CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206500Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Donna J. Griebel, MD
Subject	Division Director Summary Review
NDA	206500
Applicant Name	Tesaro, Inc.
Date of Submission	September 5, 2014
PDUFA Goal Date	September 5, 2015
Proprietary Name / Established (USAN) Name	Varubi rolapitant
Dosage Forms / Strength	Oral tablet/90 mg
Proposed Indication(s)	1. " in combination with other antiemetic agents, is indicated in adults for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy".
Recommended Action for NME:	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Aisha Peterson Johnson, MD, MPH
Statistical Review	Wen Jen Chen, PhD/Yeh-Fong Chen, PhD
Pharmacology Toxicology Review	Tracy Behrsing, PhD/Sushanta Chakder, PhD
Product Quality Review	See Quality Review Team table following this table
DPMH Maternal Health Team	Erica Radden, MD/Hari Cheryl Sachs, MD/Lynne Yao, MD Miriam Dinatale, DO/Tamara Johnson, MD, MS/Lynne Yao, MD
Clinical Pharmacology Review	Insook Kim, PhD/Sue-Chih Lee, PhD Jee Eun Lee, PhD/Nitin Mehrotra, PhD Sarah Dorff, PhD/Christian Grimstein, PhD
CSS	Katherine Bonson, PhD/Alicja Lerner, MD, PhD/Michael Klein, PhD
OPDP	Adewale Adeleye, PharmD, MBA/Kathleen Klemm, PharmD
OSI	Susan Leibenhaut, MD/Susan D. Thompson, MD/Kass Ayalew, MD, MPH
OSE/DMEPA	Sherly Abraham, RPH/Kendra Worthy, Pharm D/Lubna Merchant, MS, Pharm D Todd D Bridges, RPh
DMPP	Karen Dowdy, RN, BSNJ/Adewale Adeleye, Pharm.D.,

	MBA/Shwna Hutchins, MPH,BSN,RN/LaShawn Griffiths, MSHS-PH, BSN, RN
SEALD	Michelle Campbell/Elektra Papadopoulos, MD

OND=Office of New Drugs
DPMH=Division of Pediatric and Maternal Health
CSS= Controlled Substance Staff
OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
OSI=Office of Scientific Investigations
DMPP= Division of Medical Policy Programs
SEALD=Study Endpoints and Labeling
DRISK=Division of Risk Management

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Charles Jewell, Ph.D.	OPQ/ONDP/NDAPI/Branch 1
Drug Product	Hitesh Shroff, Ph.D.	OPQ/ONDP/NDPII/Branch V
Process	Akm Khairuzzaman, Ph.D.	OPQ/OPF/DIV-1/BRANCH-1
Microbiology	Bryan Riley, Ph.D.	OPQ/OPF/DMA/BII
Facility	Christina Capacci-Daniel, Ph.D.	OPQ/OPF/DIA/IABII
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Project/Business Process Manager	Olga Simakova, Ph.D.	OPRO/Div I/ Branch-I
Application Technical Lead	Moo-Jhong Rhee, Ph.D.	OPQ/ONDP/NDPII/Branch V
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ORA Lead	Sharon Thoma, Pharm.D.	ORA/OMPTO/MIN-DO
Environmental Assessment (EA)	James Laurenson, Ph.D.	OPQ/ONDP

Division Director Review

1. Introduction

The applicant has submitted an NDA for an oral NK-1 inhibitor, rolapitant 90 mg, a new molecular entity intended to prevent chemotherapy induced nausea and vomiting (CINV). There are currently two NK-1 inhibitors in the U.S. approved for prevention of CINV: Emend, which is approved in both oral and intravenous (IV) dosage forms, and Akynzeo, which is an oral fixed dose combination of an NK-1 inhibitor (netupitant) plus a 5HT3 antagonist (palonosetron). The product labeling for Emend states that it should be administered in combination with a 5HT3 antagonist and dexamethasone. The product label for Akynzeo, which contains the 5HT3 antagonist palonosetron, states that it should be administered with dexamethasone. Dexamethasone dosing with these NK-1 inhibitors is daily on Days 1-4 in the setting of highly emetogenic chemotherapy (HEC), and Day 1 only in moderately emetogenic chemotherapy (MEC). (It should be noted that the MEC approvals for both products were based on clinical trials that enrolled patients receiving anthracycline plus cyclosphosphamide [AC] chemotherapy regimens, which are now considered HEC regimens. Despite the new HEC designation, the Day 1 dexamethasone regimen was found to be effective for AC.)

The multiple 5HT3 antagonists approved for CINV are generally associated with efficacy in the first 24 hours after chemotherapy, i.e., the "acute phase". NK-1 inhibition is important for prevention of nausea and vomiting during the delayed phase, which is generally defined as the time period between 24 and 120 hours post initiation of chemotherapy; however, clinical trials have demonstrated that NK-1 inhibition can also improve prevention of acute phase CINV when added to a 5HT3 antagonist and dexamethasone. Emend (aprepitant) and Akynzeo (netupitant and palonosetron) both have indications for prevention of acute and delayed phase nausea and vomiting, and indications for highly emetogenic and moderately emetogenic chemotherapy (HEC and MEC, respectively). The technical details of each product's indications will be discussed in the following section of this review. (b) (4) (b) (4) (b) (4) Additional review issues were identified related to rolapitant's pharmacokinetics. Its long half-life results in prolonged impact on the metabolism of some coadministered drugs. In addition, unlike the other two approved NK-1 inhibitors it does not have a substantive impact on dexamethasone metabolism. Both aprepitant and netupitant (the NK-1inhibitor component of Akynzeo) require dose reduction of dexamethasone in their combination antiemetic regimens. Rolapitant does not.

All disciplines have recommended approval of this NDA for an indication limited to prevention of delayed phase nausea and vomiting associated with emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. I concur. My review will focus on the key review issues and will also serve as the CDTL review for this NDA. Please note that, in keeping with the USP salt policy, the rolapitant hydrochloride

product label will refer to 90 mg (rolapitant) (b) (4) that is the amount of rolapitant contained within the (b) (4) The administered dose will be two (b) (4) or 180 mg of rolapitant. The NDA and the FDA reviews refer to the amount of rolapitant *hydrochloride* administered in the clinical trials, i.e., a 200 mg total dose. All references to 200 mg rolapitant in my review are references to 200mg rolapitant *hydrochloride*, which is equivalent to the 180 mg total dose of rolapitant referred to in final product labeling.

2. Background

Please refer to the Clinical review for a comprehensive summary of the regulatory history. I will briefly summarize key highlights of interactions between FDA and the applicant during product development, and then I will cover:

1. the general approach to establishing antiemetic effectiveness for CINV
2. the labeled indications that have been granted to reflect CINV trial outcomes
3. the impact of changes in emetogenicity designation for anthracycline plus cyclophosphamide (AC) combination chemotherapy (from MEC to HEC) on indication statements in product labels.

Rolapitant development program regulatory history highlights.
In the October 6, 2005 pre-IND meeting, the FDA stated that the proposed primary endpoint of Complete Response in the overall phase, i.e., 0-120 hours post initiation of chemotherapy, was acceptable; (b) (4) FDA recommended conducting two of the program's three major clinical trials in the HEC setting.

In the April 5, 2010 End of Phase 2 meeting, the applicant was informed that statistically significant evidence of efficacy must be established (b) (4)

In a July 5, 2011 Type C meeting, the FDA stated the delayed phase should be tested as the primary endpoint, or as a co-primary endpoint. The FDA also stated that a favorable outcome in two HEC trials would support a favorable outcome in a single MEC trial to support a MEC indication. FDA stated it was important that the program evaluate efficacy in the setting of cisplatin and in a setting of doxorubicin chemotherapy, as both are associated with delayed phase nausea and vomiting. FDA expected to see at least half of the subjects enrolled in the MEC trial to have received AC. FDA stated the primary efficacy analyses should be based on the Intent-to-Treat patient population, defined as all randomized subjects who received at least one dose of study drug. Subjects with missing data should be considered treatment failures.

In the July 2, 2014 Pre-NDA meeting, FDA informed the sponsor that the Division was moving away from including MEC and HEC designations in indication statements, given the change in designation of AC from MEC to HEC.

Regulatory history of CINV drug development. CINV antiemetic drug development programs have generally included individual clinical trials dedicated to either HEC (usually,

cisplatin-based chemotherapy) or MEC. Recently, MEC trials have enrolled a substantive proportion (if not 100%) of patients who were treated with AC. Until the recent approval of the fixed combination Akynzeo (5HT3 antagonist plus NK-1 inhibitor), the indications of antiemetics had evolved to stating the product prevents chemotherapy induced nausea and vomiting in MEC and/or HEC, depending on the trial outcomes in each of these two settings.

Specific labeling for the (b) (4) delayed phase (25-120 hours) evolved with the development of the NK-1 inhibitors, which, given their mechanism of action, are intended to impact the delayed phase. (5HT-3 antagonists with long half-lives, such as palonosetron, have also been subject to development plans examining the delayed phase, due to the prolonged antiemetic exposure post chemotherapy.) Drug development plans for products intended to prevent delayed phase nausea and vomiting initially utilized a primary endpoint of "overall phase", which encompasses the full 0-120 hour period; acute phase (first 24 hours) and delayed phase (25-120 hours) were secondary endpoints. The Division later began recommending delayed phase as the appropriate primary endpoint for these products due to concern that a product intended to provide benefit in the delayed phase could have a favorable outcome in the "overall phase" when in fact the treatment effect is driven by its impact in the acute phase, or vice versa.

The following table summarizes CINV indications that have been granted over the years.

Table 1. Summary of CINV Indications Granted for Various 5-HT3 Inhibitor and NK-1 Inhibitors

DRUG	Dosage form	HEC/MEC	Acute/Delayed
5HT-3 inhibitor			
Zofran (ondansetron)		HEC and MEC	Acute Plus: Day 2 and 3 dosing instructions for MEC only.
Anzemet (dolasetron)	IV and PO	IV = "Prevention of [CINV], including high dose cisplatin" PO = MEC	acute based on Clinical Studies Section says first 24 hours
Kytril (granisetron)		"Prevention of [CINV], including high dose cisplatin" Clinical Studies Section includes a MEC trial.	acute based on Clinical Studies Section says 24 hours.
Aloxi (palonosetron)	IV	HEC	Acute
		MEC	Acute and Delayed
Aloxi	PO	MEC	Acute
NK1 inhibitor			
Emend	PO and IV	HEC	Acute and Delayed
		MEC	"prevention of nausea and vomiting" Clinical Studies Section refers to "overall phase, 0-120

			hours". Individual analyses for acute, delayed not statistically significant in one of two MEC studies.
Fixed combination of NK-1 + 5HT3 inhibitors			
Akynzeo (netupitant + palonosetron)	PO	"prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Oral palonosetron prevents nausea and vomiting during the acute phase and netupitant prevents nausea and vomiting in both the acute and delayed phase after cancer chemotherapy."	

Early review articles and treatment guidelines designated anthracyline chemotherapy as MEC; however, guidelines were subsequently updated to reclassify AC combination chemotherapy as HEC. This reclassification impacts regulatory review of development plans and NDAs proposing MEC indications because MEC trials have enrolled a substantive proportion of subjects who received AC. It should be noted that even though AC was changed from MEC to HEC in treatment Guidelines, the information provided to support the change suggests that this regimen is not as emetogenic as cisplatin chemotherapy. [The lower limit for HEC categorization is causing vomiting in 90% of patients not treated with antiemetic prophylaxis. The ASCO Guidelines, (www.asco.org/guidelines/antiemetics) state the Update Committee changed the emetogenicity category for AC after considering placebo controlled data indicating that 85% of patients treated with AC would be expected to vomit without antiemetic prophylaxis.]

The Division addressed the reclassification of AC chemotherapy to HEC in its review of the Akynzeo NDA, as its dedicated "MEC" trial for the netupitant component enrolled only patients who had received AC chemotherapy. The Division ultimately concluded it is reasonable to approve a general CINV indication (i.e., not limit the indication to HEC) if a product's development program has limited the efficacy evaluation to HEC trials. It is of key importance for an antiemetic development program to establish whether a new product is effective in the setting of cisplatin chemotherapy, and it seemed reasonable to expect that a product that has been shown to be effective for CINV HEC, should be effective for CINV MEC. To verify this, as part of the Akynzeo NDA review, the Division's antiemetic approval history was evaluated to identify examples of products in which efficacy could only be established in the setting of HEC, i.e., the product specifically failed in MEC trials while at the same time "winning" in HEC. After considering the reviews of the trials that supported the specific indications limited to HEC (based on labeling), the Division concluded there was an absence of persuasive evidence that a product effective in HEC would not also be expected to be effective in the setting of MEC.

Of note, the review of the regulatory history of antiemetic labeling revealed that the NK-1 inhibitor Emend carries an indication for both the acute and delayed phases of HEC, but only general wording regarding MEC, i.e., no specific reference to acute and delayed phases for MEC. The primary endpoint for the Emend trials was "overall phase". The single trial that supported the approval of the MEC indication (which followed the HEC approval) enrolled only subjects with breast cancer who were administered combination chemotherapy with AC. At the time of initial approval of the MEC indication, the primary endpoint "overall phase" was statistically significant (N= 438 Emend arm vs. 428 control arm); (b) (4) [redacted]. A subsequent post-marketing trial was submitted for review that also evaluated Emend in MEC (N=430 Emend arm vs. 418 control arm). The trial enrolled a larger percentage of males than the original "MEC" trial (23%); however, approximately half of the overall trial population had breast cancer and received AC chemotherapy. (b) (4) [redacted]

Ultimately, in its review of the Akynzeo NDA, the Division concluded that a more general approach to CINV labeling such as, "indicated for the prevention of nausea and vomiting associated with cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy" would be appropriate if a product has been shown to be effective in the setting of cisplatin based chemotherapy. (Note that ondansetron, the first 5HT3 antagonist, was approved in January 1991 with a general indication, "Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy," based on cisplatin studies.) The Akynzeo indication for the netupitant component reflects the acute and delayed phase efficacy observed in a development program that included a HEC study and a "MEC" study that enrolled only subjects receiving AC. The Akynzeo indication for the palonosetron component states that its efficacy is limited to the acute phase in both the MEC and HEC settings. The sample sizes of the Akynzeo trials are important to note in light of the review issues that arose during the review of this rolapitant NDA. The netupitant "MEC" AC trial enrolled over 700 subjects in each arm (N= 726 netupitant arm vs 729 control arm), a much larger sample size than in the netupitant HEC trial (N=136 netupitant arm vs. 143 control arm) and the Emend NDA's "MEC" AC trial.

Overview of key rolapitant NDA review issues, in the context of other NK-1 inhibitor approvals. The applicant for the current NDA originally proposed that rolapitant should be (b) (4) [redacted] whether rolapitant should be (b) (4) was the major review issue in this NDA because (b) (4) [redacted]

(b) (4)
half of subjects received AC chemotherapy). Therefore, in this NDA, there was no dedicated MEC trial according to updated emetogenicity classifications (since half of the subjects in the MEC trial were treated with AC), and the trials submitted did not show (b) (4) the HEC or "MEC" trials.

The applicant argued that cross study comparisons of their phase 3 MEC trial to the phase 3 netupitant MEC trial (Akynzeo NDA) reveal (b) (4) and that the sample size of the netupitant trial (approximately 1455, all treated with AC chemotherapy) was much larger than the rolapitant trial (N= 544, of whom approximately 52% received AC). (b) (4) The applicant also conducted subset efficacy analyses in the AC "MEC" subgroup vs. the non-AC "MEC" subgroup of its phase 3 rolapitant trial, (b) (4) The applicant asked the FDA to (b) (4)

In light of the absence of consistent and persuasive efficacy results across the three phase 3 trials submitted in the NDA, (b) (4) from the phase 2 dose ranging trial conducted in the HEC setting. The Statistical reviewers identified substantive issues with the phase 2 trial which led to their recommendation that it could not be considered an adequate and well controlled trial that provides substantial evidence of efficacy. Senior CDER leadership concurred with this conclusion. (b) (4) Refer to Section 7 of this review for further description of these review issues.

3. CMC/Product Quality

I concur with the conclusions reached by the Quality Review Team regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. The Categorical Exclusion for the Environmental Assessment was granted. There are no outstanding issues and no recommendations for PMCs. In keeping with the USP salt policy for active ingredients, the product labeling will reflect the 90 mg strength (rolapitant), instead of 100 mg (rolapitant hydrochloride).

(b) (4)

The Quality Review Team reached agreement with the applicant on the specification criteria for these two specific (b) (4) (NMT (b) (4) ppm for each). (b) (4) (b) (4) The commercial batch data presented in the NDA demonstrated that (b) (4) are typically present at < (b) (4) ppm and < (b) (4) ppm, respectively. The Quality Review Team also agreed to a separate specification criterion of NMT (b) (4) ppm for other (b) (4), for testing performed for release of the drug substance (b) (4) In light of the proposed specifications and proposed dose of rolapitant (180 mg), the Pharmacology/Toxicology reviewers determined that the maximum intake of the (b) (4) would be (b) (4) micrograms per dose, *based on the overall* (b) (4) *ppm specification* (b) (4) which is below the (b) (4)

As explained to me by the Drug Substance reviewer, the chemical test traditionally used to monitor for these latter toxic (b) (4) is not reliable to quantitatively test for (b) (4) (b) (4) states that the oral PDEs for (b) (4) micrograms/day, and the Pharmacology/Toxicology team leader informed me that the (b) (4) ppm specification set for each is a limit equivalent to (b) (4) micrograms each. Therefore, I agree with the reviewers' conclusions that the specifications for (b) (4) and the (b) (4) ppm specification for the overall (b) (4) is well within the PDE cited in (b) (4)

Three (b) (4) potential genotoxic impurities, have the potential for formation during manufacture of drug substance, related to use of (b) (4) (b) (4) The Quality Review team agreed with the applicant's proposal to control for these three (b) (4) impurities at (b) (4) ppm in total for the three together. The detection limit of the assay is (b) (4) ppm and the assay's quantitative limit is (b) (4) ppm. The applicant calculated a (b) (4) of (b) (4) ppm, based on ICH M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals, to support this limit. The Pharmacology/Toxicology review team evaluated the information supporting the (b) (4) ppm control level and the calculated (b) (4) and concurred. They noted the proposed limit (b) (4) ppm) will be (b) (4) lower than the calculated (b) (4) Rolapitant will be administered on an intermittent basis (one dose no more frequently than every 2 weeks, with the most common interval being at least 3 weeks) and has a long half-life (approximately 7 days, see Section 5 Clinical Pharmacology). (b) (4)

(b) (4) (b) (4) : (b) (4)

(b) (4)

ICH M7 addresses situations in which drugs are dosed intermittently, and in these cases the acceptable daily intake of mutagenic impurities is based on the total number of dosing days, without adjustment for drug half-life. Although rolapitant's half-life is long, the (b) (4) half-life is unknown. However, the Drug Substance Reviewer stated (in a meeting to discuss this issue) that the (b) (4) half-life is expected to be brief, given the reactivity of (b) (4) The reviewers evaluated whether it was reasonable to assume a patient's total lifetime exposure would be 30 days. The proposed dose regimen is one dose on Day 1 of each chemotherapy

cycle, with chemotherapy regimens cycled no more frequently than every 2 weeks. Based on a q 2 week chemotherapy schedule, thirty doses would be equivalent to covering about 13months of chemotherapy. The applicant stated it would be more likely that a patient would receive 6 cycles of chemotherapy over a 5-6 month period. With that pattern, a total of 30 doses would be equivalent to 5 courses of chemotherapy over a patient's lifetime. Although it is actually possible that a patient could exceed 30 doses over a lifetime, the (b) (4) margin between (b) (4) ppm and (b) (4) ppm would be anticipated to cover those additional doses.

Based on computational toxicology quantitative structure activity relationship methods (QSAR) and Leadscope Genotox Database, the applicant identified (b) (4) These included (b) (4) The Quality Review Team stated in the review of the drug substance that the potential for production of these impurities was "remote". The assay developed to detect (b) (4) had a limit of detection of < (b) (4) ppm and there were no detectable levels in 11 lots. The < (b) (4) ppm specification set by the applicant for (b) (4) was deemed acceptable by the Product Quality review team, again noting the relatively large calculated (b) (4) of (b) (4) ppm. The reviewer found the information the applicant submitted to support that the two (b) (4) cannot survive the reactions and work-up conditions acceptable, and concurred that these two potential impurities (b) (4)

The drug product specification for individual unspecified impurities met the ICH Q3B(R2) Impurities in New Drug Products identification threshold for products with maximum daily doses >10 mg to 2g.

The drug product contains lactose monohydrate, which is derived from a bovine source. The applicant stated that it complies with all bovine spongiform encephalopathy and transmissible spongiform encephalopathy US and EU regulations. The Quality review Team evaluated the certificate of analysis submitted to address this issue and found it satisfactory.

Biopharmaceutics. The reviewers determined that the data submitted to the NDA supported bridging of the various formulations used across the different phases of studies/trials in the development program. They determined that the final commercial formulation is bioequivalent to the 50 mg capsules that were used in the phase 3 clinical trials (each single daily dose in the phase 3 trials consisted of 4 capsules, whereas the single dose of the commercial formulation will consist of 2 tablets). The applicant conducted two trials to establish bioequivalence of the phase 3 formulation to the commercial formulation. Although they failed to demonstrate bioequivalence in the first trial, they were successful in the second trial. (b) (4) The reviewers concluded that the explanation was reasonable and that the favorable outcome of the second trial was reliable.

The results of multiple food effect studies were submitted for review. One was conducted within the first bioequivalence study (described above). In the food effect portion of this trial (one of 3 arms; subjects fed a high fat meal), the CI for the Cmax fell slightly outside the BE criteria [Mean Ratio (fed/fasting) 90% CI = 1.16 (1.06,1.27) in fed subjects who were administered the commercial formulation. The Clinical Pharmacology reviewers commented on these data in their review and concluded that because a concomitant high fat meal did not significantly affect rolapitant's bioavailability, it can be taken without regard to food. The Tmax changed from 3.79 hours in fasted state to 4.01 hour in fed state for the commercial product. Two additional studies were conducted to evaluate food effect. One, which evaluated the effect of food on the clinical trial formulation, found that fat consumption delayed Tmax from 3 hours in the fasted condition to 5 hours in the fed condition; however, overall exposure was otherwise not affected. The Dosage and Administration section of the product label will state that rolapitant can be administered without regard to meals.

The Biopharmaceutics reviewers found the dissolution method acceptable and the dissolution acceptance criterion appropriate.

4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the Pharmacology/Toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. Potential signals identified in the nonclinical program, including convulsions, ataxia, and minimal hepatocellular necrosis, were considered when the NDA's clinical safety data were reviewed.

The half-lives of rolapitant and its major metabolite (SCH 720881) are markedly longer in humans than in animals studied in the toxicology studies (rolapitant in humans =169-183 h vs. Cynomolgus monkeys and rats = 6-8 h). These differences complicated comparisons of rolapitant exposures between the animal studies and humans. Furthermore, because humans are dosed no more frequently than once every 2 weeks (once per cycle of chemotherapy), comparison of the human single dose $AUC_{0-\infty}$ value to animal steady-state AUC_{0-24h} values does not take into consideration the total cumulative animal exposures over time. (Animals were dosed every day in chronic toxicity studies.) The reviewers stated that in light of these complexities, exposure multiples were estimated based on body surface area for product labeling purposes.

The liver and thyroid were identified as target organs in repeat-dose oral toxicology studies in rodents. In the 26-week oral toxicology study in rats, liver findings included hepatocellular hypertrophy and secondary effects on the thyroid (follicular cell hypertrophy). These affects were considered related to the induction of hepatic enzymes by the drug and for this reason the reviewers stated that they may not be relevant to humans. In a chronic dosing monkey study, hepatocellular necrosis (minimal focal necrosis) was observed in ¾ males administered the highest dose of 30 mg/kg/day x 39 weeks vs. 0/4 controls. The reviewers did not conclude that these findings were adverse, treatment-related effects since the findings were characterized as focal and minimal, there were no associated changes in clinical chemistry, and the applicant indicated that this "was reported to represent a common finding in laboratory monkeys".

Furthermore, this finding was not observed in the females. Hepatocellular necrosis was not observed in a 3 month oral dosing monkey study in which the highest dose was 15 mg/kg/day.

Convulsions were observed after acute and/or subchronic administration of rolapitant hydrochloride in rat and monkey studies (single dose of 1000 mg/kg administered intraperitoneally in rats; a 3-month oral toxicity study in rats at a dose of 125 mg/kg/day; single dose oral administration study in monkeys at a 200 mg dose; a two week IV daily dose study in monkeys at a dose of 20 mg/kg [also associated with ataxia]; and in a one-month repeat dose oral dosing study in monkeys at 60 mg/kg/day and 100 mg/kg/day [also associated with ataxia]). However, convulsions were not observed in the chronic oral toxicity studies in rats and monkeys, in which animals were administered lower doses than the acute/subacute dose studies (100 mg/kg/day x 26 weeks in rats;15 mg/kg/day x 3 months in monkeys; and up to 30 mg/kg/day x 39 weeks in monkeys). The doses administered in the chronic dose toxicology studies exceed the clinical dose. Cmax values (in single dose studies) associated with a 100 mg/kg oral dose in monkeys were 6480 ng/mL for rolapitant and 875 ng/mL for its metabolite 720881. In another trial, the Cmax of the drug in monkeys after administration of 100 mg/kg dose ranged 5550-8980 ng/ml. The human Cmax after 200 mg rolapitant hydrochloride dose is 968 ng/ml. The Pharmacology/Toxicology reviewer stated, "In the 26-week oral toxicity study in rats there were no incidences of convulsions at the highest dose tested (100 mg/kg/day rolapitant hydrochloride; equivalent to 90 mg/kg/day rolapitant free base). This dose (90 mg/kg/day) is 4.9-times the recommended human dose (180 mg rolapitant, 3 mg/kg for a 60 kg adult) on a body surface area basis. In the 39-week oral toxicity study in monkeys, the NOAEL was the highest dose tested (30 mg/kg/day rolapitant hydrochloride; equivalent to 27 mg/kg/day rolapitant free base). This dose is approximately 2.9 times the recommended human dose on a body surface area basis."

Rolapitant hydrochloride and its metabolite SCH720881 were both negative in the Ames test and chromosome aberration assay. Rolapitant hydrochloride was also negative in the mouse bone marrow micronucleus test. The 2 year carcinogenicity studies in mice and rats revealed no statistically significant findings considered treatment related. See also Section 3 above regarding the Pharmacology/Toxicology reviewers' assessment of the specifications set for the potential genotoxic impurities.

The applicant conducted studies to evaluate reproductive and developmental toxicology. The reviewers worked with the Maternal Health Team from the Division of Pediatric and Maternal Health to include the study findings in Sections 8.1 and 8.2 of product labeling.

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.

Rolapitant has a relatively high bioavailability (>90%) and a long elimination half-life, i.e., approximately 7 days. The systemic exposure over 120 hours (AUC_{0-120}), which is the period over which drug efficacy was assessed, was about 40% of its AUC_{0-inf}. Peak plasma concentrations are achieved in a median of 4 hours (min = 1.5 hours; max = 12 hours). It has a

large volume of distribution, and plasma concentrations are measurable a month after single-dose administration. The Clinical Pharmacology reviewers determined that accumulation would not occur with a dosing interval of q 2 weeks, the shortest dosing interval studied in clinical trials and proposed for product labeling. Most chemotherapy regimens won't be repeated more frequently than every 3 weeks. The major metabolite, SCH720881, forms slowly and has a Tmax of 120 hours.

The major route of excretion is via hepatic/biliary route (73%), followed by urine (14%). Hepatic and renal impairment studies established that rolapitant dose adjustment isn't necessary in patients with mild to moderate hepatic or renal impairment, as there was no significant effect on rolapitant systemic exposure. However, patients with severe hepatic impairment were not studied and an insufficient number of severely renally impaired patients were studied (n=1). The Clinical Pharmacology reviewers noted that although healthy subjects have been shown to tolerate a single rolapitant dose of 720 mg, which resulted in a 3.3-fold higher Cmax and 3.9-fold higher AUC than the 180 mg dose that will be approved for marketing, the drug's long half-life in healthy subjects could potentially be even longer in patients with severe hepatic or renal impairment, resulting in accumulation after repeated dosing in these patients to levels that could result in toxicity. During labeling discussions, the review team agreed that Section 8.6 Hepatic Impairment should state "There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh Class C). Avoid use of rolapitant in patients with severe hepatic impairment. If use cannot be avoided, monitor patients for adverse reactions related to rolapitant." Because the renal route of elimination is minor, and there was little impact of rolapitant PK noted in patients with moderate renal impairment, the reviewers concluded that accumulation would not be expected to have the safety impact that severe hepatic impairment would. Therefore, they determined that it was not necessary to include a section on renal impairment in Section 8 of the product label.

Rolapitant is metabolized by CYP 3A4. Rifampin, a strong CYP3A4 inducer, was shown to decrease the rolapitant AUC by 87%. Because this substantial decrease could diminish rolapitant's efficacy, Section 7.2 of the product label will state, "Strong CYP3A4 Inducers (e.g., rifampin): significantly reduced plasma concentrations of rolapitant can decrease the efficacy of Varubi; avoid use of Varubi in patients who require chronic administration of such drugs." Rolapitant itself does not inhibit or induce CYP3A4, which is an important distinguishing feature from the currently approved NK-1 inhibitors, which both inhibit metabolism of dexamethasone, necessitating dose reduction of dexamethasone when they are coadministered in a combination antiemetic regimen. (Emend is both an inhibitor and inducer of CYP3A4.) Rolapitant was shown not to significantly affect the PK of the 5HT3 antagonist ondansetron, and based on granisetron's (another 5HT3 antagonist) major route of metabolism (expected to be via CYP3A4), it is also not expected to affect granisetron exposures. Because there is no drug drug interaction with dexamethasone, there were review concerns that health care providers would mistakenly reduce the dexamethasone dose when using rolapitant, assuming that dose reduction is required similar to the currently approved NK-1 inhibitors; this would result in an inadequate dexamethasone dose and reduced antiemetic regimen efficacy. The applicant stated that they would work with the ASCO supportive care practice guidelines group to assure that the guidelines address these differences between the products in the Fall of 2015.

Although rolapitant's impact on other CYP enzymes, including CYP2B6, CYP2C8, CYP2C9, and CYP2C19 were not considered clinically significant, rolapitant is a moderate inhibitor of CYP2D6. In light of its long half-life, rolapitant's inhibition of CYP2D6 through 7 days after a single dose was evaluated, and the study revealed a comparable level of CYP2D6 inhibition continued through 7 days post exposure. This prolonged impact was also observed in transporter interactions, which are described in Table 2 below. This is important to consider in a setting of coadministration with drugs metabolized via CYP2D6 that have significant toxicities associated with higher exposures. In light of the important safety implications of this CYP2D6 interaction, it was addressed in multiple sections of the product label:

> 4 Contraindications
>
> Varubi is contraindicated in patients receiving thioridazine, a CYP2D6 substrate. A significant increase in plasma concentrations of thioridazine may result in QT prolongation and Torsades de Points.
>
> 5 Warnings and Precautions
>
> 5.1 Interaction with CYP2D6 Substrates with a Narrow Therapeutic Index
>
> The inhibitory effect of Varubi on CYP2D6 lasts at least for 7 days and may last longer after a single dose administration of Varubi [see Contraindications , Drug Interactions, Clinical Pharmacology]. Avoid use of Varubi in patients who are receiving pimozide, a CYP2D6 substrate. An increase in plasma concentrations of pimozide may result in QT prolongation. Monitor for adverse reactions if concomitant use of Varubi and other CYP2D6 substrates with a narrow therapeutic index cannot be avoided.
>
> 7.1 Effect of Varubi on Other Drugs
>
> CYP2D6 Substrates with a Narrow Therapeutic Index: Increased plasma concentration of CYP2D6 substrates may result in potential adverse reactions. A three-fold increase in the exposure of dextromethorphan, a CYP2D6 substrate, was observed 7 days after a single dose of BRAND NAME. The duration of CYP2D6 inhibition was not studied beyond 7 days and may last longer [see Clinical Pharmacology]. Concomitant use with thioridazine is contraindicated [see Contraindications]. (b) (4) Monitor for adverse reactions if concomitant use with CYP2D6 substrates with a narrow therapeutic index cannot be avoided.

Pimozide is included in the Warning and Precaution, but not in the Contraindication, because rolapitant is a moderate inhibitor of CYP2D6. The pimozide label states that it should not be used concomitantly with strong inhibitors of CYP2D6. The Emend label carries a

Contraindication for concomitant use with pimozide, based on the fact that Emend is an inhibitor of CYP3A4. Pimozide is primarily metabolized through CYP3A4 (and to a lesser extent by CYP2D6).

Transporter data revealed that rolapitant itself is not a substrate of P-glycoprotein (P-gp), OATP1B1 and OATP1B3; however, rolapitant inhibits P-gp and BCRP efflux transporters. When co-administered with digoxin (a P-gp substrate), a 70% increase in digoxin Cmax was observed. When co-administered with sulfasalazine (a BCRP substrate), a 2.3-fold increase in exposure was observed. Day 8 evaluation after a single rolapitant dose revealed sustained transporter inhibition of BCRP; however, the Day 8 sulfasalazine exposure had decreased relative to the Day 1 increase. There was no 7-day study of P-gp effects. The table below, which is reproduced from the Clinical Pharmacology review, summarizes these data.

Table 2 Summary of significant effects of rolapitant on systemic exposure to concomitant medications on Day 1 and Day 8, after a single rolapitant exposure on Day 1.

Enzyme/ transporter	Co-administered drug	Day 1 Mean ratio (90% CI)		Day 8 Mean ratio (90% CI)	
	Name and Dose	Cmax	AUC	Cmax	AUC
CYP2D6	Dextromethorphan 30mg	2.3 (1.9, 2.7)	2.6 (2.1, 3.1)	2.8 (2.3, 3.3)	3.3 (2.8, 4.0)
BCRP	Sulfasalazine 500 mg	2.4 (2.0, 2.9)	2.3 (2.0, 2.7)	1.2 (1.0, 1.4)	1.3 (1.1, 1.6)
P-gp	Digoxin 0.5 mg	1.7 (1.5, 2.0)	1.3 (1.2, 1.4)	--	--

Section 7.1 of the product label will state:

> "BCRP Substrates with a Narrow Therapeutic Index (e.g., Methotrexate, topotecan, or irinotecan): Increased plasma concentrations of BRCP substrates may result in potential adverse reactions. Monitor for adverse reactions related to the concomitant drug if use of Varubi cannot be avoided. Use the lowest effective dose of rosuvastatin (see prescribing information for additional information on recommended dosing).
>
> P-gp Substrates with a Narrow Therapeutic Index: Increased plasma concentrations of digoxin, or other P-gp substrates, may result in potential adverse reactions [see Clinical Pharmacology]. Monitor for increased digoxin concentrations. Monitor for adverse reactions if concomitant use of Varubi with other P-gp substrates with a narrow therapeutic index cannot be avoided."

Based on the demonstration of prolonged effect of inhibition through 7 days after dosing, and the absence of data to establish when this effect resolves, the approval letter will include the following PMC:

2879-4 In vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of Varubi (rolapitant)

The following additional PMCs will be included in the approval letter to further evaluate rolapitant's impact on additional transporters:

2879-5 In vitro studies to evaluate the inhibitory potential of Varubi (rolapitant) on renal transporters, i.e., organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE) transporters, organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3).

2879-6 In vitro study to evaluate the inhibitory potential of Varubi (rolapitant) on OATP1B1 and OATP1B3. The in vitro study results will determine the need for a subsequent clinical assessment of a drug interaction between Varubi (rolapitant) and other concomitant medications.

Thorough QT study. Drug effects on QTC interval were evaluated after a single dose of rolapitant 180 mg or 720 mg in healthy subjects. The study included a moxifloxacin control. The rolapitant upper bound of the 90% CI was 4.4ms at the 720 mg dose level; whereas, the upper bound for the moxifloxacin arm was 13.2.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

The applicant proposed the following indication at the time of NDA submission: "indicated in adults for use in combination with other antiemetic agents for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy." Section 14 Clinical Studies of the proposed label stated that there were (b) (4) adequate and well controlled studies conducted, and it included the results of two phase 3 HEC trials, one phase 3 MEC trial (b) (4)
The trials were placebo controlled, add-on trials in which rolapitant or placebo were administered in a combination regimen that included a 5HT3 antagonist (granisetron) and dexamethasone. Rolapitant or placebo was administered on Day 1 only, along with the 5HT3 antagonist and dexamethasone. Dexamethasone dosing continued on Days 2-4 in the HEC trials. It was administered on Day 1 only in the "MEC" trial.

The primary endpoint in the phase 3 trials was complete response in the delayed phase (b) (4)-120 hours post initiation of chemotherapy). (b) (4)

Complete Response (CR) in all (b) (4) trials was defined as no vomiting, retching or rescue

medication. The label's proposed Section 14 included the primary endpoint results and key secondary endpoint results, i.e., (b) (4) (b) (4) (b) (4) (b) (4)

All three phase 3 trials established superiority of rolapitant over placebo in the delayed phase; (b) (4) (b) (4) The table below summarizes these results, as reported by the applicant in the NDA. The Statistical reviewers did not concur with the results reported by the applicant for the phase 2 dose ranging trial (TS-P04351), which I will discuss in detail below.

Table 3. Summary Overview of the Applicant's Reported P-values Associated with the CR Comparison of Rolapitant to Placebo in the Phase 3 Trials and the Phase 2 Dose Ranging Trial

Study	Acute Phase	Delayed Phase*	Overall Phase
Phase 3			
TS-P04832 (HEC)	(b) (4)	**<0.001**	(b) (4)
TS-P04833 (HEC)		**0.043**	
TS-P04834 (MEC)		**<0.001**	
Phase 2			
TS-P04351 (HEC)		0.045	

*primary endpoint.

The CR percentages associated with each trial and the deltas between rolapitant and placebo, as presented by the applicant, are summarized in table below:

Table 4. Summary of the Proportion of Subjects with CR by Treatment Arm and By Trial, Applicant's Analyses

	TS-P04832 HEC		**TS-P04833 HEC**		**TS-P04834 MEC**		**TS-P04351 Ph2 -HEC**	
	Rolapitant	Control	Rolapitant	Control	Rolapitant	Control	Rolapitant (200 mg)	Control
N	264	262	271	273	666	666	**88**	**90**
Delayed	72.7%	58.4%	70.1%	61.9%	71.3%	61.6%	63.6%	48.9%
Δ	14.3		8.2		9.7		14.7	
Acute	(b) (4)							
Δ								
Overall								
Δ								

N= modified ITT

(b) (4)

(b) (4)

(b) (4) The key issues identified by the Statistical reviewers and points made by the applicant to counter the issues, are summarized here:

1. The trial included an unblinded interim analysis of efficacy, for which there was no formal independent data monitoring committee. The applicant was unable to establish that adequate procedures were in place to ensure that the results of the interim analysis were not revealed to persons connected with the study. The applicant pointed out that it was not the sponsor of the trial, and despite their efforts to obtain records to document the procedures to maintain the blind from the original sponsor, the applicant was unable to retrieve this key documentation.
2. Differing numbers of patients included in various efficacy analyses prompted the Statistical reviewers to request the SAS analysis programs. In their examination of the SAS analysis program they identified 3 patients (2 rolapitant arm; 1 placebo arm) who were not included in the primary analysis submitted in the original NDA submission. The applicant stated that the removal of all 3 subjects from the ITT population was consistent with protocol criteria and/or the Data Analysis Plan (DAP); which raised further concern, as the DAP was not finalized until after study completion (3 months post). Based on the phase 2 trial's definition of ITT and plan for managing missing data, 2 patients were excluded from the ITT analysis because they had no post randomization assessment, whereas the third subject was excluded, despite being in the ITT population, because of missing data limited to the delayed phase. When the impact of removal of these patients from the primary analysis was explored, the reviewers concluded that the phase 2 trial could not be relied upon to support (b) (4) because the statistical significance in the delayed phase results was sensitive to the removal and/or imputation value for a single subject in the ITT population defined by the applicant.

   The Statistical reviewers noted that, based on the mITT population and missing data imputation method that had been recommended by the FDA (which was applied by the applicant to the three phase 3 trials), it was appropriate to include these subjects in the analysis and to include them as nonresponders. They stated that from a regulatory standpoint, it is appropriate to include patients who received study drug (as was the case with all 3 of the subjects), without a condition based on whether there was a post randomization assessment, in modified ITT analyses. The Statistical reviewer recommended that all 3 should be treated as nonresponders for the period in which there is missing data, consistent with the missing data imputation method used in the three phase 3 trials. In fact, in a July 5, 2011 Type C meeting, the FDA had advised the applicant o impute missing data to failure.

As summarized in Table 3 above, the applicant had reported in the original NDA submission that all key outcomes of this phase 2 trial, including (b) (4) delayed phase (b) (4) were statistically significant. The p value from the applicant's delayed phase CR analysis was 0.045 (b) (4) However, when all three patients with missing data were included in the delayed phase analysis as nonresponders, the p value shifted to nonsignificant at 0.056. Nonsignificant results in the delayed phase stops the sequential analyses, (b) (4) The statistical reviewer further explored the impact of excluding missing data by conducting an analysis that excluded the two patients with no assessments post baseline and included only the patient who was missing the delayed phase assessment – as a nonresponder. The results of that analysis also yielded a nonsignificant p value = 0.053.

The following tables, reproduced from the Statistical review, summarize the results of these analyses. The first table represents the Statistical reviewers' replication of the applicant's analysis submitted in the original NDA (excluding all 3 patients), the second table includes all 3 patients as nonresponders, and the third table includes only the patient whose missing data were limited to the delayed phase (and categorized as nonresponder). The p value for the applicant-defined analysis replicated by the Statistical reviewer (first table) is slightly lower than that reported by the applicant. Note the small difference in the proportions of delayed phase CR in the rolapitant arm between the applicant's original analysis and the analyses in which subjects were included as nonresponders.

Table 5: Statistical Reviewer's Delayed Phase Efficacy Analysis Excluding Three Subjects with Missing Data (as per the analysis performed by the applicant in original NDA submission) – Study TS-P04351.

Treatment Group	n	Number (%) of Patients Responding	Rolapitant versus Control[a]	
			% Difference	P-value
Control Regimen	90	44 (48.9%)		
Rolapitant Regimen	88	56 (63.6%)	14.7	0.042*

[a]: Analysis via applicant's Logistic regression SAS codes stratified by gender and CEC.

Table 6: Statistical Reviewer's Delayed Phase Efficacy Analysis Including Two Subjects with Missing Data Post Baseline and One Subject with Missing Data Limited to the Delayed Phase, All as Treatment Failures – Study TS-P04351

Treatment Group	N	Number (%) of Patients Responding	Rolapitant versus Control[a]	
			% Difference	P-value
Control Regimen	91	44 (48.4%)	NA	
Rolapitant Regimen	90	56 (62.2%)	13.8	0.056

[a]: Analysis via applicant's Logistic regression SAS codes stratified by gender and CEC.

Table 7: Statistical Reviewer's Delayed Phase Efficacy Analysis Excluding Two Subjects with Missing Data Post Baseline but Including One Subject with Missing Data Limited to the Delayed Phase (this single subject counted as treatment failure) – Study TS-P04351

Treatment Group	n	Number (%) of Patients Responding	Rolapitant versus Control[a] % Difference	P-value
Control Regimen	90	44 (48.9%)		
Rolapitant Regimen	89	56 (62.9%)	14.0	0.053

[a]: Analysis via applicant's Logistic regression SAS codes stratified by gender and CEC.

3. Finally, the phase 2 dose ranging trial was never intended to be "pivotal" trial that provided substantial evidence of efficacy. As such, the sample size per treatment arm was small relative to the sample sizes of the phase 3 trials submitted in support of this application. The Statistical reviewers pointed out that only about 90 subjects were enrolled in each arm, whereas more than 260 per arm were enrolled in the phase 3 HEC trials. It is my conclusion that while the small sample size may be expected to contribute to the observed instability of the p value (as the applicant pointed out), (b) (4) particularly in light of a negative outcome in one of the large phase 3 HEC trials and the single larger MEC trial (666 subjects enrolled in each arm). Examination of the CR rates for this trial relative to the other HEC trials (see Table 4 above) illustrates this potential.

The Statistical review concludes, (b) (4) (b) (4) (b) (4) conclusion.

These review issues were discussed in multiple meetings with the applicant. The applicant stated that the phase 2 data should reasonably be considered evidence (b) (4) for reasons that included:

1) The p value of 0.056 in the delayed phase analysis that included all 3 subjects as nonresponders was close to 0.05.
2) The CR rates in the delayed phase were similar between the analysis that included the patient with missing delayed phase data as a nonresponder and the analyses that dropped the patient from the ITT population. They further argued that since this
3) (b) (4)
4) They stated the fragility of the p value merely reflects the fact that the study was underpowered. The applicant pointed to large differences between the sample size of this study vs. the other trials in their application. They pointed to similarity of

the deltas observed in their trials relative to those observed in the Emend and Akynzeo programs.

5) They pointed to the FDA's willingness to accept a phase 2 dose ranging trial as substantial evidence of efficacy in HEC (cisplatin based chemotherapy) for netupitant in the Akynzeo NDA. They also pointed to available information on the 2003 and 2005 Emend approvals, which suggested missing data had been imputed based on LOCF. (b) (4) However, the applicant acknowledged that missing data for delayed phase was imputed to failure for netupitant in the Akynzeo NDA, which was approved more recently in 2014.

(b) (4) To support their position, the applicant presented exploratory subgroup analyses from the trial, in which the AC subgroup (n= 703) vs. the non-AC subgroup (629) were examined. The AC subgroup represented approximately 50% of the trial population. (b) (4) In addition, the applicant pointed to the results of the Akynzeo MEC trial, which enrolled only subjects treated with AC, and noted that the delta between netupitant (b) (4) The sample size was 1449. These results suggested that a "MEC" trial that enrolls a substantive number of subjects treated with AC requires a larger sample size than the applicant's MEC trial enrolled.

The applicant also presented exploratory subgroup analyses of the MEC trial to evaluate the (b) (4). They felt the U.S. subgroup analysis should be relevant and impact decisions, as the NDA supports U.S. approval. (b) (4)

Office of Biostatistics leadership was involved in these discussions with the applicant. After considering the applicant's points, the FDA concluded that the phase 2 dose ranging trial could not be considered an adequate and well controlled trial that provided substantial evidence of efficacy to support the NDA. The Biostatistics reviewers state in their review, "Accordingly, (b) (4) as they were exploratory in nature and had been conducted after the

prespecified key secondary analysis had failed to achieve statistical significance. The indication will be (b) (4) prevention of delayed phase CINV.

The following table, which summarizes the delayed phase efficacy observed in the phase 3 trials will appear in the product label:

Table 8. Percent of Patients Receiving Emetogenic Chemotherapy Responding by Treatment Group for the HEC Studies 1 and 2 and for the MEC Study 3

Endpoint	HEC Study 1			HEC Study 2			MEC Study 3		
	BRAND NAME† (N=264) Rate (%)	Control† (N=262) Rate (%)	P-Value (Treatment Difference, 95% C.I.)	BRAND NAME† (N=271) Rate (%)	Control† (N=273) Rate (%)	P-Value (Treatment Difference, 95% C.I.)	BRAND NAME† (N=666) Rate (%)	Control† (N=666) Rate (%)	P-Value (Treatment Difference, 95% C.I.)
Primary Endpoint: Complete Response -- Delayed	72.7	58.4	<0.001* 14.3 (6.3,22.4)	70.1	61.9	0.043* 8.2 (0.3, 16.1)	71.3	61.6	<0.001* 9.8 (4.7, 14.8)

† Granisetron and dexamethasone were used as companion drugs.
* Results were obtained based on the Cochran-Mantel-Haenszel test stratified by gender.

(b) (4)

(b) (4)

Efficacy in repeat cycles of treatment. The applicant proposed inclusion of "initial and repeat courses of emetogenic cancer chemotherapy" in the indication statement. They also proposed inclusion of a paragraph in Section 14 of the label regarding efficacy observed in the multiple cycle extensions of the three phase 3 trials (b) (4)

(b) (4)

(b) (4)

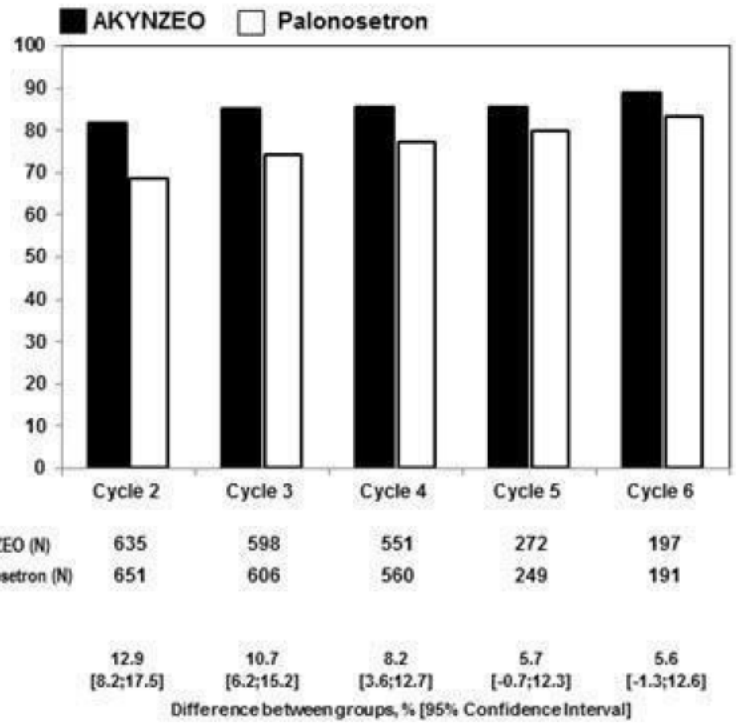
(b) (4)

1) In Cycle 1 the definition of CR was no vomiting/retching plus no use of rescue medication, whereas the efficacy measure in subsequent cycles was no vomiting/retching and no nausea that interfered with quality of life.
2) In Cycle 1, the efficacy information was collected by diary, whereas in subsequent cycles it was captured via recall, i.e., the patient was asked at the one week post chemotherapy follow-up visit (7 days +/- one day) about vomiting/retching and nausea that interfered with normal daily life.

The Clinical reviewer noted that 1-week post recall is a less than ideal way to capture these efficacy data. Differences between the endpoint components and methodology of collection could have contributed to the marginal differences demonstrated between arms in these tertiary exploratory analyses in the rolapitant phase 3 trials. (See Figure 3 below.)

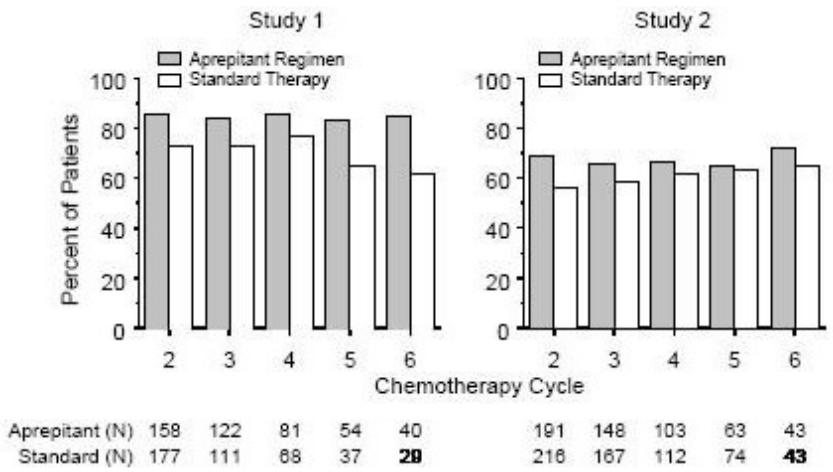
The two approved NK-1 inhibitors include "initial and repeat courses" in their indication statements. Section 14 of the Akynzeo label includes a bar graph describing the delayed phase complete response results by cycle for the program's phase 3 trial that had a multi-cycle extension. That bar graph includes information on the total number of patients treated in each arm in each cycle and confidence intervals that communicate that although the CR rate is higher than the control in subsequent cycles, the differences are not nominally statistically significant. The Emend label (first NK-1 inhibitor approved, 2003) also included bar graphs summarizing the efficacy data from cycles that followed cycle 1 (for a different efficacy endpoint of no emesis and no significant nausea and in the overall phase) by study for two individual HEC studies; however, the confidence intervals were not presented. The Emend data were derived from a two question questionnaire called Emetic Episodes and Nausea Assessment worksheet that the patient filled out instead of a diary. No bar graphs were presented for MEC; (b) (4) The following bar graphs are reproduced from the Akynzeo and Emend labels.

Figure 1. Akynzeo Label Bar Graphs for a multiple-Cycle extension study (response defined as no emesis/retching and no use of rescue medication in the delayed phase)



Proportion of Patients with Complete Response in the Delayed Phase by Treatment Group and Cycle in Study 2

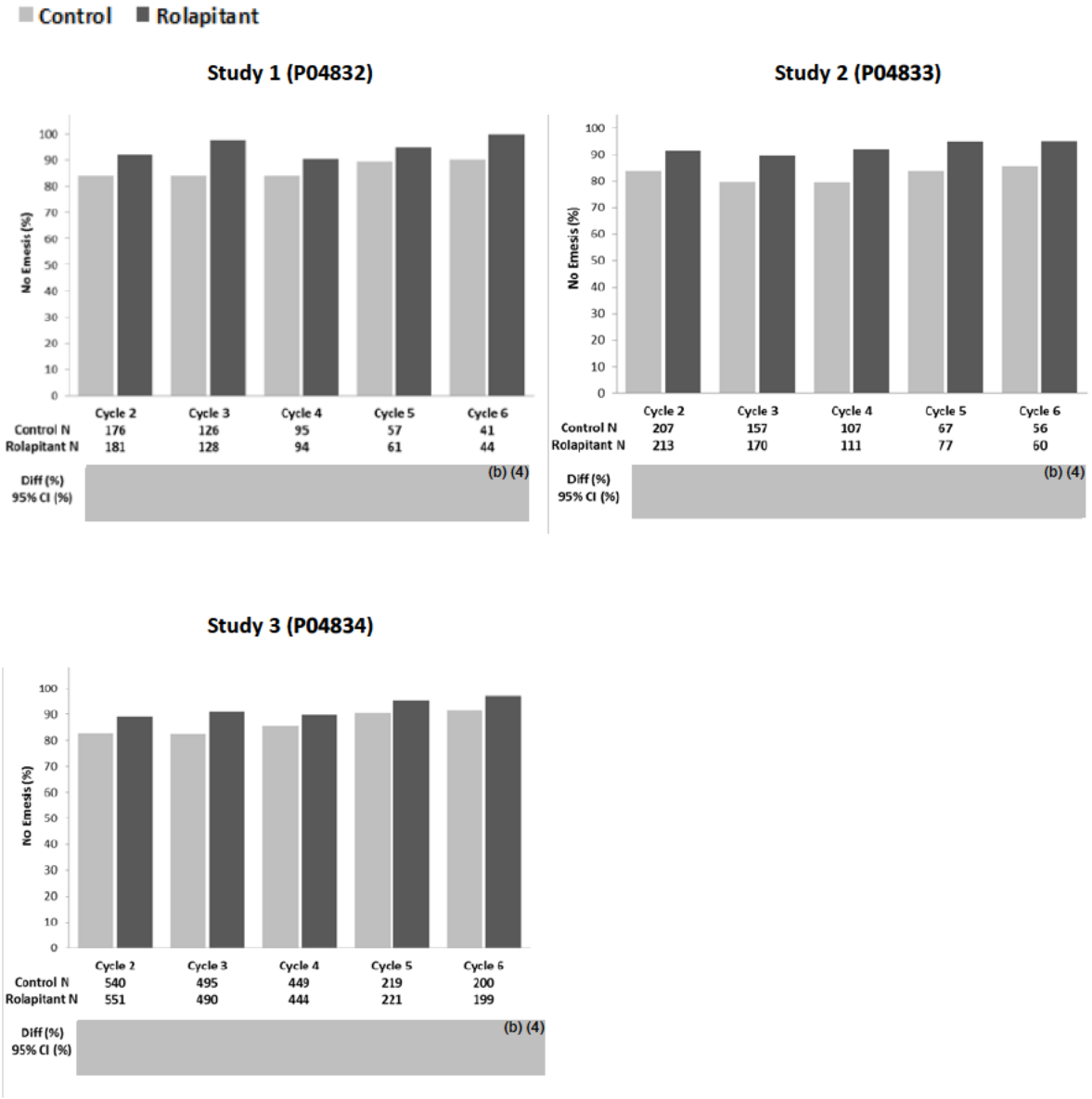
Figure 2. Emend Label Bar Graphs for two phase 3 HEC trials (response was defined as no emesis and no significant nausea in the overall phase):



EMEND Proportion of Patients Receiving Highly Emetogenic Chemotherapy with No Emesis and No Significant Nausea by Treatment Group and Cycle

The following bar graphs were requested from the applicant to support inclusion of references to repeat cycles in the product label. They are limited to delayed phase efficacy in Cycles after Cycle 1 in the phase 3 trials only. The pattern of relative efficacy between arms over time appears similar to the other NK-1 inhibitors; however, the definition of the endpoint presented in the Emend label differed and appears to be a presentation of overall phase and the repeat cycle assessment methodologies differ across the 3 programs. These bar graphs, which are considered descriptive in nature and include the sample size and confidence intervals associated with each cycle, will be included in Section 14 of the label, to be consistent with the labels of the other two NK-1 inhibitors. There will be no summary conclusion statement(s) regarding these descriptive data presentations.

Figure 3. [redacted] (b) (4) **No vomiting/retching and no "nausea that interfered with daily life"** [redacted] (b) (4)



Subgroup analyses based on sex, race and age.

The results of subgroup analyses of efficacy (based on sex, race and age) are presented below, by phase 3 trial.

In Study TS-P04832 (HEC):

1) 43% of the population was female; the delta between rolapitant and control for delayed phase was similar between females and males (15.5% vs. 13.3%), and nominally statistically significant in both subgroups.

2) 26% of the population was ≥ 65 years of age; the delta between rolapitant and control for delayed phase was numerically higher in the older subgroup (20% vs. 12%), and nominally statistically significant in both subgroups
3) 32% of the population was non-White; the delta between rolapitant and control for delayed phase was numerically higher in the non-White subgroup (19.4% vs. 12.1%), and nominally statistically significant in both subgroups.

In Study TSP-04833 (HEC):

1) 33% of the population was female; the delta between rolapitant and control for delayed phase was higher in females than males (23.3% vs. 1.1%), and nominally statistically significant in only females. Note that the low CR rate relative to control arm observed in males in this trial was based on a control arm CR rate of 67.2% in males, whereas the control arm CR rate in females was 50.6%. Furthermore, the control arm CR rate observed in males in the other phase 3 HEC trial (TSP-04832, described above), was 62.0% and the control arm rate in females was 53.6%. The disparity of CR rates between males and females observed in Study TSP-04833 appears linked to a very high CR rate in males in the control arm.
2) 27% of the population was ≥ 65 years of age; the delta between rolapitant and control for delayed phase was numerically higher in the younger subgroup (11% vs. 1.0%), and nominally statistically significant in only the younger subgroup.
3) 20% of the population was non-White; the delta between rolapitant and control for delayed phase was numerically higher in the non-White subgroup (13.2% vs. 6.7%); the differences between rolapitant and control were not nominally statistically significant in either subgroup.

In Study TSP-04834 (MEC):

1) 80% of the population was female; the delta between rolapitant and control for delayed phase was numerically lower in females than males (9.1% vs. 12.2%), but nominally statistically significant in both subgroups.
2) 28% of the population was ≥ 65 years of age; the delta between rolapitant and control for delayed phase was numerically higher in the older subgroup (11% vs. 9.0%), but nominally statistically significant in both subgroups.
3) 23% of the population was non-White; the delta between rolapitant and control for delayed phase was numerically higher in the White subgroup (10.5% vs. 7.5%); the differences between rolapitant and control were nominally statistically significant in only the White subgroup.

Summary. The applicant has presented data from three phase 3 trials that establish the efficacy of rolapitant for preventing delayed phase of CINV. Two trials were conducted in the setting of cisplatin based HEC. Approximately 53% of patients enrolled in the single MEC trial were treated with AC, which ASCO guidelines have reclassified as HEC. As stated in Section 2 of this review, the Division has determined that it is reasonable to grant a broad indication that encompasses MEC chemotherapy if the major trials submitted to support an approval are limited to study of HEC chemotherapy. This decision was prompted by the review of the Akynzeo NDA, in which the major "MEC" trial enrolled only patients who

received AC chemotherapy. A review of prior approvals found little evidence that an antiemetic that is effective for HEC would not also be effective in the setting of MEC. Consistent with this finding, the subset analyses of the non-AC subgroup in the rolapitant MEC trial in this application found a numerically favorable treatment effect of rolapitant, which was associated with a nominally significant p value. For this reason the indication for rolapitant will be general, and will state:

> VARUBI is indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

As noted in (b) (4) Clinical Pharmacology, unlike the two currently approved NK-1 inhibitors, rolapitant does not have a drug interaction with dexamethasone that increases dexamethasone exposure. The review team discussed its concerns that health care providers may mistakenly lower the dexamethasone dose when it is administered with rolapitant, based on the inaccurate assumption that all NK-1 inhibitors share this interaction. This dose reduction in the setting of combination antiemetic regimens that incorporate rolapitant could result in decreased antiemetic regimen efficacy. The applicant agreed to contact ASCO Supportive Care Working Group to educate providers regarding the lack of an interaction associated with rolapitant. The Dosage and Administration section of the product label (b) (4) will state: "There is no drug interaction between rolapitant and dexamethasone, so no dosage adjustment for dexamethasone is required." The section also provides the Day 1 dexamethasone dose (for both the MEC and HEC settings) and the dose for subsequent days (HEC setting).

8. Safety

The combined safety database from the phase 2 dose ranging trial and the three phase 3 trials consisted of 1567 patients who had taken at least one dose of rolapitant. There were 1294 patients exposed at the dose proposed for marketing. Over 300 patients received 6 cycles of exposure. The number of subjects with exposures by cycle number and within each trial is summarized in the table below, which is reproduced from the Clinical Review (Table 34 of the Clinical Review). Study P04351 is the phase 2 dose ranging trial; Study P04832 and Study P04833 are the HEC trials; and Study P04834 is the "MEC" trial (half of the patients received AC chemotherapy) trial.

Table 9. Number of Rolapitant Exposures by Cycle and by Trial

Cycle	P04351 <200mg	P04351 200mg	P04832 200mg	P04833 200mg	P04834 200mg	Total
Cycle 1	273	89	263	272	670	1567
Cycle 2	187	61	181	214	555	1198
Cycle 3	146	46[a]	128	171	492	983
Cycle 4	96	33	94	112	446	781
Cycle 5	58	19	61	78	223	439
Cycle 6	48	15	44	61	199	367
Total Rolapitant Exposures	**808**	**263**	**771**	**908**	**2585**	**5335**
Total Rolapitant Exposures @ 200mg	**N/A**	**262[b]**	**770[b]**	**908**	**2584[b]**	**4524**

Abbreviation: N/A, not applicable.
Note: Dose groups are based on actual treatment/assigned dose groups.
[a] P04351 study report notes 47 rolapitant exposures at 200mg. However, one subject (4351-091-610) had a protocol deviation indicating the subject was not dosed during Cycle 3.
[b] The following subjects did not receive a 200mg dose of rolapitant (P04351-041-0493 [Cycle 1; reason unknown]; P04832-506-2007 [Cycle 1; subject could not swallow remaining capsules due to dysphagia]; P04834-226-4020 [Cycle 1; due to a mistake]).

TEAEs led to drug discontinuation in 3.1% in both the rolapitant and placebo arms. SAE rates were also essentially identical between rolapitant and control arms (18.5% and 18.8%, respectively). The Clinical reviewer reported in her Addendum review that the incidence of TEAEs was highest in the first cycle of treatment and decreased with successive cycles. The exceptions occurred in Cycles 4 and 5 for AEs of CGC Grade 3+, and Cycle 5 for AE leading to discontinuation and AE outcome of death; however, for those, the rates were the same or higher in the control arm. There was no evidence of cumulative rolapitant toxicity. The incidence of TEAEs was also explored based on length of chemotherapy cycle. The proportion of TEAEs (based on all TEAE data pooled after Cycle 1) was similar between the rolapitant arm and control arm regardless of cycle length. There was no evidence that cycles less than 3 weeks were associated with a higher rate of TEAEs (of interest due to the long half-life of rolapitant).

Deaths. A higher number of deaths occurred in the rolapitant arms vs. placebo (48 vs. 31). Most deaths in both arms occurred in the first cycle. There was no evidence of a trend to increasing rate of deaths with subsequent cycles (and increased exposure to rolapitant) in the rolapitant arms. The deaths by cycle are summarized in the Table below, which is reproduced from the Clinical Review (Table 36).

Table 10. Number of deaths reported by Treatment Arm and by Cycle

Cycle Number	Overall Control		Rolapitant 200 mg		All Rolapitant Doses	
	N	n (%)	N	n (%)	N	n (%)
All: Cycles 1-6	1301	31 (2.4)	1294	38 (2.9)	1567	48 (3.1)
Cycle 1	1301	15 (1.2)	1294	21 (1.6)	1567	24 (1.5)
Cycle 2	998	5 (0.5)	1011	10 (1.0)	1198	13 (1.1)
Cycle 3	834	7 (0.8)	837	3 (0.4)	983	5 (0.5)
Cycle 4	695	3 (0.4)	685	1 (0.1)	781	2 (0.3)
Cycle 5	365	1 (0.3)	381	3 (0.8)	439	4 (0.9)
Cycle 6	314	0	319	0	367	0

For the rolapitant arms, the rate of adverse events resulting in death was higher in the HEC trials than in the MEC trial (3.8% vs. 1.0%). With regard to pattern of adverse reaction associated with death, there was no real signal suggesting rolapitant was causing a specific fatal drug reaction, although there was a numerically higher proportion of subjects with respiratory/thoracic and mediastinal disorders in the rolapitant arm vs. control arm, distributed across a variety of event terms. The distribution did not suggest a common adverse reaction related to study drug. In addition, there was a numerically higher rate of nervous system disorders in the rolapitant arms than in the control arms (0.3% vs. 0). There was no clear consistent pattern of event types suggesting the study drug was the underlying cause (i.e., mixture of hemorrhagic, thrombotic and metabolic). The 4 events in subjects treated with 200 mg rolapitant included cerebral haematoma (hemorrhagic), cerebrovascular accident (not clearly defined as hemorrhagic; however the Clinical reviewer considered the narrative consistent with hemorrhagic), ischemic stroke (thrombotic), and hepatic encephalopathy. There were two additional events in subjects exposed to rolapitant 25 mg: a cerebral infarction and cerebral ischaemia (both thrombotic). These data are summarized in the table below, which is reproduced from the Clinical Review (Table 37).

Table 11: Treatment Emergent Adverse Events with Outcome of Death by MedDRA System Organ Class and Preferred Term in Decreasing Order by Rolapitant 200 mg Group, All Cycles Combined – Subject Incidence.

System Organ Class Preferred Term	HEC (P04832, P04833, P04351)[a]			MEC (P04834)		Overall CINV		
	Control N = 627 n (%)	<200 mg N = 273 n (%)	200 mg N = 624 n (%)	Control N = 674 n (%)	200 mg N = 670 n (%)	Control N = 1301 n (%)	200 mg N = 1294 n (%)	Rolapitant[a] N = 1567 n (%)
Subjects with ≥1 Incidence	24 (3.8)	10 (3.7)	25 (4.0)	7 (1.0)	13 (1.9)	31 (2.4)	38 (2.9)	48 (3.1)
Respiratory, thoracic and mediastinal disorders	**2 (0.3)**	**2 (0.7)**	**7 (1.1)**	**2 (0.3)**	**5 (0.7)**	**4 (0.3)**	**12 (0.9)**	**14 (0.9)**
Respiratory failure	0	0	2 (0.3)	2 (0.3)	1 (0.1)	2 (0.2)	3 (0.2)	3 (0.2)
Acute respiratory failure	1 (0.2)	0	1 (0.2)	0	1 (0.1)	1 (<0.1)	2 (0.2)	2 (0.1)
Haemoptysis	0	0	1 (0.2)	0	1 (0.1)	0	2 (0.2)	2 (0.1)
Pulmonary embolism	0	1 (0.4)	0	0	1 (0.1)	0	1 (<0.1)	2 (0.1)
Obstructive airways disorder	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Pneumonia aspiration	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Pneumonitis	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Respiratory distress	0	0	0	0	1 (0.1)	0	1 (<0.1)	1 (<0.1)
Dyspnoea	1 (0.2)	0	0	0	0	1 (<0.1)	0	0
Pulmonary artery thrombosis	0	1 (0.4)	0	0	0	0	0	1 (<0.1)
Infections and infestations	**3 (0.5)**	**0**	**4 (0.6)**	**2 (0.3)**	**3 (0.4)**	**5 (0.4)**	**7 (0.5)**	**7 (0.4)**
Sepsis	1 (0.2)	0	1 (0.2)	0	2 (0.3)	1 (<0.1)	3 (0.2)	3 (0.2)
Pneumonia	1 (0.2)	0	2 (0.3)	0	0	1 (<0.1)	2 (0.2)	2 (0.1)
Neutropenic sepsis	0	0	0	1 (0.1)	1 (0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Parotitis	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Encephalitis herpes	1 (0.2)	0	0	0	0	1 (<0.1)	0	0
Fungaemia	0	0	0	1 (0.1)	0	1 (<0.1)	0	0
Infection	1 (0.2)	0	0	0	0	1 (<0.1)	0	0
Lobar pneumonia	0	0	0	1 (0.1)	0	1 (<0.1)	0	0

System Organ Class Preferred Term	HEC (P04832, P04833, P04351)[a]			MEC (P04834)		Overall CINV		
	Control N = 627 n (%)	<200 mg N = 273 n (%)	200 mg N = 624 n (%)	Control N = 674 n (%)	200 mg N = 670 n (%)	Control N = 1301 n (%)	200 mg N = 1294 n (%)	Rolapitant[a] N = 1567 n (%)
General disorders and administration site conditions	**9 (1.4)**	**2 (0.7)**	**6 (1.0)**	**1 (0.1)**	**0**	**10 (0.8)**	**6 (0.5)**	**8 (0.5)**
Disease progression	2 (0.3)	0	3 (0.5)	0	0	2 (0.2)	3 (0.2)	3 (0.2)
Sudden death	0	0	2 (0.3)	0	0	0	2 (0.2)	2 (0.1)
General physical health deterioration	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Death	4 (0.6)	2 (0.7)	0	0	0	4 (0.3)	0	2 (0.1)
Asthenia	1 (0.2)	0	0	0	0	1 (<0.1)	0	0
Multi-organ failure	2 (0.3)	0	0	1 (0.1)	0	3 (0.2)	0	0
Cardiac disorders	**3 (0.5)**	**2 (0.7)**	**1 (0.2)**	**0**	**3 (0.4)**	**3 (0.2)**	**4 (0.3)**	**6 (0.4)**
Cardio-respiratory arrest	2 (0.3)	1 (0.4)	0	0	2 (0.3)	2 (0.2)	2 (0.2)	3 (0.2)
Cardiac arrest	1 (0.2)	0	1 (0.2)	0	1 (0.1)	1 (<0.1)	2 (0.2)	2 (0.1)
Cardiopulmonary failure	0	1 (0.4)	0	0	0	0	0	1 (<0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**3 (0.5)**	**0**	**3 (0.5)**	**3 (0.4)**	**1 (0.1)**	**6 (0.5)**	**4 (0.3)**	**4 (0.3)**
Neoplasm progression	0	0	1 (0.2)	2 (0.3)	1 (0.1)	2 (0.2)	2 (0.2)	2 (0.1)
Metastases to central nervous system	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Oral neoplasm	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Bronchial carcinoma	1 (0.2)	0	0	0	0	1 (<0.1)	0	0
Metastases to peritoneum	0	0	0	1 (0.1)	0	1 (<0.1)	0	0
Neoplasm malignant	2 (0.3)	0	0	0	0	2 (0.2)	0	0
Nervous system disorders	**0**	**2 (0.7)**	**2 (0.3)**	**0**	**2 (0.3)**	**0**	**4 (0.3)**	**6 (0.4)**
Cerebral haematoma	0	0	0	0	1 (0.1)	0	1 (<0.1)	1 (<0.1)
Cerebrovascular accident	0	0	0	0	1 (0.1)	0	1 (<0.1)	1 (<0.1)
Hepatic encephalopathy	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)

System Organ Class Preferred Term	HEC (P04832, P04833, P04351)[a]			MEC (P04834)		Overall CINV		
	Control N = 627 n (%)	<200 mg N = 273 n (%)	200 mg N = 624 n (%)	Control N = 674 n (%)	200 mg N = 670 n (%)	Control N = 1301 n (%)	200 mg N = 1294 n (%)	Rolapitant[a] N = 1567 n (%)
Ischaemic stroke	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Cerebral infarction	0	1 (0.4)	0	0	0	0	0	1 (<0.1)
Cerebral ischaemia	0	1 (0.4)	0	0	0	0	0	1 (<0.1)
Renal and urinary disorders	**0**	**0**	**1 (0.2)**	**0**	**1 (0.1)**	**0**	**2 (0.2)**	**2 (0.1)**
Renal failure	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Renal failure acute	0	0	0	0	1 (0.1)	0	1 (<0.1)	1 (<0.1)
Metabolism and nutrition disorders	**1 (0.2)**	**1 (0.4)**	**1 (0.2)**	**0**	**0**	**1 (<0.1)**	**1 (<0.1)**	**2 (0.1)**
Hypoglycaemia	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Tumour lysis syndrome	0	1 (0.4)	0	0	0	0	0	1 (<0.1)
Dehydration	1 (0.2)	0	0	0	0	1 (<0.1)	0	0
Vascular disorders	**1 (0.2)**	**1 (0.4)**	**1 (0.2)**	**0**	**0**	**1 (<0.1)**	**1 (<0.1)**	**2 (0.1)**
Circulatory collapse	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Hypovolaemic shock	0	1 (0.4)	0	0	0	0	0	1 (<0.1)
Embolism	1 (0.2)	0	0	0	0	1 (<0.1)	0	0
Gastrointestinal disorders	**1 (0.2)**	**0**	**0**	**2 (0.3)**	**0**	**3 (0.2)**	**0**	**0**
Gastrointestinal haemorrhage	1 (0.2)	0	0	0	0	1 (<0.1)	0	0
Small intestinal obstruction	0	0	0	2 (0.3)	0	2 (0.2)	0	0
Blood and lymphatic system disorders	**1 (0.2)**	**0**	**0**	**0**	**0**	**1 (<0.1)**	**0**	**0**
Agranulocytosis	1 (0.2)	0	0	0	0	1 (<0.1)	0	0

Abbreviations: CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

[a] Subjects who received any rolapitant doses are combined.

The medical officer concluded after her review of the deaths that there was no evidence that the deaths were causally related to rolapitant. She concluded the deaths were expected in a patient population with advanced cancer. I concur.

Nonfatal SAEs. The proportion of patients with a nonfatal serious adverse event (SAE) was similar between rolapitant treated subjects and placebo (2.7% vs. 3.0%, respectively). Furthermore, the proportion of subjects who discontinued study participation due to TEAEs was similar between rolapitant and placebo (3.1% vs. 3.7%).

Adverse events of interest based on nonclinical data. Given the nonclinical study finding of convulsions in acute and subacute animal toxicity studies (which was not replicated in subsequent chronic dosing nonclinical studies; see Section 4 above), the clinical safety data were evaluated for evidence of adverse events that could be related to seizures. Neurological examinations were systematically performed in the trials at the start of each treatment cycle, including assessments of cranial nerves, gait, station, reflexes, sensation and cerebellar function. A similar proportion of patients had TEAEs related to the nervous system between study arms. Most were headache or dizziness. Similar proportions of patients had TEAEs reported as "convulsions" (0.3% in the overall rolapitant treated subjects vs. 0.2% in the placebo control group vs. 0.2% of the rolapitant subjects who were treated with 200 mg rolapitant dose). The Clinical reviewer noted that the narratives of the patients with convulsions indicated that most had brain metastases or another condition known to be associated with seizures (such as hyponatremia). The proportions of patients with syncope were identical between placebo and the overall rolapitant treated group. The proportion with presyncopal events was slightly numerically higher in the rolapitant group than the control (0.3% in 200 mg rolapitant vs. 0.2% control). The rates of individual types of TEAEs in the nervous system disorders system organ class were similar among the overall rolapitant treated subjects, the rolapitant 200 mg treated subjects, and control subjects. The CNS related deaths have already been discussed above, and did not appear to be related to rolapitant toxicity.

In her evaluation of liver safety, the reviewer noted that 5 cases of Hy's law were identified in the safety database, of which 4 occurred on the control arm and 1 occurred in a subject who was treated with a low dose of rolapitant (10mg). The laboratory abnormalities in the latter patient (a 58 yo female with squamous cell carcinoma of the tongue treated with cisplatin and 5FU) occurred two days post treatment and included an increase in ALT from normal at baseline to approximately 5 X ULN and a total bilirubin >2 X ULN (50 micromole/L); however, the patient's baseline bilirubin was also greater than ULN. Alkaline phosphatase and AST were normal. The patient had no evidence of jaundice, pruritis, abdominal symptoms or rash. She had concomitant electrolyte abnormalities, including hyponatremia, low HCO3, and high BUN and Creatinine. Her concomitant medications included acetomeniphen 500 mg every 8 hours and ranitidine 150 mg every 8 hours. All laboratory values normalized in time for the next cycle of treatment (q 4 weeks schedule). She experienced elevations again in subsequent cycles, although lower and not meeting Hy's criteria. These abnormalities resolved in time for administration of each cycle of chemotherapy. She completed 4 cycles of chemotherapy on study, and when she left the study her ALT and bilirubin were normal. (See Addendum Clinical review.) The applicant concluded that the lack of clinical signs and signs "do not suggest DILI" in this subject. Her multiple other medications (including 5HT3

antagonist, chemotherapy drugs, acetomeniphen and ranitidine) could also have caused the shifts in ALT and Bilirubin, and the patient had a high bilirubin before starting treatment.

The Clinical reviewer requested an analysis of proportion of subjects who had >3X, >5X and <10X ULN in AST, as well as >2X ULN total bilirubin. Small numerical differences between rolapitant 200 mg and control were noted for AST>5X ULN in Cycle 1 (0.2% rolapitant vs. 0.1% control), Cycle 2 (0.1% vs. 0%), and Cycle 3 (0.5% vs. 0.1%) only. For AST >10, a small numerical difference was noted in Cycle 2 (0.1% vs. 0.0%) only. For bilirubin, the proportion with >2X elevation was higher in the control arm than in the rolapitant arm in Cycle 1 and all subsequent cycles, with the exception of Cycle 2, in which rolapitant = 0.7% and control = 0.4%, and in Cycle 5, in which rolapitant = 0.8% and control = 0.5%. I concur with the Clinical Reviewer that there was no convincing signal of hepatoxicity attributable to rolapitant identified.

Common adverse reactions. The most common adverse reactions will be summarized in the label as follows (based on adverse reaction in which the rate was higher than the control arm and the rate was ≥3%):

Table 12. Most Common Adverse Reactions in Patients Receiving Cisplatin Based Highly Emetogenic Chemotherapy (Cycle 1)*

	BRAND NAME Regimen (BRAND NAME, Dexamethasone, and $5HT_3$ Receptor Antagonist) N = 624	**Control (Placebo, Dexamethasone, and $5HT_3$ Receptor Antagonist) N = 627**
Neutropenia	9%	8%
Hiccups	5%	4%
Abdominal Pain	3%	2%

*all reactions occurring at ≥ 3% in the BRAND NAME group and for which the rate for BRAND NAME exceeds the rate for control

Table 13. Most Common Adverse Reactions in Patients Receiving Moderately Emetogenic Chemotherapy and Combinations of Anthracycline and Cyclophosphamide (Cycle 1)*

	BRAND NAME Regimen (BRAND NAME, Dexamethasone, and $5HT_3$ Receptor Antagonist) N = 670	**Control (Placebo, Dexamethasone, and $5HT_3$ Receptor Antagonist) N = 674**
Decreased appetite	9%	7%
Neutropenia	7%	6%
Dizziness	6%	4%
Dyspepsia	4%	2%
Urinary tract infection	4%	3%

	BRAND NAME Regimen (BRAND NAME, Dexamethasone, and $5HT_3$ Receptor Antagonist) N = 670	**Control (Placebo, Dexamethasone, and $5HT_3$ Receptor Antagonist) N = 674**
Stomatitis	4%	2%
Anemia	3%	2%

*all reactions occurring at ≥ 3% in the BRAND NAME group and for which the rate for BRAND NAME exceeds the rate for control.

Adverse reactions related to drug drug interactions. The Clinical reviewer examined the safety database for evidence of clinically relevant adverse reactions attributable to rolapitant's interactions with concomitant medications. As stated in Section 5 of this review, rolapitant is a moderate CYP2D6 inhibitor, a weak P-gp inhibitor and a moderate inhibitor of the BCRP transporter. The reviewer found that in the subset of patients who were taking a concomitant CYP2D6 substrate drug, the incidence of treatment emergent adverse events was similar between rolapitant and control, and there were higher rates of TEAEs in the patients taking concomitant CYP2D6 substrate drugs in both arms compared to patients who were not taking substrate drugs. When specific adverse events were examined, there was a slightly higher rate of neutropenia in patients treated with both rolapitant and a CYP2D6 substrate vs. control (9.2% vs 7.7%), a slightly higher rate of diarrhea (10.4% vs. 9.9%), a higher rate of dizziness (6.5% vs. 3.5%), and alopecia (7.5% vs. 6.4%). These differences were small, and it was difficult to attribute them to the drug interactions.

Since rolapitant is only a weak inhibitor of p-GP, the clinical reviewer focused on the potential clinical safety implications of drug interactions related to rolapitant's inhibition of BCRP transporter. Doxorubicin, fluorouracil and docetaxel are BCRP substrates, and when the relative rate of adverse events was examined between rolapitant treated subjects who received one of these drugs and control subjects, the Clinical reviewer noted that the incidence of overall TEAEs was higher in patients who were treated with BCRP substrates. However, when the applicant responded to an information request to provide safety analyses for chemotherapeutic agents that are substrates for BCRP with individual tables for docetaxel, dosorubicin, epirubicin, etoposide, fluorouracil, irinotecan, methotrexate and topotecan, the Clinical reviewer found no trend of increasing TEAE incidence in events of specific interest as chemotherapy induced toxicity (e.g., cytopenia, diarrhea) in subjects who were administered concomitant BCRP substrates. I also reviewed the tables for evidence of a pattern of increase of specific types of adverse events related to underlying chemotherapy and found no persuasive evidence of a pattern of increased chemotherapy toxicity associated with coadministration of rolapitant.

Subgroup analyses of safety based on sex, age and race. The Clinical reviewer presented demographic subgroup analyses of safety in her Addendum Review.

Sex. The following table, reproduced from the Clinical Addendum review, summarizes the TEAEs by sex and by study arm (control vs. rolapitant). The relative rate between males and

females for each TEAE was similar between the rolapitant arm and control, i.e., for TEAEs that occurred at a numerically higher rate in females than males (or vice versa) in the rolapitant arm, a similar higher rate was observed in the control arm. There was little evidence of a increased risk for an adverse reaction related to rolapitant in one sex relative to the other. There are two TEAEs in the table below in which that pattern was not consistent, i.e., asthenia and neutropenia. For asthenia, there was a numerically higher difference in proportion of males with this TEAE relative to females in the rolapitant group as compared to the difference in the control group (4.8% rolapitant vs. 0.7% control). For neutropenia, there was a numerically higher difference in proportion of females with this TEAE relative to males in the rolapitant group as compared to the difference in the control group (3.6% rolapitant vs. 1.3% control). However, these differences between groups do not seem large enough to reflect an actual clinically meaningful difference in rolapitant safety between the sexes.

Table 14. TEAEs by Sex (≥10% of Subjects in Any Subgroup/Treatment Combination), Subject Incidence, Pooled Phase 3 and Phase 2 Trials, All Cycles Combined

System Organ Class Preferred Term	Overall CINV			
	Control		Rolapitant 200 mg	
	Female (N = 782) n (%)	Male (N = 519) n (%)	Female (N = 774) n (%)	Male (N = 520) n (%)
Subjects with ≥1 Incidence	*637 (81.5)*	*416 (80.2)*	*623 (80.5)*	*432 (83.1)*
Gastrointestinal disorders	**366 (46.8)**	**223 (43.0)**	**342 (44.2)**	**221 (42.5)**
Constipation	141 (18.0)	74 (14.3)	120 (15.5)	66 (12.7)
Diarrhoea	102 (13.0)	58 (11.2)	102 (13.2)	62 (11.9)
Nausea	121 (15.5)	80 (15.4)	93 (12.0)	58 (11.2)
General disorders and administration site conditions	**325 (41.6)**	**198 (38.2)**	**320 (41.3)**	**204 (39.2)**
Fatigue	183 (23.4)	70 (13.5)	177 (22.9)	79 (15.2)
Asthenia	112 (14.3)	78 (15.0)	94 (12.1)	88 (16.9)
Skin and subcutaneous tissue disorders	**242 (30.9)**	**71 (13.7)**	**224 (28.9)**	**78 (15.0)**
Alopecia	191 (24.4)	36 (6.9)	163 (21.1)	41 (7.9)
Blood and lymphatic system disorders	**190 (24.3)**	**131 (25.2)**	**215 (27.8)**	**142 (27.3)**
Neutropenia	108 (13.8)	65 (12.5)	129 (16.7)	68 (13.1)
Anaemia	72 (9.2)	41 (7.9)	84 (10.9)	52 (10.0)
Nervous system disorders	**229 (29.3)**	**90 (17.3)**	**205 (26.5)**	**120 (23.1)**
Headache	114 (14.6)	29 (5.6)	85 (11.0)	30 (5.8)
Infections and infestations	**167 (21.4)**	**81 (15.6)**	**186 (24.0)**	**109 (21.0)**
Metabolism and nutrition disorders	**175 (22.4)**	**133 (25.6)**	**172 (22.2)**	**133 (25.6)**
Decreased appetite	98 (12.5)	74 (14.3)	102 (13.2)	72 (13.8)

Age. The following table, reproduced from the Clinical Addendum review, summarizes the TEAEs by age and by study arm (control vs. rolapitant), which are presented using four age cutpoints: <45 years, 45-<65 years, ≥ 65 years and <75 years and ≥75 years. Twenty-six percent of the overall pooled phase 3 and phase 2 trial population was ≥65 years of age, and 25% of the pooled rolapitant population was ≥65 years of age. The following TEAEs occurred at a higher rate in the greater than ≥75 years subgroup treated with rolapitant than both the younger subgroups in the rolapitant arm AND the ≥75 years subgroup in the control arm: diarrhea, stomatitis, peripheral edema, anemia, leukopenia, dizziness, dyspnea, hypotension and cardiac disorders.

Table 15. TEAEs by Age Group and Dose Group, All Cycles Combined (≥10% of Subjects in Any Subgroup/Treatment Combination) – Subject Incidence, Pooling Group 1

System Organ Class Preferred Term	Overall CINV							
	Control				Rolapitant			
	<45 y (N = 174) n (%)	≥45 to <65 y (N = 766) n (%)	≥65 to <75 y (N = 295) n (%)	≥75 y (N = 66) n (%)	<45 y (N = 184) n (%)	≥45 to <65 y (N = 787) n (%)	≥65 to <75 y (N = 265) n (%)	≥75 y (N = 58) n (%)
Subjects with ≥1 Incidence	*141 (81.0)*	*606 (79.1)*	*247 (83.7)*	*59 (89.4)*	*153 (83.2)*	*628 (79.8)*	*228 (86.0)*	*46 (79.3)*
Gastrointestinal disorders	**75 (43.1)**	**346 (45.2)**	**141 (47.8)**	**27 (40.9)**	**82 (44.6)**	**327 (41.6)**	**124 (46.8)**	**30 (51.7)**
Constipation	21 (12.1)	131 (17.1)	50 (16.9)	13 (19.7)	32 (17.4)	105 (13.3)	38 (14.3)	11 (19.0)
Diarrhoea	15 (8.6)	93 (12.1)	43 (14.6)	9 (13.6)	18 (9.8)	93 (11.8)	41 (15.5)	12 (20.7)
Nausea	34 (19.5)	112 (14.6)	44 (14.9)	11 (16.7)	23 (12.5)	88 (11.2)	32 (12.1)	8 (13.8)
Stomatitis	9 (5.2)	37 (4.8)	26 (8.8)	4 (6.1)	12 (6.5)	42 (5.3)	9 (3.4)	6 (10.3)
General disorders and administration site conditions	**62 (35.6)**	**301 (39.3)**	**131 (44.4)**	**29 (43.9)**	**64 (34.8)**	**315 (40.0)**	**113 (42.6)**	**32 (55.2)**
Fatigue	31 (17.8)	152 (19.8)	51 (17.3)	19 (28.8)	28 (15.2)	152 (19.3)	60 (22.6)	16 (27.6)
Asthenia	22 (12.6)	99 (12.9)	58 (19.7)	11 (16.7)	25 (13.6)	103 (13.1)	43 (16.2)	11 (19.0)
Oedema peripheral	1 (0.6)	21 (2.7)	18 (6.1)	2 (3.0)	1 (0.5)	23 (2.9)	9 (3.4)	6 (10.3)
Blood and lymphatic system disorders	**38 (21.8)**	**191 (24.9)**	**78 (26.4)**	**14 (21.2)**	**46 (25.0)**	**211 (26.8)**	**80 (30.2)**	**20 (34.5)**
Neutropenia	25 (14.4)	102 (13.3)	41 (13.9)	5 (7.6)	30 (16.3)	118 (15.0)	43 (16.2)	6 (10.3)
Anaemia	6 (3.4)	74 (9.7)	29 (9.8)	4 (6.1)	11 (6.0)	79 (10.0)	36 (13.6)	10 (17.2)
Leukopenia	7 (4.0)	36 (4.7)	26 (8.8)	3 (4.5)	10 (5.4)	45 (5.7)	14 (5.3)	6 (10.3)
Infections and infestations	**34 (19.5)**	**130 (17.0)**	**62 (21.0)**	**22 (33.3)**	**38 (20.7)**	**187 (23.8)**	**54 (20.4)**	**16 (27.6)**
Urinary tract infection	10 (5.7)	38 (5.0)	12 (4.1)	9 (13.6)	3 (1.6)	52 (6.6)	14 (5.3)	7 (12.1)
Nervous system disorders	**40 (23.0)**	**189 (24.7)**	**71 (24.1)**	**19 (28.8)**	**48 (26.1)**	**185 (23.5)**	**77 (29.1)**	**15 (25.9)**
Headache	26 (14.9)	83 (10.8)	28 (9.5)	6 (9.1)	27 (14.7)	65 (8.3)	18 (6.8)	5 (8.6)
Dizziness	15 (8.6)	52 (6.8)	21 (7.1)	3 (4.5)	16 (8.7)	52 (6.6)	22 (8.3)	7 (12.1)

System Organ Class Preferred Term	Overall CINV							
	Control				Rolapitant			
	<45 y (N = 174) n (%)	≥45 to <65 y (N = 766) n (%)	≥65 to <75 y (N = 295) n (%)	≥75 y (N = 66) n (%)	<45 y (N = 184) n (%)	≥45 to <65 y (N = 787) n (%)	≥65 to <75 y (N = 265) n (%)	≥75 y (N = 58) n (%)
Skin and subcutaneous tissue disorders	**49 (28.2)**	**192 (25.1)**	**63 (21.4)**	**9 (13.6)**	**52 (28.3)**	**177 (22.5)**	**62 (23.4)**	**11 (19.0)**
Alopecia	37 (21.3)	140 (18.3)	45 (15.3)	5 (7.6)	37 (20.1)	119 (15.1)	39 (14.7)	9 (15.5)
Metabolism and nutrition disorders	**33 (19.0)**	**173 (22.6)**	**87 (29.5)**	**15 (22.7)**	**32 (17.4)**	**177 (22.5)**	**76 (28.7)**	**20 (34.5)**
Decreased appetite	19 (10.9)	96 (12.5)	48 (16.3)	9 (13.6)	21 (11.4)	99 (12.6)	45 (17.0)	9 (15.5)
Dehydration	8 (4.6)	37 (4.8)	26 (8.8)	5 (7.6)	3 (1.6)	26 (3.3)	22 (8.3)	6 (10.3)
Respiratory, thoracic and mediastinal disorders	**25 (14.4)**	**123 (16.1)**	**58 (19.7)**	**13 (19.7)**	**26 (14.1)**	**131 (16.6)**	**66 (24.9)**	**20 (34.5)**
Dyspnoea	3 (1.7)	26 (3.4)	14 (4.7)	3 (4.5)	4 (2.2)	35 (4.4)	12 (4.5)	7 (12.1)
Musculoskeletal and connective tissue disorders	**29 (16.7)**	**111 (14.5)**	**56 (19.0)**	**20 (30.3)**	**25 (13.6)**	**121 (15.4)**	**43 (16.2)**	**9 (15.5)**
Vascular disorders	**13 (7.5)**	**77 (10.1)**	**33 (11.2)**	**10 (15.2)**	**15 (8.2)**	**78 (9.9)**	**30 (11.3)**	**9 (15.5)**
Hypotension	1 (0.6)	19 (2.5)	9 (3.1)	0	2 (1.1)	14 (1.8)	10 (3.8)	6 (10.3)
Investigations	**13 (7.5)**	**75 (9.8)**	**37 (12.5)**	**9 (13.6)**	**11 (6.0)**	**74 (9.4)**	**34 (12.8)**	**9 (15.5)**
Psychiatric disorders	**13 (7.5)**	**71 (9.3)**	**33 (11.2)**	**6 (9.1)**	**14 (7.6)**	**61 (7.8)**	**19 (7.2)**	**7 (12.1)**
Renal and urinary disorders	**7 (4.0)**	**37 (4.8)**	**20 (6.8)**	**7 (10.6)**	**7 (3.8)**	**38 (4.8)**	**18 (6.8)**	**4 (6.9)**
Cardiac disorders	**2 (1.1)**	**28 (3.7)**	**18 (6.1)**	**4 (6.1)**	**5 (2.7)**	**30 (3.8)**	**12 (4.5)**	**6 (10.3)**

Note: This table includes all SOCs and PTs that were reported in ≥10% of subjects in any group; for SOCs that did not have PTs that met this threshold, only the SOC is listed.

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However, many of these TEAEs did not occur at a higher rate in the older age group when the age used as the cutpoint for comparisons was 65 years and older. The applicant was asked to submit the same summary of TEAEs using only the age of 65 as a cutpoint for subgroup analyses, i.e., <65 years of age vs. ≥65 years of age. The TEAEs in the following table occurred in ≥1% in the age ≥65 years subgroup and exceed both the <65 year rate and the ≥65 years subgroup in the control arm by 1%. The percentage not enclosed by parentheses in the table correspond to the percentages for overall cycles in the pooled phase 3 and phase 2 dose ranging trials. The percentages in parentheses correspond to Cycle 1 only, and only appear if the same criteria were met (rate of ≥1% and exceeds each of the other subgroups by 1%). As can be seen there are no marked differences in rates between the subgroup ≥65 years of age treated with rolapitant and those younger than 65 years in the SEAEs listed below that would indicate rolapitant is tolerated poorly in geriatric patients ages 65 years and older. When compared to the summary data above for the ≥75 years subgroup, the overlapping TEAEs that were noted to occur at a higher rate than the younger age groups and control between the ≥75 year old and ≥65 year old subgroups were: diarrhea, anemia, dizziness and hypotension. In each of those TEAEs, the rates were higher in the rolapitant treated patients that were ≥75 years of age than in those that were ≥65 years of age. However, the very small sample size of the ≥75 year old subgroup relative to the other subgroups makes it difficult to conclude that these observed differences in the more advanced age group are secondary to rolapitant.

Table 16. TEAEs in which the proportions where higher in the rolapitant arm ≥65 years subgroup than in the rolapitant arm <65 years subgroup AND the control arm subgroup ≥65 years

TEAE	Rolapitant	Rolapitant	Control arm
	≥ 65 years	<65 years	≥ 65 years
	N=323	N=971	N=361
	Overall cycles % (Cycle 1 %)		
Anemia	14.2% (5%)	9.3% (2.5%)	9.1% (3.6%)
Abdominal Pain	(3.4%)	(2.6%)	(1.9%)
Abdominal Pain, upper	(2.8%)	(0.9%)	(1.1%)
Diarrhea	16.4%	11.4%	14.4%
Fatigue	23.5%	18.5%	19.4%
Candidiasis	2.2% (1.9%)	1.1% (0.7%)	1.1% (0.3%)
Hypomagnesemia	7.7%	4.6%	5.3%
Hyperglycemia	2.2%	1.1%	1.1%
Hypocalcemia	1.5%	0.5%	0
Dizziness	9.0% (5.6%)	7.0% (4.4%)	6.6% (2.8%)
Hypoaesthesia	2.8%	0.9%	0.8%
Dyspnoea	5.9%	4.0%	4.7%
Epistaxis	3.1% (1.5%)	0.4% (0.1%)	1.9% (0.0%)
Deep Vein thrombosis	1.9%	0.5%	0.3%
Hypotension	5.0% (2.2%)	1.6% (0.7%)	2.5% (1.1%)

Race. The following table, reproduced from the Clinical Addendum review, summarizes the TEAEs by race and by study arm (control vs. rolapitant). The vast majority of subjects were white. Only 64 patients were Black, of which 35 were treated with rolapitant. I concur with the Clinical reviewer that it is difficult to draw any conclusion regarding relative safety of rolapitant based on race, given this very low sample size. TEAEs in which the observed rate was numerically higher in the small subset of Black subjects treated with rolapitant compared to White subjects treated with rolapitant AND in which the difference between groups exceeded the difference between those two race subgroups in the control arm included: diarrhea, dyspepsia, abdominal pain, stomatitis, neutropenia, leukopenia, headache, dizziness and bone pain. The deltas between the differences observed between races in the rolapitant on control group ranged 6-32%. In contrast, the rates of TEAEs in the numerically larger Other subgroup and White subgroup treated with rolapitant were similar between subgroups.

Table 17. TEAEs by Race and Rolapitant Dose Group (≥10% of Subjects in Any Subgroup), All Cycles Combined – Subject Incidence, Pooled Phase 3 and Phase 2 trials

System Organ Class Preferred Term	Overall CINV					
	Control			Rolapitant 200 mg		
	White (N = 966) n (%)	Black/African American (N = 35) n (%)	Other (N = 300) n (%)	White (N = 968) n (%)	Black/African American (N = 29) n (%)	Other (N = 297) n (%)
Subjects with ≥1 Incidence	*764 (79.1)*	*33 (94.3)*	*256 (85.3)*	*778 (80.4)*	*27 (93.1)*	*250 (84.2)*
General disorders and administration site conditions	**389 (40.3)**	**20 (57.1)**	**114 (38.0)**	**396 (40.9)**	**14 (48.3)**	**114 (38.4)**
Fatigue	198 (20.5)	17 (48.6)	38 (12.7)	188 (19.4)	11 (37.9)	57 (19.2)
Asthenia	151 (15.6)	2 (5.7)	37 (12.3)	147 (15.2)	1 (3.4)	34 (11.4)
Gastrointestinal disorders	**428 (44.3)**	**22 (62.9)**	**139 (46.3)**	**388 (40.1)**	**22 (75.9)**	**153 (51.5)**
Diarrhoea	120 (12.4)	6 (17.1)	34 (11.3)	121 (12.5)	4 (13.8)	39 (13.1)
Constipation	154 (15.9)	8 (22.9)	53 (17.7)	116 (12.0)	12 (41.4)	58 (19.5)
Nausea	150 (15.5)	9 (25.7)	42 (14.0)	114 (11.8)	4 (13.8)	33 (11.1)
Dyspepsia	51 (5.3)	1 (2.9)	19 (6.3)	55 (5.7)	4 (13.8)	20 (6.7)
Abdominal pain	43 (4.5)	2 (5.7)	11 (3.7)	48 (5.0)	4 (13.8)	12 (4.0)
Stomatitis	59 (6.1)	4 (11.4)	13 (4.3)	38 (3.9)	5 (17.2)	26 (8.8)
Vomiting	82 (8.5)	5 (14.3)	30 (10.0)	32 (3.3)	0	18 (6.1)
Blood and lymphatic system disorders	**245 (25.4)**	**14 (40.0)**	**62 (20.7)**	**290 (30.0)**	**11 (37.9)**	**56 (18.9)**
Neutropenia	138 (14.3)	7 (20.0)	28 (9.3)	159 (16.4)	9 (31.0)	29 (9.8)
Anaemia	89 (9.2)	7 (20.0)	17 (5.7)	112 (11.6)	7 (24.1)	17 (5.7)
Leukopenia	59 (6.1)	4 (11.4)	9 (3.0)	62 (6.4)	5 (17.2)	8 (2.7)
Febrile neutropenia	29 (3.0)	4 (11.4)	16 (5.3)	30 (3.1)	1 (3.4)	11 (3.7)
Nervous system disorders	**244 (25.3)**	**14 (40.0)**	**61 (20.3)**	**238 (24.6)**	**12 (41.4)**	**75 (25.3)**
Headache	111 (11.5)	7 (20.0)	25 (8.3)	80 (8.3)	8 (27.6)	27 (9.1)
Dizziness	61 (6.3)	5 (14.3)	25 (8.3)	60 (6.2)	6 (20.7)	31 (10.4)
Dysgeusia	42 (4.3)	6 (17.1)	3 (1.0)	36 (3.7)	6 (20.7)	8 (2.7)
Skin and subcutaneous tissue disorders	**248 (25.7)**	**11 (31.4)**	**54 (18.0)**	**234 (24.2)**	**11 (37.9)**	**57 (19.2)**
Alopecia	183 (18.9)	8 (22.9)	36 (12.0)	160 (16.5)	6 (20.7)	38 (12.8)
Infections and infestations	**180 (18.6)**	**12 (34.3)**	**56 (18.7)**	**226 (23.3)**	**11 (37.9)**	**58 (19.5)**
Urinary tract infection	52 (5.4)	7 (20.0)	10 (3.3)	58 (6.0)	3 (10.3)	15 (5.1)
Upper respiratory tract infection	11 (1.1)	4 (11.4)	10 (3.3)	18 (1.9)	2 (6.9)	5 (1.7)
Metabolism and nutrition disorders	**195 (20.2)**	**19 (54.3)**	**94 (31.3)**	**213 (22.0)**	**10 (34.5)**	**82 (27.6)**
Decreased appetite	98 (10.1)	10 (28.6)	64 (21.3)	116 (12.0)	4 (13.8)	54 (18.2)
Hypomagnesaemia	42 (4.3)	6 (17.1)	6 (2.0)	52 (5.4)	4 (13.8)	14 (4.7)
Dehydration	60 (6.2)	7 (20.0)	9 (3.0)	49 (5.1)	1 (3.4)	7 (2.4)
Hypokalaemia	35 (3.6)	6 (17.1)	6 (2.0)	30 (3.1)	3 (10.3)	7 (2.4)
Respiratory, thoracic and mediastinal disorders	**160 (16.6)**	**12 (34.3)**	**47 (15.7)**	**187 (19.3)**	**9 (31.0)**	**47 (15.8)**
Dyspnoea	37 (3.8)	4 (11.4)	5 (1.7)	45 (4.6)	4 (13.8)	9 (3.0)
Musculoskeletal and connective tissue disorders	**161 (16.7)**	**12 (34.3)**	**43 (14.3)**	**147 (15.2)**	**13 (44.8)**	**38 (12.8)**
Arthralgia	32 (3.3)	3 (8.6)	9 (3.0)	24 (2.5)	3 (10.3)	6 (2.0)
Bone pain	43 (4.5)	1 (2.9)	8 (2.7)	39 (4.0)	4 (13.8)	3 (1.0)

Summary. I concur with the Clinical Reviewer's conclusion that there were no safety issues identified in the NDA review that preclude approval or warrant further evaluation post approval. She did not recommend any safety PMRs or PMCs, and I concur that none are warranted at this time.

9. Advisory Committee Meeting

There was no advisory committee meeting held to discuss this NDA. This is the third drug approved in this class. There were no significant public health questions that required the input of the committee or outside expertise.

10. Pediatrics

This NDA triggered PREA. The applicant submitted an iPSP prior to NDA submission, and the agreed upon iPSP was filed by FDA on September 4, 2014. Pediatric studies will be deferred for patients birth to 17 years of age because the product is ready for approval for use in adults and the pediatric studies have not been completed. The iPSP was presented to PeRC prior to filing the agreed upon iPSP and the plan was presented to PeRC again on April 29, 2015, during the course of the NDA review. PeRC agreed with the plan for deferral of pediatric studies. The approval letter will include the following PMRs to address PREA:

2879-1 A GLP toxicology study in juvenile rats.

Final Report Submission: 1/30/2017

2879-2 A dose-ranging study assessing the pharmacokinetics, safety, tolerability, and effectiveness of Varubi (rolapitant) in pediatric patients ages 0-17 years old

Final Protocol Submission: 2/28/2017
Study Completion: 7/31/2020
Final Report Submission: 11/30/2020

2879-3 A study to evaluate the efficacy and safety of a single oral dose of Varubi (rolapitant) in pediatric patients ages 0-17 years old.

Final Protocol Submission: 11/30/2020
Study Completion: 04/30/2026
Final Report Submission: 08/30/2026

The Division of Pediatric and Maternal Health participated in labeling meetings and their recommendations are reflected in final labeling. Section 8.4 Pediatrics will state, "Safety and efficacy of Varubi have not been established in pediatric patients." The Maternal Health team revised the proposed labeling in Sections 8.1 Pregnancy and 8.2 Lactation, so that it was updated to comply with the Pregnancy and Lactation Labeling Rule (PLLR). They noted that a

review of published literature did not reveal any use of rolapitant in pregnant or lactating women. There were two women who became pregnant during phase 2 studies of rolapitant, and the pregnancies were "unremarkable". There was no information available on a patient who became pregnant in a phase 1 trial. She received a high dose of rolapitant (800 mg). The pregnancy outcome information on this pregnancy was not available at the time the Maternal Health Team reviewer filed her review. The applicant's attempts to obtain follow-up information on this pregnancy during the course of the review clock were unsuccessful. The subject had moved and no forwarding address could be identified.

Postnatal rat studies have detected the presence of rolapitant in milk from lactating rats. The Maternal Health team noted the drug's low molecular weight, high volume of distribution in humans and long half-life suggest that it may be present in human breast milk. However, no serious potential risks to the breastfed infant were identified. For this reason the Maternal Health team recommended that product labeling state:

> "The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VARUBI and any potential adverse effects on the breastfed infant from VARUBI or from the underlying maternal condition or the use of concomitant chemotherapy."

The Maternal Health team consult recommended including language regarding waiver of Pregnancy, Labor and Delivery, and Nursing Mothers subsections of product labeling in the approval letter; however, in a follow-up email, the team leader clarified that the language is not necessary because the final approved label complies with the Pregnancy and Lactation Labeling Rule, which became effective on June 30, 2015.

(b) (4)

11. Other Relevant Regulatory Issues

Controlled Substance Staff (CSS). CSS was consulted to evaluate abuse-related nonclinical and clinical data, as rolapitant is active in the CNS. They concluded there were no signals of abuse or withdrawal in primate self-administration and physical dependence studies. Limitations in the clinical data for assessing abuse potential precluded conclusions based on the human data. (The applicant did not evaluate for physical dependence or withdrawal symptoms.) Two other drugs in the class have been approved without scheduling. CSS concluded rolapitant should not be recommended for scheduling. (b) (4)

The review team determined that a PMC or PMR was

not necessary to address this recommendation because the drug is administered as a single dose no more frequently than every two weeks. The team considered whether the drug's long half-life in the context of q 2 week dosing should impact this decision, but the Clinical Pharmacology reviewers stated that accumulation would not be expected on the q two week schedule and the clinical reviewers noted that q two week dosing would be expected to be the least common dosing schedule used in the clinical setting. The applicant reported that only 59 patients in their clinical trials were treated on a q 2 week schedule, which confirms that this is expected to be an uncommon treatment schedule.

OSI investigated nine clinical investigation sites and the applicant. They determined that data from all clinical sites were reliable and the sponsor had adequately fulfilled its responsibilities. There were a number of protocol violations across 3 sites (involving the phase 2 dose finding trial, the phase 3 HEC trial and the phase 3 MEC trial), which were related to not administering rolapitant/placebo at the protocol specified time 1-2 hours before cisplatin or not administering dexamethasone 30 minutes prior. These violations are summarized below:

- In the phase 2 dose ranging trial, the site inspected had administered rolapitant 4.5 hours prior to cisplatin in 6/15 subjects and 7 hours prior in 4/15 subjects (b) (4)
- In one of the phase 3 HEC trials, 4 subjects treated on the rolapitant arm at one site did not receive the drug 1-2 hours before cisplatin or did not receive dexamethasone at the correct time, i.e., 30 minutes prior to rolapitant. Review of the line listings for these patients revealed one patient received docetaxel 3 hours before their cisplatin dose, and received their 5HT3 antagonist and dexamethasone before the docetaxel dose (b) (4) The other 3 patients received their 5HT3 antagonist and dexamethasone more than 30 minutes before cisplatin, (b) (4) In addition, one of the patients received their rolapitant dose less than an hour prior to cisplatin.
- In the other phase 3 HEC trial, the events referred to as rolapitant administration timing violations were related to administering docetaxel prior to cisplatin administration instead after cisplatin, similar to the findings in the site inspection above; however, in this study only the dexamethasone was administered prior to the docetaxel. The 5HT3 antagonist and rolapitant were administered at the correct time prior to cisplatin. This impacted one placebo arm patient and three rolapitant arm patients.

The OSI reviewer stated the test article administration in these cases "appears to have been accurately captured in the data listings submitted to the NDA, so this data is considered reliable."

The OSI inspection of the applicant involved evaluation of its compliance with sponsor responsibilities for the three phase 3 trials, which were conducted by Tesaro as the sponsor, and the phase 2 dose ranging trial, which was conducted by Schering-Plough from October 2006 to March 2008, prior to Tesaro acquiring rights to the study. Merck subsequently purchased Schering, and the FTC required Merck to divest the IND because Merck had a similar IND. Although OSI determined the applicant had fulfilled its responsibilities in the conduct of the trials, a Form FDA 483 was issued because the sponsor had not promptly brought clinical investigators in compliance. However, this only involved two sites and a total of 8 subjects.

As stated in Section 7 Efficacy, the applicant proposed that the FDA should consider the phase 2 dose ranging trial an adequate and well controlled trial (b) (4) The trial was not conducted by the applicant and there were questions raised by the FDA Statistical reviewers regarding the adequacy of blinding of the trial's interim analysis. The NDA did not provide adequate documentation regarding the actions taken by the trial's sponsor's statisticians to assure adequate blinding. OSI sought this documentation during the inspection of the applicant; however, the applicant was unable to provide the confidentiality agreements during the inspection. Instead, the applicant provided a notarized statement from the Independent Statistician who conducted the interim analysis stating that the interim results were not shared with other study personnel.

Financial Disclosures: The Clinical Reviewer evaluated the information that the applicant submitted to address financial disclosures. She stated in her review that there were no investigators with disclosable financial interests/arrangements, including employment by the sponsor.

12. Labeling

OPDP, DMEPA and DMPP (patient labeling) reviewed the proposed labeling and their recommendations were addressed during labeling negotiations. DMEPA informed the applicant that their proposed proprietary name, Varubi, was conditionally acceptable in correspondence dated March 31, 2015. The proprietary name remains acceptable and approved labeling will include this proprietary name.

Section 12.2 Pharmacodynamics: The applicant proposed inclusion of the following statement, "At the 180 mg dose of rolapitant, the mean NK_1 receptor occupancy was 73% in the striatum (b) (4) at 120 hours after a single dose administration in healthy subjects." The Clinical Pharmacology and Clinical reviewers did not agree with inclusion of the receptor occupancy (b) (4), as they could not identify evidence that established that (b) (4) in delayed phase chemotherapy induced nausea and vomiting.

See previous Sections of this review for summary comments regarding other labeling review issues. The label will include a Patient Package Insert. A Medication Guide is not necessary as there were no safety issues identified that warranted a Medication Guide.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action - Approval

- Risk Benefit Assessment – The applicant has established that rolapitant is effective in prevention of delayed phase CINV, including in the setting cisplatin chemotherapy, when administered in a combination antiemetic regimen with a 5HT3 antagonist and dexamethasone. No safety issues were identified that preclude approval, and the risk benefit assessment supports approval of this indication. There are two other approved NK-1 inhibitors, and both are available in an oral dosage form, similar to rolapitant. Like rolapitant, one of those products, Akynzeo, only requires a single dose each cycle of chemotherapy; however, it is a fixed combination with the 5HT3 antagonist palonosetron, which eliminates the ability to individualize the 5HT3 antagonist used in the overall antiemetic regimen according to a patient's need (e.g., if a patient is hypersensitive to palonosetron). The other NK-1 inhibitor's oral dose regimen (Emend) requires daily dosing x 3. (b) (4)

(b) (4)

  There are some key differences in drug drug interactions among the products, which could influence which one is selected for individual patients, based on a patient's concomitant medication use. Unlike the other two NK-1 inhibitors, rolapitant is not a CYP3A4 inhibitor, and does not require dose reduction of dexamethasone in the combination regimen. Unlike Emend, rolapitant and Akynzeo are not CYP3A4 inducers, so they are less likely than Emend to increase levels of the active metabolite of ifosfamide that causes neurotoxicity. However, rolapitant is a CYP2D6 inhibitor, and its long half-life has been shown to result in prolonged drug interactions, which persist at least a week after administration. This is an important interaction which must be considered in patients who are taking concomitant medications that are CYP2D6 substrates and have significant toxicities with increased exposures (e.g., arrhythmias). In addition, rolapitant is an inhibitor of the p-GP transporter. Clinical data from rolapitant's co-administration with digoxin revealed increased digoxin exposure. The label recommends monitoring digoxin levels if rolapitant is administered with digoxin. The labels of both Akynzeo and Emend state that those drugs have been shown not to significantly impact digoxin levels. Rolapitant's product labeling addresses the safety and efficacy issues associated with these drug drug interactions.
- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies – None.

- Recommendation for other Postmarketing Requirements and Commitments

See Section 5 for the PMCs recommended by the Clinical Pharmacology reviewer, which will be included in the approval letter. In addition, see Section 10 Pediatrics for the PREA PMRs that will appear in the approval letter.

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/s/

DONNA J GRIEBEL
09/01/2015