

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**206500Orig1s000**

**MEDICAL REVIEW(S)**

# DIVISION OF GASTROENTEROLOGY AND INBORN ERRORS PRODUCTS

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## NDA 206,500 Clinical Addendum

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This document provides an addendum to the original Clinical Review of NDA 206,500 finalized in DARRTS on May 12, 2015

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## Rolapitant Clinical Review Addendum

The purpose of this clinical addendum to the Rolapitant Clinical NDA 206,500 review entered in DARRTS on May 12, 2015 is to correct errors in the original review and address answers to Information Requests received from the Applicant since the review was entered in DARRTS.

### 1. Correction to Section 7.4.2 in the original Review

#### **Excerpt from Original Review (with error strikeout and addition double underline)**

In the rolapitant program five cases met Hy's Law criteria. Four cases occurred in patients taking control. One case occurred in a patient in Study 51 taking rolapitant 10 mg. In this patient, Hy's Law criteria were first met at Cycle 1/Visit 2. The elevations resolved by the next Visit. The patient went on to receive rolapitant for three additional cycles and lab elevations did not ~~resolve~~ recur.

#### *MO Comment:*

*The lab elevations that met Hy's Law criteria did not recur after Cyce 1/Visit 2.*

### 2. Correction and addition to Section 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects in the original Review

#### **Excerpt from Original Review (with error strikeout and addition double underline)**

The confirmatory studies support the efficacy of Rolapitant 200mg for the prevention of CINV in the delayed phase (>24-120 hours post chemotherapy). (b) (4)

While the primary and key secondary endpoints for rolapitant were based on the first cycle of chemotherapy, the primary rolapitant studies included up to a total of six cycles of chemotherapy including up to six doses of rolapitant. In cycles 2-6, the efficacy was measured using a different endpoint than the complete response endpoint (no emesis, no use of rescue medication) used in the confirmatory phase 3 trials. For Cycles 2-6, efficacy was evaluated by asking patients on Visit 2 (Days 6-8) whether, since the start of the chemotherapy cycle, they had any episode of vomiting or retching or any nausea that interfered with their normal daily life. Also, patients were not re-randomized after cycle 1. Efficacy results in Cycles 2-6, while measured differently than in cycle 1, provide supportive evidence of the persistence of the activity of rolapitant for the prevention of CINV and no tolerance effects associated with the use of rolapitant. Regarding safety, the incidence of TEAEs did not increase with repeat exposure to rolapitant over multiple cycles. In fact, the incidence of TEAEs decreased with successive cycles. See Table in 3b below.

#### *MO Comment:*

Patient recall for events of nausea that occurred 5-7 days prior is not the ideal way to collect such data. Further, it would have been preferable to measure efficacy in Cycles 2-6 in using the same primary endpoint definition of complete response used in the confirmatory trials. Given

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*these limitations in interpreting the efficacy data in cycles 2-6, I recommend that Section 14 of the label discuss the “activity”* (b) (4)

3. Information Request Response Received May 14, 2015, Submission 022

a. **Agency Request**

Please provide an analysis comparing the rate of rescue medication use vs. responder rates based only on VAS <25 (no significant nausea) and VAS<5 (no nausea).

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**Applicant Response****Table 1: Proportion of Patients using Rescue Medication**

	Overall CINV Phase (0-120h)		
Study P04832	VAS<5 (No Nausea)	VAS<25 (No Significant Nausea)	Overall (Any VAS)
Rolapitant	3 / 131 (2.3 )	12 / 189 (6.3 )	46 / 264 (17.4 )
Control	0 / 103 (0.0 )	14 / 165 (8.5 )	71 / 262 (27.1 )
Total	3 / 234 (1.3 )	26 / 354 (7.3 )	117 / 526 (22.2 )
Study P04833			
Rolapitant	4 / 149 (2.7 )	12 / 197 (6.1 )	51 / 271 (18.8 )
Control	3 / 120 (2.5 )	15 / 185 (8.1 )	70 / 273 (25.6 )
Total	7 / 269 (2.6 )	27 / 382 (7.1 )	121 / 544 (22.2 )
Study P04832/P04833			
Rolapitant	7 / 280 (2.5 )	24 / 386 (6.2 )	97 / 535 (18.1 )
Control	3 / 223 (1.3 )	29 / 350 (8.3 )	141 / 535 (26.4 )
Total	10 / 503 (2.0 )	53 / 736 (7.2 )	238 / 1070 (22.2 )
Study P04834			
Rolapitant	7 / 303 (2.3 )	39 / 470 (8.3 )	148 / 666 (22.2 )
Control	18 / 280 (6.4 )	48 / 443 (10.8 )	195 / 666 (29.3 )
Total	25 / 583 (4.3 )	87 / 913 (9.5 )	343 / 1332 (25.8 )

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**MO Comment:**

*Complete Response (CR) was defined as no use of rescue medication and no emesis. In the rolapitant clinical program, nausea was measured using a visual analog scale (VAS) where a VAS score of <5 was consistent with no nausea and a VAS score of <25 was consistent with no significant nausea. The results of the IR show that for patients with no nausea and no significant nausea, the use of rescue medication was low in rolapitant and control groups. These results support the use of a complete response definition that includes only emesis and rescue medication use as this definition is adequate to determine how effectively rolapitant controls nausea.*

**b. Agency Request**

Please provide the incidence of TEAEs by Cycle for patients in Pooling Group 1.

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## Applicant Response

Table 13 Overview of TEAEs by Cycle, Overall CINV Pooling Group 1						
	Cycle 1 n (%)	Cycle 2 n (%)	Cycle 3 n (%)	Cycle 4 n (%)	Cycle 5 n (%)	Cycle 6 n (%)
<b>Total No. of Subjects</b>						
Control	1301	998	834	695	365	314
200 mg Rolapitant	1294	1011	837	685	381	319
All Rolapitant [1]	1567	1198	983	781	439	367
<b>No. of Subjects with &gt;=1 AE</b>						
Control	840(64.6)	565(56.6)	416(49.9)	311(44.7)	143(39.2)	106(33.8)
200 mg Rolapitant	828(64.0)	566(56.0)	405(48.4)	299(43.6)	158(41.5)	87(27.3)
All Rolapitant	1021(65.2)	681(56.8)	498(50.7)	363(46.5)	204(46.5)	121(33.0)
<b>No. of Subjects with &gt;=1 Treatment-Related AE[2]</b>						
Control	82( 6.3)	38( 3.8)	27( 3.2)	27( 3.9)	6( 1.6)	2( 0.6)
200 mg Rolapitant	90( 7.0)	33( 3.3)	35( 4.2)	15( 2.2)	10( 2.6)	4( 1.3)
All Rolapitant	135( 8.6)	44( 3.7)	37( 3.8)	17( 2.2)	12( 2.7)	6( 1.6)
<b>No. of Subjects with an AE Leading to Study Drug Discontinuation</b>						
Control	48( 3.7)	29( 2.9)	19( 2.3)	9( 1.3)	8( 2.2)	0
200 mg Rolapitant	40( 3.1)	32( 3.2)	21( 2.5)	6( 0.9)	7( 1.8)	0
All Rolapitant	49( 3.1)	39( 3.3)	24( 2.4)	10( 1.3)	8( 1.8)	0
<b>No. of Subjects with &gt;=1 AE of CTC Grade 3+[3]</b>						
Control	214(16.4)	121(12.1)	86(10.3)	63( 9.1)	37(10.1)	25( 8.0)
200 mg Rolapitant	211(16.3)	118(11.7)	92(11.0)	74(10.8)	49(12.9)	20( 6.3)
All Rolapitant	262(16.7)	153(12.8)	119(12.1)	90(11.5)	59(13.4)	31( 8.4)
<b>No. of Subjects with &gt;=1 Serious AE(SAE)</b>						
Control	126( 9.7)	54( 5.4)	42( 5.0)	24( 3.5)	17( 4.7)	13( 4.1)
200 mg Rolapitant	102( 7.9)	67( 6.6)	40( 4.8)	28( 4.1)	15( 3.9)	7( 2.2)
All Rolapitant	133( 8.5)	82( 6.8)	51( 5.2)	38( 4.9)	18( 4.1)	12( 3.3)
<b>No. of Subjects with &gt;=1 Treatment-Related SAE</b>						
Control	0	0	0	0	0	0
200 mg Rolapitant	0	0	2( 0.2)	0	0	0
All Rolapitant	3( 0.2)	0	2( 0.2)	0	0	0
<b>No. of Subjects with AE Outcome of Death</b>						
Control	15( 1.2)	5( 0.5)	7( 0.8)	3( 0.4)	1( 0.3)	0
200 mg Rolapitant	21( 1.6)	10( 1.0)	3( 0.4)	1( 0.1)	3( 0.8)	0
All Rolapitant	24( 1.5)	13( 1.1)	5( 0.5)	2( 0.3)	4( 0.9)	0
<b>No. of Subjects with Treatment-Related AE Outcome of Death</b>						
Control	0	0	0	0	0	0
200 mg Rolapitant	0	0	0	0	0	0
All Rolapitant	0	0	0	0	0	0

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

[2] Any AE that is possibly, probably, or definitely related to Study Drug according to AE CRF.

[3] NCI Common Toxicity Criteria.

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**MO Comment:**

*Overall, the incidence of TEAEs was highest during the first cycle and reduced with successive cycles. This trend is not unexpected given that in cycle 1, patients were naïve to many drugs including chemotherapy. These results provide data to show that repeat dosing of rolapitant separated by at least 14 days is not associated with an increased incidence of TEAEs.*

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**c. Agency Request**

Given that the cycle lengths varied (and therefore, the interval of time between rolapitant dosing), please provide an assessment of TEAEs by rolapitant dosing interval. Please use cut-offs of 2 weeks, 3 weeks, and 4 weeks. Please provide information for both rolapitant and control patients in Pooling Group 1.

Applicant Response

The Sponsor Submitted, Table 94 (first row excerpt below).

System Organ Class Preferred Term	Overall CINV					
	<21 days (N=119) n (%)	Control 21 - <28 days (N=742) n (%)	>=28 days (N=138) n (%)	<21 days (N=135) n (%)	Rolapitant 200 mg 21 - <28 days (N=730) n (%)	>=28 days (N=147) n (%)
Subjects with >=1 Incidence	96 (80.7)	532 (71.7)	107 (77.5)	109 (80.7)	532 (72.9)	115 (78.2)

**MO Comment:**

*Incidence of TEAEs did not show a trend by cycle length for either the control or rolapitant groups. These results provide evidence that a shorter rolapitant dosing interval is not associated with a higher rate of TEAEs. Overall, the incidence of TEAEs by dosing interval was similar in the control and rolapitant groups.*

**d. Agency Request**

Please provide an assessment of patients in each treatment group (Pooling Group 1) with the following:

- i. AST >3xULN
- ii. AST 5xULN
- iii. AST >10xULN
- iv. Tbili >2xULN

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**Table 2: Proportion of Patients with Select Laboratory Tests by Cycles and All Cycles Combined**

	Pooling Group 1 (All Studies)		
Cycle 1	Control	200mg	Rolapitant[1]
Parameter, n(%)	(N=1301)	(N=1294)	(N=1567)
AST>3 xULN	17( 1.3)	18( 1.4)	21( 1.3)
AST>5 xULN	1(<0.1)	3( 0.2)	4( 0.3)
AST>10 xULN	0	0	0
TBILI>2.0 xULN	16( 1.2)	12( 0.9)	16( 1.0)
Cycle 2	Control	200mg	Rolapitant[1]
Parameter, n(%)	(N=998)	(N=1011)	(N=1198)
AST>3 xULN	11( 1.1)	8( 0.8)	9( 0.8)
AST>5 xULN	0	1(<0.1)	2( 0.2)
AST>10 xULN	0	1(<0.1)	1(<0.1)
TBILI>2.0 xULN	4( 0.4)	7( 0.7)	8( 0.7)
Cycle 3	Control	200mg	Rolapitant[1]
Parameter, n(%)	(N=834)	(N=837)	(N=983)
AST>3 xULN	5( 0.6)	8( 1.0)	9( 0.9)
AST>5 xULN	1( 0.1)	4( 0.5)	5( 0.5)
AST>10 xULN	0	0	0
TBILI>2.0 xULN	6( 0.7)	4( 0.5)	4( 0.4)
Cycle 4	Control	200mg	Rolapitant[1]
Parameter, n(%)	(N=695)	(N=685)	(N=781)
AST>3 xULN	5( 0.7)	2( 0.3)	2( 0.3)
AST>5 xULN	1( 0.1)	0	0
AST>10 xULN	0	0	0
TBILI>2.0 xULN	3( 0.4)	1( 0.1)	2( 0.3)
Cycle 5	Control	200mg	Rolapitant[1]
Parameter, n(%)	(N=365)	(N=381)	(N=439)
AST>3 xULN	3( 0.8)	2( 0.5)	4( 0.9)
AST>5 xULN	2( 0.5)	1( 0.3)	1( 0.2)
AST>10 xULN	0	0	0
TBILI>2.0 xULN	2( 0.5)	3( 0.8)	4( 0.9)

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	Pooling Group 1 (All Studies)		
Cycle 6	Control	200mg	Rolapitant[1]
Parameter, n(%)	(N=314)	(N=319)	(N=367)
AST>3 xULN	3( 1.0)	1( 0.3)	2( 0.5)
AST>5 xULN	3( 1.0)	0	0
AST>10 xULN	1( 0.3)	0	0
TBILI>2.0 xULN	3( 1.0)	2( 0.6)	2( 0.5)
All Cycles Combined	Control	200mg	Rolapitant[1]
Parameter, n(%)	(N=1301)	(N=1294)	(N=1567)
AST>3 xULN	32( 2.5)	29( 2.2)	35( 2.2)
AST>5 xULN	6( 0.5)	8( 0.6)	10( 0.6)
AST>10 xULN	1(<0.1)	1(<0.1)	1(<0.1)
TBILI>2.0 xULN	28( 2.2)	24( 1.9)	30( 1.9)

[1] Subjects who received any rolapitant dose are combined.

**MO Comment:**

*The number and proportion of patients with abnormal aminotransferases and/or bilirubin was generally low and similar in rolapitant and treatment groups. There was only one rolapitant patient who met Hy's Law criteria (see #1 above).*

## 4. Information Request and Response Received May 19, 2015, Submission 023

**Agency Request**

Please provide safety analyses for chemotherapeutic agents that are substrates of BCRP or CYP2D6 used in Pooling Group 1 by drug. The safety analyses should include total TEAE, TESAEs, and a breakdown of these events by SOC and PT.

**Applicant Response**

The tables of TEAEs by chemotherapeutic agent and SOC/PT that are substrates of BCRP (docetaxel, doxorubicin, epirubicin, etoposide, fluorouracil, irinotecan, methotrexate and topotecan) and CYP2D6 (tamoxifen) used in Pooling Group 1 were provided.

**MO Comment:**

*The multiple tables of TEAEs by SOC and PT were briefly reviewed for patients taking BCRP substrate chemotherapy agents and study drug (rolapitant and control). No trend of increasing TEAE incidence was seen for patients taking BCRP substrates and rolapitant.*

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5. Information Request and Response Received July 17, 2015, Submission 030

**Agency Request**

Posterior Reversible Encephalopathy Syndrome (PRES) was seen in two rolapitant patients and no placebo patients. Each of the rolapitant patients was taking a concomitant BCRP receptor substrate—one was taking 5-FU and another was taking irinotecan.

Please provide information regarding the background rate of this syndrome in the general population, the expected rate in the cancer population, and the rate expected with 5-FU exposure and with irinotecan exposure.

Please provide information to explain how the concomitant use of rolapitant with the BCRP substrates 5-FU and irinotecan would not be expected to contribute to increased risk of this syndrome. In addition, please provide narratives for these two patients that may help identify other contributing factors.

**Applicant Response**

The Sponsor would like to clarify that there was only one subject who experienced Posterior Reversible Encephalopathy Syndrome (PRES) in the rolapitant treated group and none in the placebo group. Since this subject (1574036) received both irinotecan and fluorouracil (5-FU), this single event of PRES was captured twice (once for each agent) in the safety tables provided previously. In addition to 5-FU and irinotecan, this subject also received bevacizumab, which is associated with PRES.

The epidemiology of PRES in the general population is not well characterized, although the syndrome is associated with hypertension, eclampsia and immunosuppressive agents. In the oncology population, there are few case reports of PRES. Irinotecan and 5-FU have not been definitively linked to PRES. When PRES does occur in patients receiving these agents, it is most commonly associated with concomitant use of vascular-acting agents.

The Sponsor concluded that given that 5-FU and irinotecan are eliminated via multiple pathways including BCRP, the concomitant use of rolapitant with irinotecan and 5-FU would not be anticipated to increase the risk of PRES.

*MO Comment:*

*A single patient experienced PRES in the development program and that patient was treated with rolapitant and multiple chemotherapeutic agents. One of those agents, bevacizumab, is known to be associated with PRES (labeled in Warnings and Precautions). Therefore, it is reasonable that this event of PRES is attributable to the use of bevacizumab. In the absence of other data, a single case of PRES in a patient taking a drug known to be associated with PRES is not a safety signal that requires further investigation.*

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## 6. Information Request and Response Received August 12, 2015, Submission 033

## a. Agency Request

A Controlled Substance Staff Consult review received during the review cycle recommended the following:

- i. The label for rolapitant should (b) (4)  
(b) (4)
- ii. Rolapitant should not be recommended for scheduling under the Controlled Substances Act.
- iii. (b) (4)

(b) (4) The shortest dosing interval planned in the rolapitant phase 3 development program was 14 days. In an effort to determine the extent to which patients in the phase 3 clinical studies were dosed at 14 day intervals, we asked the Applicant to provide the proportion of patients treated with rolapitant at a 14 day dosing interval.

## Applicant Response

	Received rolapitant at 14-day ( $\pm$ 3 days) interval	Received at least 2 cycles of rolapitant	Received at least 1 cycle of rolapitant
Number of patients	59	951	1205

*MO Comment:*

(b) (4) this reviewer believes that 14 day dosing intervals (b) (4) for rolapitant given the drug's 7-day half-life. The Applicant estimates that accumulation will be ~1.3 fold if rolapitant is given every 14 days. Therefore, formal physical dependence studies are not needed at this time.

Of the 951 patients who received rolapitant in at least two cycles, only 6.2% of those patients received rolapitant at 14-day ( $\pm$ 3 days) interval. This number provides some insight into how the drug could be used in the HEC and MEC real-world populations (given that patients were treated for a variety of cancers with a variety of regimens). Currently, proposed rolapitant labeling states, "Administer BRAND NAME prior to the

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*initiation of each chemotherapy cycle, but at no less than 2 week intervals.” This labeling appears adequate at this time.*

**b. Agency Request**

Please provide any available update on the pregnancy outcome of Patient 00306, Study P04852. An initial request for an update was made in February 2015.

**Applicant Response**

At the end of July, the Sponsor was contacted [REDACTED] (b) (4) [REDACTED] that records for Study P04852 have been identified. The Sponsor plans to review these records and will provide FDA with an update. The Division requested that the Applicant complete their review and respond to provide updated information regarding the pregnancy outcome by August 21, 2015.

In a subsequent submission (#35, August 20, 2015), the Applicant provided additional information regarding the pregnancy reported in Study 52. During this single dose study, the patient received 800 mg of rolapitant and became pregnant approximately 16 days later (based on quantitative HCG testing). However, the Applicant reports that the outcome of the pregnancy is unknown. In submission #35, the Applicant details unsuccessful efforts to get follow-up information on this patient.

7. Correction and addition to Section 7.5.3 Drug-Demographic Interactions in the original Review

**Excerpt from Original Review (with error strikeout and addition double underline)**

~~No particular explorations for drug-demographic interactions related to adverse events were conducted.~~

(Note: The entire section below is an addition to the original clinical review. The section is not underlined for ease of reading.)

A review of safety analyses by sex, age, and race for patients in the rolapitant patients in Pooling Group 1 was completed.

Sex

Overall, male and female patients had similar incidence rates for TEAEs whether they were part of the control or rolapitant treatment groups. See Table below. A review of TEAEs within treatment groups by MedRA SOC and PT terms revealed that for most SOC and PT terms, there was a gender-based difference in incidence of less than 5% in both the control and treatment groups. Notable exceptions include the terms fatigue, alopecia, headache, musculoskeletal and

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connective tissue disorders, respiratory, thoracic, and mediastinal disorders, and investigations (control subgroup only). For each of these terms, except investigations, in both treatment groups, the incidence was higher in females. The consistency of these results between treatment groups provides evidence that the safety of rolapitant is similar between genders.

**TEAEs by Gender (≥10% of Subjects in Any Subgroup/Treatment Combination), Subject Incidence, Pooling Group 1, 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 (%)
<i>Subjects with ≥1 Incidence</i>	637 (81.5)	416 (80.2)	623 (80.5)	432 (83.1)
<b>Gastrointestinal disorders</b>	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)
<b>General disorders and administration site conditions</b>	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)
<b>Skin and subcutaneous tissue disorders</b>	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)
<b>Blood and lymphatic system disorders</b>	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)
<b>Nervous system disorders</b>	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)
<b>Infections and infestations</b>	167 (21.4)	81 (15.6)	186 (24.0)	109 (21.0)
<b>Metabolism and nutrition disorders</b>	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)

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 (%)
<b>Musculoskeletal and connective tissue disorders</b>	151 (19.3)	65 (12.5)	133 (17.2)	65 (12.5)
<b>Respiratory, thoracic and mediastinal disorders</b>	106 (13.6)	113 (21.8)	112 (14.5)	131 (25.2)
<b>Psychiatric disorders</b>	82 (10.5)	41 (7.9)	73 (9.4)	28 (5.4)
<b>Vascular disorders</b>	79 (10.1)	54 (10.4)	71 (9.2)	61 (11.7)
<b>Investigations</b>	58 (7.4)	76 (14.6)	63 (8.1)	65 (12.5)

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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Age

The majority of patients in Pooling Group 1 were ages 45 to 64 years old (inclusive). The fewest number of patients were in the  $\geq 75$  years age group in both the control and rolapitant groups. In all age groups, all cycles combined, the incidence of TEAEs was higher in the rolapitant than the control age groups with the exception of the  $\geq 75$  years age group (79.3% vs 89.4%, respectively). Given the relatively low number of patients, it is difficult to make conclusions based on the  $\geq 75$  years age group. In general, there were no marked differences in incidence of TEAEs seen between the age groups.

### TEAEs by Age Group and Dose Group, All Cycles Combined ( $\geq 10\%$ 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 (%)	$\geq 45$ to <65 y (N = 766) n (%)	$\geq 65$ to <75 y (N = 295) n (%)	$\geq 75$ y (N = 66) n (%)	<45 y (N = 184) n (%)	$\geq 45$ to <65 y (N = 787) n (%)	$\geq 65$ to <75 y (N = 265) n (%)	$\geq 75$ y (N = 58) n (%)
<b>Subjects with <math>\geq 1</math> Incidence</b>	141 (81.0)	606 (79.1)	247 (83.7)	59 (89.4)	153 (83.2)	628 (79.8)	228 (86.0)	46 (79.3)
<b>Gastrointestinal disorders</b>	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)
<b>General disorders and administration site conditions</b>	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)
<b>Blood and lymphatic system disorders</b>	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)
<b>Infections and infestations</b>	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)
<b>Nervous system disorders</b>	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)

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

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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#### Race

The white race group was the only one with numbers large enough to make drawing safety conclusions possible. The majority of the patients in Pooling Group 1 were white race (966 control, 968 rolapitant). There were very few black patients (35 control, 29 rolapitant). A brief review of the safety data of black patients did not reveal any striking safety differences between control and rolapitant patients. However, the small number of patients in each group makes drawing safety conclusions for black race patients difficult. The race category "other" had the second highest numbers of patients (300 control, 297 rolapitant). This group included any race other than black and white. Making safety conclusions for the separate races that make up this group is not possible given the low numbers of patients of these separate races.

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**TEAEs by Race and Rolapitant Dose Group (≥10% of Subjects in Any Subgroup),  
All Cycles Combined – Subject Incidence, Pooling Group 1**

System Organ Class Preferred Term	Overall CNV					
	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 (%)
<i>Subjects with ≥1 Incidence</i>	764 (79.1)	33 (94.3)	256 (85.3)	778 (80.4)	27 (93.1)	250 (84.2)
<b>General disorders and administration site conditions</b>	<b>389 (40.3)</b>	<b>20 (57.1)</b>	<b>114 (38.0)</b>	<b>396 (40.9)</b>	<b>14 (48.3)</b>	<b>114 (38.4)</b>
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)
<b>Gastrointestinal disorders</b>	<b>428 (44.3)</b>	<b>22 (62.9)</b>	<b>139 (46.3)</b>	<b>388 (40.1)</b>	<b>22 (75.9)</b>	<b>153 (51.5)</b>
Diarhoea	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)
<b>Blood and lymphatic system disorders</b>	<b>245 (25.4)</b>	<b>14 (40.0)</b>	<b>62 (20.7)</b>	<b>290 (30.0)</b>	<b>11 (37.9)</b>	<b>56 (18.9)</b>
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)
<b>Nervous system disorders</b>	<b>244 (25.3)</b>	<b>14 (40.0)</b>	<b>61 (20.3)</b>	<b>238 (24.6)</b>	<b>12 (41.4)</b>	<b>75 (25.3)</b>
Headache	111 (11.5)	7 (20.0)	25 (8.3)	80 (8.3)	8 (27.6)	27 (9.1)

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**TEAEs by Race and Rolapitant Dose Group (≥10% of Subjects in Any Subgroup),  
All Cycles Combined – Subject Incidence, Pooling Group 1 (cont'd)**

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 (%)
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)
<b>Skin and subcutaneous tissue disorders</b>	<b>248 (25.7)</b>	<b>11 (31.4)</b>	<b>54 (18.0)</b>	<b>234 (24.2)</b>	<b>11 (37.9)</b>	<b>57 (19.2)</b>
Alopecia	183 (18.9)	8 (22.9)	36 (12.0)	160 (16.5)	6 (20.7)	38 (12.8)
<b>Infections and infestations</b>	<b>180 (18.6)</b>	<b>12 (34.3)</b>	<b>56 (18.7)</b>	<b>226 (23.3)</b>	<b>11 (37.9)</b>	<b>58 (19.5)</b>
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)
<b>Metabolism and nutrition disorders</b>	<b>195 (20.2)</b>	<b>19 (54.3)</b>	<b>94 (31.3)</b>	<b>213 (22.0)</b>	<b>10 (34.5)</b>	<b>82 (27.6)</b>
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)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>160 (16.6)</b>	<b>12 (34.3)</b>	<b>47 (15.7)</b>	<b>187 (19.3)</b>	<b>9 (31.0)</b>	<b>47 (15.8)</b>
Dyspnoea	37 (3.8)	4 (11.4)	5 (1.7)	45 (4.6)	4 (13.8)	9 (3.0)
<b>Musculoskeletal and connective tissue disorders</b>	<b>161 (16.7)</b>	<b>12 (34.3)</b>	<b>43 (14.3)</b>	<b>147 (15.2)</b>	<b>13 (44.8)</b>	<b>38 (12.8)</b>
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)

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*MO Comment:*

*Noticeable safety differences within sex, age, and race subgroups were not identified.*

8. Information Request Response Received August 20, 2015, Submission 035

**a. Agency Request**

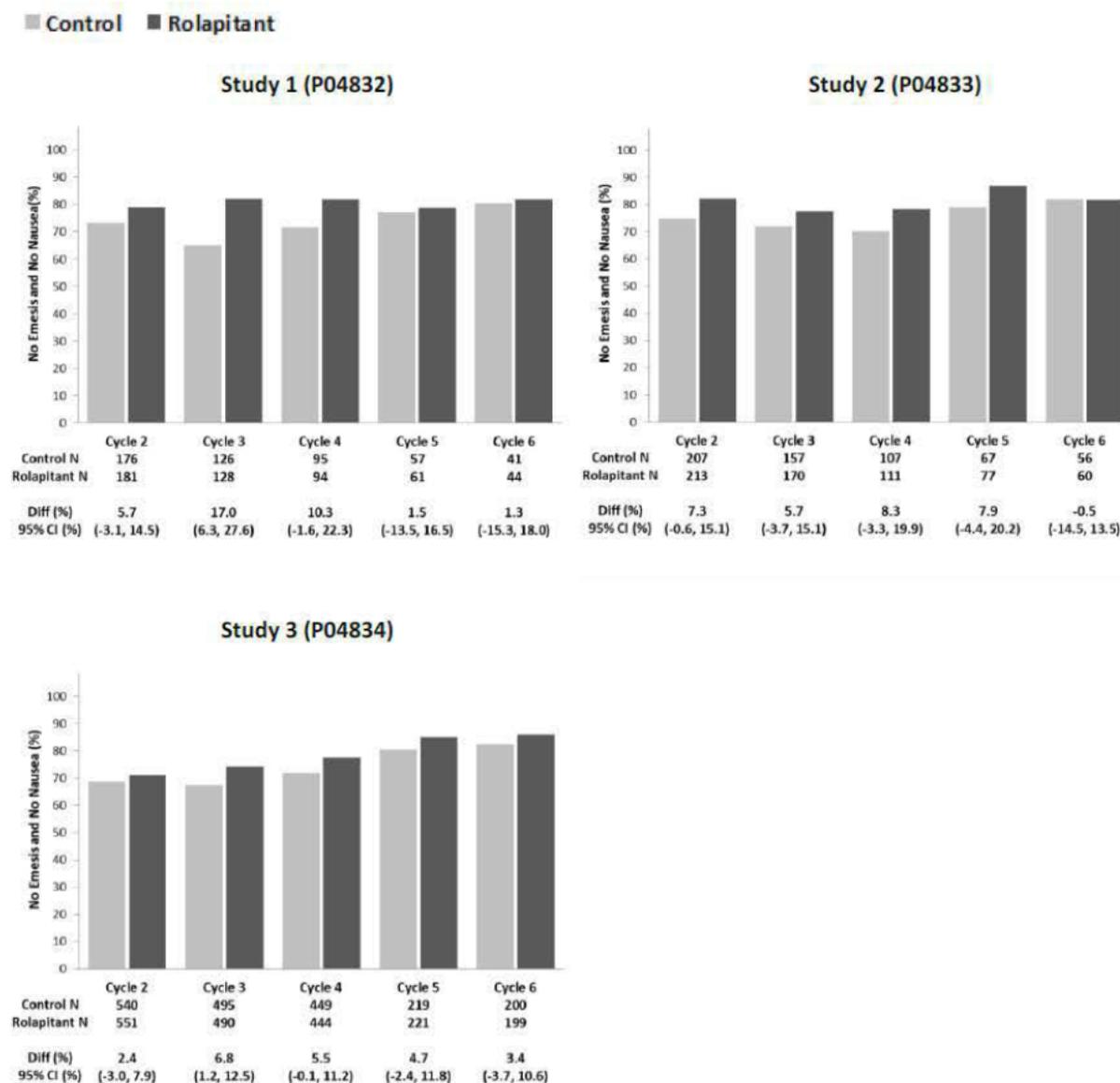
Please provide three bar graphs showing the results cycles 2 through 6 of studies 1, 2, and 3 for the proportion of patients with no vomiting/retching and no nausea that interfered with normal day activities. The graphs should include the number of patients in each treatment cycle and the confidence interval by study.

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## Applicant Response

Figure: No Emesis and No Nausea Interfering with Daily Life Over Cycles 2-6



For Cycles 2-6, efficacy was evaluated by asking patients on Visit 2 (Days 6-8) whether, since the start of the chemotherapy cycle, they had any episode of vomiting or retching or any nausea that interfered with their normal daily life (See #2 above). However, the Applicant is proposing to include (b) (4) as part of the information in the label for

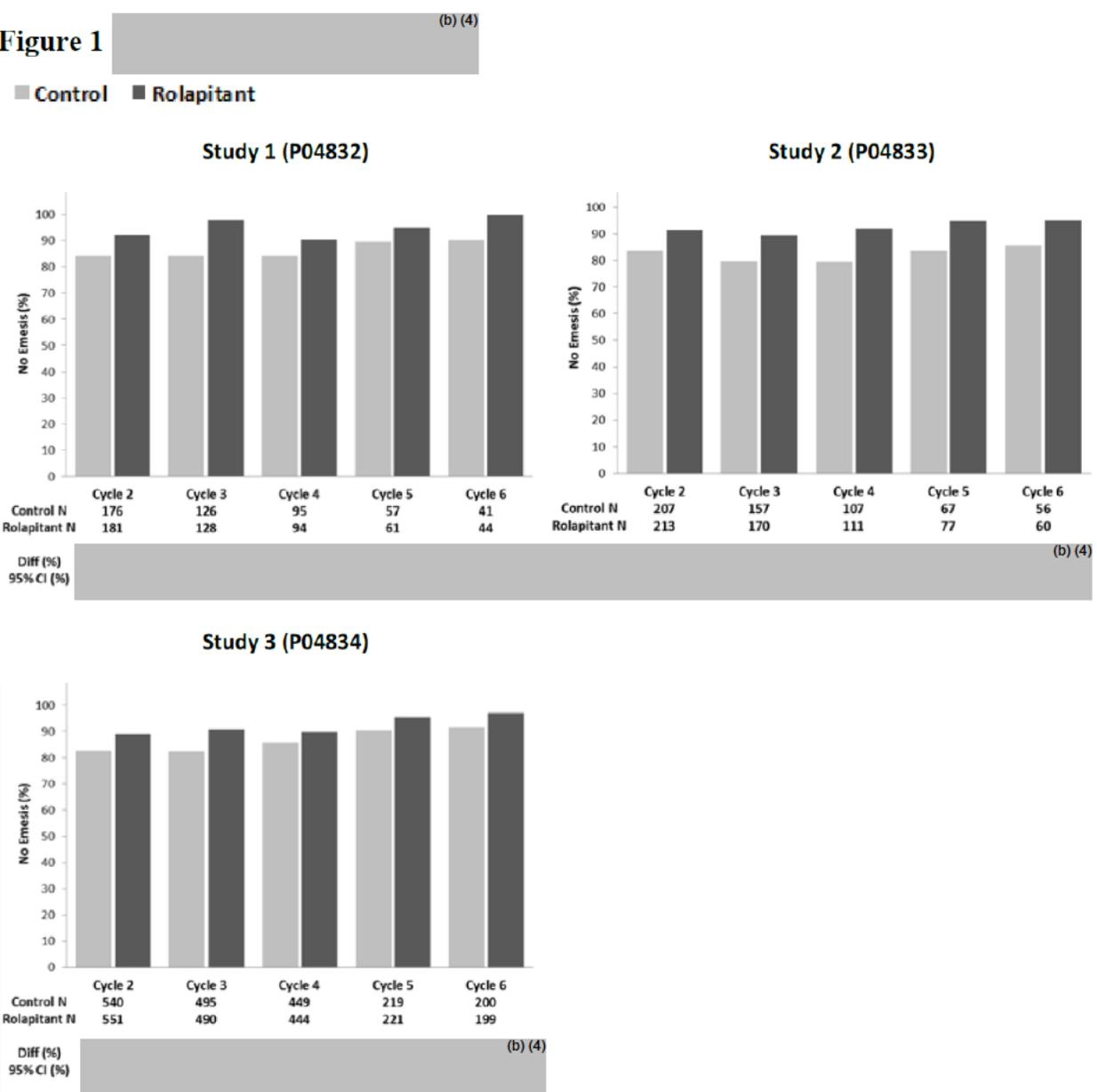
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the multiple Cycle Extension section (see graphs below). The Applicant provides the following rationale:



Figure 1



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**MO Comment:**

I agree with including the bar graphs of the information on no retching/emesis and nausea (the first set of graphs). The label should ideally reveal a complete picture of the information collected.

**b. Agency Request**

For patients in Studies 32, 33, and 34, please provide TEAE data by age using the following cut point: < 65 and ≥ 65.

**Applicant Response**

Table 82  
TEAEs by Age Group, All Cycles Combined - Subject Incidence, Overall CINV  
Pooling Group 1

System Organ Class Preferred Term	Control		Overall CINV	
	<65 yrs (N=940) n (%)	≥65 yrs (N=361) n (%)	<65 yrs (N=971) n (%)	≥65 yrs (N=323) n (%)
Subjects with ≥1 Incidence	747 (79.5)	306 (84.8)	781 (80.4)	274 (84.8)
Blood And Lymphatic System Disorders	229 (24.4)	92 (25.5)	257 (26.5)	100 (31.0)
Cardiac Disorders	30 ( 3.2)	22 ( 6.1)	35 ( 3.6)	18 ( 5.6)
Nervous System Disorders	229 (24.4)	90 (24.9)	233 (24.0)	92 (28.5)

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**MO Comment:**

When comparing the TEAE data across all cycles combined, the incidence rate was only slightly higher overall in patients 65 years of age and older. For patients in the control group, the incidence rate of TEAEs was 84.8% in patients 65 years of age and older, compared with 79.5% in patients younger than 65 years. In the rolapitant group, the incidence rate was 84.8% in the older age group compared with 80.4% in those patients less than 65 years old. Similarly, the incidence within significant SOCs, namely Blood and Lymphatic System Disorders, Cardiac Disorders, and Nervous System Disorders showed a difference between those less than 65 years old and the older age group of less than 5% for patients taking both control and active study drug. A trend of increasing TEAEs with age is expected, unrelated to study drug. In the rolapitant program, the rate of TEAEs in those 65 years of age and greater was only slightly higher than those less than 65 years of age and nearly identical in both control and rolapitant groups suggesting that the safety profile of rolapitant is similar across age groups.

9. Information Request Response Received August 21, 2015, Submission 036

**Agency Request**

Please provide a complete patient narrative for patient 020-00537 in Study 51 who met criteria for Hy's Law. Specifically, we are interested in the following:

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1. Did this patient have any symptoms associated with the increased liver enzymes?
2. What were the patient's concomitant medications?
3. Was the patient jaundiced?

**Applicant Response**

Subject 020-00537 was a 58 year old multiracial female diagnosed with squamous cell carcinoma of the tongue at the time of study (P04351) participation. On 11APR2007 (Cycle 1) this subject was administered oral rolapitant (10 mg) 2 hours prior to receiving cisplatin (159 mg IV) and 5-Fluorouracil (1590 mg IV).

**Table 1: Concomitant Medications Received by Subject 020-00537 During Cycle 1**

Study Day	Study Date	Time	Drug	Dose	Route	Notes
<b>Chemotherapy/Study Regimen</b>						
1	11APR07	9:10	ROLAPITANT	10 mg	po	Per protocol study medication
1	11APR07	10:40	ONDANSETRON	32 mg	iv	Per protocol study medication
1	11APR07	10:40	DEXAMETHASONE	20 mg	po	Per protocol study medication
1	11APR07	11:10	CISPLATIN	159 mg	iv	Per protocol study medication
1	11APR07	Not available	5-FLUORACIL	1590 mg	iv	Additional planned chemotherapy
2	12APR07	08:00	DEXAMETHASONE	8 mg	po	Per protocol study medication
2	12APR07	20:00	DEXAMETHASONE	8 mg	po	Per protocol study medication
3	13APR07	08:00	DEXAMETHASONE	8 mg	po	Per protocol study medication
3	13APR07	20:00	DEXAMETHASONE	8 mg	po	Per protocol study medication
4	14APR07	08:00	DEXAMETHASONE	8 mg	po	Per protocol study medication
4	14APR07	20:00	DEXAMETHASONE	8 mg	po	Per protocol study medication
<b>Concomitant Medications</b>						
1	11APR07	Not available	NORMAL SALINE	2000 cc	iv	Renal toxicity prophylaxis
5	15APR07	Not available	RANITIDINE	150 mg	Po q8h	Heartburn
6	16APR07	Not available	ACETAMINOPHEN	500 mg	Po q8h	Headache; Times one day
10	20APR07	Not available	FLUCONAZOLE	150 mg	Po qd	Oral Candidiasis; Times 14 days
10	20APR07	Not available	NISTATINE	20 cc	Po q6h	Oral Candidiasis; Times 14 days

NOTE: Except for receiving dexamethasone 16 mg po qd (instead of 8 mg po bid in Cycle 1), the chemotherapy/study regimen listed below was followed for each subsequent Cycle (Cycles 2-4) as well.

In summary, subject 020-0537 met basic Hy's Law criteria after exposure to the chemotherapy/study regimen and concomitant medications (ranitidine and acetaminophen) during Cycle 1 of this study. Elevations of ALT (without AST or ALK-P elevation) and increased elevations of TBil were detected 5 days after receiving a very low dose (10 mg) of rolapitant in addition to single therapeutic doses of cisplatin, 5-Fluoracil, ondansetron and multiple doses of dexamethasone (over 3 days). She experience dyspepsia, which is most likely related to cisplatin and/or 5-Fluoracil, headache and mild urinary retention and, 4 days later was found to have asymptomatic elevations of ALT, TBil, BUN, and creatinine, and decreases in serum sodium and bicarbonate. These laboratory abnormalities spontaneously resolved by 08MAY07. She was not jaundiced nor did she report other signs or symptoms (including jaundice, pruritis, or rash) which might be associated with hepatobiliary injury. She exhibited similar, though milder, asymptomatic elevations of ALT and TBil not meeting Hy's Law criteria and similar changes in Na, bicarbonate, BUN and/or creatinine at Visit

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2 of subsequent Cycles 2 – 4, which also resolved spontaneous. She completed 4 cycles of the study, at which time she discontinued the study for reasons not related to study treatment at which time ALT and TBil were within normal limits.

**Table 3: Hepatobiliary Function values during Cycle 1**

Day	Date	AST (U/L)	ALT (U/L)	ALK-P (U/L)	TBil (umol/L)
-13	29MAR07	13	16	92	27 <sup>H</sup>
1	11APR07	15	16	87	22 <sup>H</sup>
6	16APR07	22	171 <sup>H</sup>	97	50 <sup>H</sup>
28	08MAY07	17	33	103	9

Note: H=HIGH, L=LOW

**Table 2: Serum Electrolyte values during Cycle 1**

Day	Date	NA (mmol/L)	K (mmol/L)	BICARB (mmol/L)	BUN (mmol/L)	CREAT (umol/L)
-13	29MAR07	141	4.0	20	5.0	80
1	11APR07	142	4.0	21	4.3	80
6	16APR07	129 <sup>L</sup>	3.7	16 <sup>L</sup>	12.9 <sup>H</sup>	133 <sup>H</sup>
28	08MAY07	138	3.9	22	5.0	97

Note: H=HIGH, L=LOW

**MO Comment:**

*Additional information on the single rolapitant patient who met Hy's Law Criteria in the clinical development program was requested and received. The patient's laboratory elevations did not recur after Visit 2. In addition, the patient was on concomitant acetaminophen and a chemotherapy regimen that included 5-FU and cisplatin. Given the possible confounding of other hepatotoxic medications and the Hy's law imbalance in favor of rolapitant (4 control cases, 1 rolapitant case), there is no further investigation into drug induced liver injury that needs to be done at this time. Once approved, a larger cohort of patients will be exposed to the drug and routine safety monitoring will provide additional data to reveal if indeed a DILI signal is exists.*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AISHA P JOHNSON  
09/01/2015

DONNA J GRIEBEL  
09/01/2015

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206,500
Priority or Standard	Standard, Program NME Review
Submit Date(s)	05 September 2014
Received Date(s)	05 September 2014
PDUFA Goal Date	04 September 2015
Division / Office	Division of Gastroenterology and Inborn Errors Products Office of Drug Evaluation (ODE) III
Reviewer Name(s)	Aisha P. Johnson, MD, MPH, MBA
Review Completion Date	05 May 2015
Established Name	rolapitant
(Proposed) Trade Name	(Varubi)
Therapeutic Class	NK-1 inhibitor
Applicant	Tesaro, Inc
Formulation(s)	rolapitant 90 mg tablets
Dosing Regimen	180 mg 1-2 hours prior to chemotherapy
Indication(s)	BRANDNAME 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
Intended Population(s)	Adult Patients

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

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

In the opinion of this reviewer, rolapitant should be approved for marketing in the United States for use 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.

### 1.2 Risk Benefit Assessment

Overall, rolapitant has been found to be efficacious for the prevention of CINV during the delayed phase and relatively safe. Therefore, rolapitant was found to have an acceptable risk/benefit profile.

Chemotherapy-induced nausea and vomiting (CINV) is a potentially severe and debilitating side effect of chemotherapy. Highly emetogenic chemotherapy (HEC) agents are those associated with CINV in >90% of treated patients. Moderately emetogenic chemotherapy (MEC) agents are those associated with CINV in 31% to 90% of patients. Female patients and younger patients are at greater risk for developing CINV. The emetogenicity categories used for the trials submitted with the current application are listed in Table 1 below.<sup>1</sup> However, in 2011 the American Society of Clinical Oncology recommended changing the emetogenicity category from MEC to HEC for anthracyclines (including doxorubicin, epirubicin, idarubicin and daunorubicin) administered in combination with cyclophosphamide. For a discussion of the *post-hoc* rolapitant study results using the newer emetogenicity categories, see Section 6.1.10.

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<sup>1</sup> Hesketh PJ, Chemotherapy-Induced Nausea and Vomiting. N Engl J Med 2008;358:2482-94.

Table 1. Emetogenic levels of IV Administered Antineoplastic Agents\*

Level 1 (minimal risk, <10%)	Level 2 (low risk, 10–30%)	Level 3 (moderate risk, 31–90%)	Level 4 (high risk, >90%)
Bevacizumab	Bortezomib	Carboplatin	Carmustine
Bleomycin	Cetuximab	Cyclophosphamide	Cisplatin
Busulfan	Cytarabine ( $\leq 100$ mg/m <sup>2</sup> of body-surface area)	( $\leq 1.5$ g/m <sup>2</sup> )	Cyclophosphamide
Cladribine		Cytarabine (>1 g/m <sup>2</sup> )	(>1.5 g/m <sup>2</sup> )
Fludarabine	Docetaxel	Daunorubicin	Dacarbazine
Vinblastine	Etoposide	Doxorubicin	Mechlorethamine
Vincristine	Fluorouracil	Epirubicin	Streptozocin
Vinorelbine	Gemcitabine	Idarubicin	
	Ixabepilone	Ifosfamide	
	Lapatinib	Irinotecan	
	Methotrexate	Oxaliplatin	
	Mitomycin		
	Mitoxantrone		
	Paclitaxel		
	Pemetrexed		
	Temsirolimus		
	Topotecan		
	Trastuzumab		

\* Percentages indicate the risk of vomiting with intravenously administered antineoplastic agents in the absence of anti-emetic prophylaxis.

Electronically copied and reproduced from Hesketh, 2008

Two distinct phases of CINV have been identified. The acute phase happens within the first 24 hours following chemotherapy administration. The delayed phase occurs after 24 hours until 120 hours. The 5-HT<sub>3</sub> receptor antagonists form the cornerstone of the treatment of CINV. However, studies have shown that the efficacy of this class is reduced during the delayed phase. The rolapitant studies provided support the efficacy of the drug for the prevention of CINV during the delayed phase. Rolapitant is to be used in combination with other antiemetic agents. In the confirmatory studies, rolapitant was used with dexamethasone and a 5-HT<sub>3</sub> antagonist. (b) (4)

Rolapitant was found to be relatively safe and associated with relatively few adverse events. No black boxed warnings are proposed. The most common adverse events associated with the use of rolapitant during clinical trials were fatigue, neutropenia, and decreased appetite. The deaths reported during the development program were expected given the population of cancer patients. No safety signals were identified.

### 1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

### 1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant submitted plans for a pediatric program for rolapitant. The Division issued correspondence confirming agreement with sponsor's initial Pediatric Study Program (iPSP). The sponsor was granted a deferral for studies in patient's (b) (4) years of age because adult studies are complete and ready for approval.

**PMR Study #1**

(b) (4) PK/PD and clinical effectiveness in pediatric patients

Protocol submission: Nov 2016

First Dose: Aug 2017 (assuming protocol agreed with FDA by Mar 2017)

Final clinical study report submission: Nov 2020

**PMR Study #2:** Confirmatory Clinical effectiveness and safety study in pediatric patients

Protocol submission: Nov 2020

First Dose: Aug 2023

Final clinical study report submission: Aug 2026

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Trade Name:

(Varubi)

Generic Name:

rolapitant

Chemical Name:

(b) (4)

Structural Formula:

(b) (4)

Therapeutic Class:

neurokinin-1 receptor antagonist

Formulation:

100 mg tablet rolapitant hydrochloride

*MO Comment:*

*In labeling, the dose of rolapitant is reported as 180 mg representing the weight of rolapitant in the non-salt form. New FDA Chemistry Manufacturing and Controls (CMC) guidelines require the weight used for labeling be the non-salt form of the compound. However, for the entirety of this review, the term “rolapitant” refers to the rolapitant hydrochloride salt formulation which weighs 200 mg.*

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Ondansetron	5-HT3 antagonist
Palonosetron	5-HT3 antagonist
Granisetron	5-HT3 antagonist
	5-HT3 antagonist
Dolasetron	5-HT3 antagonist
Aprepitant/fosaprepitant	NK-1 antagonist
palonosetron and netupitant	5-HT3 and NK-1 antagonist

## 2.3 Availability of Proposed Active Ingredient in the United States

Rolapitant is a new molecular entity (NME). There are currently no approved drugs containing this active moiety.

## 2.4 Important Safety Issues With Consideration to Related Drugs

There are currently two NK-1 products on the market in the U.S.—Emend and Akynzeo.

Emend is available in two formulations- oral (aperepitant) and solution for injection (fosaprepitant). Akynzeo is a fixed combination of netupitant, a substance P/neurokinin1 receptor antagonist, and palonosetron, a 5-HT3 receptor antagonist.

### Contraindications

#### Aprepitant (excerpt from 08/2014 label)

*EMEND is contraindicated in patients who are hypersensitive to any component of the product. EMEND is a dose-dependent inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4). EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions [see Drug Interactions (7.1)]*

#### Fosaprepitant (excerpt from 10/2014 label)

##### *4.1 Hypersensitivity*

*EMEND for Injection is contraindicated in patients who are hypersensitive to EMEND for Injection, aprepitant, polysorbate 80 or any other components of the product. Known hypersensitivity reactions include: flushing, erythema, dyspnea, and anaphylactic reactions [see Adverse Reactions (6.2)]*

*4.2 Concomitant Use with Pimozide or Cisapride. Aprepitant, when administered orally, is a moderate cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor following the 3-day antiemetic dosing regimen for CINV. Since fosaprepitant is rapidly converted to aprepitant, do not use fosaprepitant concurrently with pimozide or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions [see Drug Interactions (7.1)]*

Akynzeo has no contraindications in the current version of the label (10/2014).

## Warnings and Precautions

### Aprepitant

- 5.1 CYP3A4 Interactions
- 5.2 Coadministration with Warfarin (a CYP2C9 substrate)
- 5.3 Coadministration with Hormonal Contraceptives
- 5.4 Patients with Severe Hepatic Impairment
- 5.5 Chronic Continuous Use

### Fosaprepitant

- 5.1 CYP3A4 Interactions
- 5.2 Hypersensitivity Reactions
- 5.3 Coadministration with Warfarin (a CYP2C9 substrate)
- 5.4 Coadministration with Hormonal Contraceptives
- 5.5 Chronic Continuous Use

The Akynzeo label has no Warnings and precautions related to the netupitant part of the fixed dose combination product.

See Section 7.2.6.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

Date	Selected Regulatory Action(s)
04 September 2014	NDA 206,500 submitted
02 July 2014	<p>Pre-NDA meeting: Key Clinical Agreements</p> <ul style="list-style-type: none"> <li>▪ The Division stated that the final indication is a review issue.</li> <li>▪ The Division stated that the indication statement granted may not contain the terms (b) (4) as the Division is moving away from these designations and currently embracing a broader CINV indication.</li> <li>▪ The Division requested the following safety analyses to address potential neurotoxicity issues based on the long half-life of the product and its cumulative effects over multiple chemotherapy cycles: <ul style="list-style-type: none"> <li>• Clarification on the most frequent dosing regimen tested during the clinical development program</li> <li>• How you intend to label your drug product with respect to dosing</li> <li>• How you will address the possibility of more frequent dosing</li> <li>• Clarification on whether you plan to label your product for administration every (b) (4)</li> <li>• The differential CNS toxicity over 3 weeks vs. 4 weeks</li> <li>• Toxicities associated with ifosfamide exposure</li> </ul> </li> <li>▪ Size of the safety database deemed acceptable by the Division. The total number of patients in the Phase 3 HEC and MEC studies combined with the Phase 2 HEC study exposed to rolapitant 200mg for one cycle was 1294. The total number of patients in the Phase3 HEC and MEC studies as well as in the Phase 2 HEC study exposed to rolapitant 200mg for 6 cycles was approximately 319.</li> </ul>
05 July 2011	<p>Type C meeting: Key Clinical Agreements:</p> <ul style="list-style-type: none"> <li>▪ If supported by a successful phase 2/3 HEC program, the Division stated that a single MEC study would be acceptable (if the proposed number of patients (approximately 1350) and at least 50% receiving anthracycline-cyclophosphamide (AC) based therapy are enrolled).</li> <li>▪ The Division re-iterated that the Applicant should test the delayed phase as the primary or co-primary endpoint. It is important that the phase 3 studies show that the drugs works given that cisplatin (HEC) and adriamycin (MEC) are associated with delayed nausea and vomiting.</li> </ul>
05 April 2010	<p>EOP2 meeting. Key Clinical Agreements:</p> <ul style="list-style-type: none"> <li>▪ Based on the results of a phase 2b, dose-finding study, the Division agreed with the Applicant's choice to carry the 200 mg dose forward into phase 3.</li> <li>▪ In the phase 2b study, 2 cases of convulsions and renal failure were observed in the rolapitant group with no cases in the placebo group. Therefore, the Division requested that neuro exams be done at Visit 2 and renal assessments be obtained at screening, -2.5 hours, and Visits 2 and 3 in Cycle 1.</li> <li>▪ The Division stated that in order to have an indication of "the prevention of (b) (4) delayed nausea and vomiting associated</li> </ul>

	<p>with initial and repeat courses of (b) (4) the Applicant would need to show statistical significance in (b) (4) delayed time frame (b) (4)</p> <ul style="list-style-type: none"><li>▪ The Division counseled the Applicant against stratifying by more than one variable in phase 3.</li></ul>
06 October 2005	<p>Type B, Pre-IND meeting. Key Clinical Agreements:</p> <ul style="list-style-type: none"><li>▪ Proposed primary (Complete Response During 0-120 hours) and secondary endpoints found to be acceptable</li><li>▪ (b) (4)</li><li>▪ FDA recommended performing two of three studies in patients taking HEC</li></ul>

## 2.6 Other Relevant Background Information

None known, except as discussed in other parts of the review.

## 3 Ethics and Good Clinical Practices

### 3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was well organized and easily navigable.

The Office of Scientific Investigations (OSI) performed site investigations and found that the confirmatory efficacy studies were conducted adequately overall, and the data generated by the sites appear acceptable in support of the indication. For further details regarding site violations, see the reports in DARRTS by Dr. Susan Leibenhaut for this application.

### 3.2 Compliance with Good Clinical Practices

According to the Applicant, all studies were performed in accordance with the Monitoring Plan and the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization

(ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements of the countries in which they were conducted.

### 3.3 Financial Disclosures

Covered Clinical Study (Name and/or Number): P04382, P04383, P04384

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <b><u>not relevant because no investigator had financial disclosures</u></b>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <b><u>0</u></b>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <b><u>0</u></b>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): <b><u>n/a</u></b></p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/> <b><u>n/a</u></b>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input type="checkbox"/> <b><u>n/a</u></b>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <b><u>0</u></b>		
Is an attachment provided with the reason:	Yes <input type="checkbox"/> <b><u>n/a</u></b>	No <input type="checkbox"/> (Request explanation from applicant)

None of the reported financial disclosures affect the approvability of the application.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

See the complete CMC review in DARRTS.

### **4.2 Clinical Microbiology**

N/A

### **4.3 Preclinical Pharmacology/Toxicology**

A comprehensive toxicology program was undertaken to support the oral administration of rolapitant in humans. These studies included single-dose toxicity studies in rats and monkeys, up to 6-month (rat) and 9-month (monkey) repeat dose toxicity studies in rats and monkeys, genotoxicity studies, two year carcinogenicity studies in rats and mice, developmental and reproductive studies in rats and rabbits, abuse potential liability studies in monkeys, and safety studies on the rolapitant major metabolite SCH 720881.

Convulsions were observed in monkeys administered 60 and 100 mg/kg. See Section 7.3.5 for a further discussion of the convulsions seen in the rolapitant clinical program.

For further discussion of these studies and their results, see the pharmacology/toxicology review in DARRTS by Tracy Behrsing, PhD.

### **4.4 Clinical Pharmacology**

The rolapitant program included 14 Phase 1 studies including single- and multiple-dose pharmacokinetic (PK), absorption, distribution, metabolism and elimination (ADME), biopharmaceutic, drug-drug interaction (DDI), and thorough QT/QTc studies in approximately 800 healthy volunteers. No significant effects on systemic exposure to rolapitant was seen in patients with mild to moderate hepatic or renal impairment.

Studies were not conducted in patients with severe hepatic or renal impairment. Therefore, according to Dr. Insook Kim, potentially high plasma concentrations cannot be ruled out due to a possible decrease in clearance of rolapitant in patients with severe hepatic or renal impairment and potential accumulation after repeated dosing. In the rolapitant program, the median interval between cycles was 21 days and the shortest interval between cycles was 2 weeks.

#### 4.4.1 Mechanism of Action

Rolapitant is a neurokinin-1 (NK-1) receptor antagonist. These receptors are broadly distributed in central and peripheral nervous systems. Studies have shown that rolapitant binds to the NK-1 receptor with high affinity and has little or no activity for the other NK receptors. The endogenous activator of the NK-1 receptor is the neuropeptide, Substance P.

A clinical PET study demonstrated that after a 200 mg dose of rolapitant, over 90% of central NK1 receptors remained blocked for at least 120 hours.

#### 4.4.2 Pharmacodynamics

No significant efficacy or safety issues related to pharmacodynamics were identified.

#### 4.4.3 Pharmacokinetics

In PK studies using rolapitant 200 mg, the mean maximum plasma concentration ( $C_{max}$ ) was approximately 1000 ng/mL. The mean terminal half-life ( $t_{1/2}$ ) following single oral doses ranged from 169 to 183 hours (~7 days) and was independent of dose. Rolapitant was found to be highly protein bound to human plasma (99.8%) with an apparent volume of distribution ( $V_d$ ) of ~ 460 L, indicating an extensive tissue distribution of rolapitant.

The PK profiles of rolapitant were evaluated in subjects with mild and moderate hepatic impairment. The changes seen in hepatically impaired patients compared to controls were not determined to be clinically meaningful; therefore, no dosage adjustment was recommended in patients with hepatic impairment

For further clinical pharmacology details of rolapitant, see the final label and the clinical pharmacology review in DARRTS by Dr. Insook Kim.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

Table 2. Primary Evidence of Efficacy, Rolapitant Clinical Development Program

Study Identifier Location Start Date Status/Date	Study Objectives	Study Design; Diagnosis	Study Drug and Control, Regimen, Route, Duration of Treatment <sup>a</sup>	Subjects: Planned/ Actual <sup>b</sup> /Completed <sup>c</sup> ; Mean Age (Range); No. M/F	Primary Endpoint
P04832 76 sites: North America, Central/South America, Europe, Asia and South Africa Start: 06 March 2012 Complete: 03 April 2014	Efficacy: Prevention of CINV Safety and tolerability	Phase 3, MC, R, DB, Active control Cancer patients receiving HEC (≥60 mg/m <sup>2</sup> cisplatin-based chemotherapy)	Rolapitant 200 mg single dose or placebo in combination with granisetron and dexamethasone PO Maximum: 6 cycles Median number of cycles: 2.0 Median cycle duration: 21-22 days Cycle length (range): 13 to 70-days	Overall: 530/526/491 Rolapitant: 265/264/251 Control: 265/262/240  Overall: 57.3 yrs (20-90) Overall: M=304; F=222	CR rate (no emesis and no use of rescue medication) in the delayed phase (>24 to 120 hours following initiation of chemotherapy)
P04833 79 sites: North America, Central/South America, Europe, Asia and South Africa Start: 20 Feb 2012 Complete: 24 Jan 2014	Efficacy: Prevention of CINV Safety and tolerability	Phase 3, MC, R, DB, Active control Cancer patients receiving HEC (≥60 mg/m <sup>2</sup> cisplatin-based chemotherapy)	Rolapitant 200 mg single dose or placebo in combination with granisetron and dexamethasone PO Maximum: 6 cycles Median number of cycles: 3.0 Median cycle duration: 21-23 days Cycle length (range): 13 to 42 days	Overall: 530/544/518 Rolapitant: 265/271/259 Control: 265/273/259  Overall: 58.5 yrs (18-83) Overall: M=369; F=175	CR rate (no emesis and no use of rescue medication) in the delayed phase (>24 to 120 hours following initiation of chemotherapy)
P04834 170 sites: North America, Central/South America, Europe, Asia and South Africa Start: 02 Mar 2012 Complete: 22 Jan 2014	Efficacy: Prevention of CINV Safety and tolerability	Phase 3, MC, R, DB, Active control  Cancer patients receiving MEC <sup>d</sup>	Rolapitant 200 mg single dose or placebo in combination with granisetron and dexamethasone PO Maximum: 6 cycles Median number of cycles: 4.0 Median cycle duration: 21 days Cycle length (range): 12 to 62 days	Overall: 1350/1332/1276 Rolapitant: 675/666/636 Control: 675/666/640  Overall: 56.7 yrs (22-88) Overall: M=265; F=1067	CR rate (no emesis and no use of rescue medication) in the delayed phase (>24 to 120 hours following initiation of chemotherapy)

Abbreviations: CINV = chemotherapy-induced nausea and vomiting; CR = complete response; DB = double-blind, F = female; HEC = highly emetogenic chemotherapy; IV = intravenous; M = male; MC = multicenter; MEC = moderately emetogenic chemotherapy; MITT = modified intent-to-treated; NR = not reported; PO = oral administration; R = randomized

<sup>a</sup> Duration of treatment is presented maximum number of cycles planned, median number of cycles administered, and actual range of days per cycle reported.

<sup>b</sup> Actual refers to the MITT population for Studies P04832, P04833 and P04834 and for Study P04351 was based on all randomized subjects who received cisplatin-based chemotherapy and a dose of study medication and had at least one post-treatment efficacy assessment in Cycle 1 recorded.

<sup>c</sup> Completed primary endpoint of Cycle 1.

<sup>d</sup> Subjects were to receive a first course of one or more of the following agents IV: cyclophosphamide (<1500 mg/m<sup>2</sup>), or doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, or cytarabine (>1 g/m<sup>2</sup>).

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### 5.2 Review Strategy

For this NDA submission, the original plan was to review Phase 3 Studies 51, 32, 33, and 34 as primary evidence of safety and efficacy. (b) (4)

Study 51

contained 91 patients taking the same dose of rolapitant (200 mg) included in the phase 3 studies.

However, after a great deal of discussion throughout the review cycle and a CDER management-level discussion on April 17, 2015 involving Lisa LaVange, PhD, Director, CDER Office of Biostatistics, and Robert Temple, MD, CDER Deputy Director for Clinical Science it was decided that

(b) (4)

(b) (4)

### **5.3 Discussion of Individual Studies/Clinical Trials**

#### **General Information Regarding Controlled Efficacy Studies**

Unless specifically stated, all efficacy results discussed are from Cycle 1 of all studies.

#### **5.3.1 Protocol Summary**

##### **Title**

##### **Studies 32 and 33**

A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study of the Safety and Efficacy of Rolapitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Subjects Receiving Highly Emetogenic Chemotherapy (HEC)

##### **Study 34**

A Phase 3, Multicenter, Randomized, Double-Blind, Active-Controlled Study of the Safety and Efficacy of Rolapitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Subjects Receiving Moderately Emetogenic Chemotherapy (MEC)

##### **Study Centers**

##### **Study 32**

A total of 76 sites randomized at least 1 patient. The geographic location of these study sites is shown below in Table 3.

Table 3. Geographic Location of Investigator Sites, MITT Population, Study 32

Cycle 1	Statistic	Rolapitant (N=264)	Control (N=262)	All (N=526)
Region	No. of Subjects	264	262	526
North America	n (%)	42 (15.9)	45 (17.2)	87 (16.5)
Central/South America	n (%)	28 (10.6)	28 (10.7)	56 (10.6)
Europe	n (%)	133 (50.4)	134 (51.1)	267 (50.8)
Asia/South Africa	n (%)	61 (23.1)	55 (21.0)	116 (22.1)

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### Study 33

A total of 79 sites randomized at least 1 patient during Study 33. See Table 4 below.

Table 4. Geographic Location of Investigator Sites, MITT Population, Study 33

Cycle 1	Statistic	Rolapitant (N=271)	Control (N=273)	All (N=544)
Region	No. of Subjects	271	273	544
North America	n (%)	17 (6.3)	19 (7.0)	36 (6.6)
Central/South America	n (%)	37 (13.7)	43 (15.8)	80 (14.7)
Europe	n (%)	173 (63.8)	165 (60.4)	338 (62.1)
Asia/South Africa	n (%)	44 (16.2)	46 (16.8)	90 (16.5)

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### Study 34

A total of 170 sites randomized at least one patient during Study 34, See Table 5 below.

Table 5. Geographic Location of Investigator Sites, MITT Population, Study 34

Cycle 1	Statistic	Rolapitant (N=666)	Control (N=666)	All (N=1332)
Region	No. of Subjects	666	666	1332
North America	n (%)	216 (32.4)	229 (34.4)	445 (33.4)
Central/South America	n (%)	31 (4.7)	32 (4.8)	63 (4.7)
Europe	n (%)	312 (46.8)	299 (44.9)	611 (45.9)
Asia/South Africa	n (%)	107 (16.1)	106 (15.9)	213 (16.0)

## **Study Period**

### Study 32

First patient enrolled: 25 April 2012

Last patient last visit: 03 April 2014

### Study 33

First patient enrolled: 20 February 2012

Last patient last visit: 24 January 2014

### Study 34

First patient enrolled: 02 March 2012  
Last patient last visit: 22 January 2014

## **Study Objective**

### Studies 32 and 33

The primary objective of this study was to determine whether administration of rolapitant with granisetron and dexamethasone improved CINV in the delayed phase (>24 to 120 hours) of CINV compared with administration of placebo with granisetron and dexamethasone in patients receiving HEC.

### Study 34

The primary objective of this study was to determine whether administration of rolapitant with granisetron and dexamethasone improved CINV in the delayed phase (>24 to 120 hours) of CINV compared with administration of placebo with granisetron and dexamethasone in patients receiving MEC.

## **Study Design**

### Studies 32 and 33

Studies 32 and 33 were global, Phase 3, multicenter, randomized, parallel-group, double-blind, active-controlled studies of rolapitant in patients receiving HEC ( $\geq 60$  mg/m<sup>2</sup> of cisplatin-based chemotherapy). Randomization was stratified by gender. In each stratum, patients were randomized in a 1:1 ratio to the study medication arms. Rolapitant or placebo was administered orally 1 to 2 hours prior to the initiation of chemotherapy on Day 1. Granisetron (10  $\mu$ g/kg intravenous [IV]) and dexamethasone (20 mg orally) were administered approximately 30 minutes before initiation of chemotherapy on Day 1, except in patients receiving taxanes as a part of cisplatin-based chemotherapy. Because of the potential for hypersensitivity reactions to taxanes, patients receiving taxanes received doses of dexamethasone according to the respective taxane package insert, in lieu of the 20 mg PO dose of dexamethasone on Day 1.

For Paclitaxel:

Day -1: Dexamethasone 20 mg PO, 12 hours prior to paclitaxel

Day 1: Dexamethasone 20 mg PO, 6 hours prior to paclitaxel

For Docetaxel:

Day -1: Dexamethasone 8 mg PO BID (one in the morning and one in the evening)

Day 1: Dexamethasone 8 mg PO, 30 minutes prior to the first administered chemotherapeutic agent and another 8 mg dose in the evening

All patients continued to receive dexamethasone (8 mg PO twice daily [BID]) on Days 2, 3, and 4.

The primary efficacy endpoint was the CR rate in the delayed phase (>24 through 120 hours).

See the section below entitled “Design Elements Common to Studies 32, 33, and 34” for further details on the design of Studies 32 and 33.

#### Study 34

Study 34 was a global, phase 3, multicenter, randomized, parallel-group, double-blind, active-controlled study of rolapitant in patients receiving MEC. Rolapitant or placebo was administered orally 1 to 2 hours prior to the initiation of chemotherapy on Day 1. Granisetron (2 mg PO) and dexamethasone (20 mg PO) were administered approximately 30 minutes before initiation of chemotherapy, except in patients taking taxanes. In those patients taking taxanes, the following regimen was used in lieu of the usual 20 mg oral dexamethasone dose:

For Paclitaxel:

-1: Dexamethasone 20 mg PO, 12 hours prior to paclitaxel

1: Dexamethasone 20 mg PO, 6 hours prior to paclitaxel

For Docetaxel:

-1: Dexamethasone 8 mg PO BID (twice a day, one in the morning and one in the evening)

Day 1: Dexamethasone 8 mg PO, 30 minutes prior to MEC and another 8 mg dose in the evening

Day 2: Dexamethasone 8 mg PO BID (one in the morning and one in the evening)

All study patients had to have an established diagnosis of malignancy, be naive to MEC and HEC, and be scheduled to receive a first course of MEC (cyclophosphamide IV [ $<1500$  mg/m<sup>2</sup>], doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, or cytarabine IV [ $>1$  g/m<sup>2</sup>]) to be eligible for the study. At least 50% of the study patients were to receive anthracycline in combination with cyclophosphamide IV. This percentage was agreed upon in an end-of-phase 2 meeting.

#### Design Elements Common to Studies 32, 33, and 34

The population for these studies included adult patients with Karnofsky performance score of  $\geq 60$ , and a life-expectancy of  $\geq 3$  months who had adequate bone marrow, kidney, and liver function and had never received chemotherapy for treatment of their underlying malignancy.

Episodes of vomiting and rescue medication use, as well as symptoms of nausea were self-reported by the study patients in the Nausea Vomiting Subject Daily (NVSD) Diary through Day 6 of Cycle 1. The NVSD contains 6 questions: one question on date and time diary was completed (Question 1), one question on nausea (Question 2), two questions on emesis (Questions 3 and 4) and two questions on the use of rescue medications (Questions 5 and 6). To ensure understanding and compliance with

reporting, telephone contact was made with each patient on Days 2 to 5 of Cycle 1 at approximately the same time each day. Health-related quality of life was measured by the FLIE Questionnaire on Day 6 of Cycle 1.

Safety and tolerability were assessed by clinical review of adverse events, physical examinations, vital signs, electrocardiograms (ECGs), and safety laboratory values. Blood samples were collected for SCH 619734 pharmacokinetic assessments. At the end of Cycle 1, eligible patients were allowed to continue the same treatment regimen for up to five additional cycles. Patients were asked the following CINV Assessment questions on Days 6, 7, or 8 in Cycles 2 to 6:

- Have you had any episode of vomiting or retching since your chemotherapy started in this cycle?
- Have you had any nausea since your chemotherapy started in this cycle that interfered with normal daily life?

Table 6. Rolapitant Registration Trials Endpoint Definitions

	Endpoint	Definition
1 <sup>o</sup> Endpoint	Complete Response	No emesis, no use of rescue medication
2 <sup>o</sup> Endpoint	No emesis	No vomiting, retching, or dry heaves (includes patients who receive rescue medication)
	No nausea	Maximum VAS <5 mm
	No significant nausea	Maximum VAS <25 mm
	Complete protection	No emesis, no rescue medication, and maximum VAS <25 mm
	Total Control	No emesis, no rescue medication, and maximum VAS <5 mm

VAS=visual analog scale

For all studies, the primary analysis was based on all randomized patients who received cisplatin-based chemotherapy and a dose of study medication and had at least one post treatment efficacy assessment in Cycle 1 recorded. These patients were labeled the modified intent-to-treat (MITT) population.

### Analysis Populations

For all studies, the primary analysis was based on the Modified intent-to-treat population. Analyses for the primary, key secondary, and secondary endpoints were repeated on the As-Treated (AT) and PP Populations. All safety analyses were performed on the Safety Population.

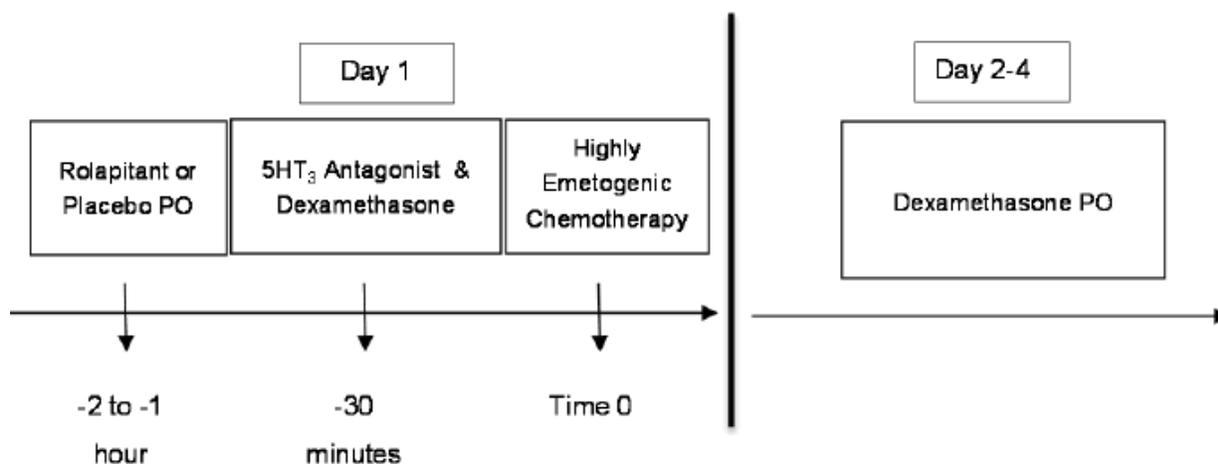
- Modified Intent-to-Treat Population (Cycle 1)

The modified intent to treat (MITT) population consisted of all randomized patients who received at least 1 dose of study drug. Patients were analyzed in the treatment group into which they were randomized.

The following criteria were used to exclude patients from the MITT population:  
Patient was enrolled at a noncompliant site with major GCP violations  
Patient did not provide informed consent  
Patient did not receive at least one dose of study drug (rolapitant or placebo)

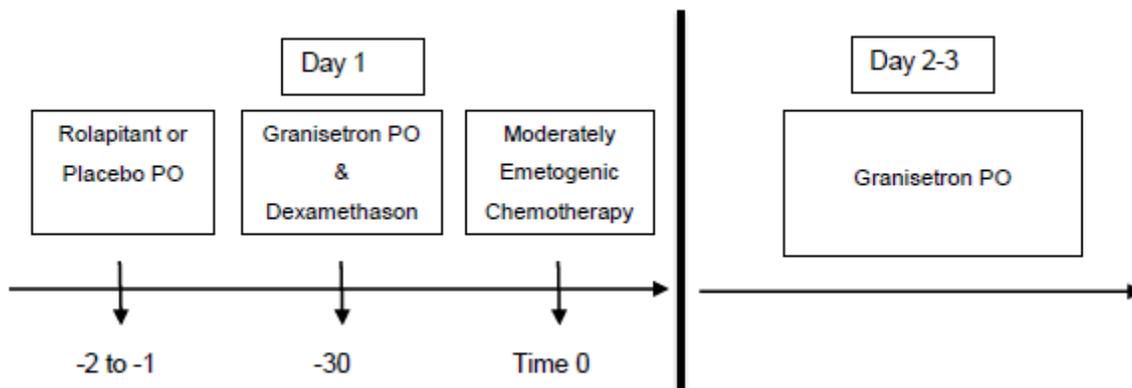
- **As-Treated Population (Cycle 1)**  
The AT population consisted of all randomized patients who received at least 1 dose of study drug. Patients were analyzed in the group in which they actually received treatment in Cycle 1.
- **Per Protocol Population (Cycle 1)**  
The PP population consisted of all randomized patients who received at least 1 dose of study drug, received emetogenic chemotherapy (Hesketh Level 5), and did not have protocol deviations significantly affecting the interpretation of the study results. In addition, if a patient had missing diary data and determination of CR could not be made from the remaining data, this patient was excluded from the respective phase of the efficacy analysis. Patients were analyzed based on actual treatment received in Cycle 1.
- **Safety Population (Cycle 1)**  
The Safety population consisted of all patients who were randomized to treatment groups and who received at least 1 dose of study drug. Safety analysis was based on actual treatment received in Cycle 1.

Figure 1. Flow Chart for Drug Administration – Days 1 thru 4, HEC Studies



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Figure 2. Flow Chart for Drug Administration – Days 1thru 3, MEC Study



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Table 7. Key Design Elements across Rolapitant Registration Trials

	Phase 3, Studies 32 and 33	Phase 3, Study 34
Complete Response Primary efficacy endpoint	CR rate in delayed phase (>24-120 hours post chemotherapy)	CR rate in delayed phase (>24-120 hours post chemotherapy)
Emetogenicity Severity	Highly	Moderately
5-HT3 antagonist	granisetron	granisetron
Granisetron dose	10 µg/kg IV	2 mg PO
Stratification factors	Gender	Gender
Day 1 dexamethasone dose adjustment for patients taking taxanes	Adjustment according to taxane package insert	Adjustment according to taxane package insert
Interim Analysis	No	No
Statistical Method of primary analysis	CMH	CMH

Reviewer's Table.

### 5.3.2 Key Inclusion Criteria

#### Studies 32 and 33

##### Cycle 1

1. Patient was 18 years of age or older.
2. Patient had never been treated with cisplatin and was to receive the first course of cisplatin-based chemotherapy ( $\geq 70 \text{ mg/m}^2$ )
3. Patient had a Karnofsky performance score of 60
4. Patient had a predicted life expectancy of 3 months

5. Patient had adequate bone marrow, kidney, and liver function as evidenced by
6. absolute neutrophil count  $\geq 1500/\text{mm}^3$  and white blood cell (WBC) count  $\geq 3000/\text{mm}^3$
7. platelet count  $\geq 100,000/\text{mm}^3$ ,
8. aspartate aminotransferase (AST)  $\leq 2.5$  x upper limit of normal (ULN),
9. alanine aminotransferase (ALT)  $\leq 2.5$  x ULN,
10. bilirubin  $\leq 1.5$  x ULN, except for patients with Gilbert's syndrome,
11. creatinine  $\leq 1.5$  x ULN.

### Cycles 2 to 6

Each patient was required to meet all of the following inclusion criteria prior to being permitted entry into additional cycles of the study:

1. Participation in the study during the next cycle of chemotherapy was considered appropriate by the investigator and would not pose an unwarranted risk to the patient.
2. Satisfactory completion of the preceding cycle of chemotherapy and related study procedures.

### 5.3.3 Key Exclusion Criteria

1. Any current treatment or medical history (eg, patient was mentally incapacitated or had a psychiatric disorder) that, in the opinion of the investigator, would confound the results of the study or pose any unwarranted risk in administering study drug to the patient.
2. Patient had a contraindication to the administration of cisplatin, ondansetron, or dexamethasone including, but not limited to, a history of hypersensitivity to the drugs or their components, severe renal impairment, severe bone marrow suppression, hearing impairment, or systemic fungal infection.
3. Patient was a woman of childbearing potential with a positive urine pregnancy test within 3 days prior to study drug administration.
4. Patient had previously received cisplatin.
5. Patient had participated in a clinical trial receiving the last dose of the investigational agent within 30 days prior to the start of administration of study drug.
6. Patient had taken the following agents within the last 5 days prior to the start of treatment with study drug until Day 6 of the study unless these agents were used as rescue medication or as part of the study treatment:
  - a) 5-HT<sub>3</sub> antagonists (ondansetron, granisetron, dolasetron, tropisetron, etc)
  - b) phenothiazines (prochlorperazine, fluphenazine, perphenazine, thiethylperazine, chlorpromazine, etc)
  - c) antipsychotics (haloperidol, droperidol, olanzepin, etc)
  - d) benzamides (metoclopramide, alizapride, etc)
  - e) Domperidone
  - f) Cannabinoids
  - g) neurokinin-1 (NK1) receptor antagonist (aprepitant)
  - h) benzodiazepines

- i) sedative antihistamines (dimenhydrinate, diphenhydramine, etc)
  - j) excessive alcohol consumption (ie, more than two drinks per day)
7. Patient was scheduled to receive any other chemotherapeutic agent with an emetogenicity level of 3 or above (Hesketh scale) from Day -2 through Day 6. There was no restriction for Day 1.
  8. Patient was scheduled to receive any radiation therapy to the abdomen or pelvis from Day -5 through Day 6.
  9. Patient had received systemic corticosteroids within 72 hours of Day 1 of the study, except as premedication for chemotherapy. Patients who were receiving chronic daily steroid therapy could be enrolled provided that the daily steroid dose was  $\leq 10$  mg of prednisone, or equivalent.
  10. Patient had symptomatic primary or metastatic central nervous system (CNS) disease.
  11. Patient had ongoing vomiting caused by any etiology or had a history of anticipatory nausea and vomiting.
  12. Patient was planning to receive multiple days of cisplatin in a single cycle.
  13. Patient had vomited and/or had had dry heaves/retching within 24 hours prior to the start of cisplatin-based chemotherapy on Day 1 in Cycle 1.

#### 5.3.4 Study Medication, 5-HT<sub>3</sub> and Dexamethasone use, and Prohibited Concomitant Medications

The use of 5-HT<sub>3</sub> receptor antagonists, phenothiazines, benzamides, domperidone, cannabinoids, NK<sub>1</sub> receptor antagonists and benzodiazepines was prohibited within 48 hours prior to the start of study treatment. Palonosetron was not permitted within 7 days prior to the start of study treatment. Systemic corticosteroids or sedative antihistamines (e.g., dimenhydrinate, diphenhydramine) were prohibited within 72 hours of Day 1 except as premedication for chemotherapy (e.g., taxanes).

#### 5.3.5 Study Visits and Procedures

All study visits occurred in an outpatient setting. The study visits and related safety assessments are summarized in the tables below.

Table 8. Study procedures, Studies 32 and 33, Cycle 1

Study Procedures	Screening Visit	Visit 1 <sup>a</sup> (Baseline/Treatment)							Treatment Follow-up Period				Visit 2	Visit 3	30-Day Poststudy Follow-up
		Day 1 (hours)							Day	Day	Day	Day			
		Days -30 to 1	Up to -3	-2 to -1	-.5	0	1	3	2	3	4	5			
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Medical history	X	X <sup>b</sup>										X <sup>b</sup>	X <sup>b</sup>		
Alcohol consumption assessment (units per week)	X														
Physical examination including neurological assessment	X	X										X	X		
Review of concomitant medications	X	X										X	X		
Height	X														
Body weight	X	X										X	X		
Karnofsky Performance Status	X	X										X	X		
12-Lead electrocardiogram	X	X						X <sup>i</sup>				X			
Vital signs	X	X						X <sup>i</sup>				X	X		
Pregnancy testing <sup>c</sup>	X	X											X <sup>j</sup>		
Laboratory tests including BUN and creatinine <sup>e</sup>	X <sup>d</sup>	X										X	X		
Collect biomarker sample	X														
Randomization	X <sup>h</sup>	X <sup>h</sup>													
Prehydration				X-----X <sup>f</sup>											
Administer rolapitant or placebo				X---X											

Study Procedures	Screening Visit	Visit 1 <sup>a</sup> (Baseline/Treatment)							Treatment Follow-up Period				Visit 2	Visit 3	30-Day Poststudy Follow-up
		Day 1 (hours)							Day	Day	Day	Day			
		Days -30 to 1	Up to -3	-2 to -1	-.5	0	1	3	2	3	4	5			
Administer granisetron and dexamethasone <sup>g</sup>					X										
Administer dexamethasone (8 mg PO BID)								X	X	X					
Administer cisplatin and additional chemotherapy								X-----X							
Daily recording on NVSD		X-----X							X-----X						
Review/collect NVSD												X			
Functional Living Index-Emesis Questionnaire												X			
Daily telephone contact								X	X	X	X				
Adverse event evaluation	X-----X												X		
Evaluate treatment eligibility for subsequent cycles													X		

Study procedures, Studies 32 and 33, cont'd

Study Procedures	Screening Visit	Visit 1 <sup>a</sup> (Baseline/Treatment)						Treatment Follow-up Period				Visit 2	Visit 3	30-Day Poststudy Follow-up
		Day 1 (hours)						Day	Day	Day	Day	Day	Day	
	Days -30 to 1	Up to -3	-2 to -1	-1.5	0	1	3	2	3	4	5	6	19-29 <sup>b</sup>	
Abbreviations: BID, twice daily; BUN, blood urea nitrogen; NVSD, Nausea Vomiting Subject Diary; PO, orally <sup>a</sup> Visit 1 (Day 1) study procedures could be performed in 2 days (Day -1 or Day 1). If the screening visit and Visit 1 were conducted on the same day, only one of the identical procedures required at separate visits was conducted, eg, only 1 laboratory sample was collected. <sup>b</sup> Interim medical history. <sup>c</sup> Female subjects of childbearing potential had to have a serum or urine beta-human chorionic gonadotropin pregnancy test that was performed locally within 3 days prior to study drug administration. <sup>d</sup> Laboratory evaluation at the screening visit were conducted within 7 days prior to study drug administration. <sup>e</sup> A local laboratory was used for scheduled laboratory tests and final analysis. <sup>f</sup> Additional postcisplatin hydration may also have been administered. <sup>g</sup> See Section 9.4.5 for details regarding subjects receiving taxanes as a part of the cisplatin-based chemotherapy. <sup>h</sup> For the subjects who were going to continue in the study, Visit 3 was conducted as close as possible to the next chemotherapy administration or merged with Cycle 2 Day 1 visit and not earlier than 4 days prior to the Cycle 2 Day 1 visit. Exact window depended on the duration of chemotherapy cycle in each individual case. For the subjects who did not proceed to Cycle 2, all efforts were made to ensure Visit 3 was completed and all procedures performed as specified. The Visit 3 of Cycle 1 could be combined with Day 1 of Cycle 2. <sup>i</sup> Electrocardiogram and vital signs were performed as soon as possible following completion of the cisplatin-based infusion. <sup>j</sup> Serum or urine sample for pregnancy test was collected only if the subject did not continue to Cycle 2. <sup>k</sup> Subjects could be randomized through the Interactive Web-based Randomization System on Day -2, Day -1, or Day 1 provided the subject was determined to be eligible for the study.														

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Table 9. Study Procedures, Study 34, Cycle 1

Study Procedures	Screening Visit	Visit 1 <sup>a</sup> (Baseline/Treatment)						Treatment Follow-Up Period				Visit 2	Visit 3	End of Study 30 day follow up
		Day 1 (Hours)						Day	Day	Day	Day	Day	Day	
	Days -30 to -1	Up to -3	(-2 to -1)	-1.5	0	1	3	2	3	4	5	6	10-29 <sup>e</sup>	
Informed Consent	X													
Inclusion/Exclusion Criteria	X	X												
Medical History	X	X <sup>b</sup>										X <sup>b</sup>	X <sup>b</sup>	
Alcohol consumption assessment (units per week)	X													
Physical Exam including neurological assessment	X	X										X	X	
Review of Concomitant Medications	X	X										X	X	
Height	X													
Body Weight	X	X										X	X	
Karnofsky Performance Status	X	X										X	X	
12-Lead ECG	X	X					X <sup>h</sup>					X		
Vital Signs	X	X					X <sup>h</sup>					X	X	
Pregnancy Testing <sup>f</sup>	X	X											X <sup>i</sup>	
Laboratory Tests including BUN and creatinine <sup>a</sup>	X <sup>d</sup>	X										X	X	
Collect Biomarker sample	X													

Study Procedures	Screening	Visit 1 <sup>a</sup> (Baseline/Treatment)							Treatment Follow-Up Period				Visit 2	Visit 3	End of Study 30 day follow up
	Visit	Day 1 (Hours)							Day	Day	Day	Day	Day	Day	
	Days -30 to -1	Up to -3	(-2 to -1)	-1.5	0	1	3	2	3	4	5	6	10-29 <sup>e</sup>		
Randomization	X <sup>j</sup>	X <sup>j</sup>													
Administer Rolapitant or Placebo			X-----X												
Administer Granisetron and Dexamethasone <sup>f</sup>					X										
Administer Granisetron (2 mg PO daily)								X	X						
Administer Moderately-Emetogenic Chemotherapy						X-----X									
Daily Recording on NVSD		X-----X						X-----X							
Review/Collect NVSD													X		
FLIE Questionnaire													X		
Daily Telephone Contact								X	X	X	X				
Adverse Event Evaluation		X-----X											X		X
Evaluate Treatment Eligibility for Subsequent Cycles														X	

BUN=blood urea nitrogen; ECG=electrocardiogram; FLIE= Functional Living Index-Emesis Questionnaire; MEC=moderately emetogenic chemotherapy; NV=nausea and vomiting; PO=oral; NVSD= Nausea Vomiting Subject Diary

- Visit 1 (Day 1) study procedures could be performed on Day -1, or Day 1. If the screening visit and Visit 1 were conducted on the same day only one of the identical procedures required at separate visits were conducted, e.g., only one laboratory sample was collected.
- Interim medical history.
- Female subjects of childbearing potential had to have a serum or urine  $\beta$ -hCG pregnancy test that was performed locally within 3 days prior to study drug administration.
- Laboratory evaluation at the screening visit had to be conducted within 7 days prior to study drug administration.
- A local laboratory had to be used for scheduled laboratory tests and final analysis.
- See Section 9.4.5.1 for details regarding subjects who received taxanes as a part of the MEC.

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### 5.3.6 Control Procedures

#### Randomization

##### Studies 32 and 33

Randomization occurred centrally during Cycle 1 using an interactive web based randomization system. Randomization was stratified by gender only. Patients were randomized in a 1:1 ratio to receive rolapitant or placebo.

In subsequent cycles, patients remained in the same treatment group from Cycle 1.

##### Study 34

Randomization occurred centrally during Cycle 1 using an interactive web based randomization system. Randomization was stratified by gender only. Patients were randomized in a 1:1 ratio to receive rolapitant or placebo.

In subsequent cycles, patients remained in the same treatment group from Cycle 1.

## Placebo and Blinding

### 32, 33, and 34

A double-blind technique was used. The placebo capsules were identical in appearance to rolapitant capsules. Blinding of rolapitant and placebo was preserved throughout the studies.

### 5.3.7 Primary Efficacy Endpoint

The primary endpoint was complete response in all studies. Complete response was defined for all studies as having no emesis and no rescue medication use over the period from >24 through 120 hours following initiation of chemotherapy.

### 5.3.8 Secondary Efficacy Endpoint(s)

#### Studies 32 and 33

The key secondary endpoints were the CR rates for the acute (0 through  $\leq 24$  hours) and overall (0 through  $\leq 120$  hours) phases of CINV.

The secondary efficacy endpoints for this study included the following:

- No emesis (no vomiting, retching, or dry heaves) during the acute, delayed, and, overall phases of CINV
- No significant nausea (maximum VAS  $< 25$  mm) during the overall phase of CINV
- Time to first emesis or to use of rescue medication

The tertiary efficacy endpoints for this study included the following:

- No significant nausea during the acute and delayed phases of CINV
- No nausea (maximum VAS  $< 5$  mm) and complete protection (no emesis, no rescue medication, and maximum nausea VAS  $< 25$  mm on a 0- to 100-mm scale) during the acute, delayed, and overall phases of CINV
- No impact on daily life (total score  $> 108$ ) as assessed using the FLIE Questionnaire

The key secondary endpoints were tested in a stepwise fashion. First, the primary endpoint was evaluated, and if this was significant ( $p \leq 0.05$ ), the acute phase of CINV was evaluated. If the acute phase of CINV was significant ( $p \leq 0.05$ ), the overall phase of CINV was evaluated.

#### Study 34

The same secondary and tertiary endpoints used for Studies 32 and 33 (see above) were used for Study 34.

### 5.3.9 Major Protocol Amendments

#### Study 32

The original protocol was amended once. The amendment was dated 12 October 2011 which was prior to the enrollment of any patients.

#### Study 33

There were 3 amendments to the original study protocol.

The first amendment was dated 09 and 16 December 2011 was not country-specific and was finalized prior to enrolling any patients. Protocol amendment 1 included Administrative changes, clarification to exclusion criteria, change in study drug dosage form (i.e. 1 × 200 mg to 4 × 50 mg), updates to study flow chart and reporting period for AEs.

Protocol Amendments 2 and 3 were country-specific amendments and were implemented following the initiation of the study.

Protocol Amendment 2: Korea-specific Amendment dated 16 July 2012

Wording to describe the PP population was added. The amendment also specified that the detailed specifications of the PP population would be provided prior to database lock and breaking the blind. Also, for this analysis, patients would be analyzed according to the actual treatment received in Cycle 1.

Protocol Amendment 3: South Africa-specific Amendment dated 03 October 2012

The timing of administration of granisetron and dexamethasone before the administration of chemotherapy on Day 1 in patients receiving certain taxanes as part of HEC based chemotherapy was revised. A footnote was added that specified that if requested by the site, the Sponsor was to provide dexamethasone (commercial source) for the prevention of hypersensitivity reactions for patients requiring taxanes as part of their HEC.

#### Study 34

There were 7 amendments to the original study protocol. Four amendments were implemented following the initiation of the study. Of these, 3 were country-specific and 1 was site-specific.

Korea-specific Amendment dated 16 July 2012

Wording to describe the PP Population was added which was defined as all randomized patients who received at least one dose of study drug, received MEC, and did not have protocol deviations significantly affecting the interpretation of the efficacy results (i.e., study medication dosing deviations, concomitant medication deviations, and incomplete diaries with no evidence of failure). The amendment also specified that the detailed specifications of the PP Population would be provided prior to database lock and breaking the blind. Also, for this analysis, patients would be analyzed according to the actual treatment received in Cycle 1.

South Africa-specific Amendment dated 03 October 2012

Timing of administration of granisetron and dexamethasone before the administration of chemotherapy on Day 1 in patients receiving certain taxanes as part of MEC based chemotherapy was revised. A footnote was added that specified that if requested by the site, the Sponsor was to provide dexamethasone (commercial source) for the prevention of hypersensitivity reactions for patients requiring taxanes as part of their MEC.

Thailand-specific Amendment dated 12 December 2012

The timing of administration of granisetron and dexamethasone before the administration of chemotherapy on Day 1 in patients receiving certain taxanes as part of MEC based chemotherapy was revised. A footnote was added that specified that if requested by the site, the Sponsor was to provide dexamethasone (commercial source) for the prevention of hypersensitivity reactions for patients requiring taxanes as part of their MEC.

Site-specific amendment (Monter Cancer Center) dated 18 April 2013

The inclusion criterion related to birth control was revised to specify that females of childbearing potential had to have a negative serum or urine pregnancy test at Screening and again on Day 1, prior to study drug administration. In addition, to the use of a medically accepted method of birth control prior to Visit 1 which was to continue to be used during the study and for at least 30 days after the study, it was added that female patients could agree to continued abstinence from heterosexual intercourse during this time period.

## 6 Review of Efficacy

### Efficacy Summary

The clinical studies submitted in support of this indication support the approval of rolapitant 200 mg for the prevention of nausea and vomiting used in combination with 5HT-3 agonists and steroids in the delayed phase (>24-120 hours) after cancer chemotherapy (including highly emetogenic chemotherapy). The Applicant submitted two phase 3 studies in patients receiving HEC. The Applicant submitted a single MEC study (phase 3).

Table 10. Statistical Significance by CINV Phase and Study

	32	33	34 (MEC)
Delayed	<0.001	0.043	<0.001
Acute	(b) (4)		
Overall			

## 6.1 Indication

The Sponsor has proposed the following indication statement for rolapitant:

BRAND NAME is a substance P/neurokinin-1 (NK-1) receptor antagonist indicated in adults for use in combination with other antiemetic agents for the prevention of <sup>(b) (4)</sup> delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.

*MO Comment:*

(b) (4)

### 6.1.1 Methods

Section 5.3 contains a discussion of the study protocols; Section 6 contains the study results.

### 6.1.2 Demographics

Baseline demographic characteristics for the modified intent-to-treat (MITT) population of confirmatory Studies 32, 33, and 34 are presented below. These populations represent the primary efficacy analysis populations of each of these studies. All studies randomized a predominance of white patients who were primarily less than 65 years of age. In the HEC Studies, there were more males than females. In the MEC study, there were more females than males. For the HEC studies, the most common site of the primary tumor was the lung. For the MEC study, the most common site of the primary tumor was the breast.

Table 11. Demographic and Baseline Characteristics, Studies 32, 33, and 34

Characteristic	HEC (P04832)		HEC (P04833)		HECs Pooled		MEC (P04834)	
	Rolapitant 200 mg (N=264)	Control (N=262)	Rolapitant 200 mg (N=271)	Control (N=273)	Rolapitant 200 mg (N=535)	Control (N=535)	Rolapitant 200 mg (N=666)	Control (N=666)
Age (yrs)								
Mean (SD)	57.0 (10.08)	57.7 (11.15)	58.5 (10.05)	58.5 (9.25)	57.8 (10.09)	58.1 (10.22)	56.7 (11.65)	56.6 (12.01)
Median	58.0	58.0	59.0	59.0	59.0	59.0	58.0	56.0
Range	27, 86	20, 90	21, 80	18, 83	21, 86	18, 90	22, 86	22, 88
Age (yrs), n (%)								
<45	33 (12.5)	27 (10.3)	23 (8.5)	18 (6.6)	56 (10.5)	45 (8.4)	107 (16.1)	105 (15.8)
≥45 - <65	166 (62.9)	166 (63.4)	175 (64.6)	182 (66.7)	341 (63.7)	348 (65.0)	388 (58.3)	365 (54.8)
≥65 - <75	60 (22.7)	56 (21.4)	62 (22.9)	66 (24.2)	122 (22.8)	122 (22.8)	131 (19.7)	152 (22.8)
≥75	5 (1.9)	13 (5.0)	11 (4.1)	7 (2.6)	16 (3.0)	20 (3.7)	40 (6.0)	44 (6.6)
Sex, n (%)								
Female	110 (41.7)	112 (42.7)	88 (32.5)	87 (31.9)	198 (37.0)	199 (37.2)	531 (79.7)	536 (80.5)
Male	154 (58.3)	150 (57.3)	183 (67.5)	186 (68.1)	337 (63.0)	336 (62.8)	135 (20.3)	130 (19.5)
Race, n (%)								
White	178 (67.4)	179 (68.3)	226 (83.4)	212 (77.7)	404 (75.5)	391 (73.1)	508 (76.3)	512 (76.9)
Asian	61 (23.1)	56 (21.4)	34 (12.5)	41 (15.0)	95 (17.8)	97 (18.1)	92 (13.8)	84 (12.6)
Black/African-American	2 (0.8)	3 (1.1)	2 (0.7)	3 (1.1)	4 (0.7)	6 (1.1)	24 (3.6)	29 (4.4)
American Indian or Alaska Native	2 (0.8)	0	2 (0.7)	8 (2.9)	4 (0.7)	8 (1.5)	7 (1.1)	6 (0.9)
Other <sup>a</sup>	21 (8.0)	24 (9.2)	7 (2.6)	9 (3.3)	28 (5.2)	33 (6.2)	35 (5.3)	35 (5.3)
Characteristic	HEC (P04832)		HEC (P04833)		HECs Pooled		MEC (P04834)	
	Rolapitant 200 mg (N=264)	Control (N=262)	Rolapitant 200 mg (N=271)	Control (N=273)	Rolapitant 200 mg (N=535)	Control (N=535)	Rolapitant 200 mg (N=666)	Control (N=666)
Ethnicity, n (%)								
Hispanic or Latino	33 (12.5)	34 (13.0)	36 (13.3)	38 (13.9)	69 (12.9)	72 (13.5)	77 (11.6)	70 (10.6)
Not Hispanic or Latino	231 (87.5)	228 (87.0)	235 (86.7)	235 (86.1)	466 (87.1)	463 (86.5)	584 (88.4)	593 (89.4)
BSA (m <sup>2</sup> )								
Mean (SD)	1.77 (0.224)	1.78 (0.259)	1.80 (0.227)	1.81 (0.211)	1.78 (0.226)	1.79 (0.236)	1.80 (0.228)	1.82 (0.235)
Median	1.75	1.76	1.80	1.79	1.77	1.78	1.78	1.79
Primary Tumor Site, n (%) <sup>b</sup>								
Breast	7 (2.7)	9 (3.4)	5 (1.8)	17 (6.2)	12 (2.2)	26 (4.9)	417 (62.6)	428 (64.3)
Lung	106 (40.2)	98 (37.4)	129 (47.6)	134 (49.1)	235 (43.9)	232 (43.4)	102 (15.3)	118 (17.7)
Head & Neck	52 (19.7)	55 (21.0)	45 (16.6)	45 (16.5)	97 (18.1)	100 (18.7)	5 (0.8)	6 (0.9)
Stomach	11 (4.2)	9 (3.4)	23 (8.5)	25 (9.2)	34 (6.4)	34 (6.4)	8 (1.2)	9 (1.4)
Colon/Rectum	1 (0.4)	0	1 (0.4)	0	2 (0.4)	0	38 (5.7)	27 (4.1)
Ovary	23 (8.7)	25 (9.5)	10 (3.7)	6 (2.2)	33 (6.2)	31 (5.8)	33 (5.0)	23 (3.5)
Alcohol Consumption, n (%) <sup>c</sup>								
0 drinks/wk	225 (85.9)	197 (75.5)	209 (78.0)	217 (79.8)	434 (81.9)	414 (77.7)	540 (81.2)	533 (80.0)
>0 to ≤5 drinks/wk	26 (9.9)	35 (13.4)	33 (12.3)	34 (12.5)	59 (11.1)	69 (12.9)	96 (14.4)	92 (13.8)
>5 to ≤10 drinks/wk	5 (1.9)	15 (5.7)	7 (2.6)	8 (2.9)	12 (2.3)	23 (4.3)	15 (2.3)	17 (2.6)
>10 drinks/wk	6 (2.3)	14 (5.4)	19 (7.1)	13 (4.8)	25 (4.7)	27 (5.1)	14 (2.1)	24 (3.6)

Table 11, cont'd.

Characteristic	HEC (P04832)		HEC (P04833)		HECs Pooled		MEC (P04834)	
	Rolapitant 200 mg (N=264)	Control (N=262)	Rolapitant 200 mg (N=271)	Control (N=273)	Rolapitant 200 mg (N=535)	Control (N=535)	Rolapitant 200 mg (N=666)	Control (N=666)
Geographic Regions, n (%)								
Europe	133 (50.4)	134 (51.1)	173 (63.8)	165 (60.4)	306 (57.2)	299 (55.9)	312 (46.8)	299 (44.9)
Eastern Europe	82 (31.1)	85 (32.4)	37 (13.7)	44 (16.1)	119 (22.2)	129 (24.1)	159 (23.9)	154 (23.1)
Central Europe	5 (1.9)	8 (3.1)	69 (25.5)	74 (27.1)	74 (13.8)	82 (15.3)	79 (11.9)	68 (10.2)
Western Europe	46 (17.4)	41 (15.6)	67 (24.7)	47 (17.2)	113 (21.1)	88 (16.4)	74 (11.1)	77 (11.6)
North America	42 (15.9)	45 (17.2)	17 (6.3)	19 (7.0)	59 (11.0)	64 (12.0)	216 (32.4)	229 (34.4)
Asia/South Africa	61 (23.1)	55 (21.0)	44 (16.2)	46 (16.8)	105 (19.6)	101 (18.9)	107 (16.1)	106 (15.9)
Central/South America	28 (10.6)	28 (10.7)	37 (13.7)	43 (15.8)	65 (12.1)	71 (13.3)	31 (4.7)	32 (4.8)

Abbreviations: BSA = body surface area; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; MITT = modified intent to treat; SD = standard deviation.

Note: number of subjects in each analysis = MITT population (i.e., no missing data) unless otherwise noted

\* Other includes: Native Hawaiian or Other Pacific Islander, Multiracial, Other, Unknown

<sup>b</sup> Only tumor sites occurring in 5% of more of subjects in either treatment group in the pooled HEC studies or MEC study are presented; see [Appendix Table 2A](#) for complete list.

<sup>c</sup> Data were self-reported and are missing for 8 subjects: HEC P04832: 2 and 1 subject in the rolapitant and control groups, respectively; HEC P04833: 3 and 1 subject, respectively; MEC P04834: 1 and 0 subjects, respectively.

Source: [Appendix Table 2A](#)

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**MO Comment:**

*In general, randomization produced demographic subgroups which were well-balanced between treatment groups.*

**6.1.3 Patient Disposition**

In Studies 32, 33, and 34 most randomized patients completed Cycle 1 (the primary efficacy evaluation period). See

Table 12 below for an overview of Patient disposition in Studies 32, 33, and 34. A more detailed discussion of patient disposition for individual studies is located in this section.

Table 12. Studies 32, 33, and 34, Patient Disposition, Cycle 1

Number of Subjects:	HEC (P04832)		HEC (P04833)		HECs Pooled		MEC (P04834)	
	Rolapitant 200 mg n (%)	Control n (%)						
Randomized <sup>a</sup>	266	266	278	277	544	543	684	685
Included in MITT Population <sup>b,c</sup>	264 (100)	262 (100)	271 (100)	273 (100)	535 (100)	535 (100)	666 (100)	666 (100)
Received Chemotherapy	262 (99.2)	262 (100)	271 (100)	272 (99.6)	533 (99.6)	534 (99.8)	666 (100)	665 (99.8)
Completed Cycle <sup>d</sup>	251 (95.1)	240 (91.6)	258 (95.2)	258 (94.5)	509 (95.1)	498 (93.1)	632 (94.9)	632 (94.9)
Discontinued During Cycle 1	13 (4.9)	22 (8.4)	13 (4.8)	15 (5.5)	26 (4.9)	37 (6.9)	34 (5.1)	34 (5.1)
Adverse event	2 (0.8)	5 (1.9)	2 (0.7)	2 (0.7)	4 (0.7)	7 (1.3)	6 (0.9)	7 (1.1)
Consent withdrawal	6 (2.3)	7 (2.7)	5 (1.8)	4 (1.5)	11 (2.1)	11 (2.1)	9 (1.4)	15 (2.3)
Death	2 (0.8)	4 (1.5)	2 (0.7)	1 (0.4)	4 (0.7)	5 (0.9)	7 (1.1)	2 (0.3)
Lack Of Efficacy	0	0	1 (0.4)	1 (0.4)	1 (0.2)	1 (0.2)	2 (0.3)	4 (0.6)
Lost To Follow-Up	1 (0.4)	2 (0.8)	0	3 (1.1)	1 (0.2)	5 (0.9)	4 (0.6)	0
Protocol Non-Compliance	1 (0.4)	4 (1.5)	3 (1.1)	3 (1.1)	4 (0.7)	7 (1.3)	4 (0.6)	6 (0.9)
Study Completed <sup>e</sup>	0	0	0	0	0	0	2 (0.3)	0
Other <sup>f</sup>	1 (0.4)	0	0	1 (0.4)	1 (0.2)	1 (0.2)	0	0

Abbreviations: GCP = Good Clinical Practices; HEC = highly emetogenic chemotherapy; MEC = moderately emetogenic chemotherapy; MITT = modified intent-to-treat.

<sup>a</sup> Subjects are counted in the treatment group in which they were randomized.

<sup>b</sup> Percent is calculated using the number of subjects in the MITT population. All rows (except randomized) are based on the MITT population.

<sup>c</sup> MITT is defined as subjects who were randomized, received study drug, and were not enrolled at the site with major GCP violations.

<sup>d</sup> Subjects are considered as having completed Cycle 1 if they completed the last visit of the cycle or entered into the next cycle.

<sup>e</sup> Collected as chemotherapy course completed or change in therapy

<sup>f</sup> Including investigator judgment.

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### Study 32

For Study 32, a total of 532 patients were randomized to receive study medication. Of these patients, 266 were randomized to receive active rolapitant with granisetron and dexamethasone (active study treatment) and 266 patients were randomized to receive placebo with granisetron and dexamethasone (control). Six randomized patients (2 rolapitant and 4 control patients) did not receive study drug and were, therefore, excluded from the MITT population. The following patients did not receive study drug:

- Patient 136-2008 (rolapitant) experienced an adverse event of ventricular bigeminy
- Patient 413-2009 (rolapitant) \* send IR (other: renewal EC approval letter is pending)
- Patient 122-2001 (placebo) experienced an adverse event of coronary artery disease
- Patient 178-2012 (placebo) withdrew consent
- Patient 410-2001 (placebo) experienced an adverse event of superior vena cava syndrome
- Patient 416-2005 did not have the study drug available at the site

Overall, 262 rolapitant patients (99.2%) and 262 control patients (100%) in the MITT population received  $\geq 1$  chemotherapeutic agent during Cycle 1; 2 patients in the rolapitant group did not receive chemotherapy due to a TEAE on Cycle 1, Day 1 (C1D1).

- Patient 204-2024, a patient with pre-existing myocardial ischemia, cardiac and respiratory failure, had worsening cardiac failure post-rolapitane dose and during infusion of cisplatin and cyclophosphamide.
- Patient 506-2007 withdrew consent on C1D1 after receiving 1 of 4 capsules of rolapitane.

While all placebo patients received  $\geq 1$  chemotherapeutic agents during Cycle 1, one patient did not receive cisplatin-based chemotherapy. Patient 175-2005 (placebo) received cyclophosphamide/doxorubicin.

The mean and median cisplatin dose administered in Cycle 1 was similar in the 2 treatment groups (see Table 13 below). The majority of patients who received cisplatin in the rolapitane and control groups received 60 to  $<80$  mg/m<sup>2</sup> of cisplatin in Cycle 1.

Table 13. Study 32, Dose of Cisplatin Administered, Cycle 1

<b>Dose (mg/m<sup>2</sup>) IV</b>	<b>Rolapitane (N = 264) n (%)</b>	<b>Control (N = 262) n (%)</b>
Number of Subjects <sup>a</sup>	262	261
<60 <sup>b</sup>	10 (3.8)	14 (5.4)
60- <80	171 (65.3)	175 (67.0)
80-<100	50 (19.1)	43 (16.5)
$\geq 100$	31 (11.8)	29 (11.1)
Mean (SD)	77.2 (12.62)	76.4 (14.11)
Median	75	75
Min, Max	56, 113	47, 161

Abbreviations: MITT = Modified Intent-to Treat; SD = standard deviation  
Electronically copied and reproduced from Study 32 (pdf #2) p 79/1803

An additional characteristic of study patients that is important to address is the site of the primary tumor. Cisplatin is used to treat a variety of cancers. In Study 32, the most common primary tumor sites were lung, head and neck, ovarian, stomach and uterine.

Table 14. Study 32, Most Common Primary Tumor Sites

Primary Tumor Site	Rolapitant N=264 n (%)	Control N=262 n (%)	Total N=256 n (%)
Lung	106 (40.2)	98 (37.4)	204 (38.8)
Head and Neck	52 (19.7)	55 (21.0)	107 (20.3)
Ovarian	23 (8.7)	25 (9.5)	48 (9.1)
Stomach	11 (4.2)	9 (3.4)	20 (3.8)
Uterine	9 (3.4)	11 (4.2)	20 (3.8)
Other tumor sites	63 (23.9)	64 (24.4)	127 (24.1)

Reviewer's Table. Source Study 32 CSR, Table 14.1.8

### Study 33

For Study 33, a total of 555 patients were randomized to receive study medication. Of these patients, 278 were randomized to receive active rolapitant with granisetron and dexamethasone (active study treatment) and 277 patients were randomized to receive placebo with granisetron and dexamethasone (control).

Overall, 272 rolapitant patients (97.8%) and 262 control patients (98.9%) in the MITT population received  $\geq 1$  study drug during Cycle 1. Six patients randomized to the rolapitant group did not receive study drug for the following reasons:

- Patient 180-3064 and Patient 418-3013- consent withdrawn
- Patient 182-3001- IV Granisetron not available at study site
- Patients 304-3024, 318-3001, and 387-3001- protocol violations

Three patients randomized to the control group in Study 33 did not receive study drug. Patients 228-3013 and 253-3005 withdrew consent. Patient 419-3012 discontinued due to protocol violations.

During Study 33, all rolapitant patients who received rolapitant and 99.6% of control patients in the MITT population received  $\geq 1$  chemotherapeutic agent during Cycle 1. One patient in the control group (Patient 180-3043) did not receive chemotherapy due to worsening hypertension and was withdrawn from the Study on Day 1.

Overall, 270 (99.6%) rolapitant patients and 270 (98.9%) control patients received at least one dose of cisplatin based chemotherapy during Cycle 1. One patient treated with rolapitant and 2 patients that received control did not receive cisplatin-based chemotherapy during this cycle. Specifically, the following patients did not receive cisplatin-based chemotherapy:

- Patient 239-3003 (rolapitant) received carboplatin
- Patient 239-3004 (placebo) received carboplatin/etoposide
- Patient 239-3001 (placebo) received dacarbazine

The mean and median cisplatin dose administered in Cycle 1 was similar in the 2 treatment groups. The majority of patients who received cisplatin in the rolapitant (72.6%) and control groups (67.8%) received 60-<80 mg/m<sup>2</sup> of cisplatin in Cycle 1.

Table 15. Study 33, Dose of Cisplatin Administered, Cycle 1

Dose (mg/m <sup>2</sup> ) IV	Rolapitant (N=271) n (%)	Control (N=273) n (%)
Number of Subjects <sup>a</sup> 270		270
<60 <sup>b</sup>	8 (3.0)	7 (2.6)
60- <80	196 (72.6)	183 (67.8)
80-<100	39 (14.4)	49 (18.1)
≥100	27 (10.0)	31 (11.5)
Mean (SD)	75.8 (12.77)	76.8 (14.57)
Median 75		75
Min, Max	30, 154	57, 190

<sup>a</sup> Four subjects did not receive cisplatin: Subject 180-3043 received study drug, but not chemotherapy; Subject 239-3003 received only carboplatin; Subject 239-3004 received carboplatin/etoposide; and Subject 239-3001 received dacarbazine.

<sup>b</sup> Fourteen of the 15 subjects who received <60 mg/m<sup>2</sup> of cisplatin received a cisplatin dose ≥50 mg/m<sup>2</sup>, which is considered HEC. Subject 418-3009 in the rolapitant group received cisplatin 30 mg/m<sup>2</sup>.

Electronically copied and reproduced, Study 33 CSR p 82/1911

In Study 33, the most common primary tumor sites were lung, head and neck, stomach, breast, and ovarian. See Table below.

Table 16. Study 33, Most Common Primary Tumor Sites

Primary Tumor Site	Rolapitant N=271 n (%)	Control N=273 n (%)	Total N=544 n (%)
Lung	129 (47.6)	134 (49.1)	263 (48.3)
Head and Neck	45 (16.6)	45 (16.5)	90 (16.5)
Stomach	23 (8.5)	25 (9.2)	48 (8.8)
Breast	5 (1.8)	17 (6.1)	22 (4.0)
Ovarian	10 (3.7)	6 (2.2)	16 (2.9)
Other tumor sites	59 (21.8)	46 (16.8)	105 (19.3)

Reviewer's Table. Source CSR Study 33, Table 14.1.8

### Study 34

Study 34 was the single trial submitted in support of the current NDA that treated patients with moderately emetogenic chemotherapy (MEC) agents. A total of 1,369 patients were randomized to receive study medication (684 rolapitant, 685 placebo).

Overall, 670 rolapitant patients (98.0%) and 674 control patients (98.4%) in the MITT population received  $\geq 1$  study drug during Cycle 1. Fourteen patients randomized to the rolapitant group did not receive study drug for the following reasons:

- Patients 123-4006- protocol violation(s)
- Patient 163-4006- protocol violation(s)
- Patient 184-4004- protocol violation(s)
- Patient 164-4005- consent withdrawn
- Patient 231-4004- protocol violation(s)
- Patient 241-4001- consent withdrawn
- Patient 254-4019- protocol violation(s)
- Patient 260-4002- consent withdrawn
- Patient 261-4001- consent withdrawn
- Patient 270-4001- IP not received into clinic on C1D1
- Patient 270-4004- protocol violation(s)
- Patient 323-40060- consent withdrawn
- Patient 332-4020- protocol violation(s)
- Patient 430-4002- consent withdrawn

Eleven patients randomized to the control group in Study 34 did not receive study drug for the following reasons:

Patient 113-4007- consent withdrawn  
Patient 123-4009- protocol violation(s)  
Patient 126-4002- protocol violation(s)  
Patient 143-4009- protocol violation(s)  
Patient 161-4001- consent withdrawn  
Patient 164-4004- consent withdrawn  
Patient 258-4043- consent withdrawn  
Patient 262-4001- consent withdrawn  
Patient 282-4009- consent withdrawn  
Patient 383-4027- consent withdrawn  
Patient 457-4004- protocol violation(s)

Twenty-five patients did not receive study drug and an additional twelve patients were treated at Site 181. During a scheduled monitoring visit to Site 181, major study assessment deviations and non-GCP compliant practices were noted. Regulatory bodies were notified and the data from the 12 patients enrolled at this site were deemed unreliable and unusable and these patients were not included in the MITT population. Therefore, the MITT population included 666 patients randomized to each treatment group.

During Study 34, 670 rolapitant patients (98.1%) and 673 placebo patients (98.2%) received  $\geq 1$  chemotherapeutic agent during Cycle 1.

In Study 34, the most common primary cancer types being treated were cancers of the breast, lung, colon/rectum, and ovary. See Table 17 below.

Table 17. Study 34, Most Common Primary Tumor Sites

<b>Primary Tumor Site</b>	<b>Rolapitant N=666 n (%)</b>	<b>Control N=666 n (%)</b>	<b>Total N=1332 n (%)</b>
<b>Breast</b>	417 (62.6)	428 (64.3)	845 (63.4)
<b>Lung</b>	102 (15.3)	118 (17.7)	220 (16.5)
<b>Colon/Rectum</b>	38 (5.7)	27 (4.1)	65 (4.9)
<b>Ovary</b>	33 (5.0)	23 (3.5)	56 (4.2)
<b>Other tumor sites</b>	76 (11.4)	70 (10.5)	146 (11.0)

Reviewer's Table. Source CSR Study 34, Table 14.1.8

#### 6.1.4 Analysis of Primary Endpoint(s)

For all studies, the primary efficacy endpoint was complete response (CR) defined as having no emesis and no rescue medication use in the delayed phase. No emesis was defined as no vomiting, retching, or dry heaving. The primary analysis population was all randomized patients who received chemotherapy and a dose of study medication who also had at least one post treatment efficacy assessment in Cycle 1. The data for cycle 1 were the primary analysis set.

Missing efficacy data were handled as follows:

- If either the acute or delayed phase outcome value was assessed as a failure and the other outcome was missing, the patient's overall outcome was counted as a failure; or
- If either the acute or delayed phase value was assessed as a success and the other outcome was missing or both phase outcome values were missing, the patient's outcome was considered as missing both overall and in the phase(s) in which data were missing.

#### Studies 32 and 33

Patients taking HEC were enrolled in Studies 32 and 33. In these studies, the primary endpoint was the CINV complete response rate during the delayed phase, i.e., >24 to 120 hours after taking chemotherapy. The MITT population was the pre-specified analysis set.

In Study 32, the complete response rate in the delayed phase was statistically significantly higher in the rolapitant 200 mg compared to the placebo group. The control rate seen in rolapitant patients was 72.7% while the control rate seen in placebo patients was 58.4%,  $p < 0.001$ . This treatment difference of 14.3% was the highest seen among the confirmatory studies reviewed for current NDA.

Table 18. Complete Response, Delayed Phase, Study 32, MITT Population

	Rolapitant 200 mg	Placebo	Treatment Difference	p-value	Odds Ratio (95% CI)
Complete Response, Delayed Phase (>24-120 hours)	72.7% (192/264)	58.4% (153/262)	14.3%	<0.001	1.9 (1.3, 2.7)

Odds ratio, CI, and p-value are calculated using the CM test adjusted for gender

### Study 33

In Study 33, the complete response rate in the delayed phase was statistically significantly higher in the rolapitant 200 mg group compared to the placebo group. The control rate seen in rolapitant patients was 70.1% while the control rate seen in placebo patients was 61.9%,  $p = 0.043$ . This treatment difference of

The complete response rate treatment difference (rolapitant-placebo) seen in Study 32 was 14.3% ( $p < 0.001$ ). In Study 33, the treatment difference was 8.2% ( $p = 0.043$ ). The primary endpoint results for Study 32 were highly statistically significant while the results for Study 33 were closer to marginal statistical significance.

Table 19. Complete Response, Delayed Phase, Study 33, MITT Population

	Rolapitant 200 mg	Placebo	Treatment Difference	p-value	Odds Ratio (95% CI)
Complete Response, Delayed Phase (>24-120 hours)	70.1% (190/271)	61.9% (169/273)	8.2%	0.043	1.4 (1.0, 2.1)

Odds ratio, CI, and p-value calculated using Cochran-Mantel-Haenszel test adjusted for gender

While the primary analysis set was the modified intent-to-treat (MITT) population, an examination of the complete response rates in other populations supports the conclusion that there is a statistically significant difference in complete response rates in the delayed phase between rolapitant 200 mg and placebo (in favor of rolapitant).

Study 34

In the single MEC trial, Study 34, the complete response rate for patients taking rolapitant in the delayed phase was 71.3% compared with a 61.6% complete response rate seen in placebo patients, p<0.001. The treatment difference of 9.7% was higher similar to the treatment differences seen in the similarly-designed HEC studies.

Table 20. Complete Response, Delayed Phase, Study 34, MITT Population

	Rolapitant 200 mg	Placebo	Treatment Difference	p-value	Odds Ratio (95% CI)
Complete Response, Delayed Phase (>24-120 hours)	71.3% (475/666)	61.6% (410/666)	9.7%	<0.001	1.6 (1.2, 2.0)

Odds ratio, CI, and p-value calculated using Cochran-Mantel-Haenszel test adjusted for gender

*MO Comment:*

*The primary efficacy results from studies 32, 33, and 34 support the efficacy of rolapitant 200 mg for the prevention of CINV in the delayed phase (>24-120 hours) following the administration of HEC and MEC.*

(b) (4)

(b) (4)

6.1.5 Analysis of Secondary Endpoints(s)

Study 32

The key secondary endpoints assessed were complete response in the acute phase and complete response in the overall phase. The key secondary endpoints were assessed in a step-wise fashion. Other secondary and tertiary endpoints included no emesis, no nausea, no significant nausea, complete protection and total control each assessed in the acute, delayed and overall phases, as well as no impact of CINV on daily life. In addition, the time to first emesis or use of rescue medication was assessed.

Table 21. Study 32, Key Secondary Endpoints, MITT

Complete Response	Rolapitant 200 mg	Placebo	p-value	Odds Ratio (95% CI)
Acute (0-24 hours)	(b) (4)			

Overall (0-120 hours)	(b) (4)
-----------------------	---------

Given that the key secondary endpoints were statistically significant, the other secondary endpoints were evaluated and p-values were calculated. Tests of statistical significance were not calculated for the tertiary endpoints. See Table 22 below.

Table 22. Study 32, Other Secondary and Tertiary Endpoints, MITT

Efficacy Variable	CINV Phase	Rolapitant (N=264) Rate (%)	Control (N=262) Rate (%)	Unadjusted P-Value	Adjusted P-Value	Statistical Significance	Method of Determination
<b>Other Secondary</b>							
No Emesis <sup>b</sup>	Acute	(b) (4)				Yes	Bonferroni-Holm
No Emesis	Delayed	(b) (4)				Yes	Bonferroni-Holm
No Emesis	Overall	(b) (4)				Yes	Bonferroni-Holm
No Significant Nausea <sup>c</sup>	Overall	(b) (4)				Yes	Bonferroni-Holm
Median Time (hr) to 1 <sup>st</sup> emesis or use of rescue medication <sup>d</sup>	Overall	(b) (4)				Yes	Bonferroni-Holm
<b>Tertiary</b>							
No Significant Nausea	Acute	(b) (4)				N/A	Not Done
No Significant Nausea	Delayed	(b) (4)				N/A	Not Done
No Nausea <sup>e</sup>	Acute	(b) (4)				N/A	Not Done
No Nausea	Delayed	(b) (4)				N/A	Not Done
No Nausea	Overall	(b) (4)				N/A	Not Done
Complete Protection <sup>f</sup>	Acute	(b) (4)				N/A	Not Done
Complete Protection	Delayed	(b) (4)				N/A	Not Done
Complete Protection	Overall	(b) (4)				N/A	Not Done
No Impact on Daily Life <sup>g</sup>	Overall	(b) (4)				N/A	Not Done

Abbreviations: CINV = chemotherapy-induced nausea and vomiting; FLIE = Functional Living Index-Emesis; N/C=not calculated; N/A=not applicable; NE=not estimable; VAS = visual analogue scale

<sup>a</sup> No emesis and no use of rescue medication.

<sup>b</sup> No vomiting, retching, or dry heaves.

<sup>c</sup> Maximum VAS <25 mm on the scale of 0 to 100 mm for the Nausea and Vomiting Subject Diary Question 2.

<sup>d</sup> Event rates (%) for each treatment group were provided for all efficacy variables except for "median time (hr) to" variable where median time was presented instead.

<sup>e</sup> Maximum VAS <5 mm on the scale of 0 to 100 mm for the Nausea and Vomiting Subject Diary Question 2.

<sup>f</sup> No emesis, no rescue medication, and max nausea VAS <25 mm on the scale of 0 to 100 mm for the Nausea and Vomiting Subject Diary Question 2.

<sup>g</sup> FLIE total score >108. Denominator was based on the number of subjects with valid questionnaire.

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No emesis was defined as no vomiting, retching, or dry heaves, and included patients who received rescue medication. For the acute, delayed, and overall phases, there was a statistically significant difference (in favor of rolapitant) in the rate of no emesis between the rolapitant and the control group. No significant nausea was defined as a maximum reported VAS of <25 mm. No significant nausea was reported by significantly more rolapitant than control treated patients in the overall phase (b) (4)

**MO Comment:**

In Study 32, the primary, secondary, and tertiary study results support the use of rolapitant 200 mg for the prevention of CINV in (b) (4) delayed phases. The results of the 200 mg rolapitant group primary endpoint results were statistically

*significantly different from placebo (in favor of rolapitant) for the prevention of CINV. The statistical significance of the tertiary endpoints was not determined. However, for each tertiary endpoint, a higher proportion of rolapitant 200 mg patients (compared with placebo) reported outcomes consistent with prevention of CINV.*

The time to first emesis or use of rescue medication reported in Study 32 is shown graphically in a Kaplan-Meier Plot in Figure 3 below. At time 0, 100% of patients in both treatment groups are in CR (i.e. no one has experienced emesis or rescue medication use). Separation of the curves occurs at about 12 hours (during the acute phase) and the separation continues through 120 hours. After about 50 hours, the rolapitant curve reaches a plateau which suggests that after 50 hours, if a patient remains in CR, this state is likely to continue for the remainder of the 120 hours.

Figure 3. Study 32, Kaplan-Meier Plot of Proportions of Patients without Emesis or Use of Rescue Medication (MITT Population)

(b) (4)

### Study 33

Studies 32 and 33 were identical in design. See the section above for an explanation of the secondary and tertiary endpoints. See study results below.

Table 23. Study 33, Key Secondary Endpoint Results, MITT

Complete Response	Rolapitant 200 mg	Placebo	p-value	Odds Ratio (95% CI)
Acute (0-24 hours)	(b) (4)			
Overall (0-120 hours)				

Efficacy Variable	Phase	Study 33		
		Rolapitant N=271	Placebo N=	p-value
<b>Other Secondary</b>				
No emesis	Acute	(b) (4)		
No emesis	Delayed			
No emesis	Overall			
<b>Tertiary</b>				
No significant nausea	Acute	(b) (4)		
No significant nausea	Delayed			
No nausea	Acute			
No nausea	Delayed			
No nausea	Overall			
Complete protection	Acute			
Complete protection	Delayed			
Complete protection	Overall			
No impact on daily life				

*MO Comment:*

(b) (4)

The complete response (CR) rate for patients randomized to receive rolapitant was not found to be statistically significantly different from the CR rate observed in patients taking placebo during the acute and overall phases. Given that Study 51 was determined not to be an adequate and well-controlled study, there are only two studies –Study 32 and Study 33—that can be used to determine the efficacy of rolapitant.

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

Study 34

Table 24. Study 34, Key Secondary Endpoints Results, MITT

Complete Response	Rolapitant 200 mg	Placebo	p-value	Odds Ratio (95% CI)
Acute (0-24 hours)	(b) (4)			
Overall (0-120 hours)				

*MO Comment:*

(b) (4)

6.1.6 Other Endpoints

At the Division's request, the Applicant conducted a *post-hoc* analysis of CR in the acute phase among the subset of patients who achieved CR in the delayed phase.

Table 25. CR in the Acute Phase in Subset of Patients with CR in the Delayed Phase

Study	Rolapitant	Control
32	(b) (4)	
33		
34		

Source: Applicant's IR Response, Submission 010, Received 01/21/2015

*MO Comment:*

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

*Both treatment groups received granisteron and dexamethasone, drugs known to be effective in the acute phase.*

6.1.7 Subpopulations

Studies 32 and 33 were identical in design; however, the efficacy outcomes by gender were very different. In Study 33, the response for CR during the delayed, acute and overall phases of CINV was similar for males in the rolapitant and control groups. In contrast, in females in this study the rates were consistently higher for the rolapitant

group over control. These results were not consistent with the results obtained in any of the other CINV studies. See below.

In HEC Study 33, CR rates for males in the delayed phase were 68.3% and 67.2% in the rolapitant and control groups, respectively; (b) (4) respectively, in the acute phase; and (b) (4) in both groups in the overall phase.

In contrast, in HEC Study 32, CR rates for males were consistently higher than placebo in all phases: delayed phase rates were 75.3% and 62.0% in the rolapitant and control groups, respectively; acute phase rates were (b) (4) respectively.

Table 26. Complete Response by Gender, Acute Phase, HEC Studies

	Number of pts (%)		Complete Response (%)			
	Male	Female	Male		Female	
			Rolapitant	Control	Rolapitant	Control
Study 32	304 (58)	222 (42)	(b) (4)			
Study 33	369 (68)	175 (32)				

Reviewer's Table.

A brief review of efficacy by age subgroups did not reveal any significant differential efficacy based on age. The majority of patients enrolled in the confirmatory studies were white race. Therefore, the meaning of differential efficacy results by race is difficult to interpret.

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The confirmatory trials evaluated a single dose of rolapitant—200 mg. Therefore, information regarding other doses was not reviewed.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The confirmatory studies support the efficacy of Rolapitant 200mg for the prevention of CINV in the delayed phase (>24-120 hours post chemotherapy). This is the extent of persistence of effects described in the Applicant's submission.

### 6.1.10 Additional Efficacy Issues/Analyses

Analysis of the rate of complete response in the delayed phase across studies supports the efficacy of rolapitant for the prevention of CINV in the delayed phase. (b) (4)



(b) (4)

HEC Summary, Acute Phase

Study	p-value
32	(b) (4)
33	(b) (4)

Reviewer's Table

The rolapitant categorization of emetogenic severity was based on the precedent set by previous CINV drug approvals. However, in 2011 the American Society of Clinical Oncology published new antiemetic guidelines that presented changes in emetogenicity category (from MEC to HEC) for anthracyclines (including doxorubicin, epirubicin, idarubicin and daunorubicin) administered in combination with cyclophosphamide.<sup>2</sup> At the Division's request, the Applicant conducted a *post-hoc* analysis of CR rates by re-categorizing patients as HEC or MEC according to the ASCO 2011 guidelines. With this additional pool of HEC patients, (b) (4) See Table 27 below for the number of HEC and MEC patients in Study 34 by ASCO 2011 criteria.

Table 27. Emetogenicity Categorization according to ASCO 2011 Guidelines, Study 34

	Rolapitant (N)	Placebo (N)
HEC	351	360
MEC	315	306
Total	666	666

The CR results for the HEC patients (according to ASCO 2011 Guidelines) (b) (4) in Studies 32 and 33—the CR rate seen in rolapitant patients was not statistically significantly different from the CR rate seen in placebo patients.

<sup>2</sup> Basch E, Prestrud A, Hesketh P, et al. Antiemetics; American Society of Clinical Oncology Clinical Practice Guideline Update. JCO. 2011. Vol 29:4189-4198.

Table 28. CR, HEC Patients (by ASCO 2011 Guidelines), Study 34

Efficacy Variable	CINV Phase	Rolapitant 200mg	Control	Rolapitant 200mg vs Control	
		n /N (%)	n /N (%)	Odds Ratio (95%CI)	P-Value[1]
Complete Response	Delayed	234 / 351 (66.7)	215 / 360 (59.7)	1.3 (1.0, 1.8)	0.073
	Acute				(b) (4)
	Overall				

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*MO Comment:*

(b) (4)

## 7 Review of Safety

### Safety Summary

In general, the use of rolapitant for the proposed indication of the prevention of CINV in the delayed phase appears to represent an acceptable risk. See the Risk Benefit Assessment Section 1.2.

### 7.1 Methods

Adverse events and medical histories were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15.0. All medications were coded using the World Health Organization (WHO) Drug Dictionary (March 2012 version).

All safety analyses were performed on the Safety Population. The safety population included all patients who were randomized to any treatment group and received at least one dose of study drug. Safety analysis was based on actual treatment received in Studies 51, 32, 33, and 34. While not adequate for safety, Study 51 provided important safety information. Safety information of healthy patients who received single doses of rolapitant as monotherapy will not be discussed briefly in Pooling Group 2 as described below.

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Rolapitant was evaluated in 1,567 patients with cancer undergoing treatment with MEC or HEC in controlled phase 2 and 3 studies. During Study 51, a phase 2 trial, 273 patients were exposed to doses of rolapitant less than 200 mg. In Studies 32, 33, 34, and 51 there were 1,294 patients exposed to 200 mg of rolapitant.

### 7.1.2 Categorization of Adverse Events

Number of Subjects with:	HEC (P04832, P04833, P04351)			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 <sup>a</sup> N = 1567 n (%)
≥1 TEAE	393 (62.7)	193 (70.7) <sup>b</sup>	397 (63.6)	447 (66.3)	431 (64.3)	840 (64.6)	828 (64.0)	1021 (65.2)
≥1 Treatment-related TEAE <sup>c</sup>	30 (4.8)	45 (16.5) <sup>d</sup>	26 (4.2)	52 (7.7)	64 (9.6)	82 (6.3)	90 (7.0)	135 (8.6)
TEAE leading to study drug discontinuation	32 (5.1)	9 (3.3)	26 (4.2)	16 (2.4)	14 (2.1)	48 (3.7)	40 (3.1)	49 (3.1)
≥1 TEAE of CTCAE Grade ≥3	125 (19.9)	51 (18.7)	116 (18.6)	89 (13.2)	95 (14.2)	214 (16.4)	211 (16.3)	262 (16.7)
≥1 TESAE	78 (12.4)	31 (11.4)	58 (9.3)	48 (7.1)	44 (6.6)	126 (9.7)	102 (7.9)	133 (8.5)
≥1 Treatment-related TESAE	0	3 (1.1)	0	0	0	0	0	3 (0.2)
TEAE with outcome of death	12 (1.9)	3 (1.1)	13 (2.1)	3 (0.4)	8 (1.2)	15 (1.2)	21 (1.6)	24 (1.5)
Treatment-related TEAE with outcome of death	0	0	0	0	0	0	0	0

Abbreviations: AE, adverse event; CINV, chemotherapy-induced nausea and vomiting; CTCAE, Common Terminology Criteria for Adverse Events; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

<sup>a</sup> Subjects who received any rolapitant doses are combined.

<sup>b</sup> The incidence of TEAEs across active treatment groups and the control group in Study P04351 were similar, but was higher than those observed in Studies P04832, P04833, and P04834.

<sup>c</sup> Any TEAE that is possibly, probably, or definitely related to study drug according to AE CRF.

<sup>d</sup> The incidence of treatment-related TEAEs across active treatment groups and the control group in Study P04351 were similar, but slightly higher than those observed in Studies P04832, P04833, and P04834.

Source: Appendix Table 11

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

For the analysis of safety, patients were separated into two primary analysis sets. Pooling Group 1 was the primary safety set and included all patients from the adequate, well-controlled, double-blind, randomized, parallel comparison studies conducted in patients at risk for CINV in studies 51, 32, 33, and 34. The safety assessment included analysis of AEs, clinical laboratory parameters, vital signs, ECGs, neurological parameters, and concomitant medications. The effect of intrinsic factors (age, gender, body weight, race, and ethnicity) and extrinsic factors (geographic region and cycle length) were evaluated. Potential drug interactions with substrates of CYP2D6 and BCRP were assessed.

Table 29. Safety Pooling Groups

Pooling Group	Subjects	Studies
Group 1	CINV subjects	P04351, P04832, P04833, P04834
Group 2	Healthy subjects receiving single-dose rolapitant as monotherapy	P03670, P04328, P04852, P04854, PR-10-5000-C, PR-10-5004-C, PR-10-5007-C, PR-10-5013-C, PR-10-5014-C

Abbreviation: CINV, chemotherapy-induced nausea and vomiting  
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For Pooling Group 1, patients were analyzed according to the actual treatment received during the first treatment cycle. Therefore, patients who were randomized to the control group but who received rolapitant were analyzed in the rolapitant group. Two levels of integrated summaries were presented. For Level 1 integration (HEC studies), patient data from the rolapitant 200mg dose group in the HEC studies were pooled as a single group. Data from the MEC study was presented as a separate group. For Level 2 integration (HEC and MEC studies), patient data from the rolapitant 10, 25, and 100mg dose groups in HEC Study 51 were pooled as another single group. Data were summarized by the pooled treatment group, defined as <200 mg and 200 mg rolapitant dose and control groups.

Patients in any rolapitant dose group were pooled to form the “all rolapitant doses combined” group.

Table 30. Pooled Treatment Groups for Pooling Group 1

Level 1 Integration					Level 2 Integration		
HEC (P04832, P04833, P04351) <sup>a</sup>			MEC (P04834) <sup>a</sup>		Overall CINV <sup>a</sup>		
Control	<200 mg Rolapitant	200 mg Rolapitant	Control	200 mg Rolapitant	Control	200 mg Rolapitant	All Rolapitant Doses Combined

Abbreviations: CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy

<sup>a</sup> Subjects in control and active drug cohorts received dexamethasone and ondansetron (Study P04351) or dexamethasone and granisetron (Studies P04832, P04833, and P04834) as adjunct therapy.

Source: SAP, Table 2

The overall incidence of TEAEs across the 550 healthy patients who received single-dose rolapitant was 30.7%; the incidence was highest among patients who received >200 mg rolapitant (54.2%) compared with those who received 200 mg (28.7%) or <200 mg (23.2%) doses. In general, the incidence of TEAEs increased with increasing rolapitant dose. In these healthy patient studies, no patients discontinued due to AEs and there were no deaths in any of the Pooling Group 2 patients. See Table 33 below.

The overall incidence of TEAEs across the 1,567 patients who received rolapitant (all doses) in Pooling Group 1 was 65.2% (Cycle 1). The percentage of patients reporting TEAEs leading to study drug discontinuation was the same among control- and rolapitant-treated patients, 3.1%. Similarly, the incidence of SAEs and deaths was similar among control- and rolapitant-treated patients. Results were similar when the results for all cycles were combined.

Table 31. Pooling Group 1 Safety Summary, Cycle 1

Number of Subjects with:	HEC (P04832, P04833, P04351)			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 <sup>a</sup> N = 1567 n (%)
≥1 TEAE	393 (62.7)	193 (70.7) <sup>b</sup>	397 (63.6)	447 (66.3)	431 (64.3)	840 (64.6)	828 (64.0)	1021 (65.2)
≥1 Treatment-related TEAE <sup>c</sup>	30 (4.8)	45 (16.5) <sup>d</sup>	26 (4.2)	52 (7.7)	64 (9.6)	82 (6.3)	90 (7.0)	135 (8.6)
TEAE leading to study drug discontinuation	32 (5.1)	9 (3.3)	26 (4.2)	16 (2.4)	14 (2.1)	48 (3.7)	40 (3.1)	49 (3.1)
≥1 TEAE of CTCAE Grade ≥3	125 (19.9)	51 (18.7)	116 (18.6)	89 (13.2)	95 (14.2)	214 (16.4)	211 (16.3)	262 (16.7)
≥1 TESAE	78 (12.4)	31 (11.4)	58 (9.3)	48 (7.1)	44 (6.6)	126 (9.7)	102 (7.9)	133 (8.5)
≥1 Treatment-related TESAE	0	3 (1.1)	0	0	0	0	0	3 (0.2)
TEAE with outcome of death	12 (1.9)	3 (1.1)	13 (2.1)	3 (0.4)	8 (1.2)	15 (1.2)	21 (1.6)	24 (1.5)
Treatment-related TEAE with outcome of death	0	0	0	0	0	0	0	0

Abbreviations: AE, adverse event; CINV, chemotherapy-induced nausea and vomiting; CTCAE, Common Terminology Criteria for Adverse Events; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

<sup>a</sup> Subjects who received any rolapitant doses are combined.

<sup>b</sup> The incidence of TEAEs across active treatment groups and the control group in Study P04351 were similar, but was higher than those observed in Studies P04832, P04833, and P04834.

<sup>c</sup> Any TEAE that is possibly, probably, or definitely related to study drug according to AE CRF.

<sup>d</sup> The incidence of treatment-related TEAEs across active treatment groups and the control group in Study P04351 were similar, but slightly higher than those observed in Studies P04832, P04833, and P04834.

Source: Appendix Table 11

Table 32. Pooling Group 1 Safety Summary, All Cycles Combined

Number of Subjects with:	HEC (P04832, P04833, P04351)			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 <sup>a</sup> N = 1567 n (%)
≥1 TEAE	502 (80.1)	234 (85.7) <sup>b</sup>	508 (81.4)	551 (81.8)	547 (81.6)	1053 (80.9)	1055 (81.5)	1289 (82.3)
≥1 treatment-related TEAE <sup>c</sup>	35 (5.6)	51 (18.7) <sup>d</sup>	38 (6.1)	92 (13.6)	80 (11.9)	127 (9.8)	118 (9.1)	169 (10.8)
TEAE leading to study drug discontinuation	76 (12.1)	24 (8.8)	71 (11.4)	37 (5.5)	34 (5.1)	113 (8.7)	105 (8.1)	129 (8.2)
≥1 TEAE of CTCAE Grade ≥3	215 (34.3)	98 (35.9)	216 (34.6)	174 (25.8)	179 (26.7)	389 (29.9)	395 (30.5)	493 (31.5)
≥1 TESAE	141 (22.5)	63 (23.1)	138 (22.1)	103 (15.3)	89 (13.3)	244 (18.8)	227 (17.5)	290 (18.5)
≥1 treatment-related TESAE	0	3 (1.1)	2 (0.3)	0	0	0	2 (0.2)	5 (0.3)
TEAE with outcome of death	24 (3.8)	10 (3.7)	25 (4.0)	7 (1.0)	13 (1.9)	31 (2.4)	38 (2.9)	48 (3.1)
Treatment-related TEAE with outcome of death	0	0	0	0	0	0	0	0

Abbreviations: CINV, chemotherapy-induced nausea and vomiting; CTCAE, Common Terminology Criteria for Adverse Events; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

<sup>a</sup> Subjects who received any rolapitant doses are combined.

<sup>b</sup> The incidence of TEAEs across active treatment groups and the control group in Study P04351 were similar, but were slightly higher than those observed in the other three CINV studies.

<sup>c</sup> Any TEAE that is possibly, probably, or definitely related to study drug according to AE CRF.

<sup>d</sup> The incidence of treatment-related TEAEs across active treatment groups and the control group in Study P04351 were similar, but were slightly higher than those observed in the other three CINV studies.

Source: Appendix Table 12

Pooling Group 2 was the secondary analysis set and included select patients in phase 1 healthy volunteer studies who received single doses of rolapitant as monotherapy. The overall incidence of TEAEs across the 550 healthy patients who received single-dose rolapitant was 30.7%; the incidence was highest among patients who received >200 mg rolapitant (54.2%) compared with those who received 200 mg (28.7%) or <200 mg (23.2%) doses. In general, the incidence of TEAEs increased with increasing rolapitant dose. In these healthy patient studies, no patients discontinued due to AEs and there were no deaths in any of the Pooling Group 2 patients. See Table 33 below.

Table 33. Pooling Group 2 Safety Summary

Number of Subjects with:	Placebo (N = 56) n (%)	<200 mg (N = 69) n (%)	200 mg (N = 422) n (%)	>200 mg (N = 59) n (%)	Rolapitant (N = 550) n (%)
≥1 TEAE	29 (51.8)	16 (23.2)	121 (28.7)	32 (54.2)	169 (30.7)
≥1 Treatment-related TEAE <sup>a</sup>	12 (21.4)	6 (8.7)	70 (16.6)	18 (30.5)	94 (17.1)
TEAEs leading to study drug discontinuation	0	0	0	0	0
≥1 TESAE	0	0	2 (0.5)	0	0
≥1 Treatment-related TESAE <sup>b</sup>	0	0	1 (0.2)	0	0
TEAE without outcome of death	0	0	0	0	0

<sup>a</sup> Any TEAE that was possibly, probably, or definitely related to study drug.

<sup>b</sup> Any TESAE that was possibly, probably, or definitely related to study drug.

Source: Appendix Table 26, Appendix Table 28, CSR P03670, CSR P04328, CSR P04852, CSR P04854, CSR PR-10-5000-C, CSR PR-10-5004-C, CSR PR-5007-C, CSR PR-10-5013, CSR PR-10-5014-C

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## 7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. Safety variables included adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, and physical examination parameters. Patients who were given at least one dose of the study medication were included in the safety analysis populations described in Section 7.1.

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

In Pooling Group 1, a total of 1,567 patients received at least one dose of rolapitant across the CINV studies. Cumulatively, these patients received 5,335 exposures of rolapitant. Compliance with dosing was over 99% in the overall rolapitant and control group in each cycle.

Overall, 422 healthy patients received 200 mg rolapitant, 69 patients received <200 mg rolapitant, and 59 patients received >200 mg rolapitant as a single dose.

Table 34. Rolapitant Exposures in Pooling Group 1

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 <sup>a</sup>	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 <sup>b</sup>	770 <sup>b</sup>	908	2584 <sup>b</sup>	4524

Abbreviation: N/A, not applicable.

Note: Dose groups are based on actual treatment/assigned dose groups.

<sup>a</sup> 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.

<sup>b</sup> 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]).

In Cycle 1, the use of concomitant medications was high in the overall CINV group: rolapitant 200 mg (89.5%), all rolapitant group (90.7%), and control group (91.8%). The most commonly used classes of concomitant medications were IV solution additives (primarily sodium chloride and potassium chloride), drugs for peptic ulcer and GERD (primarily omeprazole and ranitidine), and IV solutions (primarily mannitol and glucose). The percentage of patients receiving each concomitant medication was similar across the rolapitant 200 mg, overall rolapitant, and control groups.

Results were similar for all cycles combined.

## 7.2.2 Explorations for Dose Response

In the phase 3 studies, there was a single rolapitant dosing regimen—200 mg. Therefore, it was not possible to detect a trend of higher incidences of AEs with increasing rolapitant dose. In Study 51, a phase 2 dose-ranging study, the incidence of TEAEs was similar across dose groups. There was no clear trend of increasing TEAEs with increasing rolapitant dose; although placebo patients had the lowest incidence of TEAEs (82%) and patients in the 200 mg dose group had the highest incidence of TEAEs (89%). See Table 35 below.

Table 35. Overall Summary of Adverse Events, All Cycles, Study 51

	No. (%) of Subjects				
	Placebo (n=91)	SCH 619734 10 mg (n=91)	SCH 619734 25 mg (n=91)	SCH 619734 100 mg (n=91)	SCH 619734 200 mg (n=90)
Any treatment-emergent AE	75 (82)	78 (86)	76 (84)	80 (88)	80 (89)
Related treatment-emergent AEs	8 (9)	15 (16)	14 (15)	22 (24)	12 (13)
SAEs <sup>a</sup>	22 (24)	30 (33)	20 (22)	20 (22)	22 (24)
Related SAEs <sup>a</sup>	0	1 (1)	0	2 (2)	1 (1)
AEs leading to study drug discontinuation <sup>a</sup>	11 (12)	8 (9)	9 (10)	7 (8)	10 (11)
SAEs leading to study drug discontinuation <sup>a</sup>	9 (10)	6 (7)	6 (7)	4 (4)	6 (7)
Deaths due to AEs <sup>a</sup>	3 (3)	3 (3)	6 (7)	2 (2)	5 (6)

AE = adverse event; SAE = serious adverse event.

a: Not limited to treatment-emergent AEs.

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### 7.2.3 Special Animal and/or In Vitro Testing

N/A

### 7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments in the three submitted studies. See Section 5.3.5 for detailed information on study visits and procedures.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

For more information, see the Clinical Pharmacology Review in DARRTS by Insook Kim, PhD.

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

Use of drugs in the NK-1 antagonist class has not known to be associated with any specific adverse events. None of the drugs in this class has a black box warning. The Warnings and Precautions section of labels for drugs in this class include the following:

Aprepitant Capsules/Emend (label revised 8/2014)

- *Coadministration of aprepitant with warfarin (a CYP2C9 substrate) may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. (5.2)*
- *The efficacy of hormonal contraceptives during and for 28 days following the last dose of EMEND may be reduced. Alternative or back-up methods of contraception should be used. (5.3, 7.1)*
- *EMEND is a dose-dependent inhibitor of CYP3A4, and should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. (5.1)*
- *Caution should be exercised when administered in patients with severe hepatic impairment. (2.5, 5.4, 12.3)*

Netupitant and palonosetron/Akynzeo (label revised 10/2014)

There are no Warnings and precautions related to the netupitant part of the fixed dose combination product.

### **7.3 Major Safety Results**

During the Pooling Group 1 studies (controlled efficacy studies in CINV patients) 12-week, placebo-controlled studies, 82.3% of rolapitant patients and 80.9% of placebo patients reported any adverse event. The incidence of SAEs was nearly identical in the rolapitant and control groups, 18.5% and 18.8%, respectively. See Table 32 above.

#### **7.3.1 Deaths**

There were 79 deaths reported in Pooling Group 1. Of these, 48 occurred in rolapitant patients and 31 occurred in placebo patients. The greatest number of deaths occurred during Cycle 1 in both rolapitant and control groups. See Table 36 below.

The overall incidence of TEAEs leading to death in Cycles 1-6 for the rolapitant 200 mg group was higher in the HEC group (4.0%) compared with the MEC group (1.9%); this difference was also observed in the placebo group (3.8% compared with 1.0%). The Applicant attributes this difference to the fact that HEC studies included a higher proportion of male patients with lung cancer, compared with the MEC group which included a higher proportion of females with breast cancer.

Table 36. Number of Deaths Reported, Pooling Group 1

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

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Of the Pooling Group 1 deaths that were reported, the most common primary malignancy was lung cancer, most patients were 60 years of age or older, most were male, and most had significant comorbidities in addition to their malignancy. The causes of death for Pooling Group 1 are presented below.

Table 37. TEAEs 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, Pooling Group 1

System Organ Class Preferred Term	HEC (P04832, P04833, P04351) <sup>3</sup>			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 <sup>2</sup> N = 1567 n (%)
<i>Subjects with ≥1 Incidence</i>	24 (3.8)	10 (3.7)	25 (4.0)	7 (1.0)	13 (1.9)	31 (2.4)	38 (2.9)	48 (3.1)
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>2 (0.3)</b>	<b>2 (0.7)</b>	<b>7 (1.1)</b>	<b>2 (0.3)</b>	<b>5 (0.7)</b>	<b>4 (0.3)</b>	<b>12 (0.9)</b>	<b>14 (0.9)</b>
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)
<b>Infections and infestations</b>	<b>3 (0.5)</b>	<b>0</b>	<b>4 (0.6)</b>	<b>2 (0.3)</b>	<b>3 (0.4)</b>	<b>5 (0.4)</b>	<b>7 (0.5)</b>	<b>7 (0.4)</b>
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

Table 36 Continued

System Organ Class Preferred Term	HEC (P04832, P04833, P04351) <sup>a</sup>			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 <sup>b</sup> N = 1567 n (%)
<b>General disorders and administration site conditions</b>	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
<b>Cardiac disorders</b>	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)
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>	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
<b>Nervous system disorders</b>	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)

Table 36 continued

System Organ Class Preferred Term	HEC (P04832, P04833, P04351) <sup>a</sup>			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 <sup>a</sup> 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)
<b>Renal and urinary disorders</b>	<b>0</b>	<b>0</b>	<b>1 (0.2)</b>	<b>0</b>	<b>1 (0.1)</b>	<b>0</b>	<b>2 (0.2)</b>	<b>2 (0.1)</b>
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)
<b>Metabolism and nutrition disorders</b>	<b>1 (0.2)</b>	<b>1 (0.4)</b>	<b>1 (0.2)</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.1)</b>	<b>1 (&lt;0.1)</b>	<b>2 (0.1)</b>
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
<b>Vascular disorders</b>	<b>1 (0.2)</b>	<b>1 (0.4)</b>	<b>1 (0.2)</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.1)</b>	<b>1 (&lt;0.1)</b>	<b>2 (0.1)</b>
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
<b>Gastrointestinal disorders</b>	<b>1 (0.2)</b>	<b>0</b>	<b>0</b>	<b>2 (0.3)</b>	<b>0</b>	<b>3 (0.2)</b>	<b>0</b>	<b>0</b>
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
<b>Blood and lymphatic system disorders</b>	<b>1 (0.2)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (&lt;0.1)</b>	<b>0</b>	<b>0</b>
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

<sup>a</sup> Subjects who received any rolapitant doses are combined.

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There were no deaths reported in Pooling Group 2 (healthy patients receiving single-dose rolapitant as monotherapy).

**MO Comment:**

*The deaths reported in the rolapitant program were expected given the patient population of cancer patients.*

**7.3.2 Nonfatal Serious Adverse Events**

In Pooling Group1, all cycles, 18.5% of rolapitant and 18.8% of placebo patients reported a serious adverse event. The most commonly reported SAE preferred term was febrile neutropenia—3.0% of placebo patients, and 2.7% of rolapitant patients. See Table 38 below.

**MO Comment:**

*It appears reasonable and not drug-related that the most common SAE PT seen in all CINV patients was febrile neutropenia given that these patients were receiving myelosuppressive chemotherapy.*

Table 38. SAEs by MedDRA SOC and PT (≥1% of Patients in Any Treatment Group), All Cycles Combined – Patient Incidence, Pooling Group 1

System Organ Class Preferred Term	HEC (P04832, P04833, P04351)			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 <sup>a</sup> N = 1567 n (%)
<i>Subjects with ≥1 Incidence</i>	141 (22.5)	63 (23.1)	138 (22.1)	103 (15.3)	89 (13.3)	244 (18.8)	227 (17.5)	290 (18.5)
<b>Blood and lymphatic system disorders</b>	30 (4.8)	24 (8.8)	35 (5.6)	43 (6.4)	24 (3.6)	73 (5.6)	59 (4.6)	83 (5.3)
Febrile neutropenia	14 (2.2)	9 (3.3)	19 (3.0)	25 (3.7)	14 (2.1)	39 (3.0)	33 (2.6)	42 (2.7)
Neutropenia	13 (2.1)	11 (4.0)	9 (1.4)	13 (1.9)	7 (1.0)	26 (2.0)	16 (1.2)	27 (1.7)
Anaemia	3 (0.5)	2 (0.7)	6 (1.0)	5 (0.7)	2 (0.3)	8 (0.6)	8 (0.6)	10 (0.6)
Thrombocytopenia	2 (0.3)	3 (1.1)	4 (0.6)	1 (0.1)	1 (0.1)	3 (0.2)	5 (0.4)	8 (0.5)
<b>Infections and infestations</b>	27 (4.3)	13 (4.8)	22 (3.5)	18 (2.7)	25 (3.7)	45 (3.5)	47 (3.6)	60 (3.8)
Pneumonia	10 (1.6)	3 (1.1)	7 (1.1)	4 (0.6)	4 (0.6)	14 (1.1)	11 (0.9)	14 (0.9)
<b>Respiratory, thoracic and mediastinal disorders</b>	15 (2.4)	7 (2.6)	19 (3.0)	10 (1.5)	14 (2.1)	25 (1.9)	33 (2.6)	40 (2.6)
Pulmonary embolism	6 (1.0)	1 (0.4)	5 (0.8)	4 (0.6)	5 (0.7)	10 (0.8)	10 (0.8)	11 (0.7)
<b>Gastrointestinal disorders</b>	22 (3.5)	14 (5.1)	20 (3.2)	12 (1.8)	7 (1.0)	34 (2.6)	27 (2.1)	41 (2.6)
Vomiting	9 (1.4)	5 (1.8)	2 (0.3)	0	0	9 (0.7)	2 (0.2)	7 (0.4)
Dysphagia	0	3 (1.1)	1 (0.2)	1 (0.1)	0	1 (<0.1)	1 (<0.1)	4 (0.3)
Nausea	4 (0.6)	4 (1.5)	1 (0.2)	2 (0.3)	0	6 (0.5)	1 (<0.1)	5 (0.3)
<b>General disorders and administration site conditions</b>	23 (3.7)	7 (2.6)	19 (3.0)	4 (0.6)	6 (0.9)	27 (2.1)	25 (1.9)	32 (2.0)
Asthenia	6 (1.0)	1 (0.4)	5 (0.8)	0	1 (0.1)	6 (0.5)	6 (0.5)	7 (0.4)
<b>Nervous system disorders</b>	8 (1.3)	5 (1.8)	12 (1.9)	0	9 (1.3)	8 (0.6)	21 (1.6)	26 (1.7)
<b>Metabolism and nutrition disorders</b>	15 (2.4)	8 (2.9)	12 (1.9)	5 (0.7)	7 (1.0)	20 (1.5)	19 (1.5)	27 (1.7)
Dehydration	10 (1.6)	5 (1.8)	6 (1.0)	4 (0.6)	6 (0.9)	14 (1.1)	12 (0.9)	17 (1.1)
<b>Vascular disorders</b>	10 (1.6)	7 (2.6)	13 (2.1)	6 (0.9)	5 (0.7)	16 (1.2)	18 (1.4)	25 (1.6)
<b>Cardiac disorders</b>	5 (0.8)	4 (1.5)	8 (1.3)	6 (0.9)	7 (1.0)	11 (0.8)	15 (1.2)	19 (1.2)

System Organ Class Preferred Term	HEC (P04832, P04833, P04351)			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 <sup>a</sup> N = 1567 n (%)
<b>Renal and urinary disorders</b>	8 (1.3)	6 (2.2)	5 (0.8)	3 (0.4)	2 (0.3)	11 (0.8)	7 (0.5)	13 (0.8)
Renal failure acute	4 (0.6)	3 (1.1)	2 (0.3)	2 (0.3)	1 (0.1)	6 (0.5)	3 (0.2)	6 (0.4)
<b>Investigations</b>	6 (1.0)	1 (0.4)	1 (0.2)	5 (0.7)	4 (0.6)	11 (0.8)	5 (0.4)	6 (0.4)

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

<sup>a</sup> Subjects who received any rolapitant doses are combined.

Note: This table includes all SOC and PTs that were reported in ≥1% of subjects in any group; for SOC that did not have PTs that met this threshold, only the SOC is listed.

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### 7.3.3 Dropouts and/or Discontinuations

In Pooling Group 1, 3.1% of rolapitant patients and 3.7% of placebo patients reported a TEAE that led to study discontinuation. Of these events most were classified as GI disorders—stomatitis, nausea, and dysphagia.

Table 39. TEAEs Leading to Study Discontinuation ( $\geq 0.2\%$  of Patients in the Overall Rolapitant 200 mg Group or  $\geq 1\%$  of Patients in Any Treatment Group), Cycle 1 –Patient Incidence, Pooling Group 1

System Organ Class Preferred Term	HEC (P04832, P04833, P04351)			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 <sup>a</sup> N = 1567 n (%)
<i>Subjects with <math>\geq 1</math> Incidence</i>	32 (5.1)	9 (3.3)	26 (4.2)	16 (2.4)	14 (2.1)	48 (3.7)	40 (3.1)	49 (3.1)
Gastrointestinal disorders	4 (0.6)	0	7 (1.1)	4 (0.6)	2 (0.3)	8 (0.6)	9 (0.7)	9 (0.6)
Stomatitis	0	0	2 (0.3)	0	1 (0.1)	0	3 (0.2)	3 (0.2)
Nausea	1 (0.2)	0	1 (0.2)	0	2 (0.3)	1 (<0.1)	3 (0.2)	3 (0.2)
Dysphagia	0	0	2 (0.3)	0	0	0	2 (0.2)	2 (0.1)
Nervous system disorders	1 (0.2)	3 (1.1)	2 (0.3)	0	3 (0.4)	1 (<0.1)	5 (0.4)	8 (0.5)
Cardiac disorders	3 (0.5)	1 (0.4)	2 (0.3)	1 (0.1)	2 (0.3)	4 (0.3)	4 (0.3)	5 (0.3)
Respiratory, thoracic and mediastinal disorders	4 (0.6)	3 (1.1)	2 (0.3)	3 (0.4)	1 (0.1)	7 (0.5)	3 (0.2)	6 (0.4)
Blood and lymphatic system disorders	4 (0.6)	2 (0.7)	2 (0.3)	5 (0.7)	1 (0.1)	9 (0.7)	3 (0.2)	5 (0.3)
Febrile neutropenia	1 (0.2)	1 (0.4)	1 (0.2)	3 (0.4)	1 (0.1)	4 (0.3)	2 (0.2)	3 (0.2)
Immune system disorders	0	0	1 (0.2)	2 (0.3)	2 (0.3)	2 (0.2)	3 (0.2)	3 (0.2)
Drug hypersensitivity	0	0	0	1 (0.1)	2 (0.3)	1 (<0.1)	2 (0.2)	2 (0.1)
Infections and infestations	3 (0.5)	2 (0.7)	3 (0.5)	3 (0.4)	0	6 (0.5)	3 (0.2)	5 (0.3)
Investigations	1 (0.2)	1 (0.4)	1 (0.2)	0	2 (0.3)	1 (<0.1)	3 (0.2)	4 (0.3)
Alanine aminotransferase increased	0	0	0	0	2 (0.3)	0	2 (0.2)	2 (0.1)
Aspartate aminotransferase increased	0	0	0	0	2 (0.3)	0	2 (0.2)	2 (0.1)
Vascular disorders	4 (0.6)	1 (0.4)	3 (0.5)	0	0	4 (0.3)	3 (0.2)	4 (0.3)
General disorders and administration site conditions	3 (0.5)	1 (0.4)	1 (0.2)	2 (0.3)	1 (0.1)	5 (0.4)	2 (0.2)	3 (0.2)
Metabolism and nutrition disorders	3 (0.5)	1 (0.4)	2 (0.3)	0	0	3 (0.2)	2 (0.2)	3 (0.2)

Abbreviations: CINV, chemotherapy-induced nausea and vomiting; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SOC, system organ class; TEAE, treatment-emergent adverse event

<sup>a</sup> Subjects who received any rolapitant doses are combined.

Note: This table includes all SOCs and PTs that were reported in  $\geq 0.2\%$  of subjects in the overall rolapitant 200 mg group or  $\geq 1\%$  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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**MO Comment:**

*Given that for each cycle, rolapitant was given as a single dose, dropout rates by cycle do not provide as much valuable information as do the dropout rate for multiple dose drug programs. For each cycle, patients did not have to make the decision as to whether or not they would continue taking the study drug because study drug was only taken once per chemotherapy cycle.*

The discontinuation due to AEs results for all cycles combined were similar to the results for Cycle 1.

**7.3.4 Significant Adverse Events**

There were no significant adverse events reported in the rolapitant development program.

### 7.3.5 Submission Specific Primary Safety Concerns

#### Nervous System Disorders

The Division requested safety analyses to address potential neurotoxicity issues based on the long half-life of potential for product's cumulative effect over time. In the non-clinical studies convulsions were observed in monkeys administered 60 and 100 mg/kg. To further evaluate the finding of convulsions two single-dose non-clinical studies were conducted. In one study eight female monkeys were administered a single oral dose of 100 mg/kg. In a second study, four female monkeys were a single oral dose of 100 mg/kg. Similarly, no convulsions were observed.

In the rolapitant clinical studies, the incidence of TEAEs in the nervous system SOC was 25.4% in patients taking rolapitant and 24.5% in control patients (Pooling Group 1). The most common nervous system PTs reported were headache and dizziness. Neurologic exams were conducted in all patients during each treatment cycle. These examinations included assessments of cerebellar function, cranial nerves, gait and station, reflexes, and sensation. No pattern of clinically significant neurological events associated with rolapitant use was detected. In addition, no trend of increasing incidence of TEAEs was seen in successive cycles.

Table 40. Treatment-emergent Adverse Events in the Nervous System Disorders System Organ Class ( $\geq 0.1\%$  of Subjects in the Overall Rolapitant 200 mg Group), All Cycles Combined – Subject Incidence, Pooling Group 1

Preferred Term	HEC (P04832, P04833, P04351)			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 <sup>a</sup> N = 1567 n (%)
<i>Subjects with <math>\geq 1</math> Incidence</i>	107 (17.1)	73 (26.7)	122 (19.6)	212 (31.5)	203 (30.3)	319 (24.5)	325 (25.1)	398 (25.4)
Headache	34 (5.4)	37 (13.6)	33 (5.3)	109 (16.2)	82 (12.2)	143 (11.0)	115 (8.9)	152 (9.7)
Dizziness	20 (3.2)	23 (8.4)	28 (4.5)	71 (10.5)	69 (10.3)	91 (7.0)	97 (7.5)	120 (7.7)
Dysgeusia	13 (2.1)	8 (2.9)	21 (3.4)	38 (5.6)	29 (4.3)	51 (3.9)	50 (3.9)	58 (3.7)
Paraesthesia	10 (1.6)	3 (1.1)	8 (1.3)	11 (1.6)	17 (2.5)	21 (1.6)	25 (1.9)	28 (1.8)
Hypoesthesia	7 (1.1)	2 (0.7)	2 (0.3)	6 (0.9)	16 (2.4)	13 (1.0)	18 (1.4)	20 (1.3)
Peripheral sensory neuropathy	5 (0.8)	2 (0.7)	3 (0.5)	16 (2.4)	15 (2.2)	21 (1.6)	18 (1.4)	20 (1.3)
Syncope	11 (1.8)	1 (0.4)	11 (1.8)	3 (0.4)	6 (0.9)	14 (1.1)	17 (1.3)	18 (1.1)
Neuropathy peripheral	7 (1.1)	3 (1.1)	4 (0.6)	18 (2.7)	10 (1.5)	25 (1.9)	14 (1.1)	17 (1.1)
Somnolence	1 (0.2)	2 (0.7)	3 (0.5)	4 (0.6)	6 (0.9)	5 (0.4)	9 (0.7)	11 (0.7)
Tremor	0	1 (0.4)	2 (0.3)	5 (0.7)	6 (0.9)	5 (0.4)	8 (0.6)	9 (0.6)
Disturbance in attention	2 (0.3)	5 (1.8)	1 (0.2)	1 (0.1)	5 (0.7)	3 (0.2)	6 (0.5)	11 (0.7)
Balance disorder	0	0	3 (0.5)	3 (0.4)	2 (0.3)	3 (0.2)	5 (0.4)	5 (0.3)
Lethargy	0	1 (0.4)	2 (0.3)	3 (0.4)	3 (0.4)	3 (0.2)	5 (0.4)	6 (0.4)
Dizziness postural	1 (0.2)	0	2 (0.3)	3 (0.4)	2 (0.3)	4 (0.3)	4 (0.3)	4 (0.3)
Dysarthria	0	0	2 (0.3)	0	2 (0.3)	0	4 (0.3)	4 (0.3)
Neurotoxicity	2 (0.3)	1 (0.4)	1 (0.2)	1 (0.1)	3 (0.4)	3 (0.2)	4 (0.3)	5 (0.3)
Presyncope	1 (0.2)	0	0	2 (0.3)	4 (0.6)	3 (0.2)	4 (0.3)	4 (0.3)
Cerebrovascular accident	1 (0.2)	0	2 (0.3)	0	1 (0.1)	1 (<0.1)	3 (0.2)	3 (0.2)
Convulsion	2 (0.3)	2 (0.7)	3 (0.5)	0	0	2 (0.2)	3 (0.2)	5 (0.3)
Peripheral motor neuropathy	0	0	2 (0.3)	0	1 (0.1)	0	3 (0.2)	3 (0.2)

Preferred Term	HEC (P04832, P04833, P04351)			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 <sup>a</sup> N = 1567 n (%)
Dysaesthesia	0	5 (1.8)	2 (0.3)	0	0	0	2 (0.2)	7 (0.4)
Ischaemic stroke	2 (0.3)	0	2 (0.3)	0	0	2 (0.2)	2 (0.2)	2 (0.1)
Movement disorder	0	0	0	0	2 (0.3)	0	2 (0.2)	2 (0.1)
Polyneuropathy	0	0	0	1 (0.1)	2 (0.3)	1 (<0.1)	2 (0.2)	2 (0.1)
Restless legs syndrome	0	0	1 (0.2)	1 (0.1)	1 (0.1)	1 (<0.1)	2 (0.2)	2 (0.1)
Sinus headache	0	0	0	0	2 (0.3)	0	2 (0.2)	2 (0.1)
Transient ischaemic attack	2 (0.3)	0	1 (0.2)	0	1 (0.1)	2 (0.2)	2 (0.2)	2 (0.1)

<sup>a</sup> Subjects who received any rolapitant doses are combined.  
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A brief history of the patients who reported convulsions is presented in the Table below. Most patients either had metastases of the primary cancer to the brain or exposure to concomitant medications known to lower the seizure threshold.

Table 41. Listing of Subjects Experiencing Seizure-like Treatment-emergent Adverse Events in Studies Included in Pooling Group 1

Study	Subject	Treatment	Preferred Term	Event onset	Severity	SAE	Chemotherapy	Cancer & PMH & Concurrent event	Relationship	Action Taken	Outcome
P04351	000010	Rolapitant 100 mg	Convulsion	C1D5	Grade 2	Yes	cisplatin capecitabine cetuximab	Esophageal Cancer History of seizure secondary to hyponatremia Event concurrent with hyponatremia	Possibly (investigator noted previous seizures history)	Drug discontinued	Recovered/resolved
P04351	000516	Rolapitant 25 mg	Convulsion	C1D21	Grade 4	Yes	cisplatin paclitaxel	Stage IV ovarian cancer, metastasis History of unstable pleural effusion Event concurrent with cardiopulmonary failure	Unlikely	Drug discontinued	Recovered/resolved
P04832	411-2002	Rolapitant 200mg	Convulsion	C1D6	Grade 2	Yes	cisplatin etoposide	NSCLC, metastatic Event concurrent with diagnosis of brain metastases	Unrelated	Drug discontinued	Recovered/resolved
P04833	420-3004	Rolapitant 200 mg	Convulsion	C4D83	Grade 2	Yes	cisplatin paclitaxel	Stomach cancer, metastatic Event concurrent with diagnosis of brain metastases	Unrelated	None	Recovered/resolved
P04833	430-3004	Rolapitant 200 mg	Convulsion	C1D2	Grade 3	No	cisplatin gemcitabine	Unknown metastatic cancer Event concurrent with diagnosis of brain metastases	Unlikely related	None	Recovered/resolved
P04834	253-4020	Rolapitant 200 mg	Partial seizures	C6D130	Grade 1	Yes	carboplatin etoposide	Lung cancer, metastatic Liver and bone metastases Event concurrent with diagnosis of brain metastases	Unrelated	None	Recovered/resolved
P04832	291-2016	Control	Convulsion	C6D160	Grade 3	Yes	cisplatin docetaxel	Frontal metastatic lesion History of seizure disorder	Unrelated	None	Recovered/resolved
Study	Subject	Treatment	Preferred Term	Event onset	Severity	SAE	Chemotherapy	Cancer & PMH & Concurrent event	Relationship	Action Taken	Outcome
P04833	380-3014	Control	Convulsion	C2D43	Grade 2	No	cisplatin	Head and neck cancer Event concurrent with neutropenic fever	Unrelated	None	Recovered/resolved

Abbreviations: C, cycle; D, day; IV, intravenous; NSCLC, non-small-cell lung cancer; PMH, previous medical history; SAE, serious adverse event  
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**MO Comment:**

*Overall, there does not appear to be a safety signal for convulsions or other nervous system disorders seen in the rolapitant clinical studies.*

The use of aprepitant has been associated with ifosfamide-induced neurotoxicity. Seven patients in the rolapitant Phase 2/3 program received ifosfamide (four rolapitant:three control). None of these patients experienced TEAEs in the MedDRA *Nervous system disorders* SOC.

**Acute Renal Failure**

The incidences of TEAEs included in the MedDRA SMQ of acute renal failure were evaluated. In Pooling Group 1 (across all cycles), 3.5% of patients in the rolapitant group reported acute renal failure-associated TEAEs compared with 4.0% of control patients. No evidence of increasing AE incidence was seen with subsequent dosing.

Table 42. TEAEs Derived from SMQs for Acute Renal Failure by MedDRA System Organ Class and Preferred Term, All Cycles Combined – Subject Incidence, Pooling Group 1

Sub-SMQ Preferred Term	HEC (P04832, P04833, P04351)			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 <sup>a</sup> N = 1567 n (%)
<b>Acute renal failure</b>	<b>41 (6.5)</b>	<b>16 (5.9)</b>	<b>35 (5.6)</b>	<b>11 (1.6)</b>	<b>10 (1.5)</b>	<b>52 (4.0)</b>	<b>45 (3.5)</b>	<b>61 (3.9)</b>
Blood creatinine increased	22 (3.5)	6 (2.2)	11 (1.8)	3 (0.4)	3 (0.4)	25 (1.9)	14 (1.1)	20 (1.3)
Renal failure	10 (1.6)	4 (1.5)	8 (1.3)	1 (0.1)	2 (0.3)	11 (0.8)	10 (0.8)	14 (0.9)
Renal failure acute	8 (1.3)	3 (1.1)	9 (1.4)	4 (0.6)	1 (0.1)	12 (0.9)	10 (0.8)	13 (0.8)
Blood urea increased	9 (1.4)	3 (1.1)	4 (0.6)	1 (0.1)	2 (0.3)	10 (0.8)	6 (0.5)	9 (0.6)
Proteinuria	0	3 (1.1)	2 (0.3)	4 (0.6)	3 (0.4)	4 (0.3)	5 (0.4)	8 (0.5)
Azotaemia	1 (0.2)	0	2 (0.3)	1 (0.1)	0	2 (0.2)	2 (0.2)	2 (0.1)
Acute prerenal failure	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Hypercreatininaemia	1 (0.2)	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Nephropathy toxic	1 (0.2)	0	1 (0.2)	0	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Oliguria	0	0	1 (0.2)	0	0	0	1 (<0.1)	1 (<0.1)
Renal impairment	0	1 (0.4)	0	0	0	0	0	1 (<0.1)
Blood urea nitrogen/creatinine ratio increased	0	0	0	1 (0.1)	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; SMQ, Standardized MedDRA Query; TEAE, treatment-emergent adverse event

<sup>a</sup> Subjects who received any rolapitant doses are combined.

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## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

Table 43. TEAEs by MedDRA Preferred Term with Incidence of  $\geq 3\%$  of Patients in the Overall Rolapitant 200 mg Group or  $\geq 10\%$  of Patients in Any Group in the Order of Decreasing Frequency Based on the Overall Rolapitant 200mg Group, Cycle 1 – Patient Incidence, Pooling Group 1

Preferred Term	HEC (P04832, P04833, P04351)			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 <sup>a</sup> N = 1567 n (%)
<i>Subjects with <math>\geq 1</math> Incidence</i>	393 (62.7)	193 (70.7)	397 (63.6)	447 (66.3)	431 (64.3)	840 (64.6)	828 (64.0)	1021 (65.2)
Fatigue	40 (6.4)	34 (12.5)	43 (6.9)	106 (15.7)	110 (16.4)	146 (11.2)	153 (11.8)	187 (11.9)
Constipation	56 (8.9)	32 (11.7)	47 (7.5)	95 (14.1)	70 (10.4)	151 (11.6)	117 (9.0)	149 (9.5)
Neutropenia	48 (7.7)	16 (5.9)	56 (9.0)	40 (5.9)	50 (7.5)	88 (6.8)	106 (8.2)	122 (7.8)
Decreased appetite	53 (8.5)	21 (7.7)	42 (6.7)	47 (7.0)	59 (8.8)	100 (7.7)	101 (7.8)	122 (7.8)
Alopecia	29 (4.6)	13 (4.8)	21 (3.4)	83 (12.3)	77 (11.5)	112 (8.6)	98 (7.6)	111 (7.1)
Diarrhoea	30 (4.8)	29 (10.6)	36 (5.8)	59 (8.8)	51 (7.6)	89 (6.8)	87 (6.7)	116 (7.4)
Headache	24 (3.8)	27 (9.9)	26 (4.2)	77 (11.4)	55 (8.2)	101 (7.8)	81 (6.3)	108 (6.9)
Asthenia	65 (10.4)	23 (8.4)	43 (6.9)	35 (5.2)	33 (4.9)	100 (7.7)	76 (5.9)	99 (6.3)
Nausea	59 (9.4)	55 (20.1)	39 (6.3)	45 (6.7)	33 (4.9)	104 (8.0)	72 (5.6)	127 (8.1)
Dizziness	11 (1.8)	18 (6.6)	18 (2.9)	30 (4.5)	43 (6.4)	41 (3.2)	61 (4.7)	79 (5.0)
Dyspepsia	20 (3.2)	15 (5.5)	22 (3.5)	15 (2.2)	30 (4.5)	35 (2.7)	52 (4.0)	67 (4.3)
Mucosal inflammation	28 (4.5)	12 (4.4)	28 (4.5)	15 (2.2)	20 (3.0)	43 (3.3)	48 (3.7)	60 (3.8)
Stomatitis	13 (2.1)	7 (2.6)	17 (2.7)	16 (2.4)	25 (3.7)	29 (2.2)	42 (3.2)	49 (3.1)
Hiccups	24 (3.8)	8 (2.9)	34 (5.4)	8 (1.2)	7 (1.0)	32 (2.5)	41 (3.2)	49 (3.1)
Anaemia	22 (3.5)	10 (3.7)	17 (2.7)	13 (1.9)	23 (3.4)	35 (2.7)	40 (3.1)	50 (3.2)
Urinary tract infection	10 (1.6)	3 (1.1)	9 (1.4)	23 (3.4)	30 (4.5)	33 (2.5)	39 (3.0)	42 (2.7)
Vomiting	40 (6.4)	32 (11.7)	17 (2.7)	21 (3.1)	2 (0.3)	61 (4.7)	19 (1.5)	51 (3.3)

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

<sup>a</sup> Subjects who received any rolapitant doses are combined.

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## 7.4.2 Laboratory Findings

In general, the mean baseline values and mean changes from baseline over time observed in the hematology and chemistry parameters were similar between the rolapitant 200 mg and control groups.

In the rolapitant program five cases met Hy's Law criteria. Four cases occurred in patients taking control. One case occurred in a patient in Study 51 taking rolapitant 10 mg. In this patient, Hy's Law criteria were first met at Cycle 1/Visit 2. The elevations resolved by the next Visit. The patient went on to receive rolapitant for three additional cycles and lab elevations did not resolve.

## 7.4.3 Vital Signs

No clinically significant abnormal vital signs were noted.

#### 7.4.4 Electrocardiograms (ECGs)

In a human ECG study, rolapitant demonstrated no effects on QTc interval prolongation at both therapeutic dose (200 mg) and supra-therapeutic dose (800 mg).

During the clinical studies no clinically significant changes were observed in ECG parameters and no patient had a QTcF >450 msec.

#### 7.4.5 Special Safety Studies/Clinical Trials

No special clinical safety studies were submitted.

#### 7.4.6 Immunogenicity

N/A

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

There was no clear trend of increasing AEs for increasing rolapitant dose. However, only one dose of rolapitant was studied in phase 3.

#### 7.5.2 Time Dependency for Adverse Events

No particular explorations for time dependency of adverse events were conducted.

#### 7.5.3 Drug-Demographic Interactions

No particular explorations for drug-demographic interactions related to adverse events were conducted.

#### 7.5.4 Drug-Disease Interactions

No particular explorations for drug-disease interactions were conducted.

### 7.5.5 Drug-Drug Interactions

Rolapitant is a moderate CYP2D6 inhibitor, a weak inhibitor of P-glycoprotein (P-gp), and a substrate for CYP3A4. Rolapitant is a moderate inhibitor of the BCRP transporter. The incidence of TEAEs and SAEs in Cycle 1 and all cycles was higher among subjects who received concomitant treatment with CYP2D6 and Breast-Cancer-Related-Protein (BCRP) substrates compared with those who did not; however, the rates were generally similar between the respective rolapitant and control groups. See Tables 44 and 45 below.

The most commonly administered CYP2D6 substrates in the rolapitant 200 mg group were ondansetron, metoclopramide, and ranitidine. The incidence of TEAEs was higher in patients who reported concomitant use of CYP2D6 substrates. However, the incidence of TEAEs was similar in CYP2D6 substrate users between control (68.1%) and rolapitant (67.4%) patients. Among CYP2D6 substrate users, the incidence of neutropenia was only slightly higher in the rolapitant group (9.2%) compared with the control group (7.7%). Similarly, the incidence of diarrhea was 10.4% in the rolapitant group compared with the 9.9% in the control group. See Table 44 below.

The most commonly administered BCRP substrates were doxorubicin, fluorouracil, and docetaxel. The incidence of TEAEs was higher in patients who reported concomitant use of BCRP substrates.

*MO Comment:*

*At the time of this review, an information request was outstanding which requested a safety analysis by chemotherapeutic agent for the BCRP substrates.*

Table 44. Incidence of TEAEs by Concomitant Use of CYP2D6 Substrate Drug, Cycle, Pooling Group 1

System Organ Class Preferred Term	Overall CINV			
	Concomitant Use of CYP2D6 Substrate		No Concomitant Use of CYP2D6 Substrate	
	Control (N = 715) n (%)	Rolapitant (N = 797) n (%)	Control (N = 586) n (%)	Rolapitant (N = 770) n (%)
<i>Subjects with ≥1 Incidence</i>	546 (76.4)	618 (77.5)	294 (50.2)	403 (52.3)
<b>Gastrointestinal disorders</b>	<b>296 (41.4)</b>	<b>343 (43.0)</b>	<b>106 (18.1)</b>	<b>171 (22.2)</b>
Constipation	101 (14.1)	103 (12.9)	50 (8.5)	46 (6.0)
Nausea	92 (12.9)	95 (11.9)	12 (2.0)	32 (4.2)
Diarrhoea	71 (9.9)	83 (10.4)	18 (3.1)	33 (4.3)
Dyspepsia	28 (3.9)	44 (5.5)	7 (1.2)	23 (3.0)
Vomiting	52 (7.3)	43 (5.4)	9 (1.5)	8 (1.0)
<b>General disorders and administration site conditions</b>	<b>230 (32.2)</b>	<b>246 (30.9)</b>	<b>93 (15.9)</b>	<b>139 (18.1)</b>
Fatigue	101 (14.1)	125 (15.7)	45 (7.7)	62 (8.1)
Asthenia	72 (10.1)	59 (7.4)	28 (4.8)	40 (5.2)
<b>Nervous system disorders</b>	<b>125 (17.5)</b>	<b>161 (20.2)</b>	<b>65 (11.1)</b>	<b>84 (10.9)</b>
Headache	63 (8.8)	71 (8.9)	38 (6.5)	37 (4.8)
Dizziness	25 (3.5)	52 (6.5)	16 (2.7)	27 (3.5)
<b>Metabolism and nutrition disorders</b>	<b>147 (20.6)</b>	<b>154 (19.3)</b>	<b>36 (6.1)</b>	<b>65 (8.4)</b>
Decreased appetite	84 (11.7)	81 (10.2)	16 (2.7)	41 (5.3)
Dehydration	36 (5.0)	29 (3.6)	6 (1.0)	7 (0.9)
<b>Blood and lymphatic system disorders</b>	<b>99 (13.8)</b>	<b>135 (16.9)</b>	<b>69 (11.8)</b>	<b>83 (10.8)</b>
Neutropenia	55 (7.7)	73 (9.2)	33 (5.6)	49 (6.4)
<b>Infections and infestations</b>	<b>76 (10.6)</b>	<b>127 (15.9)</b>	<b>36 (6.1)</b>	<b>64 (8.3)</b>
Respiratory, thoracic and mediastinal disorders	101 (14.1)	111 (13.9)	20 (3.4)	43 (5.6)

System Organ Class Preferred Term	Overall CINV			
	Concomitant Use of CYP2D6 Substrate		No Concomitant Use of CYP2D6 Substrate	
	Control (N = 715) n (%)	Rolapitant (N = 797) n (%)	Control (N = 586) n (%)	Rolapitant (N = 770) n (%)
<b>Skin and subcutaneous tissue disorders</b>	<b>81 (11.3)</b>	<b>105 (13.2)</b>	<b>72 (12.3)</b>	<b>77 (10.0)</b>
Alopecia	46 (6.4)	60 (7.5)	66 (11.3)	51 (6.6)
<b>Musculoskeletal and connective tissue disorders</b>	<b>101 (14.1)</b>	<b>89 (11.2)</b>	<b>28 (4.8)</b>	<b>36 (4.7)</b>
<b>Vascular disorders</b>	<b>53 (7.4)</b>	<b>63 (7.9)</b>	<b>20 (3.4)</b>	<b>24 (3.1)</b>
<b>Investigations</b>	<b>52 (7.3)</b>	<b>62 (7.8)</b>	<b>24 (4.1)</b>	<b>22 (2.9)</b>
<b>Psychiatric disorders</b>	<b>58 (8.1)</b>	<b>55 (6.9)</b>	<b>10 (1.7)</b>	<b>18 (2.3)</b>

Note: This table includes all SOCs and PTs that were reported in ≥5% 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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Table 45. TEAEs by MedDRA System Organ Class and Preferred Term and by Concomitant Use of BCRP Substrate Drug(≥5% of Subjects in Any Subgroup), Cycle 1 – Subject Incidence, Pooling Group 1

System Organ Class Preferred Term	Overall CINV			
	Concomitant Use of BCRP Substrate		No Concomitant Use of BCRP Substrate	
	Control (N = 831) n (%)	Rolapitant (N = 933) n (%)	Control (N = 470) n (%)	Rolapitant (N = 634) n (%)
<i>Subjects with ≥1 Incidence</i>	566 (68.1)	629 (67.4)	274 (58.3)	392 (61.8)
<b>Gastrointestinal disorders</b>	<b>275 (33.1)</b>	<b>315 (33.8)</b>	<b>127 (27.0)</b>	<b>199 (31.4)</b>
Constipation	103 (12.4)	90 (9.6)	48 (10.2)	59 (9.3)
Diarrhoea	65 (7.8)	79 (8.5)	24 (5.1)	37 (5.8)
Nausea	60 (7.2)	73 (7.8)	44 (9.4)	54 (8.5)
Vomiting	37 (4.5)	28 (3.0)	24 (5.1)	23 (3.6)
<b>General disorders and administration site conditions</b>	<b>223 (26.8)</b>	<b>260 (27.9)</b>	<b>100 (21.3)</b>	<b>125 (19.7)</b>
Fatigue	113 (13.6)	139 (14.9)	33 (7.0)	48 (7.6)
Asthenia	58 (7.0)	61 (6.5)	42 (8.9)	38 (6.0)
<b>Nervous system disorders</b>	<b>143 (17.2)</b>	<b>161 (17.3)</b>	<b>47 (10.0)</b>	<b>84 (13.2)</b>
Headache	85 (10.2)	70 (7.5)	16 (3.4)	38 (6.0)
Dizziness	31 (3.7)	54 (5.8)	10 (2.1)	25 (3.9)
<b>Blood and lymphatic system disorders</b>	<b>121 (14.6)</b>	<b>142 (15.2)</b>	<b>47 (10.0)</b>	<b>76 (12.0)</b>
Neutropenia	61 (7.3)	79 (8.5)	27 (5.7)	43 (6.8)
<b>Metabolism and nutrition disorders</b>	<b>115 (13.8)</b>	<b>141 (15.1)</b>	<b>68 (14.5)</b>	<b>78 (12.3)</b>
Decreased appetite	66 (7.9)	78 (8.4)	34 (7.2)	44 (6.9)
<b>Infections and infestations</b>	<b>88 (10.6)</b>	<b>134 (14.4)</b>	<b>24 (5.1)</b>	<b>57 (9.0)</b>
<b>Skin and subcutaneous tissue disorders</b>	<b>121 (14.6)</b>	<b>132 (14.1)</b>	<b>32 (6.8)</b>	<b>50 (7.9)</b>
Alopecia	98 (11.8)	89 (9.5)	14 (3.0)	22 (3.5)
<b>Musculoskeletal and connective tissue disorders</b>	<b>85 (10.2)</b>	<b>78 (8.4)</b>	<b>44 (9.4)</b>	<b>47 (7.4)</b>
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>72 (8.7)</b>	<b>76 (8.1)</b>	<b>49 (10.4)</b>	<b>78 (12.3)</b>

System Organ Class Preferred Term	Overall CINV			
	Concomitant Use of BCRP Substrate		No Concomitant Use of BCRP Substrate	
	Control (N = 831) n (%)	Rolapitant (N = 933) n (%)	Control (N = 470) n (%)	Rolapitant (N = 634) n (%)
<b>Vascular disorders</b>	<b>46 (5.5)</b>	<b>57 (6.1)</b>	<b>27 (5.7)</b>	<b>30 (4.7)</b>
<b>Investigations</b>	<b>45 (5.4)</b>	<b>48 (5.1)</b>	<b>31 (6.6)</b>	<b>36 (5.7)</b>
<b>Psychiatric disorders</b>	<b>46 (5.5)</b>	<b>45 (4.8)</b>	<b>22 (4.7)</b>	<b>28 (4.4)</b>

Note: This table includes all SOC's and PT's that were reported in ≥5% of subjects in any group; for SOC's that did not have PT's that met this threshold, only the SOC is listed.  
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Proposed Rolapitant Labeling (as of 4/26/2015, see approved label for final wording)

## 12.3 Pharmacokinetics

### Drug Interaction Studies

#### *Effect of Other Drugs on BRAND NAME*

Rolapitant is a substrate for CYP3A4.

#### CYP3A4 inducers

Concomitant administration of a CYP3A4 inducer significantly decreased the systemic exposure to rolapitant. When 600 mg rifampin was administered 7 days before and 7 days after administration of a single 180 mg dose of BRAND NAME, mean C<sub>max</sub> of rolapitant was reduced by 30% and mean AUC was reduced by 85% compared to (b) (4) administration of rolapitant alone. The mean half-life of rolapitant was decreased (b) (4) [see Drug Interactions (b) (4)].

CYP3A4 inhibitors

No clinically significant (b) (4) was seen on the pharmacokinetics of rolapitant when ketoconazole was administered with BRAND NAME. (b) (4)

(b) (4) did not significantly affect C<sub>max</sub> while AUC<sub>t</sub> was increased by 21%.

(b) (4)

Rolapitant is a moderate inhibitor of CYP2D6. [see Contraindications (4), Warning and Precautions (5.1), and Drug Interactions (7)].

Dextromethorphan

(b) (4)

[REDACTED] (b) (4)

P-glycoprotein substrate

Rolapitant is (b) (4) inhibitor of P-gp transporter. [REDACTED] (b) (4)

[REDACTED] (b) (4)

CYP3A4 substrates

Rolapitant is neither an inhibitor nor an inducer of CYP3A4.

Midazolam

[REDACTED] (b) (4)

Ondansetron

BRAND NAME had no significant effects on the pharmacokinetics of intravenous ondansetron concomitantly administered with BRAND NAME on the same day.

Dexamethasone

BRAND NAME had no significant effects on the pharmacokinetics of dexamethasone when oral dexamethasone was administered on Days 1-3 [REDACTED] (b) (4)

[REDACTED]

---END OF PROPOSED LABEL EXCEPT---

**MO Comment:**

*A significant drug-drug interaction seen with the both Emend and Akynzeo is an increased concentration of dexamethasone with concomitant use. Current labeling for Emend and Akynzeo states that a reduced dose of dexamethasone should be used with these drugs. However, it should be noted that unlike the other NK1 antagonists (Emend and Akynzeo), a lower dose of dexamethasone is not required with the use of rolapitant.*

**7.6 Additional Safety Evaluations**

### 7.6.1 Human Carcinogenicity

The carcinogenicity potential of rolapitant was assessed in two-year carcinogenicity studies in mice and rats as recommended by the FDA Carcinogenicity Assessment Committee (CAC). There were no statistically significant drug-related neoplastic findings in the mice or rat studies.

For further details see the pharmacology/toxicology review by Dr. Tracy Behrsing, PhD.

### 7.6.2 Human Reproduction and Pregnancy Data

Adequate and well-controlled studies with rolapitant have not been conducted in pregnant women. There were 3 patients in the clinical development program noted to have become pregnant while taking rolapitant. Pregnancy narratives missing from the NDA submission were received in answer to an information request (03February2015, Division of Pediatrics and Maternal Health, Dr. Miriam Dinatale). Of the 3 known pregnancies, the outcome of one pregnancy is not known (Patient 00306, Study P04852). At the time of this review, the sponsor was involved in efforts to acquire information about this patient from a Contract Research Organization that has changed ownership since the time of study conduct.

Information regarding the other two known pregnancies is included below (electronically copied and reproduced from Sponsor's submission).

A summary of the information gathered for Subject 0161284 is included below:

- Study drug and dose assigned: Rolapitant 200 mg once and then placebo
- Duration of study drug treatment: Received on 06 May 2008; 1 day of therapy
- Estimated duration of fetal exposure: Date of conception not provided; on 05 Jun 2008 ultrasound stated 7 weeks, 2 days gestation
- Pregnancy outcome: On 30 Dec 2008 a baby boy was born premature by elective C-section. Relatively healthy.
- Gestational age at delivery or termination: Not provided
- Pregnancy complications: Elective C-section, gestational diabetes
- Infant outcomes: Healthy premature boy (no details on why premature except for elective C-section was done)
- Fetal malformations: None
- Interpretation: Subject had a negative urine pregnancy and serum HCG <5 on 06 May 2008. Subsequent transvaginal ultrasound indicated the subject was pregnant approximately 3 weeks prior to study drug administration. The investigator reported that the baby was born healthy and he was premature due to elective C-section and hypoglycemia due to glyburide. Based on CIOMS report, there were no safety concerns on the pregnancy outcome related to rolapitant administered during the pregnancy.

A summary of the information gathered for Subject 0321314 is included below:

- Study drug and dose assigned: Rolapitant 70 mg once and then placebo
- Duration of study drug treatment: Received Rolapitant on 03 June 2008; 1 day of therapy
- Estimated duration of fetal exposure: On 09 July 2008 the pregnancy was confirmed, probably date of conception not provided.
- Pregnancy outcome: 03 Mar 2009 Healthy baby girl, Wt 3860gm, length 20.5cm, APGAR score at 1 min 7, and at 5 min 9.
- Gestational age at delivery or termination: Not provided
- Pregnancy complications: None
- Infant outcomes: Healthy girl
- Fetal malformations: None
- Interpretation: Subject had a negative pregnancy on 03 Jun 2008. On 09 Jul 2008 serum pregnancy was positive. The investigator considered the pregnancy with no adverse event unlikely related to blinded study drug. Based on CIOMS report, there were no safety concerns on the pregnancy outcome related to rolapitant.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

The rolapitant program for this NDA included only adult patients. PMRs for the rolapitant pediatric program

### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

## 7.7 Additional Submissions / Safety Issues

On 09 April 2015, the Applicant submitted a safety update report that covered the 4 month period beginning on 07 May, 2014 (the database lock date of the final study P04832 included in the rolapitant New Drug Application submission) through 07 September, 2014. During this time period (07 May, 2014 through 07 September, 2014), no study patients were enrolled, no study patients were exposed to rolapitant treatment, and no new safety information (adverse events or other safety assessments) was generated.

## 8 Postmarket Experience

Rolapitant is not currently marketed in the United States or any other country.

## **9 Appendices**

### **9.1 Literature Review/References**

See footnotes in text and the following Appendices below:

Appendix A: Nausea and Vomiting Subject Diary

Appendix B:

### **9.2 Labeling Recommendations**

See the final approved label for final labeling recommendations.

### **9.3 Advisory Committee Meeting**

N/A

Appendix A: Nausea and Vomiting Subject Diary

Principal Investigator:	Study Site No: _____	Tesaro Study TS-P01832	Subject Initials: <input type="checkbox"/> F <input type="checkbox"/> M <input type="checkbox"/> L	Subject No: _____	Date: ____/____/____ DD MM YY
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**Nausea & Vomiting Subject Diary (NV Subject Diary)**

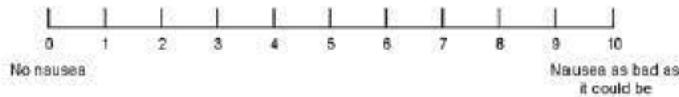
The following questions ask you about your experience with nausea and vomiting over the past 24 hours. Please complete a new daily diary each day between 0800 and 1000 (8:00AM and 10:00AM). Please only include how nausea and vomiting has affected you in the past 24 hours up to and including the present time.

1. When did you complete this questionnaire?

Date: \_\_\_\_/\_\_\_\_/\_\_\_\_ Time: \_\_\_\_:\_\_\_\_ Record in 24hr clock  
DD/MM/YYYY HH:MM

For the following question, please place a vertical mark on the line to show how you would rate your nausea over the past 24 hours.

2. How would you rate your nausea over the last 24 hours?



A vomiting episode occurs when you vomit (expel your stomach contents through your mouth) or experience dry heaves (an attempt to vomit but nothing is expelled through your mouth). If more than a minute passes between the time that you vomit or experience dry heaves, treat these as separate episodes.

3. Did you vomit or have dry heaves over the last 24 hours?

\_\_\_\_ No \_\_\_\_ Yes

Note: If response to question 3 is 'NO' skip to question 5.

Nausea and Vomiting Subject Diary continued

4. Please record the date and times that you had a vomiting or dry heaves episode over the last 24 hours:

DD/MM/YYYY	HH:MM Record in 24hr clock	(circle one)	
Date: ___/___/___	Time: ___:___	Vomited	Dry Heaves
Date: ___/___/___	Time: ___:___	Vomited	Dry Heaves
Date: ___/___/___	Time: ___:___	Vomited	Dry Heaves
Date: ___/___/___	Time: ___:___	Vomited	Dry Heaves
Date: ___/___/___	Time: ___:___	Vomited	Dry Heaves

5. Did you need to take any medication for nausea or vomiting over the last 24 hours?

No  Yes

Note: If response to question 5 is 'NO' skip question 6.

6. What medication did you take for either nausea or vomiting over the last 24 hours? (Please record the dates and times for each medication each time you took it. Include any "rescue medication," prescription drugs, over the counter medications, herbal remedies or vitamins):

	DD/MM/YYYY	HH:MM Record in 24hr clock
Name: _____	Date: ___/___/___	Time: ___:___
Name: _____	Date: ___/___/___	Time: ___:___
Name: _____	Date: ___/___/___	Time: ___:___
Name: _____	Date: ___/___/___	Time: ___:___
Name: _____	Date: ___/___/___	Time: ___:___

Nausea and Vomiting Subject Diary Continued

**Nausea & Vomiting Subject Diary (NV Subject Diary)  
Scoring Algorithm**

**Measuring the Visual Analogue Scale for a Question**

Place a metric ruler below the line for the question so that the "0" on the ruler is directly below the left hand end of the line.

**Calculating the Score for a Visual Analogue Scale Question**

Follow the instructions below to calculate the score for question 2.

1. The distance in mm is the score for the question (Score=Distance)
2. The minimum score is 0 and the maximum score is 100.

## Appendix B: Functional Living Index-Emesis (FLIE)

### PATIENT INSTRUCTIONS:

In the following questionnaire you are asked to rate how much nausea and vomiting have affected your quality of life. The first set of 9 questions refers to nausea and the second set of 9 questions refers to vomiting. The questionnaire should take approximately 10 minutes or less to complete. Please read the instructions before you begin. Think carefully about each question because your answers may help to develop treatments that will improve the quality of life for future patients.

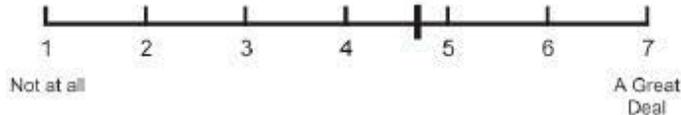
For each question, you will rate how much nausea (or vomiting) has affected an aspect of your quality of life during the past five days. Please focus on your experiences **over that time period**. We are interested in **your opinions**, not those of family members or friends. Your answers will remain confidential.

You must answer every question using a black ballpoint pen. Press firmly so that your mark is clear.

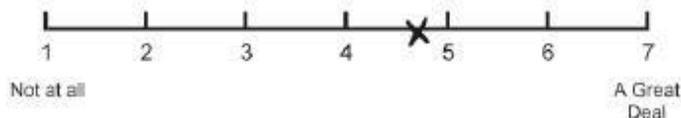
If you are unsure of your answer or do not understand the question, read the question again carefully and make a vertical mark ( | ) on the line based upon your best understanding of the question. If you want to change your answer, please do the following: make a new vertical mark ( | ); draw an arrow to the correct mark; initial and date the correction.

Each question uses a visual analogue scale. Think about how you rate your feelings and place a vertical mark ( | ) on the line at a point corresponding to how much your nausea (or vomiting) has affected that aspect of your quality of life. **Please read the question carefully because in some questions, a "1" indicates no effect on your quality of life and in other questions a "1" indicates a great deal of an effect on your quality of life.** You may place your vertical mark ( | ) at any point along the line. Be sure that you make your vertical mark ( | ) so that it intersects the horizontal line. Do not circle a number. Use a single vertical mark ( | ) as shown below.

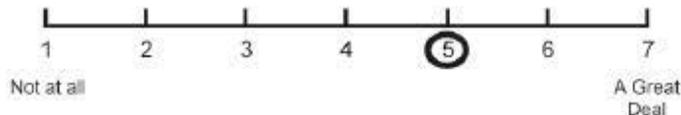
#### Correct: Vertical mark



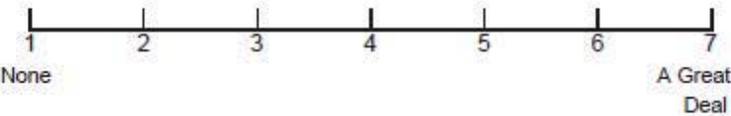
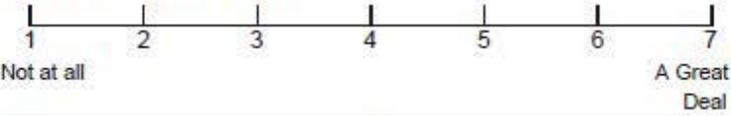
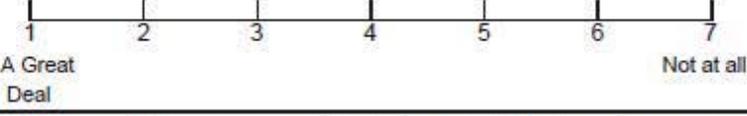
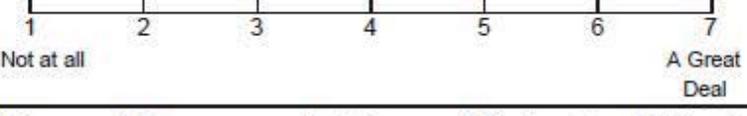
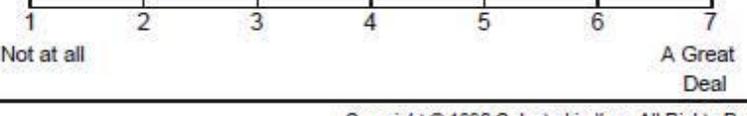
#### Incorrect: Single "x"



#### Incorrect: Circle number



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FUNCTIONAL LIVING INDEX – EMESIS	
<i>Information should be entered onto this questionnaire only by the patient</i>	
<b>NAUSEA</b>	
Think about the times you felt nauseated during the past 5 days. (Please mark your answers with a vertical mark (   ) so that it intersects the horizontal line.)	
1. How much nausea have you had in the past 5 days?  	<i>Study Coordinator Use Only</i>  Q1 _____
2. Has nausea affected your ability to maintain usual recreation or leisure activities in the past 5 days?  	Q2 _____
3. Has nausea affected your ability to make a meal or do minor household repairs during the past 5 days?  	Q3 _____
4. How much has nausea affected your ability to enjoy a meal in the past 5 days?  	Q4 _____
5. How much has nausea affected your ability to enjoy drinking liquids in the past 5 days?  	Q5 _____
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FUNCTIONAL LIVING INDEX – EMESIS (Continued)	
Information should be entered onto this questionnaire only by the patient	
NAUSEA	
Think about the times you felt nauseated during the past 5 days. (Please mark your answers with a vertical mark (   ) so that it intersects the horizontal line.)	
<p>6. How much has nausea affected your willingness to see and spend time with family and friends in the past 5 days?</p> <p style="text-align: center;"> </p>	<p><i>Study Coordinator Use Only</i></p> <p>Q6 _____</p>
<p>7. Has nausea affected your daily functioning in the past 5 days?</p> <p style="text-align: center;"> </p>	<p>Q7 _____</p>
<p>8. Rate the degree to which your nausea has imposed a hardship on you (personally) in the past 5 days?</p> <p style="text-align: center;"> </p>	<p>Q8 _____</p>
<p>9. Rate the degree to which your nausea has imposed a hardship on those closest to you in the past 5 days?</p> <p style="text-align: center;"> </p>	<p>Q9 _____</p>
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FUNCTIONAL LIVING INDEX – EMESIS (Continued)	
VOMITING	
Think about the times you vomited during the past 5 days. (Please mark your answers with a vertical mark (   ) so that it intersects the horizontal line.)	
<p>10. How much vomiting have you had in the past 5 days?</p> <p style="text-align: center;"> <span style="margin-right: 20px;">1</span> <span style="margin-right: 20px;">2</span> <span style="margin-right: 20px;">3</span> <span style="margin-right: 20px;">4</span> <span style="margin-right: 20px;">5</span> <span style="margin-right: 20px;">6</span> <span>7</span>                      Not at all <span style="float: right;">A Great Deal</span> </p>	<p><i>Study Coordinator Use Only</i></p> <p>Q10 _____</p>
<p>11. Has vomiting affected your ability to maintain usual recreation or leisure activities during the past 5 days?</p> <p style="text-align: center;"> <span style="margin-right: 20px;">1</span> <span style="margin-right: 20px;">2</span> <span style="margin-right: 20px;">3</span> <span style="margin-right: 20px;">4</span> <span style="margin-right: 20px;">5</span> <span style="margin-right: 20px;">6</span> <span>7</span>                      A Great Deal <span style="float: right;">Not at all</span> </p>	<p>Q11 _____</p>
<p>12. Has vomiting affected your ability to make a meal or do minor household repairs during the past 5 days?</p> <p style="text-align: center;"> <span style="margin-right: 20px;">1</span> <span style="margin-right: 20px;">2</span> <span style="margin-right: 20px;">3</span> <span style="margin-right: 20px;">4</span> <span style="margin-right: 20px;">5</span> <span style="margin-right: 20px;">6</span> <span>7</span>                      Not at all <span style="float: right;">A Great Deal</span> </p>	<p>Q12 _____</p>
<p>13. How much has vomiting affected your ability to enjoy a meal in the past 5 days?</p> <p style="text-align: center;"> <span style="margin-right: 20px;">1</span> <span style="margin-right: 20px;">2</span> <span style="margin-right: 20px;">3</span> <span style="margin-right: 20px;">4</span> <span style="margin-right: 20px;">5</span> <span style="margin-right: 20px;">6</span> <span>7</span>                      Not at all <span style="float: right;">A Great Deal</span> </p>	<p>Q13 _____</p>
<p>14. How much has vomiting affected your ability to enjoy drinking liquids in the past 5 days?</p> <p style="text-align: center;"> <span style="margin-right: 20px;">1</span> <span style="margin-right: 20px;">2</span> <span style="margin-right: 20px;">3</span> <span style="margin-right: 20px;">4</span> <span style="margin-right: 20px;">5</span> <span style="margin-right: 20px;">6</span> <span>7</span>                      Not at all <span style="float: right;">A Great Deal</span> </p>	<p>Q14 _____</p>
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FUNCTIONAL LIVING INDEX – EMESIS (Continued)	
<b>VOMITING</b>	
Think about the times you vomited during the past 5 days. (Please mark your answers with a vertical mark (   ) so that it intersects the horizontal line.)	
<p>15. How much has vomiting affected your willingness to see and spend time with family and friends in the past 5 days?</p> <p style="text-align: center;"> </p>	<p><i>Study Coordinator Use Only</i></p> <p>Q15 _____</p>
<p>16. Has vomiting affected your daily functioning in the past 5 days?</p> <p style="text-align: center;"> </p>	<p>Q16 _____</p>
<p>17. Rate the degree to which your vomiting has imposed a hardship on you (personally) in the past 5 days?</p> <p style="text-align: center;"> </p>	<p>Q17 _____</p>
<p>18. Rate the degree to which your vomiting has imposed a hardship on those closest to you in the past 5 days?</p> <p style="text-align: center;"> </p>	<p>Q18 _____</p>
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**FUNCTIONAL LIVING INDEX – EMESIS  
Measurement Instructions**

The Functional Living Index Emesis (FLIE) has 18 questions. These questions are divided into two domains: nausea (questions 1-9) and vomiting (questions 10-18).

**Measuring the Visual Analogue Scale for a Question**

Follow the instructions below to measure the visual analogue scale for each question.

1. Place a metric ruler below the line for the question so that the “0” on the ruler is directly below the left hand end of the line. Measure the distance to where the patient has marked his or her vertical mark through the line.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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AISHA P JOHNSON  
05/12/2015

DONNA J GRIEBEL  
05/12/2015