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RESEARCH**

APPLICATION NUMBER:

022445Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA#	022445
Applicant Name	Heron Therapeutics, Inc.
Date of Submission	July 17, 2015
PDUFA Goal Date	January 17, 2016
Proprietary Name / Established (USAN) Name	Sustol extended-release injection, for subcutaneous use granisetron
Dosage Forms / Strength	Injection/ 10 mg/0.4 mL single use
Proposed Indication(s)	(b) (4) NDA 022445/Original 1: in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens. (b) (4)
Action/Recommended Action for NME:	NDA 022445/Original 1: Approval (b) (4)

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Third Cycle: This review serves as the Clinical review for the 3 rd cycle. First and Second Cycle: Karyn Berry, MD/ Ruyi He, MD
Statistical Review	Third Cycle: Yeh-Fong Chen, PhD/Mike Welch, PhD Second Cycle: Freda W. Cooner, PhD/Mike Welch, PhD First Cycle: Wen Jen Chen, PhD/Mike Welch, PhD
Pharmacology Toxicology Review	Tamal K. Chakraborti, Ph.D./ Sushanta Chakder, Ph.D.
CMC Review	Third Cycle: See table that follows
Biopharmaceutics	Second Cycle: Zhengfang Ge, PhD/Moo-Jhong Rhee,

	PhD Second Cycle: Tapash Ghosh, PhD/Angelica Dorantes, PhD
CMC Microbiology Review	Steven P. Donald, MS/Bryan S Riley
Clinical Pharmacology Review	Sandhya K. Apparaju, PhD/ Sue Chi Lee, PhD
CDRH CDRH/ODE/DAGRID	Third cycle: John McMichael/Alan Stevens Second Cycle: Jacqueline S. Ryan Quynh Nhu Nguyen/Ron Kaye
CDTL Review	Third Cycle: This review serves as the CDTL review for this cycle. First and Second Cycles:Ruyi He, MD
DPMH	Amy Taylor, MD, MHS/Hari Sachs, MD/Lynne Yao, MD
OSE/DMEPA	Third Cycle: Matthew Barlow, BSN, RN/Mishale Mistry, PharmD, MPH/Lubna Merchant, PharmD, MS Second Cycle:Teresa McMillan, PharmD/Lubna Merchant, PharmD, MS/Kellie Taylor, PharmD, MPH
QTIRT	Second Cycle review: Janice Brodsky/Qianyu Dang/Jee Lee/Kevin Krudys/Norman Stockbridge
DOP1	Gwynn Ison, MD/Julia Beaver, MD

DPMH=Division of Pediatric and Maternal Health
 OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 DMEPA=Division of Medication Error Prevention and Analysis
 DOP1= Division of Oncology Products-1
 CDTL=Cross-Discipline Team Leader
 CDRH=Center for Devices and Radiological Health
 ODE= Office of Device Evaluation
 DAGRID = Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices
 QTIRT=- QT Interdisciplinary Review Team

Third Cycle Quality Review Team:

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Xavier Ysern, Ph.D.	ONDP/ DNDAPI/ Branch II
Drug Product	Zhengfang Ge, Ph.D.	ONDP /DIVISION II/BRANCH V
Process	Li-Shan Hsieh, Ph.D.	OPF/Division III /Branch VIII
Microbiology	Erika Pfeiler, Ph.D.	OPF/DMA/Branch I
Facility	Tony Wilson	OPF/DIA/Branch III
Biopharmaceutics	Peng(Vincent) Duan, Ph.D.	DB II/ONDP/OPQ
Regulatory Business Process Manager	Truong Quach, Pharm. D.	OPRO/OPQ
Application Technical Lead	Danuta Gromek-Woods, Ph.D.	ONDP /DIVISION II/BRANCH V
Laboratory (OTR)	NA	NA
ORA Lead	Paul Perdue	ORA/OO/OMPTO/DMPTPO/MD TP/
Environmental Assessment (EA)	Zhengfang Ge, Ph.D.	ONDP /DIVISION II/BRANCH V

Division Director Summary Review

1. Introduction

This is the third cycle submission for this 505(b)(2) NDA. The applicant was issued Complete Response (CR) letters at the end of the first and cycle reviews. The second CR letter, dated March 27, 2013, identified the following deficiencies to address prior to approval.

“FACILITY INSPECTIONS

1. During a recent inspection of the (b) (4) A.P. Pharma (Redwood City, CA), and (b) (4) manufacturing facilities for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

CONTAINER/ CLOSURE SYSTEM

2. Your completed human factors validation study (XP-1179-045 Report) did not confirm that users could adequately administer Sustol with the proposed product design and its labeling, including instructions for use. Participants in the study reported difficulty pushing the plunger due to the viscosity of the product. We are concerned that, given the amount of force needed to administer this product, the instructions for use tested in the human factors study will result in administration errors. The instructions required that a health care professional use a single hand to both push the plunger and stabilize the syringe while administering the product. The force required to expel the viscous product from the syringe will make it difficult to maintain the injection in the correct tissue plane with use of a single hand.

You have proposed revised instructions for use that include an alternative technique to administer the product. Therefore, you must conduct additional human factors validation testing to demonstrate that Sustol can be safely and effectively administered with the modified instructions for use. Please see the FDA correspondence dated March 26, 2013, containing our comments on your formative human factors testing and our recommendations on your proposed human factors validation study protocol.

CLINICAL

3. (b) (4)
(b) (4)
Sustol was (b) (4) effective for prevention of both acute and delayed phase nausea and vomiting associated with moderately emetogenic chemotherapy (MEC). The proposed indication should be revised to reflect the populations that will benefit from Sustol in both the acute and delayed phase.

To support this revision, provide the dataset and identify the variables used to determine if a patient was in the “HEC” or “MEC” stratum for randomization in trial C2006-01, the major efficacy trial submitted in this NDA. Please also 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.

PRODUCT QUALITY

4. Your proposed acceptance criteria for the *in vitro* drug release (IVR) test are not adequate. There is a high level of variability for the different lots, especially (b) (4) the IVR profiles. Development of a new IVR method may be necessary to reduce the variability that is currently observed at different time points of the drug release profile of your product. (b) (4)

While we are aware of the complexity of the release of granisetron from this product, the acceptance criteria for the IVR test will be used as a major attribute to control the quality of your product. Therefore, generate new data using new IVR methodology (as appropriate) to set the acceptance criteria of your product. The proposed criteria should also include specification-ranges for the (b) (4) release profile.”

Furthermore, the second cycle CR letter included two “ADDITIONAL COMMENTS”, which the letter stated were “not approvability issues at this time, we request that you address them in your resubmission”. One asked for the timeframe for submission of the final study reports of a two-year carcinogenicity study in the rat and SHE cell assay. FDA had agreed that both could be performed as postmarketing studies. The other was a comment stating that the FDA was considering the need for a postmarketing, randomized, controlled safety trial that evaluates patients who receive Sustol doses as frequently as every 7 days over the course of a year. (The proposed dosage and administration instructions for Sustol allowed for administration every 7 days.) The comment stated this additional safety data may be required because the applicant’s metabolic fate study (C2011-01) had only accounted for approximately 1/3 of the polymer, and the major phase 3 trial (C2006-01) did not include a control arm beyond Cycle 1 that did not receive Sustol, to allow for interpretation of safety data. The FDA noted that this phase 3 trial had also not collected serum chemistries in the subsequent cycles beyond Cycle 1.

In this third submission, the applicant proposes a product presentation that includes a prefilled sterile glass syringe for injection that contains 10 mg granisetron/0.4 mg for single use, a sterile 18 gauge 5/8 inch special thin walled administration needle, two sodium acetate syringe warming pouches, one Point Lok needle protection device, Instructions for Use (IFU) and Package Insert. Efficacy and safety data from a new large phase 3 trial that enrolled patients treated with HEC chemotherapy was submitted for review, but this trial was limited to a single cycle of treatment. (b) (4)

. The applicant

also presented a reassessment of samples from their previously reviewed metabolic fate study, in addition to data from a repeat dosing study in healthy volunteers, in which the subjects were randomized between subcutaneous (SQ) saline injections and Sustol SQ, administered every 7 days. Study C2013-02 included serum chemistry evaluations and had the advantage of not having concomitant chemotherapy to add to background toxicities. These data are intended to address the “additional comments” described above from the second cycle CR letter.

During the current review cycle, the review team found that the majority of the second cycle CR issues had been adequately addressed; [REDACTED] (b) (4)

[REDACTED] The indication will be limited to MEC and a specific type of HEC regimen, i.e., combination anthracycline plus cyclophosphamide chemotherapy (AC).

See Section 3 CMC of this review for information regarding the review of the response to the CR issues related to product quality and facility inspection issues. See Section 8 Safety regarding the review of the human factors issue related to the container/closure system cited in the last CR letter. See Section 7 Clinical/Statistical-Efficacy for a discussion of the applicant’s response to the previously cited clinical review issues.

Please note that this review will also serve as the Clinical and CDTL reviews. I have reviewed a draft review from the Clinical reviewer, in addition to her summary responses to my questions about the NDA safety data.

2. Background

The proposed product is a new dosage form of granisetron, a 5HT3 inhibitor antiemetic that has been marketed in intravenous (IV) and oral formulations as Kytril, and as a transdermal patch called Sancuso. Multiple generics of granisetron are marketed. Sustol is a new formulation of granisetron in a polymer vehicle, intended for subcutaneous injection. It is comprised of granisetron (2%) and the vehicle [REDACTED] (b) (4) which consists primarily of a tri(ethylene glycol) based poly(ortho ester) polymer (TEG-POE) and MPEG [REDACTED] (b) (4). [REDACTED] (b) (4) The polymeric formulation is intended to provide a sustained release of granisetron. The applicant is seeking an indication for prevention of acute and delayed phase chemotherapy induced nausea and vomiting (CINV) associated with highly emetogenic chemotherapy (HEC) and moderately emetogenic chemotherapy (MEC). The currently approved granisetron product CINV indications are summarized in the table below.

Table 1. Approved granisetron products, doses and indications.

	Dose	Indication	Supporting Trials
Granisetron Tablet, 1 mg Oral solution, 2 mg/10 mL	2 mg once daily or 1 mg twice daily	Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high- dose cisplatin. Prevention of nausea and vomiting associated with radiation,	Two MEC studies Two HEC studies Two radiotherapy studies
Granisetron Injection, 1 mg/1 ml in 1 ml single- use and 4 mg multi-use vials 0.1 mg/1 ml in 1 ml single-use vial	10 mcg/kg administered intravenously and infused over 5 minutes	Prevention of nausea and/or vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high- dose cisplatin.	A placebo controlled study with cisplatin A dose response study with cisplatin A dose response study for high and low dose cisplatin Randomized trial in MEC
Granisetron Transdermal Patch	52 cm ² patch containing 34.3 mg of granisetron. The patch releases 3.1 mg of granisetron per 24 h for up to 7 days.	Prevention of nausea and vomiting in patients receiving MEC and/or HEC for up to 5 consecutive days	Single randomized study. Control arm = oral granisetron 2 mg once daily in patients receiving multi-day chemotherapy.

Note that none of the indications include the indication qualifiers “acute phase” or “delayed phase”. However, the oral granisetron product labels state, in the Dosage and Administration section, “Continued treatment, while not on chemotherapy, has not been found to be useful.” This statement indicates that the approved granisetron products have not been shown to be effective in delayed phase CINV. The intravenous (IV) product label states it should be only administered on the day chemotherapy is administered (the efficacy data in the Clinical Studies section is limited to 24 hours). The Sancuso transdermal product label, which provides sustained exposure to granisetron over days, clarifies that the transdermal product is for multiday chemotherapy exposure, i.e., not specifically for delayed phase CINV, but for acute phase CINV associated with daily chemotherapy dosing.

The 5HT3 antagonist drug class is generally associated with CINV acute phase efficacy. The only 5HT3 antagonist product that carries a specific “delayed phase” indication statement in

product labeling is intravenous palonosetron, where the delayed phase indication is limited to moderately emetogenic chemotherapy (MEC). However, it must be noted that the trials conducted to support approval of IV palonosetron for delayed phase MEC enrolled a substantial proportion of patients who were treated with anthracycline + cyclophosphamide chemotherapy (AC), i.e., approximately 60%. *AC has been reclassified from MEC to HEC since the time of palonosetron's approval.* Furthermore, although the product labeling for ondansetron, the first approved 5HT3 antagonist, does not include the words “acute phase” or “delayed phase” in the indication statement, the label’s Clinical Studies section presents two “MEC” trials in which efficacy over 3 days was described. The MEC trials reported in the ondansetron label, *like the MEC trials supporting the delayed phase indication for palonosetron,* included patients who received AC. The ondansetron label only reports 24 hour efficacy for the HEC trials, which were cisplatin based regimens. There are publications in the literature describing clinical trials that evaluated multi-day dosing of ondansetron compared to placebo or active control, and found that ondansetron was superior in the delayed phase for AC chemotherapy (Kaizer, et al. JCO. Vo 12, No5, 1994:1050-1057).

The delayed phase of CINV is generally recognized as a distinct entity from acute phase nausea and vomiting, and is thought to be caused by different mechanism(s). The NK-1 antagonist class was specifically developed to target the delayed phase of CINV. The approval of the only 5HT3 antagonist that carries a delayed phase indication (IV palonosetron) did not occur until after the approval of the first NK1 inhibitor, Emend.

Current Cycle Clinical Review Issues. In the initial Sustol NDA submission, the applicant submitted a single phase 3 trial, Study 2006-01, which enrolled patients treated with moderately or highly emetogenic chemotherapy. The trial was intended to support the applicant’s initial proposed product indication: MEC (acute and delayed) and HEC (acute).

(b) (4)

(b) (4)

During the second review cycle, assessment of the product's role in MEC and HEC was further complicated by the reviewers' questioning the applicant's emetogenicity assignment (MEC vs. HEC categories) of the various other chemotherapy regimens administered in Study 2006-01. In the current resubmission, the applicant has submitted re-analyses of Study 2006-01 efficacy data using revised emetogenicity categorization of individual regimens. These exploratory analyses yielded outcomes that were generally consistent with those observed in the original analyses.

In addition, in the current cycle, the applicant submitted the results of a new randomized, controlled trial (Study 2013-01) intended to establish the delayed phase efficacy of Sustol for HEC. The trial was designed to demonstrate superiority of a combination of Sustol, dexamethasone and Emend vs. IV ondansetron, dexamethasone and Emend (plus placebo polymer vehicle SQ injection). In the latter combination, the ondansetron was administered on Day 1 only (consistent with IV ondansetron labeling for HEC, cisplatin based); however, inconsistent with ondansetron labeling, only a single dose of ondansetron was administered in the trial instead of 3 doses on Day 1, as described in IV ondansetron product labeling ["The recommended adult intravenous dosage of ondansetron is three 0.15 mg/kg doses up to a maximum of 16 mg per dose. The first dose is infused over 15 minutes beginning 30 minutes before the start of emetogenic chemotherapy. Subsequent doses (0.15 mg/kg up to a maximum of 16 mg per dose) are administered 4 and 8 hours after the first dose of ondansetron]. Based on the results of the two phase 3 trials in this application, the applicant initially proposed in this resubmission that Sustol should be indicated for both acute and delayed phases of CINV associated with both MEC and HEC.

(b) (4)

(b) (4)



(b) (4)

the option of approving Sustol for prevention of acute and delayed phase CINV associated with MEC or AC was considered; the indication would be written to specifically identify “AC”, since AC is currently classified as HEC (b) (4)

Such an approval would not be inconsistent with the approval of IV palonosetron for acute and delayed phases of MEC, as the two MEC trials that supported its approval for delayed phase MEC included AC chemotherapy; however, the palonosetron label only specifies “MEC”. (Of note, although the ondansetron label does not have a specific delayed phase indication, the Clinical Studies section includes a description of MEC trials that supported its approval with dosing after the first 24 hours, and those MEC trials enrolled patients receiving AC.)

(b) (4)

(See page 1 of this review, Proposed Indications: NDA 22445/Original 1

(b) (4)

With this labeling approach for Sustol, given the availability of IV single dose palonosetron for MEC acute and delayed phase (based on trials that enrolled patients treated with AC), the safety risks associated with the Sustol, had to be carefully considered in the risk/benefit analysis. The reviewers were particularly concerned about the increase in injection site adverse reactions associated with Sustol in the new trials submitted in this third review cycle, compared to the previous Sustol trials. Although most of the reactions were graded as mild, there was an increase in higher grade events. As evidenced by the injection site reaction grade descriptors utilized in the patient diaries in Study 2013-01, some of these events impacted how patients felt and functioned:

1. Injection site bleeding “mild” grade definition included oozing that lasts for multiple days.
2. Injection site “swelling” of “moderate” grade description included decreased ability to perform daily activities.
3. Injection site pain descriptors for moderate and severe pain indicated these reactions required intervention and impacted ability to function.
 - a. The “moderate” grade of site pain included required treatment with non-narcotic pain medication and/or patient had decreased ability to perform daily activities.
 - b. The severe category of site pain included required treatment with opiates and patient had decreased ability to perform daily activities.

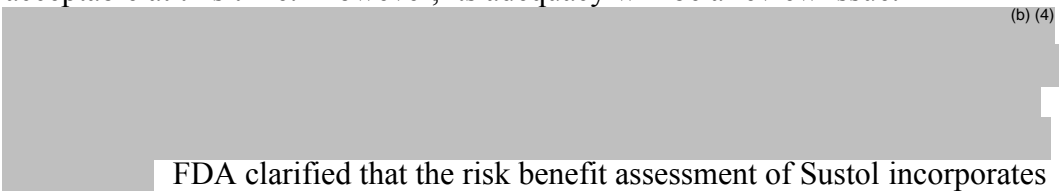
Furthermore, there were injection site infections that required treatment with antibiotics.

Current Cycle CMC/Container Closure System/ Product Presentation Review issues. As noted in Section 1 Introduction, above, container/closure system issues precluded approval in the previous review cycle as the applicant had not established that providers could adequately administer Sustol with the proposed product design and labeling, including instructions for use. There was concern that product viscosity resulted in difficulty pushing the plunger during administration, and that the force necessary to push the product could lead to administration errors due to loss of control, which might result in injection into an unintended tissue compartment. The applicant now proposes inclusion of a warming device in the product presentation to warm the product prior to administration, to decrease the amount of force necessary to deliver the product. Although the CDRH reviewer identified device deficiencies during this review cycle regarding the new presentation, which left unaddressed would have been grounds for CR, the applicant adequately addressed these deficiencies during the current review cycle. See Section 3 CMC and the Human Factors review presented in Section 8 Safety of this review.

Recent Regulatory History. I will briefly summarize here the record of interactions between the applicant and FDA in the interim period since issuance of the 2nd cycle CR letter.

March 27, 2013: Second CR letter issued.

October 30, 2013: Meeting between FDA and AP Pharma Inc. to discuss AP Pharma's plans to address the Container/Closure system and clinical issues cited in the CR letter.

- 1) The FDA agreed that the proposed warmed and prefilled syringe was a combination product, and noted that the warmer is proposed to ensure safety and effectiveness of the combination. The device will be a constituent part of the combination and part of co-packaging. The FDA clarified that the warmer device would not be considered a standalone class-1 exempt device; it would be reviewed under the NDA.
- 2) In response to a question regarding the evidence to support that the warmer resulted in reduction of the force necessary to deliver the product, FDA stated: "It appears from your normative data that the 95th percentile for three point grip among women is 65 N and the lowest peak and average grip forces would be 58N and 42 N, respectively. Heating the syringe to 37 degrees C prior to injection appears to reduce expulsion forces below 20N, which is acceptable. However, your usability study will be critical in determining if the combination product with the syringe warmer results in safe drug administration."
- 3) In response to AP Pharma's request for comments on the Validation and Verification and Use testing for the new product presentation, FDA noted that adequacy of the Validation and Verification depended on the acceptability of performance testing to assure the warmer meets design specifications. With regard to Use Testing, FDA noted that a revised validation protocol to reflect the new product design configuration, which included the warmer pouch, had not been submitted. The FDA stated the protocol should include assessment of critical steps and user tasks associated with use of the warmer pouch and assessment of understanding of the instructions for use (IFU) related to the warmer pouch. There should also be a user-related risk analysis describing the potential negative consequence of use errors and task failures related to the use of the pouch. FDA requested submission of the revised protocol for evaluation. FDA recommended IFU changes to clarify procedures for use of the warmer pouch.
- 4) FDA said the sponsor's reclassification description of the MEC and HEC reclassification in Study C2006, according to ASCO 2011 definitions, "appears to be acceptable."
- 5) FDA said the Study C2006 dataset package for both the Hesketh algorithm emetogenic classification and the ASCO 2011 emetogenic classification "seems acceptable at this time. However, its adequacy will be a review issue."
- 6)  (b) (4)
FDA clarified that the risk benefit assessment of Sustol incorporates the safety issues associated with the route/method of administration.
- 7) AP Pharma asked if the FDA concurred with the drug combination in the control arm and the doses proposed in the phase 3 clinical study protocol. The FDA stated that they were acceptable. Furthermore, the FDA stated the following in a response to a question regarding whether the proposed phase 3 trial would support "demonstration of superiority/activity of APF530 for prevention of CINV in the

delayed phase for patients receiving HEC”: “The protocol design appears adequate....we recommend that your protocol plan for continuing treatment with repeat cycles focusing on safety data, i.e., laboratory, injection site reactions, and refusal to receive repeat dosing.” The sponsor stated that evaluating repeat dosing would be prohibitive in terms of cost and duration of study. FDA responded that they recommend at least 4 cycles to assess a safety concern. The FDA also recommended that instead of the proposed Fischer’s exact test for the primary and secondary efficacy analyses, the Cochran-Mantel-Haenszel (CMH) test stratified by variable be used for these analyses.

- 8) FDA commented on the sponsors’ proposed metabolic fate analysis plan and noted the CR letter clinical comment pertained to lack of safety information beyond the first cycle of treatment in the clinical trials. To address this question, additional clinical data are needed; however, FDA stated these additional clinical safety data could “potentially” be a post-approval requirement. FDA also commented in response to the applicant’s proposal to address metabolic fate: “A near complete recovery of polymer dose and the time course of such recovery would certainly be informative in understanding accumulation potential following multiple weekly injections of Sustol. However, it is possible that the incomplete recovery in study C2011-02 could have been due to inadequate sampling duration (10 days). In addition, your exploratory analyses suggested propionic acid to be a significant breakdown product (theoretical quantitative estimate similar to TEG and PE). However, this metabolite wasn’t identified in your clinical study due to lack of analytical sensitivity. Your plan for assay improvements and reanalyses do not seem to address propionic acid assay. Therefore, reanalysis may not still account for total recovery.”
- 9) The FDA agreed with the proposed timeline for the rat carcinogenicity study and SHE cell assay. (The CR letter had included a comment that a 2-year carcinogenicity study in rats and a SHE cell assay would be required as a postmarketing study.)

December 5, 2013: Meeting between FDA CMC reviewers and AP Pharma Inc. to address CMC issues related to consolidation of the manufacture supply chain sites, product presentation and revised *in vitro* release method. The FDA agreed that CMC data (not clinical bioequivalence studies – (b)(4) site manufacture polymer vs. (b)(4) site manufactured polymer) would be acceptable to qualify the (b)(4) site; however, IVR profile comparison would be required. However, for qualification of the manufacture of bulk drug product at Lifecore, a bioequivalence study would be required to assess for differences from the product manufactured at (b)(4) (which was the source of the clinical trial study product). The original clinical batches were not available for purposes of this comparison, and the FDA reviewers stated that the current stability registration batches manufactured at (b)(4) should be appropriate. The reviewers found AP Pharma’s proposed approach to qualifying a syringe and tip cap from an additional vendor acceptable, with regard to compatibility data and leachables data. AP Pharma asked if the (b)(4) IVR method adequately controlled variability and would be acceptable to set drug product acceptance criteria. The reviewers stated that based on the information provided, the IVR method seemed reasonable if properly

justified and validated. The reviewers stated that the last time point in the (b) (4) IVR should be selected at the point where the mean of the tested units just passes 80%.

December 5, 2013. The applicant submitted a proposal to address the repeat dosing safety issues discussed in the CR letter (in the context of the comment about future post marketing safety) and at the October 30, 2013 meeting. There is no record of review comments going to the applicant regarding this study proposal

January 22, 2014. The applicant submitted their proposed Human Factors Study protocol for comment. The review comments were conveyed to the applicant in a letter dated April 2, 2014.

February 4, 2014. The applicant notified the FDA that the corporation name had changed from AP Pharma to Heron.

3. CMC/Device

I concur with the CMC and CDRH reviewers' recommendations supporting approval of this NDA in this third review cycle. The manufacturing sites have been evaluated and determined to be acceptable.

In the second review cycle, the CMC reviewer found that many of the first review cycle CR issues related to product quality had been adequately addressed, however, Dr. Ge did not recommend approval in her review dated 3/5/2013, for the following three reasons:

- 1) An overall "Acceptable" recommendation had not been issued from the Office of Compliance for all sites
- 2) There was inadequate specification for the drug product due to unresolved in-vitro release testing. (The final Biopharmaceutics review was pending at the time that Dr. Ge filed the 3/5/2013 review.)
- 3) Labeling issues had not been finalized. Labeling was not completed during this review cycle due to continued presence of issues that precluded approval.

The second cycle CR letter contained two deficiencies related to CMC/Biopharmaceutics:

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) A.P. Pharma (Redwood City, CA), and (b) (4) manufacturing facilities for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRODUCT QUALITY

Your proposed acceptance criteria for the *in vitro* drug release (IVR) test are not adequate. There is a high level of variability for the different lots, especially (b) (4) of the IVR profiles. Development of a new IVR method may be necessary to

reduce the variability that is currently observed at different time points of the drug release profile of your product. (b) (4)

While we are aware of the complexity of the release of granisetron from this product, the acceptance criteria for the IVR test will be used as a major attribute to control the quality of your product. Therefore, generate new data using new IVR methodology (as appropriate) to set the acceptance criteria of your product. The proposed criteria should also include specification-ranges for the (b) (4) release profile.

During this review cycle, the manufacturing facility inspections were ultimately found acceptable. The (b) (4) district initially issued a withhold recommendation for (b) (4) the facility responsible for identity release testing of commercial drug product by ¹H-NMR and ¹³C-NMR. However, the firm (b) (4) responded and submitted an amendment to the NDA, which was reviewed and determined to be adequate. The district office determined the firm's responses and corrective actions were adequate. (b) (4)/DIA ultimately recommended approval of this NDA, as all facilities had been evaluated and determined acceptable.

The applicant responded to the IVR deficiency (b) (4)

(b) (4) The FDA accepted the revised proposed IVR specification (b) (4), "pending on the future evaluation of the drug release and stability data once they are available. We strongly recommend the applicant submit these data to the agency for review once they are available." The Biopharmaceutics reviewers recommended approval, stating these additional data could be submitted for review post approval, in the Annual Report. The Biopharmaceutics reviewers and OPQ leadership stated that the request for submission of this information post-approval did not constitute a PMC for the approval letter.

In this resubmission, the applicant proposed a revised granisetron related impurity testing drug product specification of (b) (4)% "Other Individual Impurities", which covered previously identified impurity (b) (4). The CMC reviewer found the proposed revision acceptable because (b) (4)% is consistent with ICH Q3B. The viscosity range was revised, tightening the limit at release, which the CMC reviewer found acceptable. The applicant removed testing for heavy metal in the drug product as the heavy metals are tested and controlled for the drug substance. The CMC reviewer found this acceptable.

In this resubmission, the applicant proposed moving the manufacturing site from (b) (4) to Lifecore Biomedical, and scaled up to (b) (4) kg. Quality control (lot release and stability) were also moved to Lifecore Biomedical (from Heron Therapeutics). This move was the subject of pre-submission meetings with the FDA. The applicant submitted stability study data for batches manufactured at the new site, in accordance with FDA's presubmission meeting recommendations. The CMC reviewers found the stability data "confirmed that the products manufactured at Lifecore is equivalent to the products submitted in the previous submission. The IVR results met the proposed acceptance criteria." Furthermore, relative bioavailability bioequivalence data supported the manufacturing change. See Section 5 Clinical Pharmacology.

A potential GMP issue was identified by Dr. Li-Shan Hsieh, PhD, related to an increase in total duration of time in the manufacturing process outside the (b) (4) degrees C range, i.e. from (b) (4) hours, which occurred with scale up to (b) (4) kg. Dr. Hsieh requested that the manufacturing site inspector evaluate the batch record to see whether any failure lots had been observed with this increase in time outside (b) (4) degrees C. In an addendum review, Dr. Hsieh documented that the inspector provided information "that no objectionable observations were noted for the (b) (4) kg commercial batch APF530, therefore, the above increase in manufacturing time outside of (b) (4) degrees C is no longer a concern." The reviewer concluded, "From a manufacturing process perspective, the set duration time of (b) (4) hours is acceptable."

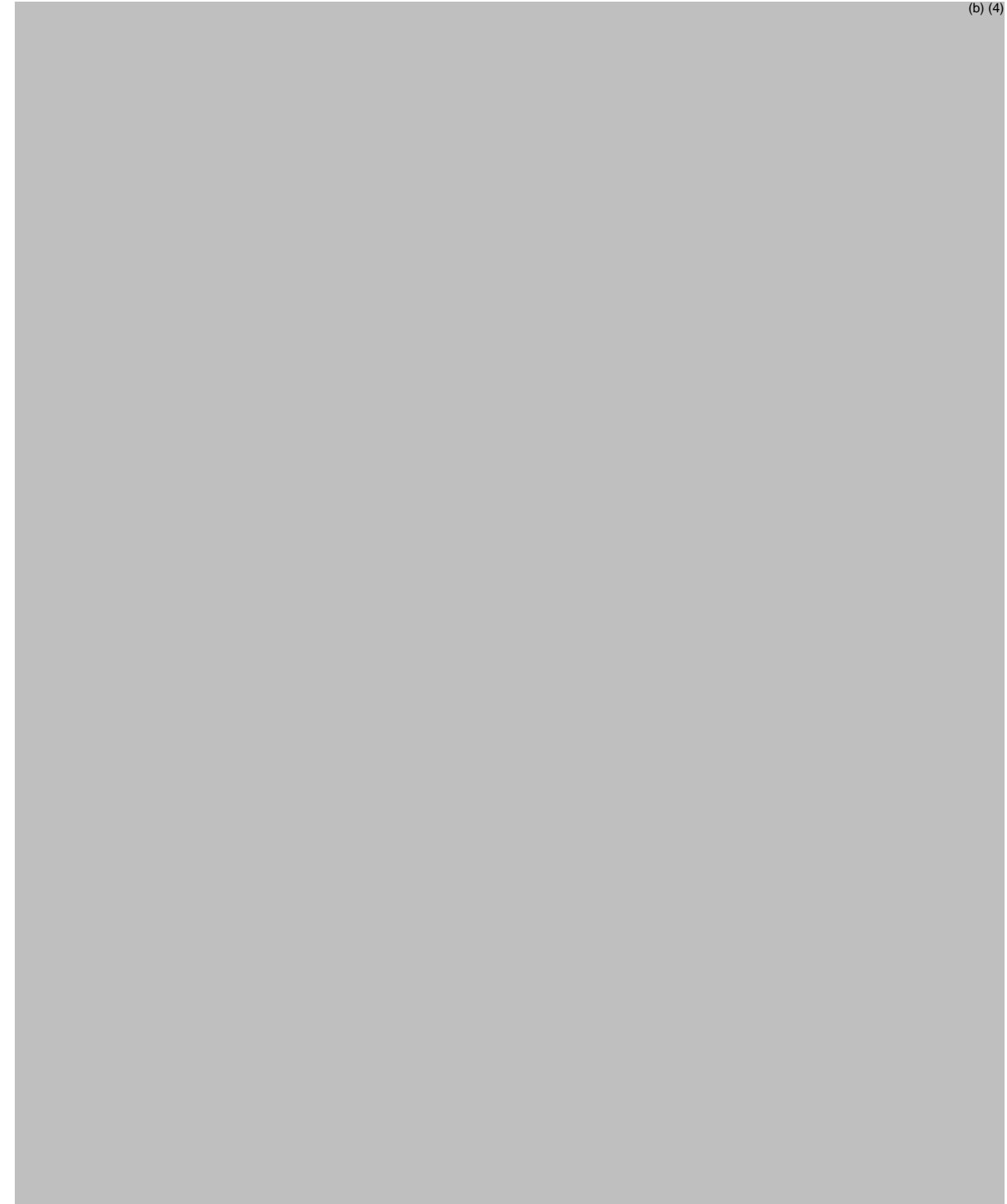
Device.

The applicant proposed changes in the container closure system in the resubmission (change from (b) (4) syringe to (b) (4) syringe, change from (b) (4) tip cap to (b) (4) tip cap, addition of finger flange). The proposed Sustol Delivery System is comprised of the following:

- (b) (4) 1 ml (long) glass syringe with (b) (4) Tip Cap
- (b) (4) Grey stopper
- (b) (4) Flange
- (b) (4)
- (b) (4) Plunger (b) (4)
- (b) (4) needle, 18 ga x 5/8", (b) (4) Thin Wall (b) (4)
- Smiths Medical Point-Lok[®] Needle Safety Device

Images of the components and the assembled container/closure system are shown below:

(b) (4)



The (b) (4) syringe with tip cap is filled with drug product (b) (4); this assembly is sterilized by gamma irradiation.

(b) (4) This syringe assembly is placed into a tray with the injection needle, Point-Lok needle safety device, Instructions for Use, package insert, and two syringe warmers. The tray is then packaged into a unit box. Storage is refrigeration at 2-8° C.

The Microbiology reviewer found the data for the new components of the container closure system, including the DMFs, the container closure integrity studies, the terminal sterilization (by radiation) and stability testing “adequate to ensure the microbiological quality of the drug product.” They recommended approval.

See Section 4 Nonclinical Pharmacology/Toxicology below for a summary of the evaluation of the extractables/leachables associated with the two new components in direct contact with the drug product.

The Applicant proposed co-packaging the product with two surgical warmers, for activation by the healthcare provider during the preparation of the product to soften the drug product for injection (reducing the force needed for subcutaneous injection of the viscous polymer product). The warmers warm the drug product-filled syringe to 37-40 degrees from room temperature, within 5-6 minutes. The applicant stated that two warmers are provided in each kit “in case the syringe needs additional warming before injection.” The CMC reviewer evaluated in-use stability data for the drug product after warming to 40 degrees C before use. These tests were conducted with samples pulled after storage of 0, 3 months, 12 months and 24 months. The CMC review states, “Warmer temperature cycling had no significant impact on the drug product. All the results fall within product specifications.” The application referred to (b) (4) warmer and (b) (4) warmer. The following table summarizes the characteristics of these two devices.

Table 2: Comparison of (b) (4) Warmers.

Parameter	(b) (4)	
Dimensions	125 ± 5 mm x 85 ± 5 mm	120 ± 5 mm x 85 ± 5 mm
Pouch Material	(b) (4)	
Fill Solution	Sodium Acetate, (b) (4)	Sodium Acetate, (b) (4)
Activation Mechanism	(b) (4)	
Fastener	Hook & Loop Strips	Hook & Loop Strips

CDRH (General Hospital Devices Branch, Division of Anesthesiology, General Hospital, Respiratory, Infection Control and Dental Devices in the Office of Device Evaluation) was consulted to evaluate the changes that the applicant made in the pre-filled syringe presentation, including the addition of the syringe warmers. The CDRH reviewers issued a number of information requests during the review. The applicant was asked to provide further justification of their proposal to increase the injection force specification from (b) (4) N to (b) (4) N “from marketing input to the final specification.” The reviewer had noted that in the current submission the applicant listed the required injection force as (b) (4) N; however, data indicated the injection force is 33N at 35° C and 24.6 N for 40°C. (b) (4)

(b) (4) The following data table, submitted by the applicant, summarizes the injection force needed with specific temperatures.

Table 3. Temperature versus Injection force (Study RPT-ENG-04)

Measured Product Temperature (°C)	Measured Injection Force (N)
20	72.1
25	51.9
30	45.8
35	30.5
40	23.2

The following figure summarizes the data for injection force required by time syringe is kept in a warmer.



The applicant's table summarizing their literature review of the hand grip strength (reproduced below from the CDRH consult) indicates that 40 N is the lowest strength identified in their review.

Table 4: Applicant’s summary of literature values of hand grip and pinch strength

Condition	Subjects (n)	Age Range or Mean	Sex	Grip Force Mean or Range (N)	3 Point Pinch Force Range (N)	Reference
Rheumatoid Arthritis	130	18-81	F	92		Björk, 2007
Rheumatoid Arthritis	59	18-80	M	185		
Healthy	62	21-89	F	198		
Healthy	61	21-89	M	343		
Rheumatoid Arthritis	20	33-70	F	62		Brorsson, 2012
Healthy	20	33-70	F	213		
Polymyositis or Dermatomyositis	18	56.1 (mean)	F	151		Regardt, 2011
Polymyositis or Dermatomyositis	13	56.1 (mean)	M	241		
Healthy	318	20 - 75+	F	309 - 165 (reduction w/age)	76 - 51 (reduction w/age)	Mathiowetz, 1985
Healthy	310	20 - 75+	M	532 - 242 (reduction w/age)	117 - 81 (reduction w/age)	
Healthy	78	20 - 62	F	301 - 234 (reduction w/age)	79 - 68 (reduction w/age)	Phillips, 2013
Healthy	101	20 - 62	M	529 - 453 (reduction w/age)	110 - 99 (reduction w/age)	
Healthy	50	20-60	F		58-177	Van der Ploeg, 1991
Healthy	50	23-60	M		88-192	
Rheumatoid Arthritis	19	36-69	F	42		Nordenskjold, 1993
Fibromyalgia	14	46-59	F	77		
Healthy	105	20-69	F	229		
Healthy	64	20-69	M	432		

The reviewer found the applicant’s responses to this issue adequate.

The CDRH reviewers identified the following additional concerns during their review:

- 1) The applicant only provided real-time aging data of 1-year duration for both the proposed syringe warmers, which wasn’t adequate to support the proposed ^(b)₍₄₎year expiry for the proposed combination product. The CDRH reviewer also noted that differences between the tested warmers and the final to-be-marketed design of the warmers could impact the aging testing results. The reviewer stated that the “real-time age testing of device samples should incorporate performance testing according to the essential performance requirements of the device as laid out in the [applicant’s] design verification testing.”
- 2) The reviewer noted that the ^(b)₍₄₎ warmers being tested in the applicant’s shelf-life study have a ^(b)₍₄₎ lower fill volume than the ^(b)₍₄₎ warmers the applicant intends to market.

The reviewer concluded that the difference in the warmers tested vs. those that the applicant plans to market, “in conjunction with the limited amount of stability data (27 weeks), is inadequate for the Agency to recommend approval for the commercial release of the (b) (4) syringe warmers with the PFS.” The reviewer stated that “performance testing on real-time aged device samples should be conducted on the to-be-marketed syringe warmers from (b) (4) up to the abled date of expiry, currently labeled as (b) (4), before the Agency can recommend approval. The performance testing of the syringe warmers should include verification of essential performance requirements of the device and be in accordance with the indications for use of the device. The acceptance criteria of the performance testing on the aged device samples should be identical to that in the design verification documentation already provided by the [applicant]. Real-time aged performance testing should be conducted every 2 months in order to assess any trends in device performance over time up until the labeled date of expiry.”

The applicant was contacted via teleconference on February 11, 2016 to discuss the remaining device deficiencies related to real-time aging testing of the syringe warmers and the conditions under which verification testing of the syringe stopper break force was conducted. A follow-up email to provide the deficiencies in writing to the applicant was sent on the following day, and this email included two additional issues, one related to the syringe stopper break force requirement set by the applicant and the other related to the absence of Letters of Authorization (LOA) for the device constituent parts described as (b) (4) in the NDA submission.

On February 18, 2016, the applicant provided new data for review in response to the identified deficiencies. The CDRH reviewers concluded the information “verified that the (b) (4) warmers have undergone real-time aging up to the labeled date of expiry (b) (4) months for the combination product) and have passed all acceptance criteria....Therefore, the reviewer finds the response adequate to ensure the performance of both warmers of the labeled date of expiry of the combination product.”

Regarding the stability testing for break force, the reviewers concluded that the remaining issues could be addressed as post-approval commitments. The applicant has not provided real-time stability data regarding injection force for the entire shelf-life of the combination product. The applicant completed accelerated aging stability testing. Real-time stability testing will supplement the accelerated aging stability data. The reviewer stated, “the Sponsor has provided adequate justification for providing injection force testing as a part of the stability use study in lieu of lot release testing.” The applicant submitted a post-approval stability protocol. The approval letter will include a PMC to address this issue:

3094-7 An addition to the stability protocol to test the break force, glide force, and peak force of injection of Sustol (granisetron) extended-release injection, for subcutaneous use.

Final Report Submission:

09/2018

The LOAs were reviewed and the reviewer stated, “The sponsor has also provided Use Stability Testing results as well as results of the ongoing Engineering study of the (b) (4) Point-Lok and needle constituent parts. The results of these studies in combination with the clinical validation of the parts (no failures in performance have been noted to date) are sufficient to the reviewer for the verification of these device constituent parts.”

The applicant also adequately addressed the final comment regarding the break force specification requirement. The reviewer stated that the applicant will revise their Technical Specification and Validation Protocol to reflect the break force specification of (b) (4) N maximum, and it will be submitted in the next Annual Report. The reviewer found this plan acceptable. The reviewer concluded that data submitted after implementation and testing of the syringe warmer supported that the risk associated with high injection force “has been sufficiently lowered.”

Ultimately, the CDRH reviewers found that the applicant had provided sufficient information to support a shelf-life of (b) (4) years for the device constituent parts of the combination product.

See also the Human Factors discussion in Section 8 Safety.

4. Nonclinical Pharmacology/Toxicology

The Pharmacology/Toxicology (Pharm/Tox) reviewers have recommended approval, from a nonclinical standpoint. During this review cycle, the Pharm/Tox reviewers evaluated the extractable and leachable information submitted to support the safety of components of the container/closure system. In this submission, the applicant proposed new components of the system that would be in contact with the drug product, i.e. a change to (b) (4) syringe from the original planned (b) (4) syringe and a change in the tip cap to (b) (4) tip cap. The components of the two systems (past and current) are summarized in the table below, which is reproduced from the CDRH review.

Table 3: Primary Container Closure System Configurations

(b) (4)



There was some lack of clarity in the submission regarding whether the applicant intended to market the product with only one or both of the tip caps; however, in an email dated January 28, 2016, the applicant confirmed that they only intended to market a presentation that included the (b) (4) Tip Cap.

The Pharm/Tox reviewers evaluated extractable and leachable studies submitted to support the safety of the (b) (4) tip cap and the (b) (4) syringe. They stated, “Overall daily exposures to leachables from the container closure system for APF530 appear to be reasonably safe.” The Associate Director of Pharmacology, Dr. Abby Jacobs, documented her concurrence with this conclusion in an email dated January 28, 2016. The Pharm/Tox review refers to earlier assessments of the (b) (4) syringe and the (b) (4) Tip Cap (made of (b) (4)); review of the regulatory record for this NDA indicates that the leachable/extractable studies for the originally proposed product presentation was performed by the CMC reviewers. In the current Pharm/Tox review, Dr. Chakraborti presents highlights of Extractable/Leachable study data submitted to support the previous product presentation, i.e., the (b) (4) syringe; however, I will limit my summary below to the review findings from the studies for the currently relevant proposed container closure system (for the (b) (4) Tip cap and the (b) (4) syringe).

As stated above, the tip cap leachable study was conducted in combination with the (b) (4) syringe, i.e., leachables were assessed with the drug product in the container closure system with both components contributing exposure intact (i.e. tip cap and the syringe). No leachables exceeded Method Detection Limits. The reviewers concluded no additional data are needed because results were observed under accelerated conditions.

Summary. The Pharm/Tox reviewers recommended approval. They ultimately recommended that a SHE-cell assay and a carcinogenicity study be conducted as PMCs. The decision to allow these studies to be conducted post approval was critically re-evaluated in this review cycle. FDA had informed the sponsor in two prior meeting responses that the studies would not be required pre-approval:

- 1) Meeting minutes from a December 13, 2006 meeting state, “The Division concluded that it would be okay for the sponsor to initiate the necessary carcinogenicity studies in two species at ‘about the time of’ NDA submission....[a clinical team leader] suggested that the carcinogenicity study might be accepted as a Phase 4 commitment]”.
- 2) Meeting minutes from a February 25, 2011 meeting to discuss the CR letter date March 16, 2010, noted as a point of ‘Additional Meeting Discussion’, “The 2 year carcinogenicity study in the rat and SHE cell assay will be performed as a postmarketing study per previous agreement.” The applicant had not submitted a formal question about the carcinogenicity study in their formal meeting package.

The ICH Guideline: Guideline on the Need for Carcinogenicity Studies of Pharmaceuticals S1A was considered in determining the appropriateness of adhering to the previous agreement to delay the carcinogenicity studies to post approval. S1A states “The fundamental considerations in assessing the need for carcinogenicity studies are the maximum duration of patient treatment and any perceived cause for concern arising from other investigations. Other factors may also be considered such as the intended patient population, prior assessment of carcinogenic potential, the extent of systemic exposure, the dissimilarity to endogenous substances, the appropriate study design or the timing of study performance relative to clinical development.” The guidelines state that “results from genotoxicity studies, toxicokinetics, and mechanistic studies can now be routinely applied in preclinical safety assessment. These additional data are important not only in considering whether to perform carcinogenicity studies but for interpreting study outcomes with respect to relevance for human studies.” The Guidelines state that “When carcinogenicity studies are required they usually need to be completed before application for marketing approval....For pharmaceuticals developed to treat

certain serious disease, carcinogenicity testing need not be conducted before market approval although these studies should be conducted post-approval.” The following factors should be considered for carcinogenicity testing:

- a. “Carcinogenicity studies should be performed for any pharmaceutical whose expected clinical use is continuous for at least 6 months.” Note that this does not state this must be done preapproval.
- b. Causes for concern such as “previous demonstration of carcinogenic potential in the product class relevant to humans, structure-activity relationship suggesting risk, evidence of preneoplastic lesions in repeat dose toxicity studies, and long term tissue retention of parent compound or metabolites resulting in local tissue reactions or other pathophysiological responses.”
- c. Genotoxicity
- d. Indication and Patient population – the Guidelines state “In instances where the life-expectancy in the indicated population is short (i.e., less than 2-3 years) no long term carcinogenicity studies may be required..... In cases where the therapeutic agent for cancer is generally successful and life is significantly prolonged there may be later concerns regarding secondary cancers. When such pharmaceuticals are intended for adjuvant therapy in tumour free patients....carcinogenicity studies are usually needed.” The latter does not address timing.
- e. Extent of systemic exposure.
- f. Endogenous peptides and protein substances or their analogs

The following issues relevant to the Sustol review were considered.

1. Any risk of carcinogenicity associated with the polymer is purely theoretical.
2. Theoretical risk of carcinogenicity is less of a concern in patients with metastatic disease. The indication will be prevention of CINV in the setting of MEC and AC. While MEC chemotherapy regimens are commonly used in patients with metastatic disease, AC is generally used as an adjuvant chemotherapy regimen. Furthermore, oxaliplatin is considered MEC chemotherapy and it is used in adjuvant regimens for colon cancer. Both cyclophosphamide and doxorubicin are components of treatment of non-Hodgkins lymphomas, which are curable. Doxorubicin, which is considered MEC when not given in combination with cyclophosphamide, is a component of a chemotherapy regimen used in Hodgkins Disease, which is also a curable disease. However, adjuvant chemotherapy regimens are generally less than or equal to 6 months in duration. Curative treatments for hematological malignancies can range from <6 months to ≤ 1 year. Treatments of metastatic cancer can be prolonged over months and even years.
3. Many chemotherapy regimens, including those for hematological malignancies and adjuvant treatments for solid tumors, are known to be associated with increased risk of secondary malignancies.

4. The time to actual complete clearance of the polymer in humans is still unknown, and the Clinical Pharmacology reviewer estimates that it takes at least a month for the polymer to clear.
5. Genotoxicity studies of the polymer revealed that the Ames test for APF530 (drug plus polymer vehicle) was negative; the Ames test for (b) (4) the polymer vehicle, was negative; the L5178Y TK+/- Mouse Lymphoma forward mutation assay with APF530 was negative; the L5178Y TK+/- Mouse Lymphoma forward mutation assay with (b) (4) (polymer vehicle) was negative; In Vivo Rat micronucleus assay with APF530 and (b) (4) by subcutaneous route was negative (harvests were done at 24 and 48 hours).
6. Toxicokinetics of the polymer were characterized in rats using polymer in which the triethylene glycol molecule was radiolabeled. Radioactivity was noted extensively distributed throughout the body with measurable quantities in multiple tissues through 672 hours post dose, when only approximately 1-2% of the radiolabeled does was detected, with the majority eliminated (76%) in the first 24 hours post administration. Higher radioactivity concentrations were in the injection site, liver, urinary bladder and kidney. A 90 day SQ toxicity study in rats treated once every 24 hours with APF530 revealed the primary target organs of toxicity were the injection site, lymph node (lymphoid hyperplasia), bone marrow (myeloid hyperplasia) and spleen (hematopoiesis); similar doses administered once every 72 hours for 28 days did not produce similar histopathological changes in the lymph nodes, bone marrow and spleen. The 90 day SQ toxicity study in beagle dogs treated daily revealed no target organ of toxicity. Chronic toxicity studies of the polymer did not reveal any evidence of premalignant lesions.

Taking into consideration the lack of evidence for polymer genotoxicity and the lack of premalignant lesions in the chronic toxicity studies, along with the human populations to be treated, the expected treatment duration with respective population subgroups, and the likelihood that the population would be receiving other medications known to be associated with secondary malignancies, the review team concluded that it was acceptable to approve Sustol with the carcinogenicity study conducted as a post approval requirement.

The Division of Oncology Products 1 (DOP1) was consulted during these deliberations, and the oncology consultants initially questioned whether the product's indication statement should be modified to limit use to patients receiving chemotherapy without curative intent, given the findings of liver tumors currently reported in the Kytril label's Section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility for Kytril, which states (emphasis added in bold by me):

“In a 24-month carcinogenicity study, rats were treated orally with granisetron 1, 5 or 50 mg/kg/day (6, 30 or 300 mg/m²/day). The 50 mg/kg/day dose was reduced to 25 mg/kg/day (150 mg/m²/day) during week 59 due to toxicity. For a 50 kg person of average height (1.46 m² body surface area), these doses represent 16, 81 and 405 times the recommended clinical dose (0.37 mg/m², iv) on a body surface area basis. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in males treated with 5 mg/kg/day (30 mg/m²/day, **81 times the recommended human dose based on body surface area**) and above,

and in females treated with 25 mg/kg/day (150 mg/m²/day, **405 times the recommended human dose based on body surface area**). No increase in liver tumors was observed at a dose of 1 mg/kg/day (6 mg/m²/day, 16 times the recommended human dose based on body surface area) in males and 5 mg/kg/day (30 mg/m²/day, 81 times the recommended human dose based on body surface area) in females. In a 12-month oral toxicity study, treatment with granisetron 100 mg/kg/day (600 mg/m²/day, **1622 times the recommended human dose** based on body surface area) produced hepatocellular adenomas in male and female rats while no such tumors were found in the control rats. A 24-month mouse carcinogenicity study of granisetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive.

Because of the tumor findings in rat studies, KYTRIL Injection should be prescribed only at the dose and for the indication recommended [*see Indications and Usage (1) and Dosage and Administration (2)*].

Granisetron was not mutagenic in an in vitro Ames test and mouse lymphoma cell forward mutation assay, and in vivo mouse micronucleus test and in vitro and ex vivo rat hepatocyte UDS assays. It, however, produced a significant increase in UDS in HeLa cells in vitro and a significant increased incidence of cells with polyploidy in an in vitro human lymphocyte chromosomal aberration test.”

A meeting was held between the reviewers, DOP1 consultants and senior leadership from Pharm/Tox, i.e., the Director of Division of Hematology Oncology Toxicology (DHOT), Dr. John Leighton, PhD, and Associate Directors of Pharmacology and Toxicology Karen Davis-Bruno, PhD, and Abby Jacobs, PhD, regarding including a Warning and Precaution related to the nonclinical carcinogenicity findings for granisetron and the current status of the evaluation of the polymer. Senior leadership firmly advised against a Warning/Precaution or modification of the indication statement based on the information in Section 13.1 regarding granisetron. They also stated that the current information available on the polymer did not warrant a Warning/Precaution or modification of the indication statement. They stated that it may even be reasonable, based on what is known about the polymer and its metabolites, to not require a formal carcinogenicity study with the polymer. The Pharm/Tox team leader and senior Pharm/Tox leadership entered a memo in DARRTS with their recommendations and the scientific support for the recommendations, which are summarized below.

1. Regarding granisetron:
 - a. The 24-month rat carcinogenicity study revealed no increase in liver tumors at a dose of 1 mg/kg/day, which is 16 times the recommended human dose based on BSA in males and at 5 mg/kg/day, which is 81 times the recommended human dose based on BSA in females.
 - b. The hepatocellular tumor findings in rats aren't relevant to humans because hepatocellular tumors are common in rodents, usually occur by modes of action not relevant to humans and occurred at doses which provide ≥ 81 times exposure multiples of ≥ 34 times the SQ dose.

- c. Granisetron was not mutagenic in an *in vitro* Ames test or the mouse lymphoma cell forward mutation assay, or genotoxic in the *in vivo* mouse micronucleus test and the *in vitro* and *ex vivo* rat hepatocyte UDS assays. The “weight of evidence approach outlined in ICH S2(R1) Guidance Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use” supports the conclusion that granisetron is not genotoxic, despite additional nonclinical *in vitro* data that revealed granisetron produced an increase in unscheduled DNA synthesis in HeLa cells and an increased incidence of polyploidy in an *in vitro* human lymphocyte chromosomal aberration test.
2. Polymer vehicle
 - a. The findings of the acute and subacute/subchronic (28- and 90-day studies toxicology in rats and dogs, revealed the major target organ was the injection site (inflammatory reactions). As stated above, other findings were limited to lymphoid hyperplasia of draining lymph nodes, splenic hematopoiesis and bone marrow myeloid hyperplasia.
 - b. The polymer was negative in the Ames test, mouse lymphoma assay and the *in vivo* rat bone marrow micronucleus test. The polymer + drug product (Sustol) was also negative in a standard battery of genotoxicity studies.
 - c. Regarding the putative breakdown products of the polymer, which include pentaerythritol, triethylene glycol, propionic acid and glycolic acid:
 - i. Triethylene glycol was not found to be genotoxic in the Ames test, CHO cell gene mutation assay, chromosomal aberration assay in CHO cells and sister chromatid exchange assays. This information comes from the Final Report on the Safety Assessment of Triethylene Glycol and PEG-4, Int J Toxicol, 25 (Suppl 2): 121-138, 2006; Reregistration Eligibility Decision for Triethylene Glycol, USEPA, September 26, 2003. It had no carcinogenicity potential in studies conducted at doses up to the testing limit established by the US EPA (same report).
 - ii. Pentaerythritol was not genotoxic in the Ames test and chromosomal aberration assay in Chinese hamster lung (CHL) cells. This information comes from the Organization for Economic Cooperation and Development, Screening Information DataSet, Pentaerythritol, Initial Assessment Report for 8th SIAM, 1998. It was not carcinogenic in rats and mice in 2-year carcinogenicity studies. This information comes from J Appl Toxicol, 10 (5):353-357; National Toxicology Program, US Department of Health and Human Services, Public Health Service, NIH, Toxicology and Carcinogenesis Studies of Pentaerythriol Tetranitrate in F344/N Rats and B6C3F1 Mice, Technical Report Series, No. 365, August 1989, NIH Publication No. 89-2820.
 - iii. Propionic acid was not genotoxic in Ames test and an *in vivo* micronucleus test using Chinese Hamsters (OECD, SIDS, SIAM 25 2007). In addition, the European Food Safety Authority Panel on Food Additives and Nutrient Sources Added to Food concluded

there is no concern with respect to its genotoxicity and carcinogenicity [Scientific Opinion on the Re-evaluation of Propionic Acid, Sodium Propionate, Calcium Propionate and Potassium Propionate as Food Additives, EFSA Journal, 12 (7):3779, 2014].

- iv. Glycolic acid wasn't genotoxic in the Ames test [European Food Safety Authority, Glycolic Acid, Scientific Opinion on the Safety Evaluation of the Substance Glycolic Acid for use in Food Contact Materials, EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids, EFSA Journal 8 (12):1927, 2010]. There were also no tumor findings in rats in a chronic dietary carcinogenicity study [Cosmetic Ingredient Review; Journal of American College of Toxicology 17 (Suppl 1):1-242]. The US EPA has not classified glycolic acid as a human carcinogen and the NTP has not listed glycolic acid as a human carcinogen.

I discussed the Pharm/Tox memo with senior leadership from DOP1, and they concurred with not proceeding with a Warning/Precaution or modification of the indication statement. A memo from DOP1 was entered on July 26, 2016, stating that it doesn't recommend label modification to address potential carcinogenic risk, when administered as approved.

Based on this, the product label's Section 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility will state:

Long-term studies in animals with SUSTOL have not been performed to evaluate the carcinogenic potential of the polymer vehicle of SUSTOL. In a 24-month carcinogenicity study of granisetron hydrochloride, rats were treated orally with 1, 5 or 50 mg/kg/day. The 50 mg/kg/day dose was reduced to 25 mg/kg/day during week 59 due to toxicity. For a 60 kg person, the 1, 5, and 25 mg/kg/day doses represent approximately 7, 34 and 169 times, respectively, the maximum recommended human dose (MRHD) (10 mg granisetron/week, approximately 6.2 mg/m²/week) of SUSTOL 10 mg/week, based on body surface area. There was a statistically significant increase in the incidence of hepatocellular carcinomas and adenomas in male rats treated with 5 mg/kg/day (approximately 34 times the MRHD of SUSTOL 10 mg/week, based on body surface area) and above, and in female rats treated with 25 mg/kg/day (approximately 169 times the MRHD of SUSTOL 10 mg/week, based on body surface area). No increase in liver tumors was observed at a dose of 1 mg/kg/day (approximately 7 times the MRHD of SUSTOL 10 mg/week, based on body surface area) in male rats and 5 mg/kg/day (approximately 34 times the MRHD of SUSTOL 10 mg/week, based on body surface area) in female rats.

In a 12-month oral toxicity study with granisetron hydrochloride, rats were treated at 100 mg/kg/day (approximately 677 times the MRHD of SUSTOL 10 mg/week, based on body surface area). This dose produced hepatocellular adenomas in male and female rats while no such tumors were found in the control rats. A 24 month mouse

carcinogenicity study of granisetron did not show a statistically significant increase in tumor incidence, but the study was not conclusive. Because of the tumor findings in rat studies, SUSTOL should be prescribed only at the dose and for the indication recommended [*see Indications and Usage ()*, *Dosage and Administration ()*].

Granisetron hydrochloride was not mutagenic in an *in vitro* Ames test and mouse lymphoma cell forward mutation assay, and *in vivo* mouse micronucleus test and *in vitro* and *ex vivo* rat hepatocyte unscheduled DNA synthesis (UDS) assays. However, granisetron hydrochloride was positive in a mouse lymphoma assay with metabolic activation and produced a significant increase in UDS in HeLa cells *in vitro* and a significant increased incidence of cells with polyploidy in an *in vitro* human lymphocyte chromosomal aberration test.

Neither SUSTOL nor the polymer vehicle for SUSTOL was mutagenic in the Ames test, mouse lymphoma assay, and the *in vivo* rat bone marrow micronucleus test.

Granisetron hydrochloride at subcutaneous doses up to 6 mg/kg/day (approximately 40 times the MRHD of SUSTOL 10 mg/week, based on body surface area), and oral doses up to 100 mg/kg/day (approximately 677 times the MRHD of SUSTOL 10 mg/week, based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

The polymer vehicle for SUSTOL at subcutaneous doses up to 0.295 g per day (approximately 45 times the amount of polymer vehicle present in the maximum recommended /weekly single human dose of SUSTOL, based on body surface area) was found to have no adverse effect on fertility and reproductive performance of male and female rats.

Furthermore, we have determined that the carcinogenicity study and SHE cell assay can be conducted as PMCs instead of PMRs. The PMCs will state:

3094-5 A 2-year subcutaneous carcinogenicity study in rats with the (b) (4) vehicle used in the formulation of Sustol (granisetron) extended-release injection, for subcutaneous use.

3094 – 6 A Syrian Hamster Embryo (SHE) cell transformation assay with the (b) (4) vehicle used in the formulation of Sustol (granisetron) extended-release injection, for subcutaneous use.

5. Clinical Pharmacology

I concur with the conclusions reached by the Clinical Pharmacology reviewers that there are no outstanding clinical pharmacology issues that preclude approval. There were no Clinical Pharmacology deficiencies identified in the March 27, 2013 CR letter. However, the applicant submitted two new bioavailability/bioequivalence trials and an addendum to their previously reviewed polymer metabolic fate study (Study C2011-02) in this resubmission. The two new relative bioavailability trials included:

- 1) C2013-03: comparing product from the manufacturing sites that provided product in the clinical trials ((b) (4) manufacture; Lifecore fill) to product from new commercial manufacturing sites (Lifecore manufacture and fill).
- 2) C2011-02: comparing exposures associated with product administration via abdominal subcutaneous tissue injection vs. upper arm subcutaneous tissue injection.

With regard to the addendum to the previously reviewed metabolic fate study, the applicant applied improved analytical methods and internal standards to stored urine samples from Study C2011-02, to further characterize TEG (triethylene glycol), TEG-acid and PEMPA (pentaerythritol monopropionate); however, the interpretability of the updated data was called into question by the reviewers because the reanalyses were performed on urine samples outside the established storage stability of TEG, TEG-acid and PEMPA. Therefore, these additional analyses did not address the issues presented as ADDITIONAL COMMENTS in the second cycle CR letter. (See further discussion below.)

Bioequivalence evaluation of the clinical trial product (Reference: from (b) (4)) vs. proposed commercial product (Lifecore). The results of the open-label, randomized, two-way crossover bioequivalence study indicated the products were bioequivalent, i.e., AUC and C_{max} fell within the bioequivalence 90% confidence interval of 80-125%. The reviewers identified a trial design issue, i.e., there were two additional steps in drug administration in the study that were not used in the clinical trials submitted to establish efficacy/safety of the product, i.e., the drug product was transferred from a pre-filled glass syringe into a tuberculin syringe, and drug product from two prefilled syringes was used to prepare one dose in the single tuberculin syringe. The applicant was contacted regarding this difference. The reviewer states in her review that the applicant responded that the transfer into the tuberculin syringe was performed to avoid use of the warmer pouches; however, the quote from the sponsor included in her review states that the transfer to the plastic tuberculin syringes from the glass syringes was performed to “maintain blinding”. The applicant noted the reference product (b) (4) was filled into (b) (4) 1.0 ml Long syringes with a plastic rigid tip cap, which is a plastic sheath on the outside of the rubber tip cap. The commercial product was provided in the (b) (4) 1.0 mL Long syringes, which do not have the plastic rigid tip caps. The tip cap for the commercial product in this study was solid rubber. The applicant stated the second step was performed because additional product was needed in order to fill the tuberculin syringe with the intended dose, given that some of the product was caught up and “lost” in the transfer space created by the luer-lock and luer-lock transfer device for the transfer between syringes. The Clinical Pharmacology reviewer discussed the applicant’s

response with the CMC reviewer and the Clinical team, and concluded that despite these design issues, the data from the study were interpretable and supported bioequivalence.

Comparison of sites of administration – abdominal tissue vs upper arm tissue. The results of the open-label, randomized, two-way crossover evaluation of bioavailability of Sustol 500 mg administered SQ into abdominal skin vs. upper non-dominant arm) in healthy subjects indicated the routes are bioequivalent, i.e., AUC and C_{max} fell within the bioequivalence 90% confidence interval of 80-125%. However, the data suggested that exposures, both C_{max} and AUC, are slightly higher with administration in the upper arm, i.e., the lower bound of the confidence interval exceeded 100%. The lower bound for all parameters fell below 120%. The following table, summarizing the data, is reproduced from the Clinical Pharmacology review.

Table 6. Bioavailability comparison of subcutaneous injection in abdominal tissue vs. upper arm tissue. (T= upper arm; R=abdomen)

Parameter	T/R (%)	90 % confidence bounds
C _{MAX}	111.52	[105.95-117.37]
AUC _T	107.45	[103.72-111.32]
AUC _{INF}	106.28	[102.37-110.34]
AUC ₂₄	111.93	[105.60 – 118.65]

Evaluation of metabolic fate of the polymeric component of Sustol. The CR letter from the second review cycle included a comment (not a CR deficiency), which stated:

“The metabolic fate study (C2011-02) you submitted in this resubmission only accounted for approximately 1/3 of the polymer. The proposed dosage and administration instructions allow for administration of Sustol every 7 days. Although the major trial submitted to support this NDA, C2006-01, included patients who were exposed to up to 4 doses of Sustol, there was no control arm beyond the first cycle to allow for optimal interpretation of the safety data in this complex patient population with underlying malignancies. In addition, serum chemistries from patients who received subsequent doses of Sustol were not submitted for review in the NDA. For these reasons, we are considering whether a postmarketing, randomized, controlled safety trial that evaluates patients who receive Sustol doses as frequently as every 7 days over the course of a year will be a condition for future approval.”

The applicant submitted re-analyses with improved methods in the current submission, which suggest that the recovery of the polymer load as breakdown products is higher than presented in the previous submission. The recovery in urine samples increased from 34% to approximately 47%. The reviewer noted this increase was primarily attributable to “the ability to quantify additional triethylene glycol (TEG) as TEG-COOH and additional pentaerythritol (PE) as pentaerythritol monopropionate (PEMPA) in the urine samples.” However, the reviewers noted that the validity of the data cannot be supported because the long term storage stability data supporting re-assay of stored samples is not currently available.

Summary. The new relative bioavailability/bioequivalence trials submitted in this application support the proposed change in manufacturing facility and that the product may be administered in the subcutaneous tissue of the upper arm of the non-dominant arm or the subcutaneous tissue of the abdomen.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The second cycle included the following deficiency related to efficacy:

Clinical

(b) (4)

Sustol was (b) (4) effective for prevention of both acute and delayed phase nausea and vomiting associated with moderately emetogenic chemotherapy (MEC). The proposed indication should be revised to reflect the populations that will benefit from Sustol in both the acute and delayed phase.

To support this revision, provide the dataset and identify the variables used to determine if a patient was in the “HEC” or “MEC” stratum for randomization in trial C2006-01, the major efficacy trial submitted in this NDA. Please also 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.

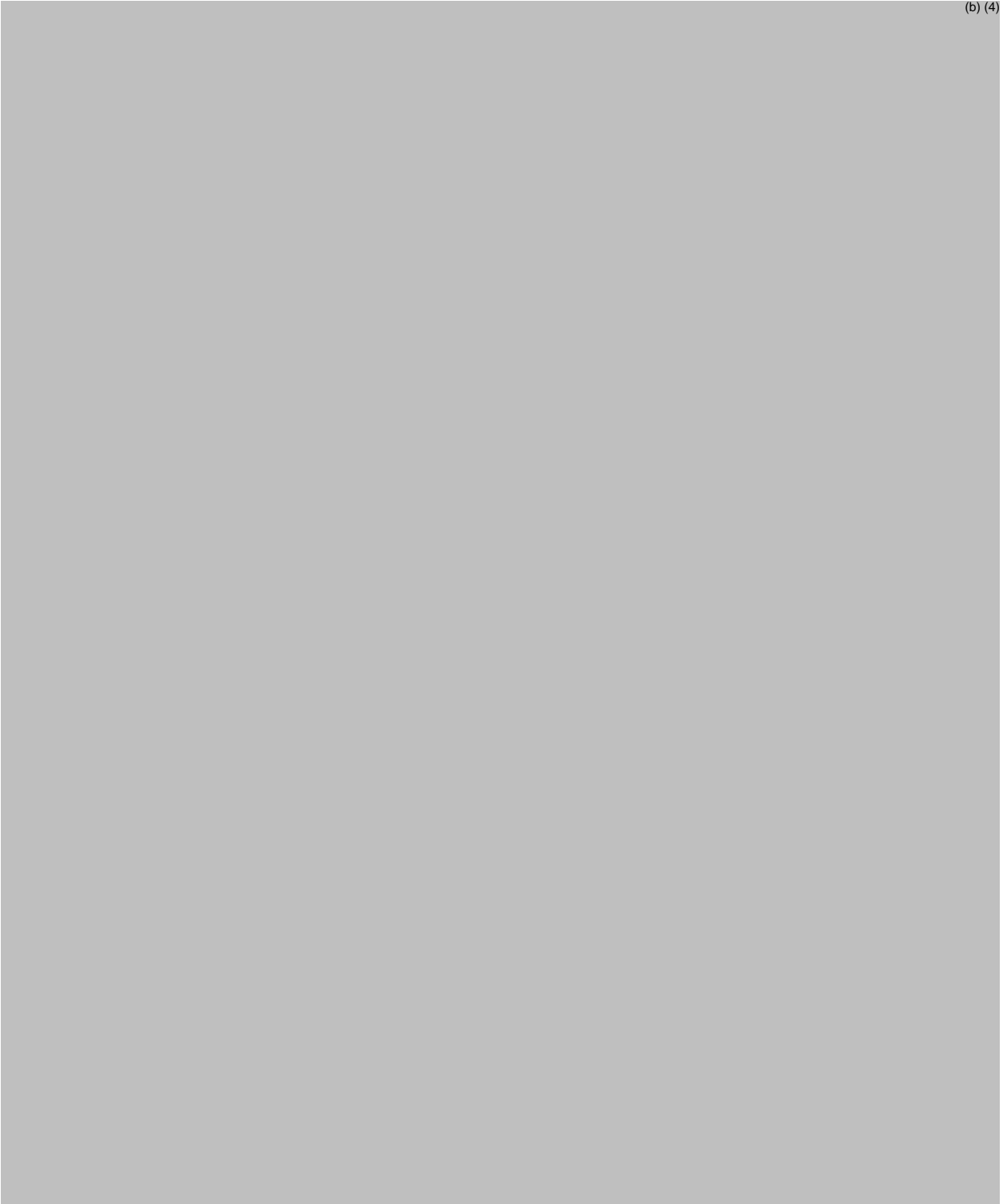
(b) (4) the applicant has submitted:

1. the results of a new randomized, controlled and double blind phase 3 trial (Study C2013-01), which enrolled patients treated with HEC chemotherapy, where the HEC categorization was based on the updated 2011 ASCO Guidelines (anthracycline plus cyclophosphamide (AC) was categorized HEC). The NK-1 inhibitor fosaprepitant and dexamethasone were administered in both arms. The comparator arm differed from the Sustol arm in that ondansetron IV was the 5HT3 antagonist administered, as a single 0.15 mg/kg dose on Day 1 only. A vehicle (polymer only) injection was also administered in the ondansetron control arm.
2. New analyses of the previously submitted noninferiority trial, Study C2006-01, based on reclassification of the chemotherapy received by patients, using the updated 2011 ASCO Guidelines.

In this section of my review, (b) (4) a summary of the review of the resubmitted efficacy analyses from Study C2006-01 for which the emetogenicity categories had been revised. Note that two Sustol

doses were studied (250 mg and 500mg, which correspond to granisetron doses of 5 mg and 10 mg) in Study C2006-01, while only the higher dose (500mg) was studied in Study C2013-01. The applicant seeks approval of only the high dose. In my review I will refer to the Sustol dose as both 500 mg (referring to overall product) and 10 mg (referring to granisetron).

(b) (4)



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7.2 Reanalysis of Study C2006-01 based on reclassification of HEC/MEC categories according to the 2011 ASCO Guidelines.

Study C2006-01 was a randomized, controlled, patient and investigator blinded (pharmacist was not blinded), double dummy, parallel group study that enrolled patients who received HEC or MEC chemotherapy. Patients could be treated with multiple cycles of therapy; however, the primary efficacy analysis was limited to the first cycle. Two Sustol dose levels were evaluated (250 mg and 500 mg). The active control was a single IV injection of palonosetron 0.25 mg, which is approved for: 1) acute CINV in HEC and 2) acute and delayed CINV in MEC.

In the review of the 2012 resubmission,

(b) (4)

the reviewers raised concerns that the Hesketh emetogenicity classification was used to determine the emetogenicity of the chemotherapeutic agents administered. An algorithm assigned a HEC designation to some combinations of chemotherapy based on the emetogenicity of a single component that would not by itself be considered HEC. If one or more of the agents was an emetogenicity “level 2 or greater”, the emetogenicity level of the combination was assigned a one level higher emetogenicity than the most emetogenic drug in the regimen. The 2011 ASCO Guidelines only mention the anthracycline plus cyclophosphamide (AC) combination as HEC; otherwise, the guidelines state combination regimens should be categorized based on the most emetogenic component drug in the regimen, with no elevation of the emetogenicity of that agent because it is present in a combination. The Hesketh list of Level 5 drugs used in the

trial included the following: carmustine, cisplatin, cyclophosphamide $\geq 1500 \text{ mg/m}^2$, dacarbazine, mechlorethamine, streptozotocin. The ASCO 2011 guidelines include the same five individual drugs as highly emetogenic, plus an additional drug: dactinomycin.

In response to the CR letter, the applicant has provided retrospective analyses in which the emetogenicity category for each patient was reclassified based on the 2011 ASCO Guidelines. Hochberg’s sharper Bonferroni approach was applied within each emetogenic stratum (HEC or MEC) to control overall Type I error rate at 5% for 4 simultaneous comparisons (each of the two Sustol doses compared to palonosetron for each of two endpoints, i.e., delayed phase and acute phase). This approach was also used in the original analysis plan. Confidence intervals of 95%, 97.5%, 98.33% and 98.75% were constructed, and if all 4 lower limits (the 4 comparisons in each stratum) of the 95% CI were not greater than -15%, the 97.5% CIs could be examined. As stated in the Statistical review, “If 3 of the 4 lower limits of the 97.5% CIs were greater than -15%, non-inferiority was declared for each [Sustol] dose/phase combination which met the criterion and was not declared for the [Sustol] dose/phase combination which did not meet the criterion. If 3 of the 4 lower limits of the 97.5% CIs were not greater than -15%, the 98.33% CIs were reviewed. If 2 of the 4 lower limits of the 98.33% CIs were greater than -15%, non-inferiority was declared for the 2 [Sustol] dose/phase combinations which were met. The step-down procedure was to continue to the fourth stage as needed.” (b) (4)

The Statistical reviewer for the previous review cycle focused on the mITT analysis. The Statistical reviewer for the current review cycle has determined that the mITT analysis is the primary analysis to evaluate for decisional purposes and for product labeling.

The mITT efficacy analysis results in the original Statistical review, prior to recategorization based on the ASCO Guidelines emetogenicity categories, are presented in the table below. The presentation of results is limited to the 98.75% CI.

Table 17: Study C2006-01 mITT efficacy analysis results from the original FDA Statistical review
Primary Results of Complete Response in Cycle 1 (mITT Population)

Phase	Statistic	MEC		
		5 mg Sustol	10 mg Sustol	0.25 mg Aloxi [®]
	N	214	212	208
Acute	CR	160 (74.8%)	163 (76.9%)	156* (75.0%)
	98.75% CI (%)	(-10.9, 10.4)	(-8.6, 12.4)	-
Delayed	CR	110 (51.4%)	125 (59.0%)	120 (57.7%)
	98.75% CI (%)	(-18.4, 5.8)	(-10.7, 13.3)	-

* The sponsor reported 160 but with percentage 75.0%, presumably was a typographic error.

Source: Reviewer’s Table (the results concur with those from the sponsor except noted in *)

The following mITT analyses (reproduced from the current FDA Statistical review), are based on the ASCO guideline re-categorization and were submitted in this third review cycle resubmission package. The applicant’s prespecified noninferiority analysis was based on the mITT population. Although labeling should be limited to prespecified analyses, these re-

analyses were the most relevant to labeling because the results reflect Sustol’s efficacy in the actual setting of the emetogenic regimen categories proposed for approval and labeling.

Table 18. Applicant’s mITT Reanalysis of C2006-01 based on ASCO Guideline Recategorization. Content submitted to initiate third cycle review.

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

(b) (4)

Source: Sponsor’s Table 9.9 of CSR Addendum

In the MEC subgroup, the absolute CR rates observed in the mITT analyses in both the Sustol 500mg and palonosetron arms numerically increased in the ASCO recategorization analysis compared to the CR rates observed in the original Hesketh category analysis, in both the acute phase (from Sustol 500 mg 76.9% and Aloxi 75.0%, to 83.4% and 88.6%, respectively) and delayed phase (Sustol 500 mg 59.0% and Aloxi 57.7%, to 69.3% and 69.7%, respectively) analyses. The increase in CR rates in the Aloxi arm was numerically greater than in the Sustol 500 mg arm, in both the acute and delayed phase. The sample size shift in MEC was:

Acute MEC mITT Original:
 Acute MEC mITT Reassignment Analysis:

Sustol N=212
 Sustol N=205

Palo N=208
 Palo N=211.



(b) (4)



(b) (4)

in the per protocol analysis of MEC acute phase based on the ASCO Guideline re-categorization of MEC acute phase, the delta between Sustol 500 mg and Aloxi increased from 5.2% observed in the mITT analysis to 6.7%, both favoring Aloxi (see Table 19 below). Examination of the MEC acute phase mITT data in Table 19 reveals that the confidence interval for the difference between Sustol and Aloxi approaches -15 for the 98.75% CI. All confidence intervals for the mITT acute phase analyses include zero. However, for the per protocol analysis of acute phase (see table below), not only does the lower bound of the 98.75% CI cross -15%, the 95% confidence interval excludes zero.

Table 19. Applicant's Per Protocol Reanalysis of C2006-01 based on ASCO Guideline Recategorization. Content submitted to initiate third cycle review.

	APF530 250 mg	APF530 500 mg	Aloxi 0.25 mg
MEC (ASCO)			
Acute Phase CR			
CR, n/N (%)	148/176 (84.1)	153/180 (85.0)	177/193 (91.7)
P-value vs. Aloxi	0.03	0.05	
95% CI (diff w/Aloxi)	-14.7, -0.9	-13.6, -0.2	
97.5% CI (diff w/Aloxi)	-15.7, 0.0	-14.6, 0.7	
98.33% CI (diff w/Aloxi)	-16.3, 0.5	-15.2, 1.2	

	APF530 250 mg	APF530 500 mg	Aloxi 0.25 mg
98.75% CI (diff w/Aloxi)	-16.7, 0.8	-15.6, 1.6	
Delayed Phase CR			
CR, n/N (%)	118/176 (67.0)	126/180 (70.0)	139/193 (72.0)
P-value vs. Aloxi	0.31	0.73	
95% CI (diff w/Aloxi)	-14.4, 4.5	-11.3, 7.2	
97.5% CI (diff w/Aloxi)	-15.8, 5.8	-12.6, 8.5	
98.33% CI (diff w/Aloxi)	-16.5, 6.5	-13.3, 9.2	
98.75% CI (diff w/Aloxi)	-17.0, 7.0	-13.9, 9.7	

(b) (4)

Source: Sponsor's Table 9.10 of CSR Addendum

(b) (4)

The analyses above also support noninferiority in the delayed phase of MEC. The per protocol exploratory analyses presented above don't support the noninferiority of Sustol to Aloxi in the acute phase of MEC. The patients treated with AC in this trial were designated as having received HEC in these analyses. Nevertheless, previously approved antiemetic products that carry MEC/HEC labeling were granted approval of the MEC indication based on trials that enrolled patients receiving AC, given the previous categorization of AC as MEC. This is important to consider when relying on Aloxi as the active control in a MEC noninferiority trial. Technically, the noninferiority (NI) analyses in Study C2006-01 should be based on analyses that compare Sustol and Aloxi in populations comparable to those studied in the trials for which Aloxi was granted its indications.

In neither of the applicant's original or updated MEC analyses was AC included as a MEC regimen, as it was in the Aloxi trials that were the basis for its approval for MEC, (b) (4)

the reviewers conducted additional analyses to assess NI when the chemotherapy regimens were grouped in a similar fashion to the trials that supported Aloxi's approval. Before doing so, the reviewers assessed the adequacy of the applicant's recategorization based on ASCO and found that some anthracycline regimens were miscoded as AC. I will summarize the FDA's assessment of the re-categorization of Study C2006-01 and additional exploratory analyses conducted by FDA in

the sections that follow. The high level summary list of the content of the following sections is provided below:

- 1) Assessment of the applicant's reassignment of emetogenicity based on ASCO Guidelines and definition of per protocol in Study C2006-01
- 2) Reanalysis of NI of Sustol vs. Aloxi in MEC subgroup of Study C2006-01 – using the corrected ASCO Guideline derived reassignment data base, based on FDA's evaluation in #1.
- 3)  (b) (4)
- 4) Reanalysis of NI of Sustol vs Aloxi in the AC + MEC subgroup of Study C2006-01, where the MEC assignment is based on the ASCO guidelines. This analysis population should be comparable to the overall population studied in the trials that supported Aloxi's approval for MEC - using the corrected reassignment database, based on FDA's evaluation in #1.
- 5) Reanalysis of NI of Sustol vs Aloxi based on the AC subgroup only of Study C2006-01 (the majority of the population studied to support the MEC indication for Aloxi) – using the corrected reassignment database, based on FDA's evaluation in #1.
- 6)  (b) (4)
- 7)  (b) (4)
- 8)  (b) (4)

Overall, these analyses provided support that Sustol is effective for acute and delayed phase of MEC and AC. I will end this section with the applicant's exploratory analyses of impact of age on efficacy, using the corrected MITT population of Study C2006-01, and limiting to the analysis to the MEC and AC subpopulations of the trial.

7.2.1 Assessment of applicant's reassignment of emetogenicity based on ASCO Guidelines and application of the per protocol definition. The clinical reviewers evaluated the dataset for accuracy and consistency of application of the ASCO Guidelines emetogenicity

categorization. They noted discrepancies attributable to the applicant’s decision to include liposomal doxorubicin as HEC chemotherapy when combined with cyclophosphamide, and as MEC when not combined with cyclophosphamide. Because liposomal doxorubicin is considered only mildly emetogenic, the reviewers sent an information request to the applicant asking for reanalyses in which liposomal doxorubicin combination regimens were correctly categorized. Furthermore, the reviewers noted there appeared to have been inconsistent application of the per protocol definition, in terms of whether or not the dexamethasone dose stated in the protocol had been administered. The information request also asked the applicant to address those inconsistencies in the reanalyses. The applicant submitted those analyses and the Statistical reviewer confirmed the results. The reanalyses are described in the sections below.

7.2.2 Reanalysis of NI of Sustol vs. Aloxi – using the corrected reassignment data base for MEC, based on FDA’s evaluation in #1. The “corrected” updated analyses for the MEC subgroup are presented in the tables below, where “New” refers to the reclassification of liposomal doxorubicin to low emetogenicity. In these reanalyses, Sustol 500 mg was noninferior to palonosetron in the per protocol and mITT analyses of both the acute and delayed phases in MEC. The red font rows refer to analyses in which the per protocol population was revised to ensure consistent application of the per protocol definition based on dexamethasone administration.

Table 20: Study C2006-01 Cycle 1 Acute, Delayed and Overall CR Results by ASCO MEC Classification before and after correction of liposomal doxorubicin emetogenicity category

Endpoint/ Population	APF 500 mg (Sustol 10 mg) n/N (%)	Aloxi n/N (%)	Difference (%) (APF-Aloxi)	95% CI	Fisher’s p-value
ASCO MEC – Acute CR (Original, 0-24 hours post-chemotherapy)					
ITT	176/216 (81.5)	188/219 (85.8)	-4.3	(-11.5, 2.7)	0.2438
mITT	171/205 (83.4)	187/211 (88.6)	-5.2	(-12.1, 1.5)	0.1566
PP	153/180 (85.0)	177/193 (91.7)	-6.7	(-13.6, -0.2)	0.0514
ASCO MEC – Acute CR (NEW, 0-24 hours post-chemotherapy)					
ITT	171/210 (81.4)	184/214 (86.0)	-4.6	(-11.6, 2.5)	0.2367
mITT	166/200 (83.0)	183/206 (88.8)	-5.8	(-12.6, 0.9)	0.1155
PP	148/175 (84.6)	173/189 (91.5)	-6.9	(-13.6, -0.3)	0.0506
PP (IV Dex Revised)	148/175 (84.6)	171/187 (91.4)	-6.8	(-13.6, -0.2)	0.0512
ASCO MEC – Delayed CR (Original, 24-120 hours post-chemotherapy)					
ITT	147/216 (68.1)	148/219 (67.6)	0.5	(-8.3, 9.4)	0.9187
mITT	142/205 (69.3)	147/211 (69.7)	-0.4	(-9.4, 8.5)	1.0000
PP	126/180 (70.0)	139/193 (72.0)	-2.0	(-11.3, 7.2)	0.7320
ASCO MEC – Delayed CR (NEW, 24-120 hours post-chemotherapy)					
ITT	142/210 (67.6)	145/214 (67.8)	-0.2	(-9.0, 8.8)	1.0000
mITT	137/200 (68.5)	144/206 (69.9)	-1.4	(-10.4, 7.6)	0.8298

PP	121/175 (69.1)	136/189 (72.0)	-2.9	(-12.2, 6.6)	0.5669
PP (IV Dex Revised)	121/175 (69.1)	135/187 (72.2)	-3.1	(-12.4, 6.3)	0.5641
ASCO MEC – Overall CR (Original, 0-120 hours post-chemotherapy)					
ITT	139/216 (64.4)	143/219 (65.3)	-0.9	(-9.9, 8.0)	0.8416
mITT	134/205 (65.4)	142/211 (67.3)	-1.9	(-11.1, 7.2)	0.6797
PP	120/180 (66.7)	136/193 (70.5)	-3.8	(-13.3, 5.7)	0.4369
ASCO MEC – Overall CR (NEW, 0-120 hours post-chemotherapy)					
ITT	134/210 (63.8)	140/214 (65.4)	-1.6	(-10.7, 7.5)	0.7610
mITT	129/200 (64.5)	139/206 (67.5)	-3.0	(-12.2, 6.2)	0.5317
PP	115/175 (65.7)	133/189 (70.4)	-4.7	(-14.2, 4.9)	0.3687
PP (IV Dex Revised)	115/175 (65.7)	132/187 (70.6)	-4.9	(-14.5, 4.7)	0.3663

Includes Site 504 in ITT, excludes from mITT and PP. Grouped by ADEM.EMETOGA. PP selected from ADEF2012.PERPRORE less those exclusions due to stratification and dexamethasone infractions in PP2010.PPREASON. “Original” indicates results from Addendum CSR. “New” reclassifies 11 APF 500 mg and palonosetron subjects given liposomal doxorubicin from Moderately to Low (i.e., removes them). “PP (IV Dex Revised)” excludes 2 subjects from the prior PP row who did not receive IV dexamethasone on Day 1

(b) (4)

(b) (4)



7.2.4 Reanalysis of NI based on the AC + MEC (ASCO designation) population only (the population studied to support the MEC indication for Aloxi) – using the corrected reassignment database and the revised per protocol definition based on dexamethasone.

Aloxi’s approval for MEC acute and delayed phase was based on trials in which over 50% of patients received AC chemotherapy (approximately 50-60% across the trials). For this reason, the “corrected” analyses were also conducted in the population that received MEC plus AC chemotherapy. Those analyses, summarized in the table below, also demonstrate NI in both the acute and delayed phases of MEC. In these re-analyses, Sustol 500 mg was noninferior to palonosetron in the per protocol and mITT analyses of both the acute and delayed phases. The red font rows refer to analyses in which the per protocol population was revised to ensure consistent application of the per protocol definition based on dexamethasone administration.

Table 22. Study C2006-01: Cycle 1 Acute, Delayed and Overall CR Results for the subpopulation treated with AC or MEC as per ASCO Guidelines, after correction of liposomal doxorubicin emetogenicity category

Endpoint/ Population	APF 500 mg (Sustol 10 mg) n/N (%)	Palonosetron n/N (%)	Difference (%) (APF-Palo)	Confidence Intervals ¹		Fisher’s p-value
				Size	Interval	

MEC + AC – Acute CR (0-24 hours post-chemotherapy)						
ITT	254/328 (77.4)	255/325 (78.5)	-1.1	95% 97.5% 98.33% 98.75%	(-7.4, 5.3) (-8.3, 6.2) (-8.8, 6.7) (-9.1, 7.1)	0.7775
mITT	249/317 (78.5)	254/315 (80.6)	-2.1	95% 97.5% 98.33% 98.75%	(-8.4, 4.2) (-9.3, 5.1) (-9.8, 5.6) (-10.1, 5.9)	0.5542
PP	229/284 (80.6)	241/288 (83.7)	-3.1	95% 97.5% 98.33% 98.75%	(-9.3, 3.2) (-10.2, 4.1) (-10.7, 4.6) (-11.0, 4.9)	0.3825
PP (IV Dex Revised)	229/284 (80.6)	239/286 (83.6)	-3.0	95% 97.5% 98.33% 98.75%	(-9.2, 3.4) (-10.1, 4.3) (-10.6, 4.7) (-10.9, 5.1)	0.3832
MEC + AC – Delayed CR (24-120 hours post-chemotherapy)						
ITT	196/328 (59.8)	195/325 (60.0)	-0.2	95% 97.5% 98.33% 98.75%	(-7.8, 7.3) (-8.8, 8.4) (-9.4, 8.9) (-9.8, 9.3)	1.0000
mITT	191/317 (60.3)	194/315 (61.6)	-1.3	95% 97.5% 98.33% 98.75%	(-8.9, 6.3) (-10.0, 7.4) (-10.6, 8.0) (-11.0, 8.4)	0.7449
PP	174/284 (61.3)	181/288 (62.8)	-1.5	95% 97.5% 98.33% 98.75%	(-9.5, 6.4) (-10.7, 7.5) (-11.3, 8.1) (-11.7, 8.6)	0.7306
PP (IV Dex Revised)	174/284 (61.3)	180/286 (62.9)	-1.6	95% 97.5% 98.33% 98.75%	(-9.6, 6.3) (-10.8, 7.4) (-11.4, 8.1) (-11.8, 8.5)	0.7299
Endpoint/ Population	APF 500 mg (Sustol 10 mg) n/N (%)	Palonosetron n/N (%)	Difference (%) (APF-Palo)	Confidence Intervals ¹		Fisher's p-value
				Size	Interval	
MEC + AC – Overall CR (0-120 hours post-chemotherapy)						
ITT	184/328 (56.1)	183/325 (56.3)	-0.2	95%	(-7.8, 7.4)	1.0000

Endpoint/ Population	APF 500 mg (Sustol 10 mg) n/N (%)	Palonosetron n/N (%)	Difference (%) (APF-Palo)	Confidence Intervals ¹		Fisher's p-value
				Size	Interval	
MEC + AC – Overall CR (0-120 hours post-chemotherapy)						
mITT	179/317 (56.5)	182/315 (57.8)	-1.3	95%	(-9.0, 6.4)	0.7484
PP	164/284 (57.7)	173/288 (60.1)	-2.4	95%	(-10.4, 5.7)	0.6103
PP (IV Dex Revised)	164/284 (57.7)	172/286 (60.1)	-2.4	95%	(-10.5, 5.7)	0.6095

¹Two-sided confidence intervals are given that correspond to the original Hochberg simultaneous testing of 4 primary hypotheses (acute and delayed CR for each of 2 Sustol doses versus palonosetron).

Includes Site 504 in ITT, excludes from mITT and PP. Group selected first by ADEM.EMETOGA=Moderately plus [ADEM.EMETOGA=Highly AND Regimen=AC AND EMETOGL=Moderately]. PP selected from ADEF2012.PERPRORE less those exclusions due to stratification and dexamethasone infractions in PP2010.PPREASON. **“PP (IV Dex Revised)” excludes 2 subjects from the prior PP row who did not receive IV dexamethasone on Day 1.**

When the sample sizes in the new analyses are compared between the MEC only vs. the MEC plus AC analyses in Tables 20 and 22 above (to determine the number of AC patients vs. the total number of patients in the MEC plus AC analysis), it is apparent that the proportion of AC patients in the MEC+AC analysis (34-38% in the mITT and PP analyses of acute phase analyses and delayed phase analyses) is lower than that in the Aloxi trials that supported its MEC approval. When the point estimate for the difference between the CR rates in the Sustol and palonosetron arms is compared between the MEC-only and the MEC+AC analyses, the difference is numerically smaller between arms in the MEC+AC analyses, which suggests that one might predict that had there been a higher proportion of AC patients in the analysis, the NI analysis results would not have been unfavorably impacted, assuming that the additional AC patients had similar responses as those patients treated with AC in the trial. A summary of the deltas and lower bound of the confidence intervals for the two subgroups and the two phases is presented in Table 23 below. For both phases (acute and delayed) and for both the mITT and PP analyses, the CR point estimates were numerically higher in the palonosetron arm.

Table 23. Summary of deltas (CR Sustol minus CR Aloxi) and associated lower bounds of the 95% confidence intervals by phase for the MEC vs. MEC+AC subgroups of Study C2006-01.

		Sustol CR minus Palonosetron CR		Lower bound of 95% CI	
		MEC only	MEC+AC	MEC only	MEC+ AC
Acute Phase	mITT	-5.8	-2.1	-12.6	-8.4
	PP	-6.9	-3.1	-13.6	-9.3
Delayed phase	mITT	-1.4	-1.3	-10.4	-8.9
	PP	-2.9	-1.5	-12.2	-9.5

See Sections 7.2.7 and 7.2.8 below for exploratory analyses of the AC-only subgroup of Study C2013 -01.

7.2.5 Reanalysis of NI of Sustol vs Aloxi based on the AC population only (the majority of the population studied to support the MEC indication for Aloxi) – using the corrected reassignment database, based on FDA’s evaluation in #1. An exploratory analysis of efficacy in the AC-only subgroup of Study C2006-01, conducted by the Statistical reviewer, is presented in Table 24 below. In this subgroup there was a numerically higher CR rate in the Sustol treated patients than the Aloxi treated patients, primarily in the acute phase. The higher CR point estimates in the Sustol arm compared to the palonosetron arm contribute to the more favorable NI results observed in the tables above in the MEC+AC subgroup relative to the MEC-only subgroup.

Table 24. Study C2006-01: AC Subgroup Analysis – Acute and Delayed Phases

Acute Phase	AC Subgroup		
	Sustol-10 mg	Palo	p-value/95% CI
ITTA	70.3% (N=118)	64% (N=111)	0.31 (-5.8, 18.5)
MITTA	70.9% (N=117)	65.1% (N=109)	0.35 (-6, 18)
PPREV (ONLY PTS IN MITTA)	74.3% (N=109)	68.7% (N=99)	0.37 (-6.7, 17.9)

Delayed Phase	AC Subgroup		
	Sustol-10 mg	Palo	p-value/95% CI
ITTA	45.8% (N=118)	45.1% (N=111)	0.91 (-12, 14)
MITTA	46.2% (N=117)	45.9% (N=109)	0.97 (-13, 13.3)
PPREV (ONLY	48.6%	45.5%	0.65

Delayed Phase	AC Subgroup		
	Sustol-10 mg	Palo	p-value/95% CI
PTS IN MITTA)	(N=109)	(N=99)	(-10, 17)

These analyses of Study C2006-01 provide support that Sustol is effective for acute and delayed phase of MEC and AC. (b) (4)

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7.2.9 Age Subgroup analyses of Study C2006-01 using the corrected MITT population, and limiting the analyses to the populations treated with MEC or AC.

The applicant submitted the following age subgroup analyses, based on the analysis population from Study C2006-01 that would be labeled.

Table 28. Study C2006-01: Delayed Phase CR, Applicant’s age subgroup analysis in MITT population limited to MEC plus AC.

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

Source: Sponsor’s Revised Table 2.1.1.1 from SN0113

The analyses in the above table suggest that in the delayed phase, patients ≥65 years of age tend to have a higher response to both Sustol (500mg) and Aloxi than patients <65 years of

age. The nominal p value for Sustol 500 mg suggested a trend, and the nominal p value for Aloxi suggested a significantly higher response among older patients. Comparisons between the two products (Sustol 500 mg vs. Aloxi) demonstrated a similar rate of CR between drugs in the younger age subgroup, whereas a numerically higher response with Aloxi was observed in the older age subgroup (which was not nominally significant).

Table 29. Study C2006-01: Acute Phase CR, Applicant’s age subgroup analysis in MITT population limited to MEC plus AC.

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

Source: Sponsor’s Revised Table 2.1.1.2 from SN0113

The analyses in the above table suggest that in the acute phase, patients ≥65 years of age tend to have a numerically higher response to both Sustol (500mg) and Aloxi than patients <65 years of age. The nominal p value for Aloxi suggested a significantly higher response among older patients than in younger patients, whereas the numerically higher CR rate in the older age group vs. younger patients treated with Sustol 500mg was not nominally significant. (Note that the lower Sustol dose tested is associated with a nominally significant p value in this exploratory analysis.) Comparisons between the two products (Sustol 500 mg vs. Aloxi) demonstrated numerically higher rate of CR between drugs in the younger age subgroup treated with Sustol 500mg, whereas there was a numerically higher response observed in the older age subgroup treated with Aloxi. Neither difference was statistically significant.

The differences observed in these exploratory analyses of the Sustol dose that will be approved were not statistically persuasive, and therefore these data were not included in Section 8.5 Geriatric Use of the product label.

Summary. Reanalyses of the combined HEC/MEC trial (Study C2006-01) submitted in the original application support that Sustol is effective for CINV in the acute and delayed phase of MEC. These analyses support the efficacy of Sustol for CINV in the setting of MEC and subgroup analyses support the efficacy of Sustol for CINV in the setting of AC. (This population (MEC or AC) is consistent with the populations enrolled in the palonosetron trials that supported its approval for the MEC acute and delayed phase indication).

Given that the comparator arm of Study C2006-01, Aloxi IV, is approved for MEC based on clinical trials that enrolled a mixture of patients receiving MEC or AC, the reviewers determined that the favorable results of the subgroup MEC + AC subgroup of Study C2006-01 are adequate to support approval of Sustol for acute and delayed phase CINV associated with

MEC or AC. Study C2006-01 did not include an NK-1 inhibitor as part of the antiemetic regimen administered to patients in that trial; however, the trial was a noninferiority trial, and the Aloxi IV comparator was approved based on clinical trials that did not utilize an NK-1 inhibitor (for both the MEC and HEC indications). ASCO Guidelines (Basch E, Prestrud A, et al. 2011 Antiemetics: American society of Clinical Oncology Clinical Practice Guideline Update) recommend use of an NK-1 inhibitor in the HEC setting, including AC. Use of an NK-1 inhibitor is optional for MEC. The ASCO Antiemetics Focused Update published online on November 2, 2015 states that all patients who receive HEC, including AC, should be offered “a three-drug combination of an NK1 receptor antagonist, a 5-THE receptor antagonist, and dexamethasone.”

(b) (4)

Ultimately, the review team concluded that the efficacy data provided in this NDA support approval of Sustol for the following indication:

“SUSTOL is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.”

Given that the approval is based on the results of Study C2006-01, the efficacy data presented in Section 14 Clinical Studies of the product label will be limited to the results of Study C2006-01, and will only include the results for the AC + MEC subgroup of Study C2006-01. The following table summarizing efficacy will be included in the label:

Table 30. Efficacy table to be included in Section 14 Clinical Studies of the Sustol product label.

Number and Percentage of Patients Who Achieved Complete Response with MEC or AC Combination Chemotherapy[‡]

Moderately Emetogenic Chemotherapy

Complete Response	SUSTOL 10 mg subcutaneous N=200 n (%)	Palonosetron hydrochloride, 0.25 mg intravenous N=206 n (%)	Difference (95% CI[§]): SUSTOL minus Palonosetron
Acute Phase (0 – 24 hours)	166 (83)	183 (89)	-6 (-13, 1)
Delayed Phase (>24 – 120 hours)	137 (69)	144 (70)	-1 (-10, 8)

[‡] Complete response defined as no emetic episodes and no use of rescue medications.

[§] This study was designed to show non-inferiority in the acute phase or delayed phase for patients receiving moderately emetogenic chemotherapy. A lower bound greater than -15% demonstrates non-inferiority between SUSTOL and comparator.

AC Combination Chemotherapy

Complete Response	SUSTOL 10 mg subcutaneous N=171 n (%)	Palonosetron hydrochloride, 0.25 mg intravenous N=156 n (%)	Difference (95% CI^{§§}): SUSTOL minus Palonosetron
Acute Phase (0 – 24 hours)	120 (70)	99 (64)	6 (-3, 17)
Delayed Phase (>24 – 120 hours)	85 (50)	74 (47)	2 (-9, 13)

^{§§} This study was designed to show non-inferiority in the acute phase and superiority in the delayed phase. A lower bound greater than -15% demonstrates non-inferiority between SUSTOL and comparator. Because a lower bound did not exceed 0%, superiority was not demonstrated between SUSTOL and comparator.

The Statistical reviewer recommended presentation of the analysis utilizing the 95% confidence interval.

Study C2006-01 utilized two different dexamethasone regimens for HEC and MEC. The Dosage and Administration section will include the dexamethasone dose used in the clinical trials for MEC and AC (HEC), respectively. The Dosage and Administration section will state that if an NK-1 receptor antagonist is added to the combination regimen, the dexamethasone dose should be modified to be consistent with the dexamethasone dose recommended in the NK-1 receptor antagonist label, given that there are drug-drug interactions between dexamethasone and some NK-1 receptor antagonists, which requires dexamethasone dose reduction. It was important to mention NK-1 receptor antagonists in the Sustol label, even though they were not studied in combination with Sustol in Study C2006-01, because 1) NK-1 receptor antagonists are recommended by ASCO Guidelines for use in AC, and are mentioned in the Guidelines as optional in the setting of MEC, and 2) there is a significant drug-drug interaction between dexamethasone and NK-1 antagonists that require dose modification to assure safety. Sustol has been studied in combination with an NK-1 receptor antagonist in Study C2013-01; (b) (4)

(b) (4) there were no safety issues identified in Study C2013-01 attributable to the use of Sustol with an NK-1 receptor antagonist. Section 6 Adverse Reactions will include the safety data from both Studies C2006-01 and C2013-1, and the introductory paragraph will inform users that some patients in the safety database were treated with a concomitant NK-1 inhibitor. The strong trend toward superiority in the AC subgroup of that trial, in the delayed phase, indicates that there is little reason to recommend against adding Sustol to an NK-1 antagonist combination antiemetic regimen from an efficacy standpoint.

The applicant had initially proposed in this resubmission that Studies C2006-01 and C2013-01 supported approval of an indication that included prevention of acute and delayed phases of CINV (b) (4)

as shown below:

NDA 022445/Original 1: Sustol is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.

(b) (4)

8. Safety

The major safety issues considered during the previous (second) review cycle were:

- 1) time to resolution of injection site reactions
- 2) the ability of the health care providers to administer the product (Human Factors Study)
- 3) potential for glycolic acid toxicity.

The second cycle CR letter deficiency list included a safety issue related to the Human Factors Study, and also included a non-CR issue (in additional comments) related to safety, i.e., the potential need for a postmarketing, randomized, controlled safety trial to evaluate patients who receive Sustol doses as frequently as every 7 days over the course of a year. (The proposed Dosage and Administration instructions for Sustol allowed for administration every 7 days.) The CR letter stated that q 7 day dosing safety data may be required because the applicant's metabolic fate study (Study C2011-01) had only accounted for approximately 1/3 of the polymer, and the major phase 3 trial (Study C2006-01) didn't include a non-Sustol control arm beyond Cycle 1, to allow for interpretation of safety data. Furthermore, the phase 3 trial had not collected serum chemistries in cycles beyond Cycle 1.

The applicant has now submitted additional Human Factors data to support changes in administration procedures proposed for labeling, including a change to a smaller gauge needle (18 gauge) and use of syringe warming devices. The current submission also included new clinical trials not previously reviewed by FDA, which provide new safety data. These trials include a new phase 3 randomized, controlled trial that enrolled patients treated with HEC chemotherapy for only one cycle (Study C2013-01). The additional new trials (Studies C2013-02, C2013-03 and C2014-01) were smaller and all enrolled healthy volunteers. They were conducted to further evaluate the safety of repeat dosing (Study C2013-02), evaluate

bioequivalence between administration in SQ tissue of the abdomen vs. nondominant arm (Study C2014-01), and to evaluate bioequivalence of Sustol produced at a new commercial site vs. Sustol used in the phase 3 clinical trials. The two bioequivalence studies utilized randomized cross over designs, with 2 week washout periods.

The following tables, reproduced from the applicant's ISS, summarize the sizes of the safety database from the original submission, the first resubmission and the current resubmission. Table 31 below summarizes the exposures in the clinical trials that enrolled patients; the only new patient trial is the new phase 3 HEC trial, Study C2013-01, which was a single cycle trial (in bold). Table 32 summarizes the studies that enrolled healthy volunteers. The three new healthy volunteer studies (Studies C2013-02, 2013-03, and 2014-01) are all marked in bold. Note that with the exception of the trials submitted in this current resubmission, the control arm was a saline injection.

Table 31. Enumeration of Subjects Phase 2-3 (Safety Population)

Study	Number of cycles of administration	APF530 250 mg N	APF530 500 mg N	APF530 750 mg N	Total APF530 N	Aloxi 0.25 mg N	Ondansetron 0.15 mg/kg N
Phase 2 C2005-01	Single APF530 dose	17	15	13	45		
Phase 3 C2006-01	≥1 APF530 dose ^a	636	642		1278	463 ^b	
	1 APF530 or Aloxi dose total + saline injection placebo	147	164		311		
	2 APF530 doses total	119	122		241		
	3 APF530 doses total	165	165		330		
	4 APF530 doses total	205	191		396		
Phase 2b C2007-01	Single APF530 dose	17	18		35		
Phase 3 C2013-01	Single APF530 or Ondansetron + polymer dose		456		456		459
All Cycles (Phase 2-3 Studies)	Total Subject Study Participations	670	1131	13	1814	463 ^b	459
	Total Unique Subjects ^c	668	1130	13	1806	463 ^b	459
Cycle 1 (Phase 2-3 Studies)	Total Subject Study Participations	498	957	13	1468	463 ^b	459
	Total Unique Subjects ^c	497	956	13	1461	463 ^b	459

^a APF530 N's contain Cycle 1 Aloxi subjects who received APF530 in Cycles 2-4.

^b Of the 463 subjects who received Aloxi in C2006-01 Cycle 1, 172 received APF530 250 mg and 174 received APF530 500 mg in subsequent C2006-01 cycles.

^c Cannot sum APF530 individual dose N's across columns to obtain Total APF530 N, given some subjects received a different APF530 dose across studies.

Source: [Module 5.3.5.3, Table 1.1](#)

Table 32: Enumeration of Healthy Subjects Phase 1 (Safety Population)

Study	Number of cycles of administration	APF530 125 mg N	APF530 250 mg N	APF530 500 mg N	APF530 1000 mg N	Total APF530 N
Phase 1 C2004-01	Single APF530 dose	6	8	6	6	26
Phase 1 C2011-01	Single APF530 dose				56	56
Phase 1 C2011-02	Single APF530 dose				10	10
Phase 1 C2013-02	≥ 1 APF530 dose			50		50
	1 APF530 dose total			2		2
	2 APF530 doses total			–		–
	3 APF530 doses total			–		–
Phase 1 C2013-03	≥ 1 APF530 dose			150		150
	1 APF530 dose total			6		6
	2 APF530 doses total			144		144
	3 APF530 doses total			–		–
Phase 1 C2014-01	≥ 1 APF530 dose			120		120
	1 APF530 dose total			7		7
	2 APF530 doses total			113		113
APF530 All Periods (Phase 1 Studies)	Total Subject Study Participations	6	8	326	72	412
	Total Unique Subjects ^a	6	8	321	72	407
APF530 Period 1 (Phase 1 Studies)	Total Subject Study Participations	6	8	326	72	412
	Total Unique Subjects ^a	6	8	321	72	407

Note that the product and saline control in the original application was delivered via a (b) (4) [REDACTED], whereas in the trials submitted in the current resubmission, the product was administered via a smaller 18 gauge x 5/8 inch needle. Another difference between the methods of administration in the trials was the use of warming devices: in the current submission, a warming device was used in the phase 3 trial (Study C2013-01) and two of the 3 smaller trials (Study C2013 – 02, i.e., the repeat dosing study, and Study 2014-01, i.e., BE trial evaluating abdominal vs. upper arm administration).

During the review of the newly submitted safety data, the Clinical reviewers identified additional safety concerns from what had been identified in previous cycles. In this section of my review, I will first present the results of the review of the new Human Factors data, as Human Factors issues related to safe SQ administration of this new polymeric granisetron dosage form were cited in the last CR letter. I will then present a high level overview of the adverse event rates observed in the new phase 3 trial (Study C2013-01) submitted for review in this resubmission, followed by a summary of the deaths, SAEs and discontinuations due to AEs in the newly submitted clinical trials. My review will then focus on the new safety review issues identified in this review cycle, which related to injection site reactions, adverse gastrointestinal events potentially attributable to sustained granisetron exposure associated with Sustol's dosage form, and CPK elevations that could potentially be related to muscle injury from the SQ polymer. I will discuss the overall tolerability of the regimen as evidenced by the reported injection site reactions and the study drop out rates. Finally, I will describe the safety findings from the newly submitted multi-dose study, Study C2013-02, (weekly x 4) which enrolled healthy volunteers, which is the only repeat-dosing study using the proposed commercial product presentation and administration technique. The applicant conducted the latter study to address the non-deficiency comment in the second cycle CR letter related to the safety of repeated exposure to polymer vehicle.

8.1 Human Factors Study Results. The second cycle CR letter included the following deficiency:

CONTAINER / CLOSURE SYSTEM

2. Your completed human factors validation study (XP-1179-045 Report) did not confirm that users could adequately administer Sustol with the proposed product design and its labeling, including instructions for use. Participants in the study reported difficulty pushing the plunger due to the viscosity of the product. We are concerned that, given the amount of force needed to administer this product, the instructions for use tested in the human factors study will result in administration errors. The instructions required that a health care professional use a single hand to both push the plunger and stabilize the syringe while administering the product. The force required to expel the viscous product from the syringe will make it difficult to maintain the injection in the correct tissue plane with use of a single hand.

You have proposed revised instructions for use that include an alternative technique to administer the product. Therefore, you must conduct additional human factors validation

testing to demonstrate that Sustol can be safely and effectively administered with the modified instructions for use. Please see the FDA correspondence dated March 26, 2013, containing our comments on your formative human factors testing and our recommendations on your proposed human factors validation study protocol.

In response to the CR letter, the applicant modified the device for administration as follows: 1) switched to a smaller gauge needle (18 gauge instead of the previous (b) (4)), 2) added a non-removable finger flange for better leverage, and 3) added warming gel packs (to lessen drug product viscosity). The applicant performed additional human factors studies to address the deficiency in the CR letter and to support the changes in the device/product presentation. The reviewers from the Division of Medication Error Prevention and Analysis (DMEPA) concluded that the studies demonstrated that health care providers “are able to use the product safely and effectively with the availability of Instructions for Use.” They noted that user errors observed in the study would not result in harm to the patient. The reviewers recommended the applicant modify the Instructions for Use to include a step clarifying that the user must remove the hub cover from the needle.

8.2 Overall Adverse Event Distribution in Study C2013-01. In this section, I have summarized the overall treatment emergent adverse events (TEAEs) in the new phase 3 trial, Study C2013-01, and have included summary TEAE data from the previously reviewed phase 3 trial, C2006-01, for comparison.

The following table summarizes the treatment emergent adverse events reported in Study C2013-01, excluding injection site reactions. The only adverse event in this table for which the rate in the Sustol arm exceeded the control arms was constipation (21.9% vs. 15.3%). Excluding injection site reactions, in the previously reviewed phase 3 trial, C2006-01, constipation was also the most common treatment emergent adverse event. The rate of constipation TEAEs in the first cycle of Study C2006-01 was 13.4% in the Sustol 250 mg arm, 15.4%, in the Sustol 500 mg arm, and 13.4% in the Aloxi arm. Numerically, the proportion of patients with constipation TEAEs was even higher in Study 2013-01, including in the control arm (21.9% and 15.3%, respectively).

Table 33. Study 2013-01: Treatment-Emergent Adverse Events (Excluding Injection Site Reactions) that Occurred in ≥5.0% of Subjects in Any Treatment Group (Safety Population) Copied from Study report

System Organ Class/ Preferred Term	Sustol 500 mg N=456 n (%)	Ondansetron 0.15 mg/kg N=459 n (%)
Subjects with at Least One Event	347 (76.1%)	354 (77.1%)
Blood and lymphatic system disorders	38 (8.3%)	50 (10.9%)
Neutropenia	26 (5.7%)	30 (6.5%)
Gastrointestinal disorders	223 (48.9%)	197 (42.9%)
Constipation	100 (21.9%)	70 (15.3%)

System Organ Class/ Preferred Term	Sustol 500 mg N=456 n (%)	Ondansetron 0.15 mg/kg N=459 n (%)
Nausea	76 (16.7%)	74 (16.1%)
Diarrhoea	40 (8.8%)	35 (7.6%)
Dyspepsia	27 (5.9%)	32 (7.0%)
General disorders and administration site conditions	131 (28.7%)	148 (32.2%)
Fatigue	95 (20.8%)	109 (23.7%)
Metabolism and nutrition disorders	60 (13.2%)	54 (11.8%)
Decreased appetite	24 (5.3%)	23 (5.0%)
Dehydration	23 (5.0%)	18 (3.9%)
Nervous system disorders	106 (23.2%)	133 (29.0%)
Headache	56 (12.3%)	82 (17.9%)
Dizziness	25 (5.5%)	25 (5.4%)
Psychiatric disorders	34 (7.5%)	47 (10.2%)
Insomnia	21 (4.6%)	29 (6.3%)

Abbreviations: N=total number of subjects in the Safety population; n=number of subjects with an event.
Reference: [Table 14.3.1.2.2](#)

The following table, which is reproduced from the applicant’s ISS compares the proportion of patients with any treatment emergent adverse event (TEAE) in Cycle 1 of the previous phase 3 trial, Study C2006-01, to the new phase 3 trial, Study C2013-01. This summary included injection site reactions. Note that there is a higher rate of overall TEAEs in the most recent trial than the previous trial, and a higher proportion of moderate and severe TEAEs, including in the control arms. The control in the previous trial, Study C2006-01, was Aloxi plus SQ saline injection. The control in the most recent trial, Study C2013-01, was ondansetron and a SQ polymer vehicle injection.

Table 34. Overall Summary of Treatment-Emergent Adverse Events, Including Injection Site Reactions, in Study C2013-01 and in Cycle 1 of Study C2006-01 (Using the Conventions from the 2015 Safety Update)

Category	C2006-01 Cycle 1		C2013-01	
	APF530 500 mg (N=468) n (%)	Aloxi+ saline (N=463) n (%)	APF530 500 mg (N=456) n (%)	Ond + polymer (N=459) n (%)
Subjects With Any Treatment-Emergent Adverse Event	328 (70.1)	292 (63.1)	413 (90.6)	411 (89.5)
Subjects Who Died	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)

Category	C2006-01 Cycle 1		C2013-01		
	APF530 500 mg (N=468) n (%)	Aloxi+ saline (N=463) n (%)	APF530 500 mg (N=456) n (%)	Ond + polymer (N=459) n (%)	
Subjects With Serious Adverse Events	20 (4.3)	10 (2.2)	28 (6.1)	16 (3.5)	
Subjects With Treatment-Related ^a Serious Adverse Event	0	0	2 (0.4)	1 (0.2)	
Subjects Who Discontinued Due to an Adverse Event	12 (2.6)	3 (0.6)	6 (1.3)	3 (0.7)	
Subjects Who Discontinued Due to a Treatment-Related ^a Adverse Event	1 (0.2)	0	0	0	
Subjects With an Adverse Event by Severity:	Mild	189 (40.4)	159 (34.3)	170 (37.3)	164 (35.7)
	Moderate	97 (20.7)	95 (20.5)	154 (33.8)	158 (34.4)
	Severe	42 (9.0)	38 (8.2)	89 (19.5)	89 (19.4)
Subjects With Treatment-Related ^a Adverse Event	159 (34.0)	84 (18.1)	302 (66.2)	295 (64.3)	

^a Possible, probable, definite, or missing relationship to study drug.

Note: A subject with events in more than one severity category is counted at the maximum severity category, with unknown or missing assumed to be severe.

Source: [Module 5.3.5.3 Table 4.1.2.1](#) and [C2013-01 CSR Table 14.3.1.1.1](#)

The following table, which is also reproduced from the applicant’s ISS compares the proportion of patients with treatment emergent adverse events (TEAEs) in Cycle 1 of the previous phase 3 trial, Study C2006-01, to the new phase 3 trial, Study C2013-01, excluding ISRs. While the overall proportions decrease in both arms of Study C2013-01 with removal of ISRs, the numerically higher rate in Study C2013-01 compared to Study C2006-01 remains. With elimination of the ISRs, the relative difference between arms diminishes.

Table 35. Overall Summary of Treatment-Emergent Adverse Events (Excluding Injection Site Reactions) in Study C2013-01 and in Cycle 1 of Study C2006-01 (Using the Conventions From the 2015 Safety Update)

Category	C2006-01 Cycle 1		C2013-01	
	APF530 500 mg (N=468) n (%)	Aloxi + saline (N=463) n (%)	APF530 500 mg (N=456) n (%)	Ond + polymer (N=459) n (%)
Subjects With Any Treatment-Emergent Adverse Event	284 (60.7)	283 (61.1)	347 (76.1)	354 (77.1)
Subjects Who Died	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)
Subjects With Serious Adverse Events	20 (4.3)	10 (2.2)	27 (5.9)	16 (3.5)
Subjects With Treatment-Related ^a Serious Adverse Event	0	0	1 (0.2)	1 (0.2)

Category	C2006-01 Cycle 1		C2013-01	
	APF530 500 mg (N=468) n (%)	Aloxi + saline (N=463) n (%)	APF530 500 mg (N=456) n (%)	Ond + polymer (N=459) n (%)
Subjects Who Discontinued Due to an Adverse Event	11 (2.4)	3 (0.6)	6 (1.3)	3 (0.7)
Subjects Who Discontinued Due to a Treatment-Related Adverse Event	1 (0.2)	0	0	0
Subjects With an Adverse Event by Severity:				
Mild	152 (32.5)	152 (32.8)	161 (35.3)	159 (34.6)
Moderate	90 (19.2)	93 (20.1)	121 (26.5)	136 (29.6)
Severe	42 (9.0)	38 (8.2)	65 (14.3)	59 (12.9)
Subjects With Treatment-Related ^a Adverse Event	53 (11.3)	41 (8.9)	75 (16.4)	79 (17.2)

^a Possible, probable, definite, or missing relationship to study drug.

Note: A subject with events in more than one severity category is counted at the maximum severity category, with unknown or missing assumed to be severe.

Source: [Module 5.3.5.3 Table 4.1.7.1](#) and [C2013-01 CSR Table 14.3.1.1.2](#)

The applicant attributed the differences observed between trials to the following: 1) non-US sites were included in the earlier trial (suggesting that AE reporting is lower at non-US sites), 2) there was more frequent and direct questioning about ISRs in 2013-01, 3) the instructions for ISR reporting in Study 2013-01 stated that the injection site reactions should be coded as treatment related, 4) inclusion of patients receiving MEC in the earlier trial, 5) and use of a prespecified grading scale for ISRs in Study 2013-01. The applicant attributed the higher reporting in general to higher reporting of injection site reactions and stated that these reactions “appear to be qualitatively similar with no new or unexpected safety findings identified between these 2 studies.” However, the reviewers were concerned about the higher rate of reporting of the injection site reactions in the most recent trial and could not agree with the applicant that the reactions were qualitatively similar between trials. The new reporting system employed in Study C2013-01 would be expected to have been more likely to reflect the patient’s experience and indicate that the injections can have a negative impact on how a patient feels and/or functions. (See discussions of ISRs in Section 8.4.1 below.)

8.3 Deaths, SAEs and Discontinuations for AEs.

This Section will focus primarily on the events observed in the new large phase 3 trial, Study C2013-01. However, there were additional new healthy subject trials submitted in this review cycle. The ISR events associated with those trials will be presented along with the ISR data from the phase 3 trials (8.4.2). Other events observed in those healthy volunteer trials will be described in subsections specifically labeled with those trial codes (Study C2013-02 in Section 8.5 and Study C2013-03 in Section 8.3.2.5).

8.3.1 *Deaths.* Although there were 5 deaths in Study C2013-01, (3 in the Sustol arm and 2 in the ondansetron arm), none were determined to be related to study drug, and I concur with this assessment. Note that in the previous safety review of C2006-01, the deaths observed in patients exposed to Sustol (either the 500mg or 250 mg dose), were not attributed to study drug by either the applicant or the Clinical reviewer. The patient population was receiving cytotoxic chemotherapy and had underlying malignancy.

8.3.2 *Serious Adverse Events.* There was an imbalance in serious adverse events (SAEs) between arms in Study C2013-01: Sustol=42 and Ondansetron =28. See table below for list of treatment emergent SAEs in Study 2013-01. Treatment emergent SAEs were reported in a numerically higher proportion of patients in the Sustol arm than in the ondansetron arm: 6.1% vs. 3.5%. Five of the Sustol SAEs [injection site infection (n=1), muscular weakness (n=1), atrial fibrillation (n=1), febrile neutropenia (n=1) and pneumonia (n=1)] were considered treatment related by the investigator, whereas only 1 of the ondansetron SAEs was considered treatment related [dehydration (n=1)]. I do not concur with the assessment that the muscle weakness event, febrile neutropenia and pneumonia were attributable to Sustol. I also question whether the atrial fibrillation was treatment related.

The table below lists the SAEs. There were 3 pancreatitis SAEs, all on the Sustol arm. There were SAEs of constipation and faecaloma (impaction) on the Sustol arm, and there was an SAE of an injection site infection. An equal number of renal failure SAEs occurred between arms. Although this table counts 4 SAEs of acute renal failure, review of the applicant’s narratives indicates that there were 5 acute renal failure SAEs: two on the Sustol arm and 3 on the ondansetron + polymer placebo arm.

Table 36. Treatment Emergent Serious Adverse Events

System Organ Class/ Preferred Term	APF530 500 mg N=456 n (%)	Ondansetron 0.15 mg/kg N=459 n (%)
Subjects with at Least One Event*	28 (6.1%)	16 (3.5%)
Blood and lymphatic system disorders	4 (0.9%)	1 (0.2%)
Febrile neutropenia	4 (0.9%)	1 (0.2%)
Cardiac disorders	1 (0.2%)	0
Atrial fibrillation	1 (0.2%)	0
Gastrointestinal disorders	10 (2.2%)	5 (1.1%)
Vomiting	3 (0.7%)	3 (0.7%)
Nausea	2 (0.4%)	3 (0.7%)
Pancreatitis	2 (0.4%)	0
Abdominal pain	1 (0.2%)	1 (0.2%)
Constipation	1 (0.2%)	0
Diarrhoea	1 (0.2%)	0
Faecaloma	1 (0.2%)	0

System Organ Class/ Preferred Term	APF530 500 mg N=456 n (%)	Ondansetron 0.15 mg/kg N=459 n (%)
Pancreatitis acute	1 (0.2%)	0
Diverticular perforation	0	1 (0.2%)
General disorders and administration site conditions	1 (0.2%)	0
Pyrexia	1 (0.2%)	0
Infections and infestations	1 (0.2%)	3 (0.7%)
Injection site infection	1 (0.2%)	0
Breast abscess	0	1 (0.2%)
Peritonitis	0	1 (0.2%)
Pneumonia	0	1 (0.2%)
Injury, poisoning and procedural complications	1 (0.2%)	0
Traumatic intracranial haemorrhage	1 (0.2%)	0
Metabolism and nutrition disorders	2 (0.4%)	1 (0.2%)
Dehydration	2 (0.4%)	1 (0.2%)
Neoplasms benign, malignant and unspecified including cysts and polyps	2 (0.4%)	0
Malignant neoplasm progression	2 (0.4%)	0

System Organ Class/ Preferred Term	APF530 500 mg N=456 n (%)	Ondansetron 0.15 mg/kg N=459 n (%)
Nervous system disorders	3 (0.7%)	3 (0.7%)
Cerebrovascular accident	2 (0.4%)	1 (0.2%)
Convulsion	1 (0.2%)	0
Presyncope	0	1 (0.2%)
Syncope	0	1 (0.2%)
Psychiatric disorders	0	1 (0.2%)
Mental status changes	0	1 (0.2%)
Renal and urinary disorders	2 (0.4%)	2 (0.4%)
Renal failure acute	2 (0.4%)	2 (0.4%)
Reproductive system and breast disorders	1 (0.2%)	0
Breast pain	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	3 (0.7%)	1 (0.2%)
Dyspnoea	2 (0.4%)	0
Haemoptysis	1 (0.2%)	0
Chronic obstructive pulmonary disease	0	1 (0.2%)

Note: A subject is counted once if the subject reported one or more events in each system organ class/preferred term. Preferred terms within each system organ class are sorted by decreasing APF530 500 mg frequency. This table summarizes all treatment-emergent SAEs, including treatment-emergent SAEs leading to death.

* Narratives have been written for 70 subjects with serious adverse events, of which 44 subjects had treatment emergent serious adverse events, which are displayed in the above table. The remaining subjects had serious adverse events which were not treatment emergent.

Abbreviations: N=total number of subjects in the Safety population; n=number of subjects with an event

I will describe the specific SAEs of interest below (an injection site infection, acute renal failure, constipation and pancreatitis) from Study C2013-01. I will also describe two additional SAEs from a healthy volunteer bioequivalence study, Study C2013-03. I have evaluated the narrative for the SAE of muscle weakness, which was considered treatment related by investigator, and will not present it here as I concur with the applicant that it was not related to study drug (brachial plexus injury from “pulmonary artery catheter insertion”).

8.3.2.1 Injection site infection.

[ID (b) (6)] Sustol treated 56 year old patient with breast cancer, treated with AC. She had no concomitant illness that would increase her risk of skin infection. She was treated on Feb 19, and developed a fever on March 4 (approx. 13 days post treatment). She was admitted to hospital with warmth, redness and swelling around her abdominal injection site. Her admission laboratory tests revealed neutropenia. She was treated with IV antibiotics for “abdominal cellulitis” and was discharged 4 days later.

See Section 8.4.3 below for a description of overall injection site infection AEs in the NDA database.

8.3.2.2 Acute renal failure. Although the number of renal failure events was similar between arms, given that the polymer vehicle raised concerns during previous review cycles and that patients in the ondansetron control arm received polymer injections, I evaluated the narratives for those events for evidence that they could have been attributable to polymer; however, all these SAEs occurred in elderly patients who received cisplatin combination chemotherapy, which was the most likely cause of the change in BUN and creatinine.

(Pt (b) (6)) Sustol treated 76 yo male patient who received cisplatin and premetrexed for nonsmall cell lung carcinoma. The patient had multiple medical conditions, including hypertension and coronary artery disease. He presented to the ER for weakness six days later and was diagnosed with acute renal failure; his creatinine had increased from 1.47 to 4.7 mg/dL. Additional diagnoses included hypokalemia, cytopenia and C. difficile infection. His hospital course was complicated by venous thrombosis and presumed aspiration pneumonia. The patient died. I concur with the investigator’s conclusion that the renal failure was not related to Sustol. It was more likely related to the chemotherapy.

(Pt (b) (6)) Ondansetron treated 77 yo male patient who received cisplatin and docetaxel for nonsmall cell lung carcinoma. His concomitant medical conditions included mild renal insufficiency, COPD, hypokalemia and hypomagnesaemia and left atrial enlargement. His baseline creatinine was 100 micromol/L. He presented to the ER six days after treatment after

a syncopal episode. He complained of chest tightness and dyspnea and was found to be tachycardic at 126 bpm. He was cytopenic, and his creatinine was 3.3 mg/dL (BUN was 85 mg/dL) at the time of admission. The patient died. I concur with the investigator that the event was not related to the placebo (polymer) + ondansetron. The most likely etiology was the patient's chemotherapy.

(Pt (b) (6)) Sustol treated 67 yo male with head and neck cancer and lung cancer who received cisplatin and gemcitabine. At a follow up visit one week after treatment his creatinine had elevated to 2.9 mg/dL. GFR was 22 ml/min/1.73 m². He was given IV fluids and 3 days later his creatinine was 2.7 mg/dL, and he was admitted to the hospital. The acute kidney injury was considered related to the cisplatin; I concur. Although he was discharged from the hospital with improved creatinine, the following day he developed shortness of breath and back pain, became unresponsive and did not respond to cardiopulmonary resuscitation.

(Pt ID (b) (6)) Ondansetron treated 73 yo female with ovarian cancer received cisplatin and gemcitabine, and presented with elevated creatinine (2.08 mg/dL) and BUN (54 mg/dL) seven days after treatment. The diagnosis of ARF was made 4 days later. Renal function improved with IV saline.

(Pt (b) (6)) Ondansetron (plus polymer placebo) treated 62 year old female with breast carcinoma, received AC chemotherapy. She had a past medical history significant for hypertension, hyperuricemia, and hypercalcemia. The day after treatment she presented with grade 4 anasarca and grade 4 bilateral lower extremity edema. Five days later she was found to have ARF and was admitted. Her creatinine was 1.4 mg/dL and BUN was 35 mg/dL. She was cytopenic. She was treated with diuretics and prednisone "for her anasarca". She improved and was discharged 25 days later; she was withdrawn from the trial. The investigator did not consider the event treatment related. It is not clear what the underlying etiology of the event was, however, and the laboratory values provided do not clearly indicate that the patient actually had ARF.

8.3.2.3 Constipation. There was a numerically higher proportion of patients in the Sustol arm of Study C2013-01 who had TEAEs of constipation. There were also SAEs related to constipation. The reviewers expressed concern that the prolonged exposure to granisetron associated with Sustol may increase the risk of constipation associated with granisetron relative to the currently approved granisetron products. The currently marketed IV granisetron product's Section 6.1 Clinical Trials Experience section of the label reports that constipation was the second most common adverse reaction reported in the clinical trials (3%). The granisetron patch (Sancuso, which provides sustained granisetron exposure over days) label reports constipation as the most common adverse reaction reported in the clinical trials; the rate (5%) was numerically higher on the Sancuso arm than on the oral granisetron control arm (3%).

(Pt ID (b) (6)) Sustol treated 62 yo female with metastatic adenocarcinoma of the lung received cisplatin and vinorelbine. The patient had history of constipation and was taking MS Contin and Vicodin at study entry. Her ongoing bowel medications included Miralax. Seven

days after study treatment, she presented to the ER complaining of abdominal pain and not having had a bowel movement for 4 days. The investigator attributed the episode to constipation from pain medication and unrelated to study medication. Although this patient was taking significant narcotics and was taking Miralax at study entry, presumably to manage opioid induced constipation, it is possible that the granisetron exposure over multiple days from the Sustol injection contributed to worsened constipation.

(Pt (b) (6)) Sustol treated 51 yo female with bladder cancer received cisplatin and gemcitabine. The constipation led to hospitalization. Her concomitant medical conditions included history of constipation, type 2 DM, hypothyroidism, adrenal insufficiency, “colitis”, hypertension, urinary incontinence, fibromyalgia. Baseline medications included duloxetine, fentanyl, morphine sulfate insulin, hydrocortisone, losartan, atorvastatin, sulfasalazine, senna and lactulose. She developed abdominal pain 2 days post chemotherapy. She was treated with methylnaltrexone. Abdominal CT revealed a midline 8 cm mass and a 4 cm mass in the RLQ. The investigator considered the event unlikely related to study medication. The patient was on chronic opioid narcotics and baseline medications to manage constipation, presumably from her opioid use. It is possible that the addition of granisetron could have increased her baseline constipation from her opioids. As stated above, the granisetron product label reports constipation as an adverse reaction observed in the clinical trials.

(Pt ID (b) (6)) Sustol treated 58 yo male with head and neck carcinoma received cisplatin and docetaxel. He was admitted 6 days later with a 5 day history of constipation associated with nausea and vomiting. CT revealed a large amount of stool in the descending/sigmoid colon. His constipation was attributed to narcotics for his tumor pain. His medical history included constipation. His baseline medications included MS Contin, Vicodin and Effexor. His only baseline bowel medication for constipation was docusate. Although this patient was taking narcotics and docusate at study entry, the latter to presumably manage opioid induced constipation, it is possible that the granisetron exposure over multiple days from the Sustol injection contributed to worsened constipation.

8.3.2.4 Acute pancreatitis. There were no TEAEs or SAEs of pancreatitis on the ondansetron control arm. Although one of the 3 pancreatitis events in the Sustol arm of Study C2013-01 occurred in a patient with a history of pancreatitis, the fact that all 3 events occurred in the Sustol arm raises questions about the potential causal relationship granisetron may have had with these events. I have summarized the cases below. Review of the applicant’s study report for the previously reviewed phase 3 trial, Study C2006-01, revealed no cases of pancreatitis. The approved IV granisetron label and the granisetron patch label do not mention pancreatitis, including in the postmarketing experience section. There was no rechallenge to further assess causality, as there was only 1 cycle of treatment administered in Study C2013-01; however, if the event was related to polymer vehicle, the continued exposure from the subcutaneous depot site might have been thought to cause persistent and ongoing signs and symptoms of pancreatitis. As described above, all of these events resolved in <10 days. I examined the most recent NDA reviews for antiemetics for evidence of pancreatitis. The rolapitant NDA had one case of pancreatitis in 1567 patients exposed to any dose of rolapitant. The episode occurred in a second cycle of treatment. In the recently reviewed Emend 150 mg

IV NDA supplement for MEC, there was one case of pancreatitis in the control group of the trial submitted for review. Given the lack of cases in Study C2006-01, the fact that one patient had a history of pancreatitis, and the evidence of pancreatitis in other antiemetic applications, I have concluded that the 3 events in Study C2013-01 do not constitute a safety signal.

[ID (b) (6)] Sustol arm: 53 yo female with breast CA was treated with AC and presented 4 days later with a complaint of “stomach burning”, which was treated with a proton pump inhibitor. The following day she was admitted with vomiting, elevated pancreatic enzymes and a diagnosis of acute pancreatitis. No gallstones were detected on imaging. The event, which lasted 7 days, resolved and she was discharged. She had a past medical history of hyperlipidemia and hypertension.

[ID (b) (6)] Sustol arm: 38 yo female with breast CA treated with AC presented 4 days later with acute pancreatitis. The event lasted 6 days.

[ID (b) (6)] Sustol arm: 65 yo female with breast CA treated with AC was hospitalized for pancreatitis 4 days after treatment. She presented with severe abdominal pain, bloating and vomiting, rising lipase. The event lasted 8 days. She had a past medical history of pancreatitis.

8.3.2.5 SAEs from Study 2013-03. There were also two SAEs in one of the small healthy volunteer studies, i.e., C2013-03, which was the bioequivalence trial conducted to evaluate Sustol produced at a new manufacturing facility. Drug was administered in this study on Days 1 and 15. The trial enrolled a total of 150 subjects. The two SAEs, a case of HaNDL syndrome (a neurological syndrome of transient headache and neurologic deficits with cerebrospinal fluid lymphocytosis) and a case of elevated AST, are summarized below.

HaNDL syndrome. The subject [ID (b) (6)] developed syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL syndrome), which was graded severe, on Study Day 8, a week after the first dose of study drug. It resolved on Day 20. The second dose was not administered. The SAE was not considered related to study drug by the applicant; however, the Clinical reviewer could not rule out a causal relationship, given the timing of onset and resolution after drug discontinuation. The underlying etiology of HaNDL syndrome is unknown and is believed to be underdiagnosed. It typically present like migraines. Headaches are among the common adverse reactions associated with 5-HT₃ receptor antagonists.

ALT/LDH/CK elevation. The subject [ID (b) (6)], a 19 year old male, developed elevated AST (233 U/L; ULN = 37), associated with an increase in ALT (91 U/L; ULN=78), LDH (436; ULN=227) and CK (13,868 U/L; ULN=308), which was attributed to a strenuous exercise routine 4 days prior to the blood draw (3 days after administration of the reference product SQ in the lower right abdominal quadrant, and 17 days after the initial injection of the test product SQ in the upper left quadrant of the abdomen). The exercise was described as weight lifting, pushups and abdominal exercises. Onset was Day 22, 7 days after the second injection (reference product administered into lower right quadrant of abdomen); resolution was Day 31 (9 days later). Baseline AST was 20 U/L, and the Day 14 AST prior to the second

dose on study (reference) was also 20 U/L. Although the applicant determined this event wasn't study drug related, the Clinical reviewer noted other subjects experienced transaminase, LDH, and CK elevations after Sustol administration, which were not graded serious.

Cases of non-SAE elevations occurred in Study C2013-03, including a subject who discontinued due to CPK elevations. I will present the other CPK elevations in Study C2013-03 here. Refer to Section 8.5.1.4 for a presentation of the CPK elevations observed in the healthy subject repeat dose trial, Study C2013-02. The subject who discontinued from Study C2013-03, [ID (b)(6)], was a 22 year old male who was noted to have CPK elevation on the Day 14 laboratory assessment before the second dose of study drug. This subject had received the reference product by SQ injection into the upper left quadrant of the abdomen on Day 1. The baseline CK was normal and was elevated to 9696 U/L on Day 14. The level had dropped somewhat to 6371 U/L the following day, and had normalized 9 days later. AST and LDH were also elevated on Day 14: AST= 149 U/L (4 x ULN), LDH = 337 (1.5 x ULN). These values had normalized when CK had normalized. ALT was normal at all checks.

There were 10 subjects (6.7%) in this same study that had elevated CK values at the end of Period 2 compared to baseline; 3 were reported as TEAEs. However, the applicant reported that there were also 10 subjects who had high CPKs at baseline, and of those subjects, 6 normalized on study. I reviewed the serial CK data listed in the applicant's study report for Study C2013-03 (Table 14-18) and identified:

7 subjects who had a high baseline value (either at screening or on Day 1 prior to the first dose on study) and high value at study end (Day 22);

9 subjects who had a high baseline value and a normal level at study end; and

7 subjects that had a normal baseline who developed a high CPK on study (the latter group included the SAE described above and the subject who discontinued from the study due to high CPK described above).

In the first group (high baseline; high end of study), the baseline levels were all minimally elevated (range 310-366; ULN=308), with the exception of one subject with a baseline CPK of 994 (ULN=308). (There was also one subject whose CK was elevated over a different ULN laboratory reference value =192; their measured CK was 214.) End of study levels in this group ranged 315-748. The high (748) was observed on Day 22 in a subject whose baseline level was 310. This subject had experienced an even higher interim level of 9696 U/L. The subject with the second highest Day 22 value, i.e., 577 U/L, had a Day 1 value of 366 U/L.

In the second group (high baseline, normal end of study), the baseline values ranged 321- 952 (in the subjects whose ULN laboratory reference value =308; two subjects had elevations above a laboratory ULN of 192, i.e. 202 and 266).

Among the 7 subjects with normal baseline value and elevations on study, the highest value was documented before Day 22 in 4 subjects (on Day 14). All 4 normalized by Day 22. The elevated levels ranged 329-974 (in subjects whose ULN reference laboratory value =308); one subject had a maximum value on Day 14 of 211 (reference laboratory ULN = 192). All but the subject whose value was 974 U/L had elevations in the 300's range. The remaining subjects included the SAE described above, another subject whose maximum level was documented at

362 on Day 22 and a subject whose CK increased to 4270 on Day 22 and was even higher on Day 28, i.e., 6677 U/L.

The Clinical reviewer raised concern that the elevations might be related to muscle injury from study drug. Although there were many elevations at baseline observed in this trial, those levels were not markedly increased, in contrast to the five subjects noted above, i.e., the SAE, the discontinuation for elevated CK, the elevation to 9696 U/L, 6677 U/L and 974 U/L. CKs were not evaluated in the phase 3 trials; however, the repeat dosing healthy volunteer study (Study C2013-02) submitted in this resubmission did evaluate CKs. Marked elevations were not observed in that study. See CPK discussion of that trial in Section 8.5.1.4 below.

8.3.3 *AEs leading to study discontinuation in Study C2013-01.* There were 6 AEs that led to study discontinuation in the Sustol arm of Study C2013-01 and 4 in the ondansetron arm. I did not consider these events treatment related, with the exception of an AE of constipation in the Sustol arm. There was one discontinuation for acute renal failure in the Sustol arm and two in the ondansetron arm. The remaining events were: CVAs (one in each arm), a traumatic intracranial hemorrhage in the Sustol arm, a seizure in the Sustol arm (patient with history of seizure disorder and a low phenytoin level), dyspnea (patient with pulmonary metastases, history of pleurodesis, and pericardial effusion which acutely exacerbated on the date dyspnea event) in the Sustol arm, and disease progression in the ondansetron arm.

8.3.3.1 AEs leading to discontinuation in other studies. There was a discontinuation for elevated CPK in a healthy volunteer enrolled in Study C2013-03. This event and the SAE described above raised concerns about whether SQ injections of Sustol can cause local muscle injury. See further review of this issue in Sections 8.3.2.5 above (Study C2013-03) and 8.5.1.4 below (Study C2013-02).

8.4 TEAEs of Particular Interest. The safety review of injection site reactions, GI/pancreas events, and CK elevations will be presented below. The primary focus will be the new safety data from Study C2013-01; however, these results will also be presented in the context of findings from the previously reviewed phase 3 trial Study C2006-01, and the safety data from the newly submitted multi-dose healthy volunteer trial.

8.4.1 Injection Site Reactions.

Evaluation of the injection site reactions across trials interpretation of ISS data for injection site reactions (ISRs) is hampered by changes the applicant made over the course of time in how information on the ISRs were evaluated and captured for the safety data set. In two of the new trials submitted in this resubmission, the patients/subjects themselves captured specific information regarding the injection site in a daily diary, which included self-grading of the severity (Studies C2013-01 and C2013-02) . The diary was one source of ISR TEAE data; the investigators could also record observations. The patient's daily diary was collected and distributed on a weekly basis (Days 1, 8, 15, 22, 29 and 59). There was also an injection site assessment by the investigator on a weekly basis. In the smaller bioequivalence studies (Studies C013-03 and 2014-01), the injection site was assessed by investigators on Days 1-8 and Days 15-21). In both the latter trials, patient diaries were not used.

The Clinical Study report in Section 2.7.4 page 24 provides the following summary of how ISR data were collected in the various trials in the development program:

“Throughout the APF530 development program, ISRs could be captured in 3 different ways:

- (1) on the ISR Case Report Form (CRF) page (C2013-02, C2013-03, C2014-01)*,
- (2) on the **AE CRF page** (C2005-01, C2011-02, **and C2013-01****), and
- (3) on **both the ISR and AE CRF pages** (C2004-01, C2011-01, **C2006-01**, and C2007-01).

* Note that for Studies C2013-02, C2013-03, and C2014-01, injection site reactions were collected for the most part on the injection site reaction CRF page only. However, if any injection site reactions occurred at either a time outside of the scheduled injection site reaction collection time points or any injection site reaction types occurred that were not collected on the injection site reaction CRF page (e.g., discoloration, stinging, etc.), then those injection site reactions were collected on the adverse event CRF page only.

** Note that the original C2013-01 protocol required both investigator- and subject-reported injection site reactions only be recorded on an injection site reaction page of the CRF. Protocol Amendment 3 changed this to also record injection site reactions, whether investigator-assessed or subject-reported, on the adverse event CRF page. The week of 25 August 2014, sites were trained via web conference to only record injection site reactions on the adverse event page of the CRF using specified conventions outlined in updated CRF completion instructions. Any injection site reactions recorded only on the injection site reaction CRF page prior to that were mapped to the adverse event CRF page by the sites. The CRF instructions said to pick one type of reaction (e.g., either hematoma or bruising) for the subjects that had the injection site reaction CRF page data moved to the adverse event CRF page. The diary had Swelling and Bruising, but the original injection site reaction CRF page (that was eventually dropped after Protocol Amendment 3 [Protocol Version 4]) had Induration/Swelling and Hematoma/Bruising. In addition, relationship to any investigational product was to be entered as “possible.”

Initially, during the conduct of Study C2013-01, ISRs were intended to be captured on a CRF page dedicated to ISRs (both patient and investigator reported information); however, a protocol amendment changed the procedure to limiting entry of the ISR data into the CRF adverse event pages. This amendment necessitated going back to pre-amendment entries on the dedicated ISR page, to transfer them to the Adverse Event page. There was an algorithm for the terminology to be used in moving reported events from one page to the other. The analysis plan for mapping ISRs included the following “rules”:

- 1) MedDRA Lower Level Terms (LLT), PT, and SOC variables were assigned for each verbatim with terms specifically mentioned as a component manifestation in the patient’s diary. It is important to note that the diary referred to “induration/swelling” as a single manifestation for grading. Similarly, the patient diary referred to hematoma/bruising as a single item for grading. For each of those

two records in the diary data, i.e., INDURATION/SWELLING and HEMATOMA/BRUISING cases, two separate AE records were created.

- 2) An AE dataset record was created for each ISR at the first time a grade ≥ 1 was observed for each dose period. Any ISR that resolved and restarted within the same dose period was considered a separate event, with a separate dataset record for each occurrence.
- 3) A flag variable in AE analysis dataset was included to indicate if the source for the record was the investigator's ISR assessment page. Any ISR with a Grade of 4 was to be captured on the AE CRF. If an investigator's AE page was completed, that ISR record was not to be outputted to the AE dataset, for the grade 4 events (to prevent redundancy). Any ISR that led to discontinuation was to be captured on the AE CRF. If an AE page was completed, the ISR record was not to be outputted to the AE dataset, again to prevent redundancy.

ISRs captured on the ISR CRF page and the investigator assessment of the injection site were mapped retrospectively to AEs, using the conventions referenced in the individual study SAPs and included attributing all ISRs as at least "possibly" related to treatment. The outcome categories collected differed by study, so all studies were mapped in the integrated database to the outcomes collected for Study C2006-01 (normal, redness, tenderness/pain, lump, bruising, itching, and other)." [Note that the Study 2013-01 diary response options were: Redness/erythema; tenderness; pain; nodule; induration/swelling; bruising/hematoma; bleeding.]

In contrast, for the trials submitted in the original submission, including Study C2006-01, only the investigator evaluated the injection site, prompted by the CRF, which asked the investigator to check off any descriptor that applied from a list of 7 terms (normal, redness, tenderness/pain, lump, bruising, itching and other). The CRF then prompted the investigator to also report "each check item....on the Adverse Events form." The adverse events form was a separate page in the CRF and prompted the investigator to record the adverse event description, start and stop dates, severity "mild, moderate, severe", relationship to study drug, action taken, outcome and whether it was serious.

As mentioned above, the ability to compare the ISR data from the separate submissions was further complicated by differences in terminology used as descriptors for ISR manifestations in various study documents among the trials. The injection site form in the CRF for the investigators in the earlier studies from the previous NDA submission contained a list of "prompts" for the investigator on the Subcutaneous Injection Site Assessment page of the CRF (a separate page from the AE reporting page in the CRF) that differed from the list of terms captured in the patient diary used in the most recent trials submitted in this current resubmission. Furthermore, the grading scale used by study staff for ISRs in the most recent trials to train patients in how to interpret their diary choices for ISR grading introduced additional terms: "induration" with "Swelling" and "hematoma" with "bruising". The Adverse event pages in the trials did not contain specific "prompts". When Study C2013-01 was amended to eliminate the Injection Site page, which included a checklist of specific prompts

used in the patient diary for data entry from both the patient diary and the investigator, it is not clear what terminology the investigator was utilizing for the clinician descriptors of similar manifestations. The following table summarizes the ISR terminology used for the “prompts” in the various records.

Table 37. Summary of ISR terminology used for “prompts” in study records.

CRF Prompt for Injection Site Assessment Page for Investigator 2006-01 Early Submissions	Patient Diary in C2013-01	CRF Prompt for Injection Site Assessment Page for + 2013-01 Current Submission	Grading Scale Terminology for Clinic Staff
		Check whether Subject or Clinician	
-	Pain	Pain	Pain
-	Tenderness	Tenderness	Tenderness
Tenderness/Pain			
Redness	Redness	Erythema/Redness	Erythema/Redness
-	Swelling	Induration/Swelling	Induration/Swelling
-	Nodules	Nodules	Nodules
Lump			
-	Bleeding	Bleeding	Bleeding
Bruising	Bruising	Hematoma/Bruising	Hematoma/Bruising
Itching			
Other			

+ CRF Subcutaneous Injection Site Assessment page used throughout the trial duration in C2006-01; however, in C2013-01, this page was discontinued and the data was entered directly into the Adverse Event page of the CRF.

In addition to differences in the terminology used, the grading system for ISRs changed with the new trials submitted in the most recent resubmission. Grading was performed exclusively by the investigators in the previously conducted trials, and was based on the following descriptors found in the protocol appendix:

- Mild = easily tolerated and does not interfere with normal daily activities
- Moderate = causes some interference with daily activities
- Severe = all normal daily activities are completely halted

The applicant changed the ISR grading system in the new trials; patients were trained to grade their ISRs in the daily diary, which included prompts for each of the specific manifestations listed in the table below, along with prompts for severity, as listed in the table below.

Table 38. Study 2013-01: Patient Diary Self-Reported Grading System for Injection Site Reactions.

Local Reaction to Injectable Product	Grade 1 (Mild)	Grade 2 (Moderate)	Grade 3 (Severe)	Grade 4 (Severe ¹)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever >24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness*	2.5 to 5.0 cm	5.1 to 10 cm	>10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling**	2.5 to 5.0 cm and does not interfere with activity	5.1 to 10 cm OR interferes with activity	>10 cm OR prevents daily activity	Necrosis
Nodules	Nodules to palpation 1 to 2 cm in diameter	Visible nodules 1 to 2 cm in diameter	Visible or palpable nodules 2–4 cm in diameter	Visible or palpable nodules >4 cm in diameter
Bleeding	Repeated oozing over several days	Requires bandage with change more than 3 times a day	Requires bandage with change more than 6 times a day	Emergency room (ER) visit or hospitalization
Hematoma	<2 cm in diameter	2 to 4 cm in diameter	>4 cm in diameter	ER visit or hospitalization
Bruising	<2 cm in diameter	2 to 4 cm in diameter	>4 cm in diameter	ER visit or hospitalization

As will be shown below, a higher ISR rate was observed in the newly submitted trials and there were more patients/subjects with moderate and severe ISRs. The applicant attributed these apparent increases to the changes in methodology used to capture and grade ISRs. The applicant stated that the investigator-reported severity from the earlier trials was more reliable and informative as it was based on “impact on function”, as per the descriptors listed earlier. In contrast, the applicant stated that the severity grading reported by patients/subjects in the new trials was primarily based on measurement of size of visible manifestations of reactions, e.g., bruise size. The applicant said these measurements were not likely accurate because of difficulty patients would have measuring these sites on their own bodies. The reviewers considered alternative explanations for the higher proportion of injection site reactions in the most recent trials. They questioned whether the smaller needle size and use of syringe warmers in the new phase 3 trial, Study C2013-01, had enabled application of a higher injection force that increased tissue injury from the force of the polymer entering the tissue. After evaluating the changes made in the methodology for capture and grading ISRs, the Clinical reviewer concluded that the differences would be expected to impact the severity of reporting, but not

the absolute proportion of injection site reaction events. However, I think it is conceivable that if the site personnel were reviewing the patient diary at subsequent visits and noted that a patient had reported adverse events related to the injection, there could have been higher ascertainment than if only the investigator's assessment was relied upon. The investigator may have been more likely to dismiss the site reactions as unimportant in Study C2006-01, where there was no specific feedback collected from the subjects themselves. I believe the higher number and grade of the reactions in Study C2013-01 are more accurately reflective of the patient experience than the ISR data from Study C2006-01. I am less concerned that the apparent increase reflects altered safety attributable to smaller needle and use of syringe warmers, and more likely related to patient reporting.

A number of the diary's grading response prompts were "double-barreled", in that the description associated with the score included two potential descriptions of the patient's experience connected with an "or", and the form did not capture which of the two (or perhaps both) contributed to the patient's actual selection of the score. For example, in the table above "Induration/Swelling" Grade 2 was defined as "5.1-10 cm OR interferes with activity". If a patient rated swelling as Grade 2, it is not clear whether they were reporting the size or a detrimental impact on their activity level. Nevertheless, it is difficult to dismiss patients' reports of their own experience, and in the absence of data captured to establish otherwise, one can't assume the grade was selected based swelling size only. The applicant pointed to patient reports of satisfaction with study treatment as evidence that patient daily function/well-being was not negatively impacted by these reactions. I can't agree the "subject satisfaction" data inform actual impact on function, as these data were based on subjects' response to a global question in the patient diary that did not specifically target the local injection experience. Instead, the global question targeted control of nausea and vomiting, i.e., "How satisfied are you with the study medication's *ability to control your nausea and vomiting during these 24 hours* [emphasis added]?" and "Overall, how satisfied are you with the study medication's *ability to control your nausea and vomiting during this 5 day period* [emphasis added]?"

In the following subsections, I'll present information regarding the apparent differences in **proportions** of overall ISRs, proportions of specific manifestations of ISRs, **severity**, and **duration** of ISRs among trials. I'll focus on the two phase 3 trials, but will also present ISR data from the newly submitted multi-dose healthy volunteer trial, Study 2013-02, as the monitoring procedures (including the subject diary) and the administration procedures were similar to those used in Study 2013-01. ISRs observed in this healthy volunteer study also differed from the previously submitted healthy volunteer studies. Finally, I'll explore the tolerability of the SQ injections through exploration of study **discontinuation**. It should be noted that in the most recent phase 3 trial, Study C2013-01, study discontinuation is not a good exploratory measure of tolerance of the product, as it was a single cycle trial. However, the originally submitted phase 3 trial, Study C2006-01, was a multi-cycle trial, and discontinuations over time can be explored.

8.4.1.1 Overall Proportion of Injection Site Reactions. The following table, reproduced from the applicant's ISS (Table 35; Section 2.7.4.2.1.6.1.1), summarizes the relative overall proportions of ISRs reported in the two major phase 3 trials in this application (the new Study

2013-01 and Cycle 1 of the previously reviewed trial, Study 2006-01). Note that the control arm of the new trial utilized a vehicle polymer control injection in the comparator arm, whereas in the older trial, the control arm utilized a saline injection. The polymer vehicle used in the ondansetron control arm of Study 2013-01 did not contain granisetron; therefore, the ISR rate was similar between arms within that trial. Note the overall higher ISR rate in Study 2013-01, including a higher rate in the control arm polymer vehicle control injection compared to the saline injection control in Study 2006-01. In terms of severity, like Study C2006-01, the ISRs in Study C2013-01 tended to be mild; however, a higher proportion of subjects had moderate or severe ISRs than in Study C2006-01. Among Sustol treated patients who had ISRs in Study 2013-01, 27% (77/282) had moderate reactions vs. 7% (13/175) in Study C2006-01. Likewise, among Sustol treated who had ISRs in Study 2013-01, 10% (28/282) had severe reactions vs. 0% in Study C2006-01.

Table 39: Overall Summary of ISRs in Study C2013-01 and Cycle 1 of Study C2006-01 (Table 35 in the applicant’s ISS).(35 in 2.74.2.1.6.1.1 in Summary of Clinical Safety)

Category	C2006-01 Cycle 1		C2013-01	
	APF530 500 mg (N=468) n (%)	Aloxi +saline (N=463) n (%)	APF530 500 mg (N=456) n (%)	Ond+polymer (N=459) n (%)
Subjects With Any Treatment-Emergent Injection Site Reaction	175 (37.4)	71 (15.3)	282 (61.8)	273 (59.5)
Subjects Who Died	0	0	0	0
Subjects With Serious Injection Site Reactions	0	0	1 (0.2)	0
Subjects Who Discontinued Due to an Injection Site Reaction	1 (0.2)	0	0	0
Subjects With an Injection Site Reaction by Severity: Mild	162 (34.6)	69 (14.9)	177 (38.8)	166 (36.2)
Moderate	13 (2.8)	2 (0.4)	77 (16.9)	74 (16.1)
Severe	0	0	28 (6.1)	33 (7.2)

Note: A subject with events in more than one severity category is counted at the maximum severity category, with unknown or missing assumed to be severe.

Source: [Module 5.3.5.3 Table 4.10.1.1.1](#) and [C2013-01 CSR Table 14.3.1.1.3](#)

The new administration technique (smaller needle, use of syringe warmers) proposed for the to be marketed product was utilized in both Study C2013-01 and a multi-dose (weekly x4) trial, Study C2013-02, which was conducted in healthy volunteers. Unlike Study 2013-01, the control arm in Study 2013-02 employed a saline injection instead of polymer vehicle control. As in Study C2013-01, subjects in C2013-02 (like C2013-01) captured ISR data (with grading) in a diary, and both the subject and the physician performed injection site assessments. The subjects’ grading system was the same used by the patients in Study C2013-01. The investigator evaluated the injection site weekly, in addition to 1 and 3 hours following each dose. Subjects conducted self-evaluations on Days 2-7, 9-14, 16-21, Day 23 and Day 28. Subjects with an ISR were to return to the study site within 24 hours for ISR evaluation.

ISR data from the new healthy volunteer study, Study C2013-02 (which employed a subject diary), shown in Table 40 below, are of interest as the rate is higher than previously observed in healthy volunteer studies, and higher than reported in Study C2013-01 (compared to Table 39 above). Of note, the proportion with moderate severity ISRs is also higher in healthy subjects than in Study C2013-01 (patients). The proportion of subjects with moderate and severe ISRs was also higher in Study C2013-02 than in the combined data for all the phase 1 trials (healthy subject trials), as shown by comparing the severity rows in Tables 40 and 41 below. In the saline control arm, the overall rate of ISRs and rate of mild ISRs was similar to the saline control arm of Study C2006-01 (Table 39); however, the moderate and severe ISR rate was numerically higher in the saline control in the healthy subject trial than in Study C2006-01, (4% vs. 0.4%). The most common ISR manifestation reported in this healthy subject trial was pain, whereas in the patient trials, bruising was the most common..

Table 40. Study C2013-02: Summary of injection site reactions – subject (healthy volunteers) and investigator assessed. (Table 12.6 in the applicant’s Study Report for Study C2013-02)

Parameter	APF530 500 mg SC (N=50)	Granisetron 1.0 mg IV + Saline SC (N=25)	Total (N=75)
Subjects with at Least One ISR	45 (90.0%)	4 (16.0%)	49 (65.3%)
Subjects with at Least One Treatment Related	45 (90.0%)	4 (16.0%)	49 (65.3%)
Subjects with at Least One Serious ISR	0	0	0
Subjects with at Least One ISR with Outcome	0	0	0
Mild	26 (52.0%)	3 (12.0%)	29 (38.7%)
Moderate	16 (32.0%)	1(4.0%	17 (22.7%)
Severe	3 (6.0%)	0	3 (4.0%)

Data Source: [End of Text Table 14.3.1.1.5](#); [Listing 16.2.7.1 \(Appendix 16.2\)](#).

[1] A subject is counted once in the most severe category if the subject reported one or more events, but different severities. Unknown severity is treated as severe.

Table 41. Overall Summary of ISRs in all periods in the Phase 1 healthy volunteer subject trials included in the NDA (including, but not limited to Study C2013-02). Reproduced from applicant’s ISS Table 37.

Category	APF530 ≤ 250 mg (N=14) n (%)	APF530 ≥ 500 mg (N=398) n (%)	Total APF530 (N=412) n (%)
Subjects With Any Treatment-Emergent Injection Site Reaction	13 (92.9)	365 (91.7)	378 (91.7)
Subjects Who Died	0	0	0
Subjects With Serious Injection Site Reaction	0	0	0
Subjects Who Discontinued Due to an Injection Site Reaction	0	2 (0.5)	2 (0.5)

Category		APF530 ≤ 250 mg (N=14) n (%)	APF530 ≥ 500 mg (N=398) n (%)	Total APF530 (N=412) n (%)
Subjects With an Injection Site Reaction by Severity:	Mild	12 (85.7)	286 (71.9)	298 (72.3)
	Moderate	1 (7.1)	69 (17.3)	70 (17.0)
	Severe	0	10 (2.5)	10 (2.4)

Note: A subject with events in more than one severity category is counted at the maximum severity category, with unknown assumed severe.

Source: [Module 5.3.5.3 Table 4.10.1.2](#)

Most ISRs in the healthy subject trial, Study C2013-02, which utilized repeat dosing, were grade 1; however, two subjects on the Sustol arm had Grade 3 ISRs. The following table compares severity grading between subjects and investigators (based on maximum severity grading overall) in that trial. On the Sustol arm, the investigators tended to grade events lower severity than subjects did (primarily in the Grade 1 vs. 2 range). Within the saline injection arm, the investigators reported more events than the subjects did (4 vs. 2).

Table 42. Study C2013-02: Proportion of healthy subjects with Grade 1-4 Maximum Severity ISRs – as assessed by subjects vs. investigator (From Tables 14.3.1.9 and 14.3.1.10 in the study report)

Severity Grade	Sustol 500 mg N=50	Granisetron +Saline injection N=25
Subject		
Grade 1	25 (50%)	1 (4%)
Grade 2	12 (24%)	1 (4%)
Grade 3	2 (4%)	0
Grade 4	0	0
Investigator		
Grade 1	29 (58%)	4 (16%)
Grade 2	9 (18%)	0
Grade 3	2 (4%)	0
Grade 4	0	0

8.4.1.2 Specific ISR manifestations. The following table was presented in the applicant’s study report. It summarizes the relative proportion of each ISR manifestation in Study C2013-01 and StudyC2006-01. When evaluating the data presented in this table, one must take into consideration differences between trials in how data were captured and differences in the ISR manifestation terminology used. There was no patient diary in Study C2006-01, and the investigators were specifically prompted to report on a limited number of terms (redness, “tenderness/pain”, “lump”, “bruising”, “itching” and “other”) that appeared on the ISR Evaluation page of the CRF; there was no prompt for “bleeding”. The individual prompts listed in the patient diary in Study C2013-01 (i.e., pain, tenderness, redness, swelling, nodules, bleeding, bruising) are highlighted in yellow in the table below. Note that in Study 2006-01

the investigator prompt combined pain and tenderness into a single item, whereas the patient diary separated these concepts. The “tenderness” patient diary response is not listed in the applicant’s table below. It is my understanding that the additional items listed in the table below were written in the CRF by the investigator at follow up visits.

Table 43. Studies C2006-01 and C2013-01: Proportion of patients in each arm of the phase 3 trials with various manifestations of injection site reactions. (Source Table 38 in the ISS)

Preferred Term	C2006-01 Cycle 1		C2013-01	
	APF530 500 mg (N=468) n (%)	Aloxi +saline (N=463) n (%)	APF530 500 mg (N=456) n (%)	Ondansetron +polymer (N=459) n (%)
Total subjects with at least one event	175 (37.4)	71 (15.3)	282 (61.8)	273 (59.5)
Injection site bruising	93 (19.9)	40 (8.6)	191 (41.9)	154 (33.6)
Injection site cellulitis	1 (0.2)	0	0	0
Injection site discoloration	4 (0.9)	0	2 (0.4)	0
Injection site discomfort	0	0	0	1 (0.2)
Injection site erythema	51 (10.9)	14 (3.0)	77 (16.9)	127 (27.7)
Injection site hematoma	1 (0.2)	0	15 (3.3)	11 (2.4)
Injection site hemorrhage	18 (3.8)	11 (2.4)	23 (5.0)	36 (7.8)
Injection site induration	3 (0.6)	0	3 (0.7)	2 (0.4)
Injection site infection	1 (0.2)	0	3 (0.7)	0
Injection site inflammation	0	0	0	1 (0.2)
Injection site irritation	1 (0.2)	0	0	0
Injection site mass	47 (10.0)	3 (0.6)	0	0
Injection site nodule	3 (0.6)	0	82 (18.0)	45 (9.8)
Injection site pain	33 (7.1)	6 (1.3)	141 (30.9)	163 (35.5)
Injection site paresthesia	1 (0.2)	0	0	0
Injection site pruritus	5 (1.1)	1 (0.2)	0	0
Injection site rash	0	0	0	0
Injection site reaction	0	1 (0.2)	0	0
Injection site scab	1 (0.2)	1 (0.2)	0	0
Injection site scar	0	1 (0.2)	0	0
Injection site swelling	0	0	45 (9.9)	53 (11.5)
Injection site thrombosis	0	1 (0.2)	0	0
Injection site vesicles	0	0	1 (0.2)	0
Injection site warmth	0	0	0	0

Note: Note: A subject with more than one event represented by a given Preferred Term is counted only once for that

Preferred Term.

Preferred Terms are presented alphabetically.

Yellow highlighted terms appeared in the Patient Diary of C2013-01

Source: [Module 5.3.5.3 Table 4.10.2.2.1](#) and [C2013-01 CSR Table 14.3.1.2.3](#)

Notable differences between the phase 3 trials in qualitative nature of ISRs include:

- 1) Doubling of proportion of patients with bruising in Study C2013-01, compared to the earlier trial. This increase may reflect the impact of changes in the administration procedure; however, an alternative explanation could be that even though there was a specific prompt for “bruising” on the CRF ISR evaluation page in Study C2006-01, the investigator did not find the bruising important to report.
- 2) Marked increase in pain reported in Study C2013-01, despite the specific prompt on the CRF ISR evaluation page in Study C2006-01 for “tenderness/pain”. This may reflect the impact of administration procedure changes. An alternative explanation is that pain, which is a subjective experience known only to the patient, was more effectively ascertained through the patient diary used in Study C2013-01.
- 3) Doubling of the proportion of patients with injection site bleeding, taking into consideration the polymer vehicle control arm rate, in Study C2013-01. This may reflect changes in the administration procedure. Alternative explanations include the lack of a “bleeding” prompt in the ISR evaluation page of the CRF for Study C2006-01 and/or changes in ascertainment related to involving patients in the reporting. Specific diary “bleeding” prompts in Study C2013-01 could have resulted in capture of previously unobserved bleeding.
- 4) Marked increase in proportion of patients with a “nodule” in Study C2013-01; however, the prompt in the CRF for the investigator evaluation of ISRs in C2006-01 used the term “lump”, which does not appear in the table above, but was apparently substituted with “mass”. Even comparing those two rows in the tables, there is a numerically higher proportion in the Sustol arm of Study C2013-01 vs. Study C2006-01.
- 5) Numerically higher proportion of patients with injection site infections in Study C2013-01 vs. Study C2006-01.

The most common ISR manifestation in Study C2013-01 was bruising. The second most common was pain (30.9% in the Sustol arm and 35.5% in the vehicle control arm).

The following tables, reproduced from the applicant’s Clinical Summary of Safety (2.7.4 in Clinical Safety report and Clinical Study report for C2013-02), summarize the relative severity of the most common specific individual manifestations of ISRs reported in the two phase 3 trials (Cycle 1 of Studies C2006-01 and C2013-01 in Table 44). I have highlighted in yellow the terms that appeared in the patient diary in Study C2013-01. There was no CRF prompt on the ISR evaluation page for the investigator in Study C2006-01. As noted above, the ISR evaluation page included a “lump” prompt for the investigator that did not appear in the patient diary for Study C2013-01. The term “mass” did not appear in the terminology used in the documents for either study. The patient diary in Study C2013-01 included an individual term “tenderness” that is not included in the table below. The Clinical reviewer explained that the reports of pain and tenderness were combined under the common term “pain”.

Table 44. Severity of the ISR manifestations in the two phase 3 trials – Studies C2006-01 and C2013-01. Reproduced Table 42 from applicants 2.7.4 Summary of Clinical Safety.

Preferred Term		C2006-01 Cycle 1		C2013-01	
		APF530 500 mg (N=468) n (%)	Aloxi +saline (N=463) n (%)	APF530 500 mg (N=456) n (%)	Ondansetron + polymer (N=459) n (%)
Subjects With at Least One Event	Overall	175 (37.4)	71 (15.3)	282 (61.8)	273 (59.5)
	Grade 1	162 (34.6)	69 (14.9)	177 (38.8)	166 (36.2)
	Grade 2	13 (2.8)	2 (0.4)	77 (16.9)	74 (16.1)
	≥ Grade 3 ^a	0	0	28 (6.1)	33 (7.2)
Injection site bruising	Grade 1	87 (18.6)	38 (8.2)	110 (24.1)	74 (16.1)
	Grade 2	6 (1.3)	2 (0.4)	60 (13.2)	55 (12.0)
	≥ Grade 3	0	0	21 (4.6)	25 (5.4)
Injection site pain	Grade 1	32 (6.8)	6 (1.3)	123 (27.0)	142 (30.9)
	Grade 2	1 (0.2)	0	15 (3.3)	14 (3.1)
	≥ Grade 3	0	0	3 (0.7)	7 (1.5)
Injection site nodule	Grade 1	1 (0.2)	0	76 (16.7)	39 (8.5)
	Grade 2	2 (0.4)	0	4 (0.9)	4 (0.9)
	≥ Grade 3	0	0	2 (0.4)	2 (0.4)
Injection site erythema	Grade 1	48 (10.3)	14 (3.0)	69 (15.1)	106 (23.1)
	Grade 2	3 (0.6)	0	6 (1.3)	20 (4.4)
	≥ Grade 3	0	0	2 (0.4)	1 (0.2)
Injection site swelling	Grade 1	0	0	41 (9.0)	47 (10.2)
	Grade 2	0	0	2 (0.4)	6 (1.3)
	≥ Grade 3	0	0	2 (0.4)	0
Injection site hemorrhage	Grade 1	18 (3.8)	11 (2.4)	19 (4.2)	31 (6.8)
	Grade 2	0	0	4 (0.9)	4 (0.9)
	≥ Grade 3	0	0	0	1 (0.2)
Injection site mass	Grade 1	46 (9.8)	3 (0.6)	0	0
	Grade 2	1 (0.2)	0	0	0
	≥ Grade 3	0	0	0	0

Table only shows injection site reactions that were reported by ≥ 5% of subjects in any treatment group in Cycle 1.

^a There was only 1 subject with a Grade 4 ISR that was subsequently reassessed as a Grade 3 ISR after database lock

Yellow highlighted terms appeared in the Patient Diary of C2013-01

Note: A subject with more than one event represented by a given Preferred Term is counted once at the maximum severity category that applies within that Preferred Term, with unknown assumed severe.

Source: [Module 5.3.5.3 Table 4.10.3.1.2](#) and [C2013-01 CSR Table 14.3.1.3.2](#)

The summary phase 3 ISR data in Table 44 above reveal a higher proportion of all grades of bruising and erythema, and a marked increase in pain, nodule and swelling in Study C2013-01 relative to Study C2006-01. The higher proportion of bruising suggests either a detrimental impact of the new administration procedure or a tendency of investigators not to report bruises relative to the patient who actually experiences them. A strikingly higher rate of Grade 2 and ≥ Grade 3 bruising was observed in Study C2013-01; grading was based only on size of bruise.

Although the applicant stated that bruising ISRs were primarily cosmetic in nature, a narrative for a Sustol patient who experienced Grade 4 bruising at the injection site suggests that bruising can be more impactful, as it can reflect a significant underlying hematoma. The patient was a 55 year old with breast cancer, treated with AC. She developed injection site pain and bruising on the day of treatment and had taken ibuprofen the following day “for a headache”. Three days later, she reported grade 2 injection site swelling, pain and erythema. On a clinic evaluation 4 days later, the site was dark blue/purple, with a diameter >4 cm. Four days after the clinic visit she called to report that the bruising was increasing in size and was extremely painful, so much so that she was going to go to urgent care center or the ER. The investigator returned the call and the patient said that the pain had subsided, without being seen in an urgent care center.

The applicant investigated concomitant patient features that might have contributed to grade 3 or greater (severe) bruising and found use of concomitant medications that affect platelet function or coagulation increased the risk of grade 3 bruising/hemorrhage/hematoma ISRs (odds ratio 2.7, CI: 1.2, 6.2), when the analysis was limited to the Sustol treated group. However, when hemorrhage/bleeding was analyzed alone, the risk appeared similar between patients taking anticoagulants vs. patients who were not. White subjects appeared to be at greater risk of developing injection site bruising/hemorrhage/hematoma than non-White subjects, when both arms were evaluated together (odds ratio 1.8, CI: 1.3, 2.6).

With regard to hemorrhage, the overall higher rate of hemorrhage in Study C2013-01 was primarily manifested as grade 1 reactions; however, unlike Study C2006-01, there were 8 patients (4 in the Sustol arm and 4 in the vehicle polymer control arm) who had grade 2 hemorrhages, compared to none in the earlier phase 3 trial. In addition, there was one grade 3 hemorrhage in the polymer vehicle control arm of Study C2013-01, compared to none in the earlier trial. The reviewers were concerned that even Grade 1 bleeding was described as “repeated oozing over several days,” which would likely be undesirable to patients. Grade 2 bleeding was described as requiring bandage change more than 3 times a day. Grade 3 was described as requiring bandage change more than 6 times a day. Note that there was an SAE of intractable bleeding reported in the original submission of this application, which I presented in my original review. That patient (with normal PT/PTT) didn’t respond to 5 hours of compression to the site and had to be seen by a surgical oncologist, who applied an abdominal binder. The patient had to return to the ER because brisk oozing continued from the puncture site. Bleeding ultimately stopped with application of oxidized cellulose and pressure.

A higher proportion of pain ISRs and a higher proportion of Grade 2 and $\geq$ Grade 3 pain were reported in Study C2013-01 than in Study C2006-01. Grade 2 pain was described in the patient diary as “repeated use of non-narcotic pain reliever for over 24 hours or interferes with activity”; grade 3 pain was described as “any use of narcotic pain reliever or prevents daily activity.” The apparent increase could reflect an actual increase in pain attributable to the administration technique, or could reflect the impact of change from investigator to patient reporting for a reaction only known to the patient. The applicant responded to the FDA review team’s concerns regarding the pain severity reports and said, “Only one patient out of the 456 subjects receiving Sustol in Study C2013-01 took an analgesic for injection site pain (rate of

0.22%).” However, it is unclear whether the use of pain medication for injection site reactions was accurately captured in this trial. The patient diary included a section that asked patients to record medications they took; however, that section was connected with the questions about retching, vomiting and nausea. It was not connected with ISR reporting. Presumably patients recorded medications that they took for nausea in that section; the diary did not clearly prompt patients to record pain medications. However, even if patients did not take medication for their grade 2/3 pain, the response item included descriptors that the pain interfered with their activity (including grade 2 pain), which indicates that ISR pain was impactful. Furthermore, patients reported pain and tenderness separately in the diary. The tenderness reports were counted as pain in the safety dataset. Therefore, some of the “pain” events could have been “tenderness”, for which grading did not include a description of requiring pain medication or impact on daily activity. See Table 46 below for a breakdown of tenderness vs. pain in the diary responses of healthy volunteers in Study C2013-02. In the latter, the proportion of tenderness ISRs reported was higher than pain, and the grade associated with tenderness was higher than with pain.

As discussed above, “induration/swelling” did not appear as an investigator prompt in the Study C2006-01 CRF ISR evaluation page. There are no ISR reports of “swelling” from Study C2006-01 reported in the table above, likely related to the absence of this terminology in the CRF. In Study C2013-01, most of the swelling ISRs were Grade 1 in severity. The reviewers were concerned about Grade 2 swelling ISRs in Study C2013-1 (2 in the Sustol arm and 6 in the polymer vehicle control arm) and one Grade 3 event (in the polymer vehicle control), because the double barreled descriptors for these grades included a negative impact on patient function. Grade 2 included a measurement of the swelling OR *interfered with daily activity*; Grade 3 included a measurement OR *prevented daily activity*. The applicant stated that the events reported by patients in the swelling/induration reflected physical measurement of the swelling, not necessarily activity interference; the applicant noted that it was difficult for patients to accurately measure the area given the position of the swelling/induration. However, the patients didn’t specifically record whether the graded was based on impact on daily activity, so we cannot rule out that this ISR negatively impacted patient function.

The following tables, reproduced from the applicant’s Clinical Summary summarize the relative severity of the most common specific individual ISR manifestations reported in the repeat dose healthy subject study, Study C2013-02.

Table 45. Study C2013-02: Number and percent of healthy subjects (repeat dosing study) with specific manifestations of injection site reactions – subject and investigator assessed. (Table 12.7 in the applicant’s Study Report)

<i>System Organ Class Preferred Term</i>	APF530 500 mg SC (N=50)	Granis 1.0 mg IV + saline SC (N=25)	Total (N=75)
<i>Subjects with at Least One Event</i>	45 (90.0%)	4 (16.0%)	49 (65.3%)
General disorders and administration site conditions	45 (90.0%)	4 (16.0%)	49 (65.3%)
<i>Injection site pain</i>	38 (76.0%)	2 (8.0%)	40 (53.3%)

System Organ Class Preferred Term	APF530 500 mg SC (N=50)	Granis 1.0 mg IV + saline SC (N=25)	Total (N=75)
<i>Injection site erythema</i>	29 58.0%	3 (12.0%)	32 (42.7%)
<i>Injection site bruising</i>	27 54.0%	2 (8.0%)	29 (38.7%)
<i>Injection site haematoma</i>	27 54.0%	2 (8.0%)	29 (38.7%)
<i>Injection site induration</i>	27 54.0%	0	27 (36.0%)
<i>Injection site swelling</i>	27 54.0%	0	27 (36.0%)
<i>Injection site nodule</i>	25 50.0%	0	25 (33.3%)
<i>Injection site haemorrhage</i>	1 (2.0%)	1 (4.0%)	2 (2.7%)
<i>Injection site pruritus</i>	0	1(4.0%	1 (1.3%)

Source: End of Text Tables 14.3.1.2.1, 14.3.1.2.5 and 14.3.1.3.2.1; Listing 16.2.7.1 (Appendix 16.2).

Note: ISR events were to be collected on both the ISR and AE CRFs, however, all ISRs were not collected simultaneously and Table 14.3.1.2.1 integrates both CRFs versus Table 14.3.1.2.5 which counts one fewer injection site pain, injection site induration and injection site pruritus.

Yellow highlighted terms appeared in the Subject Diary of C2013-02

The following table summarizes the maximum severity of each ISR manifestation, as reported by healthy subjects vs. investigators in Study C2013-02. Healthy subjects reported a greater proportion of events and higher grades for subjective events such as pain, tenderness and induration/swelling than investigators. The investigators reported more nodules and bleeding. Subjects reported somewhat higher numbers of hematoma/bruising than investigators and were more likely than investigators to grade these as grade 2 than grade 1. (Note that the diary captured hematoma and bruising separately, but these manifestations were combined for the tabulation in the study report.) Regarding ISR severity, most were Grade 1; however, 2 subjects on the Sustol arm had Grade 3 ISRs. The investigators graded more ISRs on the Sustol arm Grade 1 than the subjects did.

Table 46. Study C2013-02: Injection site manifestation maximum severity as graded by the healthy volunteer subjects vs. investigator (from Study Report Tables 14.3.1.9 and 14.3.1.10)

Severity Grade	Sustol 500 mg N=50	Granisetron +Saline injection N=25	Sustol 500 mg N=50	Granisetron +Saline injection N=25
	SUBJECT		INVESTIGATOR	
PAIN				
Grade 1	21 (42%)	2 (8%)	13 (26%)	0
Grade 2	0	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
TENDERNESS				
Grade 1	34 (68%)	2 (8%)	24 (48%)	0
Grade 2	3 (6%)	0	0	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
INDURATION/SWELLING				

Severity Grade	Sustol 500 mg N=50	Granisetron +Saline injection N=25	Sustol 500 mg N=50	Granisetron +Saline injection N=25
	SUBJECT		INVESTIGATOR	
Grade 1	20 (40%)	0	19 (38%)	0
Grade 2	2 (4%)	0	1 (2%)	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
BLEEDING				
Grade 1	-	-	1 (2%)	1 (4%)
Grade 2	-	--	0	0
Grade 3	-	-	0	0
Grade 4	-	-	0	0
Hematoma/Bruising				
Grade 1	15 (30%)	0	18 (36%)	2 (8%)
Grade 2	9 (18%)	1 (4%)	4 (8%)	0
Grade 3	2 (4%)	0	2 (4%)	0
Grade 4	0	0		0
ERYTHEMA				
Grade 1	23 (46%)	0	14 (28%)	3 (12%)
Grade 2	2 (4%)	0	6 (12%)	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0
NODULE				
Grade 1	17 (34%)	0	21 (42%)	0
Grade 2	2 (4%)	0	2 (4%)	0
Grade 3	0	0	0	0
Grade 4	0	0	0	0

The Sustol arm had a higher proportion of all reports of ISR manifestations in the healthy subject trial than in the phase 3 trials, with the exception of hemorrhage, which was numerically lower in the healthy subject trial. Notably, a higher proportion of ISR manifestations were reported in the saline injection control of the healthy subject trial relative to the saline injection control arm of Study C2006-01, with the exception of bruising, which was similar between saline control arms of the two trials. This higher rate of reporting relative to patients may reflect the nature of this study and the subjects who entered. Healthy subjects were likely more focused on study procedures relative to patients, who had meaningful distractions of chemotherapy and their underlying malignancy.

Study C2013-02 was the only repeat dosing study conducted with the new administration technique. The following table summarizing the proportion of reports by weekly cycle in this healthy subject study indicates that between Cycles 1 and 2 there was a marked decrease in proportion of pain, swelling, induration and hemorrhage reports. Reduced reporting may have been related to a reduced acute focus on the study procedures and anxiety among subjects after experiencing the initial dose. The other manifestations remained essentially stable, with the exception of an increase in nodule reports at the fourth dose.

Table 47. Incidence of ISR Type in Study C2013-02 healthy subject study over each of 4 doses of Sustol 500 mg XC by Period (Subject and Investigator Assessed). Reproduced from table 12.9 in applicants Clinical Study report for Study C2013-02

ISR	Dose 1 N=50	Dose 2 N=48	Dose 3 N=48	Dose 4 N=48
Pain	30 (60.0%)	21 (43.8%)	22 (45.8%)	23 (47.9%)
Haematoma	21 (42.0%)	20 (41.7%)	17 (35.4%)	11 (22.9%)
Swelling	22 (44.4%)	13 (27.1%)	10 (20.8%)	8 (16.7%)
Induration	21 (42.0%)	12 (25%)	10 (20.8%)	8 (16.7%)
Erythema	17 (34%)	13 (27.1%)	17 (35.4%)	17 (35.4%)
Bruising	15 (30%)	16 (33.3%)	15 (31.3%)	11 (22.9%)
Nodule	10 (20%)	11 (22.9%)	11 (22.9%)	17 (35.4%)
Haemorrhage	1 (2%)	0	0	0

Overall Summary of ISR Severity. The applicant stressed that even though the rate of adverse event reporting related to ISRs had increased in the new trials, the events were primarily low grade in severity. The Clinical reviewers expressed concern that even the lowest grade bleeding was described as a prolonged reaction, i.e., oozing over several days, and even grade 2 bleeding required bandage changes more than three times a day. Furthermore, relatively low grade pain (less than severe) was associated with the need to take multiple doses of non-narcotic pain medicine or interfered with daily activity. Similarly, lower grade induration/swelling was associated with interference with daily activity in the response description. Even low and moderate grade scores in these specific manifestation categories may not be acceptable to patients, particularly in light of alternative antiemetic treatments that are not associated with the adverse reactions. The applicant countered that subject satisfaction with study treatment was not negatively impacted by these reactions; however, this conclusion was based on subjects’ response to a global question in the patient diary that did not specifically target the local injection experience; the global question targeted control of nausea and vomiting, “How satisfied are you with the study medication’s *ability to control your nausea and vomiting during these 24 hours* [emphasis added]?” and “Overall, how satisfied are you with the study medication’s *ability to control your nausea and vomiting during this 5 day period* [emphasis added]?”

The applicant expressed concern that patient reporting and the scales exaggerated ISR severity; they pointed to the hematoma and bruising components as evidence of this and stated patients could not accurately measure the size of the hematomas and bruises. However, the events of

particular concern to the reviewers included those in which patients reported a negative impact on their activity/function. Nevertheless, the “double-barreled” nature of some of the diary responses for grading those reactions could lead to misleading conclusions about the actual impact on the patient, i.e., the use of the word “OR” could mean that a patient may have had only one component of the response that did not impact function. For example, for Grade 2 induration/swelling, the response is “5.1-10 cm OR interferes with activity”. It is possible a patient graded their reaction Grade 2 on the basis of swelling size, but experienced no interference with activity; however, there is no information available to determine whether this was the case. We can’t exclude that a patient was reporting interference with activity.

Although the Clinical reviewers expressed concern that the increase in proportion of higher grade severity events may be secondary to product administration changes, I think that having the patient report severity instead of the investigator could well have been the underlying etiology for the increase. I think the proportions of moderate and severe events reported by patients in the most recently submitted phase 3 trial are more likely to reflect the true rate and level of severity of ISRs, although the double-barreled nature of some of the grading descriptions leaves it unclear how impactful they actually were. The fact that the rates reported in the smaller healthy volunteer trials are higher in the more recent trials than in the first submission raises questions that there may be something more than reporting methodology that has contributed to these differences; however, it is also possible that there was heightened investigator reporting in these trials, in light of efforts by the applicant to obtain more comprehensive reporting after the first cycle review.

8.4.1.3 Time course of ISRs: time to onset and duration. The majority of injection site reactions manifested in the first few days of administration of the product; however, injection site mass/nodule was reported later, with the longest mean onset being 6.9 days. The time to onset differed between the phase 3 trials. Onset was in the Day 4-8 range in Study C2006-01 compared to earlier onset in Study C2013, likely reflecting the timing of investigator assessment in Study C2006-01 vs. the daily assessment by patients in Study C2013-01.

The mean and median durations of ISR manifestations were generally longer in Study C2006-01 compared to Study C2013-01, with the exception of injection site nodule, for which the mean duration was doubled in the patient reported ISR trial, Study C2013-01. The mean duration of nodules in Study C2006-01 was 6.0 days vs. 13.9 days in C2013-01. Nodules persisted for a median of 15 days in the combined data from the two trials. Six percent of patients had a nodule for longer than 21 days. The duration of hemorrhage was similar between the two trials; the mean was 7.9 days in the Sustol arm of Study C2006-01 and 6.8 days in the Sustol arm of Study C2013-01. The median duration of hemorrhage was much longer in Study C2013-01: 7.0 days vs. 2.0 days. The mean duration of pain in Study C2006-01 was 12.4 days vs. 5.5 days in Study C2013-01. The median duration in the combined data from the two trials was 5 days. Six percent of patients had pain lasting longer than 7 days.

For low grade reactions, these durations do not raise concerns; however, for higher severity ISRs, these durations seem likely to be unacceptable to patients in a setting of treatment alternatives that don’t involve SQ injections.

In the new repeat dosing study conducted in healthy subjects (Study C2013-02), date of onset of the manifestations of injection site reactions was the first day. The mean ISR duration appears somewhat longer in this healthy volunteer study. The mean duration of the individual ISR manifestations in the Sustol arm ranged from 5 days for erythema to 12.2 days for nodules. The mean and median duration of pain in the Sustol arm were 8.0 and 6.0 days, which was longer than in the saline injection control arm (4.0 days for both mean and median). The mean duration of injection site induration and swelling was 5 days (compared to 0 days on the saline control arm). A hemorrhage was observed in a single subject on each arm, lasting 2 days. Injection site hematomas occurred on both arms; mean duration on the Sustol arm was 9.0 days, compared to 3.5 days on the control arm. Bruising lasted a mean of 9.8 days on the Sustol arm and 3.5 days on the saline control arm. Mean duration of a nodule on the Sustol arm was 12.2 days (median was 8 days) compared to 0 days on the saline injection control.

8.4.2 Discontinuations. The Clinical reviewer for the earlier submissions noted in her review that although she did not consider the ISRs observed with Sustol treatment to be grounds for not approving the product, patients may not desire repeat treatment with the product if they experience one of these reactions. Willingness to continue in a repeat dosing trial could inform how impactful patients find these reactions. The newly submitted phase 3 trial (Study C2013-01) was only a single cycle study, so there are no repeat dosing data from patients that evaluated the new administration procedures (smaller needle and warming). Although the newly submitted repeat dosing study, Study C2013-02, utilized the new administration procedure, it was conducted in healthy volunteers who were reimbursed for their participation. It is not clear that those data are generalizable to patients. It is also difficult to conclude that the discontinuation pattern observed in the first repeat dose phase 3 trial (Study C2006-01) is generalizable to the current administration procedures, given the apparent higher proportion and severity of reactions observed in Studies C2013-01 vs. C2006-01.

The Clinical Review from the original submission noted that in Cycle 1 of Study C2006-01 a numerically higher proportion of subjects treated with Sustol 250 mg or 500 mg prematurely discontinued from the trial due to treatment emergent adverse events than in the Aloxi (+ saline injection) control arm: **2.7% vs 3.0% vs. 1.5%**, respectively. It is important to note that in Cycles 2-4, there was no Aloxi (+ saline injection) control arm; patients who agreed to continue in the trial either remained on the original assigned Sustol dose if they were originally randomized to Sustol in the first cycle, or they were randomized between the two Sustol dose levels after Cycle 1 if they had been treated with Aloxi in Cycle 1. (Patients originally treated on the Aloxi arm received a placebo saline injection in the first cycle.) In the subsequent cycles, 4.2% and 4.9% of the Sustol 250 mg and 500 mg arm patients discontinued prematurely. The reviewer stated “Across all cycles combined, a total of 36 subjects (5.3%) who received $\leq$ 250 mg APF530 and 41 (5.9%) who received $\geq$ 500 mg APF530 experienced treatment-emergent AEs associated with premature discontinuation of trial participation.” However, this type of analysis does not clearly address patients who withdrew from the study, including between cycles, because they no longer wished to receive SQ injections of study drug.

The following table, reproduced from the original review cycle’s Clinical review (Table 6 of Dr. Berry’s review), summarizes the reasons for discontinuation from Study C2006-01 during Cycle 1.

Table 48. Distribution of reasons for discontinuation during Cycle 1 across arms and emetogenicity subgroup in Study C2006-01.

Reason for discontinuation	MEC			HEC		
	5mg	10 mg	Aloxi	5mg	10 mg	Aloxi
AE	0	0	0	0.4%	0.4%	0
Lost to f/u	1.4%	1.4%	1.9%	0.4%	0.4%	0
Withdrew Consent	0.5%	0.5%	0	0.4%	0.4%	0
Death	0	0	0.5%	0.8%	0.4%	0
Other	0	0	0.5%	0.8%	0.4%	0.8%

The following table, which is reproduced from the original review cycle’s Clinical review, summarizes the patient disposition by cycle, divided between whether patients received MEC or HEC chemotherapy. Discontinuation between Cycle 1 and 2 is difficult to assess because the Aloxi arm patients who remained on trial were randomized in Cycle 2 between the two Sustol dose levels (the sample size in the Sustol arms increases between Cycle 1 and Cycle 2). Therefore, some of the patients treated with Sustol in Cycle 2 received the polymer-based injection for the first time in Cycle 2. (In the Aloxi control arm, patients received a saline injection in the first Cycle, which data presented above suggest was better tolerated than the Sustol injection.) Furthermore, if having received two injections was the critical decision point to stop agreeing to SQ polymer-based drug injection, there will be a lag in actual drop out, given the contribution of former Aloxi arm patients to the Cycle 2 sample size.

Table 49: Summary of disposition of subjects in Study C2006-01 (mITT and PP Populations). Reproduced from original cycle Clinical Review (Table 4)

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

The dropout (i.e., loss of subjects) between Cycles 2 and 3 was 23% in the MEC 250 mg treated subjects, 23% in the MEC 500 mg treated subjects, 21% in the HEC 250 mg treated subjects and 23% in the HEC 500 mg treated subjects. The dropout between cycles 3 and 4 numerically increased somewhat: to 30%, 27%, 24% and 27%, respectively.

In response to an information request from the clinical review team, the applicant submitted the disposition by-cycle based on original arm of randomization, and those data are summarized in the table below. There was a slight numeric increase in loss between the Cycle 1/Cycle 2 and Cycle 3/Cycle 4, particularly in the MEC subgroup patients who were treated

with Aloxi + saline injection in the first cycle. The dropout rate from cycle to cycle otherwise appears pretty steady.

Table 50. Study C2006-01: Summary of disposition of subjects by original Cycle 1 randomization assignment.

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)
Cycle 2	171	162	163	185	179	183
% loss C1 to C2	-25%	-24%	-22%	-19%	-25%	-23%
Cycle 3	129	121	130	144	136	140
% loss C2 to C3	-25%	-25%	20%	-22%	-24%	-24%
Cycle 4	94	92	87	110	99	109
% loss C3 to C4	-27%	-24%	-33%	-24%	-27%	-22%

Some of the discontinuations were due to death, completion of chemotherapy regimen, “no additional qualifying chemotherapy”, “failed to meet dosing criteria”, and protocol violation. The remaining causes of discontinuation that might be attributed to lack of tolerance of SQ polymer administration included: adverse event, lost to follow up, withdrew consent, lack of efficacy, and other. Table 51 below summarizes the disposition by tabulating these latter potentially “intolerant” categories as a “narrow composite”. In the table below, the composites are the number and % of patients in the cycle listed above the composite rows that did not go on to the cycle listed below the “composite” rows due to the reasons listed in the (broad vs. narrow) definitions provided below the table. Note that the narrow composite data for the movement from Cycle 1 to Cycle 2 was based on the Original Clinical Review Table 6, which is limited in information and reports “reasons for discontinuation from trial during Cycle 1”; therefore, the composite rows that follow Cycle 1 may not have captured the reasons for discontinuation between Cycles 1 and 2 in a manner consistent with the subsequent cycles.

Table 51. Study C2006-01: Summary of disposition of subjects by original Cycle 1 randomization assignment broken down by composite reason for discontinuation (see composite definition below table).

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)
Broad Composite						
Narrow Composite	-4 (-2%)	-4 (-2%)	-4 (-2%)	-3 (-1%)	-3 (-1%)	-1 (0.4%)
Cycle 2	171	162	163	185	179	183
Broad Composite	-30 (-18%)	-26 (-16%)	-19 (-12%)	-16 (-9%)	-11 (-6%)	-19 (-10%)
Narrow Composite	-3 (-2%)	-6 (-4%)	-3 (-2%)	-7 (-4%)	-3 (-2%)	-7 (-4%)
Cycle 3	129	121	130	144	136	140
Broad Composite	-17 (-13%)	-13 (-11%)	-14 (-11%)	-8 (-6%)	-9 (-7%)	-8 (-6%)
Narrow Composite	-3 (-2%)	-3 (-2%)	0	-3 (-2%)	-2 (-2%)	-1 (-1%)
Cycle 4	94	92	87	110	99	109

Broad composite= Number of patients who discontinued either during or between cycles due to adverse event, lost to follow up, withdrew consent, lack of efficacy, and other.

Narrow composite = Number of patients who discontinued either during or between cycles due to adverse event, lost to follow up, withdrew consent.

As can be seen, the dropout rate for the “narrow composite” of discontinuation for adverse event, lost to follow up or withdrew consent is much smaller than the overall proportion of drop out between cycles, and appears stable over the 4 cycles.

The dropout pattern over multiple cycles in Study 2006-01 was further explored by comparing it to the dropout pattern observed in multi-cycle chemotherapy trials reviewed in the NDA for rolapitant. In that application, two trials offered treatment to patients over multiple cycles (Studies 32 and 33); both were HEC trials. Those data are presented first limited to Cycle 1, and then over the multiple cycles. The discontinuation rate during Cycle 1 of these two trials for adverse events and withdrawal of consent, summarized in the table below, was numerically higher than that observed in Cycle 1 of the Sustol trial, Study C2006-01. The proportion lost to follow up in these two rolapitant HEC trials was numerically higher than that observed in the HEC subgroup of the Sustol trial; however, the proportion of patients treated with MEC in the Sustol trial who were lost to follow up was numerically higher than observed in the HEC treated patients in the Sustol and rolapitant trials.

Table 52. Summary of Discontinuation from rolapitant HEC trials, reproduced and modified from the Clinical Review of NDA 206500 for rolapitant (Table 12)

Number of Subjects:	HEC (P04832)		HEC (P04833)	
	Rolapitant 200 mg n (%)	Control n (%)	Rolapitant 200 mg n (%)	Control n (%)
Randomized ^a	266	266	278	277
Included in MITT Population ^{b,c}	264 (100)	262 (100)	271 (100)	273 (100)
Received Chemotherapy	262 (99.2)	262 (100)	271 (100)	272 (99.6)
Completed Cycle ^d	251 (95.1)	240 (91.6)	258 (95.2)	258 (94.5)
Discontinued During Cycle 1	13 (4.9)	22 (8.4)	13 (4.8)	15 (5.5)
Adverse event	2 (0.8)	5 (1.9)	2 (0.7)	2 (0.7)
Consent withdrawal	6 (2.3)	7 (2.7)	5 (1.8)	4 (1.5)
Death	2 (0.8)	4 (1.5)	2 (0.7)	1 (0.4)
Lack Of Efficacy	0	0	1 (0.4)	1 (0.4)
Lost To Follow-Up	1 (0.4)	2 (0.8)	0	3 (1.1)
Protocol Non-Compliance	1 (0.4)	4 (1.5)	3 (1.1)	3 (1.1)
Study Completed ^e	0	0	0	0
Other ^f	1 (0.4)	0	0	1 (0.4)

Abbreviations: GCP = Good Clinical Practices; HEC = highly emetogenic chemotherapy; MEC = moderately

The following table summarizes the rolapitant exposures in subsequent cycles in Studies 32 and 33. Compared to Table 50 above (**Summary of disposition of subjects in Study C2006-01 by original Cycle 1 randomization assignment.**), the proportion lost between cycles is similar to that observed in the multi-cycle Sustol trial, Study C2006-01.

Table 53. Rolapitant exposures in Study 32 and Study 33 over Cycles 1 through 6. From Clinical review of NDA rolapitant (Table 34 of that review).

Cycle	Study 32 (n)	% drop out Study 32	Study 33 (n)	% drop out Study 33
Cycle 1	263		272	
Cycle 2	181	31%	214	21%
Cycle 3	128	29%	171	20%
Cycle 4	94	27%	112	34%
Cycle 5	61	35%	78	30%
Cycle 6	44	28%	61	22%

In the Akynzeo NDA, there were also two multi-cycle trials, NETU-08-18 (MEC) and NETU-10-29. The following table summarizes the overall trial patient disposition in the Akynzeo MEC trial (NETU-08-18). The clinical reviewer stated in her review that most patients (98.8%) completed Cycle 1.

Table 54. Overall trial patient disposition in the multicycle Akynzeo MEC Trial NETU-08-18. From Clinical review Table 3 of NDA 205718.

	NETU/PALO		PALO alone		Overall	
	n	(%)	n	(%)	n	(%)
Randomized	726	(100.0)	729	(100.0)	1455	(100.0)
Treated	724	(99.7)	726	(99.6)	1450	(99.7)
Completed Planned/Unplanned Chemotherapy Cycles	453	(62.4)	463	(63.5)	916	(63.0)
Completed Planned Chemotherapy Cycles but Discontinued During Additional Unplanned Cycle	2	(0.3)	0		2	(0.1)
Completed a Cycle But Not Continuing in the Next Planned Cycle	253	(34.8)	245	(33.6)	498	(34.2)
Discontinued After Randomization and During any Planned Chemotherapy Cycle	18	(2.5)	21	(2.9)	39	(2.7)
Reason for Not Continuing or for Discontinuation						
Inclusion/Exclusion Criteria not Met (Multiple-Cycle Extension)	55	(7.6)	66	(9.1)	121	(8.3)
Adverse event	10	(1.4)	19	(2.6)	29	(2.0)
Death	0		2	(0.3)	2	(0.1)
Protocol Violation	5	(0.7)	6	(0.8)	11	(0.8)
Lost to Follow-up	0		5	(0.7)	5	(0.3)
Withdrawal of Consent	65	(9.0)	42	(5.8)	107	(7.4)
Lack of Efficacy	1	(0.1)	3	(0.4)	4	(0.3)
Sponsor's Decision	0		0		0	
Other	136	(18.7)	123	(16.9)	259	(17.8)

In Cycle 1, treatment emergent adverse events led to discontinuation in 0/726 patients in Akynzeo arm and 2/726 (0.3%) of the control arm. In the overall multicycle extension, no patients in the Akynzeo arm and 1 (0.2%) in the control discontinued due to AE.

The following table from the Akynzeo NDA Clinical review summarizes the patient disposition by Cycle, after Cycle 1. Although the previous table indicates that approximately a

third of patients across the overall trial completed a cycle but didn't continue on to the next cycle, as can be seen in the table below, subject retention was high after Cycle 2 until cycle 4. From cycle 1 to Cycle 2, 12.5% and 10.7% of subjects did not continue into Cycle 2 in the Akynzeo and control arms, respectively. From Cycle 2 to Cycle 3, 4.4% and 5.4% of patients did not continue, respectively. From Cycle 3 to Cycle 4, 6.2% and 5.9% of patients did not continue. There was a marked decrease in patients scheduled for Cycle 5 after Cycle 4, which could reflect completion of common 4-cycle chemotherapy regimens, or patient choice. Because this trial was a "MEC" trial, in which AC was considered MEC, which is generally used as adjuvant therapy for breast cancer, the dramatic drop likely represents completion of the scheduled planned course of chemotherapy. (AC is commonly administered over 4 cycles of treatment.) The loss of patients between cycles in the first 4 cycles was much lower in this trial than in Study C2006-01 (or the rolapitant trials).

Table 55. Patient disposition by Cycle across multiple cycles in Study 08-18 in the Akynzeo NDA 205718. From Clinical review, Table 4.

	NETU/PALO FDC (N=726)		PALO alone (N=729)		Overall (N=1455)	
	n	(%)	n	(%)	n	(%)
Scheduled for Treatment Cycle 2	635	(87.5)	651	(89.3)	1286	(88.4)
Treated Cycle 2	635	(87.5)	651	(89.3)	1286	(88.4)
Completed Cycle 2	630	(86.8)	645	(88.5)	1275	(87.6)
Scheduled for Treatment Cycle 3	598	(82.4)	606	(83.1)	1204	(82.7)
Treated Cycle 3	598	(82.4)	605	(83.0)	1203	(82.7)
Completed Cycle 3	596	(82.1)	603	(82.7)	1199	(82.4)
Scheduled for Treatment Cycle 4	551	(75.9)	560	(76.8)	1111	(76.4)
Treated Cycle 4	551	(75.9)	560	(76.8)	1111	(76.4)
Completed Cycle 4	548	(75.5)	559	(76.7)	1107	(76.1)
Scheduled for Treatment Cycle 5	272	(37.5)	249	(34.2)	521	(35.8)
Treated Cycle 5	271	(37.3)	249	(34.2)	520	(35.7)
Completed Cycle 5	268	(36.9)	248	(34.0)	516	(35.5)
Scheduled for Treatment Cycle 6	197	(27.1)	191	(26.2)	388	(26.7)
Treated Cycle 6	197	(27.1)	191	(26.2)	388	(26.7)
Completed Cycle 6	197	(27.1)	191	(26.2)	388	(26.7)
Scheduled for Treatment Cycle 7	3	(0.4)	3	(0.4)	6	(0.4)
Treated Cycle 7	3	(0.4)	3	(0.4)	6	(0.4)
Completed Cycle 7	3	(0.4)	3	(0.4)	6	(0.4)
Scheduled for Treatment Cycle 8	3	(0.4)	2	(0.3)	5	(0.3)
Treated Cycle 8	3	(0.4)	2	(0.3)	5	(0.3)
Completed Cycle 8	3	(0.4)	2	(0.3)	5	(0.3)

Another multi-cycle trial, NETU 10-29, enrolled patients treated with either HEC (25%) or MEC (75%), and 37% of patients completed a cycle during the trial but didn't go on to the subsequent cycle. The following table summarizes this overall study disposition. Discontinuation for adverse event across multiple cycles occurred in 6% of Akynzeo arm patients and 11.5% of control arm patients. Withdrawal of consent across cycles occurred in 5.5% of Akynzeo patients vs. 6.7% of control. Loss to follow-up accounted for 1.6% of Akynzeo patients and 1.0 % of control arm patients.

Table 56. Summary of overall patient disposition in the Akynzeo multicycle trial NETU 10-29. From Clinical review of Akynzeo NDA 205718, Table 50

	NETU/PALO FDC		Aprepitant+ PALO		Overall	
	n	(%)	n	(%)	n	(%)
Randomized	309	(100.0)	104	(100.0)	413	(100.0)
Treated	309	(100.0)	103	(99.0)	412	(99.8)
Completed planned/unplanned chemotherapy cycles	181	(58.6)	55	(52.9)	236	(57.1)
Completed planned chemotherapy cycles but discontinued during additional unplanned cycle	0		0		0	
Completed a cycle but not continuing in the next planned cycle	111	(35.9)	43	(41.3)	154	(37.3)
Discontinued after randomization and during any planned chemotherapy cycle	17	(5.5)	6	(5.8)	23	(5.6)
Reason for not continuing or for discontinuation						
Adverse event	19	(6.1)	12	(11.5)	31	(7.5)
Death	12	(3.9)	0		12	(2.9)
Protocol violation	4	(1.3)	1	(1.0)	5	(1.2)
Lost to follow-up	5	(1.6)	1	(1.0)	6	(1.5)
Withdrawal of consent	17	(5.5)	7	(6.7)	24	(5.8)
Lack of efficacy	0		0		0	
Sponsor's decision	1	(0.3)	0		1	(0.2)
Other	70	(22.7)	28	(26.9)	98	(23.7)
Entered a within-study cardiovascular follow-up*	6	(1.9)	2	(1.9)	8	(1.9)
Entered a post-withdrawal cardiovascular follow-up*	1	(0.3)	1	(1.0)	2	(0.5)

Overall, although the drop out in the Sustol arms appears higher than observed in the Akynzeo trials, it appears similar to that observed in the rolapitant trials. These cross study comparisons are merely exploratory and are seriously limited by available information to assure that the same types of data are being compared between trials, e.g., whether dropouts occurred during a cycle vs. between cycles. There is no clear evidence that patients treated in the Sustol multi-dose phase 3 trials were more likely to have “voted with their feet” and left the trial because they preferred to avoid further SQ injections relative to patients who participated in antiemetic trials in which the product was administered IV or PO.

8.4.3 Infections. As stated earlier in my discussion of SAEs, there was one hospitalization for an injection site infection. In the recently submitted trial, Study C2013-01, there were 3 injection site infections on the Sustol arm (0.7%) and none on the ondansetron arm (for total study injection rate, counting the drug free polymer, of 0.3%). The applicant reported in the ISS that there was a total of 8 subjects (including one healthy subject from a phase 1 study) that had an infection at the injection site. Two of the subjects had a history of diabetes. One of the infections, an SAE in Study C2013-01, was described above. The following table, created for me by the Clinical Reviewer, summarizes the injection site infections across the NDA's entire ISS database.

Table 57. Injection Site Infections across NDA ISS (includes patients in Studies C2006-01 and C2013-01, and one healthy subject from Study C2011-01)

Subject ID/ Treatment Arm	Age (years)	Sex	AE Term / Treatment	AE Severity	Cycle	AE Onset (Cycle Day)	Duration (days)	Overall	Pertinent Medical History/ Data
(b) (6) Sustol 5 mg	77	F	Cellulitis Dicloxacillin	Mild	1	7	31	Resolved	None
(b) (6) Sustol 5 mg	77	M	Cellulitis Dicloxacillin	Mild	2	16	55	Resolved	Diabetes mellitus BMI 30.9 (obese)
			Cellulitis	Mild	4	1	7	Resolved	
(b) (6) Sustol 10 mg	54	M	Cellulitis Ciprofloxacin/ Erythromycin	Moderate	1	8	8	Resolved	BMI 30.2 (obese)
(b) (6) Sustol 10 mg	40	M	Infection* Cephalexin	Mild	1	8	7	Resolved	None
(b) (6) † Sustol 20 mg (healthy volunteer)	35	M	Erysipelas Cephalexin	Mild	1	7	6	Resolved	BMI 26.4 (overweight)*
(b) (6) Sustol 10 mg	56	F	Skin infection IV vancomycin + piperacillin- tazobactam	Moderate	1	14	9	Resolved	BMI 27.1 (overweight) Neutropenia**
(b) (6) Sustol 10 mg	43	F	Infection Cephalexin	Moderate	1	9	34	Resolved	None
(b) (6) Sustol 10 mg	72	M	Infection Cephalexin	Moderate	1	12	11	Resolved	Diabetes mellitus Hypothyroidism Renal insufficiency BMI 35.9 (obese)

Source:

Abbreviations: AE, adverse event; ANC, absolute neutrophil count; BMI, body mass index; CLL, chronic lymphocytic leukemia; F, female; H, high; M, male

† Subjects with available AE narrative (see)

(ANC 400) Note: All infections occurred at abdominal injection sites following administration of Sustol

Section 5.1 under the label’s Warnings and Precautions will state that seven patients in the clinical trials and one healthy subject had infections at the injection site. The warning will describe median time to onset (9 days) and that one of the infections required hospitalization.

8.4.4 Gastrointestinal adverse events of interest: Constipation and Pancreatitis.

A numerically higher rate of constipation TEAEs of all grades (except grade 4) was reported in the Sustol arm relative to the ondansetron arm in Study C2013-01. There were 3 SAEs that involved constipation. The following table summarizes the distribution of these events across

arms, including the grade. The data are derived from the applicant’s Clinical Study Report Table 14.3.1.3.3.

Table 58. Study C2013-01: Treatment Emergent Constipation AEs and distribution by Grade

Constipation Grade	Sustol 500mg	Ondansetron
Grade 1	71 (15.6%)	52 (11.3%)
Grade 2	28 (6.1%)	18 (3.9%)
Grade 3	1 (0.2%)	0
Grade 4	0	0

In the original Clinical Review of the first phase 3 trial submitted to this NDA, Study C2006-01, the reviewer noted that constipation was the most frequently reported adverse event (excluding ISRs); in Cycle 1 it occurred in 13.4% of the 250 mg group and 15.4% of the 500mg group (compared to 13.4% in the Aloxi comparator arm). There was one SAE for constipation, which led to treatment discontinuation. The distribution of constipation severity in Study C2006-01 is summarized in the table below, which is reproduced from the applicant’s study report. Grading in this trial was based on mild, moderate or severe. No patient in the Aloxi arm of Study C2006-01 experienced severe constipation, whereas 6 patients in the Sustol arms experienced severe constipation. There were twice as many patients in the Sustol arm who experienced severe constipation than in the lower dose arm. There was also a numerically higher number of patients who experienced moderate constipation in the Sustol arms relative to the Aloxi arm. The SAE of constipation in Study C2006-01 occurred in a patient treated with Sustol 5 mg who presented complaining of constipation onset 7 days after treatment. She did not have a bowel movement for 12 days. This case was not confounded by concomitant use of opioid drugs.

Table 59. Study C2006-01: Treatment Emergent Constipation in Cycle 1, by severity level and by treatment arm.

		Sustol 250 mg N=464		Sustol 500 mg N=468		Aloxi 0.25 mg N=463	
Preferred Term ^{a,b}	Severity	Related	Not	Related	Not	Related	Not
		n (%)	Related n (%)	n (%)	Related n (%)	n (%)	Related n (%)
Constipation	Mild	13 (2.8)	30 (6.5)	15 (3.2)	40 (8.5)	12 (2.6)	41 (8.9)
	Moderate	6 (1.3)	13 (2.8)	4 (0.9)	10 (2.1)	2 (0.4)	7 (1.5)
	Severe	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)	0	0

As discussed earlier, the Clinical reviewer expressed concern that the constipation reflected the sustained exposures to granisetron, which is known to be associated with constipation. The reviewer noted that the rate of constipation in Study C2006-01 was higher than reported in the

IV granisetron label (3%); however, the rate of constipation in the Aloxi control arm of Study C2006-01 was also numerically higher than that reported in the IV Aloxi product label (5%).

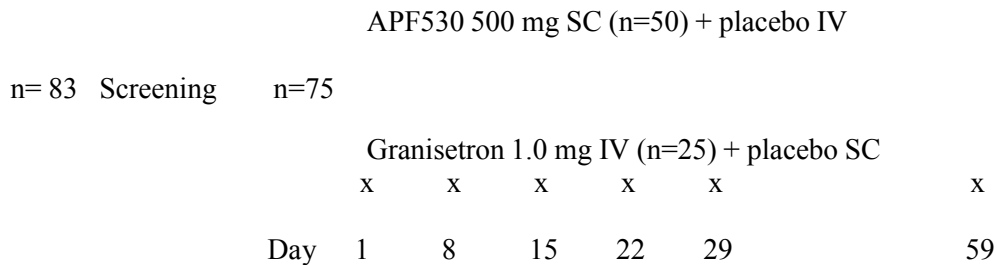
8.4.5 Pancreatitis. Three pancreatitis events were presented above in the discussion of SAEs. All three occurred on the Sustol arm of Study C2013-01. Although one of the 3 pancreatitis events occurred in a patient with a history of pancreatitis, the fact that all 3 events occurred in the Sustol arm was notable. The approved IV granisetron label and the granisetron patch label do not mention pancreatitis, including in the postmarketing experience section. See my discussion of pancreatitis in SAE Section 8.3.2.4, where I concluded that these events did not constitute a clear signal related to Sustol.

8.5 Serum Chemistry Evaluation in New Repeat dosing study (q 7 days) in healthy volunteers – Study C2013-02.

In response to the non-deficiency comment in the CR letter regarding the need for assessment of serum chemistries during repeat dosing and with q 7 day dosing, the applicant submitted the results of a multi-dose study that randomized healthy volunteers, in a 2:1 randomization, between Sustol 500 mg + IV placebo vs. granisetron IV + SQ normal saline placebo injection. The new administration directions for Sustol were utilized in this trial, with the exception that the injection sites were limited to the abdomen. Warming pouches were used, “if needed”. Enrollment of healthy volunteers instead of patients receiving chemotherapy is acceptable because it allowed assessment of impact on serum chemistries in a population that would not have confounding impact from toxicities related to the concomitant chemotherapy.

The population enrolled was 56% male and median age was 28 years. The majority (85%) were white. Subjects received 4 administrations separated by 1 week. They were discharged to home 4 hours after every injection, as long as there were no reactions that precluded discharge. This study addressed concerns about Sustol dosing as frequently as every 1 week, as had been proposed in the product labeling.

Figure 3 Study C2013-02 Flow Diagram



Safety monitoring included weekly serum chemistry, hematology, urinalysis, and physical examinations. Both the subject and the physician performed injection site assessments. The investigator evaluated the injection site weekly, in addition to 1 and 3 hours following each dose. The subjects conducted self-evaluations of the injection site on Days 2-7, 9-14, 16-21, Day 23 and Day 28. If the subject had an injection site reaction, they were to return to the

clinical study site within 24 hours to be evaluated by the investigator. The scoring system was the same used by the patients in Study C2013-01.

Very few subjects withdrew from this trial. The following table, which summarizes subject disposition, is reproduced from the Clinical Study report (Applicant's Table 10.1). One subject discontinued for an adverse reaction: constipation, stomach cramps (upper abdomen), aches, fever and sore throat, which developed 3-7 days after the first dose of Sustol. Another subject randomized to Sustol discontinued after the first dose "due to scheduling problem".

Table 60. Study C2013-02: Subject disposition

Parameter/ Category	APF530 500 mg	Granisetron 1.0 mg	Total
Number of Subjects			
Screened			83
Randomized	50	25	75
Treated (Safety Population)	50 (100.0%)	25 (100.0%)	75 (100.0%)
Completed Study	48 (96.0%)	25 (100.0%)	73 (97.3%)
Primary Reason for			
Adverse Event	1 (2.0%)	0	1 (1.3%)
Protocol Violation	0	0	0
Pregnancy	0	0	0
Withdrew Consent	0	0	0
Difficulties in Blood	0	0	0
Sponsor or Investigator Terminated	0	0	0
Lost to Follow-up	0	0	0
Other [1]	1 (2.0%)	0	1 (1.3%)

Source: End of Text Table 14.1.1.1; Listing 16.2.1 (Appendix 16.2).

The rate of treatment emergent AEs (TEAEs), excluding ISRs, was similar between arms: 22.0% Sustol arm and 20% in IV Kytril (+saline injection) arm. There were no SAEs and no deaths. Most of the AEs were graded as mild; maximum severity was moderate. Excluding ISRs, headache was the most commonly reported TEAE (6% Sustol and 12% Kytril). Constipation followed: 6% in the Sustol arm and 0% in the Kytril 1.0 mg IV arm.

In this section, I will focus on the results of serial chemistries in light of the weekly dosing in this trial. The ISRs reported in this trial were discussed earlier.

8.5.1 Serum chemistries.

8.5.1.1 Liver chemistries. One subject on the Sustol arm had an elevated total bilirubin (51.3 micromole/L; normal = 3.4 to 25.7) 11 days after the last Sustol dose, associated with an increased AST (83 IU/L) and ALT 137 IU/L. (See summary laboratory values listed below.) The subject ((b) (6)) reportedly had elevated bili, AST/ALT at baseline. At screening the AST was slightly elevated at 48 U/L (ULN=40), total bili was 25.6 micromol/L and direct bili was elevated at 6.8 (ULN=3.4 micromol/L). The Day 1 elevations included ALT= 54, AST = 59, and direct bili of 5.1 micromole/L; however, total bili was within normal range (17

micromole/L). GGT and LDH were within normal limits at baseline and Day 1. The subject’s laboratory values shifted between elevated and normal range during the dosing period, and then elevated consistently relative to baseline during follow-up after completion of 4 doses. Alkaline phosphatase was normal throughout. Hy’s Law criteria weren’t met. The serial changes are summarized in the table below, which is reproduced from the applicant’s study report (Table 12.10). The applicant reported the elevated bilirubin resolved 26 days later.

Table 61. Study 2013-02: Summary liver chemistries in Subject (b) (6).

Visit	ALT	AST	LDH	GGT	D. Bili	Total Bili	Alk. Phos
Screening	32	48 [H]	211	45	6.8416 [H]	25.656 [H]	76
Day 1	54 [H]	59 [H]	206	37	5.1312 [H]	17.104	60
Day 8	55 [H]	59 [H]	218	56	6.8416 [H]	25.656 [H]	79
Day 15	33	52 [H]	208	55	3.4208	11.9728	61
Day 22	38	44 [H]	166	64	5.1312 [H]	22.2352 [H]	65
Day 29 or ET	63 [H]	103 [H]	228 [H]	64	10.2624 [H]	51.312 [H][CS]	76
Day 59	83 [H]	137 [H][CS]	248 [H]	69	5.1312 [H]	20.5248 [H]	80

Source: End of Text Table 14.3.4.10; Listing 16.2.8.2.1 (Appendix 16.2).

ALT=alanine aminotransferase; AST=aspartate aminotransferase; LDH=lactate dehydrogenase; GGT=gamma glutamyl transferase. [H]=abnormalhigh;[CS]=clinicallysignificant;>3xULNforASTand>2xULNforTotalBilirubin.

Review of the total serum bilirubin shift tables from this trial revealed a numerically higher percentage of subjects in the control arm shifted from normal to high during the trial (8% vs. 2%). Review of the shift tables for direct bilirubin also revealed a numerically higher proportion shifted from normal to high abnormal on the control arm: 4% on Day 22 and 8% on Day 29. On the Sustol arm, 2% shifted from normal baseline to high abnormal on Day 8.

Review of the shift tables for ALT revealed that a numerically similar percentage on the Sustol and control arms shifted from normal baseline to high abnormal: Sustol = 6% on the Day 22 visit, 4% on the Day 29 visit and 2% on the Day 59 visit; Control arm = 4% on Day 8, and 1 on Day 59.

For AST, there was a numerically higher percentage of shifts on the control arm relative to the Sustol arm. The control arm: 8% at Day 8 visit, 4% at the Day 22, 29 and 59 visits. The Sustol arm: 2% on Day 22 and 29, in addition to 4% at the Day 59 follow up who had shifted from baseline normal to abnormally high.

Overall the percentages of shifts from normal baseline to high abnormal appeared comparable between arms, with the exception of a greater number of shifts to high abnormal bilirubin in the control arm.

8.5.1.2 Serum bicarbonate. Serum bicarbonate levels were evaluated for evidence of metabolic acidosis, potentially secondary to polymer degradation. The maximum bicarbonate reduction documented on the Sustol arm was -0.88 mmol/L (compared to the granisetron + saline placebo change = -1.68 mmol/L). No subject experienced a shift to a low bicarb level. These data indicate that polymer metabolism, when administered in 4 weekly doses separated by 1 week, is unlikely to induce metabolic acidosis in patients with normal renal function.

8.5.1.3 Renal function. There were no shifts from normal to high abnormal BUN on the Sustol arm, whereas there was one subject that shifted to high abnormal on the control arm. There was one subject on the Sustol arm who shifted from normal creatinine to high creatinine on the Day 22 visit only. There were no other shifts to abnormal creatinine in the study.

A subject on the Sustol arm shifted from normal to high abnormal potassium level on Day 15 (5.6 in context of ULN of 5.5), and there were two subjects that shifted from normal to high on Day 22 (5.7 in context of 5.5 ULN in one subject, who was also the subject that experienced a slight elevation on Day 15). On Day 29 there was one subject with a shift to high. At the Day 59 follow up there were two subjects who had shifted from normal at baseline to high. In contrast, on the Kytril+saline injection control arm, one subject shifted from normal to high abnormal on Day 15. In light of the 2:1 randomization of Sustol:Kytril, it is unclear whether these numeric differences are meaningful.

These shifts do not appear clinical meaningful and I cannot conclude that there is a risk of renal toxicity and electrolyte abnormalities associated with the polymer from these data.

8.5.1.4 CPK. The Clinical reviewer expressed concern about high CPK levels observed in the Sustol arm of this trial, as CPK elevation might reflect underlying muscle injury related to the SQ injection. The shift tables reveal the following shifts from normal baseline to abnormal high CPK levels on the Sustol arm: Day 8, 15 and 22 = 2 (4%), Day 29 = 4 (8%), Day 59 = 12.5%. On the Kytril + saline injection control arm, there were fewer assessment dates with shifts to abnormal, and on matched days with the Sustol arms, the proportion of subjects with shifts was numerically lower than the Sustol arm, with the exception of Day 22: Day 22 = 2 (8%), Day 29 = 1 (4%), Day 59 = 2 (8%). (There was a 2:1 randomization in this trial.) These apparent differences are difficult to interpret, given the trial's small sample size and the relatively small differences. Furthermore, some subjects in both arms had high baseline CPK's, particularly on the control arm, and the majority of those in both arms remained high during the trial.

I reviewed the applicant's study report for Study C2013-02, Table 16.2.8.2.2 Abnormal Chemistry and Serology Results and noted that in the Sustol group, there were 14 subjects who experienced elevation of CPK after a normal baseline CPK, compared to 5 on the control; however, one must keep in mind the 2:1 randomization when comparing the numbers. There were 4 additional subjects who had high screening and/or Day 1 CPKs, followed by elevated CPKs on subsequent evaluations, compared to 6 on the control arm.

- Among Sustol treated subjects with normal baseline CPK, the highest on-study CPK was 490 U/L (ULN=143) on Day 22; there was a subject with a high CPK on Day 59 follow-up visit (562U/L; ULN=143).
- In the Sustol treated subjects with high baseline CPK:
 - one subject whose baseline screening CPK was minimally elevated at 150 U/L (ULN=143 U/L) experienced a slight increase to 169 U/L on Day 29.
 - One subject with a screening CPK of 295 U/L (ULN 196 U/L) followed by a markedly elevated Day 1 level (pretreatment) of 2315 U/L, demonstrated a

general decrease on study, with some variability: on Day 15 CK was 263 U/L, Day 22=356 U/L, Day 29 =270 U/L; Day 59=242 U/L.

- Another subject had a marked elevation on Day 1 (pretreatment) of 4036 U/L (ULN=196). This subject's level dropped to 767 U/L on Day 8 and further to 370 U/L on Day 22.
- One final subject had a high screening CK of 768 U/L (ULN= 196 U/L), and the levels dropped while on study: Day 8 = 378 U/L and Day 29 = 293 U/L.

On the control arm there were only 5 subjects who experienced CPK elevations who had normal baseline CPKs. There were 6 subjects with high baseline CPKs, on screening and/or Day 1 evaluation.

- Among the control arm subjects with normal baseline CPK, the highest level documented on study was 320 U/L (ULN 196 U/L).
- Among the control subjects with high baseline CPK value:
 - one subject had a screening level of 197 U/L (ULN= 143 U/L), and on each subsequent evaluation the CPK level exceeded the ULN, but varied; the highest post baseline level was 268 on Day 22.
 - Another subject had a screening level of 202 (ULN=196 U/L), and the levels continued to climb on study: Day 8 = 434 U/L, Day 22= 401 U/L, Day 29=501 U/L, and Day 59= 574 U/L.
 - A subject with a Day 1 CPK elevation of 226 U/L (ULN=196 U/L) experienced a low rise over the course of the study: Day 15=233 U/L, Day 29= 295 U/L.
 - A subject with a high screening CPK of 319 U/L (ULN=196 U/L) had follow up values that varied but remained high: Day 8=312 U/L, Day 22= 243 U/L, Day 29 = 215 U/L, Day 59=394 U/L.
 - A subject with a mildly elevated screening CPK (153 U/L; ULN=143 U/L) had a marked increase in CPK at the Day 1 pretreatment evaluation (CPK=713 U/L). The CPK subsequently dropped to within normal range and was only mildly elevated on Day 59 (152 U/L).
 - A subject with a normal screening CPK had a markedly elevated CPK on the pretreatment Day 1 evaluation (680 U/L; ULN=143 U/L). The CPK dropped to 302 U/L on Day 8 and subsequent CPKs were within normal range for the remainder of the study.
 - Finally, a subject with a normal screening CPK had a Day 1 evaluation that was elevated at 250 U/L (ULN=143 U/L). On Day 8 the CPK increased further to 348 U/L. The remaining evaluations exceeded the ULN, but were steadily decreasing. The Day 29 value was 212 U/L.

Although there were more subjects in the Sustol arm of this trial who shifted from a normal baseline CK to an elevated CK than on the control arm, the elevations were generally not dramatic, and when the 2:1 randomization is taken into account there is no clear imbalance. In addition, the highest documented increases were on Day 1 evaluation, which was pre-dosing. The serial laboratory values demonstrate that a number of patients entered the trial with high screening and/or Day CKs, which of course could not be attributed to study drug, and the levels generally decreased while receiving repeat SQ injections.

In summary, the healthy volunteer multiple dose study did not reveal a non-ISR adverse event that signals a safety issues associated with repeat dosing of Sustol. The single patient with shifts in bilirubin and transaminases had abnormalities at baseline. The increased degree of abnormalities while on study is possibly drug related; however, elevations of liver enzymes and bilirubin have been observed in the CINV clinical trials that have investigated 5HT3 inhibitors. It is possible this patient's underlying liver pathology was worsened by continuous exposure to granisetron in this weekly repeat dose study. With regard to the elevations of CPK, given the 2:1 randomization and the relatively similar proportion of events that occurred on the control arm, I cannot conclude from the information available in this trial that the Sustol injections were associated with muscle necrosis. Conclusions are limited by the sample size and the observation that a substantive proportion of subjects already had elevated CPKs at baseline. (See also discussion of CPK elevations in Study C2013-03, in Section 8.3.2.5 above.)

Overall Safety Summary. The most common adverse reactions associated with Sustol were injection site reactions (ISRs) and constipation. I have concluded that the higher proportion of reports of ISRs in the second phase 3 trial, Study C2013-01, reflects the true rate of ISRs associated with Sustol, and that the increase observed in the second trial was primarily due to ascertainment methodology in that trial vs. the earlier trial, i.e., patient reporting via diary vs. investigator report. The vast majority of the ISR manifestations were characterized as mild, and it was difficult to interpret the meaningfulness of the higher grade reactions due to the descriptors utilized in the second trial's grading system (some of the grade descriptors were double barreled in nature). The higher grade ISR manifestations associated with double barrel descriptors (swelling and pain) suggest the patients with those reactions were experiencing a negative impact on well-being/function due to the ISR; however, swelling and pain are not life threatening, and there was no evidence of irreversible morbidity associated with these specific manifestations documented in the clinical trial safety database. Nevertheless, these are important manifestations that patients should be aware when Sustol is offered as an antiemetic for CINV, particularly since there is are approved antiemetic alternatives with the same indication.

Infection, a potentially serious ISR manifestation in the proposed population, only occurred in 0.4% across the CINV trials, and only one of the infections was considered an SAE. IV palonosetron (which is indicated for the same population for which Sustol will be approved) is administered intravenously, and any IV administration is associated with some risk of introducing infection. The healthcare providers who will administer Sustol have heightened awareness of infection risks in the patients they care for, as cytotoxic chemotherapy commonly reduces neutrophil counts. Similarly, these providers also have heightened awareness of bleeding risks, given that chemotherapy can increase the risk of developing thrombocytopenia. The risk of bleeding with Sustol administration is highest in the first 24 hours after administration, and thrombocytopenia related to chemotherapy generally is generally delayed by at least a week after chemotherapy. However, patients may be on concomitant anticoagulants or may have baseline thrombocytopenia related to their underlying malignancy. Section 5 Warnings and Precautions of the Sustol product label will contain a warning about

ISRs, 5.1 Injection Site Reactions. This warning will include information, from the overall NDA safety database, on “Bruising and/or hematomas” and “Bleeding” as follows:

Bruising and/or hematomas

Bruising and/or hematomas at the injection site occurred in 426 of 1131 (38%) patients treated with SUSTOL 10 mg with a median time to onset of 2 days. Bruising and/or hematomas with a delayed onset (onset 5 or more days following SUSTOL administration) were reported in 175 (15%) patients. Severe bruising or hematoma (e.g., greater than 4 cm bruise or hematoma) occurred in 3% of patients. Patients receiving concomitant anticoagulant and antiplatelet medications were at greater risk for severe injection site bruising and hematomas.

Bleeding

Bleeding at the injection site occurred in 70 of 1814 (4%) patients treated with SUSTOL. One patient required emergency management. Bleeding for longer than 5 days was reported in 23 (1%) patients.

The “Management of ISRs” component of this ISR Warning will state “In patients receiving antiplatelet agents or anticoagulants, consider the increased risk of bruising or severe hematoma prior to the use of Sustol.”

Section 5.1 Injection Site Reactions (ISRs) of the product label will also include information on the risk of infections at the site, pain and tenderness and nodules, as follows:

Infections

Infections at the injection site occurred in 0.4% (7 of 1814) of patients with cancer and 0.2% (1 of 412) of healthy subjects in clinical trials. Infections had a median onset of 9 days (range 7 to 16 days) following SUSTOL administration. One patient who was neutropenic at the time of the infection was hospitalized. All patients with infection were treated with antibiotics and had complete resolution.

Pain and Tenderness

In a clinical trial that collected information about injection site pain and tenderness from patient diaries, pain with or without tenderness at the injection site was reported by 91 of 456 (20%) of patients treated with SUSTOL 10 mg, and an additional 50 of 456 (11%) of patients reported tenderness without pain. Pain and/or tenderness severe enough to require taking pain medication, interfere with patient activity level, or cause significant discomfort at rest was reported in 2% of patients. Among all patients who reported pain and/or tenderness with SUSTOL 10 mg in clinical trials, the median duration was 5 days, and pain lasting longer than 7 days occurred in 6% of patients.

Nodules

Nodules at the injection site occurred in 203 of 1131 (18%) of patients treated with SUSTOL 10 mg. Nodules persisted for a median of 15 days and 73 patients (6%) had nodules with durations longer than 21 days.

The Management of ISRs component of Section 5.1 Injection Site Reactions (ISRs) will also include the following:

- Monitor patients for ISRs following SUSTOL injection. Some ISRs (infections, bruising, and hematoma) may occur up to 2 weeks or more after SUSTOL administration.
- In patients with ongoing or unresolved ISRs, administer SUSTOL at a site away from areas affected by ISRs [*see Dosage and Administration ()*].

Regarding ISRs, Section 17 will state that the health care provider should inform the patient of the following:

- Inform patients that ISRs may occur and may include infections, bruising and/or hematomas, bleeding, pain and tenderness, and nodules.
- Inform patients that some ISRs (infections, bruising, and hematoma) may occur up to 2 weeks or more after SUSTOL administration.
- Instruct patients to seek immediate medical care for the following ISRs:
 - signs of infection at the injection site.
 - injection site bleeding that is severe or lasts for longer than one day.
- Advise patients to tell their healthcare provider if they experience:
 - pain or tenderness severe enough to require treatment with pain medication or interfere with daily activity.
 - bruising and/or hematoma or a persistent nodule at the injection site

In addition, the label will include a Medication Guide that informs patients of the ISR manifestations, including potential impact on daily activity, delayed onset and potential for prolonged bleeding.

Because Sustol is a depot formulation of the 5-HT₃ antagonist, granisetron, the reviewers considered the impact of serious hypersensitivity reactions to granisetron, since the drug exposure would be expected to last for days. For this reason, the reviewers recommended that the product label reflect that Sustol should not be administered to patients with a known hypersensitivity to drugs in the 5-HT₃ class, and that health care providers should be reminded that hypersensitivity reactions may require ongoing intervention over a course of days. The product label will contraindicate Sustol in patient with hypersensitivity to granisetron, any component of Sustol or any other 5-HT₃ receptor antagonist. In addition, under Section 5 Warnings and Precautions, a warning regarding hypersensitivity reactions will state:

Hypersensitivity Reactions

Hypersensitivity reactions, including anaphylaxis, have been reported in granisetron-treated patients who have exhibited hypersensitivity to other 5-HT₃ receptor antagonists [see *Contraindications*]. Avoid SUSTOL in patients who have had hypersensitivity reactions to other 5-HT₃ receptor antagonists [see *Contraindications*].

Due to the extended-release properties of the SUSTOL polymer formulation, exposure to granisetron may continue for 5 to 7 days following administration. Hypersensitivity reactions may occur up to 7 days or longer following SUSTOL administration and may have an extended course. Inform patients of the signs and symptoms of anaphylaxis, and instruct them to seek immediate medical care should signs and symptoms occur. If hypersensitivity reactions occur, administer appropriate treatment and monitor patients until signs and symptoms resolve.

The Medication Guide will inform patients of the risk of serious allergic reactions and that the risk may be prolonged for a week after administration.

To address the concerns that the constipation associated with granisetron in Sustol may be prolonged and serious, given the prolonged release of granisetron from the polymer, the label will contain the following Warning:

Gastrointestinal Disorders

Constipation

In clinical trials, 224 of 1131 (20%) of patients treated with SUSTOL 10 mg reported constipation compared to 13% to 15% in the 5-HT₃ receptor antagonist control arms. Hospitalization due to constipation or fecal impaction was reported in 5 SUSTOL-treated patients (0.3%). Monitor patients for the development of constipation while receiving treatment with SUSTOL taking into consideration the extended release properties of the SUSTOL polymer formulation over at least 5 to 7 days, particularly in patients receiving opioid medications. Consider optimizing bowel regimens in patients using SUSTOL.

The Medication Guide will also inform patients of the risk of serious constipation, and that it may be more likely to occur in patients taking opioids.

The label will include a class warning (for 5-HT₃ receptor antagonists) for serotonin syndrome.

Section 6 Adverse Reactions of the product label will present the adverse reactions observed in both Studies C2006-01 and C2013-01. The following table of common adverse reactions observed in these trials will be presented in the product label.

Table 62. Adverse reaction table presented in Section 6 of the Sustol label: Adverse Reactions Occurring in at Least 3% of Patients Treated with SUSTOL 10 mg in Study 1 and/or Study 2

Adverse Reaction	Study 1		Study 2	
	SUSTOL 10 mg subcutaneous (N=468) %	Palonosetron hydrochloride 0.25 mg intravenous (N=463) %	SUSTOL 10 mg subcutaneous (N=456) %	Ondansetron 0.15 mg/kg intravenous (N=459) %
Injection Site Reactions, any ^a	37	15 ^b	62	See footnote ^b
Constipation	14	11	22	15
Fatigue	11	10	21	24
Headache	9	9	13	19
Diarrhea	8	7	9	8
Abdominal Pain	7	7	7	4
Insomnia	4	2	5	6
Dyspepsia	3	3	6	7
Dizziness	3	2	5	5
Asthenia	4	6	2	2
Gastroesophageal Reflux	1	1	5	4

^a Rates of individual injection site reactions (ISRs) are shown in.

^b The placebo subcutaneous injection for Study 1 was normal saline and for Study 2 was a SUSTOL-matched control consisting of the SUSTOL polymer vehicle without active drug

The applicant has agreed to submitting 15 day alert reports of some of the adverse events of interest that already appear in the label (e.g., constipation) and submission of periodic post-marketing reports, PADERS that include analyses of those reactions. They agreed to do so for the first two years post approval. (See approval letter.) The reviewers worked with the applicant to develop a standardized questionnaire that will be used by the applicant to obtain specific information from reporters of adverse reactions regarding the severity of the reactions.

The approval letter will state that “for a period of two years you submit, as 15 day alert reports, all cases of injection site reactions requiring medical attention by a healthcare provider (emergency room, urgent care center, inpatient hospitalization, or unscheduled clinic visit) and inpatient hospitalizations due to gastrointestinal conditions including constipation, gastrointestinal obstruction, ileus, pancreatitis, and gastrointestinal perforation, as 15-day alert reports. Provide detailed analyses of these clinical study and post-marketing reports as adverse events of special interest in your Periodic Benefit-Risk Evaluation Report (PBRER). These analyses should show cumulative data relative to the date of approval of Sustol (granisetron) extended-release injection, for subcutaneous use, as well as relative to the prior PBRER.

Medical literature reviews for case reports/case series of these reactions should also be provided in the PBRER.”

The applicant also agreed to

(b) (4)

There will also be a PMR trial under 505(o) to evaluate, in patients receiving chemotherapy, repeat dosing with the new administration methods utilized in Study C2013-01 (in which treatment was limited to a single dose). The approval letter will state:

“We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a signal of a serious risk of injection site reactions.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a signal of a serious risk of injection site reactions with the use of Sustol (granisetron) extended-release injection, for subcutaneous use.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3094 – 4 A repeat dose, randomized, active-controlled trial to assess the safety of Sustol (granisetron) extended-release injection, for subcutaneous use, when administered to patients receiving chemotherapy, for 6 cycles.

The timetable you submitted on 6/9/2016, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	03/2017
Trial Completion:	03/2021
Final Report Submission:	09/2021”

In summary, the safety issues identified in the review of this application were thoroughly discussed among the members of the review team. The team concluded that the risks could be appropriately managed at this time through labeling, including a Medication Guide, enhanced safety reporting and a PMR trial. The review team determined that a REMS was not necessary at this time. Postmarketing safety reporting and the results of the PMR trial will be evaluated.

If there is evidence that the current approach is inadequate, FDA will reassess and make changes as indicated by the data.

9. Advisory Committee Meeting

There was no Advisory Committee meeting for this application. There were no decisional issues that required input from an Advisory Committee.

10. Pediatrics

There was no Pediatric Study Plan at the time of the resubmission, as the original submission of the NDA was prior to 2012 when FDASIA required an agreed upon PSP before NDA submission. In the last resubmission, the applicant requested (b) (4)

. The applicant requested deferral for children (b) (4) years and older. These requests ((b) (4) deferral) remained unchanged with the current resubmission.

(b) (4)

The application will be approved this review cycle. The product label's Section 8.4 Pediatric Use will state, "The safety and effectiveness of SUSTOL in pediatric patients under 18 years of age have not been established."



The reviewers discussed the deferred pediatric plan with the applicant on May 26, 2016. The following list of PREA PMRs will be included in the approval letter. (b) (4)



3094 - 1 A pharmacokinetic/dose ranging study to determine the pediatric doses of Sustol (granisetron) extended-release injection, for subcutaneous use, and a controlled clinical trial with an active comparator to evaluate the efficacy, safety, and tolerability of Sustol (granisetron) extended-release injection, for subcutaneous use, for the prevention of acute and delayed phase nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) or anthracycline and cyclophosphamide combination chemotherapy regimens in pediatric patients ages 12-17 years old.

Final Protocol Submission:	06/2017
Study Completion:	11/2022
Final Report Submission:	03/2023

3094 – 2 A pharmacokinetic/dose ranging study to determine the pediatric doses of Sustol (granisetron) extended-release injection, for subcutaneous use, and a controlled clinical trial with an active comparator to evaluate the efficacy, safety, and tolerability for the prevention of acute and delayed phase nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (MEC) or anthracycline and cyclophosphamide combination chemotherapy regimens in pediatric patients ages 0 to less than 12 years old.

Final Protocol Submission:	06/2019
Study Completion:	11/2024
Final Report Submission:	03/2025

3094 - 3 A 1-month, GLP juvenile animal toxicology study of Sustol (granisetron) extended-release injection, for subcutaneous use, conducted in a single species. This study must be completed and submitted for review before initiating pediatric studies in patients ages 0 to less than 12 years.

Final Protocol Submission:	11/2017
Study Completion:	11/2018
Final Report Submission:	03/2019

11. Other Relevant Regulatory Issues

See review from original review cycle regarding the financial disclosure for the initially submitted clinical trials. The applicant submitted new clinical trials in the current submission. The Applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangement with their clinical investigators for the newly submitted trials in this resubmission, whereby the value of compensation to the investigator could be affected by the outcome of the trial defined by 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 CFR 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 sort.

12. Labeling

See other sections of this review for final labeling decisions related to presenting the efficacy conclusions and addressing the safety issues associated with Sustol. Class safety labeling for 5HT3 antagonist class was included in the final Sustol label. The safety and efficacy of Sustol

in the pediatric population has not been established. Sustol will not carry a pediatric indication. See Section 10 Pediatrics above.

In 2010, ONDQA and the Labeling and Nomenclature Committee designated the name for the drug product as Sustol (granisetron) injection, extended release. This name was communicated to the sponsor. In the current review cycle, the applicant used that name on the proposed carton/container labeling.

The Product Title (PT), as a part of the Prescribing Information, was reevaluated as part of the labeling review. The draft Product Title Guidance, which is in clearance and not currently public, was consulted during the review. The draft Guidance does not include an option for “extended-release, injection”. Using the FDA label search tool, no products with a similar PT were identified. The closest terminology is “extended-release injectable suspension” (Abilify Maintena, Bydureon, Invega Sustenna); however, SUSTOL is not a suspension formulation.

The review team consulted Yana Mille in OPQ to provide input on the PT. She contacted USP and requested their Nomenclature and Labeling Expert Committee provide input on the use of “extended-release” in association with “injection,” as it is unusual to combine these two terms. Taking into account the pharmacokinetics of the drug product, USP agreed to the dosage form terminology of “extended-release injection.” This recommendation differs from the ONDQA advice in 2010, in that the word “injection” is moved to the end and “extended-release” is hyphenated.

The Product Title in the PI must include the proprietary name, non-proprietary name, dosage form, and route of administration. Therefore, the following is the final, agreed upon PT:

SUSTOL® (granisetron) extended-release injection, for subcutaneous use

The carton and container labels were also aligned with the USP’s recommendation.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action –

Approval of NDA 022445/Original 1: Sustol is indicated in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.

(b) (4)

(b) (4)

- Risk Benefit Assessment –
NDA 022445/Original provides substantial evidence of the efficacy of the proposed product for prevention of CINV in the setting of MEC or AC combination chemotherapy. The major safety issues identified, injection site reactions and constipation, are not unique to this product. Injection site reactions are the most common reactions associated with this product; other SQ administered products associated with significant injection site reactions have been approved by the FDA. Constipation is a known adverse reaction associated with granisetron, which is already approved for marketing in other dosage forms. The majority of the reactions observed in the Sustol safety database were mild in nature. I agree with the reviewers that the risks associated with use of Sustol for this indication can be managed through labeling. To assure patients are aware of the reactions they might experience with the product, the labeling will include a Medication Guide. The applicant is developing healthcare provider training that will include making providers aware of the Medication Guide to inform patients of the potential risks and benefits of the product.

The benefit-to-risk balance for prevention of CINV in the setting of MEC or AC combination chemotherapy is favorable.

(b) (4)

(b) (4)

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies
Not applicable.
- Recommendation for other Postmarketing Requirements and Commitments
See Section 8 Safety of this review and the approval letter for a description of the PMR trial to evaluate injection site reactions with repeat dosing of Sustol in patients receiving chemotherapy. A description of the applicant's commitments for safety reporting for adverse reactions that already appear in the product label can be found in Section 8 of this review and the approval letter. (b) (4)
See Section 10 Pediatrics and the approval letter for the pediatric studies that will be required under PREA. The letter will also include PMCs related to the device (See Section 3) and for a carcinogenicity study and SHE cell assay (See Section 4).

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/s/

DONNA J GRIEBEL
08/09/2016