CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	206-500	*Submission Date*	09/05/2014
Brand Name		To-be-determined	
Generic Name		Rolapitant hydrochloride	
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OCP Division		Division of Clinical Pharmacology 3	
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Sponsor		Tesaro, Inc.	
Relevant IND(s)		IND 72,754	
Submission Type; Code		Original Submission	New Molecular Entity
Formulation; Strengths; Regimen		90 mg rolapitant (equivalent to 100 mg rolapitant hydrochloride) tablet Oral administration of 180 mg rolapitant at 1-2 hours prior to the start of chemotherapy. Once per chemotherapy cycle	
Proposed Indication		In combination with other antiemetic agents in adults for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy including, but not limited to, highly emetogenic chemotherapy	

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1 Executive Summary

Rolapitant is a substance P/neurokinin 1 (NK_1) -receptor antagonist and is proposed for use by the sponsor for the prevention of (b) (4) delayed nausea and vomiting associated with emetogenic cancer chemotherapy (CINV). The proposed dosage regimen is a single-dose administration of 180 mg rolapitant at 1-2 hour prior to the initiation of chemotherapy cycle in combination with a 5-HT_3 receptor antagonist and a corticosteroid.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the submission and found acceptable from a clinical pharmacology standpoint provided mutual agreement on the labeling languages is reached.

1.2 Post-Marketing Commitments

***a. Recommended study*:** In vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 7 days after a single dose administration of rolapitant

Rationale: Rolapitant is a moderate CYP2D6 inhibitor with inhibitory effects observed on 7 days after a single dose administration. The target patient population is cancer patients who will receive emetogenic chemotherapeutics and is likely to be on multiple other medications. Especially rolapitant will be administered every 2-4 weeks depending on the number of and the interval between chemotherapy cycles over a course of therapy. This PMC will be used to inform how long the inhibition of CYP2D6 enzyme lasts after a single dose administration of rolapitant as so to properly inform the labeling and to mitigate the potential risk with increased systemic exposure of concomitant CYP2D6 substrates.

b. Recommended study: In vitro study to evaluate an inhibitory potential of rolapitant on OATP1B1 and OATP1B3

Rationale: Inhibition of hepatic transporters, OATP1B1 and OATP1B3 can cause an increase in systemic exposure of OATP1B1 or OATP1B3 substrates such as statin. The inhibitory potential of rolapitant on OATP1B1 and OATP1B3 was not evaluated to assess drug interaction potential.

c. Recommended study: In vitro studies to evaluate an inhibitory potential of rolapitant on renal transporters i.e. organic cation transporter 2 (OCT2), multidrug and toxin extrusion (MATE) transporters organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3)

Rationale: Inhibition of renal transporters may lead to an increase in systemic exposure to concomitant drugs that are substrates of these transporters, which include but not limited to, metformin and cisplatin (OCT2 and MATEs), and methotrexate (OAT1, OAT3). The inhibitory

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potential of rolapitant on kidney transporters (OCT2, MATE1, MATE-2K, OAT1, and OAT3) was not evaluated to assess drug interaction potential.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The clinical efficacy and safety of rolapitant was studied in combination with a standard of care i.e. a 5-HT_3 antagonist and a corticosteroid and compared with placebo treatment which was also given with a standard of care. The efficacy was evaluated based on the proportion of patients who had complete response (CR) i.e. no emesis, and no rescue medication over 120 hours in delayed (25-120 h), acute (0-24 h) and overall (0-120 h) phases.

Dose-Response Relationship

Efficacy

The proposed dose of 180 mg rolapitant was supported by a Phase 2 dose-finding study and three Phase 3 clinical trials where the efficacy and safety of rolapitant was evaluated with 180 mg dose. (b) (4) In a Phase 2 trial in patients who received cisplatin-based chemotherapy, there was a dose-dependent increase in the CR rate in the dose range from 9 mg to 180 mg rolapitant. Only 180 mg dose but not lower doses showed, significantly higher CR rates in delayed, overall, and acute phases compared to placebo treatment.

In addition, within doses ranging from 4.5 mg to 180 mg, there was a dose-dependent increase in the NK_1 receptor occupancy in the brain at 120 hours after single-dose administration of rolapitant.

The proportion of patients with CR was significantly higher than that in placebo group in the delayed and overall phases in two phase 3 trials for highly emetogenic chemotherapy (P04832, P04833) and one phase 3 trial for moderately emetogenic chemotherapy (P04834). On the other hand, a statistically significant increase in CR rate in the acute phase was shown only in P04832 but not in Studies P04833 and P04834. For more details, see the Biostatistics Review.

Safety

Across clinical trials, nausea, anorexia, vomiting, fatigue, neutropenia and headache were the most frequently reported treatment-emergent adverse events (TEAE).

No apparent dose-dependent increase in the incident of treatment-emergent adverse events was noted in the dose range from 9 mg to 180 mg in patients receiving cisplatin-based chemotherapy (n=90-91 per dose). While doses higher than 180 mg were not studied in cancer patients, no serious adverse events were reported at 720 mg dose in healthy subjects (n=41) [1] and TEAEs were mostly mild in severity except one subject experienced moderate disorientation at 720 mg rolapitant. See the Clinical Review by Dr. Johnson for thorough review of safety.

Effects on the QT interval

No significant effects on the QTc interval were observed after single dose administration of 720 mg rolapitant in a thorough QT study.

[1] Study P0478:Through QT study

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Table 1 the Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Rolapitant and the Largest Lower Bound for Moxifloxacin[2])

Treatment	Time (h)	ΔΔQTcF (ms)	90% CI (ms)
Rolapitant 180 mg	1	1.3	(-1.5, 4.0)
Rolapitant 720 mg	0	1.7	(-1.0, 4.4)
Moxifloxacin 400 mg	1	10.4	(7.7, 13.2)

Pharmacokinetic/Biopharmaceutics Properties

Pharmacokinetics

The PK of rolapitant and the effects of rolapitant on other drugs were mainly studied after single-dose administration of rolapitant consistent with the proposed dosage regimen. In efficacy trials, rolapitant was administered once every 2-4 weeks with a median interval of 21 days depending on the chemotherapy regimen. The dosing interval of less 2 weeks was not studied in cancer patients.

The pharmacokinetics of rolapitant is characterized by a large apparent volume of distribution with plasma concentrations measurable at a month after a single-dose administration. Upon oral administration, the peak plasma concentration of rolapitant is achieved around 4 hours. Once absorbed, rolapitant is slowly eliminated from the circulation with mean elimination half-life of about 7 days. The systemic exposure ($AUC_{0\text{-}120}$) over 120 hours, during which the efficacy of rolapitant was evaluated, is about 40% of total systemic exposure ($AUC_{0\text{-}inf}$). In cancer patients the apparent total clearance (CL/F) and volume of distribution (Vd/F) is estimated to be 0.96 L/h and 387 L, respectively by a population PK analysis. Rolapitant is highly protein bound (>99%) and is metabolized to multiple metabolites mainly by CYP3A4. A metabolite, M19 (SCH720881) is a major circulating active metabolite while other metabolites were measurable only in urine or feces but not in plasma. Rolapitant is mainly excreted via hepatic/biliary route. In a mass balance study, 73% and 14% of the administered dose was excreted in feces and urine, respectively and unchanged rolapitant was not found in urine while it was predominant in feces.

The to-be-marketed formulation i.e. 90 mg rolapitant tablet was bioequivalent to the formulation used in phase 3 clinical trials i.e. 45 mg rolapitant capsules. See the review of Biopharmaceutics by Dr. Peng for more details.

Specific Population

No dosage adjustment for patients with mild to moderate hepatic or renal impairment is deemed necessary based on no significant effects of mild to moderate hepatic or renal impairment on systemic exposure to rolapitant.

Patients with severe hepatic impairment or renal impairment

PK or safety for rolapitant was not evaluated in patients with severe hepatic impairment (HI) or is insufficient in patients with severe renal impairment (RI)(n=1). In healthy subjects no remarkable safety issues were identified after a single-dose administration of 720 mg rolapitant[3] at which the Cmax and AUC were 3.3-fold and 3.9-fold higher than those at 180 mg. It seems less than likely

[2] IRT-QT review of the thorough QT study; IND 72,754 SDN076 dated 11/05/2010

[3] Supratherapeutic dose in the thorough QT study (Study P0478)

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that after a single-dose rolapitant (no repeat dose), the systemic exposure of rolapitant in severe HI or RI patients would exceed the systemic exposure observed at 720 mg. Nevertheless, considering a long half-life of rolapitant and possible decrease in clearance of rolapitant in severe HI or RI patients, potentially high plasma concentrations cannot be ruled out in patients with severe RI or HI due to accumulation after repeated dosing especially with shorter chemotherapy interval.

Drug Interactions

Effects of other drugs on rolapitant

Rolapitant is a substrate of CYP3A4. Rolapitant is not recommended in patients who are on a strong CYP3A4 inducer such as rifampin for the potential loss of efficacy due to a significant decrease in systemic exposure i.e. AUC decreased by 87% with concurrent rifampin.
Concurrent ketoconazole, a strong CYP3A4 inhibitor did not significantly affect systemic exposure to rolapitant.

In vitro studies suggest that rolapitant is not a substrate of P-glycoprotein, OATP1B1 and OATP1B3.

Effects of rolapitant on other drugs[4]

CYP2D6 substrate

Rolapitant is a moderate inhibitor of CYP2D6 based on a clinical drug interaction study. Notably an inhibitory effect of rolapitant on CYP2D6 was observed even on Day 7 after a single-dose administration of rolapitant to the comparable extent to the inhibition observed on Day 1. The inhibition of CYP2D6 was not studied beyond 7 days after rolapitant administration (Table 1).

Substrates of efflux transporters, BCRP and P-gp

Rolapitant is an inhibitor of breast-cancer-resistance-protein (BCRP) and P-glycoprotein (P-gp). Concomitant rolapitant increased the systemic exposure to sulfasalazine, a substrate of BCRP by 2.3-fold on Day 1 and the inhibitory effect was decreased on Day 7.

When co-administered with rolapitant, mean Cmax of digoxin, a substrate of P-gp was 70% higher than that without rolapitant.

CYP3A4

Rolapitant is not an inhibitor or an inducer of CYP3A4. In a clinical drug interaction study, a single-dose rolapitant did not significantly affect the PK of midazolam over 10 days.

Dosage adjustment is not necessary for dexamethasone and granisetron which were used in combination with rolapitant for efficacy. Rolapitant did not significantly affect the PK of

[4] A potential drug interaction was studied at two time points after single-dose administration of 180 mg rolapitant by evaluating PK of a substrate drug on Day 1 as well as on Day 7 after co-administration with rolapitant on Day 1. The PK of a substrate drug was compared with that after administration of substrate alone before rolapitant administration in a fixed-sequence, cross-over study.

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dexamethasone. A significant effect of rolapitant on the PK of granisetron, a CYP3A4 substrate is not expected[5].

Other CYP enzymes

No clinically significant effects of rolapitant were seen on the PK of efavirenz (CYP2B6 substrate), repaglinide (CYP2C8 substrate), and tolbutamide (CYP2C9 substrate). Rolapitant slightly increased mean Cmax of omeprazole (CYP2C19 substrate) by 44% and 38%, on Day 1 or Day 7, respectively.

In vitro studies suggest that rolapitant is not an inhibitor of CYP1A2 and CYP2E1. A significant drug interaction via an inhibition of CYP2A6 appears unlikely based on no significant effects of rolapitant on substrates of CYP enzymes for which IC_{50} values were similar to that for CYP2A6.

Table 2 Summary of significant effects of rolapitant on systemic exposure to concomitant drugs

Enzyme/ transporter	Co-administered drug	Day 1 Mean ratio (90% CI)		Day 7 Mean ratio (90% CI)	
	Name and Dose	Cmax	AUC	Cmax	AUC
CYP2D6	Dextromethorphan 30mg	2.3 (1.9, 2.7)	2.6 (2.1, 3.1)	2.8 (2.3, 3.3)	3.3 (2.8, 4.0)
BCRP	Sulfasalazine 500 mg	2.4 (2.0, 2.9)	2.3 (2.0, 2.7)	1.2 (1.0, 1.4)	1.3 (1.1, 1.6)
P-gp	Digoxin 0.5 mg	1.7 (1.5, 2.0)	1.3 (1.2, 1.4)	--	--

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What is pertinent regulatory background contributes to the current assessment of the clinical pharmacology of rolapitant?

Rolapitant is a new molecular entity and a substance P/neurokinin 1 (NK_1) receptor antagonist.

EMEND (aprepitant for oral administration and fosaprepitant for intravenous injection) is the first NK_1 receptor antagonist approved for chemotherapy induced nausea and vomiting. AKYNZEO, a fixed dose combination product of netupitant, NK_1 receptor antagonist and palonosetron, 5-HT_3 antagonist was approved in October, 2015.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of rolapitant, and the formulation of the drug product?

[5] Package Insert for Granisetron Hydrochloride

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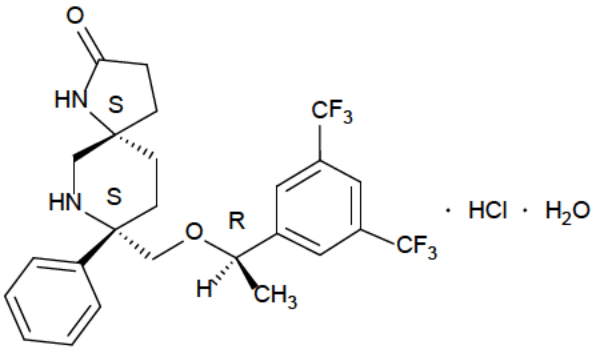

Figure 1 Structure of rolapitant hydrochloride

Solubility of rolapitant hydrochloride in aqueous solution is pH-dependent and is more soluble at lower pH (pH =< 4). Rolapitant hydrochloride has good solubility in common pharmaceutical solvents such as ethanol, propylene glycol, and 40% hydroxypropyl beta cyclodextrin.

The to-be-marketed formulation is an immediate release table which contains 90 mg rolapitant (equivalent to 100 mg rolapitant hydrochloride). On the other hand, 45 mg rolapitant in capsules were used in phase 3 trials. Bioequivalency was demonstrated between two 90 mg rolapitant tablets and four 45 mg rolapitant capsules.

Reviewer's comment:
During the development, the dosage strength and the dose were based on rolapitant hydrochloride (HCl) in clinical study reports. As the strength of dosage form should be presented based on an active ingredient i.e.90 mg rolapitant, the dose strength as presented in this review will be as either 90 mg rolapitant or 100 mg rolapitant HCl. See the Biopharmaceutics Review by Dr. Peng for more details.

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication?

Rolapitant is a substance P/neurokinin 1 (NK_1) receptor antagonist and proposed to be used in combination with a 5-HT3 antagonist and a corticosteroid.

Chemotherapeutic agents exert their emetic stimulus via processes that involve the release of serotonin and substance P and subsequent activation of the 5-HT_3 and NK_1 receptors. The release of substance P is associated with delayed emesis induced by chemotherapy while serotonin is associated with acute emesis induced by chemotherapy.

The indication proposed by the sponsor is "in combination with other antiemetic agents in adults for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy including, but not limited to, highly emetogenic chemotherapy".

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Reviewer's comment: The clinical trials were conducted to evaluate the efficacy of rolapitant based on the emetogenicity of chemotherapeutics i.e. highly or moderately emetogenic chemotherapy (HEC or MEC). Patients in studies for HEC, mostly received a cisplatin-based chemotherapy. In a MEC trial, 51% of patients received anthracycline-cyclophosphamide based chemotherapy. Of note the emetogenicity of anthracycline-cyclophosphamide regimen was recently reclassified from MEC to HEC[6]. (b) (4) See the Clinical Review for more details.

2.1.4 What is the proposed dosage regimen?

Table 3 Proposed Dosage Regimen in Combination with Dexamethasone and 5-HT$_3$ antagonist

(b) (4)

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support the efficacy and safety of rolapitant three phase 3 trials i.e. two trials for HEC and one trial for MEC were conducted in cancer patients. The dose-response relationship was studied in a phase 2 trial.

In clinical trials, the efficacy and safety of rolapitant was studied in combination with dexamethasone, a corticosteroid, and a 5-HT$_3$ antagonist. The patients in the placebo arm received dexamethasone and a 5- HT$_3$ antagonist in addition to the placebo for rolapitant.
As a 5- HT$_3$ antagonist, intravenous granisetron was used in the phase 3 HEC study and oral granisetron was in the phase 3 MEC study. Both intravenous and oral granisetron were approved for CINV including highly emetogenic chemotherapy induced nausea and vomiting and recommended to be given only on days of chemotherapy administration. On the other hand, intravenous ondansetron was used in the phase 2 trial (Table 4).

Reviewer's comment: Intravenous 32 mg ondansetron used in phase 2 trial was removed from the labeling in November 2012 due to the concern of QT prolongation.

Pharmacokinetics of rolapitant and its major metabolite was studied in healthy subjects and in cancer patients. Because a single dose rolapitant will be given prior to the start of chemotherapy, PK of rolapitant was studied mostly after single dose administration except for one multiple dose

[6] Basch et al. (2011) Antiemetics: ASCO Clinical Practice Guideline Update, J. Clin.Oncol. 29(34), 4189

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PK study. Phase 1 PK studies for comparison were done in a fixed-sequence cross-over manner for clinical drug interaction studies due to a prolonged half-life of rolapitant.

Table 4 Dosage regimens of co-administered dexamethasone and 5-HT_3 receptor antagonist in the clinical trials

Study		5-HT_3 antagonist [b]	Dexamethasone
P4832 P4833	HEC	Intravenous 10 mcg/kg granisetron on Day 1	Oral 20 mg on Day 1, 8 mg b.i.d. on Days 2-4
P4834	MEC	Oral 2 mg granisetron on Days 1-3	Oral 20 mg on Day 1 only
P4351[a]	HEC	Intravenous 32 mg ondansetron on Day 1	Oral 20 mg on Day 1, 8 mg b.i.d. on Days 2-4

[a] phase 2 trial
[b] approved regimen

2.2.2 What is the basis for selecting the endpoints in clinical pharmacology and clinical studies?

The clinical efficacy was evaluated based on the proportion of patients who had a complete response (CR) (defined as no emesis, no rescue medication) over 0-24 h (acute phase), 25-120 h (delayed phase) and 0-120 h (overall phase) post chemotherapy.

Other efficacy endpoints such as time to first emetic episode, time to first rescue medication, time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first) were also evaluated.

In a phase 1 pharmacodynamics study, the NK_1-receptor occupancy in the brain was explored in a Positron Emission Tomography (PET) study using a labeled tracer.

2.2.3 Are the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?

Yes. Rolapitant and its major active metabolite were identified and measured using a validated bioanalytical assay methods. See Section 2.6 for more details.

2.2.4 Exposure-Response Evaluation

2.2.4.1 Is the proposed dose of 180 mg appropriate?

Dose-response relationship

The dose-response relationship was explored in a phase 2 trial (P4351) in the range from 9 mg to 180 mg rolapitant (equivalent to 10 mg to 200 mg rolapitant HCl). In patients received $\geq$ 70 mg/m^2 cisplatin-based chemotherapy, there was a dose-dependent increase in the complete response rate

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(Figure 2). The study was powered to show the difference between the dose and the placebo but not for the difference between doses.

Table 5 Summary of Complete Response in the Acute, Delayed, and Overall Phases: Cycle 1[a]

	Placebo	Rolapitant			
Time interval		10 mg	25 mg	100 mg	200 mg
0-24 hr	(b) (4)				
24-120 hr	48.9%	50.5%	54.5%	58.2%	63.6%[b]
0-120 hr	(b) (4)				

[a]: n=88-91 per dose group
[b]: P-value <0.05

Reviewer's comments: The results of statistical analysis method are currently under discussion. See the Biometrics review for more details.

Figure 2 Complete Response Rate (%) in Patients who received Cisplatin-Based Chemotherapy (HEC) by Dose in Acute, Delayed, and Overall Phases: Cycle 1 (P4351)

(b) (4)

The dose of 180 mg is also supported by other secondary endpoints including time to first emesis or to rescue medication use. As shown in Figure 3, time to first emesis or to rescue medication use was significantly longer during Cycle 1 for patients with 200 mg compared to other dose groups.

Figure 3 Kaplan-Meier Plot for Time to First Emesis or Rescue Medication Use: Cycle 1

(b) (4)

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Phase 3 trials

In phase 3 trials, one dose level of 200 mg rolapitant HCl (equivalent to 180 mg rolapitant) was studied. The rate of complete response in the delayed (primary endpoint), acute and overall phases (key secondary endpoints) was evaluated in patients who received HEC e.g. cisplatin-based chemotherapy (Studies P04832 and P04833) and moderately emetogenic chemotherapy including anthracycline-cyclophosphamide based chemotherapy (Study P04834).

Reviewer's comment: Anthracycline-cyclophosphamide regimen is reclassified to HEC from MEC.

In delayed phase The CR rate in delayed phase was significantly higher after rolapitant treatment than control group while the CR rate in the control group was > 50% in all three trials. On the other hand, the effect of rolapitant on acute CINV was inconsistent as a statistically significant increase in CR rate was shown only in one trial (P04832). Notably the CR rate in acute phase is similar after rolapitant treatment across trials while the CR rate in control group varied across trials.

Table 6 Proportion of Patients with the Complete Response in Acute, Delayed and Overall Phases in Patients who received Highly Emetogenic Chemotherapy (MITT Population, Study P04832)

CINV phase	Rolapitant % (n/N) 95% CI	Control % (n/N) 95% CI	p-value
Delayed (24-120 h)	72.7 (192/264) [66.9, 78.0]	58.4 (153/262) [52.2, 64.4]	<0.001
Acute (0-24 h)	(b) (4)		
Overall (0-120 h)			

Table 7 Proportion of Patients with the Complete Response in Acute, Delayed and Overall Phases in Patients who received Highly Emetogenic Chemotherapy (MITT Population, Study P04833)

CINV phase	Rolapitant % (n/N) 95% CI	Control % (n/N) 95% CI	p-value
Delayed (24-120 h)	70.1 (190/271) [64.3, 75.5]	61.9 (169/273) [55.9, 67.7]	0.043
Acute (0-24 h)	(b) (4)		
Overall (0-120 h)			

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Table 8 Proportion of Patients with the Complete Response in Acute, Delayed and Overall Phases in Patients who received Moderately Emetogenic Chemotherapy (Study P04834)

CINV Phase	Rolapitant % (n/N) 95% CI	Control % (n/N) 95% CI	p-value
Delayed (24-120 h)	71.3 (475/666) [67.7,74.7]	61.6 (410/666) [57.7,65.3]	<0.001
Acute (0-24 h)	(b) (4)		
Overall (0-120 h)			

Receptor occupancy study

A dose-dependent NK_1 receptor occupancy was observed in an exploratory NK_1-receptor occupancy study using PET in healthy subjects[7]. The NK_1 receptor occupancy at 120 hours after single-dose administration of rolapitant was estimated. Subjects were treated with a single dose of ^{11}C-GR205171, a radiotracer alone and with rolapitant at 120 hours prior to ^{11}C-GR205171. The estimated occupancy of the NK1 receptor in the averaged cortical region was 37% at 4.5 mg, 44% at 9 mg, 67% at 21.6 mg, 76% at 45 mg, 79% at 90 mg, and 94% at 180 mg (n=2 per dose cohort). The receptor occupancy in the striatum region was 19% at 4.5 mg, 13.5% at 9 mg, 46% at 21.6 mg, 47% at 45 mg, 59% at 90 mg, and 73% at 180 mg (Figure 4). The doses higher than 180 mg were not studied.

In an exploratory PK/PD model based on the sigmoid Emax equation, rolapitant concentrations above 324 ng/ml was predicted to be correspond to > 90% NK_1 receptor occupancy based on an average across the frontal, occipital, temporal and parietal region of interests (ROI)s.

Reviewer's comment:

The striatum region represents the area with the highest NK_1 receptor expression in humans while the role of each brain regions in the modulation of the CINV is unknown[8]. An exploratory PK/PD analysis was done based on the averaged receptor occupancy in the cortical region. On the other hand, the receptor occupancy in the striatum was considered underestimated due to a high expression of NK_1 receptors in this region. Because of the high expression of NK_1 receptors in the striatum, a tracer binding at baseline was considered underestimated resulting in lower receptor occupancy by rolapitant in this region. Nevertheless, in the same study, the receptor occupancy in the striatum and in the averaged cortical region was 90.5% and 96%, respectively at 24 hours after a single dose administration of 125 mg aprepitant. While it is unclear if striatal receptor occupancy by rolapitant is underestimated due to a underestimated tracer binding at baseline, rolapitant

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[7] The estimation of receptor occupancy from brain PET scans is based upon two measurements: a first measurement of binding of the PET ligand under tracer alone conditions (baseline scan) and another measurement of binding after administration of rolapitant (blocked scan).

Receptor Occupancy: $OCC(\%) = ((Ki'_{Baseline} - Ki'_{Blocked})/Ki'_{Baseline}) \times 100$

Ki': the rate constant for the transfer of tracer from plasma to the irreversible compartment, normalized to the volume of distribution in the reference region

[8] Caberlotto L. et al., (2003) Neurokinin 1 receptor and relative abundance of the short and long isoforms in human brain. Eur J. Neurosci.17:1736-1746

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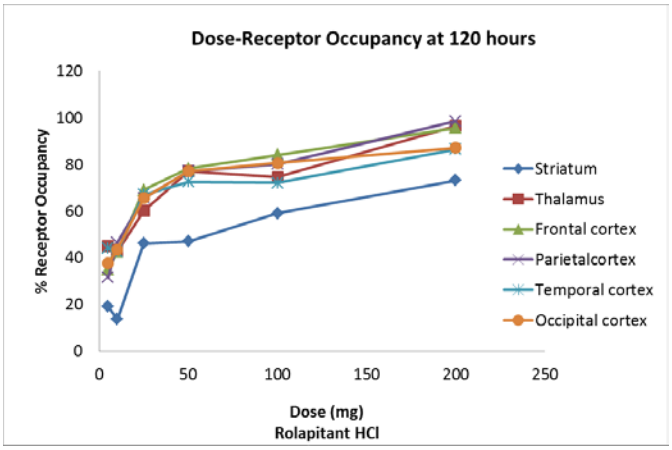
concentration needed for > 90% NK_1 receptor in the striatum may be higher than for the averaged cortical region.

Figure 4 Receptor Occupancy-Dose Relationship by Region of Interest



2.2.4.2 What are the characteristics of the dose-response relationships for safety?

In the phase 2 trial no dose-dependent increase in the adverse events was apparent in the dose range from 9 mg to 180 mg in patients receiving HEC ($\geq$70 mg/m^2 cisplatin-based chemotherapy) (Table 9). Among the most frequently reported treatment-emergent adverse events (TEAE) were nausea, anorexia, vomiting, fatigue, neutropenia and headache (Table 10). Doses higher than 180 mg were not studied in cancer patients.

In healthy subjects, there was no serious adverse event occurred after administration of 720 mg rolapitant. One out of 41 subjects experienced moderate disorientation at 720 mg while all other TEAEs were mild in severity.

For detailed review of safety is deferred to the Clinical Review by Dr. Johnson.

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Table 9 Overall Summary of adverse events by treatment: all cycles (1-6)*

Category[a]	Treatment Group				
	Control (n = 91) n (%)	Rolapitant 10 mg (n = 91) n (%)	Rolapitant 25 mg (n = 91) n (%)	Rolapitant 100 mg (n = 91) n (%)	Rolapitant 200 mg (n = 90) n (%)
Any TEAE	75 (82.4)	78 (85.7)	76 (83.5)	80 (87.9)	80 (88.9)
Treatment-related TEAE	8 (8.8)	15 (16.5)	14 (15.4)	22 (24.2)	12 (13.3)
TESAE	22 (24.2)	30 (33.0)	20 (22.0)	20 (22.0)	22 (24.4)
Treatment-related TESAE	0	1 (1.1)	0	2 (2.2)	1 (1.1)
TEAE leading to study drug discontinuation	11 (12.1)	8 (8.8)	9 (9.9)	7 (7.7)	10 (11.1)
TESAE leading to study drug discontinuation	9 (9.9)	6 (6.6)	6 (6.6)	4 (4.4)	6 (6.7)
Deaths due to TEAEs	3 (3.3)	3 (3.3)	6 (6.6)	2 (2.2)	5 (5.6)

Abbreviations: TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event

[a] Per the P04351 data analysis plan, a TEAE is one that began during the treatment phase and any days thereafter, unless the same event occurred prior to the start date of treatment with the same or greater severity. Note, this is slightly different than the definition that was used for the analysis of Pooling Group 1.

Source: CSR P04351, Table 20

*Dose as rolapitant HCl

Table 10 Most common treatment-emergent adverse events ≥ 2% during cycle 1*

Protocol No. P04351

Adverse Event[b]	No. (%) of Subjects[a]					
	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)	Total (n=454)
Subjects Reporting Any AE	**8 (9)**	**12 (13)**	**12 (13)**	**21 (23)**	**9 (10)**	**62 (14)**
Constipation	0	2 (2)	3 (3)	6 (7)	1 (1)	12 (3)
Headache	2 (2)	4 (4)	3 (3)	2 (2)	0	11 (2)
Dizziness	0	3 (3)	1 (1)	3 (3)	1 (1)	8 (2)
Fatigue	2 (2)	1 (1)	0	2 (2)	3 (3)	8 (2)
Disturbance in attention	2 (2)	1 (1)	1 (1)	2 (2)	1 (1)	7 (2)
Nausea	0	1 (1)	2 (2)	2 (2)	0	5 (1)
Anorexia	0	2 (2)	0	1 (1)	1 (1)	4 (1)
Vomiting	1 (1)	0	3 (3)	0	0	4 (1)
Abdominal pain	0	0	0	2 (2)	0	2 (<1)
Somnolence	0	0	0	0	2 (2)	2 (<1)

AE = adverse event.

a: ≥2% incidence in any treatment group.

b: AEs presented in decreasing order of frequency based on totals for all treatment groups combined.

Source Data: Section 14.3.1.1.4.

*Dose as rolapitant HCl

2.2.4.3 Does this drug prolong the QT or QTc interval?

No significant effects on the QTc interval were observed after single dose administration of 720 mg rolapitant in a thorough QT study (Table 11, Figure 5). There was no increase in ddQTcF with an increase in rolapitant concentrations (Figure 6).

Reference ID: 3748397

In a randomized, double-blind, single-dose, parallel-group study, 160 healthy subjects received rolapitant 180 mg, 720 mg, placebo, and a single oral dose of moxifloxacin 400 mg. The supratherapeutic dose (720 mg) produces mean C_{max} values of 3.1-fold higher than the mean C_{max} for the therapeutic dose (180 mg).

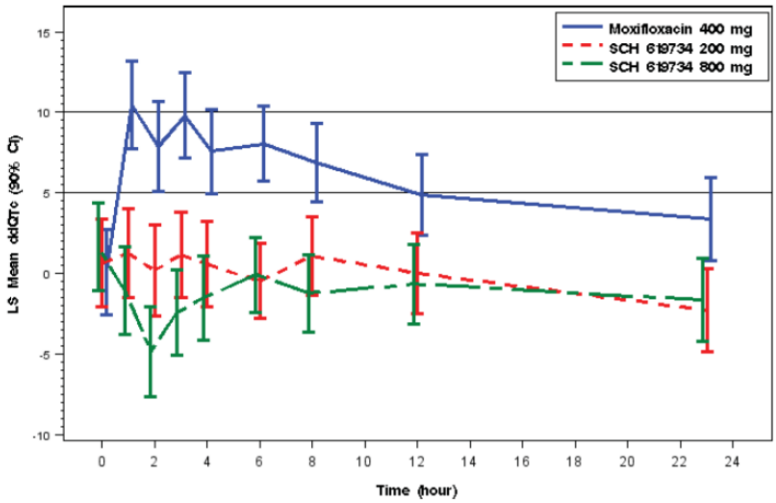
Table 11 The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for Rolapitant and the Largest Lower Bound for Moxifloxacin (Analysis by the FDA IRT-QT review team[9][10])

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
Rolapitant 200 mg	1	1.3	(-1.5, 4.0)
Rolapitant 800 mg	0	1.7	(-1.0, 4.4)
Moxifloxacin 400 mg*	1	10.4	(7.7, 13.2)

* Multiple endpoint adjustment was not applied. The largest lower bound after Bonferroni adjustment for 4 time points is 6.7 ms.

*Dose as Rolapitant HCl

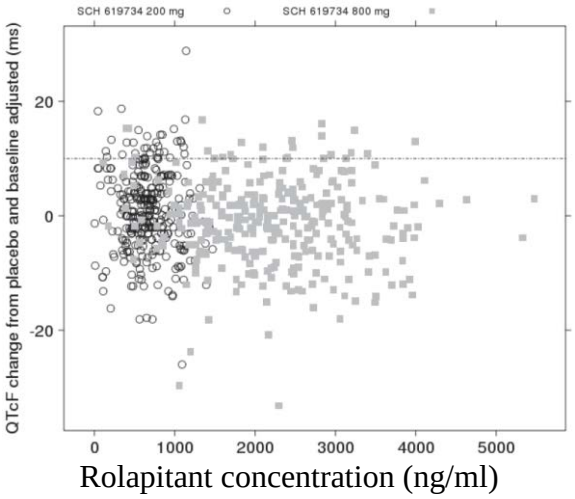
Figure 5 Mean and 90% CI of ddQTcF (Analysis by the FDA IRT-QT review team)



[9] IRT-QT review of the thorough QT study; IND 72,754 SDN076 dated 11/05/2010
[10] IRT-QT review of NDA 206-500 dated 10/23/2014

Reference ID: 3748397

Figure 6 ΔΔQTcF vs. Rolapitant concentration (ng/ml) (FDA Analysis[9])



Reviewer's comment: In the thorough QT study, the ECGs were obtained during the first 24 hour after a single-dose administration of rolapitant. While the ECGs were not obtained for peak plasma concentration of the major metabolite, which was substantially delayed compared to rolapitant, a significant effect of SCH720881 on the QT prolongation is not expected at the proposed clinical dose of 180 mg rolapitant. At the supratherapeutic dose, plasma concentrations of the metabolite, SCH720881 during 24 hours when ECG were obtained were higher than the Cmax of SCH720881 at 180 mg (Table 12).

Table 12 Mean (%CV) concentrations of SCH720881 following single dose of 720 mg rolapitant in healthy subjects

Time (h)	ng/ml
6	175 (34)
8	206 (37)
12	231 (36)
24	354 (37)
Cmax of SCH720881 at 180 mg rolapitant	175 (39)

2.2.5 Pharmacokinetic Characteristics

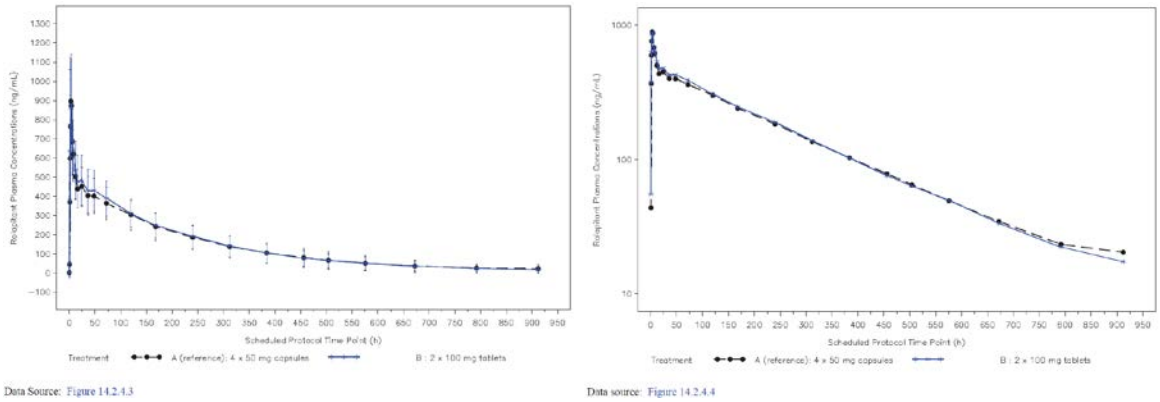
2.2.5.1 What are the PK characteristics of rolapitant?

The notable PK characteristics of rolapitant are a large apparent volume of distribution and the prolonged elimination half-life (~ 7 days) with rolapitant concentration detectable at a month after a single-dose administration of 180 mg rolapitant. The systemic exposure over 120 hours ($AUC_{0\text{-}120}$) during which the efficacy of rolapitant was assessed, was about 40% of $AUC_{0\text{-}inf}$ for rolapitant.

The formation of the major metabolite SCH720881 was slow with median Tmax of 120 hours after rolapitant administration.

Reference ID: 3748397

Figure 7 Mean (SD) Rolapitant Concentration-Time Profile after Administration of 180 mg Rolapitant (Study 5014-C)



2.2.5.2 What are the single dose and multiple dose PK parameters?

Table 13 Rolapitant PK Parameters after a Singe-Dose Administration of 180 mg Rolapitant under Fasting Condition

	Mean (%CV) (n=42)
Cmax (ng/mL)	968.1 (27.5)
T_{max} (h)	(b) (4)
$T_{1/2}$ (h)	164 (35.3)
AUC_{0-120} (µg*h/mL)	50.5 (22.5)
AUC_{0-t} (µg*h/mL)	122.8 (25.1)
AUC_{0-inf}(µg*h/mL)	127.5 (27.1)

[a] Median (min-max); *Source: CSR PR-10-5013-C Table 10*

Multiple dose PK was studied after once daily dosing of rolapitant HCl for 10 days at 10 mg, 25 mg, and 50 mg. After multiple doses, mean Cmax and AUC_{0-24} of rolapitant was 3.5- and 5-fold, respectively higher than those after a single dose consistently with the long half-life of rolapitant. PK of SCH720881 was not studied after multiple doses. Multiple dose PK was not studied at the proposed dose.

Reference ID: 3748397

Table 14 Mean (%CV) PK Parameters for Rolapitant on Days 1 and 10 following Once Daily Dosing for 10 days in Healthy Subjects*

Protocol No. P03670

Dose	Cmax (ng/mL)	Tmax (hr)[a]	t½ (hr)	AUC(0-24 hr) (ng·hr/mL)	R
Day 1					
10 mg (n=8)	48.6 (16)	3 (1.5–6)	NC	673 (13)	NC
25 mg (n=8)	139 (23)	2 (1.5–4)	NC	1950 (22)	NC
50 mg (n=8)	254 (16)	3 (1.5–6)	NC	3400 (12)	NC
Day 10					
10 mg (n=7)[b]	180 (15)	3 (2–6)	238 (30)	3590 (19)	5.33 (16)
25 mg (n=8)[c]	491 (23)	2 (1–4)	NC	9720 (28)	4.98 (18)
50 mg (n=8)	895 (13)	2.5 (1–4)	172 (45)	17700 (14)	5.25 (15)

CV = coefficient of variation; Cmax = maximum observed plasma concentration; Tmax = time of maximum observed plasma concentration; t½ = apparent terminal elimination phase half-life; AUC(0-24 hr) = area under the plasma concentration vs time curve from time 0 to 24 hours postdose; R = accumulation index; NC = not calculated.

a: Median (range).

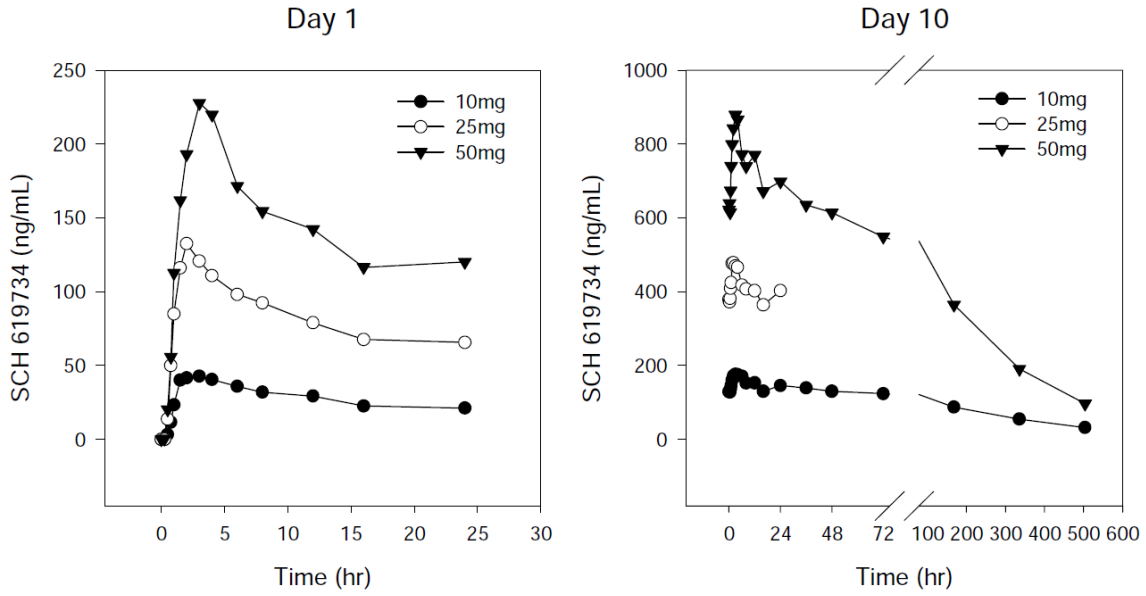
b: Subject No. 1005 was excluded because of incomplete sample collection.

c: Samples collected up to 24 hours only. DI part started on Day 11.

Source Data: Section 16.1.9.2.

*Dose based on rolapitant HCl

Figure 8 Mean Plasma Concentration-Time Profile of rolapitant (SCH619734) after Once Daily Dosing for 10 days in Healthy Subjects*



*Dose based on rolapitant HCl

Reviewer's comment: Multiple peaks were noted in the concentration-time profile after multiple doses suggesting a possibility of enterohepatic circulation of rolapitant.

Reference ID: 3748397

2.2.5.3 How is the PK of Rolapitant Compared between Healthy Volunteers and Cancer Patients?

The difference in the PK of rolapitant and the major active metabolite, SCH 720881 between in healthy subjects and in cancer patients was not formally assessed.
In healthy subjects, the apparent total clearance (CL/F) and Vd/F of rolapitant was estimated to be 1.74 L/h and 460 L, respectively. From the population PK analysis with data from cancer patients, the PK of rolapitant was characterized by a two compartment model and the apparent total clearance (CL/F) and the apparent volume of distribution (Vd/F) was estimated to be 0.962 L/h and 387 L (V2/F= 214 L and V4/F=164 L), respectively. Since the models used to estimate PK parameters are different for the datasets from two different populations, a simple comparison is not feasible. However, the population PK analysis identified body weight as a significant covariate on two volume of distribution parameters and the distribution of body weight is slightly different between healthy volunteers (mean 77.5 kg [range 58.3 – 106.1] and cancer patients (mean 68.9 kg [range 38-128]), it would be reasonable to conclude the slight difference might be caused by body weight as well as different analysis methods.

2.2.5.4 What are the characteristics of drug absorption?

After oral administration, the median Tmax was 4 hours with a range of 2-8 hours.

The oral bioavailability of rolapitant is estimated to be > 90% when the systemic exposure for rolapitant was compared between after oral administration of 200 mg rolapitant HCl and after intravenous administration of 100 mcg radiolabeled rolapitant HCl. After dose-normalization, the mean ratio of Cmax and AUC between oral administration to intravenous infusion was 49.8% (90% CI: 40, 61.9) and 101% (90% CI: 94, 108) for AUCi, respectively (Table 15, Figure 9).

Table 15 Mean (%CV) rolapitant PK parameters following a single oral administration of 200 mg rolapitant HCl and 15 min intravenous infusion of 100 mcg [^{14}C]-rolapitant HCl to healthy subjects

Protocol No. P04328

Dose Group	Cmax (ng/mL)	Tmax[a] (hr)	AUC(tf)/D (ng·hr/mL/mg)	AUC(I)/D (ng.hr/mL/mg)	t½ (hr)
Oral dose 200 mg (n=6)	1230 (12)	2 (1.5-3.92)	619 (12)	660 (10)[b]	138 (17)[b]
Micro dose 100 mcg (n=6)	1.27 (31)	0.25 (0.25-0.25)	619 (18)	622 (8)[b]	148 (21)[b]

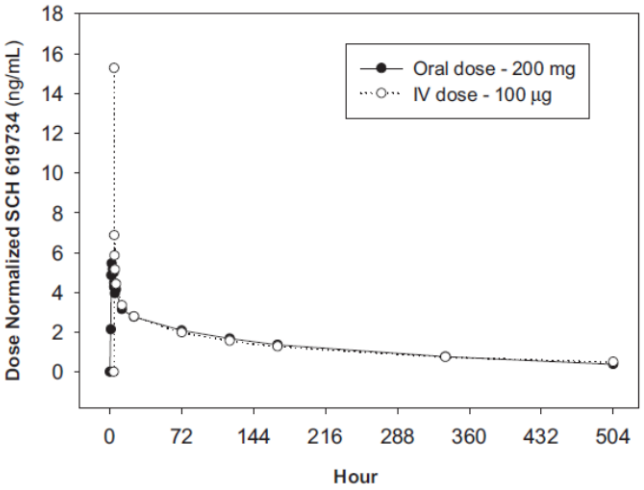
Abbreviations: CV = Coefficient of variation; IV = intravenous; Cmax = maximum observed plasma concentration; Tmax = time of maximum observed plasma concentration; AUC(tf) = area under the plasma concentration-time curve from time 0 to the time of the final quantifiable sample; AUC(tf)/D = dose normalized AUC(tf); AUC(I) = area under the plasma concentration-time curve from time 0 to infinity; AUC(I)/D = dose normalized AUC(I); t½ = half life.

a: Median (Range)

b: n = 4

Reference ID: 3748397

Figure 9 Mean Plasma Rolapitant Concentration-Time Profiles Following Oral Administration of 200 mg Rolapitant HCl and Intravenous Infusion of 100 mcg [^{14}C]-Rolapitant HCl over 15 Minutes to Healthy Subjects



Reviewer's comments: Rolapitant was analyzed by a LC/MS/MS method after oral administration and by AMS (accelerator mass spectrometry).

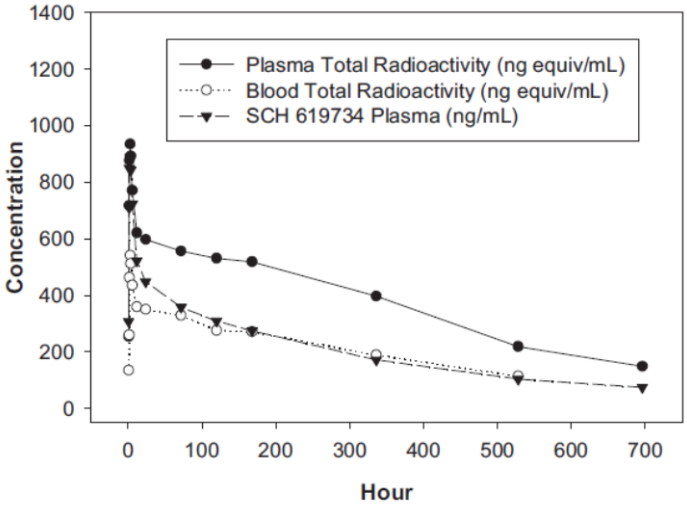
2.2.5.5 What are the characteristics of drug distribution?

Rolapitant is extensively bound to protein. In vitro the mean % protein bound fraction of rolapitant was 99.1% in humans and similar to that in animals: 99% in rats and 99.2%, in cynomolgus monkey. The major metabolite, SCH 720881 is >99% protein bound in humans.

Rolapitant has a large apparent volume of distribution of ~460 L in healthy volunteers and 387 L in cancer patients suggesting an extensive distribution to tissues upon absorption. A lack of meaningful distribution of rolapitant and its metabolites into red blood cells was suggested by about 2-fold higher total drug related radioactivity in plasma than that of whole blood (Figure 10).

Reference ID: 3748397

Figure 10 Mean Rolapitant Plasma, Total Radioactive Whole Blood and Plasma Concentration-Time Profile Following Single Administration of 180 mg ^{14}C-Rolapitant to Healthy Subjects



2.2.5.7 What are the characteristics of elimination?

Rolapitant was slowly metabolized with median Tmax of 120 ho for the major metabolite and eliminated with a mean t½ of 186 hr. The apparent clearance was approximately 1.8 L/h. Rolapitant is mainly excreted via biliary excretion while the renal excretion has a negligible role.

Metabolism

Rolapitant is metabolized to multiple metabolites (Figure 11).

In a mass balance study, the exposure (AUCt) to total plasma radioactivity was 53% higher than the exposure to rolapitant due to the metabolite species. The metabolite SCH 720881 (M19) which accounted 25% of the increased exposure to total plasma radioactivity was identified as a major circulating metabolite of rolapitant. The metabolite M19 has an affinity for the human NK_1 receptor (Ki = 0.42 nM) which is similar to that of rolapitant (Ki = 0.66 nM for human NK_1 receptor). In in vitro study, the formation of M19 was inhibited by ketoconazole.
Metabolites other than M19 were not measurable in plasma while multiple metabolites were measurable in urine and feces (Table 16).

Reference ID: 3748397

Figure 11 Proposed Metabolic Pathways of Rolapitant

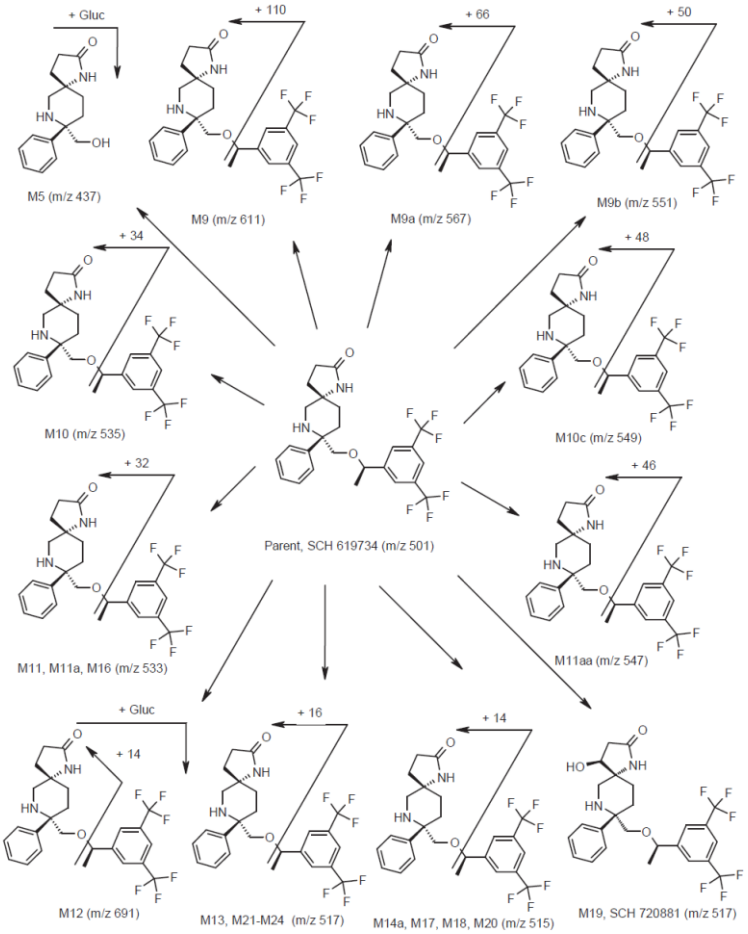


Table 16 Percent Dose for Metabolites in Pooled Urine and Feces (0-336 hr)

	% Dose (n=6)	
Analytes	Urine	Feces
Recovered radioactivity	8.3	37.8
Rolapitant	NA	12.7
M19 (SCH 720881)	NA	1.91
M5	1.57	--
M9b	1.64	4.27
M10	0.62	2.6
M10c	--	4.8
M11	0.39	2.28
M11aa	--	1.35
M13	NA	3.54
M14a	--	1.51

Reviewer's comments: Concomitant ketoconazole, a strong CYP3A4 inhibitor, did not result in clinically significant change of the systemic exposure to rolapitant. However, the median T_{max} for the major metabolite, M19 was significantly delayed from 168 hours to 336 hours. While the total

Reference ID: 3748397

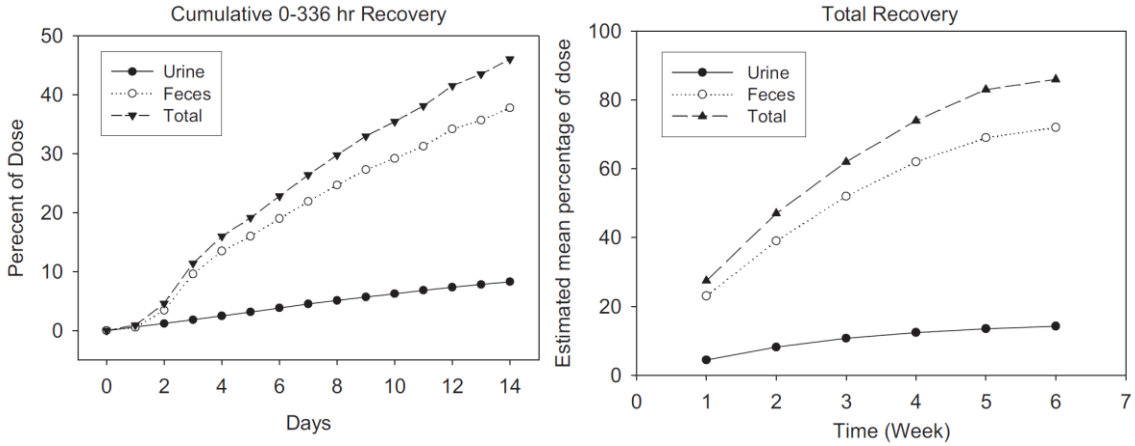
AUC of the metabolite was decreased by 16%, and AUC_{0-120} was decreased by 62%. This observation combined with the prolonged circulation of rolapitant in plasma suggests that a release from tissue appears to be a rate-limiting step for elimination of rolapitant.

2.2.5.8 What are the characteristics of drug excretion?

The total of 46% of the radioactive dose was recovered in urine and feces samples collected daily for 14 days (336 h) after single administration of radio-labeled rolapitant. In the pooled urine collected over 336 h, 8.3% of the dose was recovered and in the pooled feces 37.8% of the dose was recovered (Table 16). In feces, rolapitant was the most prominent component accounting for 12.7% of the dose while rolapitant was not measurable in urine.

The recovery of administered radioactivity was incomplete even in 6 weeks after dosing. Over 6 weeks[11] the total recovery of the radioactive dose was 85%. Of the dose 14.2% (range 9% to 20%) was recovered in the urine and 72.7% (range 52% to 89%) was recovered in the feces (Figure 12) In animals, the biliary excretion of rolapitant was evident by fecal excretion of rolapitant after intravenous administration and biliary excretion in bile duct-cannulated animals. After an intravenous dose, 54.6% and 58.4% of the dose was recovered in feces in rats and in monkeys, respectively (SN 04917). For more details, see the Pharmacology and Toxicology Review

Figure 12 Mean Cumulative and Total Recovery of Radioactivity Following a Single 180 mg Oral Administration of [^{14}C]-Rolapitant to Healthy Subjects



In animals, the biliary excretion of rolapitant was evident by fecal excretion of rolapitant after intravenous administration and biliary excretion in bile duct-cannulated animals. After an intravenous dose, 54.6% and 58.4% of the dose was recovered in feces in rats and in monkeys, respectively (SN 04917). For more details, see the Pharmacology and Toxicology Review.

[11] The urine and fecal samples were collected weekly up to 6 weeks following daily collection over the first 2 weeks after rolapitant administration. The total recovery was interpolated assuming the constant rate of excretion between the sample collections.

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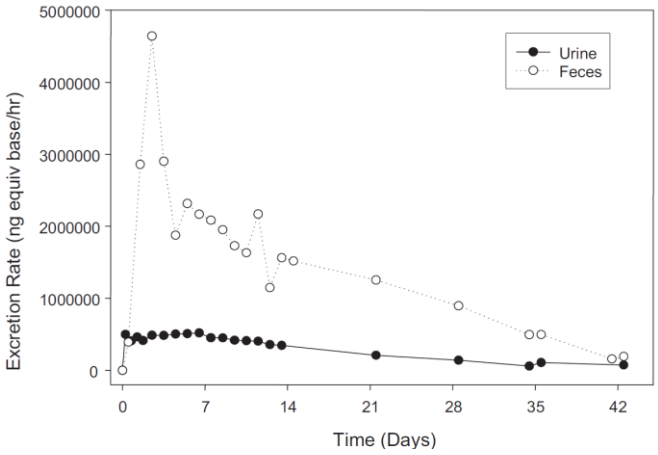
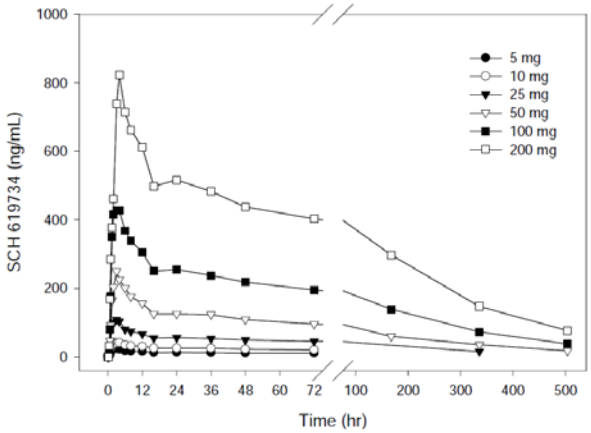
Figure 13 Mean Excretion Rate in Urine and Feces over Time



2.2.5.9 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

The dose-proportional increase in the AUC was observed within a dose range from 22.5 mg to 720 mg rolapitant. On the other hand, Cmax was increased in a dose-proportional manner in the range of 22.5 mg to 180 mg while less than dose-proportionally at doses higher than 180 mg rolapitant. Mean Cmax was 3.1-fold higher when the dose was increased by 4 fold from 180 mg to 720 mg. When the dose increased by 4-fold from 180 mg to 720 mg rolapitant, mean Cmax and AUC of the major metabolite M19 was increased by 3.4-fold and 3.9-fold, respectively similarly to those of rolapitant.

Figure 14 Mean Rolapitant Concentration-Time Profile after Single-Dose Administration in Healthy Subjects*



*Dose by rolapitant HCl

Reference ID: 3748397

Table 17 Single Ascending Dose Mean (%CV) Rolapitant Pharmacokinetic Parameters in healthy subjects

Protocol No. P03670

Dose (mg)	Cmax[a] (ng/mL)	Tmax[b] (hr)	AUC(I)[a] (ng·hr/mL)	t½[a] (hr)
5 (n=8)	27.3 (19)	2 (1.5-4)	931[c] (15)	NC
10 (n=8)	52.7 (35)	2.5 (1-4)	1820[c] (12)	NC
25 (n=8)	119 (13)	2.5 (1.5-4)	17200 [d] (38)	183[d] (43)
50 (n=8)	276 (24)	3 (1.5-4)	33600 (42)	171 (28)
100 (n=8)	475 (10)	2 (1.5-4)	74400 (47)	181 (46)
200 (n=8)	944 (29)	4 (2-6)	148000 (33)	169 (39)

Abbreviations: NC = Not calculated; CV = Coefficient of variation; Cmax = maximum observed plasma concentration; Tmax = time of maximum observed plasma concentration; hr = hour; AUC = area under the curve of plasma concentration versus time; t½ = half life.

a: Mean (%CV).

b: Median (Range).

c: AUC(0-72 hr).

d: n=6.

Reviewer's comment: PK for M19 was not studied in Study P03670.

Table 18 Mean (CV%) Pharmacokinetic Parameters for Rolapitant and SCH720881 (M19) Following Single-Dose Administration of Rolapitant to Healthy Subjects (Study P4852)

	Cmax (mcg/mL)	Tmax [e] (h)	AUCt (mcg*h/mL)	AUCi (mcg*h/mL)	$T_{1/2}$ (h)
Rolapitant					
180 mg (n=39)	0.98 (23)	4 (2-8)	106 (27)	121[a] (28)	153 [a] (34)
720 mg (n=41)	3.06 (23)	4(2-8)	412 (29)	449[b] (26)	157 [b] (37)
M19 (SCH720881)					
180 mg (n=39)	0.18 (37)	120 (24-168)	62.0 (28)	73.2[c] (26)	158[c] (32)
720 mg (n=41)	0.61 (31)	120 (72-336)	225.6 (35)	285.1[d] (31)	196 [d] (31)

a: n=33; b: n=38; c: n=15; d: n=19; e: median (min-max)

2.3 Intrinsic Factors

2.3.1 Do intrinsic factors (age, gender, race, weight, and organ dysfunction) influence PK of rolapitant?

From a population PK analysis, body weight was identified as a significant covariate on volume of distribution of rolapitant, the effect was especially great on the peripheral compartment (estimated power: 2.08). The effect of body weight on volume of distribution is summarized in Table 19. Since the covariate effect on clearance is not observed, any need for dose adjustment based on body weight was not considered.

Other than body weight, no covariates were identified to effect on rolapitant pharmacokinetics. See the Pharmacometrics Review by Dr. Jee Eun Lee for more details.

Reference ID: 3748397

Table 19 Effects of Body Weight on the Apparent Volume of Distribution

Continuous covariate		Rolapitant	
		V2/F[b] (L)	V4/F[c] (L)
WT (kg)	38	130.7	47.7
	68.8	214	164
	128	358.3	596.6

2.3.2 Is dosage adjustments recommended for any intrinsic factors?

No dosage adjustment is recommended for age, gender, and weight and mild-to-moderate renal impairment (RI) or hepatic impairment (HI).
Rolapitant will be given as a single dose and there were no significant effects of age, gender, and weight or mild-to-moderate RI or HI on PK of rolapitant.

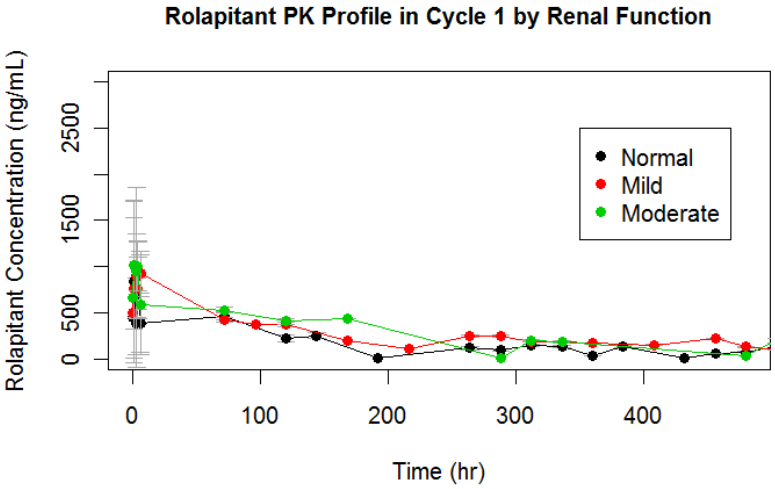
The effects of severe renal impairment or severe hepatic impairment on PK of rolapitant were not studied.

2.3.2.1 Should the dose be adjusted for patients with mild or moderate renal impairment?

No. Effect of renal impairment on the PK of rolapitant was evaluated by a population PK analysis of data from phase 2 and 3 trials. There was no dedicated PK study for the effect of renal impairment. Sparse PK blood samples were collected from patients with renal function based on creatinine clearance (29.3 ml/min to 90 ml/min): normal (n=254), mild (n =188); moderate (n=39), and severe (n=1). No significant effect of creatinine clearance on the rolapitant PK was noted in patients with mild to moderate renal impairment from a population PK analysis and it was confirmed with observed concentration profile by renal function (Figure 15). This result is consistent with the negligible renal excretion of unchanged rolapitant as unchanged rolapitant was not detected in pooled urine samples collected over 2 weeks. PK of rolapitant was not studied in patients with end-stage renal disease requiring dialysis. See the Pharmacometrics Review by Dr. Jee Eun Lee for more details (Appendix 4.1).

Reference ID: 3748397

Figure 15 Rolapitant Concentrations following 180 mg Rolapitant by Renal Function in Cancer Patients



2.3.2.2 Hepatic Impairment

The effects of hepatic impairment on PK of rolapitant were evaluated in subjects with mild (Child-Pugh Score 5-6) and moderate hepatic impairment (Child-Pugh Score 7-9). Pharmacokinetics of rolapitant were not studied in patients with severe hepatic impairment (Child-Pugh score >9).

In healthy subjects mean AUC of the major metabolite was about 53 % of rolapitant AUC indicating substantial metabolism of rolapitant (Study P4852). Nevertheless the systemic exposure to rolapitant was not significantly different in patients with mild or moderate hepatic impairment compared to that in healthy subjects.
In patients with moderate hepatic impairment, mean C_{max} and $AUC_{0\text{-last}}$ for rolapitant was lower by 25% and 19%, respectively than those in normal subjects. The mean C_{max}, $AUC_{0\text{-}120}$ and $AUC_{0\text{-last}}$ for the major metabolite, SCH720881 was also lower by 19%, 24% and 17%, respectively (**Error! Reference source not found.**). Of note the geometric mean plasma concentration at 504 h after rolapitant administration was 133 ng/ml, 93 ng/ml, and 80 ng/ml in in patients with moderate HI, mild HI, and healthy subjects, respectively. It is unclear why systemic exposure tended to be lower in patients with moderate hepatic impairment while the number of patients was small (n=6) to draw a firm conclusion.

The effect of hepatic impairment on unbound fraction[12] of rolapitant was not evident: mean unbound fraction of rolapitant 1.16%, 1.06%, and 1.26% in healthy subjects and patients with mild or moderate hepatic impairment, respectively.

Reviewer's comments:

[12] Plasma protein binding was assessed by equilibrium dialysis in PK samples collected at pre-dose, and at 3 hours, 168 hours, and 504 hours.
.

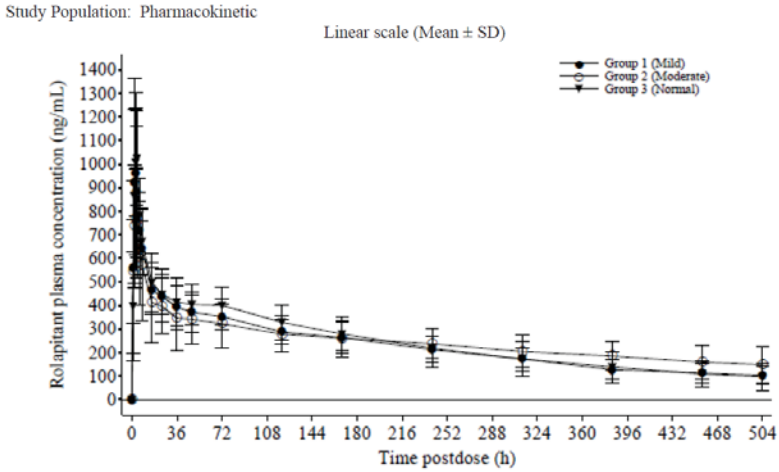
Reference ID: 3748397

Pharmacokinetics of rolapitant were not studied in patients with severe hepatic impairment (Child-Pugh score >9).
On the other hand, in healthy subjects, no significant safety issues were identified with 3.5-fold higher Cmax and 3.9-fold higher AUC than those at the proposed dose (n=41). It seems less than likely that the systemic exposure to rolapitant after a single-dose (no repeat cycle) administration would be altered to a degree requiring a dosage adjustment in patients with severe hepatic impairment. Nevertheless, potentially high systemic exposure due to accumulation after repeated dosing especially with shorter cycle chemotherapy in patients with severe hepatic impairment cannot be ruled out. In this program, the median interval of chemo cycle was 21 days and the shortest chemo cycle was 2 weeks.

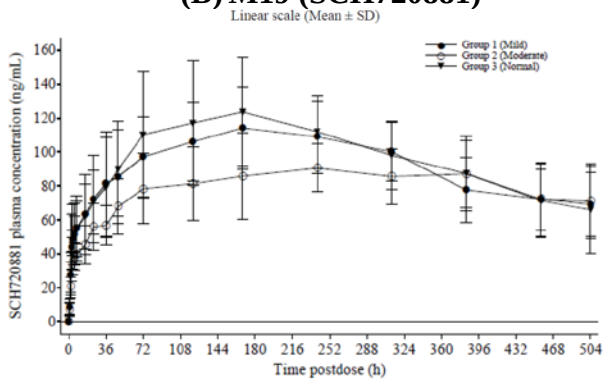
When rolapitant was administered with a strong CYP3A4 inhibitor, ketoconazole, the Tmax of M19 (SCH720881) was significantly delayed by a week and the AUC of SCH720881 was reduced by 62% during the first 120 hours post-dose. Nevertheless the overall formation of SCH720881 was reduced by 16% over 3 weeks while the $AUC_{0\text{-}120}$ and AUC_t for rolapitant was not significantly different from that after administration of rolapitant alone.

Figure 16 Mean (SD) Concentration-Time Profile for (A) Rolapitant and (B) Major metabolite after 180 mg Rolapitant Administration

(A) Rolapitant



(B) M19 (SCH720881)



Reference ID: 3748397

Figure 17 Individual $AUC_{0\text{-last}}$ value for rolapitant by a degree of hepatic impairment

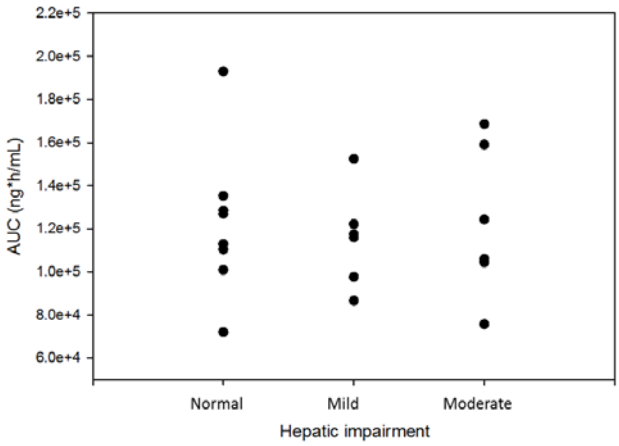


Table 20 Pharmacokinetics Parameters of Rolapitant and SCH 720881 in Subjects with Hepatic Impairment (Study PR-10-5004-C)[1,]

Treatment	N	C_{max} (ng/mL) Mean (SD)	T_{max} (hr) Median (Range)	$AUC_{0\text{-last}}$ (ng·hr/mL) Mean (SD)	$AUC_{0\text{–}120hr}$ (ng·hr/mL) Mean (SD)	$t_{1/2}$ (hr) Mean (SD)
Rolapitant						
Group 1 Mild	6	1036 (351)	3.00 (2.00 – 8.00)	115319 (22647)	47280 (8879)	235 (66.8)
Group 2 Moderate	6	840 (265)	3.00 (2.00 – 4.00)	122957 (35386)	42968 (13817)	355 (292)
Group 3 Normal	8	1093 (254)	3.96 (2.00 – 4.00)	122424 (34757)	51474 (10367)	212 (71.5)
SCH 720881						
Group 1 Mild	6	119 (22.3)	204 (120 – 240)	46180 (6634)	10309 (2812)	380 (162)
Group 2 Moderate	6	102 (14.5)	204 (120 – 384)	39937 (7020)	7965 (1836)	836 (747)
Group 3 Normal	8	128 (32.9)	168 (72.0 – 240)	48448 (9984)	11060 (3492)	366 (203)

Source: CSR PR-10-5004-C Tables 6 and 10.

2 AUC = area under the plasma concentration-time curve; C_{max} = maximum concentration; SD = standard deviation; inf = infinity; N = number; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum concentration.

[1] : PK blood samples were collected at pre-dose and at 1, 2, 3, 4, 6, 8, 16, 24, 36, 48, 72, 120, 168, 240, 312, 384, 456, and 504 hours.
2: The estimated $t_{1/2}$ was greater than half the sampling interval and $AUC_{0\text{-inf}}$ values were extrapolated to > 30% for most of subjects: 5 subjects in Group 1, all subjects in Group 2, and 4 subjects in Group 3.

Reference ID: 3748397

Table 21 Geometric Mean Ratio and 90% CI of Pharmacokinetic Parameters between Patients with Hepatic Impairment and Healthy Subjects

	Rolapitant		SCH720881	
Hepatic Impairment	Mild/normal	Moderate/normal	Mild/normal	Moderate/normal
Cmax	0.92 (0.68, 1.25)	0.75 (0.55, 1.02)	0.94 (0.77, 1.14)	0.82 (0.67,0.99)
AUCt	0.96 (0.75,1.23)	1.0 (0.78, 1.28)	0.96 (0.81, 1.14)	0.83 (0.70, 0.99)
AUC0-120	0.92 (0.73, 1.16)	0.81 (0.64, 1.02)	0.93 (0.72, 1.21)	0.73 (0.56, 0.95)

2.4 Extrinsic Factors

2.4.1 What extrinsic factors influence dose-exposure and/or response and what is the impact of any differences in exposure on response?

Concurrent rifampin, a strong CYP3A4 inducer significantly decreased systemic exposure to rolapitant as well as its active metabolite and can decrease the efficacy of rolapitant. Therefore use of rolapitant in patients who have been on strong CYP3A4 inducers is not recommended. See Section **2.4.2.8** for more details.

2.4.2 Drug-Drug Interactions

2.4.2.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

The inhibition and induction of CYP enzymes and transporters were studied in vitro for rolapitant and its major metabolite. In vitro rolapitant inhibited CYP2D6 with the lowest IC_{50} value followed by CYP2C19 and CYP2C9 (Table 22, Table 23). In vitro SCH720881 inhibited CYP2D6, 2C19, and 2B6 at 10 mcM. The IC_{50} value of SCH720881 was estimated for CYP2B6 but not for other enzymes. In healthy subjects, mean Cmax for rolapitant was 944 ng/ml (~1.7 mcM).

In vitro Inhibition of CYP enzymes

Table 22 In vitro assessment of Drug Interaction Potential via Inhibition of CYP enzymes by Rolapitant

Inhibition	IC_{50} or Ki (mcM)	$[I]/IC_{50}$ or $[I]_2/IC_{50}$	In vivo drug interaction potential	In-vivo study (yes or no)
CYP1A2	>100		Remote	No
CYP2A6	22 (10)	0.08 (0.17)	Remote/possible	No
CYP2B6	13	0.13	Possible	Yes with efavirenz
CYP2C8	23	0.07	Remote	Yes with repaglinide
CYP2C9	9.6	0.18	Possible	Yes with tolbutamide
CYP2C19	8.7	0.20	Possible	Yes with omeprazole

Reference ID: 3748397

CYP2D6	3.4 (Ki)	0.5	Possible	Yes with dextromethorphan
CYP2E1	>100		Remote	No
CYP3A4/5	49	0.035	Remote	Yes with midazolam
CYP3A4	41	0.041	Remote	

Table 23 In vitro Evaluation of Rolapitant as an Inhibitor for CYP enzymes

		Direct Inhibition				Time-Dependent Inhibition		
		Zero-Minute Pre-Incubation				30-Minute Pre-Incubation		
Enzyme	CYP Reaction	IC_{50} (μM)	Maximum Inhibition at 100 μM (%)[a]	K_i (μM)	Type of Inhibition	IC_{50} (μM)	Maximum Inhibition at 100 μM (%)[a]	Potential for Time-Dependent Inhibition[b]
CYP1A2	Phenacetin *O*-deethylation	>100	39[c]	ND	ND	90	86[c]	Yes
CYP2A6	Coumarin 7-hydroxylation	22	51[d]	ND	ND	10	79[d]	Yes
CYP2B6	Bupropion hydroxylation	13	100	ND	ND	13	100	Little or none
CYP2C8	Amodiaquine *N*-dealkylation	23, 23	87, 87	ND	ND	24, 25	85, 85	Little or none
CYP2C9	Diclofenac 4´-hydroxylation	9.6	100	ND	ND	9.3	100	Little or none
CYP2C19	S-Mephenytoin 4´-hydroxylation	8.7	100	ND	ND	7.6	100	Little or none
CYP2D6	Dextromethorphan *O*-demethylation	7.1	86	3.4	competitive	4.0	86	No
CYP2E1	Chlorzoxazone 6-hydroxylation	>100	NA	ND	ND	>100	NA	Little or none
CYP3A4/5	Testosterone 6β-hydroxylation	49	72	ND	ND	35	88	Yes
CYP3A4/5	Midazolam 1´-hydroxylation	41	81	ND	ND	28	94	Yes

Notes: Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values. IC_{50} values were calculated with XLfit.

a: Maximum inhibition (%) is calculated with the following formula and data for the highest concentration of test article for which usable data were collected (results are rounded to two significant figures): Maximum inhibition (%) = 100% - Percent solvent control.

b: Time-dependent inhibition was determined by comparison of IC_{50} values with and without pre-incubation, by comparison of the maximum inhibition (%) with and without pre-incubation and by visual inspection of the IC_{50} plot.

c: Activation was observed in incubation concentrations of SCH 619734 up to 30 μM followed by inhibition at an incubation concentration of 100 μM SCH 619734.

d: Percent inhibition reported at 30 μM SCH 619734 due to possible solubility concerns.

NA = Not applicable. The rate at 100 μM SCH 619734 was higher than that of the solvent control.

ND = Not determined.

***Reviewer's comment*:** In vitro an apparent increase in the activity of CYP2E1 and CYP1A2 was observed in presence of rolapitant while the study was designed to evaluate an inhibitory potential. Similarly the induction of CYP1A2 activity was observed when human hepatocytes were pre-treated with rolapitant for 3 days.

<u>Metabolite</u>

In vitro inhibition of CYP2B6, 2C19, and 2D6 by 10 µM SCH720881 was observed. The IC_{50} value was not estimated for other CYP enzymes except for CYP2B6 for which the greatest inhibition was shown by 10 µM SCH720881.

The IC_{50} value of SCH 720881 was estimated to be 8.65 µM for CYP2B6[13]. Based on the $[I]/IC_{50}$ value of $0.04 < 0.1$[14], drug interaction potential via inhibition of CYP2B6 by M19 appears remote. An inhibition of CYP2D6 by SCH 720881 was also observed in presence of 10 µM rolapitant.

[13] IC_{50} for ticlopidine was 0.1 µM.

[14] Mean peak plasma concentration of SCH720881 (M19) was 175 mcg/L (0.34 mcM) after 180 mg rolapitant administration (m.w.512.6).

Reference ID: 3748397

Table 24 In vitro evaluation of CYP enzyme inhibition by a major metabolite, SCH 720881

Compound ID	CYP Isozyme	CYP Substrate	Mean % Inhibition at 1 µM	Mean % Inhibition at 10 µM
SCH 720881	1A2	Phenacetin	4.1	-9.3
	2B6	Buproprion	0.5	57.1
	2C8	Amodiaquine	-23.9	-7.4
	2C9	Diclofenac	-10.1	21.1
	2C19	Mephenytoin	6.9	44.8
	2D6	Dextromethorphan	-8.1	31.4
	3A4	Midazolam	0.1	-3.2
	3A4	Testosterone	-15.1	17.5
Control Inhibitors:			Mean % Inhibition at 10 µM:	Mean % Inhibition at 50 µM:
Fluvoxamine	1A2	Phenacetin	100.6	102.7
Ticlopidine	2B6	Buproprion	101.2	103.4
Quercetin	2C8	Amodiaquine	48.0	98.5
Sulfaphenazole	2C9	Diclofenac	92.5	101.8
Omeprazole	2C19	Mephenytoin	53.6	94.0
Quinidine	2D6	Dextromethorphan	90.0	98.7
Ketoconazole	3A4	Midazolam	106.4	108.1
Ketoconazole	3A4	Testosterone	103.6	104.4

Induction of CYP enzymes

Treatment of cultured human hepatocytes with rolapitant for 3 days caused a concentration-dependent increase in CYP1A2, CYP2C8, CYP2C19 and CYP3A4/5 activity at concentrations up to 10 mcM. At 10 mcM, the induction potency of rolapitant was ~80% of omeprazole for CYP1A2 and ~68% of rifampin for CYP3A4 activity (Table 25, Table 26).

A significant induction of CYP1A2 by rolapitant in humans is unlikely based on the in-vitro induction weaker than omeprazole, which is a weak CYP1A2 inducer in vivo and no significant induction of CYP3A4 by rolapitant. A decrease in the activity of all the enzymes was observed at rolapitant concentrations above 30 mcM which is >17 fold higher than the mean peak plasma concentration of rolapitant in humans.

In an in-vitro study using cultured human hepatocytes, rolapitant did not significantly induce CYP2B6 at concentrations up to 20 mcM while a prototype inducer; phenobarbital caused a 15.4-fold increase in CYP2B6 activity (Table 27).

Reviewer's comment: In a clinical drug interaction study with midazolam, single-dose administration of 180 mg rolapitant did not inhibit or induce metabolism of midazolam by CYP3A4 over 10 days after administration.

Reference ID: 3748397

Table 25 Induction of CYP enzymes by rolapitant (enzyme activity)

Treatment	Concentration	Enzymatic activity (pmol/mg protein/min)[a]				
		Phenacetin *O*-dealkylation (CYP1A2)	Amodiaquine *N*-dealkylation (CYP2C8)	Diclofenac 4´-hydroxylation (CYP2C9)	*S*-Mephenytoin 4´-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5)
DMSO	0.1% (v/v)	48.0 ± 29.3	259 ± 95	1140 ± 830	12.7 ± 6.7	2940 ± 300
SCH 619734	0.1 μM	41.1 (n = 2)	222 (n = 2)	758 (n = 2)	13.9 (n = 2)	3350 (n = 2)
SCH 619734	1 μM	118 ± 13	374 ± 162	1330 ± 1010	15.4 ± 7.5	5560 ± 500
SCH 619734	10 μM	551 ± 57	522 ± 228	1320 ± 980	29.3 ± 13.7	8930 ± 1130
SCH 619734	30 μM	242 (n = 2)	165 (n = 2)	315 (n = 2)	29.6 (n = 2)	2450 (n = 2)
Omeprazole	100 μM	979 ± 638	1490 ± 610	1970 ± 1360	28.7 ± 19.6	7120 ± 900
Rifampin	10 μM	136 ± 77	1900 ± 460	2860 ± 1700	156 ± 84	12900 ± 3300

Rates are rounded to three significant figures and standard deviation is rounded to the same degree of accuracy.

a: Values are the mean ± standard deviation of three of human hepatocyte preparations: H684, H688 and H691, unless indicated otherwise, e.g., n = 2.

Table 26 Induction of CYP enzymes by rolapitant (Fold-Change)

Treatment	Concentration	Fold Increase[a]				
		Phenacetin *O*-dealkylation (CYP1A2)	Amodiaquine *N*-dealkylation (CYP2C8)*	Diclofenac 4´-hydroxylation (CYP2C9)	*S*-Mephenytoin 4´-hydroxylation (CYP2C19)	Testosterone 6β-hydroxylation (CYP3A4/5)*
DMSO	0.1% (v/v)	100 ± 0.61	1.00 ± 0.37	1.00 ± 0.72	1.00 ± 0.53	1.00 ± 0.10
SCH 619734	0.1 μM	1.19 (n = 2)	1.06 (n = 2)	0.999 (n = 2)	1.06 (n = 2)	1.20 (n = 2)
SCH 619734	1 μM	3.71 ± 3.13	1.43 ± 0.15	1.16 ± 0.09†	1.24 ± 0.06	1.89 ± 0.05†
SCH 619734	10 μM	18.1 ± 16.7	2.10 ± 0.82	1.16 ± 0.05†	2.42 ± 0.53*	3.03 ± 0.11¥†
SCH 619734	30 μM	11.7 (n = 2)	0.830 (n = 2)	0.458 (n = 2)	2.20 (n = 2)	0.869 (n = 2)
Omeprazole	100 μM	22.7 ± 9.2¥	5.86 ± 2.05¥	1.87 ± 0.40¥	2.18 ± 0.37	2.42 ± 0.06
Rifampin	10 μM	3.12 ± 0.89	7.78 ± 2.31¥	2.84 ± 0.73¥	12.5 ± 2.2§	4.41 ± 1.26¥

Fold increases are rounded to three significant figures and standard deviation is rounded to the same degree of accuracy.

a: Values are the mean ± standard deviation of three human hepatocyte preparations: H684, H688 and H691, unless indicated otherwise, e.g., n = 2.

¥ = Statistically significant compared to control (0.1% dimethyl sulfoxide) according to Dunnett's Test ($p<0.05$) with positive controls.

† = Statistically significant compared to control (0.1% dimethyl sulfoxide) according to Dunnett's Test ($p<0.05$) without positive controls.

* = Significantly different from 0.1% dimethyl sulfoxide according to Dunn's Method ($p<0.05$) without positive controls.

§ = Significantly different from 0.1% dimethyl sulfoxide according to Dunn's Method ($p<0.05$) with positive controls.

Table 27 No significant induction of CYP2B6 by rolapitant

Treatment	Concentration	Fold increase [a]
		Bupropion hydroxylation (CYP2B6)
Dimethyl sulfoxide	0.1% (v/v)	1.00 ± 0.78 [b]
Rolapitant	0.1 μM	0.893 ± 0.015
Rolapitant	1 μM	1.50 ± 0.30
Rolapitant	10 μM	1.78 ± 0.38
Rolapitant	20 μM	1.16 ± 0.61
Phenobarbital	750 μM	15.4 ± 8.1

a Values are the mean ± standard deviation of three determinations (human hepatocyte preparations H1082, H824 and HC3-3).

b CV (Coefficient of Variance) = Rate standard deviation / Mean Rate. CV is calculated instead of standard deviation to give a more realistic representation of variance among control samples.

Metabolite

In vitro the major metabolite, SCH720881 did not significantly induce the CYP450 isozymes 1A2, 2B6, 2C9, and 3A4 at concentrations up to 10 mcM. The effects on CYP1A2, 2B6, 2C9, and 3A4 were assessed using phenacetin, bupropion, diclofenac and testosterone were used as substrates, respectively; the control inducers were omeprazole, phenobarbital, and rifampicin, respectively.

Reference ID: 3748397

2.4.2.2 Is rolapitant a substrate of CYP enzymes?

Rolapitant is metabolized by CYP3A4 to form a major metabolite, SCH720881. In vitro the formation of SCH720881 was predominantly mediated by CYP3A4 (Figure 18) while inhibited by CYP3A4 inhibitor ketoconazole and by others partial inhibitors with an inhibitory effect on CYP3A4 (Figure 19). When radiolabeled rolapitant was inducted with human microsomes for 120 min, SCH720881 was the most prominent metabolite.

Figure 18 Summary of Total SCH 720881 Formation (% profiled radioactivity) from [14C]-SCH 619734 with Various Human P450 SUPERSOMES

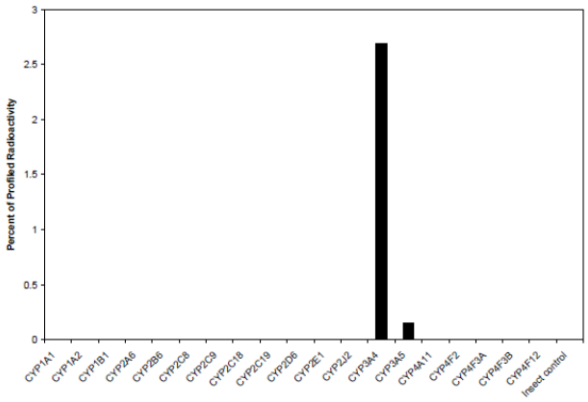


Table 28 Effect of Inhibitors on the Formation of SCH720881 from [^{14}C]-Rolapitant in human liver microsomes or CYP3A4 Supersomes™

Inhibitors	P450 Inhibitor	Inhibitor Conc. (μM)	Percent of Inhibition (IC50)	
			HLM	CYP3A4
Ketoconazole	CYP3A4/5	2	74 (1.03±0.01[a])	ND[b]
Quinidine	CYP2D6	5	15	ND
Omeprazole	CYP2C19	10	0	ND
Astemizole	CYP2J2	100	76 (22±1.7)	88
Sulfaphenazole	CYP2C9	3	0	ND
Orphenadrine	CYP2B6	300	52 (226±31)	57
Quercetin	CYP2C8	50	65 (25±3.1)	51
α-Naphthoflavone	CYP1A1/2	10	0	ND

a: ± standard error
b: not done

Reviewer's comment: The inhibition by chemical inhibitors of various CYP enzymes was studied by measuring the formation of a major metabolite SCH 720881. Because the remaining rolapitant in presence of inhibitors was not measured in this study, it is unknown which enzymes other than CYP3A4 are involved in the metabolism of rolapitant to form other metabolites. Nevertheless as SCH720881 is the major circulating metabolite of rolapitant in plasma and in liver microsomes, a clinically significant impact of inhibition of other CYP enzymes is unlikely.

Reference ID: 3748397

2.4.2.3 Is rolapitant an inhibitor and/or an inducer of CYP enzymes in humans?

Rolapitant is a moderate inhibitor of CYP2D6 in humans.

In vitro studies using human microsomes suggested that rolapitant is an inhibitor of CYPs 2B6, 2C8, 2C9, 2C19, and 2D6 among which [I]/Ki was the highest for CYP2D6.

In in vitro studies, rolapitant also caused a concentration-dependent increase in the activity of CYP1A2 and CYP3A4.

The clinical drug interaction studies were conducted first with a substrate of CYP2D6 and subsequently with substrates for other CYP enzymes with lower [I]/IC_{50} values.

Clinical drug interaction study was designed to compare substrate levels with and without 180 mg rolapitant. Two sampling days were included in order to evaluate not only the effects of rolapitant, but also the potential for an inhibitory effect of a metabolite, SCH 720881, 7 days after rolapitant and substrate administration, at maximum SCH 720881 concentrations. Effect of a single dose rolapitant on enzyme activity beyond Day 7 was not studied except for CYP3A4 for which no significant effect of rolapitant was shown up to 10 days.

Table 29 Summary of mean ratios of Cmax and AUC of substrates with or without rolapitant from clinical drug interaction studies

Enzyme/transporter	Co-administered drug	Day 1 Mean ratio (90% CI)		Day 7 Mean ratio (90% CI)	
	Name and Dose	Cmax	AUC	Cmax	AUC
CYP2B6	Efavirenz 200 mg	0.82 (0.74, 0.90)	1.08 (0.99, 1.17)	1.1 (0.99, 1.2)	1.28 (1.18, 1.39)
CYP2C8	Repaglinide 0.25 mg	1.07 (0.96, 1.19)	1.12 (1.07, 1.18)	1.29 (1.16, 1.44)	1.24 (1.18, 1.30)
CYP2C9	Tolbutamide 500 mg	0.96 (0.9, 1.0)	0.90 (0.85, 0.95)	0.98 (0.92, 1.0)	0.95 (0.90, 1.0)
CYP2C19	Omeprazole 40 mg	1.44 (1.12, 1.86)	1.23 (1.12, 1.36)	1.37 (1.05, 1.78)	1.15 (1.03, 1.27)
CYP2D6	Dextromethorphan 30mg	2.25 (1.87, 2.70)	2.58 (2.13, 3.11)	2.77 (2.30, 3.33)	3.33 (2.76, 4.02)
CYP3A4	Midazolam 3 mg	0.86 (0.78, 0.94)	0.98 (0.93, 1.03)	0.96 (0.88, 1.05)	1.07 (1.01, 1.13)
P-gp	Digoxin 0.5 mg	1.7 (1.49 1.95)	1.3 (1.2, 1.4)	--	--
BCRP	Sulfasalazine 500 mg	2.4 (2.0, 2.9)	2.28 (1.95, 2.67)	1.17 (0.98, 1.39)	1.32 (1.13, 1.55)

Reference ID: 3748397

CYP2D6 substrate

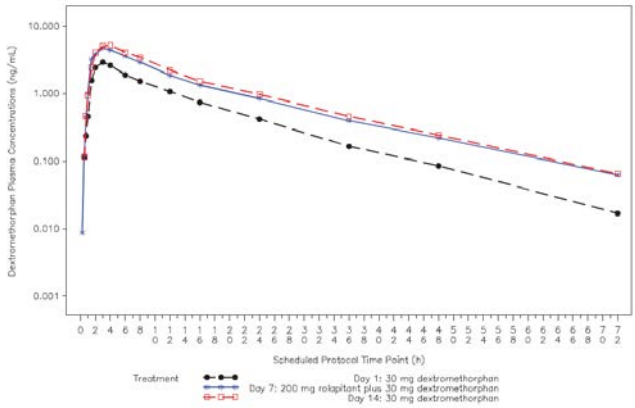
Rolapitant is a moderate inhibitor of CYP2D6 with a prolonged inhibitory effect at least for 7 days after a single dose rolapitant. When concomitantly administered with single dose 180 mg rolapitant, the Cmax and AUC to dextromethorphan was 2.2-fold and 3-fold higher, respectively than those after administrations of dextromethorphan alone. The Cmax and AUC of dextromethorphan were 2.8-fold and 3.9-fold higher, respectively on Day 7 (Table 30). In in vitro studies the time-dependent inhibition of CYP2D6 activity by rolapitant was not evident and an inhibition of CYP2D6 by SCH720881 was observed. The IC_{50} value of SCH720881 for CYP2D6 was not estimated.

Table 30 PK parameters for dextromethorphan and dextrorphan after administration of dextromethorphan alone and with rolapitant

Parameter	Day	Treatment	N	Analyte	Arithmetic Mean (SD)	Treatment Ratio [a]	90% CI for Ratio
C_{max} (ng/mL)	1	30 mg Dextromethorphan	26	Dextromethorphan	3.114 (4.1379)		
	7	30 mg Dextromethorphan + 200 mg Rolapitant	26	Dextromethorphan	5.355 (5.2793)	2.245	(1.866, 2.702)
	14	30 mg Dextromethorphan	26	Dextromethorphan	5.723 (4.8649)	2.768	(2.301, 3.331)
$AUC_{0\text{-last}}$ (ng.h/mL)	1	30 mg Dextromethorphan	26	Dextromethorphan	32.3 (51.21)		
	7	30 mg Dextromethorphan + 200 mg Rolapitant	26	Dextromethorphan	62.1 (77.78)	3.006	(2.432, 3.715)
	14	30 mg Dextromethorphan	26	Dextromethorphan	70.1 (84.83)	3.929	(3.179, 4.855)
$AUC_{0\text{-inf}}$ (ng.h/mL)	1	30 mg Dextromethorphan	24	Dextromethorphan	36.7 (53.46)		
	7	30 mg Dextromethorphan + 200 mg Rolapitant	25	Dextromethorphan	67.4 (81.10)	2.575	(2.129, 3.114)
	14	30 mg Dextromethorphan	26	Dextromethorphan	74.1 (87.67)	3.332	(2.763, 4.019)
C_{max} (ng/mL)	1	30 mg Dextromethorphan	26	Dextrorphan	4.452 (1.6462)		
	7	30 mg Dextromethorphan + 200 mg Rolapitant	26	Dextrorphan	5.031 (2.6596)	1.075	(0.948, 1.220)
	14	30 mg Dextromethorphan	26	Dextrorphan	5.286 (3.6093)	1.111	(0.979, 1.260)
$AUC_{0\text{-last}}$ (ng.h/mL)	1	30 mg Dextromethorphan	26	Dextrorphan	22.0 (8.87)		
	7	30 mg Dextromethorphan + 200 mg Rolapitant	26	Dextrorphan	26.5 (9.15)	1.229	(1.137, 1.329)
	14	30 mg Dextromethorphan	26	Dextrorphan	27.9 (10.41)	1.298	(1.201, 1.404)
$AUC_{0\text{-inf}}$ (ng.h/mL)	1	30 mg Dextromethorphan	26	Dextrorphan	23.0 (9.33)		
	7	30 mg Dextromethorphan + 200 mg Rolapitant	25	Dextrorphan	28.1 (10.18)	1.234	(1.144, 1.332)
	14	30 mg Dextromethorphan	26	Dextrorphan	29.7 (11.02)	1.313	(1.218, 1.415)

[a]Baseline reference group for all comparisons was treatment Day 1. Ratio of least squares means.

Figure 19 Mean Dextromethorphan Concentration-Time Profile with or without concomitant rolapitant



Data source: Section 14, Figure 14.2.4.3a

Reference ID: 3748397

Reviewer's comments: The inhibitory effect of rolapitant on dextromethorphan metabolism was studied in CYP2D6 intermediate and extensive metabolizers. However, a definitive conclusion on a potentially different inhibitory potency of rolapitant on CYP2D6 could not be drawn due to insufficient data with large variability of dextromethorphan PK parameters **(see also section 2.6.4).**

CYP3A4 substrate

The effect of rolapitant on PK of midazolam and 1-OH midazolam was studied over 10 days after concomitant administration with single-dose rolapitant on Day 1. There was no significant effect of rolapitant on PK of midazolam and its metabolite 1-OH midazolam over 10 days. This is consistent with the in vitro observation where an inhibitory or inductive effect of rolapitant on CYP3A4 enzyme was not significant.

Table 31 Mean (%CV) PK Parameters of Midazolam after Administration of Midazolam Alone and with Rolapitant

Treatment	Midazolam without rolapitant[a]	With a single-dose rolapitant on Day 1		
		Midazolam With rolapitant	Midazolam alone	Midazolam alone
	(n=26)	**Day 1** (n=26)	**Day 7** (n=26)	**Day 10** (n=26)
Cmax (ng/ml)	13 (26.6)	11.3 (33.5)	12.4 (27.4)	13.5 (26)
Tmax	0.5 (0.2-0.9)	0.5 (0.25, 1)	0.5 (0.25, 1)	0.6 (0.25, 1.25)
$T_{1/2}$ (h)	5.9 (38.1)	5.1 (34.3)	5.1 (30.2)	5.1 (32.7)
AUCt (ng*h/ml)	28.8 (32.6)	28.5 (37.2)	31.3 (34.3)	34.3 (33.7)
AUCinf (ng*h/ml)	30.6 (31.2)	29.8 (36.4)	31.8 (32.8)	35.7 (33.2)

[a]PK of Midazolam was studied before administration of rolapitant in a fixed-sequence, cross-over study

Reference ID: 3748397

CYP2C9 substrate

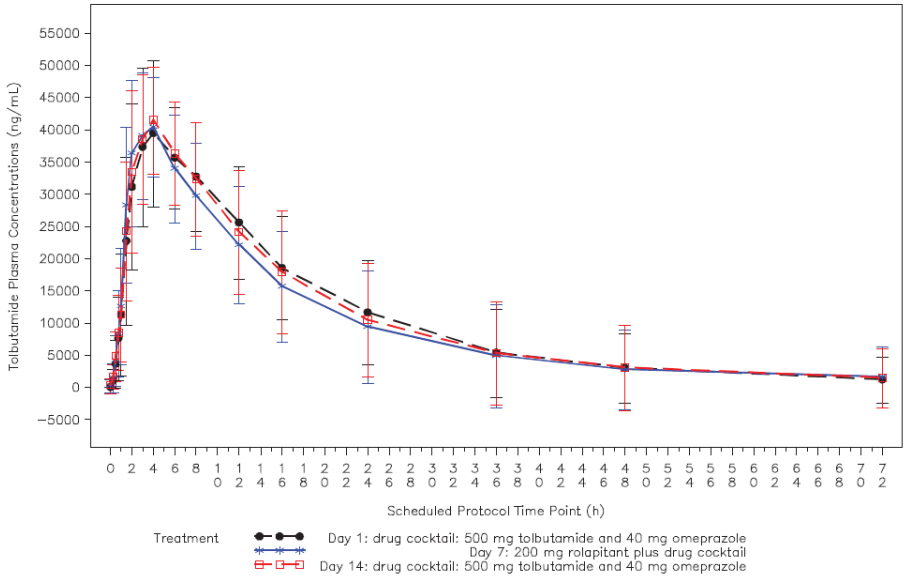
Single-dose rolapitant did not significantly affect the PK of tolbutamide, a CYP2C9 substrate and its metabolites, 4-carboxy tolbutamide and hydroxyl tolbutamide for 7 days.

Table 32 Mean PK Parameters of Tolbutamide with or without Rolapitant*

Parameter	Day	Treatment	N	Analyte	Arithmetic Mean (SD)	Treatment Ratio [a]	90% CI for Ratio
C_{max} (ng/mL)	1	Drug Cocktail: 500 mg Tolbutamide and 40 mg Omeprazole	20	Tolbutamide	43348.0000 (7212.8552)		
	7	200 mg Rolapitant + drug cocktail	20	Tolbutamide	41849.0000 (7784.8476)	0.962	(0.906, 1.022)
	14	Drug Cocktail	18	Tolbutamide	42992.778 (8455.7421)	0.977	(0.918, 1.040)
$AUC_{0\text{-last}}$ (ng.h/mL)	1	Drug Cocktail: 500 mg Tolbutamide and 40 mg Omeprazole	20	Tolbutamide	748794.9 (417504.83)		
	7	200 mg Rolapitant + drug cocktail	20	Tolbutamide	685747.6 (475892.82)	0.892	(0.846, 0.940)
	14	Drug Cocktail	18	Tolbutamide	740246.1 (492443.07)	0.947	(0.897, 1.000)
$AUC_{0\text{-inf}}$ (ng.h/mL)	1	Drug Cocktail: 500 mg Tolbutamide and 40 mg Omeprazole	20	Tolbutamide	801800.9 (596564.72)		
	7	200 mg Rolapitant + drug cocktail	20	Tolbutamide	765904.5 (773092.16)	0.899	(0.850, 0.951)
	14	Drug Cocktail	18	Tolbutamide	817760.4 (766273.48)	0.952	(0.898, 1.009)

*Effect of rolapitant on tolbutamide was studied after administration of drug cocktail consisting of 500 mg tolbutamide and 40 mg omeprazole.

Figure 20 Mean (±SD) Tolbutamide Concentration-Time Profile with and without Rolapitant



Data source: Section 14, Figure 14.2.4.2b

Reference ID: 3748397

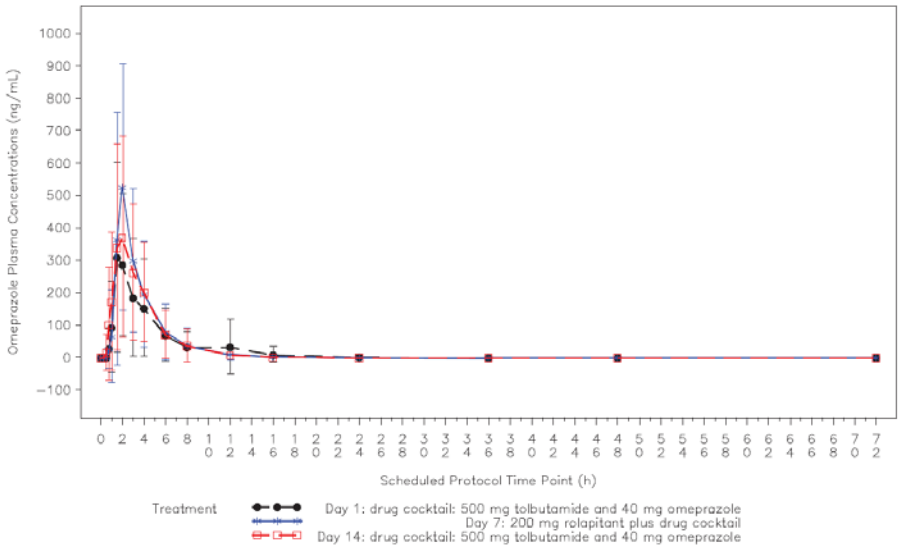
CYP2C19 substrate

Single-dose administration of rolapitant with omeprazole resulted in an increase in Cmax and AUCi of omeprazole by 44% and 23%, respectively on Day 1 compared to those after omeprazole alone. On Day 7, Cmax and AUCi of omeprazole was 37% and 15% higher, respectively.

Table 33 Mean PK Parameters for Omeprazole with or without Rolapitant

Parameter	Day	Treatment	N	Analyte	Arithmetic Mean (SD)	Treatment Ratio [a]	90% CI for Ratio
C_{max} (ng/mL)	1	Drug Cocktail: 500 mg Tolbutamide and 40 mg Omeprazole	20	Omeprazole	409.570 (254.6114)		
	7	200 mg Rolapitant + drug cocktail	20	Omeprazole	605.950 (371.3320)	1.441	(1.118, 1.856)
	14	Drug Cocktail	18	Omeprazole	510.889 (252.7600)	1.366	(1.050, 1.776)
$AUC_{0\text{-last}}$ (ng.h/mL)	1	Drug Cocktail: 500 mg Tolbutamide and 40 mg Omeprazole	20	Omeprazole	1188.0 (1021.06)		
	7	200 mg Rolapitant + drug cocktail	20	Omeprazole	1461.2 (1166.14)	1.223	(1.132, 1.320)
	14	Drug Cocktail	18	Omeprazole	1339.2 (1035.77)	1.163	(1.074, 1.259)
$AUC_{0\text{-inf}}$ (ng.h/mL)	1	Drug Cocktail: 500 mg Tolbutamide and 40 mg Omeprazole	16	Omeprazole	1150.7 (1017.00)		
	7	200 mg Rolapitant + drug cocktail	19	Omeprazole	1537.7 (1162.80)	1.233	(1.121, 1.355)
	14	Drug Cocktail	16	Omeprazole	1429.0 (1074.19)	1.146	(1.033, 1.272)

Figure 21 Mean (±SD) Omeprazole Concentration-Time Profile with and without Rolapitant



Data source: Section 14, Figure 14.2.4.5b

Reference ID: 3748397

CYP2B6 substrate

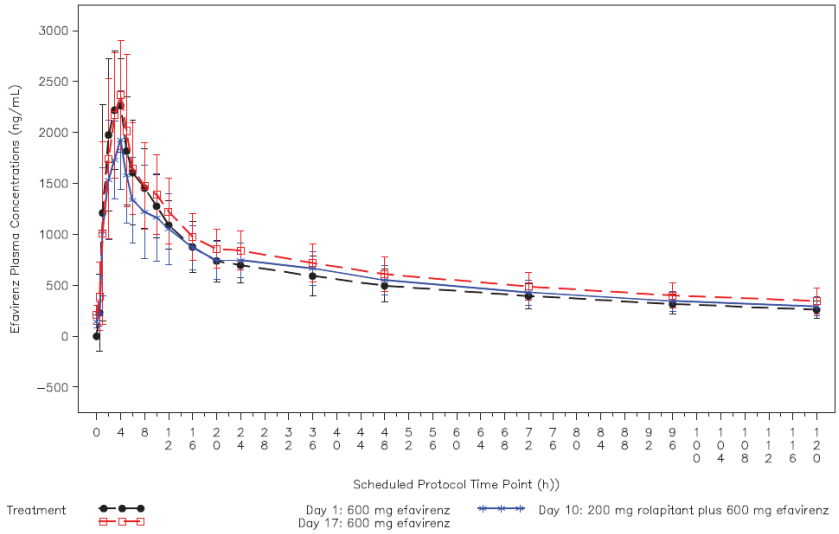
No significant effects of rolapitant on PK of efavirenz were observed on Day 1 while a weak inhibition of efavirenz, a CYP2B6 substrate metabolism was noted on Day 7. When efavirenz was co-administered with rolapitant, Cmax and AUC of efavirenz were 19% lower and 8% higher, respectively than when efavirenz was administered alone. When efavirenz was administered 7 days after rolapitant dosing, Cmax and AUC were 9% and 28% higher compared to those after efavirenz alone.

Table 34 Mean PK parameters of omeprazole with or without concomitant rolapitant

Parameter	Day	Treatment	N	Analyte	Arithmetic Mean (SD)	Treatment Ratio [a]	90% CI for Ratio
C_{max} (ng/mL)	1	600 mg Efavirenz	20	Efavirenz	2592.000 (574.2602)		
	10	200 mg Rolapitant plus 600 mg Efavirenz	20	Efavirenz	2103.000 (401.2231)	0.817	(0.742, 0.899)
	17	600 mg Efavirenz	20	Efavirenz	2817.000 (542.2672)	1.094	(0.993, 1.205)
$AUC_{0\text{-last}}$ (ng.h/mL)	1	600 mg Efavirenz	20	Efavirenz	68462.7 (14981.65)		
	10	200 mg Rolapitant plus 600 mg Efavirenz	20	Efavirenz	69945.8 (14418.88)	1.022	(0.963, 1.085)
	17	600 mg Efavirenz	20	Efavirenz	80078.7 (17048.92)	1.168	(1.101, 1.240)
$AUC_{0\text{-inf}}$ (ng.h/mL)	1	600 mg Efavirenz	20	Efavirenz	102616.9 (24402.91)		
	10	200 mg Rolapitant plus 600 mg Efavirenz	20	Efavirenz	113011.3 (35916.00)	1.079	(0.994, 1.171)
	17	600 mg Efavirenz	20	Efavirenz	135903.7 (48514.05)	1.281	(1.180, 1.390)

[a] Baseline reference group for all comparisons was treatment Day 1. Ratio of least squares means.

Figure 22 Mean (±SD) Efavirenz Concentration-Time Profile with or without Rolapitant



Data source: Section 14, Figure 14.2.4.2c

Reference ID: 3748397

CYP2C8

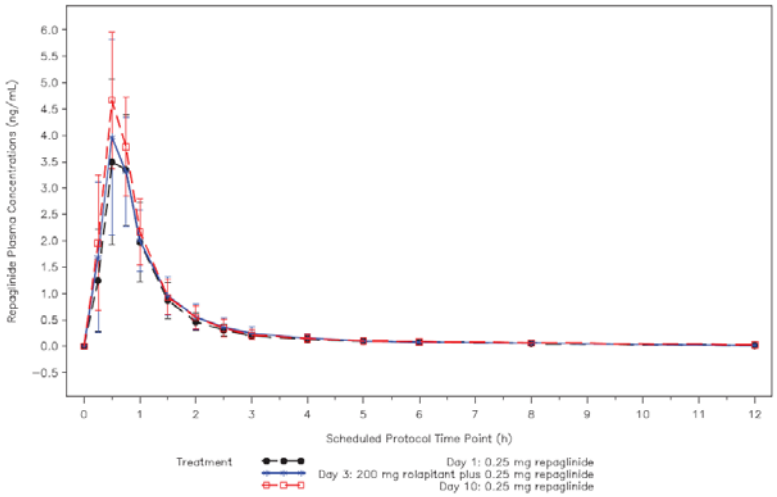
Single-dose rolapitant resulted in a slight increase in Cmax and AUC of repaglinide, a CYP2C8 substrate by 29% and 24%, respectively on 7 days after rolapitant dosing while did not significantly affect the systemic exposure on Day 1.

Table 35 Mean PK Parameters of Repaglinide with or without Rolapitant

Parameter	Day	Treatment	N	Analyte	Arithmetic Mean (SD)	Treatment Ratio [a]	90% CI for Ratio
C_{max} (ng/mL)	1	0.25 mg Repaglinide	20	Repaglinide	3.742 (1.4393)		
	3	200 mg Rolapitant plus 0.25 mg Repaglinide	20	Repaglinide	4.125 (1.6762)	1.066	(0.957, 1.188)
	10	0.25 mg Repaglinide	20	Repaglinide	4.712 (1.2470)	1.294	(1.162, 1.442)
$AUC_{0\text{-last}}$ (ng.h/mL)	1	0.25 mg Repaglinide	20	Repaglinide	4.1 (1.39)		
	3	200 mg Rolapitant plus 0.25 mg Repaglinide	20	Repaglinide	4.6 (1.52)	1.110	(1.060, 1.162)
	10	0.25 mg Repaglinide	20	Repaglinide	5.0 (1.53)	1.225	(1.170, 1.282)
$AUC_{0\text{-inf}}$ (ng.h/mL)	1	0.25 mg Repaglinide	16	Repaglinide	4.4 (1.51)		
	3	200 mg Rolapitant plus 0.25 mg Repaglinide	13	Repaglinide	5.3 (1.65)	1.124	(1.069, 1.181)
	10	0.25 mg Repaglinide	15	Repaglinide	5.6 (1.84)	1.236	(1.179, 1.295)

[a] Baseline reference group for all comparisons was treatment Day 1. Ratio of least squares means.

Figure 23 Mean (±SD) Repaglinide Concentration-Time Profile with or without Rolapitant



Data source: Section 14, Figure 14.2.4.2d

2.4.2.4 Is rolapitant a substrate and/or an inhibitor of transporters?

Substrate Potential

Rolapitant and SCH720881 are not substrates of P-glycoprotein (P-gp), nor is it a substrate of organic anion-transporting polypeptide 1B1 (OATP1B1) and 1B3 (OATP1B3).

Reviewer's comment: In in vitro studies for the evaluation of P-gp substrate, the recovery of rolapitant and SCH720881 from the receiver chamber after the apical to basal permeation was about 30% and 50%, respectively due to non-specific binding and it was significantly lower than those for control materials.

Reference ID: 3748397

Inhibition

P-glycoprotein substrate
Rolapitant is an inhibitor of p-glycoprotein based on a clinical drug interaction study.

In vitro study
Rolapitant
In vitro, inhibition of p-gp activity by rolapitant was studied using Caco-2 cells. There was rolapitant concentration-dependent inhibition of digoxin efflux observed at concentration up to 20 mcM. Rolapitant inhibited digoxin efflux by 74% at 20 mcM while cyclosporine, a p-gp inhibitor inhibited digoxin efflux by 93% at 20 mcM. The IC_{50} of rolapitant was estimated to be 7.36 µM and the $[I]/IC_{50}$ value for p-gp inhibition was estimated to be 0.23. Based on $[I]/IC_{50} > 0.1$ a potential in-vivo drug interaction via inhibition of p-gp cannot be ruled out. Based on this study, an in vivo drug interaction using digoxin as a substrate was conducted.

Metabolite
The major metabolite, SCH 720881 did not reduce the efflux of talinolol, a P-gp substrate at concentrations of 1 or 10 mcM while verapamil, a positive control reduced the efflux of talinolol from 11.3 to 0.27.

Clinical drug interaction study
Co-administration of 0.5 mg digoxin with 180 mg rolapitant increased mean digoxin Cmax by 71% and mean AUCt by 30%, respectively compared to those without rolapitant.

Table 36 Mean (%CV) PK Parameters of Digoxin

	C_{max} (ng/mL)	T_{max} [c] (hr)	$AUC_{0\text{-last}}$ (ng*hr/mL)	$T_{1/2}$ (hr)
Digoxin (n=16)	2.38 (34)	1 (1-1.5)	28.4 (32)	40.7 (11)[a]
Digoxin + Rolapitant (n=16)	3.98 (25)	1 (0.5-1.5)	36.0 (23)	42.4 (11)[b]

[a] n=9; [b] n=12; [c] median (range) *Source: Modified from CSR P05325 Tables 2 and 4*

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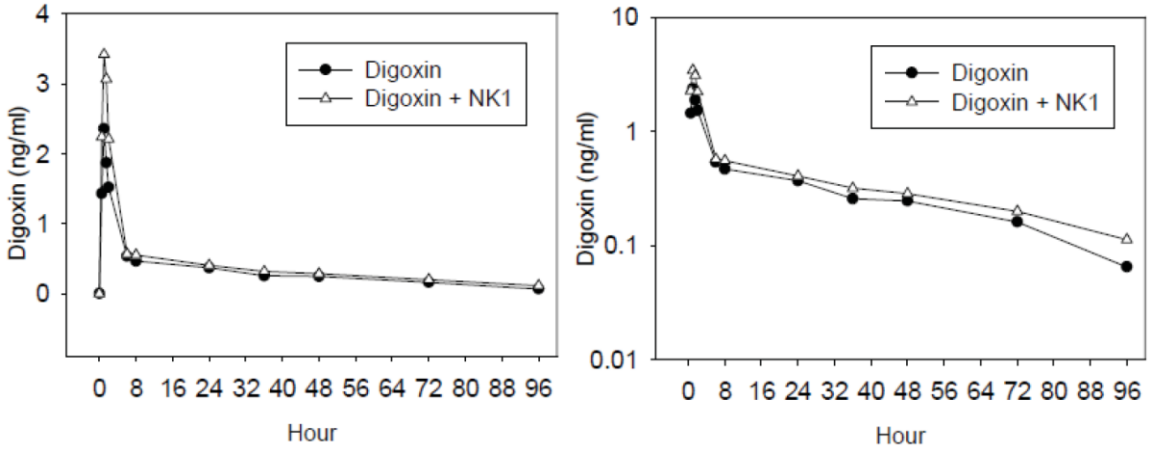
Figure 24 Mean Digoxin Concentration-Time Profile following a Single Oral Dose of 0.5 mg Digoxin with or without Rolapitant



<u>Breast cancer resistance protein (BCRP)</u>

Rolapitant is an inhibitor of BCRP based on a clinical drug interaction study.

<u>In vitro study</u>

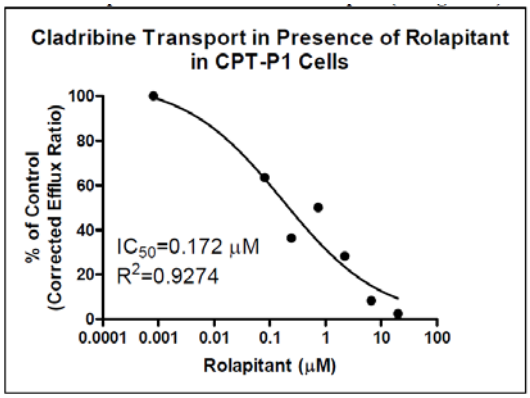
<u>Rolapitant</u>

In an in-vitro study using CPT-P1 cell line which was derived from Caco-2 cells, with lower expression of p-gp, the efflux ratio of cladribine, a substrate of BCRP was decreased in a rolapitant concentration-dependent manner. The efflux ratio of cladribine decreased from 19 to 2 in presence of 20 mcM rolapitant compared to that in absence of rolapitant. A prototype inhibitor, Ko143[15] was reduced the efflux ratio to 0.83. The IC_{50} was estimated to be 0.172 mcM and $[I]/IC_{50}$ was estimated to be about 10 suggesting potential drug interaction via inhibition of BCRP.

<u>Metabolite</u>

In vitro 3 µM SCH720881 did not affect the efflux ratio of cladribine while Ko143 decreased the efflux ratio from 9.3 to 2.0. Inhibition of BCRP was studied at SCH720881 concentration, which is about 10 times higher than mean C_{max} of SCH720881.

Figure 25 Effect of Rolapitant on Cladribine Transport in CPT-P1 cells



<u>Clinical drug interaction study</u>

[15] Allen JD et al., (2002) Mol. Can.Ther. 1(6): 417-425

Reference ID: 3748397

Co-administration with rolapitant resulted in 2.4- and 2.3-fold increase in Cmax and AUC of sulfasalazine, a BCRP substrate respectively compared to those without rolapitant. The median half-life of sulfasalazine was similar (7.7 h and 7.6 h). The inhibitory effect was weakened over time and on Day 7, Cmax and AUC was 17% and 32% higher, respectively compared to those after administration of sulfasalazine alone (Table 37, Figure 26). Rolapitant did not significantly affect the PK of sulfapyrine, a metabolite of sulfasalazine.

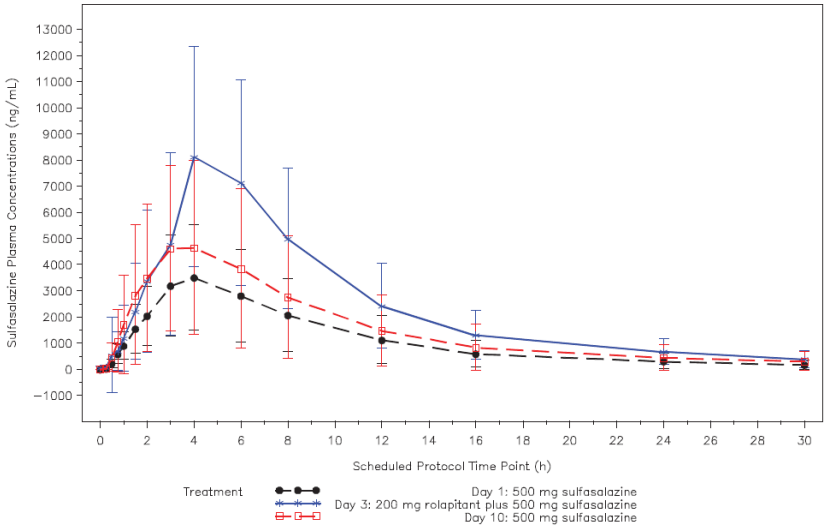
Table 37 Mean (%CV) PK Parameters of Sulfasalazine

Treatment	Day	N	C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0\text{-last}}$ (ng·hr/mL)	$AUC_{0\text{-inf}}$ (ng·hr/mL)	$t_{1/2}$ (hr)
			Mean (%CV)	Median (Range)	Mean (%CV)	Mean (%CV)	Mean (%CV)
SUL	1	20	4013 (50.7)	4.0 (2.0-8.0)	33405 (61.5)	35446 (63.9)	7.72 (11.7)
SUL + ROL	3	20	9543 (45.9)	4.0 (3.0-8.0)	72666 (49.1)	77407 (51.3)	7.85 (16.2)
SUL	10	20	5133 (67.0)	4.0 (1.5-8.0)	46946 (80.8)	51351 (84.5)	9.13 (23.7)

Source: CSR PR-10-5001-C, Table 31

AUC = area under the plasma concentration-time curve; C_{max} = maximum concentration; T_{max} = time to maximum concentration; $t_{1/2}$ = terminal elimination half-life. CV = coefficient of variation; N = number; SUL = sulfasalazine; ROL = rolapitant.

Figure 26 Mean (SD) Sulfasalazine Concentration-Time Profile with or without rolapitant



Data source: Section 14, Figure 14.2.4.3e

***Reviewer's comment*:** BCRP substrates include but not limited to, methotrexate, mitoxantrone, imatinib, irinotecan, lapatinib, rosuvastatin, sulfasalazine, and topotecan. Among these irinotecan

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is a moderately emetogenic chemotherapy while methotrexate, topotecan and mitoxantrone have low risk of emetogenicity[16].

Bile Salt Export Pump

In vitro Study

Rolapitant

In an in vitro using the BSEP-expressing membrane vesicles, concentration-dependent inhibitory effect of rolapitant on BSEP was observed. The uptake of taurocholic acid (TCA), a substrate of BSEP was inhibited by ~50% at 18 mcM while 10 mcM cyclosporine, a positive inhibitor inhibited the TCA uptake by 95%. The inhibition was not studied at concentrations higher than 18 mcM. The IC_{50} value was not estimated as the inhibition was 49.3% at the highest studied concentration. The mean peak plasma concentration of rolapitant is about 1.7 mcM and at 2 mcM, the TCA uptake by BSEP was 15% inhibited by rolapitant.

Reviewer's comment: If the IC_{50} was close to18 mcM, the $[I]/IC_{50}$ would have been close to 0.1 in which case the in vivo drug interaction potential cannot be ruled out.

Metabolite

A concentration-dependent inhibition of BSEP by SCH720881 was observed in vitro. At 3 mcM which is 10-times higher than mean Cmax of SCH720881, the uptake of [^{3}H]TCA into human BSEP vesicles was inhibited by 24%.

Table 38 Inhibition of [^{3}H]-TCA by Rolapitant into BSEP-Expressed Vesicles

Treatment	[^{3}H-TCA] Uptake Rate (pmol/min/mg protein)							Activity Remaining (%)	Inhibition (%)[b]
	Cofactor ATP			Cofactor AMP			Net Influx Rate[a]		
	R1	R2	Average	R1	R2	Average			
10 μM CsA	0.487	0.460	0.473	0.183	0.231	0.207	0.266	5.5	94.5
18 μM Rolapitant	2.57	2.68	2.62	0.171	0.188	0.180	2.44	50.7	49.3
6 μM Rolapitant	3.82	3.74	3.78	0.201	0.180	0.190	3.59	74.5	25.5
2 μM Rolapitant	4.26	4.27	4.27	0.194	0.186	0.190	4.08	84.6	15.4
0.667 μM Rolapitant	4.80	4.53	4.67	0.186	0.199	0.192	4.47	92.8	7.2
0.222 μM Rolapitant	4.59	4.68	4.63	0.188	0.209	0.199	4.43	92.0	8.0
0.0741 μM Rolapitant	4.82	4.92	4.87	0.238	0.247	0.242	4.63	96.0	4.0
[^{3}H]-TCA only	5.10	5.03	5.06	0.276	0.213	0.244	4.82	100	n.a.

[a] Net Influx Rate: average ATP value minus average AMP value.
[b] Inhibition = 100% minus remaining activity (%).
n.a: not applicable.

2.4.2.5 What is the effect of rolapitant on concomitant 5-HT_3 antagonist and corticosteroid?

Rolapitant is recommended to be used in combination with a 5-HT3 antagonist and a corticosteroid for CINV.

A clinical drug interaction study was conducted to evaluate the effect of rolapitant on dexamethasone and ondansetron and vice versa when rolapitant was co-administered with

[16] Basch et al. (2011) Antiemetics: ASCO Clinical Practice Guideline Update, J. Clin.Oncol. 29(34), 4189

Reference ID: 3748397

dexamethasone and ondansetron in a regimen studied in the phase 2 trial: 32 mg intravenous ondansetron and 20 mg oral dexamethasone on Day 1 followed by 8 mg dexamethasone twice a day on Days 2-3 and single-dose of dexamethasone on Day 4..

Concomitant rolapitant did not significantly affect the PK of ondansetron or dexamethasone compared to that after administration ondansetron and dexamethasone without rolapitant (Table 39, Table 40). Concomitant ondansetron and dexamethasone did not significantly affect the PK of rolapitant (Table 41).

Reviewer's comment: Ondansetron had been used in other NK1 receptor antagonist development program. In this program, while 32 mg intravenous ondansetron was used in a phase 2 trial either intravenous, oral granisetron was used as a 5-HT3 receptor antagonist in phase 3 trials. Single-dose intravenous ondansetron at 32 mg was removed from the labeling in November 2012 due to the risk of QT prolongation. Both oral and intravenous granisetron is approved for chemotherapy-induced nausea and vomiting including high-dose cisplatin.

On the other hand clinical drug interaction study was not done with granisetron. Nevertheless significant alteration of PK of granisetron by rolapitant to affect the efficacy comparison with the placebo group is unlikely. In vitro liver studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by CYP 3A subfamily[17] while rolapitant does not significantly inhibit or induce CYP3A4 activity and.

Dexamethasone

Concurrent administration of rolapitant did not significantly affect the Cmax and AUC of dexamethasone on Day 1. The systemic exposure was 10% lower on Day 4 when dexamethasone was given with rolapitant compared to dexamethasone alone. This result is consistent with no significant effect of rolapitant on a sensitive CYP3A4 substrate, midazolam (Table 39, Figure 27). Dexamethasone dosage was not adjusted in the efficacy and safety clinical trials based on this result.

Table 39 Mean (%CV) PK Parameters of Dexamethasone with or without Concomitant Rolapitant on Day 1*

Treatment	Cmax (ng/mL)		Tmax (hr) [a]		AUC_{0-24} (ng·hr/ml)	
	Day1	Day 4[b]	Day 1	Day 4[b]	Day 1	Day 4[b]
Dexamethasone alone (n=24)	205 (29)	84.9 (23)	2 (0.75-4)	1 (0.5-4)	1480 (31)	484 (40)
With Rolapitant (n=23)	202 (17)	79.8 (33)[c]	2 (0.5-4)	0.75 (0.5-4) [c]	1500 (29)	415 (44) [c]
Geometric Mean Ratio (90% CI) Dexamethasone with rolapitant vs. Dexamethasone alone						
	101 (93, 110)	91 (84, 98)	--	--	105 (98, 112)	89 (82, 97)

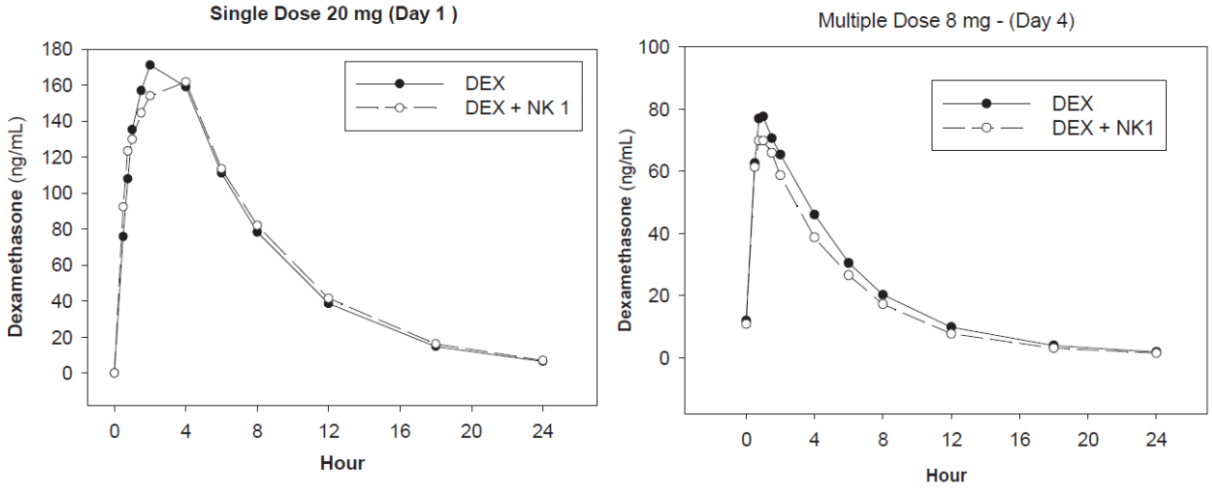
[a] median (range); [b] n=21; [c]n=20

[17] Package Insert of Granisetron hydrochloride

Reference ID: 3748397

*Dexamethasone regimen: 20 mg on Day 1 followed by 8 mg twice a day on Days 2 and 3 and single-dose of 8 mg on Day 4. 32 mg ondansetron was intravenously administered on Day 1

Figure 27 Mean Plasma Dexamethasone Concentration-Time Profiles on Day 1 Following Single Oral Administration of Dexamethasone 20 mg (Left) and on Day 4 Following Multiple Oral Administrations of Dexamethasone 8 mg (Right), With Ondansetron, With and Without Rolapitant



Ondansetron

Table 40 Mean (%CV) PK Parameters for Ondansetron after administered alone and administered with rolapitant on Day 1*

	C_{max} (ng/mL	T_{max} (h)[a]	AUC_{0-24} (ng·h/mL)	AUC_{inf} (ng·h/mL)	$T_{1/2}$ (h)
Ondansetron Alone (n=24)	339 (24)	0.5 (0.25-1)	1750 (31)	1840 (33)	5.97 (18)
With Rolapitant (n=23)	343 (35)	0.5 (0.25-1.5)	1920 (34)	2020 (36)	5.86 (15)
Geometric Mean Ratio (90% CI) Ondansetron with rolapitant vs. Ondansetron alone					
	98 (88, 109)		107 (102, 112)	107 (102, 113)	

[a] median (range);

Reference ID: 3748397

Rolapitant

Concomitant intravenous ondansetron and oral dexamethasone did not significantly affect mean AUC of rolapitant while mean Cmax was 16% lower than when rolapitant was administered alone.

Table 41 Mean (%CV) PK Parameters for Rolapitant after Administration alone or with Dexamethasone and Ondansetron

	Rolapitant alone	Rolapitant with OND and DEXA	Geometric Mean ratio (90% CI) Rolapitant alone vs. with OND+DEXA
Cmax (ng/ml)	991 (19)	1170 (19)	84 (76, 94)
AUC_{0-120} (ng·h/ml)	46800 (15)	48400 (13)	96 (89, 104)

2.4.2.7 What other co-medications are likely to be administered to the target patient population?

The target patient population is cancer patients; therefore patients will take various chemotherapeutics. In a clinical trial for MEC (P04834), 51.7% of patients received anthracycline-cyclophosphamide (AC) based chemotherapy and 47.3% of patients received non-AC based chemotherapy. In MEC trial, 5.7% (39/666) of patients received irinotecan. In clinical trials for HEC (P04832, P04833), $\geq$ 99% patients received cisplatin-based chemotherapy

In addition to cancer drugs, patients in clinical trials were on acid-reducers for gastroesophageal reflux disease (GERD) and pain medications including opioids (Table 42).

In phase 3 clinical trials, 25-50% of patients were taking acid-reducers across studies. The proportion of patients who took any acid-reducers e.g. antacid or PPI or H_2 blocker was 27%, 55% and 31% in Studies P04832, P04833, and P04834, respectively. Across the trials, the CR rate in acute phase after rolapitant was similar: 83.7%, 83.4%, and 83.5% in Studies 32, 33, and 34, respectively.

Reference ID: 3748397

Table 42 Concomitant medications used by > 10% of subjects in either the rolapitant or control group in Study P04832

WHODD ATC Level 3	Rolapitant (N = 264) n (%)	Control (N = 262) n (%)	All (N = 526) n (%)
Number of subjects with ≥1 medication reported	***245 (92.8)***	***246 (93.9)***	***491 (93.3)***
IV solution additives	129 (48.9)	135 (51.5)	264 (50.2)
IV solutions	94 (35.6)	109 (41.6)	203 (38.6)
Drugs for peptic ulcer and GERD	79 (29.9)	97 (37.0)	176 (33.5)
High-ceiling diuretics	66 (25.0)	66 (25.2)	132 (25.1)
Opioids	47 (17.8)	61 (23.3)	108 (20.5)
Other analgesics and antipyretics	52 (19.7)	48 (18.3)	100 (19.0)
Immunostimulants	47 (17.8)	52 (19.8)	99 (18.8)
Anti-inflammatory and anti-rheumatic products, non-steroids	35 (13.3)	45 (17.2)	80 (15.2)
Antithrombotic agents	28 (10.6)	49 (18.7)	77 (14.6)
Corticosteroids for systemic use, plain	36 (13.6)	41 (15.6)	77 (14.6)
Laxatives	34 (12.9)	36 (13.7)	70 (13.3)
Antiemetics and anti-nauseants	34 (12.9)	33 (12.6)	67 (12.7)
Antihistamines for systemic use	36 (13.6)	30 (11.5)	66 (12.5)
ACE inhibitors, plain	29 (11.0)	34 (13.0)	63 (12.0)
Beta blocking agents	22 (8.3)	35 (13.4)	57 (10.8)
Lipid modifying agents, plain	29 (11.0)	28 (10.7)	57 (10.8)
Propulsives	24 (9.1)	28 (10.7)	52 (9.9)

Abbreviations ACE = angiotensin-converting-enzyme; ATC = anatomic therapeutic chemical; GERD = gastro-oesophageal reflux disease; MITT = Modified Intent-to-Treat; WHODD = World Health Organization Drug Dictionary

Source: Table 14.1.12.2

2.4.2.8 What are the effects of other concomitant drugs on rolapitant?

Rolapitant is a substrate of CYP3A4 and in vitro the formation of the major metabolite of rolapitant was inhibited by ketoconazole, a CYP3A4 inhibitor. Therefore the effects of CYP3A4 inhibitor and inducer were studied in humans. In humans concurrent rifampin significantly decreased AUC of rolapitant and its active metabolite by 87% and 89%, respectively. On the other hand ketoconazole increased AUCt of rolapitant by 21% (Table 43).

Reference ID: 3748397

Table 43 Effects of Other Drugs on Rolapitant and its Major Metabolite

	Median Tmax (h)	% Change in Cmax	%Change in AUC
With Ketoconazole (n=12)[a] (one day before and for 21 days after rolapitant)			
Rolapitant	4 (alone) 4 (with Keto)	3%↑	AUC_{0-120}: 16% ↑ AUCt: 21% ↑
SCH720881	168 (alone) 336 (with Keto)	2%↓	AUC_{0-120}: 62%↓ AUCt: 16%↓
With Rifampin (n=20) (for 7 days before and for 7 days after rolapitant)			
Rolapitant	3.9 (alone) 4.0 (with Rif)	33%↓	87%↓
SCH720881	144 (alone) 6.1 (with Rif)	22%↑	89%↓

[a]: 90 mg rolapitant was administered with ketoconazole
↓: Decrease in rolapitant exposure by other drug;
↑: Increase in rolapitant exposure by other drug

CYP3A4 inducers

The mean Cmax and AUC of rolapitant was 33% and 87% reduced when single dose rolapitant was administered to healthy subjects who received 600 mg rifampin, a strong CYP3A4 inducer for 7 days before rolapitant administration and 7 days after co-administration (Table 44). On the other hand, the median Tmax for SCH 720881 was reduced to 6 h with rifampin from 144 hours without rifampin. Mean C_{max} of SCH720881 was increased by 20% while mean AUCt of SCH720881 was decreased by 89%. Concurrent rifampin enhanced both the formation and elimination of SCH720881 suggesting that the subsequent metabolism of SCH720881 is also induced by rifampin. In a mass balance study, SCH720881 was either not detected in urine or excreted as a small fraction in feces although it is a major circulating metabolite in plasma.

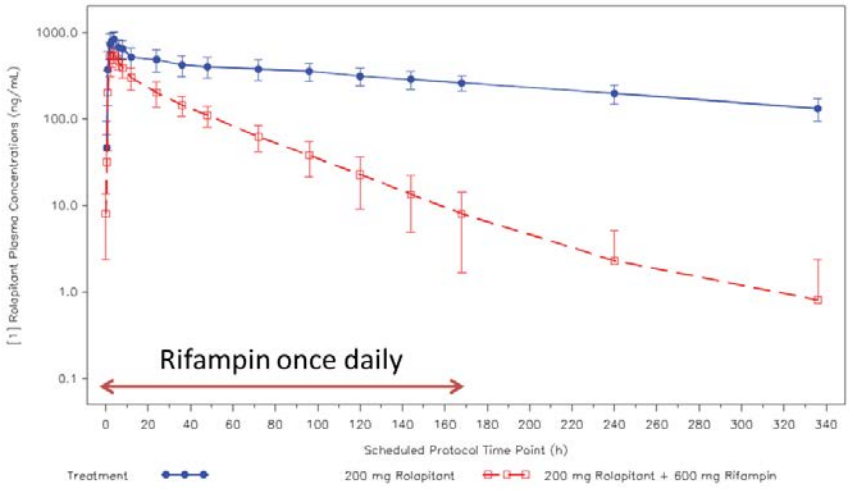
CYP3A4 inhibitor

In a clinical drug interaction study, ketoconazole (400 mg once a day) was administered one day before and 21 days after the co-administration with rolapitant. Concurrent ketoconazole did not significantly affect the Cmax of rolapitant while mean AUC_{0-120} and AUCt of rolapitant were 16% and 21% higher, respectively than those after administration of rolapitant alone (Table 45).

On the other hand the formation of the major metabolite SCH 720881 was significantly delayed with the median Tmax from 168 hr to 336 hr and reduced during the first 120 hours post-dose. The overall AUC up to 504 h post-dose for SCH 720881 was 16% lower with concurrent ketoconazole than without ketoconazole (Table 45).

Reference ID: 3748397

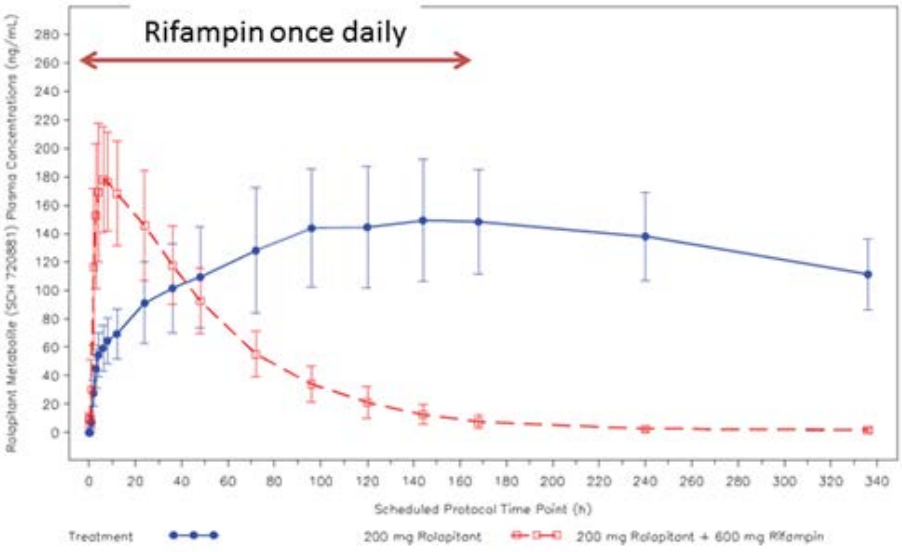
Figure 28 Mean (SD) Rolapitant Concentration-Time Profiles with or without Rifampin



[1] Logarithmic Scale
Error bars are not displayed if the difference Mean−SD <0 on the logarithmic scale
Day 1: 200 mg rolapitant dosed. Day 15−21: 600 mg rifampin dosed.
Day 22: 200 mg rolapitant + 600 mg rifampin dosed. Day 23−28: 600 mg rifampin dosed.

Data source: Figure 14.2.4.4

Figure 29 Mean (SD) Major Metabolite Concentration-Time Profiles with or without Rifampin



Day 1: 200 mg rolapitant dosed. Day 15−21: 600 mg rifampin dosed.
Day 22: 200 mg rolapitant + 600 mg rifampin dosed. Day 23−28: 600 mg rifampin dosed.

Data source: Figure 14.2.4.7

Table 44 Mean (%CV) PK Parameters for Rolapitant with or without Rifampin

	Rolapitant alone (n=20)	Rolapitant With rifampin (n=20)	Mean ratio (%) (90% CI)
Rolapitant			
C_{max} (ng/ml)	896.8 (19.5)	611.1 (26.4)	67 (62, 73)
T_{max} (h)[a]	3.9 (1.9, 8.0)	4 (2.6)	
AUC_t (mcg·h/ml)	95.8 (20.7)	16.2 (23.5)	17 (15, 18)
AUC_{inf} (mcg·h/ml)	130.9 (23.5)	16.4 (23.5)	13 (11, 14)
$T_{1/2}$ (h)	175.6 (23.4)	41 (48.3)	
SCH720881			
C_{max} (ng/ml)	157.4 (26.4)	191.0 (21.9)	122 (112,133)
T_{max} (h) [a]	144 (72-240)	6 (2-24)	
AUC_t (mcg·h/ml)	42.8 (24.1)	11.0 (22.9)	26 (24, 28)
AUC_{inf} (mcg·h/ml)	108.0 (32.9)	11.5 (24.3)	11 (9, 14)
$T_{1/2}$ (h)	397(51.4)	66 (43.9)	

[a:] Median (range)

Table 45 Mean (%CV) PK Parameters of Rolapitant after Administration of 90 mg Rolapitant Alone or with Multiple Doses of Ketoconazole

	Rolapitant alone (n=12)	Rolapitant With ketoconazole (n=12)	Mean ratio (90% CI)
Rolapitant			
C_{max} (ng/ml)	657 (17)	676 (18)	103 (92, 115)
T_{max} (h) [a]	4 (2-6) [a]	4 (1.5-6)	--
AUC_{0-120} (mcg·h/ml)	32.2 (18)	37.2 (16)	116 (104, 130)
AUC_t (mcg·h/ml)	78.4 (20)	94.4 (16)	121 (104, 141)
AUC_{inf} (mcg·h/ml)	85.4 (8) [b]	11.4 (12) [c]	--
SCH720881			
C_{max} (ng/ml)	86.7 (26)	85 (26)	98 (85,114)
T_{max} (h) [a]	168 (24, 336)	336 (168, 504)	--
AUC_{0-120} (mcg·h/ml)	7.4 (31)	2.8 (39)	38 (31, 46)
AUC_t (ng·h/ml)	35.6 (23)	30.4 (32)	84 (72, 98)

[a] median (range);[b] n=7; [c] n=8
100 mg of rolapitant HCl

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Figure 30 Mean rolapitant concentration-time profile following administration of 90 mg rolapitant alone or with ketoconazole

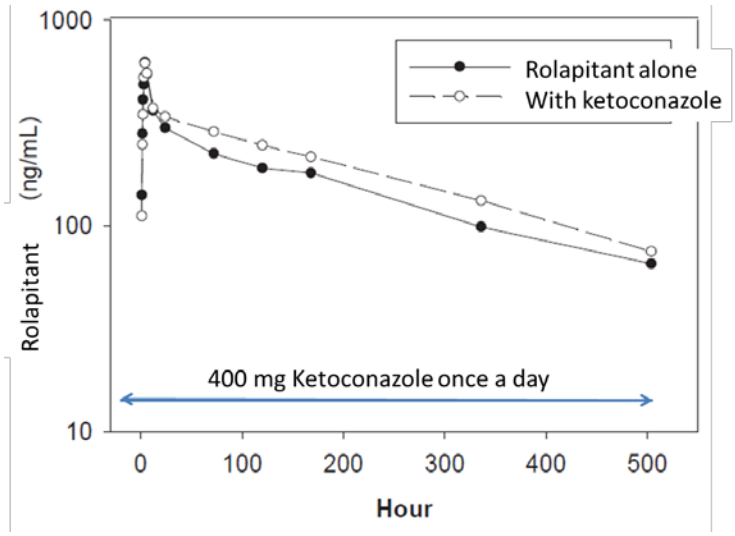
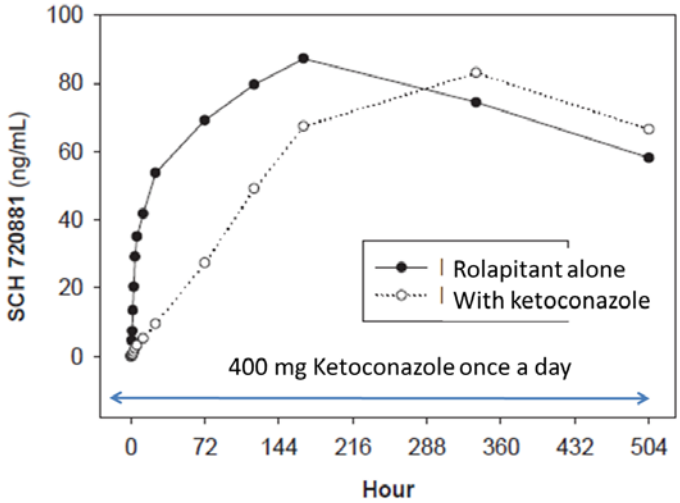


Figure 31 Mean SCH720881 Concentration-Time Profiles following Administration of 90 mg Rolapitant alone or with Ketoconazole



2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?

The clinical efficacy of anti-emetics for chemotherapy induced nausea and vomiting is based on the pharmacodynamic drug-drug interactions between rolapitant and chemotherapeutics. Rolapitant is being proposed to antagonize the off-target pharmacodynamic effects of chemotherapeutics that leads to emesis.

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2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation?

It appears that rolapitant belongs to BCS Class II with high permeability and low solubility. The absolute bioavailability was estimated to > 90% in humans. Solubility of rolapitant hydrochloride monohydrate in aqueous solution is pH-dependent (Table 46). Of note, the BCS classification for rolapitant was not formally assessed.

Table 46 Aqueous solubility of rolapitant by pH

pH	Solubility at Room Temperature (mg/mL)	Solubility at 37 °C (mg/mL)
2.0	0.44[a]	0.71[a]
4.0	0.81	0.83
6.0	0.030	0.028 (at pH = 5.9)
6.9	0.0072	0.012
7.4	0.006	0.10 t pH = 7.5)

[a] Reduced solubility due to common ion effect of hydrochloric acid used for pH adjustment

- Rolapitant dose (180 mg)/250 mg =0.72

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

Of note, in this section, the dosage strength is presented based on rolapitant HCl as originally described by the sponsor.

<u>BE study between the clinical formulation and the to-be-marketed formulation</u>

The Biopharmaceutics Reviewer concluded that a bioequivalence was demonstrated between two 90 mg to-be-marketed tablets and four 45 mg capsules used in clinical trials based on Study PR-10-5014-C.

Two bioequivalence studies i.e. PR-10-5013-C and PR-10-5014-C were conducted to compare the 50 mg capsules (equivalent to 45 mg rolapitant) used in phase 3 trials and the to-be-marketed 100 mg tablets (equivalent to 90 mg rolapitant). PK blood samples were collected up to 912 hours after single dose administration of rolapitant in both trials[18].

In Study PR-10-5014-C, a bioequivalence was demonstrated between two 100 mg tablets and four 50 mg capsules (Table 47). On the other hand, in Study PR-10-5013-C, which was conducted before PR-10-5014-C, a BE was not demonstrated for AUC as two 100 mg tablets resulted in (b)(4)% and (b)(4)% higher AUC_t and AUC_{inf}, respectively compared to four 50 mg capsules. (b) (4)

(b) (4)

[18] Blood samples for PK analysis were taken predose and at the following times postdose: 0.5,1, 1.5,2, 3,4,6,8,12,16,24,36,48,72,120,168, 240, 312, 384, 456, 504, 576, 672, 792 and 912 hours

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Reviewer's comments: While the design of two BE studies is comparable with PK sampling up to 912 hours in both studies, for Study PR-10-5014-C, the in-house stay (b) (4) to 38 days following the oral administration of the dose regimens, (b) (4) in PR-10-5013-C. See the Assessment of Biopharmaceutics Section in the Office of Product Quality Review for more details.

Table 47 Mean (%CV) PK Parameters for Rolapitant after Administration of the clinical formulation (treatment A) and the to-be-marketed formulation (treatment B) under Fasting Condition (Study 5014-C)

	Treatment A (n=42)	Treatment B (n=42)	Geometric Mean Ratio (B/A) [b] (90% CI)
	4 x 50 mg Capsules	2 x 100 mg Tablets	
C_{max} (ng/mL)	972 (24.5)	968 (27.5)	0.99 (0.89, 1.11)
T_{max} (h) [a]	3 (1.5,12)	4.0 (1.5, 12)	--
$t_{1/2}$ (h)	175 (41)	164 (35.3)	--
AUC_{0-120} (mcg*h/mL)	47.9 (21.9)	50.5 (22.5)	1.06 (0.97, 1.17)
AUC_t (mcg*h/mL)	120.1 (33)	122.8 (25.1)	1.06 (0.94, 1.19)
AUC_{inf} (mcg*h/mL)	126.6 (37.4)	127.5 (27.1)	1.05 (0.92, 1.19)

[a]: median (range)
[b]: *Source: Table 11 in CSR 5014-C*

Relative bioavailability between interim formulations

The formulation used in clinical trials was different from the to-be-marketed formulation. The to-be-marketed tablet contains 100 mg rolapitant HCl while the clinical formulation used in phase 3 trials were capsules containing 50 mg rolapitant HCl.

Phase 1, 2 and 3 clinical studies were conducted using immediate release 50 mg capsules. In (b) (4)

Reviewer's comment: In a relative bioavailability study, (b) (4) resulted in a lower bioavailability than when four 50 mg capsules were administered. The sponsor postulated that drug load might be an important determining factor for drug product bioavailability. The 100 mg tablets were developed to administer as two dosage units per dose (b) (4) The relative BA studies between 50 mg capsules and the interim formulations were not reviewed as the interim formulations were not used either in clinical pharmacology or clinical efficacy and safety trials.

2.5.2.1 What are the safety or efficacy issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

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There is no remarkable safety or efficacy issue despite an inconsistency observed between two BE studies. In Study PR-10-5014-C, a bioequivalence was demonstrated between two 100 mg tablets and four 50 mg capsules.

The deviation from BE criterion for AUC i.e. (b) (4) % higher AUCt in Study PR-10-5013-C is not expected to significantly affect the efficacy and safety of rolapitant especially because the Cmax and AUC_{0-120} was comparable when the efficacy of rolapitant is expected.

2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the dosage form?

Concomitant high fat meal did not significantly affect the bioavailability of rolapitant when rolapitant was administered as two 90 mg tablets within 5 min after finishing a high fat meal. Rolapitant can be taken without regard of food.

Table 48 Effects of a High Fat Meal* on PK of Rolapitant (Study PR-10-5013-C)

	Under fasting	Under fed condition*	Mean Ratio (fed/fasting) (90% CI)
Treatment	Geometric LS means		
Cmax (ng/ml)	(b) (4)		
Tmax[a] (h)			
AUC_{0-120} (mcg·h/ml)			
AUCt (mcg·h/ml)			
AUCi (mcg·h/ml)			
$T_{1/2}$ [b] (h)			

[a]Median (min, max)

[b] Arithmetic mean (%CV)

Figure 32 Mean (SD) Rolapitant Concentrations-Time Profiles after Administration of Rolapitant under Fed or Fasting Condition

(b) (4)

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2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Rolapitant and its major metabolite SCH 0720881 were measured in plasma using a validated liquid-chromatographic-tandem mass spectrometric method (LC/MS/MS). The bioanalytical assay method was validated in human plasma containing the anticoagulant K2-ethylenediaminetetraacetic acid (K2EDTA) using solid phase extraction in a 96-wellplate format. As the internal standard $^{13}C_3$ SCH 619734 (rolapitant) was used.

Throughout the development program, the bioanalytical assay methods had evolved and each time, it was adequately validated. The initially bioanalytical assay method was validated for rolapitant only but later validated for simultaneous analysis of rolapitant and SCH 0720881. Multiple bioanalytical assay methods were validated for different calibration range, plasma volume, changes in instrumentation and bioanalytical assay site throughout the development program.

For phase 3 trials and the pivotal BE study, a bioanalytical validation report, KB-0006-RB-BV-RPT-01 (and a subsequent partial validation report KB-0010-RB-BV-RPT-01) supported the bioanalytical assays.

Rolapitant after intravenous administration of ^{14}C-rolapitant in a microdosing study (Study P4328) was measured by accelerator mass spectrometry after protein precipitation, chromatographic separation by HPLC and analytes fraction collection.

2.6.2 Which metabolites have been selected for analysis and why?

A major active metabolite, SCH 720881 was measured in plasma.

2.6.3 What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)?

See Table 49.

2.6.4. Are the methods used to determine CYP2D6 genotype in study PR-10-5001-C acceptable?

Yes. Analyses were performed by (b) (4)

(b) (4)

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Table 49 Summary of bioanalytical assay method validation (KB-0010-RB-BV-RPT-01)

Validated Assay Summary		
Matrix and Anticoagulant	Human plasma (K_2EDTA)	
Sample Extraction Volume	25 µL	
Extraction Procedure	Solid phase (Oasis MCX 96-well plate 30µm, 10 mg)	
Analysis	APCI (positive-ion mode) Multiple-reaction-monitoring scan mode	
Regression, Weighting	Linear, $1/x^2$	
SCH 619734		
Standard Curve Range	2.00 to 2000 ng/mL	
Quality Control Concentrations	2.00 ng/mL (QC-LLOQ), 6.00 ng/mL (QC-Low), 80.0 ng/mL (QC-Mid-Int), 800 ng/mL (QC-Mid), 1600 ng/mL (QC-High), and 8000 ng/mL (QC-Dil)	
Accuracy and Precision	Accuracy (% Bias)	Precision (% CV)
Intra-Batch	-1.3 → 12.0	1.5 → 7.2
Inter-Batch	0.6 → 9.0	2.8 → 6.2
Dilution Linearity	8000 ng/mL (Dilution Factor = 5)	
Stability in Whole Blood	4 Hours at room temperature (Study No. KB-0006-RB-BV)[a]	
Short-Term Stability in Plasma	25 Hours at room temperature (Study No. KB-0006-RB-BV)[a]	
Freeze/Thaw Stability in Plasma	6 Cycles (Study No. KB-0006-RB-BV)[a]	
Reinjection Reproducibility	Maximum 5 days refrigerated	
Stock Solution Short-Term Stability	25 Hours at room temperature (Study No. KB-0006-RB-BV)[a]	
SCH 720881		
Standard Curve Range	1.00 to 1000 ng/mL	
Quality Control Concentrations	1.00 ng/mL (QC-LLOQ), 3.00 ng/mL (QC-Low), 40.0 ng/mL (QC-Mid-Int), 400 ng/mL (QC-Mid), 800 ng/mL (QC-High), and 4000 ng/mL (QC-Dil)	
Accuracy and Precision	Accuracy (% Bias)	Precision (% CV)
Intra-Batch	-4.4 → 14.0	1.3 → 7.3
Inter-Batch	-1.6 → 9.0	3.2 → 7.5
Dilution Linearity	4000 ng/mL (Dilution Factor = 5)	
Stability in Whole Blood	4 Hours at room temperature (Study No. KB-0006-RB-BV)[a]	
Short-Term Stability in Plasma	25 Hours at room temperature (Study No. KB-0006-RB-BV)[a]	
Freeze/Thaw Stability in Plasma	6 Cycles (Study No. KB-0006-RB-BV)[a]	
Reinjection Reproducibility	Maximum 5 days refrigerated	
Stock Solution Short-Term Stability	25 Hours at room temperature (Study No. KB-0006-RB-BV)[a]	

[a] Summary results obtained from the original validation study KB-0006-RB-BV.

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Table 50 CYP2D6 Alleles Detected by Assays used in study PR-10-5001-C

	Number of Subjects	CYP2D6 Alleles Detected
		(b) (4)

Although the method for phenotype classification based on CYP2D6 genotype was not provided by the applicant, different approaches may be used to determine CYP2D6 phenotype in clinical practice. In a clinical drug interaction study, there were 8 intermediate metabolizers, 17 extensive metabolizers and one ultra-metabolizer based on applicant-predicted phenotype results. When an alternative classification method was applied (phenotypes determined using the Clinical Pharmacogenetics Implementation Consortium [CPIC] guidelines for activity score [PharmGKB]) 6 intermediate metabolizers were reclassified as extensive metabolizers, leaving only 2 intermediate metabolizers. Overall, the inhibitory potency of rolapitant by CYP2D6 phenotype could not be drawn due to the limited available data and large variability of dextromethorphan PK parameters.

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3 Major Labeling Recommendations

- Inclusion of a language about the duration of CYP2D6 inhibition in Section 5
- Inclusion of examples for concomitant substrates for CYP2D6 and BCRP
- Recommend "Use of TRADENAME is not recommended in patients who are on strong CYP3A4 inducers"

- Detailed labeling recommendations including formatting will be conveyed during the labeling negotiation

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4 Appendices

4.1 Pharmacometrics Review

Submission	**NDA206500**
Submission Date	**September 05, 2014**
Generic Name	**Rolapitant Hydrochloride**
Primary Reviewers	**Jee Eun Lee, Ph.D.**
Secondary Reviewers	**Nitin Mehrotra, Ph.D.**
OCPB Division	**DPM**
ORM division	**OND/ ODE3/DGIEP**
Applicant	**Tesaro, Inc**
Formulation; Strength(s)	**Immediate release tablets; 100 mg**
Proposed Indication	**Prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat course of emetogenic cancer chemotherapy**
Proposed Dosing Regimen	**180 mg orally on Day 1, 1-2 hours prior to chemotherapy as part of a regimen to prevent nausea and vomiting induced by emetogenic chemotherapy that includes a corticosteroid and a 5-HT3 receptor antagonist**

1 KEY REVIEW QUESTIONS

1.1 Is the proposed a dose of 180 mg on Day 1, 1-2 hours prior to chemotherapy as part of a regimen to prevent nausea and vomiting induced by emetogenic chemotherapy appropriate?

Yes. A Phase 2 dose-finding study (Study P04351), 180 mg showed significantly greater complete response rates overall and in the acute and delayed phases than the placebo group. The overall complete response rate was (b) (4)% compared with (b) (4)% for placebo (odds ratio = (b) (4) (b) (4) For Acute Phase, the response was (b) (4)% vs. (b) (4)% (b) (4) for Delayed Phase, the response rate was 63.6% vs. 48.9% (IR = 1.86; p=0.045).). Complete response rates for the other dose groups did not achieve statistical significance when compared with placebo (Table 1).

Table 1. Summary of Complete Response Overall and in the Acute and Delayed Phases: Cycle 1

Time interval	Placebo (N=90)	Rolapitant			
		10 mg (N=91)*	25 mg (N=88)**	100 mg (N=91)	200 mg (N=88)**
0-24 hr	(b) (4)				
24-120 hr	48.9%	50.5%	54.5%	58.2%	63.6%
0-120 hr	(b) (4)				

*N=90 for Acute Phase, **N=89 for Acute Phase

(Source: Sponsor's report, p04351 Table 8, page 73)

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The superiority of 180 mg is also supported by other secondary endpoints including time to first emesis or to rescue medication use. As shown in Figure 1, time to first emesis or to rescue medication use was significantly longer during Cycle 1 for patients with 180 mg compared to other dose groups.

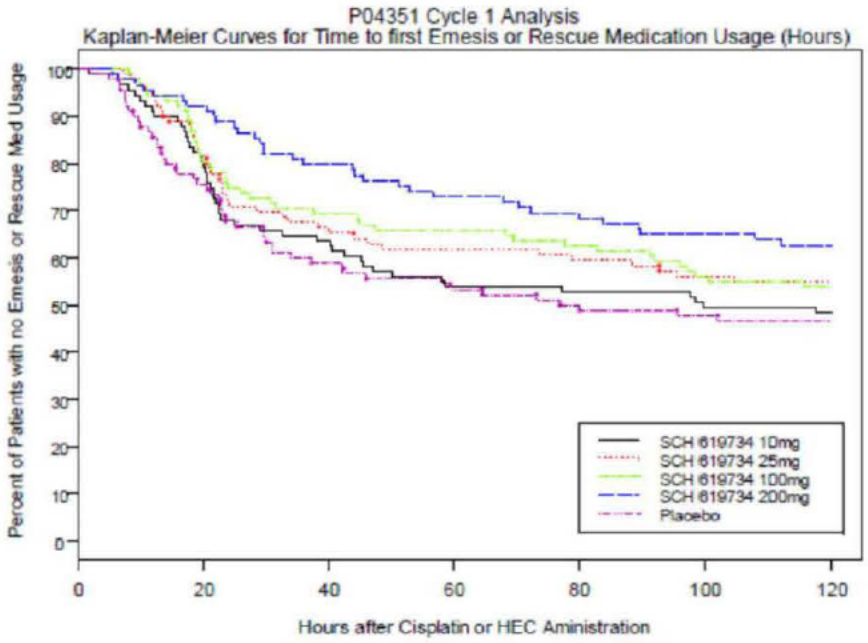

Figure 1. Kaplan-Meier curves for Time to first emesis or to rescue medication use in Cycle 1 (Sponsor's report p04351, Figure 3, page 78)

The sponsor also conducted a receptor occupancy study using PET (positron emission tomograrhy) as an exploratory analysis to support the 180 mg dose (See Clinical Pharmacology Review).

Therefore, 180 mg dose was chosen to be evaluated in the Phase 3 trials. In studies with patients receiving HEC (Study P04832) and with patients receiving MEC (Study P04834), the efficacy of a single dose of rolapitant 180 mg compared to placebo was observed. Patients who received rolapitant 180 mg showed a significantly higher response compared to placebo in both Acute Phase and Delayed Phase in Study P04832. From Study P04834, patients received rolapitant 180 mg showed a significantly higher complete response rate in the delayed phase of CIV compared to control group (71.3% vs. 61.6%; $p<0.001$). Similar safety profiles were observed between placebo and rolapitant were observed in the clinical trials with 180 mg dose and no evidence for cumulative toxicity over multiple cycles for TEAEs was observed. Therefore, the proposed dose of 180 mg appears to be acceptable.

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1.2 Should the dose be adjusted for patients with mild or moderate renal impairment?

No, there is no need for dose adjustment in patients with mild or moderate renal impairment.. Based on the population pharmacokinetic analysis, the effect of renal impairment on rolapitant pharmacokinetics was not significant. The number of patients included in the pooled dataset for each category were; normal kidney function 252, mild renal impairment 187, moderate renal impairment 39. There was only one patient whose creatinine clearance was below 30 mL/min (26.9 mL/min), therefore no clear conclusion about the effect of severe renal impairment on rolapitant PK can be made. There is no dedication PK study to evaluate the effect of renal function on rolapitant PK, however, considering low fraction of renal excretion (~14%), the conclusion appears to be reasonable. Furthermore, the reviewer's confirmatory analysis (Figure 2) also supports that the effect of mild or moderate renal impairment on rolapitant PK is not evident.

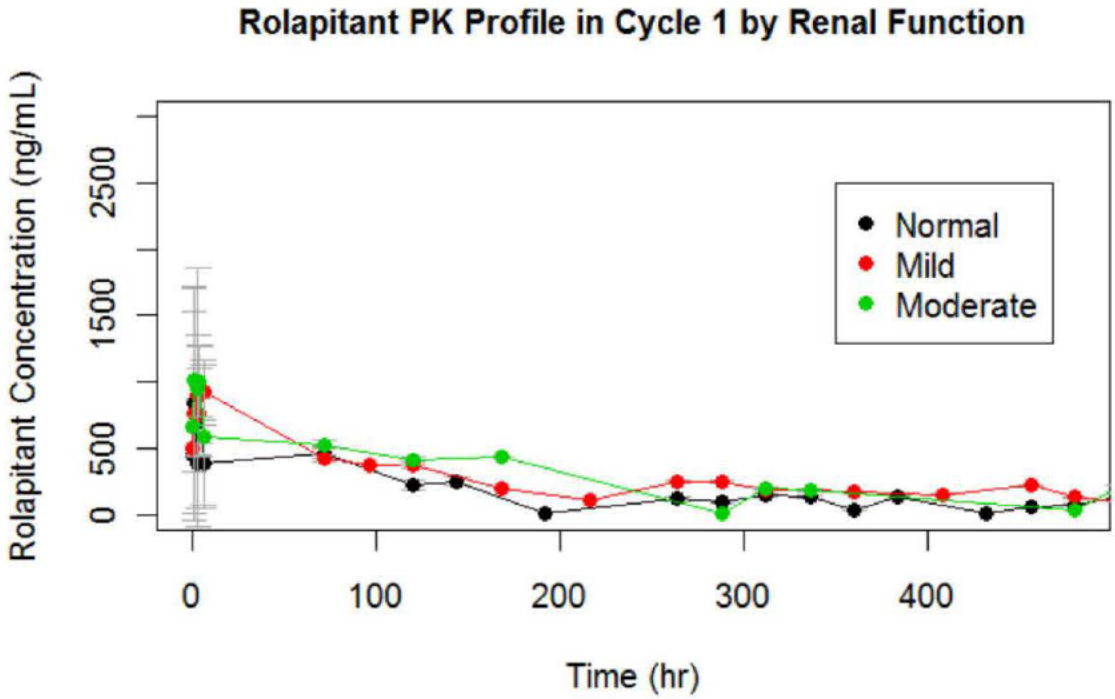

Figure 2. Rolapitant concentration versus time profile following 180180 mg during Cycle 1 by kidney function: Normal kidney function (N=109), Mild impairment (N=78), Moderate impairment (N=19). ***(Reviewer's analysis).***

1.3 Label Statements

Detailed labeling recommendation is following:

Reference ID: 3748397

Creatinine clearance at baseline did not [redacted] (b) (4) effect on rolapitant pharmacokinetics in [redacted] (b) (4) [redacted] (b) (4)

2 PERTINENT REGULATORY BACKGROUND

Rolapitant is indicated for the prevention of [redacted] (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy in combination with other antiemtic agents.

There are two described phases of chemotherapy induced nausea and vomiting (CINV), acute and delayed, mediated by neurotransmitter-driven mechanisms, primarily serotonin (5-HT) and neurokinin-1 (NK-1). Neutokinin (NK) receptors are believed to affect a variety of behavioral responses including emesis. Selective antagonists for NK1 receptors are expected to have inhibitory effect on emesis induced bychemotherapy.

The acute phase of CINV, which represent the first 24 hours following chemotherapy, is mediated in part by chemotherapy-induced incases in serotonin release and activation of 5-HT3 receptors on vagal afferent neurons in the gut. 5-HT3 receptor antagonists such as granisetron and ondansetron are clinically effective in reducing the incidence of CINV in the acute phase, particularly when given in combination with a corticosteroid such as dexamethasone. In addition to serotonin, other neurotransmitters are implicated in the etiology of acute CINV, as indicated by a further reduction in the incidence of nausea and vomiting when NK1 receptor antagonists are added to a standard antiemetic regimen that includes a 5-HT3 receptor antagonist.

The etiology of the delayed phase of CINV, which occurs 2 to 5 days following the initiation of chemotherapy, involves the release of the neurokinin peptide substance P in the brain. Antiemetic therapy with a corticosteroid and 5-HT3 receptor antagonist alone is minimally effective during the delayed phase of CINV. The combination of NK1 and 5-HT3 receptor antagonists, together with a corticosteroid, provides the greatest preventative effect from CINV. This combination of three drugs have showed efficacy for prevention of CINV following administration of chemotherapy, except for those who cannot tolerate dexamethasone. For these patients, an NK1 receptor antagonist could be an alternative option. Currently the only approved NK1 receptor antagonist is aprepitant which has shorter half-life (9-12 hours) than rolapitant.

3 RESULTS OF SPONSOR'S ANALYSIS

3.1.1 Introduction

The sponsor conducted a population PK analysis to characterize the PK of rolapitant and evaluate various covariates to explain inter-patient variability in exposure, such as body weight, body surface area, age, gender, race, baseline neutrophil count and measures for baseline

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hepatic/renal function. Chemotherapeutic regimen and Karnofsky performance status were also included in the covariate analysis and whether the patients was taking rescue medication or concomitant medication such as CYP3A4 inhibitors/substrates was considered as well.

3.1.2 Datasets

The population PK analysis was based on pooled data consisted of 8858 concentration measurement from 482 adult subjects from two Phase 3 studies (P04832 and P04833) and Study P04351.

3.1.3 Results

A two-compartment model for both parent and metabolite with first order absorption was chosen as the base model although inter-individual variability for the first order absorption rate constant (ka) was quite large (179%). The sponsor indicated various models for atypical absorption were attempted but unsuccessful to find a better alternative model fitting absorption phase of the data.

Covariates were evaluated during model development and they included but not limited to age, gender, body weight, body surface area, AST, ALT, total bilirubin, serum albumin, serum creatinine clearance and HEC/MEC and concomitant medication (CYP3A4 inhibitors). Nonetheless, body weight was the only covariate which had a significant effect on volume of distribution for peripheral compartments for parent and metabolite, but not on clearance either for parent or metabolite

Therefore, body weight was included in the final model and Table 2 summarizes the final pharmacokinetic parameter estimates for rolapitant and SCH720881.

Table 2. Population PK Parameters for Rolapitant and SCH720881

Parameter	Estimate	%RSE	95% CI
Ka (1/hr)	1.99	5.58	1.77 – 2.21
IIV	2.80	13.6	2.05 – 3.55
$CL_{,rolapitant}$ (L/hr)	0.962	4.95	0.869 -1.06
IIV	0.247	7.29	0.212 – 0.282
$CL_{,SCH720881}$(L/hr)	1.83	3.79	1.69 -1.97
IIV	0.141	10.9	0.111 -0.171
V2 (L)	214	2.07	205 - 223

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IIV	0.067	7.33	0.0574 - 0.0766
V4 (L)	164	5.11	148 - 180
IIV	0.252	16.3	0.172 – 0.332
Q (L/hr)	2.79	12.0	2.3 – 3.45
WT on V2	0.830	10.9	0.653 – 1.01
WT on V4	2.08	12.0	1.59 – 2.57
Residual (σ)	0.0826	1.01	0.0810 – 0.0842

(Source: Sponsor's population PK Study report, Table 10-6, page 34)

The sponsor conducted further analysis with predicted AUC using population PK model and compared AUC in patients with response and AUC in patients without response for the primary endpoint and secondary endpoints. The boxplots for the complete response during acute phase is shown in Figure 3

(b) (4)

Figure 3. Boxplot of complete response at 24 hours versus rolapitant AUC (ng*hr/mL) from pooled data (*Source: Sponsor's Population PK report, Figure 11-15, page 197*)

Reviewer's comments: The sponsor's final model appears to adequately explain the observed data. The effect of renal impairment was not observed from dataset included in the analysis.

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

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(b) (4)

The sponsor conducted additional analysis that only compared AUC in patients with and without response, which has little value of interpretation for dose justification or any covariate effects.

4 REVIEWER'S ANALYSIS

4.1 Introduction

The sponsor's population PK analysis did not identify the effect of renal function on rolapitant PK and thus no dose adjustment was proposed for patients with renal impairment. The reviewer performed independent analysis to confirm sponsor findings.

4.1.1 Datasets

Pooled dataset from 482 adult subjects from two Phase 3 studies (P04832 and P04833) and Study P04351was utilized.

4.1.2 Software

Graphical, statistical analysis were performed with R (version 2.13.1)

4.2 Results

As shown in Figure 2, there appears no evidence for the effect of mild or moderate renal impairment on rolapitant PK.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
NDA206500_ER.R	Exposure-response analysis with pooled data	Reviews\Ongoing PM Reviews\Rolapitant_NDA206500_JEL\ER_ Analyses

Reference ID: 3748397

4.2 OCP Filing Form

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	206-500	**Brand Name**	TBD
OCP Division (I, II, III, IV, V)	III	**Generic Name**	Rolapitant
Medical Division	DGIEP	**Drug Class**	NK1-receptor antagonist
DCP Reviewer	Insook Kim, Ph.D.	**Indication(s)**	for the prevention of (b) (4) delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy
DCP Team Leader	Sue-Chih Lee, Ph.D.		
Pharmacometrics Reviewer	Jee-Eun Lee, Ph.D.		
Pharmacometrics Team Leader	Nitin Mehrotra, Ph.D.	**Dosage Form**	90 mg tablet
Pharmacogenomics Reviewer	Sarah Dorff, Ph.D.	**Dosing Regimen**	180 mg prior to the start of chemotherapy
Pharmacogenomics Team Leader	Christian Grimstein, Ph.D.	**Route of Administration**	Oral
Date of Submission	9/5/14	**Sponsor**	Tesaro Inc.
Estimated Due Date of OCP Review	5/5/15	**Priority Classification**	Standard
PDUFA Due Date	9/4/15		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	6	6	**DM27188** (rolapitant alone) **DM27298** (rolapitant +metabolite in 96-well plate) **DM27530** (rolapitant +metabolite) **XBL11063** (rolapitant +metabolite) **BAC-KB-L002** (rolapitant in K2EDTA plasma) **BAC-KB-L003** (metabolite in K2EDTA plasma)
I. Clinical Pharmacology				
Mass balance:	x	1	1	**P04328**
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:	x	2	2	**DM27248** **Xbl12709**
Pharmacokinetics (e.g., Phase I) -	x	1		
Healthy Volunteers-				
single dose:	x	1	1	P03670
multiple dose:	x			P03670
Patients-				
single dose:	x	1		**P04351**

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:	x			P03670
fasting / non-fasting multiple dose:	x			P03670
Drug-drug interaction studies -				
In-vivo effects on primary drug:	x	2	2	**PR-10-5003:** rifampin **P04854:** Ketoconazole
In-vivo effects of primary drug:	x	4	4	**P05325:** Digoxin **PR-10-5003:** Midazolam **P04854:** Ondansetron, Dexamethasone **PR-10-5001:** Dextromethorphan, Tolbutamide, Omeprazole, Efavirenz, Repaglinide, Sulfasalzine
In-vitro:	x	15	15	**12tesa1** **12tesap2r1** **Dm27248** **Dm27353** **Dm27365** **Dm27251** **Dm27366** **Dm27427** **Dm27495** **KB-0046-DV-BA** **KB-0046-DV-DA** **KB-0046-DV-EB** **KB-0046-DV-PB** **SN04917** **Xt113090**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	x			**Population PK**
hepatic impairment:	x	1	1	**PR-10-5004**
PD -				
Phase 2:	x	1	1	**P04078 PET**
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:	x	1	1	**P04852 Thorough QT study**
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	x	1		Combined datasets from two phase 3 trials data from phase 2 trial was used to develop the model
II. Biopharmaceutics				
Absolute bioavailability	x			**P04328**
Relative bioavailability -				
solution as reference:	x			**P04328**
alternate formulation as reference:	x	2	0	**PR-10-5000-C** **PR-10-5007-C**
Bioequivalence studies -				
traditional design; single / multi dose:	x	2	2	**PR-10-5013-C** **PR-10-5014-C:** **pivotal 2x 100 mg tablets vs. 4 x 50 mg capsules**
replicate design; single / multi dose:				
Food-drug interaction studies				**PR-10-5013-C**
Bio-waiver request based on BCS				
BCS class				

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Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	x			
Literature References				
Total Number of Studies		39	36	

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements

No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	x			
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	x			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	x			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			x	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	x			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	x			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	x			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			See comment below
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	x			

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

Reference ID: 3748397

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?				
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		x		CYP2D6 genotype result is submitted without raw data for DDI study
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	x			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another language needed and provided in this submission?	x			

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
__Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

Reference ID: 3748397

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Review issue:
It appears that the significant inhibitory effect of rolapitant on CYP2D6 activity in CYP2D6 extensive metabolizers is observed 7 days after single dose administration of rolapitant. Provide any available information on how long the inhibitory effect is estimated to last.

Non-filing comments:

1) Please provide hyperlinks to individual study reports which support the clinical pharmacology related labeling sections i.e. Sections 7, 8, and 12 in the annotated labeling.

2) The location of Study report PR-10-5000-C and XBL11064-RPT02279 are switched in Section 5.3.1.2.

3) Please provide the method by which the genotype for CYP2D6 was determined in Study PR-10-5001-C.

4) Please conduct a safety analysis by renal impairment in phase 2 and 3 trials.

5) Submit all model codes or control streams for all major model building steps, e.g., base structural model (Model 006xl), covariates models, final model (Model 200o), and validation model (posterior predictive check). These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

   If you already submitted these files, locate the exact folder in the submission.

   Following comment was communicated to the sponsor and the sponsor provided a summary of in-vitro studies using human biomaterials in Section 5.3.2. with hyperlinks to the study reports in sequence No 2. The sponsor also clarified that DM27583, a pilot protein binding study report was erroneously submitted and deleted from the submission.

   - We note that the in vitro studies pertinent to pharmacokinetics using human biomaterials are submitted in Section 4 Nonclinical study reports except for one study. Please provide a separate summary table for in-vitro studies using human biomaterials in Section 5.3.2. with hyperlinks to the reports in Section 5.3.2.

Insook Kim, Ph.D.	10/29/14
Reviewing Clinical Pharmacologist	Date
Sue-Chih Lee, Ph.D.	10/29/14
Team Leader	Date

File name: 5_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement updated 082114

Reference ID: 3748397

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

INSOOK KIM
05/05/2015

JEE E LEE
05/05/2015

SARAH E DORFF
05/05/2015

MICHAEL A PACANOWSKI on behalf of CHRISTIAN GRIMSTEIN
05/05/2015

NITIN MEHROTRA
05/05/2015

SUE CHIH H LEE
05/05/2015

EDWARD D BASHAW
05/05/2015