) Emetogenic Strata During the Acute-onset Phase (0 – 24 hours) in Cycle 1 (mITT Population)

	MEC		
	APF530 5 mg (N=214)	APF530 10 mg (N=212)	Aloxi 0.25 mg (N=208)
CR (%)	160 (74.8)	163 (76.9)	160 (75.0)
P value vs. Aloxi	1.0000	0.7321	
95% CI for difference with Aloxi	-8.6, 8.1	-6.3, 10.1	
97.5% CI for difference with Aloxi	-9.8, 9.3	-7.5, 11.4	
98.33% CI for difference with Aloxi	-10.4, 9.9	-8.1, 12.0	
98.75 CI for difference with Aloxi	-10.9, 10.4	-8.6, 12.4	

(b) (4)

Source: Modified Applicant's table, Main Trial Report

2) Proportion of subjects with CR During the delayed-onset Phase (24 to 120 Hours) following the administration of chemotherapy in Cycle 1

For the moderately emetogenic stratum, the primary objective of the trial was to demonstrate the non-inferior efficacy of APF530 to Aloxi for CR during the delayed-onset phase (>24 to 120 hours).

(b) (4)

Table 8: Summary of Complete Response in Subjects in the Moderately ^{(b) (4)} Emetogenic Strata During the Delayed-onset (> 24 hours – 120 hours) Phase in Cycle 1 (mITT Population)

	MEC		
	APF530 5 mg (N=214)	APF530 10 mg (N=212)	Aloxi 0.25 mg (N=208)
CR (%)	110 (51.4)	125 (59.0)	120 (57.7)
P value vs. Aloxi	0.2048	0.8432	
95% CI for difference with Aloxi	-15.8, 3.3	-8.2, 10.7	
97.5% CI for difference with Aloxi	-17.1, 4.6	-9.5, 12.1	
98.33% CI for difference with Aloxi	-17.9, 5.4	-10.2, 12.8	
98.75 CI for difference with Aloxi	-18.4, 5.8	-10.7, 13.3	

(b) (4)

Source: Modified Applicant's table, Main Trial Report

Medical Reviewer's comments: Because of the multiple comparisons involved with this trial (i.e. multiple drug dosages, multiple primary endpoints and multiple emetogenic strata), the Statistical Reviewer recommended using a more conservative CI of 98.75%, for the primary endpoint analysis.

The lower limit of the CI for the primary endpoint of the proportion of patients with CR during the acute phase (0 to 24 hours) following the administration of chemotherapy in Cycle 1 was above -15% in both treatment groups (5 mg APF530 and 10 mg APF530)

(b) (4)

The lower limit of the CI for the primary endpoint of the proportion of patients with CR during the delayed-onset phase (24 to 120 hours) following the administration of chemotherapy in Cycle 1 was above -15% only in the 10 mg APF530 treatment group for MEC.

(b) (4)

Therefore, using a non-inferiority margin of 15%, the Applicant demonstrated non-inferiority of 5 mg APF530 and 10 mg APF530 compared with Aloxi in the prevention of acute CINV (b) (4). Non-inferiority was also demonstrated in the prevention of delayed CINV in MEC with 10 mg APF530. (b) (4)

6.1.5 Analysis of Secondary Endpoints(s)

The Applicant stated that the analysis of secondary variables were considered supportive of the primary results and therefore statistical testing was not controlled for the multiple tests performed. Selected secondary endpoints that are clinically meaningful were reviewed. These are: 1) CR (no emesis and no use of rescue medication) for the period 0 to 120 hours during Cycle 1, 2) Complete Control (Complete response with no more than mild nausea) during Cycle 1 for acute-onset (0 to 24 hours), delayed onset (>24 to 120 hours) and overall (0 to 120 hours) and 3) Total Response (Complete response with no nausea) during Cycle 1 for acute onset (0 to 24 hours), delayed onset (>24 to 120 hours) and overall (0 to 120 hours).

The percentage of subjects with CR for the period 0 to 120 hours during Cycle 1 was greater in subjects in the 10 mg APF530 dose groups (54.2% in the MEC group (b) (4) (b) (4)). See Table 9

The percentage of subjects with CC (CR with no more than mild nausea) during the acute onset phase, delayed phase, and the overall period in Cycle 1 did not vary significantly between the dosage groups of the MEC and HEC group. 70.7% to 72.0% of subjects in the MEC (b) (4) had CC during the acute onset phase. In the delayed onset phase, 46.7% to 54.2% of subjects in the MEC group (b) (4) had CC and during the overall period, 43.5% to 50.5% of subjects in the MEC group (b) (4) had CC. See Table 10

As in the above 2 secondary endpoints, the percentage of subjects with TR (CR with no nausea) during the acute onset phase, delayed phase, and the overall period in Cycle 1 did not vary significantly between the dosage groups of the MEC and HEC group. 54.3% to 63.1% of subjects in the MEC (b) (4) had TR during the acute onset phase. In the delayed onset phase, 35.5% to 42.0% of subjects in the MEC group (b) (4) had TR and during the overall period, 31.3% to 37.3% of subjects in the MEC group (b) (4) had TR. See Table 11

Table 9: Summary of CR in Subjects in the MEC (b) (4) Strata During 0 – 120 hours in Cycle 1 (mITT Population)

	MEC		
	APF530 5 mg (N=214)	APF530 10 mg (N=212)	Aloxi 0.25 mg (N=208)
CR (%)	104 (48.6)	115 (54.2)	109 (52.4)

(b) (4)

Source: Modified Applicant's table: Main trial report, C2006-01

Table 10: Summary of CC in Subjects During the Acute Onset Phase, Delayed Phase and the Overall Period in Cycle 1

	MEC		
	APF530 5 mg (N=214)	APF530 10 mg (N=212)	Aloxi 0.25 mg (N=208)
CC (%)			
Acute phase	154 (72.0)	152 (71.7)	147 (70.7)
Delayed phase	100 (46.7)	115 (54.2)	107 (51.4)
Overall period	93 (43.5)	107 (50.5)	99 (47.6)

(b) (4)

Source: Modified Applicant's table: Main trial report, C2006-01

Table 11: Summary of TR in Subjects During the Acute Onset Phase, Delayed Phase and the Overall Period in Cycle 1

	MEC		
	APF530 5 mg (N=214)	APF530 10 mg (N=212)	Aloxi 0.25 mg (N=208)
TR (%)			
Acute phase	135 (63.1)	121(57.1)	113 (54.3)
Delayed phase	76 (35.5)	89 (42.0)	73 (35.1)
Overall period	68 (31.8)	79 (37.3)	65 (31.3)

(b) (4)

Source: Modified Applicant's table: Main trial report, C2006-01

Medical Reviewer's comments: The Applicant's analysis of these secondary endpoints demonstrates that generally only small differences were seen for CR, CC, and TR within phases between treatment doses (APF530 and Aloxi) within each emetogenic stratum.

6.1.6 Other Endpoints

The Applicant submitted trial C2005-01 as a supportive trial because of the exploratory endpoint assessment. There were no primary or secondary objectives of trial C2005-01 related to efficacy. Exploratory efficacy variables included CR, CC and TR as well as the following:

- Number of vomiting episodes
- Number of retching/dry heave episodes
- Severity of nausea
- Use of rescue medication
- Time to first vomiting episode
- Time to first retching/dry heave episode
- Time to first use of rescue medication
- Time to treatment failure, based on time to first vomiting episode, time to first retching/dry heave episode, or time to rescue medication, whichever occurred first

Trial C2005-01 was an open-label, multicenter, ascending, single S.C. dose, sequential group trial to evaluate the PK, tolerability, and safety of APF530 in patients under-going moderately emetogenic chemotherapy for cancer. Patients received a single APF530 S.C. injection, administered in the abdominal area approximately 30 ± 5 minutes before

the start of moderately / highly emetogenic chemotherapy. A local anesthetic (lidocaine or ethyl chloride spray) was applied to the patient's abdomen at the injection site prior to study drug administration. Prohibited medications included antiemetics and cytochrome P450 3A4 (CYP3A4) subfamily of inhibitors within 10 days of administration of APF530. This trial was conducted at 6 clinical sites in the United States.

There were ten patients in each treatment group.

The dose groups were:

- Group A: 250 mg APF530 (5 mg of granisetron) as approximately 0.26 mL S.C. injection
- Group B: 500 mg APF530 (10 mg of granisetron) as approximately 0.48 mL S.C. injection
- Group C: 750 mg APF530 (15 mg of granisetron) as approximately 0.70 mL S.C. injection

The average (SD) ages for 250 mg, 500 mg and 750 mg were 67.4 (13), 59.9 (12.9), and 64.3 (10.6) years. No body weight information was available. There were 27 females and 18 males (7 Females & 4 Males in group A, 11 Females and 4 Males in group B, and 9 Females and 4 Males in group C. Some subjects were found to have been administered highly emetogenic chemotherapy after retrospective evaluation of their treatments by applying the Hesketh algorithm. As a result, patients were almost equally distributed between highly emetogenic chemotherapy (n=23; 51%) and moderate to minimally emetogenic chemotherapy (n=22; 49%). Dexamethasone was the steroid used.

The exploratory variables of CR, CC and TR will be reviewed. As in trial C2006-01, subjects were provided with a diary in which they were to record emetic episodes, use of rescue medication and severity of nausea. These exploratory efficacy variables were evaluated based on the diary entries.

Table 12: APF530 Acute, Delayed and Overall Onset CINV in Subjects Receiving MEC/HEC

Dose level	Period	Efficacy Measure (% of Subjects)		
		CR	CC	TR
250 mg APF530	Acute phase (0–24 h)	92.3	92.3	76.9
	Delayed (24–168 h)	92.3	92.3	69.2
	Overall (0-168 h)	84.6	84.6	53.8
500 mg APF530	Acute	93.3	93.3	93.3
	Delayed	83.3	76.9	61.5
	Overall	75.0	69.2	53.8
750 mg APF 530	Acute	69.2	69.2	61.5
	Delayed	58.3	50.0	38.5
	Overall	50.0	41.7	30.8

Source: Applicant's table, Trial Report C2005-01

Medical Reviewer's comments:

(b) (4)

This trial differed from the pivotal trial in a couple of areas (i.e. average age of subjects and the design of open label). These may limit its role as supportive.

6.1.7 Subpopulations

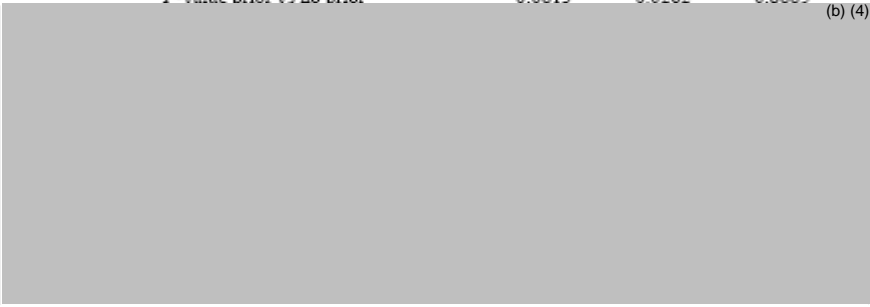
Analysis performed by the Applicant were reviewed for the following subpopulations: prior chemotherapy, chemotherapeutic regimen during Cycle 1, gender, and age.

Prior chemotherapy:

During the acute onset phase there were no significant differences in CR within any treatment comparisons or between either dose of APF530 and Aloxi for prior chemotherapy and for those subjects who were naïve to chemotherapy. A significant difference ($p=0.0441$) in the moderately emetogenic stratum was observed between treatment groups in the delayed phase CR in subjects who had prior chemotherapy. There were no significant differences between treatment groups in any other phase. In the delayed phase the percentage of subjects who experienced CR was significantly higher ($p=0.0262$) among subjects in the moderately emetogenic stratum who received 10 mg APF530 and had prior chemo-therapy than among the subjects who did not have prior chemotherapy. The percentage of subjects with CR was also higher in the 10 mg APF530 dose group than in the Aloxi group in subjects who had received prior chemotherapy, for both the acute and delayed-onset phase in each emetogenic stratum. All other within treatment comparisons were not significant.

Table 13: Summary of Complete Response in Subjects in the MEC (b) (4) Strata by Hx of Prior Chemotherapy During the Acute-onset and Delayed-onset Phases in Cycle 1 (mITT Population)

Emetogenicity Level	Prior Chemotherapy Group	Treatment		
		APF530 5 mg	APF530 10 mg	Aloxi 0.25 mg
Moderate	CR during acute-onset phase			
	Prior chemotherapy	n 101	105	102
		n (%) 74 (73.3)	84 (80.0)	75 (73.5)
	No prior chemotherapy	n 113	107	106
		n (%) 86 (76.1)	79 (73.8)	81 (76.4)
	<i>P</i> -value prior vs no prior ^a	0.6403	0.3297	0.6354
CR during delayed-onset phase	CR during delayed-onset phase			
	Prior chemotherapy	n 101	105	102
		n (%) 50 (49.5) ^b	70 (66.7) ^b	58 (56.9) ^b
	No prior chemotherapy	n 113	107	106
		n (%) 60 (53.1)	55 (51.4)	62 (58.5)
	<i>P</i> -value prior vs no prior ^a	0.6813	0.0262	0.8885



Source: Applicant's table

Chemotherapeutic regimen during Cycle 1:

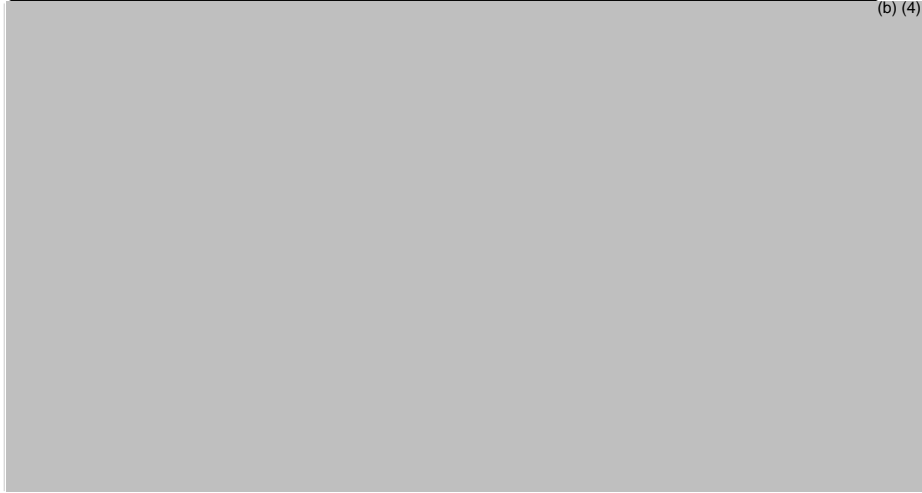
The Applicant reported a significant effect of chemotherapeutic regimen on CR in subjects in the moderately emetogenic stratum, with all other regimens showing greater CR than the cyclophosphamide/doxorubicin regimen in the 10 mg APF530 and Aloxi groups during the acute phase ($p < 0.0220$) and all other regimens showing greater CR than the cyclophosphamide/doxorubicin regimen in the 5 mg APF530, 10 mg APF530, and Aloxi groups during the delayed phase ($p < 0.0055$). (b) (4)



There were no significant differences observed between either APF530 dose groups.

Table 14: Summary of Complete Response in Subjects in the MEC (b) (4) Strata by Chemotherapeutic Regimen During the Acute-onset and Delayed-onset Phases in Cycle 1 (mITT Population)

Emetogenicity Level	Chemotherapeutic Regimen		Treatment			
			APF530 5 mg	APF530 10 mg	Aloxi 0.25 mg	
Moderate	CR during acute-onset phase					
	Cyclophosphamide/doxorubicin	n	125	116	108	
		n (%)	88 (70.4)	82 (70.7)	71 (65.7)	
	All other regimens	n	89	96	100	
		n (%)	72 (80.9)	81 (84.4)	85 (85.0)	
	<i>P</i> -value D/C vs all other regimens ^a			0.1099	0.0220	0.0014
	CR during delayed-onset phase					
	Cyclophosphamide/doxorubicin	n	125	116	108	
		n (%)	54 (43.2)	55 (47.4)	50 (46.3)	
	All other regimens	n	89	96	100	
	n (%)	56 (62.9)	70 (72.9)	70 (70.0)		
<i>P</i> -value D/C vs all other regimens ^a			0.0055	0.0002	0.0007	



Source: Applicant's table

Gender:

Overall, males showed a numerically higher CR in both acute and delayed (b) (4)

Age:

Overall, the older population showed numerically higher CR in both acute and delayed (b) (4)

Table 15: Summary of Complete Response in Subjects in the MEC (b) (4) Strata by Gender During the Acute-onset and Delayed-onset Phases in Cycle 1 (mITT Population)

Emetogenicity Level	Gender	Treatment			
		APF530 5 mg	APF530 10 mg	Aloxi 0.25 mg	
Moderate	CR during acute-onset phase				
	Female	n	189	177	177
		n (%)	138 (73.0)	132 (74.6)	130 (73.4)
	Male	n	25	35	31
		n (%)	22 (88.0)	31 (88.6)	26 (83.9)
	<i>P</i> -value female vs male [#]		0.1416	0.0817	0.2656
CR during delayed-onset phase					
Female	n	189	177	177	
	n (%)	91 (48.1)	95 (53.7)	97 (54.8)	
Male	n	25	35	31	
	n (%)	19 (76.0)	30 (85.7)	23 (74.2)	
<i>P</i> -value female vs male [#]		0.0103	0.0003	0.0498	

(b) (4)

Source: Applicant's table

Table 16: Summary of Complete Response in Subjects in the MEC (b) (4) Strata by Age during the Acute-onset and Delayed-onset Phases in Cycle 1 (mITT Population)

Emetogenicity Level	Age	Treatment			
		APF530 5 mg	APF530 10 mg	Aloxi 0.25 mg	
Moderate	CR during acute-onset phase				
	<65 years	n	162	160	149
		n (%)	117 (72.2)	121 (75.6)	107 (71.8)
	≥65 years	n	52	52	59
		n (%)	43 (82.7)	42 (80.8)	49 (83.1)
		P-value <65 years vs ≥65 years ^a	0.1458	0.5704	0.1106
Moderate	CR during delayed-onset phase				
	<65 years	n	162	160	149
		n (%)	75 (46.3)	92 (57.5)	76 (51.0)
	≥65 years	n	52	52	59
		n (%)	35 (67.3)	33 (63.5)	44 (74.6)
		P-value <65 years vs ≥65 years ^a	0.0105	0.5174	0.0019



Source: Applicant's table

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The Applicant selected two doses of APF530, 250 mg and 500 mg (5 mg and 10 mg granisetron, respectively), for evaluation in the Phase 3 trial (C2006-01) on the basis of prior clinical experience (PK data found in the Phase 1 and Phase 2 clinical trials).

The maximum dose of S.C. APF530 tested in the Phase I trial C2004-01 was 1 g (20 mg granisetron), which is equivalent to approximately 286 µg/kg for a 70 kg subject. The Applicant stated that this dose was selected on the grounds that doses of up to 300 µg/kg I.V. granisetron had been well tolerated in previous clinical trials. The Applicant reports that this dose level was also supported by the toxicology data. In rats and dogs, there was no evidence of systemic toxicity following administration of APF530, with maximum doses of granisetron of approximately 80 mg/kg and 8 mg/kg, respectively.

A range of dose levels up to the maximum of 1 g (20 mg granisetron) were evaluated in the Phase I and Phase II studies. All dose levels were reportedly well tolerated, and exploratory efficacy measures in the Phase II trial C2005-01 indicated that the 250 mg (5 mg granisetron) and 500 mg APF530 (10 mg granisetron) doses were more efficacious than the higher dose level (750 mg; 15 mg granisetron).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

NA

6.1.10 Additional Efficacy Issues/Analyses

There is concern with the significant protocol violations identified by the DSI Investigation (giving an excluded drug, methylprednisolone at the beginning of chemotherapy treatment) in 49 subjects out of a total of 86 subjects at site 03 (trial-C2006-01-Phase 3) in the US. This site enrolled 86 subjects (11 subjects were discontinued because of death, lost to follow-up or subject decision) and the trial lasted 1.5 years. See Section 3.2 and DSI consult for additional information.

7 Review of Safety

Safety Summary

Overall, the safety of APF530 S.C. injection in the prevention of nausea and vomiting in adult cancer patients who received either HEC or MEC has not been adequately demonstrated. Administration site reactions such as, bruising, nodules, erythema, pain and, hemorrhage are primary concerns in the review of this Application. The critical question that remains is whether administration site reactions are due to the use of a 1 inch 16-gauge needle for subcutaneous injections, the injection technique, or the study medication. The Applicant will need to provide additional data related to drug packaging/product kit/labeling and drug administration to assess these issues.

No deaths related to the study drug were reported by the Applicant. While a significant number of Serious Adverse Events (SAEs) were reported by the Applicant, it is possible that in this patient population SAEs may be related to the disease itself and/or complications of chemotherapeutic drugs.

In addition to administration site reactions, other observed AEs, such as constipation, diarrhea and headache, were similar to adverse events reported in other granisetron formulations. The percentage of subjects who experienced certain AEs (i.e. constipation and diarrhea) was higher though in the APF530 groups compared to the Kytril I.V. label.

The Applicant's request for a waiver of a thorough QT trial should be denied. Because of the trial design, the PK/ECG sub-trial in trial C2006-01 was inadequate to assess the effects of APF530 on QTcF.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Applicant submitted the Summary of Clinical Safety as the narrative portion of the Integrated Safety Summary (ISS). The Applicant's rationale was based on their interpretation of the *Guidance for Industry – Integrated Summaries of Effectiveness and Safety Location Within the Common Technical Document* (June 2007), since the majority of the subjects, 92.9% are in one trial (C2006-01). The Applicant stated that based on the Guidance, the summary of clinical safety is sufficiently detailed to serve as the narrative portion of the ISS, but is still concise enough to meet the suggested size limitations for Module 2, the Summary of Clinical Safety. Therefore, the Applicant submitted the Summary of Clinical Safety as the narrative of the ISS.

Safety data were reviewed from four (4) clinical trials, C2004-01 (phase 1 healthy subjects), C2005-01 (phase 2 ascending dose and PK trial), C2006-01 (phase 3 pivotal trial) and C2007-01 (phase 2 PK trial) submitted by the Applicant. The majority of the data though is supplied from trial C2006-01 which contributed 92.9% of subjects to the integrated safety database.

A total of 1038 subjects received APF530. Of this number, all but 25 received the dosage regimens used in the pivotal C2006-01 trial (250 mg APF530 or 500 mg APF530). The remaining subjects received doses of 125 mg, 750 mg or 1 g. The Applicant combined the 6 subjects who received the 125 mg dose into the 250 mg treatment group and the 19 subjects who received a dose higher than 500 mg into the 500 mg treatment group. This was based on the assumption that a subject who had a clinical or laboratory abnormality at 125 mg would be likely to experience the same AE at 250 mg. Regarding the subjects who received doses of 750 mg and 1 gm, the Applicant believed this would be a conservative approach, as a subject who experienced an AE at 750 mg or 1 gm might not have experienced that AE at a lower dose level.

For trials C2006-01 and C2007-01, dose levels of APF530 were described in terms of granisetron content. In trials C2004-01 and C2005-01, dose levels were described in terms of the total quantity of the APF530 formulation administered. Doses described as 250 mg, 500 mg, 750 mg and 1 gm APF530 in studies C2004-01 and C2005-01 were described as 5 mg, 10 mg, 15 mg, and 20 mg APF530 in trials C2006-01 and C2007-01.

7.1.2 Categorization of Adverse Events

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

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

Safety data was pooled from all 4 clinical trials. Trial C2006-01 was the only trial to use multiple doses of APF530 up to 4 cycles of chemotherapy and therefore is the only data source for the Cycle 2 to 4 analysis.

7.2 Adequacy of Safety Assessments

The database is sufficiently large to allow for adequate assessment of the safety profile of APF530. Although the assessment for these events has been adequate, there is limited data to allow for detection of adverse events that are rare. Adverse events that require a long duration exposure to occur are unlikely to be captured since the subcutaneous formulation is intended for limited use.

The Applicant reports that all patients who received a dose of the study medication were included in the safety analysis population.

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

The demographic make-up was adequate. There were no major demographic differences between treatment groups.

Table 17: Baseline Demographics – Safety Population – Pooled Dosage Regimens
 Emetogenic Status: Moderately/Highly/Non-exposed Combined

Variable	APF530 ≤ 250 mg (N=512)	APF530 ≥ 500 mg (N=526)	Aloxi (N=463)
Gender (N [%])			
Male	131 (25.6)	149 (28.3)	119 (25.7)
Female	381 (74.4)	377 (71.7)	344 (74.3)
Age (years)			
Mean	55.9	55.8	57.7
Median	56.0	55.5	59.0
SD	13.66	13.30	13.05
Range	18-87	20-91	22-85
Ethnic group (N [%])			
White or Caucasian	308 (60.2)	330 (62.7)	293 (63.3)
Black or African American	31 (6.1)	37 (7.0)	34 (7.3)
Native Hawaiian/Other Pacific Islander	5 (1.0)	4 (0.8)	3 (0.6)
American Indian/Alaskan Native	1 (0.2)	0	0
Hispanic or Latino	34 (6.6)	25 (4.8)	26 (5.6)
Asian	130 (25.4)	128 (24.3)	107 (23.1)
Other	3 (0.6)	2 (0.4)	0
Country (N [%])			
USA	318 (62.1)	333 (63.3)	307 (66.3)
India	111 (21.7)	118 (22.4)	97 (21.0)
Poland	69 (13.5)	63 (12.0)	59 (12.7)
UK	14 (2.7)	12 (2.3)	0

Source: Modified Applicant's table

7.2.2 Explorations for Dose Response

Assessment of dose response within each strata was adequate.

7.2.3 Special Animal and/or In Vitro Testing

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

7.2.4 Routine Clinical Testing

The protocol defined clinical testing and safety assessments were adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

The clinical pharmacology data submitted by the Applicant was considered adequate by the Clinical Pharmacology reviewer. CYP1A1 is the major enzyme responsible for the

metabolism of granisetron via a main 7- hydroxylation pathway and an alternative 9'-demethylation route.

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

Adverse events of particular concern for granisetron S.C. include the following: 1) constipation and 2) administration site reactions. Other than the administration site reaction concerns, which are inherent to the new formulation, the adverse event profile of granisetron S.C. is similar to other granisetron formulations per their labels.

7.3 Major Safety Results

7.3.1 Deaths

The Applicant reported a total of 34 deaths during the four APF530 clinical trials. No deaths occurred in trial C2004-01 (healthy subjects) or trial C2007-01. The Applicant did not consider any of the deaths as possibly, probably or definitely related to the study drug. The Applicant considered that there was no relationship with the study drug in 30 cases and that “a relationship with the study drug was improbable in the remaining 4 cases.” The Applicant reported that a total of 13 subjects died during Cycle 1, while 7, 8 and 6 subjects died during Cycles 2, 3, and 4 respectively. Of the 13 subjects who died during Cycle 1, 8 received 250 mg APF530 (5 mg granisetron), 3 received 500 mg APF530 (10 mg granisetron) and 2 received Aloxi. Of the 34 subjects who died across all Cycles combined, 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 and 6 had received Aloxi then 500 mg APF530. No subjects who received APF530 doses higher than 500 mg died.

Table 18: Deaths in Clinical Trials of APF530

Patient number/Cycle of Death	Preferred term	Relationship
Trial C2006-01		
APF530 (250) 5 mg		
003030/Cycle 2	Pneumonia Resp Failure	None None
003040/Cycle 1	Resp Failure	None
003084/Cycle 2	Pneumonia	None
032002/Cycle 1	Breast Ca metastatic	None
034003/Cycle 1	Sudden Death	None
034016/Cycle 1	Multi-organ failure	None
036029/Cycle 1	Dehydration Thrombocytopenia Dermatitis	Improbable Improbable Improbable
049015/Cycle 4	Resp Failure	None

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058005/Cycle 1	Sepsis	None
078012/Cycle 3	Pneumonia	None
512003/Cycle 2	Dyspnea	None
702014/Cycle 1	Cardio-pulmonary arrest	None
708015/Cycle 2	Respiratory failure	None
APF530 (500) 10 mg		
001030/Cycle 3	Multi-organ failure	None
003080/Cycle 1	Respiratory failure	None
010019/Cycle 1	Myocardial infarction	Improbable
034013/Cycle 2	Acute myocardial infarction Cardiac arrest	None None
049049/Cycle 3	Pneumonia	None
049072/Cycle 3	Febrile Neutropenia	None
066005/Cycle 3	Cardio-respiratory arrest	None
500083/Cycle 2	Malignant neoplasm progression	
Aloxi 0.25 mg		
007008/Cycle 1	Septic Shock	None
505007/Cycle 1	Sepsis	None
Aloxi – APF530 (250) 5 mg		
003035/Cycle 2	Sepsis	None
005012/Cycle 4	Staphylococcal Infection Respiratory Failure	None None
049032/Cycle 4	Sudden Death	None
Aloxi – APF530 (500) 10 mg		
500029/Cycle 3	Esophageal Carcinoma Recurrent	None
016005/Cycle 4	Sepsis	None
044004/Cycle 4	Respiratory Failure	None
058002/Cycle 3	Death	None
060008/Cycle 3	Dehydration Bladder Cancer	None None
078026/Cycle 4	Malignant Neoplasm Progression	None
Trial C2005-01		
APF530 (500) 10 mg		
00611/Cycle 1	Pyrexia	None

Medical Reviewer's comments: While the Applicant reported a total of 34 deaths during the four APF530 clinical studies, only 33 deaths are identified by the Reviewer. A total of 12 subjects died during Cycle 1, while 7, 8 and 6 subjects died during Cycles 2, 3, and 4 respectively. Of the 12 subjects who died during Cycle 1, 7 received 250 mg APF530 (5 mg granisetron), 3 received 500 mg APF530 (10 mg granisetron) and 2 received Aloxi. Of the 33 subjects who died across all Cycles combined, 14 had received 250 mg APF530 (5 mg granisetron) only, 8 had received 500 mg APF530 (10 mg granisetron) only, 2 had received Aloxi only, 3 had received Aloxi then 250 mg APF530 and 6 had received Aloxi then 500 mg APF530.

There were no deaths attributed to APF530. The Applicant states that in this patient population it is very likely that death may be related to the disease itself and/or complications of chemotherapeutic drugs and this Reviewer agrees.

7.3.2 Nonfatal Serious Adverse Events (SAE)

In Cycle 1, 44 subjects (8.6%) who received ≤ 250 mg APF530, 41 (7.8%) who received ≥ 500 mg APF530 and 27 (5.8%) who received Aloxi experienced at least one treatment emergent SAE. In Cycles 2 to 4, 61 subjects (11.6%) who received ≤ 250 mg APF530 and 73 (14.2%) who received ≥ 500 mg APF530 had at least one treatment emergent SAE. Across all cycles combined, 99 subjects (14.5%) who received ≤ 250 mg APF530 and 109 (15.6%) who received ≥ 500 mg APF530 had at least one treatment emergent SAE. No subject who received APF530 doses higher than 500 mg had an SAE.

The only treatment emergent SAE to occur in $\geq 1\%$ of subjects in any treatment group during Cycle 1 was febrile neutropenia, which occurred in 2 subjects (0.4%) in the ≤ 250 mg APF530 group, 7 subjects (1.3%) in the ≥ 500 mg APF530 group and 3 subjects (0.6%) in the Aloxi group.

In Cycles 2 to 4, febrile neutropenia occurred in 5 subjects (0.9%) in the ≤ 250 mg APF530 group and 8 (1.6%) in the ≥ 500 mg APF530 group, anemia occurred in 6 subjects (1.1%) in the ≤ 250 mg APF530 group and 2 (0.4%) in the ≥ 500 mg APF530 group, neutropenia occurred in 2 subjects (0.4%) in the ≤ 250 mg APF530 group and 6 (1.2%) in the ≥ 500 mg APF530 group, pneumonia occurred in 7 subjects (1.3%) in the ≤ 250 mg APF530 group and 4 (0.8%) in the ≥ 500 mg APF530 group, dehydration occurred in 4 subjects (0.8%) in the ≤ 250 mg APF530 group and 6 (1.2%) in the ≥ 500 mg APF530 group and pulmonary embolism occurred in no subjects in the ≤ 250 mg APF530 group and 6 (1.2%) in the ≥ 500 mg APF530 group. No other treatment-emergent SAE occurred in more than 1% of subjects in any treatment group during Cycles 2 to 4.

In all Cycles combined (Cycles 1 to 4), febrile neutropenia occurred in 7 subjects (1.0%) in the ≤ 250 mg APF530 group and in 15 subjects (2.1%) in the ≥ 500 mg APF530, anemia occurred in 9 subjects (1.3%) in the ≤ 250 mg APF530 group and in 3 subjects (0.4%) in the ≥ 500 mg APF530 group, neutropenia occurred in 4 subjects (0.6%) in the ≤ 250 mg APF530 group and in 7 subjects (1.0%) in the ≥ 500 mg APF530 group, vomiting occurred in 2 subjects (0.3%) in the ≤ 250 mg APF530 group and in 7 subjects (1.0%) in the ≥ 500 mg APF530 group, pneumonia occurred in 7 subjects in the ≤ 250 mg APF530 group and 5 subjects (0.7%) in the ≥ 500 mg APF530 group, dehydration occurred in 5 subjects (0.7%) in the ≤ 250 mg APF530 group and in 8 subjects (1.1%) in the ≥ 500 mg APF530 group, and pulmonary embolism occurred in 1 subject (0.1%) in the ≤ 250 mg APF530 group and in 7 subjects (1.0%) in the ≥ 500 mg APF530 group

The Applicant reported that one SAE was reported as related to the study drug during the course of the APF530 clinical development program: Subject 016004 in trial C2006-01, (a 75-year old female who had received 250 mg APF530) had a pulmonary embolism during Cycle 1 on Trial Day 16, for which she was hospitalized. This was considered by the investigator to be possibly related to study drug, but considered by the medical monitor to be unrelated.

Medical Reviewer' comments: After review of narratives of the SAE, the medical reviewer identified SAEs whose relationship to the study drug differed from that of the Applicant and may be related to the study drug based on known AEs associated with granisetron and the timing of the SAE.

Subject (b) (6) in trial C2006-01, (a 49-year old female who had received 250 mg APF530) had an injection site hemorrhage during Cycle 1 on Trial Day 1. The subject was in the oncology office and at approximately 1 p.m. study drug was administered subcutaneously. Subject experienced bleeding from injection site. A pressure dressing was applied for five hours. Subject was seen by the surgical oncologist. The pressure dressing was changed and an abdominal binder was applied. PT/PTT was drawn and within normal limits. Subject was discharged home in stable condition with instructions to proceed to the emergency room if bleeding continued. At 1 a.m., subject presented to the emergency room with bleeding from the injection site. Brisk active oozing from the puncture site was noted. Oxidized cellulose was applied to the area, as was pressure and the bleeding stopped. Steri-strips were applied to hold the Surgicel in place. There was no further bleeding and the subject was discharged home.

Subject (b) (6) in trial C2006-01, (a 37-year old female, being treated for adenocarcinoma of the right breast who had received 250 mg APF530) had severe constipation. Subject received study drug on (b) (6) (Cycle 1; Day 1) and SAE start date was 15 May 2007 and SAE end date was (b) (6). The Subject presented to the oncology office and reported that she did not have a bowel movement for twelve days with associated bloating, abdominal pain, and nausea. Subject was admitted to the hospital and noted also to have dehydration, neutropenia, pain in the right chest wall at the mastectomy site and low-grade fever. A kidney, ureters and bladder single view x-ray was performed and revealed nonspecific increased density at L5 and constipation. She was treated with multiple laxatives having several bowel movements over the next three days. She was treated with levofloxacin and vancomycin hydrochloride for the neutropenia. Subject also complained of back pain and lumbosacral spine films were obtained which were essentially normal. By (b) (6), she felt much improved. She had no further pain, was afebrile and the white cell count was normal. Subject was discharged home on (b) (6). The subject was discontinued from study drug due to this event. The Subject completed the trial on 12 June 2007 when she had her 30 day follow-up visit.

7.3.3 Dropouts and/or Discontinuations

In Cycle 1, 14 subjects (2.7%) who received ≤ 250 mg APF530, 16 (3.0%) who received ≥ 500 mg APF530 and 7 (1.5%) who received Aloxi experienced treatment-emergent AEs associated with premature discontinuation of trial participation.

In Cycles 2 to 4, 22 subjects (4.2%) who received ≤ 250 mg APF530 and 25 (4.9%) who received ≥ 500 mg APF530 experienced treatment-emergent AEs associated with premature discontinuation of trial participation. Across all cycles combined, a total of 36 subjects (5.3%) who received ≤ 250 mg APF530 and 41 (5.9%) who received ≥ 500 mg APF530 experienced treatment-emergent AEs associated with premature discontinuation of trial participation. Four subjects withdrew from the trial due to AEs that were considered by the investigator to be related to study drug. One subject ((b) (6)), who received Aloxi in Cycle 1 followed by 500 mg APF530 in Cycle 2, experienced an injection site reaction, which was considered by the investigator to be definitely related to study drug. One subject ((b) (6)), who received 250 mg APF530 only, experienced dyspepsia, which was considered by the investigator to be possibly related to study drug. Two subjects, who received 500 mg APF530 only, discontinued after experiencing AEs that were considered by the investigator to be possibly related to study drug (drug hypersensitivity, subject (b) (6); and vomiting, subject (b) (6)).

Medical Reviewer's comments: In Cycle 1, subject disposition was similar between the two APF530 groups (2.7% and 3.0%), but lower in the active comparator, Aloxi, group (1.5%). In Cycles 2 to 4, subject disposition was also similar between the two treatment groups.

7.3.4 Significant Adverse Events

In Cycle 1, 27.3-31.9% of APF530 subjects and 16.8% of Aloxi subjects experienced at least one mild related AE, while 5.3% - 5.9% of APF530 subjects and 2.6% of Aloxi subjects experienced at least one moderate related AE and 0.8%-1.1% of APF530 subjects and 1.1% of Aloxi subjects experienced at least one severe related AE.

In Cycles 2 to 4, 35.8% - 37.5% of subjects experienced at least one mild related AE, while 6.6%-7.4% experienced at least one moderate related AE and 0.8%-1.1% experienced at least one severe related AE. Across all cycles combined, 38.2%-40.0% of subjects experienced at least one mild related AE, while 8.6%-8.7% experienced at least one moderate related AE and 1.1%-1.3% experienced at least one severe related AE.

In all cycles combined, severe, related AEs in more than one subject who received APF530 included constipation (3 ≤ 250 mg APF530 subjects, 2 ≥ 500 mg APF530

subjects), headache (2 ≤ 250 mg APF530 subjects, 1 ≥ 500 mg APF530 subject), and pain (2 ≥ 500 mg APF530 subjects).

Table 19: Total Number of Subjects with Adverse Events by Severity and Relatedness

Cycle	Severity	≤250 mg APF530 [N (pct)]		≥500 mg APF530 [N (pct)]		Aloxi® [N (pct)]	
		Related	Not Related	Related	Not Related	Related	Not Related
Cycle 1	Mild	140 (27.3)	286 (55.9)	168 (31.9)	313 (59.5)	78 (16.8)	274 (59.2)
	Moderate	27 (5.3)	161 (31.4)	31 (5.9)	158 (30.0)	12 (2.6)	142 (30.7)
	Severe	4 (0.8)	72 (14.1)	6 (1.1)	65 (12.4)	5 (1.1)	51 (11.0)
	Unknown	1 (0.2)	0	0	0	0	0
Cycles 2-4	Mild	189 (35.8)	379 (71.8)	193 (37.5)	368 (71.5)	N/A	N/A
	Moderate	35 (6.6)	249 (47.2)	38 (7.4)	244 (47.4)	N/A	N/A
	Severe	6 (1.1)	110 (20.8)	4 (0.8)	109 (21.2)	N/A	N/A
	Unknown	0	1 (0.2)	1 (0.2)	1 (0.2)	N/A	N/A
All cycles combined	Mild	261 (38.2)	484 (70.8)	280 (40.0)	499 (71.3)	N/A	N/A
	Moderate	59 (8.6)	341 (49.9)	61 (8.7)	333 (47.6)	N/A	N/A
	Severe	9 (1.3)	168 (24.6)	8 (1.1)	160 (22.9)	N/A	N/A
	Unknown	1 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	N/A	N/A

Source: Applicant's table, Summary of Clinical Safety

7.3.5 Submission Specific Primary Safety Concerns

The AE profile of other formulations of granisetron is well documented. For this new formulation, which is designed to maintain a sustained plasma concentration of granisetron for up to 120 hours after S.C. injection, administration site reactions are a specific safety concern.

The site for the subcutaneous injection of the study drug was in the lower abdomen. A local anesthetic was applied to the injection site area prior to the study drug's administration. The study drug was subcutaneously injected using a prepackaged 16 Gauge (G) x 1 inch needle. The sponsor stated that a 16G x 1" needle was required due to the study drug's viscosity.

Administration site reactions were among the most common AEs reported across all treatment groups, and the incidence of administration site reactions was higher in the APF530 groups than in the Aloxi group. The injection site reactions were generally considered by the investigator to be related to the study drug. Administration site AEs were monitored in all 4 clinical trials

In Cycle 1, treatment emergent general and administration site AEs were reported for 240 subjects (46.9%) who received ≤ 250 mg APF530, 259 subjects (49.2%) who received ≥ 500 mg APF530 and 170 subjects (36.7%) who received Aloxi. Across all cycles, 424 subjects (62.0%) who received ≤ 250 mg APF530 and 444 (63.4%) who received ≥ 500 mg APF530 experienced treatment emergent general and administration site AEs.

The most common administration site reactions were: nodules, bruising, erythema, pain and hemorrhage. Injection site bruising was the most common AE reported in both the, ≤ 250 mg APF530 and ≥ 500 mg APF530 groups (16.4% - 18.4% of subjects in Cycle 1). Injection site erythema was reported in both APF530 groups (9.2% - 11.6% of subjects in Cycle 1). Injection site nodules were reported in both groups (4.5%, - 9.9% of subjects) and injection site pain was reported in both groups (4.5% - 8.2% of subjects) in Cycle 1. The ≥ 500 mg APF530 group reported more injection site nodules than the ≤ 250 mg APF530 group. This difference was not observed with respect to the other injection site reactions. Injection site nodule was also reported markedly more frequently in females than in males in both the ≤ 250 mg APF530 group (15.4% of females; 2.4% of males) and the ≥ 500 mg APF530 group (29.2% of females; 7.8% of males) in the moderately emetogenic stratum. There was minimal between-gender difference in the highly emetogenic stratum

On Day 1 of Cycle 1, 90.5%-91.0% of APF530 subjects and 92.6% of Aloxi subjects had normal assessments. The remaining subjects had redness (3.5%-4.1% and 2.2%), tenderness/pain (1.0%-1.6% and 0.2%), lump (0.6%-2.4% and 0.2%), bruising (2.7%-2.8% and 2.4%), itching (0 and 0.2%) or other (1.6%-2.5% and 2.4%).

On Day 5 of Cycle 1, 64.7%-74.6% of APF530 subjects and 89.9% of Aloxi subjects had normal assessments. Fewer subjects in the APF530 groups had normal assessments compared to the Aloxi group, and more subjects in the APF530 groups had each of the other assessments. Bruising was the most common abnormal finding, followed by redness, lump, and tenderness/pain, and the incidence of each of these findings was higher in the ≥ 500 mg APF530 group than in the ≤ 250 mg APF530 group. See Table 21

On Day 1 of Cycles 2, 3, and 4, most subjects (91.4%-94.7% across cycles and APF530 dose groups) had normal assessments. The percentage of subjects with normal findings on Day 5 increased from cycle to cycle, though the incidence of normal findings was always significantly lower in the 500 mg APF530 (68.8%-77.0% across cycles) group than in the 250 mg APF530 (76.9%-84.0%) group. The incidence of lump and bruising were both significantly higher in the 500 mg APF530 group than in the 250 mg APF530 group on Day 5 of Cycle 3, and the incidence of lump was significantly higher in the 500 mg APF530 group than in the 250 mg APF530 group on Day 5 of Cycle 4. The incidence of bruising, redness, lump, and tenderness/pain in both groups generally decreased from cycle to cycle.

A total of 1619 administration site reactions were reported as treatment emergent AEs in APF530 subjects (711 in the ≤ 250 mg group and 908 in the ≥ 500 mg group). The Applicant reported that 94.9% - 95.5% of the AEs severities were assessed as being mild. One administration site reaction in each dose treatment group was severe.

Administration site AEs resolved in 93.0% of cases in the ≤ 250 mg APF530 group and 88.9% of cases in the ≥ 500 mg APF530 group. Of the 44 ongoing treatment emergent administration site reactions in the ≤ 250 mg APF530 group, the most commonly reported were: bruising (16/44 [36.4%]), nodule (12/44 [27.3%]), erythema (6/44 [13.6%]), and hemorrhage (6/44 [13.6%]). Of the 99 ongoing treatment emergent administration site reactions in the ≥ 500 mg APF530 group, the most common were: nodule (41/99 [41.4%]), bruising (31/99 [31.3%]), and erythema (14/99 [14.1%]).

The Applicant reported that the time to administration site reaction resolution was not collected by actual resolution date in any of the clinical trials, but was generally collected at a patient visit. The Applicant noted that resolution of nodules could take up to 8 weeks from recorded date of onset in the MEC group as opposed to 3 weeks in the HEC group.

Table 20: Cycle 1 – Injection Site AEs
 Safety Population – Pooled Dosage Regimens

Preferred Term	APF530 ≤ 250 mg (N=512)	APF530 ≥ 500 mg (N=526)	Aloxi (N=463)
% of subjects			
Injection site bruising	16.4	18.4	8.9
Injection site erythema	9.2	11.6	3.0
Injection site nodule	4.5	9.9	0.6
Injection site pain	4.5	8.2	1.1
Injection site hemorrhage	4.3	3.6	2.2

Source: Modified from Applicant's table, ISS

Table 21: Subcutaneous Injection Site Assessment – Cycle 1 -4 - Safety Population
Pooled Dosage Regimen

Cycle	Day	Outcome	APF530 ≤ 250 mg	APF530 ≥ 500 mg	Aloxi
% of subjects					
1	1		N= 487	N= 493	N= 458
		Normal	443 (91.0)	446 (90.5)	424 (92.6)
		Redness	17 (3.5)	20 (4.1)	10 (2.2)
		Tenderness/pain	5 (1.0)	8 (1.6)	1 (0.2)
		Lump	3 (0.6)	12 (2.4)	1 (0.2)
		Bruising	13 (2.7)	14 (2.8)	11 (2.4)
		Itching	0	0	1 (0.2)
		Other	12 (2.5)	8 (1.6)	11 (2.4)
	5		N=481	N= 482	N=451
		Normal	359 (74.6)	312 (64.7)	401 (88.9)
		Redness	29 (6.0)	47 (9.8)	4 (0.9)
		Tenderness/pain	15 (3.1)	34 (7.1)	4 (0.9)
		Lump	20 (4.2)	44 (9.1)	3 (0.7)
		Bruising	80 (16.6)	93 (19.3)	40 (8.9)
		Itching	2 (0.4)	5 (1.0)	0
		Other	14 (2.9)	14 (2.9)	2 (0.4)
2	1		N=527	N=513	2 (0.4)
		Normal	486 (92.2)	469 (91.4)	
		Redness	14 (2.7)	16 (3.1)	
		Tenderness/pain	3 (0.6)	6 (1.2)	
		Lump	2 (0.4)	5 (1.0)	
		Bruising	14 (2.7)	11 (2.1)	
		Itching	0	0	
		Other	10 (1.9)	16 (3.1)	
	5		N=516	N=509	
		Normal	397 (76.9)	363 (71.3)	
		Redness	19 (3.7)	28 (5.5)	
		Tenderness/pain	13 (2.5)	22 (4.3)	
		Lump	27 (5.2)	33 (6.5)	
		Bruising	84 (16.3)	98 (19.3)	
		Itching	2 (0.4)	2 (0.4)	
		Other	8 (1.6)	11 (2.2)	
3	1		N=404	N=390	
		Normal	370 (91.6)	360 (92.3)	
		Redness	11 (2.7)	6 (1.5)	
		Tenderness/pain	1 (0.2)	0	
		Lump	4 (1.0)	4 (1.0)	
		Bruising	10 (2.5)	14 (3.6)	
		Itching	0	0	
		Other	14 (3.5)	8 (2.1)	
	5		N=400	N=385	
		Normal	317 (79.3)	265 (68.8)	
		Redness	20 (5.0)	19 (4.9)	
		Tenderness/pain	9 (2.3)	13 (3.4)	

		Lump	20 (5.0)	38 (9.9)	
		Bruising	53 (13.3)	72 (18.7)	
		Itching	0	3 (0.8)	
		Other	7 (1.8)	16 (4.2)	
4	1		N=300	N=289	
		Normal	284 (94.7)	268 (92.7)	
		Redness	4 (1.3)	1 (0.3)	
		Tenderness/pain	1 (0.3)	1 (0.3)	
		Lump	1 (0.3)	7 (2.4)	
		Bruising	3 (1.0)	8 (2.8)	
		Itching	0	0	
		Other	7 (2.3)	7 (2.4)	
	5		N=294	N=283	
		Normal	247 (84.0)	218 (77.0)	
		Redness	6 (2.0)	10 (3.5)	
		Tenderness/pain	3 (1.0)	6 (2.1)	
		Lump	11 (3.7)	25 (8.8)	
		Bruising	35 (11.9)	43 (15.2)	
		Itching	0	0	
		Other	4 (1.4)	4 (1.4)	

Note: All percentages are based on the number of subjects shown at the top of each column, which is the number of patients with an assessment at the indicated time. Each subject can check off more than one non-normal outcome. Injection site AEs occurring on intervening days or subsequent to day 5 may appear only in the AE tabulations
 Source: Applicant's table, ISS

Medical Reviewer's comments: Administration site reactions were the most common AEs reported across all treatment groups. Administration site reactions in both study drug treatment groups were significantly greater than in the Aloxi treatment group.

While the majority of administration site reactions were reported by the Applicant as mild, safety concerns related to the subcutaneous injection of this novel polymer remain. These include: 1) administration techniques in a non-controlled environment, such as a clinical trial and 2) subcutaneous injections using a much larger gauge and length of needle than is typically used for S.C. injections.

Subcutaneous injections are usually administered into the fatty tissue below the dermis and above the muscle tissue. Generally, the needle gauge and length is 5/8-inch and 23 to 27 gauge needle, not the (b) (4) needle that the Applicant proposes for APF530. (b) (4)

In the clinical trials, staff were well trained and monitored to ensure appropriate injection techniques. In other use, because of the large gauge needle (b) (4) needle length it is very likely that there will be additional administration site reactions related to inappropriate administration of the drug. If APF530 is inadvertently administered either intramuscularly or intravenously, questions are raised about the drug's pharmacokinetics.

It is unclear whether administration site reactions are due to the use of a 1 inch-16-gauge needle, the injection technique, or the study medication.

The Pharmacology Toxicology reviewer noted that the injection site (inflammatory reactions) appeared to be the major target organ in studies in rats and dogs..

Additional safety concerns related to drug packaging/product kit/labeling and administration have been identified by DMEPA (See section 4 (Significant Efficacy/Safety Issues Related to Other Review Disciplines); part 4.5.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Commonly reported AEs in Cycle 1, other than administration site reactions, were: constipation, nausea, fatigue, diarrhea, headache, neutropenia, anemia, asthenia, alopecia, abdominal pain and vomiting. In Cycles 2 to 4 and across all cycles combined, additional common treatment emergent AEs observed included: thrombocytopenia, leukopenia, dyspepsia, dysgeusia, stomatitis, edema peripheral, pyrexia, and pain. The incidence of common AEs, other than administration site reactions, was similar across treatment groups. The most common AE in any treatment group, other than administration site reactions, was constipation.

Table 22: Cycle 1 - Treatment Emergent AEs (≥ 3%)
Safety Population – Pooled Dosage Regimens

System organ class Preferred term	APF530 ≤ 250 mg (N=512)		APF530 ≥ 500 mg (N=526)		Aloxi 0.25 mg (N=463)	
Number (%) of subjects with at least one AE	377 (73.6)		395 (75.1)		319 (68.9)	
Number (%) of subjects	n	%	n	%	n	%
Blood and lymphatic system disorders						
Neutropenia	40	7.8	52	9.9	40	8.6
Anemia	49	9.6	46	8.7	36	7.8
Thrombocytopenia	20	3.9	20	3.8	13	2.8
Leukopenia	16	3.1	12	2.3	15	3.2
Gastrointestinal disorders						
Constipation	69	13.5	79	15	62	13.4
Nausea	61	11.9	66	12.5	41	8.9
Diarrhea	54	10.5	47	8.9	40	8.6
Abdominal pain	22	4.3	17	3.2	28	6.0
Vomiting	27	5.3	25	4.8	14	3.0
Dyspepsia	17	3.3	18	3.4	16	3.5
Dysgeusia	7	1.4	17	3.2	14	3.0
Hiccups	6	1.2	17	3.2	8	1.7
General disorders and administration site conditions						
Injection site bruising	84	16.4	97	18.4	41	8.9
Fatigue	64	12.5	66	12.5	52	11.2
Injection site erythema	47	9.2	61	11.6	14	3.0
Asthenia	26	5.1	23	4.4	30	6.5
Injection site nodule	23	4.5	52	9.9	3	0.6
Injection site pain	23	4.5	43	8.2	5	1.1
Pyrexia	17	3.3	17	3.2	19	4.1
Injection site hemorrhage	22	4.3	19	3.6	10	2.2
Pain	14	2.7	15	2.9	20	4.3
Metabolism and nutrition disorders						
Decreased appetite	14	2.7	17	3.2	17	3.7
Dehydration	18	3.5	15	2.9	14	3.0
Anorexia	21	4.1	11	2.1	8	1.7
Musculoskeletal and connective tissue disorders						
Bone pain	16	3.1	15	2.9	8	1.7
Nervous system disorders						
Headache	36	7.0	54	10.3	45	9.7
Insomnia	20	3.9	26	4.9	11	2.4
Dizziness	15	2.9	19	3.6	8	1.7
Respiratory, thoracic, and						

mediastinal disorders						
Dyspnea	16	3.1	16	3.0	9	1.9
Cough	11	2.1	11	2.1	14	3.0
Pharyngolaryngeal pain	9	1.8	6	1.1	15	3.2
Skin and subcutaneous tissue disorders						
Alopecia	20	3.9	32	6.1	26	5.6

A subject with more than one event represented by a given Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class)
 Source: Applicant's table, ISS

Medical Reviewer's comments: The incidence of observed AEs were similar among treatment groups. Many of the AEs (such as constipation, abdominal pain, and headache), with the exception of administration site reactions, noted in the above tables, are known to be associated with other formulations of granisetron and Aloxi. The Applicant states that these AEs are known to be associated with chemotherapy and/or with cancer.

The incidence of some of the observed Gastrointestinal AEs, such as constipation and diarrhea were greater in each of the APF530 treatment groups (APF530 constipation – 13.5%-15%; diarrhea – 8.9%-10.5%) and the Aloxi treatment group (Aloxi constipation – 13.4%;, diarrhea – 8.6%) than reported in the innovator Kytril (constipation – 3%; diarrhea – 4%, Kytril I.V. label).

7.4.2 Laboratory Findings

The protocol defined clinical testing and safety assessments were adequate.

Hematology

The Applicant reported the following mean changes from baseline for the following parameters across all treatment groups in safety population (Cycle 1):

There was a decrease in basophils (absolute and percentage), eosinophils (absolute), lymphocytes (absolute), mean corpuscular volume (MCV), monocyte (absolute and percentage), platelets and an increase in mean corpuscular hemoglobin concentration (MCHC).

Statistically significant changes from baseline were reported for the following in the > 500 mg APF530 and Aloxi groups only: A decrease in hemoglobin and hematocrit and an increase in mean corpuscular hemoglobin (MCH).

An increase in neutrophils (absolute) and a decrease in red blood cell count (RBC) were reported in the > 500 mg APF530 group only; and an increase in lymphocytes (percentage) was reported in the Aloxi group only. No significant changes from baseline were reported for eosinophils (percentage), neutrophils (percentage) or white blood cell count (WBC) in any treatment group.

Chemistry

Statistically significant mean changes from baseline were noted for following parameters across all treatment groups: An increase in ALT, serum bicarbonate total bilirubin and blood urea nitrogen. A decrease in albumin, calcium, serum chloride, serum sodium, serum uric acid and total protein. Statistically significant changes from baseline were also noted for serum phosphorus in the ≤ 250 mg APF530 and ≥ 500 mg APF530 groups only; An increase in direct bilirubin and serum glucose were noted in the ≤ 250 mg APF530 group only; and an increase in GGT and triglycerides in the ≥ 500 mg APF530 group only.

7.4.3 Vital Signs

The protocol defined vital sign testing and safety assessments were adequate.

Overall, most subjects (>90%) in each treatment group had no changes in physical examinations over any of the assessment periods and there were no notable differences in the incidence of change between treatment groups.

7.4.4 Electrocardiograms (ECGs)

The protocol defined ECG testing and safety assessments were adequate.

7.4.5 Special Safety Studies/Clinical Trials

Trial C2006-01 had a PK/Holter monitoring sub-trial component.

During Cycle 1, a planned subset of 100 to 130 subjects had 24-hour Holter monitoring with ECG assessments on Days 2 through 5 and blood drawn on Days 1 through 5 for the analysis of plasma granisetron concentration.

The planned subset were to undergo 12-lead ECGs immediately prior to PK blood sampling at approximately 48, 72, 96 and 120 hours post study drug administration in Cycle 1. Additionally, Holter monitoring was to be conducted in the same subjects for approximately 24 hours following study drug administration in Cycle 1 only. All Holter and ECG data in these subjects were evaluated by the central electrocardiography laboratory. Changes in QTcB and QTcF were plotted against mean granisetron concentrations derived from the PK trial.

Among the subjects who were randomized and initiated Cycle 1, 107 entered the PK and ECG monitoring sub-trial. These included:

- 60 subjects in the moderately emetogenic stratum: 27 subjects in the 5 mg APF530 group; 19 subjects in the 10 mg APF530 group; and 14 subjects in the Aloxi group

- 47 subjects in the highly emetogenic stratum: 14 subjects in the 5 mg APF530 group; 18 subjects in the 10 mg APF530 group; and 15 subjects in the Aloxi group.

Two subjects were discontinued from the sub-trial (one died and one discontinued for other reasons).

The Applicant reported that 0-4 subjects across times and treatment groups had either decreases (<50 bpm and >25% change from baseline) or increases in HR (>100 bpm and >25% change from baseline) and no significant differences between treatment groups were noted. One subject across times and treatment groups had a PR interval >200 msec and at least 25% increase from baseline or a QRS interval >100 msec and at least a 25% increase from baseline. No subjects had QT >500 msec and a baseline QT <500 msec, and no more than 1 subject across times and treatment groups had QTcB >500 msec and a baseline QTcB <500 msec or QTcF >500 msec and a baseline QTcF <500 msec. Maximal effects on QT interval were noted at the 12-hour time point. QTcF exceeded 500 msec only once in a subject in the palonosetron group at 8 hours. QTcB exceeded 500 msec in that subject as well as in a subject in the 5 mg APF530 group at 72 hours.

Increases in QTcB >5 msec from baseline were noted in the majority of subjects (72.0% to 82.6% across treatment groups) at the first time point (8 hours) with 30.0% to 39.1% still having a QTcB >5 msec at 120 hours. There were no significant differences between treatment groups on this parameter. Likewise, increases in QTcB >10 msec from baseline were noted in 61.5% to 78.3% of subject at 8 hours and 20.0% to 27.3% at 120 hours. The Applicant reported a significant difference between the 10 mg dose of APF530 and Aloxi was noted at 20 hours (64.7% vs. 27.3%; $p=0.0264$), but not at any other time points.

Similar results were observed for QTcF. QTcF increases >5 msec were noted in 56.0% to 65.4% of subjects at 8 hours and 30.0% to 36.4% at 120 hours and increases >10 msec were apparent in 44.0% to 60.9% of subjects at 8 hours and 18.2% to 21.7% at 120 hours, with no significant differences between treatment groups at any time. Subgroup analysis of QTcB and QTcF showed that more females than males in the APF530 treatment groups had increases of >5 msec in these parameters, but effects of age (<65 or >65 years) were less with fewer subjects in the older group.

For each dose of APF530, the highest mean plasma concentrations of granisetron (9.3 and 11.8 ng/mL, respectively) observed at 22-28 hours and were associated with the increases in mean QTcB (11.4 and 13.3 msec) and QTcF (8.9 and 11.9 msec). At all other time points, mean QTcB and QTcF values were unchanged or decreased from baseline.

There was no reported correlation between peak plasma concentration and peak QTcF changes in any of the three treatment groups. The peak change in QTcF in both APF530 groups was detected at 12 hours, but C_{max} was not detected until the 22-28 hour timepoint, by which time the change in QTcF had fallen considerably. The peak change in QTcF in the Aloxi group was not detected until 12 hours, whereas C_{max} would have occurred immediately after the I.V. injection of Aloxi. Consequently, it is not possible to conclude that the QTcF changes observed were related to the 5HT₃ antagonist employed.

The Applicant cardiology consultant concluded that “Protocol C2006-01 is not ideal for estimation of the effects of APF530 and palonosetron on QTcF because of absence of a control group to elucidate circadian change, unavailability of QTcF and PK data at important time points, incomplete PK data for palonosetron, and the likely contribution of anthracyclines and circadian variation to the observed increase in QTcF. The data suggest that the QT effects of palonosetron and APF 530 10 mg are similar, and that the lower dose of APF530 has a smaller effect on QTcF than the higher dose. However, it is not possible to accurately define the magnitudes of these effects.”

Medical Reviewer’s comments: The inability to correlate the peak plasma concentrations and QTcF changes makes it difficult to determine whether the QTcF changes seen were related to the 5HT₃ antagonists used.

A consult was therefore requested from the QT Interdisciplinary Review Team (IRT) regarding the Applicant’s request for a Thorough QT trial waiver. The QT-IRT noted that QTc prolongation was observed in trial C2006-01 in both the APF530 and Aloxi arms. They did not conduct an independent review of QT results from this trial. A summary of the findings from the QT IRT states that 1) the timing of the QT effects did not correspond to the peak plasma concentrations for APF530 and palonosetron. Peak QT effects occurred around 8 hours after dosing in all arms. Peak palonosetron concentrations occur immediately following I.V. infusion and peak APF530 concentrations occur approximately 24 hours after dosing and 2) Per the protocol for C2006-01, subjects received chemotherapy 30 – 60 minutes after APF530 or palonosetron administration. The QT IRT concluded that QT effects may be confounded by concomitant chemotherapy.”

A tQT trial has not been conducted on the innovator Kytril. APF530 will provide a more prolonged release of granisetron, than the I.V. formulation. A tQT trial should be conducted by the Applicant.

7.4.6 Immunogenicity

The Applicant did not provide any clinical or adverse event data regarding immunogenicity in this NDA.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In Cycle 1, 377 subjects (73.6%) who received $\leq$ 250 mg APF530, 395 (75.1%) who received $\geq$ 500 mg APF530 and 319 (68.9%) who received Aloxi experienced at least one treatment emergent AE. In Cycles 2 to 4, 427 subjects (80.9%) who received $\leq$ 250 mg APF530 and 421 (81.7%) who received $\geq$ 500 mg APF530 experienced at least one treatment-emergent AE. Across all cycles combined, a total of 570 (83.3%) subjects who received $\leq$ 250 mg APF530 and 580 (82.9%) who received $\geq$ 500 mg APF530 experienced at least one treatment-emergent AE.

7.5.2 Time Dependency for Adverse Events

Since APF530 was intended for single administration limited use, evaluation of time dependency was not performed.

7.5.3 Drug-Demographic Interactions

The Applicant presented an overall safety summary of gender and age.

Gender

In the Aloxi group, a higher proportion of females (73.3%) than males (56.3%) experienced treatment-emergent AEs. Similarly, there were also marked between-gender differences in the incidence of mild AEs (67.4% in females; 47.1% in males) and related AEs (20.6% in females; 15.1% in males) in the Aloxi group. Related AEs were reported more frequently in the $\geq$ 500 mg APF530 group (37.1% in females; 29.5% in males). During Cycle 2 to 4, both APF530 dose, treatment-emergent AEs were reported more frequently in females (81.6%-83.0%) than in males (77.7%-78.3%) and related AEs were reported markedly more frequently in females (41.4%-43.5%) than in males (26.1%-28.2%). However, treatment-emergent SAEs were reported more frequently in males (14.6%-18.8%) than in females (10.8%-12.5%), and markedly more males (9.0%-9.7%) than females (2.8%-3.7%) discontinued due to a treatment-emergent AE.

Age

Across all cycles combined, the incidence of treatment-emergent AEs increased with age in the $\geq$ 500 mg APF530 group, from 69.8% in the 18-39 years old subgroup, to 80.9% in the 40-64 years old subgroup and 90.8% in the $\geq$ 65 years old subgroup. However, there was no clear association between age and incidence of treatment-emergent AEs in the $\leq$ 250 mg APF530 group: the incidence was lowest in the 40-64 years old subgroup (81.4%, and 83.6% in the 18-39 year old subgroup and 87.6% in the $\geq$ 65 year old subgroup). The incidence of treatment emergent SAEs increased with age

in both APF530 groups across all cycles combined, from 4.8%-6.0% in the 18-39 years old subgroup, to 12.0%-14.7% in the 40-64 years old subgroup and 22.8%-20.8% in the ≥65 years old subgroup. The incidence of severe treatment-emergent AEs also increased in age in both APF530 groups across all cycles combined, from 12.7%-14.9% in the 18-39 years old subgroup, to 21.2%-24.8% in the 40-64 years old subgroup and 30.1%-30.9% in the ≥65 years old subgroup.

7.5.4 Drug-Disease Interactions

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

7.5.5 Drug-Drug Interactions

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

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Human carcinogenicity studies were not performed. Since the dosing is not considered chronic, the Applicant was not required to submit the final report of the two year rodent carcinogenicity studies with this NDA>

7.6.2 Human Reproduction and Pregnancy Data

The Applicant has not studied APF530 in pregnant or lactating subjects.

7.6.3 Pediatrics and Assessment of Effects on Growth

Safety and effectiveness of APF530 (Sustol) in pediatric patients (under 18 years of age) have not been established. The Applicant has requested a deferral for evaluation of APF530 in the pediatric population ages (b) (4) to 17 (b) (4). This will be evaluated once the Applicant has adequately addressed all safety issues/deficiencies.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

The Applicant states that APF530 will be administered in a controlled setting as a single fixed dose, therefore the Applicant considers overdosage unlikely. The Applicant did not report any cases of drug overdose in the clinical development program.

Granisetron is not considered to have drug abuse potential and therefore, the Applicant did not conduct any trials to investigate the abuse potential.

7.7 Additional Submissions / Safety Issues

None

8 Postmarket Experience

APF530 has not been approved for marketing in any country worldwide.

9 Appendices

9.1 Literature Review/References

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Clinical Review
Karyn L. Berry, MD, MPH
NDA 22-445
Sustol (granisetron)

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9.2 Labeling Recommendations

There are no labeling recommendations this review cycle.

9.3 Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

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

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/s/

KARYN L BERRY
03/03/2010

NANCY C SNOW
03/03/2010

I agree with recommendations of clinical reviewer.