CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208399Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA 208399 (SDN42)	VARUBI (Brand name) Rolapitant (Generic name)
Submission Date	4/25/2017
OCP Review Team	Elizabeth Y. Shang, Ph.D., R.Ph, Insook Kim, Ph.D.
OCP Final Signatory	Hae Young Ahn, Ph.D.
OCP Division	DCP3
OND division	DGIEP
Sponsor	Tesaro, Inc
Submission Type	Resubmission (Class 2)
Review Priority	Standard
Formulation; Strength(s)	Nano-emulsion/166.5 mg/92.5 mL (1.8 mg/mL, (b) (4) for Intravenous Infusion

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) has reviewed this NDA and found the application acceptable from an OCP standpoint. Labeling comments need to be conveyed to the sponsor.

In the original NDA submission, the sponsor proposed two manufacturing sites for commercial batch production. One site in (b) (4) hat made the injectable emulsion batches used in the clinical studies including the pivotal BA/BE study has failed to pass the process inspection. As for the alternative site in (b) (4) there was no in vivo bridging study conducted to support the manufacturing site change. In addition, the

comparative in vitro release test included in the original NDA was inadequate and could not be used to bridge the formulation used in the pivotal BA/BE study and the formulation manufactured in the alternative site (b) (4)

The clinical pharmacology related deficiencies identified in the Complete Response Letter are shown below.

> "You have not provided an adequate bridge between the to-be-marketed formulation manufactured at your alternative manufacturing facility (i.e., Hameln Pharmaceuticals GmbH) and the formulation utilized in your clinical trial submitted to support your application, which was manufactured at a different site (i.e., (b) (4) .
>
> You have not demonstrated the comparability between the products manufactured from the two sites (i.e., (b) (4) and (b) (4)) with adequate in vitro dissolution methods and comparable physicochemical properties.
>
> If you are not able to demonstrate the comparability with in vitro release data (see comments provided above under "Product Quality"), you need to conduct an in vivo BE study to support the alternative manufacturing facility."

In this resubmission, the data from in vitro release tests were deemed to be acceptable and can be used for a biowaiver to support the manufacturing site change. Refer to the Biopharmaceutics Review. Therefore, a biowaiver request for an in vivo BA/BE was granted and the formulations manufactured at different sites were adequately bridged.

1.2 Phase IV Commitments

1.2.1 Post-Marketing Requirement

Recommended study: In vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 28 days after single dose administration of Varubi (rolapitant) intravenously. The duration of the study should be long enough to demonstrate when the CYP2D6 inhibition is resolved.

> Rationale: Previous in vivo drug interaction study with a sensitive substrate of CYP2D6 (dextromethorphan) showed 2-fold increase in systemic exposure (AUC) to dextromethorphan 4 weeks after a single dose of rolapitant IV. Thus, we recommend contraindicating CYP2D6 substrates with narrow therapeutic indices as concomitant medications. The observed duration of inhibitory effects on CYP2D6 after a single dose of rolapitant is unexpected and the information is lacking to guide when a CYP2D6 substrate with a narrow therapeutic index may be introduced to patients after the completion of entire course chemotherapy with rolapitant administration. Therefore the study is needed to determine when the

patients can be prescribed a new medication that is a CYP2D6 substrate after finishing their chemotherapy.

1.2.2 Post-Marketing Commitments

Recommended study 1: In vitro studies to evaluate the inhibitory potential of Varubi (rolapitant) on MATE1 and OATP1B1 transporters and the IC_{50} values for each transporter

Rationale: The in vivo drug-drug interaction cannot be ruled out following IV administration of rolaptiant because IC_{50} was not determined in the in vitro studies for OATP1B1 and MATE1.

1.3 Current Submission

1.3.1 Relevant Regulatory History

Tesaro submitted NDA 208399 for rolapitant IV originally on March 11, 2016 (SDN1). The resubmission (SDN 42) occurred on April 25, 2017 in response to the Complete Response (CR) Letter of January 11, 2017 for the original NDA.

There is no new clinical pharmacology data in the resubmission. The clinical pharmacology data supporting the changes in Varubi labeling were submitted in the original NDA submission (SDN1) for the IV formulation and from results of two PMC studies issued under NDA 206500 for oral Varubi. All these clinical pharmacology data were reviewed by the Agency[1] and communicated to the sponsor in the Complete Response Letter and Fulfilment of Postmarketing Commitment Letter issued under NDA206500 on June 30, 2017. This review captures the proposed labeling changes for rolaptiant as the product label is for both oral and IV formulations. Labeling revisions are ongoing. Please refer to the final approved labeling when available.

1.3.2 Labeling Review

1.3.2.1 Recommendation for labeling changes related to CYP2D6 inhibition

Update DDI information related to CYP2D6 inhibition is applicable to both oral and IV formulations (Sections 4, 5, 7, and 12.3).

An in vivo drug interaction study showed that the duration of CYP2D6 inhibition following single dose of rolapitant IV was at least four weeks (28 days) with the peak inhibition (3-fold increase in AUC of dextromethorphan) occurring on Day 7 and Day 14 after rolapitant administration. By Day 28 following rolapitant administration, the degree of CYP2D6 inhibition is similar to that on Day 1 (a 2-fold increase in dextromethorphan).

[1] Clinical pharmacology review of NDA 208399 dated December 7, 2016

For details, refer to Clinical Pharmacology Review of original NDA 208399 for rolapitant IV filed in DARRTS on December 7, 2016.

In the in vitro studies, rolapitant inhibited CYP2D6 by competitive inhibition and no time-dependent inhibition was observed. However, the Tmax of rolapitant IV is 30 minute (end of infusion). Thus, the time course of CYP2D6 inhibition, i.e., peak inhibition occurring on Day 7 and Day 14 after dosing does not appear to be due to competitive inhibition by rolapitant. The inhibition of CYP2D6 on Day 21 and Day 28 does not appear to be due to rolapitant either. It is unknown if there are any other mechanisms that may have contributed to the inhibition of CYP2D6.

The prolonged inhibition does not appear to be caused by the active metabolite as the IC_{50} of CYP2D6 inhibition by SCH 720881 (M19) is > 10 µM. The ratio of Cmax/Ki is 0.06 assuming the IC_{50} is 10 uM with Ki of 5 uM ($Ki=IC_{50}/2$).

There were 11 other metabolites found in a mass balance study that were not detectable in plasma but detected in urine or feces. Refer to the Clinical Pharmacology Review of the original NDA 206500 for oral rolapitant. Because these metabolites were not detectable in the plasma, it is difficult to determine whether any of these metabolites contributed to the in vivo CYP2D6 inhibition.

As such the Office of Clinical Pharmacology recommends following changes to the label regarding DDI with CYP2D6 substrates. Rolapitant is currently allowed to be given repeatedly at an interval no less than every two weeks. This repeated dosing may result in additive inhibitory effect on CYP2D6 with an even longer period of inhibition. Thus, CYP2D6 substrates with a narrow therapeutic index should be contraindicated during the entire course including multiple cycles of chemotherapy and at least 28 days from the last dose of rolapitant. Before starting treatment with rolaptiant, the prescribers should consider whether patients require treatment with CYP2D6 substrates with a narrow therapeutic index. If patients require these medications, use an alternative antiemetic to rolaptiant. Otherwise, the prescriber should select medications that are not metabolized by CYP2D6.

Similarly, CYP2D6 substrates other than those with a narrow therapeutic index should be avoided when rolapitant is used. The prescribers should consult the prescribing information of CYP2D6 substrates to obtain further information about interactions with CYP2D6 inhibitors.

1.3.2.2 Recommendation for the other changes in the proposed label

The proposed clinical pharmacology related section of the labeling changes other than CYP2D6 inhibition are listed below:

1. Add new data obtained from IV formulation including ADME and DDI studies other than CYP2D6 inhibition using IV formulation (Sections 7 and 12.3). DDI study results included in the label are: warfarin, sulfasalazine (a BCRP substrate), digoxin (a P-gp substrate), caffeine (a CYP1A2 substrate), omeprazole (a CYP2C19 substrate)

   Rationale for adding warfarin to Section 7
   The sponsor conducted a study to evaluate the effect of IV rolapitant on warfarin and found that no clinical significant changes in systemic exposures to S-warfarin (Clinical Pharmacology Review of IV rolapitant, NDA208399). However, the change of INR was not measured. Since warfarin is a narrow therapeutic index drug, the prescribers should monitoring INR changes when using rolapitant concomitantly with warfarin.

2. Add drug interaction potential between IV or oral rolaptiant and renal and hepatic transporters (Section 12.3). This is based on the study results from the two PMC studies.

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/s/

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09/22/2017

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Office of Clinical Pharmacology Review

NDA or BLA Number	208399
Link to EDR	\\CDSESUB1\evsprod\NDA208399\208399.enx
Submission Date	3/11/2016
Submission Type	Original Submission
Brand Name	Varubi® Injectable emulsion
Generic Name	Rolapitant
Dosage Form and Strength	Nano-emulsion/166.5 mg/92.5 mL (1.8 mg/mL, (b) (4))
Route of Administration	Intravenous Infusion
Proposed Indication	In combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeated courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.
Applicant	Tesaro Inc.
Associated IND	117307
OCP Review Team	Elizabeth Shang, Ph.D., R.Ph., Insook Kim, Ph.D.
OCP Final Signatory	Hae Young Ahn, Ph.D.

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1. EXECUTIVE SUMMARY

Rolapitant is a substance P/neurokinin 1 (NK1) receptor antagonist indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy (CINV). The oral tablet has been approved since 2015. In this original submission, the sponsor proposes a new emulsion formulation with globule size in the nanometer scale for intravenous infusion.

The sponsor relied on the efficacy and safety findings of their own approved oral rolapitant for CINV. The sponsor conducted a relative bioavailability (BA) study to establish a bridge between the proposed emulsion formulation and the approved oral tablet for efficacy. This study showed that the systemic exposures ($AUC_{0\text{-}inf}$ and $AUC_{0\text{-}120h}$) to rolapitant and its major active metabolite were comparable. The Cmax from rolapitant IV administration was 1.9-fold that of oral rolapitant. The sponsor conducted an additional phase 1 study in healthy subjects using doses higher than the proposed therapeutic dose to support the safety of high peak plasma concentrations following intravenous administration.

The sponsor proposed two manufacturing sites for commercial batch production. One site in (b) (4) that made the injectable emulsion batches used in the clinical studies including the pivotal BA/BE study in this NDA failed to meet the process inspection. Refer to Manufacturing Facility Reviewer's final report. As for the alternative site in (b) (4) there is no bridging study conducted to support the manufacturing site change. According to the biopharmaceutics review, the comparative in vitro release test is inadequate by the FDA's standard and cannot be used for a biowaiver for in vivo BA/BE study to support the manufacturing site change.

1.1 Recommendations

The Division of Clinical Pharmacology 3 has reviewed this application and found this NDA **not** acceptable from a clinical pharmacology perspective. The proposed IV nano-emulsion has a complex dosage form. Because of the change in manufacturing site, the sponsor needs to demonstrate that the IV batches made at the new site (b) (4) are comparable to those manufactured at the (b) (4) site with comparable physicochemical characteristics and in vitro dissolution profiles. If the sponsor is unable to demonstrate the comparability between the products manufactured from the two sites with in vitro release data, then a new BE study is needed to support the site change.

The key review issues with specific recommendations/comments are summarized below:

Review Issues	Recommendations and Comments
Bridge between the "to-be-marketed" (TBM) and clinical trial formulations	Lack of a bridge between TBM formulation manufactured at a new proposed site and the clinical trial formulation manufactured at a different site failed the process inspection. We recommend that the applicant demonstrates the comparability between the products manufactured from the two sites with adequate *in vitro* dissolution methods and comparable physicochemical properties. If the applicant is not able to demonstrate the comparability with *in vitro* release data, we recommend the sponsor conduct an *in vivo* BE study to support a new site.
Concomitant use of CYP2D6 substrates with single dose or repeated dose of rolapitant IV	Labeling language needs to be updated when the product is deemed to be approvable.

1.2 Post-Marketing Requirements and Commitments

Not applicable at this review cycle.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Rolapitant is a substance P/neurokinin 1 (NK1) receptor antagonist indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Chemotherapeutic agents exert their emetic stimulus via processes that involve the release of serotonin and substance P and subsequent activation of the 5-HT3 and NK1 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 clinical pharmacokinetics data are summarized below. However, the readers should keep in mind that these data were generated from the IV batches manufactured at a site which failed to meet the process review. Refer to Section 1 – Executive Summary. In addition, the proposed IV formulation is a nano-emulsion. The measured plasma concentrations represent total concentrations of rolapitant, i.e., sum of free (unbound), protein-bound, and rolapitant (b) (4) . Refer to the discussion in Section 3.3.1 later in the review.

Following a single intravenous dose administration of 185 mg rolapitant injectable emulsion to healthy subjects, the Cmax of rolapitant was reached at the end of infusion (i.e., 30 min) and mean Cmax was 1986 ng/mL (%CV:39%). The mean terminal half-life following single intravenous dose of 185 mg of rolapitant is 161 hours.

A relative BA study between the proposed injectable emulsion and approved oral rolapitant tablet showed that the systemic exposures ($AUC_{0\text{-}inf}$ and $AUC_{0\text{-}120h}$) to rolapitant and its major active metabolite met the bioequivalence criteria. The Cmax from rolapitant IV administration was 1.9-fold that of oral rolapitant. The Cmax for the major active metabolite after administration of rolapitant tablet and the proposed emulsion met the bioequivalence criteria.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen with rolapitant IV is shown below. The proposed dose is presented as rolapitant (b) (4) The dose of 166.5 mg rolapitant as (b) (4) equivalent to 185 mg rolapitant hydrochloride.

	Day 1	Day 2	Day 3	Day 4
Prevention of Nausea and Vomiting Associated with Cisplatin-Based Highly Emetogenic Cancer Chemotherapy				
VARUBI	166.5 mg infused over 30 minutes; within 2 hours prior to initiation of chemotherapy	None		
Dexamethasone	20 mg; 30 min prior to initiation of chemotherapy	8 mg twice daily	8 mg twice daily	8 mg twice daily
$5\text{-}HT_3$ receptor antagonist	See the prescribing information for the co-administered $5\text{-}HT_3$ receptor antagonist for appropriate dosing information.	None		
Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Cancer Chemotherapy and Combinations of Anthracycline and Cyclophosphamide				
VARUBI	166.5 mg infused over 30 minutes; within 2 hours prior to initiation of chemotherapy	None		
Dexamethasone	20 mg; 30 min prior to initiation of chemotherapy	None		
5-HT3 receptor antagonist	See the prescribing information for the co-administered 5-HT3 receptor antagonist for appropriate dosing information.	See the prescribing information for the co-administered 5-HT3 receptor antagonist for appropriate dosing information.		

Source Data: Sponsor's proposed product label

Hereafter, the rolapitant dose refers to the (b) (4) form unless otherwise specified since that was the designation used by the sponsor during their drug development.

2.2.2 Therapeutic individualization

Not applicable.

2.3 Outstanding Issues

The main issue related to this NDA is that the manufacturing site (b) (4) (b) (4) in (b) (4)) producing the IV batches for the clinical studies including the pivotal BA/BE study failed to meet the process inspection. Refer to Manufacturing Facility Reviewer's final report. The bridge between the proposed alternative manufacturing site ((b) (4) (b) (4)) and the (b) (4) site has not been established with in vitro release data in this NDA. Without an adequate bridge with in vitro release data, a waiver for in vivo relative BA/BE study cannot be granted for the manufacturing site change from (b) (4) (b) (4) site) to the proposed (b) (4) (b) (4) (b) (4) site. Therefore, unless the sponsor is able to provide adequate in vitro release data demonstrating that the IV batches made by (b) (4) (b) (4) are comparable to those made by (b) (4) the sponsor needs to conduct a BA/BE study to bridge the IV product manufactured at the (b) (4) site to those that had been manufactured at the [redacted] site. A parallel design would suffice due to the long terminal half-life of rolapitant.

2.4 Summary of Labeling Recommendations

Review of label for rolapitant IV product is on hold because of the deficiency found in this NDA.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Proposed product

Rolapitant injectable emulsion for IV infusion is supplied as a translucent white homogeneous emulsion. The emulsion globules have a mean diameter of (b) (4) nm. Each sterile vial for intravenous use contains 166.5 mg rolapitant (b) (4) and the following inactive ingredients: polyoxyl 15 hydroxystearate (44 mg/mL), medium chain triglycerides (11 mg/mL), soybean oil (6.6 mg/mL), sodium chloride (6.2 (b) (4) mg/mL) dibasic sodium phosphate anhydrous (2.8 (b) (4) mg/mL), and may contain hydrochloric acid and/or sodium hydroxide to adjust for pH.

Clinical development program and relevant regulatory background

This clinical development program comprises four Phase 1 studies in healthy subjects including single and multiple-dose dose escalation pharmacokinetics studies (PR-11-5012-C and PR-11-5022-C), pivotal relative BA study (PR-11-5016-C), and drug-drug interaction study (PR-11-5021-C). The DDI study assessed the effect of rolapitant IV and its metabolite on P-gp substrate, BCRP substrate, CYP3A, CYP2C19, CYP2C9, CYP1A2 and CYP2D6.

No clinical trial was conducted to assess the efficacy of rolapitant IV. The sponsor is relying on the Agency's findings of approved rolapitant oral tablets owned by the sponsor (Tesaro Inc.) as well. The relative BA study results were summarized in Section 2.1.

For the safety of higher Cmax with intravenous administration of the proposed formulation, the sponsor submitted additional safety information in the above phase 1 studies where subjects were exposed to doses higher than the proposed therapeutic dose. The average exposure (Cmax) from the highest dose (300 mg) was twice the Cmax following single therapeutic dose (PR-11-5016-C). Defer to the Clinical Review for safety.

3.2 General Pharmacology and Pharmacokinetic Characteristics

The mechanism of action, absorption, distribution, metabolism, and excretion information can be found in the product label of approved rolapitant oral tablet (NDA 206500).

Below is a brief summary of the PK characteristics specific to the single doses of the IV formulation. For other details, refer to Section 0

Review of Individual Studies including the results of a pivotal BA/BE study.

Following a single dose administration of 185 mg rolapitant via 30 minute intravenous infusion to healthy subjects, the Cmax of rolapitant was reached at the end of infusion and mean Cmax was 1986 ng/mL (%CV:39%). The systemic exposures (Cmax and AUC) to rolapitant increased in a dose-proportional manner when the intravenous dose of rolapitant increased from 20 mg to 200 mg and from 225 mg to 300 mg in two studies.

Following various single intravenous dose levels ranging from 20 to 300 mg of rolapitant, the mean terminal half-life (t1/2) of rolapitant ranged from 135 to 205 hours and was independent of dose. This is similar to that of single oral doses (4.5 to 180 mg, (b) (4) of rolapitant which ranged from 169 to 183 hours. Rolapitant is metabolized by CYP3A to form a major active metabolite SCH 720881 (M19). Refer to oral rolapitant product label.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The sponsor relied on the efficacy and safety findings of their own approved oral rolapitant for CINV. The efficacy of rolapitant IV formulation should be supported by the results from the pivotal BA/BE study (PR-11-5016-C) in which BE criteria are met for AUC between rolapitant IV and rolapitant oral.

A relative BA study between the proposed emulsion formulation and approved oral rolapitant tablet showed that the systemic exposures ($AUC_{0\text{-}inf}$ and $AUC_{0\text{-}120h}$) to rolapitant met bioequivalence criteria. The Cmax from rolapitant IV administration was 1.9-fold that of oral

rolapitant. In addition, the systemic exposure parameters of Cmax, $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, and $AUC_{0\text{-120}}$ of the active metabolite, SCH 720881, from IV administration were comparable to those from oral administration in the pivotal BA/BE study. For details, see Section 4.2.2 Pivotal BA/BE Study: PR-11-5016-C.

Reviewer's comment: As noted in Section 4.1, the measured plasma concentrations of rolapitant represented the sum of free, protein-bound, and rolapitant (b) (4)*. Because the systemic exposures to major active metabolite from IV administration were comparable to those from oral administration using the approved tablets, it provided supportive evidence that rolapitant was released* (b) (4) *into plasma following administration of the proposed emulsion to a comparable degree as that after the approved tablet.*

The sponsor proposed a manufacture site change in this NDA as discussed earlier in this review. As the formulation of this IV product is nano-emulsion, Clinical Pharmacology Review Team does ***not*** *believe that the sponsor can rely on the current relative BA/BE study alone for approval without adequate in vitro release data demonstrating comparability between the IV batches made in the new site* (b) (4) *and those made in* (b) (4)

The safety and tolerability profile of rolapitant IV is supported by multiple studies in humans at both therapeutic and supra-therapeutic doses (PR-11-5012-C, PR-11-5016-C, PR-11-5021-C, and PR-11-5022-C). Refer to Dr. Aisha Johnson's Clinical Review for the safety of rolapitant IV.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes.

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Not applicable.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Food-drug Interactions

Since rolapitant nano-emulsion is administered by IV infusion, food-effect study is not conducted as food-drug interactions are not anticipated or applicable.

Drug-drug interactions

The effects of single dose rolapitant IV on CYP3A, 1A2, 2C9 and transporters (P-gp and BCRP) were evaluated. The results are summarized below. For details of the study results, refer to 4.2.1 Drug-Drug Interaction Study: PR-11-5021-C.

Table 1. Summary of the effects of single dose of rolapitant IV on the substrates of CYP3A, 1A2, 2C9, 2C19, P-gp, and BCRP

	Substrate	Fold Change in Cmax		Fold Change in AUC (%)	
		Day 1	Day 7	Day 1	Day 7
CYP3A	Midazolam	0.86	0.88	0.84	0.86
CYP1A2	Caffeine	0.97	0.90	1.01	1.03
CYP2C9	Warfarin	1.03	1.03	1.18	1.21
CYP2C19	Omeprazole	1.14	1.15	1.06	1.02
P-gp	Digoxin	1.21	--	1.07	--
BCRP	Sulfasalazine‡	0.98	0.82‡	1.06	0.94‡

‡ Day 10; --: not studied; Fold change: ratios of geometric mean of Cmax and AUC of each substrate.
Day 1: Co-administration of rolapitant IV and a substrate drug; Day 7: administration of a substrate drug alone

For IV rolapitant, the review team recommends: 1) monitoring INR when it is co-administered with warfarin, and 2) measuring serum digoxin concentrations before initiating concomitant drugs and reducing digoxin dose by approximately 15% to 30% or by modifying the dosing frequency and continue monitoring which is consistent with the digoxin label.

The effect of single dose rolapitant IV on CYP2D6 was evaluated. The results are summarized below. For details, refer to Section 4.2.1 Drug-Drug Interaction Study: PR-11-5021-C.

Table 2. Summary of the effect of single dose of rolapitant IV on dextromethorphan, substrate of CYP2D6

	Day 1	Day 7	Day 14	Day 21	Day 28
Fold Change in Cmax	1.7	2.4	2.7	2.2	2.0
Fold Change in AUC	2.1	3.2	3.2	2.8	2.3

Fold change: ratios of geometric mean of Cmax and AUC of dextromethorphan
Day 1: Co-administration of rolapitant IV and a substrate drug;
Day 7, 14, 21, and 28: Administration of a substrate drug alone.

A maximum 2.7-fold increase in Cmax and 3.2-fold increase in AUC were observed two weeks after the co-administration of rolapitant and dextromethorphan. By Day 28, 4 weeks after co-administration, the magnitude of CYP2D6 inhibition was similar to that on Day 1.

The same labeling language as that in the oral product label should be used in advising concomitant use of rolapitant IV with thioridazine and pimozole. Because of the prolonged inhibition of CYP2D6, concomitant use of a single dose of rolapitant with other CYP2D6 substrates with a narrow therapeutic index should be avoided.

Oral rolapitant can be given prior to the initiation of each chemotherapy cycle but at no less than two-week interval. It is unknown whether the repeated dosing of rolapitant with every two-

week interval will result in additional CYP2D6 inhibition. Thus, all CYP2D6 substrates should be avoided under this scenario. According to oral rolapitant label, thioridazine is contraindicated and pimazole should be avoided. These recommendations hold true for IV rolapitant as well. Currently there is no data indicating when these substrates may be re-started when rolapitant is discontinued.

4. APPENDICES

4.1. Summary of Bioanalytical Method Validation and Performance

Rolapitant and its major metabolite SCH 0720881 (M19) were measured in plasma using a validated liquid-chromatographic-tandem mass spectrometric method (LC/MS/MS). Validation methods (Studies KB-0006-RB-BV, KB-0010-RB-BV) were previously used to support NDA 206500 for oral rolapitant and deemed to be acceptable. Study KB-0008-RB-BL was used to evaluate the long-term storage (-20°C freezer) stability of rolapitant and its metabolite.

Validation study KB-0006-RB-BV was used to support the assay in the pivotal relative BA/BE study PR-11-5016-C. A summary of the in-study report of this BA/BE study is shown below.

Matrix and Anticoagulant	Human plasma (K_2EDTA)
Standard Curve Ranges	
SCH 619734	2.00 to 2000 ng/mL
SCH 720881	1.00 to 1000 ng/mL
QC Concentrations	
SCH 619734	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)
SCH 720881	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)
Sample Extraction Volume	25 µL
Extraction Procedure	Solid phase (Oasis MCX 96-well plate 30µm, 10 mg)
Instrumentation	API-5500
Detection	APCI (positive-ion mode) Multiple-reaction-monitoring scan mode
Regression, Weighting	Linear, $1/x^2$
Stability	
Short Term in Whole Blood	4 Hours at room temperature
Short Term in Plasma	25 Hours at room temperature
Long Term in Plasma	784 Days at -20°C 85 Days at -80°C
Freeze/Thaw in Plasma	6 Cycles (-20°C/room temperature)
Extract	70 Hours refrigerated
Reinjection Reproducibility	Maximum 5 days refrigerated
Incurred Sample Reanalysis	Acceptable

Source data: Validation Report KB-0051-RB-BS-RPT-01

Reviewer's comment: It is noteworthy that this method measured total concentrations of rolapitant, i.e., sum of free (unbound), protein-bound, and rolapitant (b) (4) .

4.2. Review of Individual Studies

4.2.1. Drug-Drug Interaction Study: PR-11-5021-C

Reviewer's comment: This study evaluated the effect of rolapitant as a perpetrator on other drugs.

Title: An Open Label, Single Dose, Three Part Study to Assess the Effects of Rolapitant (1.8 mg/mL IV solution) on the Pharmacokinetics of Digoxin (P-gp); Sulfasalazine (BCRP); and the

Cooperstown Cocktail (Midazolam [CYP3A4], Omeprazole [CYP2C19], S-Warfarin [CYP2C9], Caffeine [CYP1A2], and Dextromethorphan [CYP2D6]) in Healthy Subjects.

Study Design:

This was an open-label, 3-part DDI study of orally administered P-gp substrate, BCRP substrate, and CYP probe substrates in the presence and absence of a single dose of rolapitant (IV, 30 minute infusion) in healthy male and female subjects. This study was conducted in 3 independent parts: Part A, Part B, and Part C. See section on treatment groups below for further details.

Treatment Groups:

Part A: Subjects received a single oral dose of 0.5 mg (2 × 0.25 mg tablets) digoxin during Period 1 and, after a ≥ 8-day washout period, a single oral dose of 0.5 mg digoxin at the end of a 30 minute IV infusion of 166.5 mg (1.8 mg/mL) rolapitant IV in Period 2.

	Period 1 (5 days)	Washout	Period 2 (5 days)
Digoxin PO (0.5 mg)	X 1	≥ 8 days	X1
Rolapitant			X1
Summary table of the study design made by the reviewer			

PK blood sampling: Blood samples for digoxin were drawn on Day 1 of Period 1 predose (0 hour) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 6, 8, 24, 36, 48, 72, and 96 hours post digoxin dosing.

Blood samples for digoxin and rolapitant IV PK evaluations were drawn on Day 1 of Period 2 at the following times: at pre-infusion, at the end of rolapitant IV infusion (0.5 hour for rolapitant IV and 0 hour [predose] digoxin), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 6, 8, 24, 36, 48, 72, and 96 hours post digoxin dosing.

Reviewer's comment: The sampling time for rolapitant is acceptable as Part A of this study evaluated the effect of rolapitant on digoxin.

Part B: Subjects received an oral dose of 500 mg of sulfasalazine on Day 1 and Day 13. On Day 3, subjects were administered an oral dose of 500 mg sulfasalazine at the end of a 30 minute infusion of 166.5 mg (1.8 mg/mL) rolapitant IV. A 2-day washout period followed the Day 1 dose; a 10-day washout period followed the Day 3 dose.

	Day 1	Day 3	Washout	Day 13
Sulfasalazine PO (500 mg)	X 1	X 1	≥ 8 days	X 1
Rolapitant		X 1		
Summary table of the study design made by the reviewer				

PK blood sampling: On Days 1 and 13, blood samples for the determination of plasma concentrations of sulfasalazine were collected predose (0 hour sulfasalazine), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 30 hours postdose.

On Day 3, blood samples for the determination of plasma concentrations of sulfasalazine and rolapitant IV were collected at pre-infusion, at the end of rolapitant IV infusion (0.5 hour for rolapitant IV and 0 hour [predose] sulfasalazine), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, and 30 hours post dosing of sulfasalazine.

Part C: Subjects received an oral dose of the Cooperstown cocktail (midazolam [3 mg], omeprazole [40 mg], S-warfarin [10 mg + 10 mg vitamin K], caffeine [200 mg], and dextromethorphan [30 mg]) on Days 1 and 14, and received an oral dose of Cooperstown cocktail at the end of a 30 minute infusion of 166.5 mg (1.8 mg/mL) rolapitant IV on Day 7. On Days 21, 28, and 35, subjects received an oral dose of 30 mg dextromethorphan alone. A 6-day washout period followed the Day 1 dose and a 7-day washout period followed the Day 7, 14, 21, and 28 doses.

	Day 1	Day 7	Day 14	Day 21	Day 28	Day 35
CC	X 1	X 1	X 1			
DMX	√	√	√	X 1	X 1	X 1
Rolapitant		X 1				
√ DMX was given as part of the CC						
CC: Copperstown Cocktail; DMX: Dextromethorphan						
Summary table of the study design made by the reviewer						

PK blood sampling: On Days 1 and 14, blood samples for the determination of plasma concentrations of Cooperstown cocktail probes were collected pre-dose (0 hour cocktail probes), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours postdose. On Day 7, blood samples for the determination of plasma concentrations of Cooperstown cocktail probes and rolapitant IV were collected at pre-infusion, at the end of rolapitant IV infusion (0.5 hour for rolapitant IV and 0 hour [predose] cocktail probes), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 96 and 120 hours post the dosing of Cooperstown cocktail.

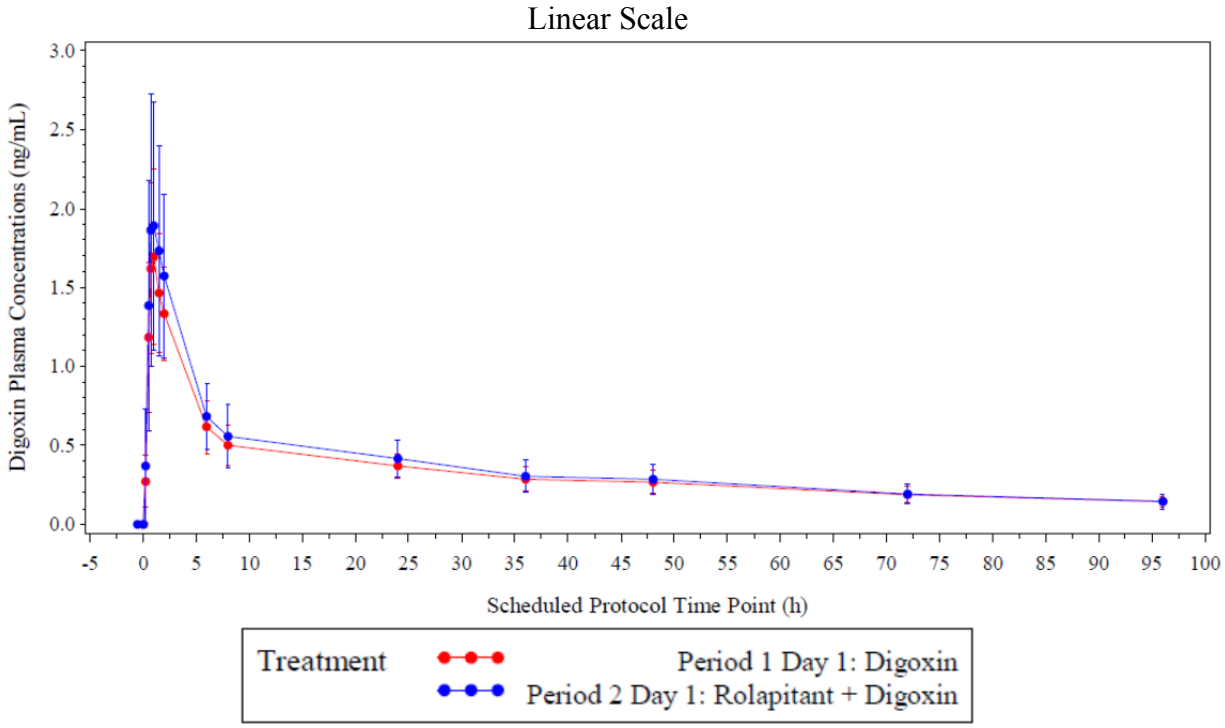
On Days 21, 28 and 35, blood samples for the determination of plasma concentrations of dextromethorphan were collected pre-dose (0 hour dextromethorphan), and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48 and 72 hours post dextromethorphan dosing.

Pharmacokinetic Results

Part A: Effect on Digoxin, a P-gp transporter substrate

Digoxin concentration-time profiles are shown below.

Figure 1. Mean (SD) Digoxin Plasma Concentration-Time Profile



Descriptive Summary of the PK parameters of digoxin estimated by non-compartmental analysis is shown below.

Treatment	Period	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
Analyte = Digoxin							
0.5 mg Digoxin	1	n	36	36	31	36	31
		Mean	1.81	1.08	44.26	29.19	38.81
		SD	0.523	0.432	13.515	7.222	8.541
		Median	1.71	1.00	42.16	29.83	39.55
		Min, Max	0.8, 3.3	0.5, 2.0	23.8, 91.3	13.3, 46.5	24.0, 60.0
		%CV	28.9	39.8	30.5	24.7	22.0
		Geometric Mean	1.74	1.02	42.59	28.24	37.91
Rolapitant IV + 0.5 mg Digoxin	2	n	29	29	23	29	23
		Mean	2.23	1.18	42.12	31.94	43.78
		SD	0.735	1.001	16.039	10.610	13.315
		Median	1.95	0.98	40.08	33.05	44.66
		Min, Max	1.1, 3.7	0.5, 6.0	26.3, 107.5	12.1, 52.6	16.2, 71.6
		%CV	33.0	84.7	38.1	33.2	30.4
		Geometric Mean	2.11	1.01	40.24	30.07	41.66

Statistical analysis of the effect of rolapitant and its active metabolite on the systemic exposures of digoxin is shown below.

Parameter	Period	Treatment	N[a]	Geometric LSM	Geometric LS Means 95% CI	Treatment Ratio[b]	90% CI for Ratio	Within Subject CV(%)[c]
C_{max} (ng/mL)	1	Digoxin	65	1.7	(1.6, 1.9)	1.212	(1.069, 1.374)	29.4
	2	Rolapitant + Digoxin		2.1	(1.8, 2.4)			
$AUC_{0\text{-last}}$ (ng•h/mL)	1	Digoxin	65	28.2	(25.8, 30.9)	1.077	(1.005, 1.155)	15.4
	2	Rolapitant + Digoxin		30.4	(26.9, 34.5)			
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	Digoxin	54	37.9	(34.7, 41.3)	1.068	(0.989, 1.153)	12.6
	2	Rolapitant + Digoxin		40.4	(35.9, 45.6)			

Abbreviations: ANOVA = analysis of variance; $AUC_{0\text{-last}}$ = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0\text{-inf}}$ = area under the plasma concentration-time curve from time 0 to infinity; C_{max} = maximum observed plasma concentration; CI = confidence interval; CV = coefficient of variation; LSM = least-squares mean

A repeated measures model with unstructured variance-covariance was applied to the log-transformed data. Least-squares means, ratio of LSMs, and 90% CIs for ratios were estimated from the model after exponential transformation back to the original scale.

[a] Number of observations used in the repeated measures analysis.

[b] Baseline reference group for all comparisons is treatment Day 1.

[c] Coefficient of variation = [exp(variance) - 1]^0.5 * 100, where variance is estimated from the residuals of the repeated measures ANOVA.

Statistical analysis of the effect of rolapitant and its active metabolite on the Tmax of digoxin using non-parametric analysis is shown below.

Analyte	Parameter[a]	Between-Treatment Comparison	N[b]	Hodges-Lehmann Estimate Median Difference[c]	90% CI for Estimate of Median Difference[d]
Digoxin	t_{max} (h)	Rolapitant + Digoxin vs. Digoxin	29	-0.008	(-0.208, 0.133)

Conclusions:

- Co-administration of rolapitant IV with digoxin had no effect on digoxin systemic exposure (90% CIs for the ratios of geometric AUC0-last and AUC0-inf were within the 0.80 to 1.25 range) or on Tmax.
- 21% increase in digoxin Cmax was observed (90% CI for the ratio of geometric means: 1.069 to 1.374).

Reviewer's comment: Although the sponsor considered the 21% increase in Cmax of digoxin as clinically insignificant, the reviewer recommends cautionary language in the product label as

digoxin is a drug with narrow therapeutic index. According to oral digoxin product label, for digoxin concentrations increased less than 50%, health care provider should "measure serum dioxin concentrations before initiating concomitant drugs. Reduce digoxin dose by approximately 15% to 30% or by modifying the dosing frequency and continue monitoring."

Part B: Effect on sulfasalazine, a BCRP transporter substrate

Sulfasalazine concentration-time profiles are shown below.

Figure 2. Mean (SD) Sulfasalazine Plasma Concentration-Time Profile

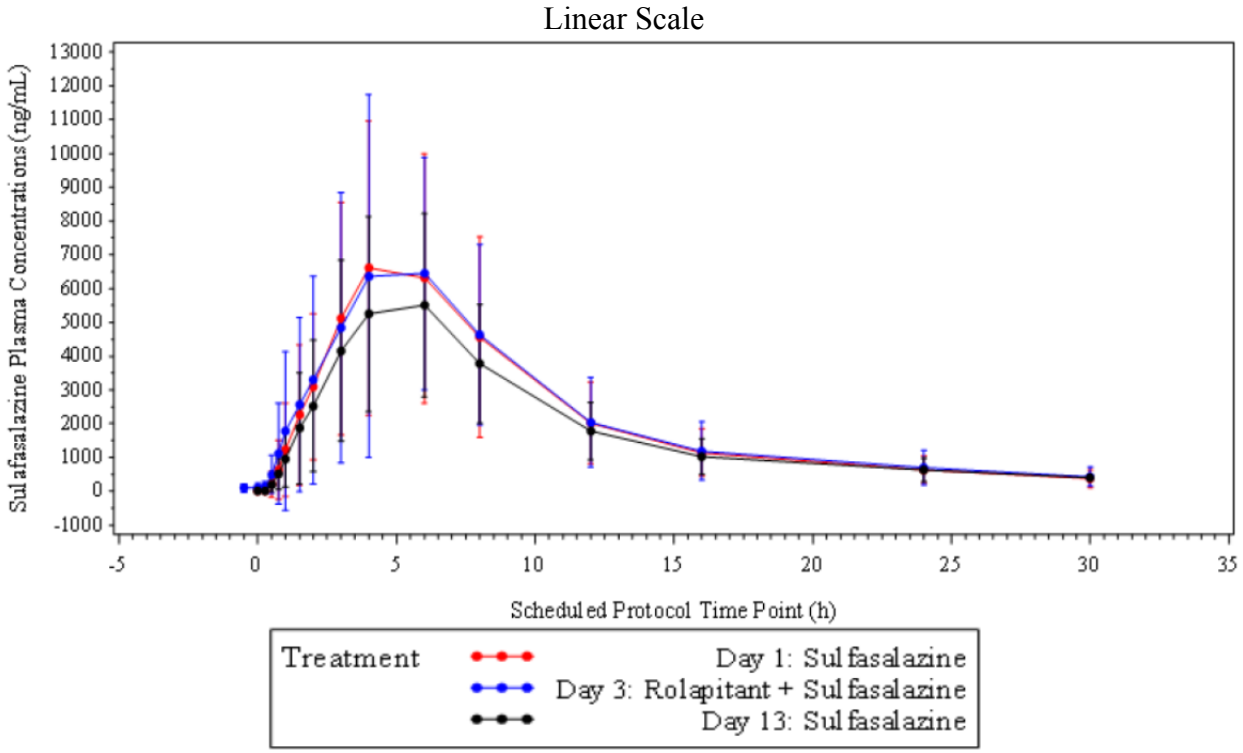
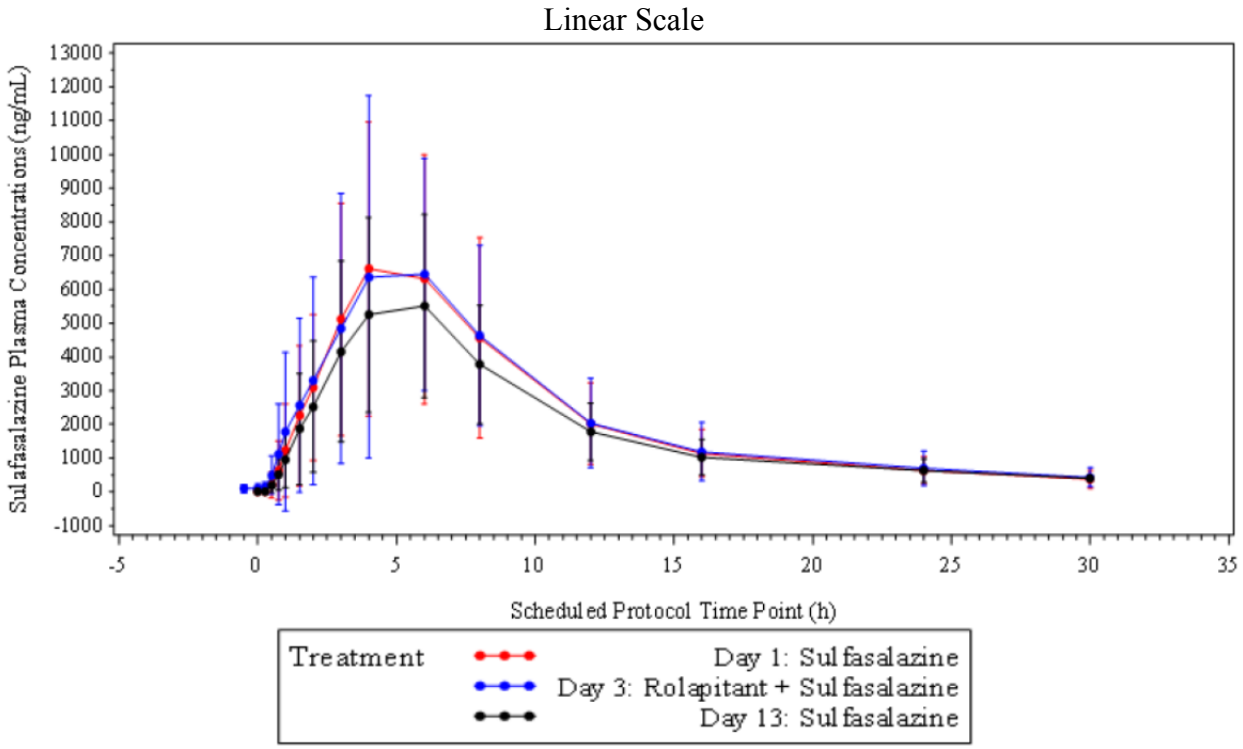


Figure 3. Mean (SD) Sulfapyridine Plasma Concentration-Time Profile



Descriptive Summary of the PK parameters of sulfasalazine and sulfapyridine estimated by non-compartmental analysis is shown below.

Treatment	Day	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
Analyte = Sulfasalazine							
500 mg Sulfasalazine	1	n	30	30	30	30	30
		Mean	7899.67	5.07	7.82	64510.96	68974.75
		SD	3915.017	1.929	1.323	35531.35	38976.92
		Median	7060.00	4.03	7.54	57018.55	60115.23
		Min, Max	1360.0, 16800.0	2.0, 12.0	5.8, 11.1	14449.5, 146609.5	15375.4, 163098.3
		%CV	49.6	38.0	16.9	55.1	56.5
		Geometric Mean	6856.97	4.77	7.72	55278.80	58760.62
Rolapitant IV + 500 mg Sulfasalazine	3	n	27	27	25	27	25
		Mean	8041.11	5.39	8.62	66141.67	75036.10
		SD	5254.081	1.669	1.673	40498.61	43663.51
		Median	7560.00	6.00	8.30	58162.81	67752.62
		Min, Max	2490.0, 25000.0	1.5, 8.0	5.5, 14.3	18118.6, 190200.4	19027.3, 205754.9
		%CV	65.3	31.0	19.4	61.2	58.2
		Geometric Mean	6804.93	5.09	8.48	56053.74	64431.01
500 mg Sulfasalazine	13	n	27	27	25	27	25
		Mean	6392.59	5.31	8.97	55289.27	60526.81
		SD	2958.011	1.314	1.861	24757.42	27585.33
		Median	7140.00	5.98	8.59	55514.53	62594.43
		Min, Max	1900.0, 12200.0	3.0, 8.2	6.1, 13.5	17660.7, 105434.8	19373.9, 114400.1
		%CV	46.3	24.7	20.7	44.8	45.6
		Geometric Mean	5656.19	5.15	8.81	49335.06	53799.47
Analyte = Sulfapyridine							
500 mg Sulfasalazine	1	n	30	30	27	30	27
		Mean	3004.33	10.27	10.19	43509.20	57060.04
		SD	717.734	3.705	4.570	15629.84	27822.94
		Median	3110.00	8.01	8.99	38676.57	44007.79
		Min, Max	1820.0, 4850.0	6.0, 24.0	4.6, 23.2	17779.9, 70726.2	18681.3, 107211.2
		%CV	23.9	36.1	44.8	35.9	48.8
		Geometric Mean	2922.00	9.76	9.31	40762.16	50708.89
Rolapitant IV + 500 mg Sulfasalazine	3	n	27	27	25	27	25
		Mean	2987.04	10.32	10.18	45683.28	60608.45
		SD	863.734	2.593	4.563	18550.89	32417.45
		Median	2880.00	12.00	9.08	39236.39	45613.87
		Min, Max	1240.0, 4870.0	6.0, 16.0	5.1, 22.0	16225.2, 74131.1	17739.4, 122977.3
		%CV	28.9	25.1	44.8	40.6	53.5
		Geometric Mean	2853.53	9.98	9.33	42027.18	52659.90
500 mg Sulfasalazine	13	n	27	27	23	27	23
		Mean	3081.11	9.78	9.80	43981.61	57902.87
		SD	892.371	3.649	4.218	14081.58	24971.10
		Median	3140.00	8.05	8.69	43345.31	46978.00
		Min, Max	1180.0, 4960.0	6.0, 24.1	4.7, 21.0	21997.9, 72927.1	23504.8, 117409.3
		%CV	29.0	37.3	43.0	32.0	43.1
		Geometric Mean	2934.90	9.29	9.03	41749.07	52998.74

Statistical analysis of the effect of rolapitant and its active metabolite on the systemic exposures of sulfasalazine and sulfapyridine is shown below.

Parameter	Day	Treatment	N[a]	Geometric LSM	Geometric LS Means 95% CI	Treatment Ratio[b]	90% CI for Ratio	Within Subject CV(%)[c]
Analyte = Sulfasalazine								
C_{max} (ng/mL)	1	Sulfasalazine	84	6857.0	(5519.1, 8519.1)			38.8
	3	Rolapitant + Sulfasalazine		6716.5	(5348.1, 8435.1)	0.980	(0.836, 1.148)	
	13	Sulfasalazine		5598.6	(4539.0, 6905.5)	0.816	(0.689, 0.968)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	Sulfasalazine	84	55278.8	(44429.2, 68777.9)			31.2
	3	Rolapitant + Sulfasalazine		55777.9	(44127.0, 70505.1)	1.009	(0.881, 1.156)	
	13	Sulfasalazine		49141.9	(40159.8, 60132.8)	0.889	(0.773, 1.022)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	Sulfasalazine	80	58760.6	(47066.6, 73360.1)			29.1
	3	Rolapitant + Sulfasalazine		61978.2	(49014.0, 78371.3)	1.055	(0.919, 1.210)	
	13	Sulfasalazine		55363.0	(44803.3, 68411.5)	0.942	(0.817, 1.086)	
Analyte = Sulfapyridine								
C_{max} (ng/mL)	1	Sulfasalazine	84	2922.0	(2669.9, 3197.9)			15.0
	3	Rolapitant + Sulfasalazine		2865.3	(2537.5, 3235.3)	0.981	(0.920, 1.045)	
	13	Sulfasalazine		2946.7	(2591.6, 3350.6)	1.008	(0.936, 1.086)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	Sulfasalazine	84	40762.2	(35444.3, 46877.9)			10.3
	3	Rolapitant + Sulfasalazine		41711.0	(35152.9, 49492.6)	1.023	(0.982, 1.066)	
	13	Sulfasalazine		41516.9	(36266.4, 47527.5)	1.019	(0.969, 1.070)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	Sulfasalazine	75	51602.8	(42478.7, 62686.5)			9.1
	3	Rolapitant + Sulfasalazine		52764.9	(41933.9, 66393.3)	1.023	(0.984, 1.063)	
	13	Sulfasalazine		53377.9	(44254.8, 64381.6)	1.034	(0.990, 1.081)	

Abbreviations: ANOVA = analysis of variance; $AUC_{0\text{-last}}$ = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0\text{-inf}}$ = area under the plasma concentration-time curve from time 0 to infinity; C_{max} = maximum observed plasma concentration; CI = confidence interval; CV = coefficient of variation; LSM = least-squares mean

A repeated measures model with unstructured variance-covariance was applied to the log-transformed data. Least squares means, ratio of LS means, and 90% CI for ratio were estimated from the model after exponential transformation back to the original scale.

Statistical analysis of the effect of rolapitant and its active metabolite on the Tmax of sulfasalazine and sulfapyridine using non-parametric analysis is shown below.

Analyte	Parameter[a]	Between-Treatment Comparison	N[b]	Hodges-Lehmann Estimate Median Difference[c]	90% CI for Estimate of Median Difference[d]
Sulfasalazine	t_{max} (h)	Day 3 (Rolapitant + Sulfasalazine) vs. Day 1 (Sulfasalazine)	27	0.242	(-0.042, 1.000)
		Day 13 (Sulfasalazine) vs. Day 1 (Sulfasalazine)	27	0.008	(-0.017, 0.992)
Sulfapyridine	t_{max} (h)	Day 3 (Rolapitant + Sulfasalazine) vs. Day 1 (Sulfasalazine)	27	0.017	(0.000, 2.000)
		Day 13 (Sulfasalazine) vs. Day 1 (Sulfasalazine)	27	-0.017	(-1.908, 0.025)

Abbreviations: CI = confidence interval; PK = pharmacokinetic(s); t_{max} = time to reach the maximum observed plasma concentration

[a] t_{max} was derived from PK concentration data.

[b] N is the number of subjects used in the analysis. This is the number of subjects with complete data for both treatment days.

[c] The difference in medians and its 90% CI are estimated using the methodology of Hodges-Lehmann for paired samples.

[d] The CI of the median difference was obtained by applying a normal approximation to the Wilcoxon Signed-Rank distribution.

Conclusions:

- Co-administration of rolapitant IV with sulfasalazine had no effect on sulfasalazine Day 3 systemic exposure (90% CIs for the ratios of geometric mean of Cmax, AUC0-last, and AUC0-inf were all contained within 0.80 to 1.25) or on tmax.
- A slight decrease in sulfasalazine Cmax (18%) and AUC0-last (11%) (but not AUC0-inf) was observed on Day 13 (Day 13 90% CI for the ratio of geometric means: 0.689 to 0.968 and 0.773 to 1.022 for Cmax and AUC0-last, respectively); however, this effect is not considered clinically significant.
- There was no effect on sulfapyridine systemic exposure on either Day 3 or Day 13.

Reviewer's comment: This reviewer concurs with sponsor's conclusions.

Part C: Effect on midazolam (CYP3A), omeprazole (CYP2C19), S-warfarin (CYP2C9), caffeine (CYP1A2), and dextromethorphan (CYP2D6)

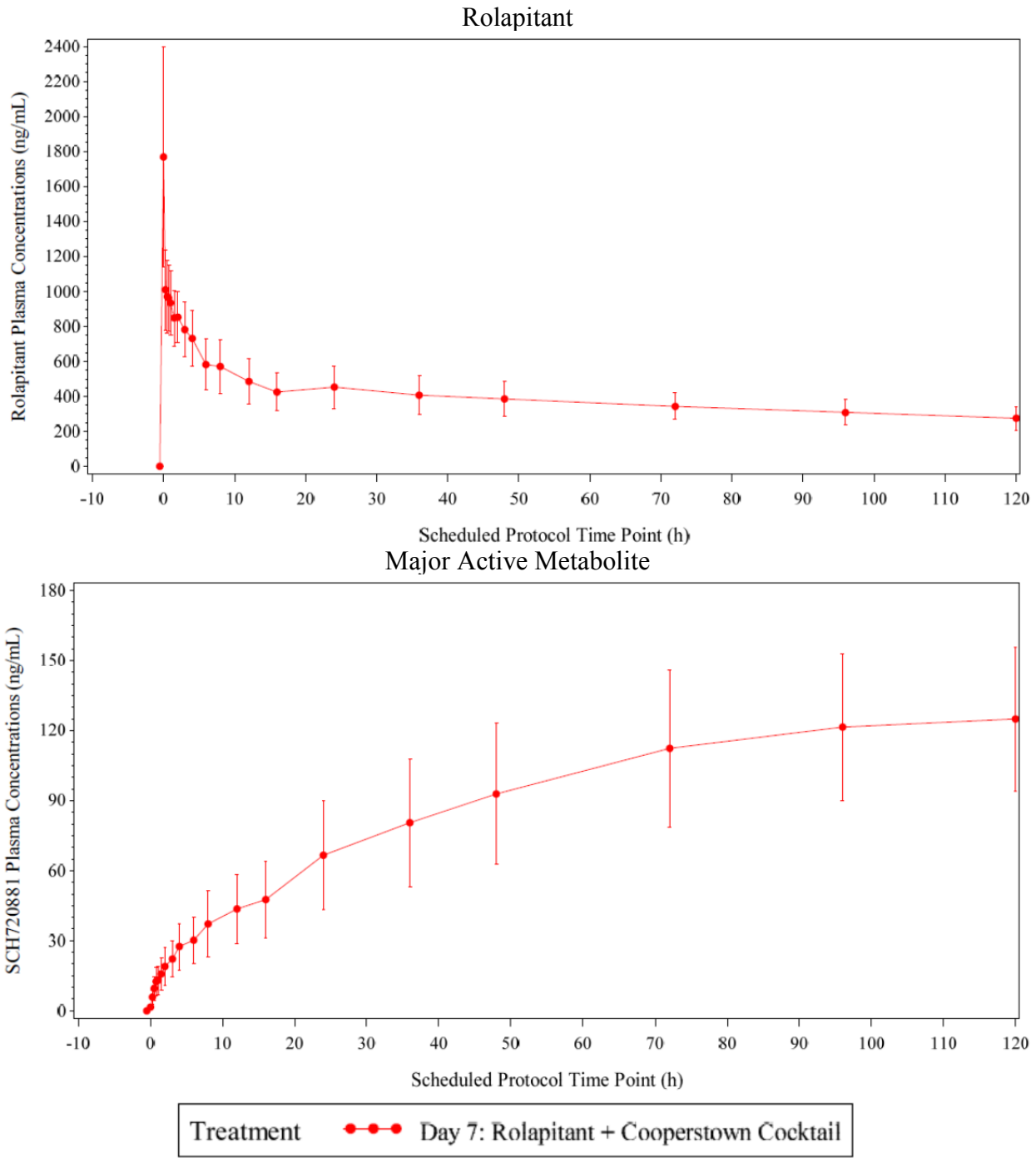
Midazolam (3 mg), omeprazole (40 mg), warfarin (10 mg), caffeine (200 mg), and dextromethorphan (30 mg) were administered together as a cocktail regimen (Copperstown

Cocktail, CC). Dextromethorphan was also administered alone 2, 3, and 4 weeks following single dose of rolapitant.

Plasma concentrations of rolapitant and its active metabolite were measured. However, the sampling time was only up to 120 hours. Given that rolapitant has a long half-life, the PK parameters of AUC0-inf would not be estimated accurately with 120 hours sampling. The estimates of Cmax and Tmax of the active metabolite would not be accurate either.

The mean concentration time profiles of rolapitant and its major active metabolite is shown below.

Figure 4. Mean (SD) Rolapitant and Its Metabolite Plasma Concentration-Time Profiles



Midazolam (CYP3A)

Midazolam concentration-time profiles are shown below.

Figure 5. Mean (SD) Midazolam Plasma Concentration-Time Profile

Linear Scale

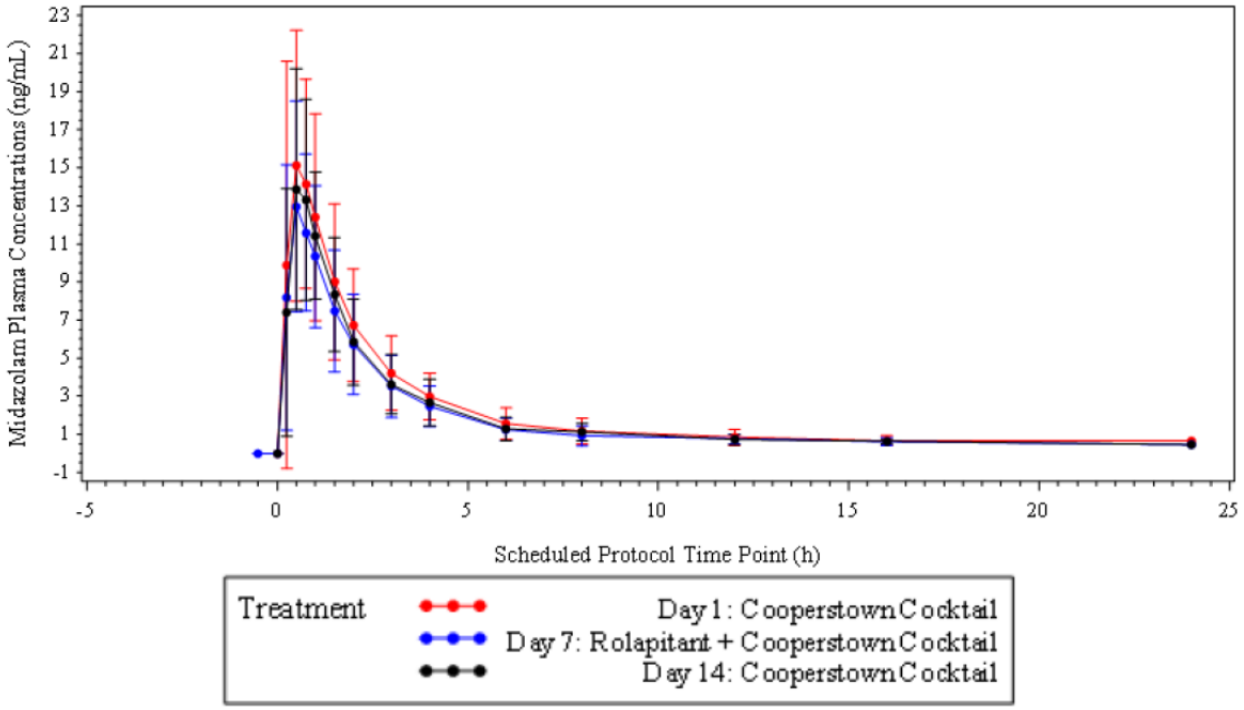
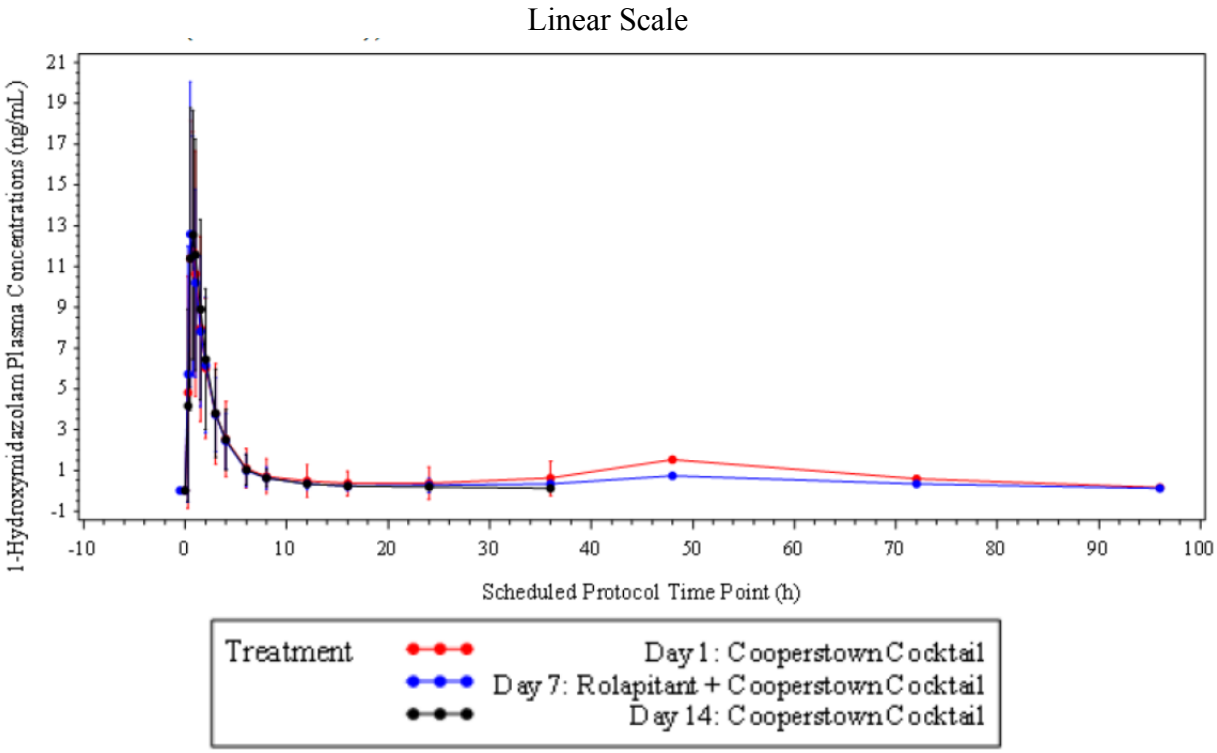


Figure 6. Mean (SD) 1'-Hydroxymidazolam Plasma Concentration-Time Profile



Descriptive Summary of the PK parameters of midazolam and its metabolite estimated by non-compartmental analysis is shown below.

Treatment	Day	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
Analyte = Midazolam							
Cooperstown Cocktail	1	n	36	36	33	36	33
		Mean	17.93	0.61	3.32	39.60	43.19
		SD	9.779	0.213	2.135	19.162	21.050
		Median	16.25	0.50	2.69	34.79	37.82
		Min, Max	4.7, 62.2	0.3, 1.0	0.9, 11.4	9.1, 92.0	10.5, 99.6
		%CV	54.5	34.7	64.2	48.4	48.7
		Geometric Mean	16.07	0.58	2.83	35.56	38.76
Rolapitant IV + Cooperstown Cocktail	7	n	32	32	28	32	28
		Mean	14.77	0.63	2.90	31.96	36.04
		SD	5.132	0.228	1.445	13.921	14.410
		Median	13.95	0.52	2.58	30.11	33.46
		Min, Max	3.9, 26.3	0.3, 1.0	1.2, 7.5	7.0, 68.9	14.2, 73.6
		%CV	34.7	36.3	49.8	43.6	40
		Geometric Mean	13.83	0.59	2.62	29.03	33.49
Cooperstown Cocktail	14	n	31	31	28	31	28
		Mean	15.56	0.70	2.97	34.22	36.65
		SD	6.517	0.238	1.656	15.020	15.322
		Median	14.90	0.75	2.56	32.86	37.12
		Min, Max	5.0, 33.0	0.3, 1.6	0.9, 7.7	6.7, 66.5	7.5, 67.6
		%CV	41.9	34.0	55.8	43.9	41.8
		Geometric Mean	14.29	0.67	2.59	30.72	33.08
Analyte = 1-OH-Midazolam							
Cooperstown Cocktail	1	n	36	36	30	36	30
		Mean	13.39	0.71	6.00	37.17	36.00
		SD	6.660	0.262	3.608	34.979	35.764
		Median	11.75	0.75	5.18	28.36	26.43
		Min, Max	4.5, 34.7	0.3, 1.5	1.8, 15.1	13.7, 211.7	14.0, 214.4
		%CV	49.8	37.2	60.1	94.1	99.4
		Geometric Mean	11.85	0.65	5.04	30.33	29.57
Rolapitant IV + Cooperstown Cocktail	7	n	32	32	27	32	27
		Mean	13.91	0.67	5.73	34.29	36.08
		SD	6.590	0.311	3.302	19.316	20.606
		Median	13.60	0.52	6.08	28.48	30.03
		Min, Max	4.6, 35.7	0.3, 2.0	1.7, 17.1	14.7, 94.8	15.6, 95.9
		%CV	47.4	46.5	57.7	56.3	57.1
		Geometric Mean	12.58	0.62	4.91	30.58	32.09
Cooperstown Cocktail	14	n	31	31	20	31	20
		Mean	14.11	0.77	6.71	34.16	32.56
		SD	7.020	0.285	4.784	18.405	13.750
		Median	12.80	0.75	5.69	27.92	28.38
		Min, Max	4.8, 34.8	0.3, 1.6	1.4, 21.7	12.3, 100.5	12.9, 58.8
		%CV	49.8	37.0	71.3	53.9	42.2
		Geometric Mean	12.68	0.72	5.39	30.32	29.76

Abbreviations: $AUC_{0\text{-last}}$ = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0\text{-inf}}$ = area under the plasma concentration-time curve from time 0 to infinity; C_{max} = maximum observed plasma concentration; CV = coefficient of variation; IV = intravenous(ly); max = maximum; min = minimum; SD = standard deviation; t_{max} = time to reach C_{max}; $t_{½}$ = terminal elimination half-life

Statistical analysis of the effect of rolapitant and its active metabolite on the systemic exposures of midazolam and 1-hydroxymidazolam is shown below.

Parameter	Day	Treatment	N[a]	Geometric LS Mean	Geometric LS Means 95% CI	Treatment Ratio[b]	90% CI for Ratio	Within Subject CV(%)[c]
Analyte = Midazolam								
C_{max} (ng/mL)	1	CC	99	16.1	(13.7, 18.8)			21.9
	7	Rolapitant + CC		13.8	(12.1, 15.8)	0.859	(0.781, 0.946)	
	14	CC		14.2	(12.3, 16.4)	0.884	(0.810, 0.965)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	CC	99	35.6	(30.3, 41.8)			17.2
	7	Rolapitant + CC		28.9	(24.7, 33.8)	0.813	(0.752, 0.879)	
	14	CC		30.4	(25.7, 35.9)	0.855	(0.787, 0.929)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	CC	89	38.1	(32.5, 44.8)			17.5
	7	Rolapitant + CC		32.0	(27.6, 37.2)	0.840	(0.775, 0.911)	
	14	CC		32.9	(27.7, 39.1)	0.863	(0.786, 0.948)	
Analyte = 1-OH-Midazolam								
C_{max} (ng/mL)	1	CC	99	11.8	(10.0, 14.1)			26.6
	7	Rolapitant + CC		12.6	(10.7, 14.8)	1.062	(0.950, 1.188)	
	14	CC		12.8	(10.9, 15.1)	1.082	(0.989, 1.184)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	CC	99	30.3	(25.1, 36.7)			16.4
	7	Rolapitant + CC		30.4	(26.1, 35.4)	1.002	(0.932, 1.077)	
	14	CC		31.7	(26.2, 38.3)	1.045	(0.981, 1.113)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	CC	77	30.9	(25.0, 38.1)			18.2
	7	Rolapitant + CC		31.4	(26.7, 36.9)	1.016	(0.933, 1.108)	
	14	CC		32.7	(25.8, 41.4)	1.058	(0.976, 1.147)	

Statistical analysis of the effect of rolapitant and its active metabolite on the Tmax of midazolam and 1-hydroxymidazolam using non-parametric analysis is shown below.

Analyte	Parameter[a]	Between-Treatment Comparison	N[b]	Hodges-Lehmann Estimate Median Difference[c]	90% CI for Estimate of Median Difference[d]
Midazolam	t_{max} (h)	Day 7 (Rolapitant + CC) vs. Day 1 (CC)	32	0.008	(-0.117, 0.125)
		Day 14 (CC) vs. Day 1 (CC)	31	0.117	(0.000, 0.133)
1-hydroxy-midazolam	t_{max} (h)	Day 7 (Rolapitant + CC) vs. Day 1 (CC)	32	0.000	(-0.125, 0.017)
		Day 14 (CC) vs. Day 1 (CC)	31	0.104	(-0.008, 0.133)

Conclusions:

- Co-administration of rolapitant IV with the Cooperstown cocktail (containing 3 mg midazolam) on Day 7 resulted in a decrease in Cmax, AUC0-last, and AUC0-inf parameters by 14%, 19%, and 16%, respectively. This slight decrease was sustained through Day 14 (12%, 14%, and 14% decrease for Cmax, AUC0-last, and AUC0-inf).
- There was no effect on 1-hydroxymidazolam systemic exposure on either Day 7 or Day 14.

Reviewer's comment: 1-hydroxymidazolam systemic exposures increased in a small magnitude (< 10%) on Day 7 and Day 14 although the 90%CI for the geometric mean ratios were contained within the 80-125% bound.

- There was no effect on midazolam or 1'-hydroxymidazolam tmax following rolapitant IV co-administration.

Omeprazole (CYP2C19)

Omeprazole concentration-time profiles are shown below.

Figure 7. Mean (SD) Omeprazole Plasma Concentration-Time Profile

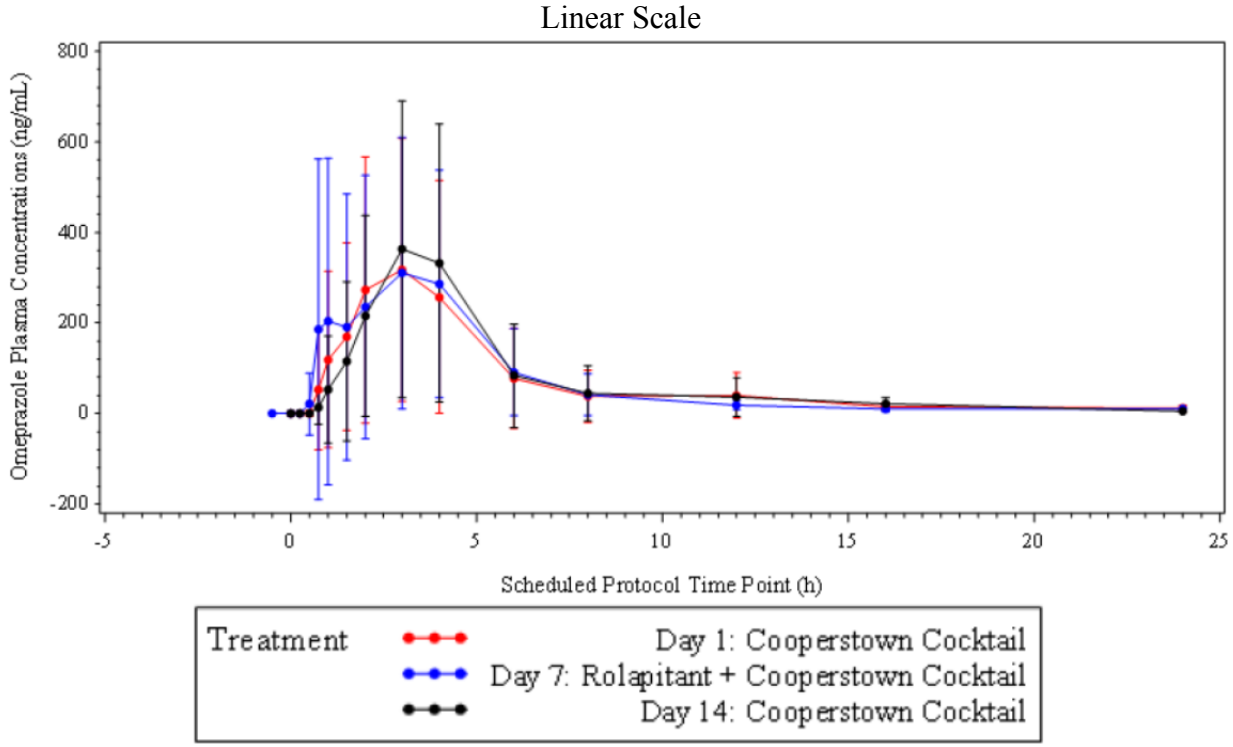
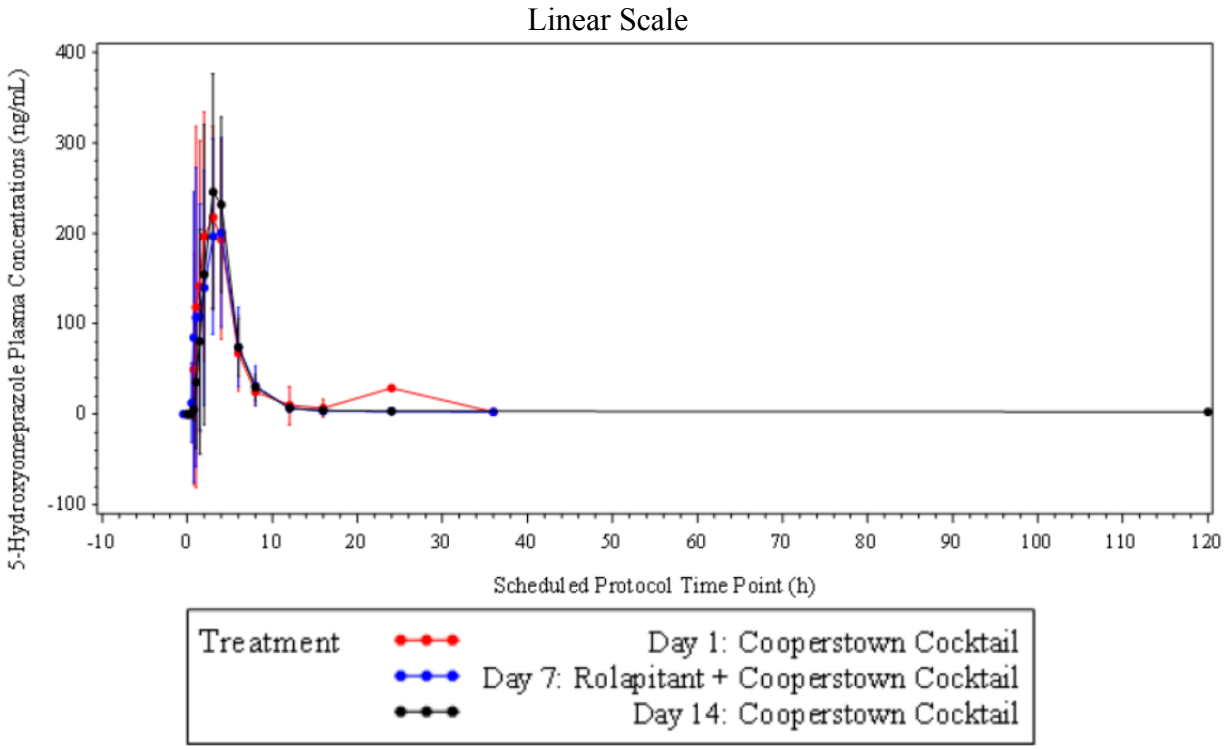


Figure 8. Mean (SD) 5-Hydroxyomeprazole Plasma Concentration-Time Profile



Descriptive Summary of the PK parameters of omeprazole and its metabolite estimated by non-compartmental analysis is shown below.

Treatment	Day	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
Analyte = Omeprazole							
Cooperstown Cocktail	1	n	36	36	24	36	24
		Mean	511.83	2.76	1.07	1212.38	1316.32
		SD	309.199	1.914	0.489	1012.517	1059.085
		Median	467.50	2.98	0.93	782.00	980.20
		Min, Max	142.0, 1570.0	0.8, 12.0	0.6, 2.9	308.0, 4789.6	354.5, 4827.1
		%CV	60.4	69.4	45.9	83.5	80.5
		Geometric Mean	433.3	2.34	0.99	945.52	1047.03
Rolapitant IV + Cooperstown Cocktail	7	n	32	32	25	32	25
		Mean	560.19	2.68	1.48	1337.43	1491.35
		SD	341.432	1.462	1.250	1120.550	1243.061
		Median	424.50	3.00	1.05	997.33	1117.25
		Min, Max	172.0, 1440.0	0.8, 6.1	0.8, 6.9	298.5, 4982.0	349.8, 5081.1
		%CV	60.9	54.5	84.2	83.8	83.4
		Geometric Mean	479.70	2.25	1.25	1052.49	1152.82
Cooperstown Cocktail	14	n	31	31	20	31	20
		Mean	552.16	2.95	1.30	1295.97	1541.79
		SD	305.470	0.861	0.622	1191.274	1287.674
		Median	464.00	3.00	1.10	766.64	1220.78
		Min, Max	123.0, 1360.0	1.0, 4.0	0.8, 3.5	263.4, 5624.4	591.0, 5651.6
		%CV	55.3	29.2	48.0	91.9	83.5
		Geometric Mean	483.44	2.81	1.20	981.88	1220.23
Analyte = 5-OH-Omeprazole							
Cooperstown Cocktail	1	n	36	36	33	36	33
		Mean	350.92	2.88	1.59	977.27	1010.51
		SD	131.793	1.923	0.270	250.907	251.512
		Median	341.50	2.99	1.57	1033.91	1062.96
		Min, Max	59.0, 639.0	0.8, 12.0	1.0, 2.2	343.5, 1474.1	366.9, 1482.0
		%CV	37.6	66.7	17.0	25.7	24.9
		Geometric Mean	320.59	2.44	1.56	939.66	972.93
Rolapitant IV + Cooperstown Cocktail	7	n	32	32	30	32	30
		Mean	329.3	2.75	1.70	940.78	957.48
		SD	100.611	1.475	0.268	203.351	211.021
		Median	320.00	3.00	1.65	1014.26	1038.03
		Min, Max	88.5, 532.0	0.8, 6.1	1.1, 2.2	401.1, 1436.6	409.4, 1450.6
		%CV	30.6	53.6	15.8	21.6	22.0
		Geometric Mean	311.19	2.30	1.68	916.47	931.53
Cooperstown Cocktail	14	n	31	31	30	31	30
		Mean	360.36	3.06	1.77	977.77	986.18
		SD	100.168	0.805	0.467	214.183	217.460
		Median	349.00	3.00	1.62	980.93	969.20
		Min, Max	96.2, 578.0	1.5, 4.0	1.0, 3.5	475.8, 1343.6	490.5, 1354.5
		%CV	27.8	26.3	26.4	21.9	22.1
		Geometric Mean	344.02	2.95	1.72	952.62	960.79

Statistical analysis of the effect of rolapitant and its active metabolite on the systemic exposures of omeprazole and 5-hydroxyomeprazole is shown below.

Parameter	Day	Treatment	N[a]	Geometric LS Mean	Geometric LS Means 95% CI	Treatment Ratio[b]	90% CI for Ratio	Within Subject CV(%)[c]
Analyte = Omeprazole								
C_{max} (ng/mL)	1	CC	99	433.3	(354.6, 529.5)			34.3
	7	Rolapitant + CC		492.7	(406.7, 596.9)	1.137	(0.994, 1.301)	
	14	CC		497.3	(413.3, 598.4)	1.148	(0.986, 1.336)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	CC	99	945.5	(751.6, 1189.6)			22.7
	7	Rolapitant + CC		1051.7	(841.6, 1314.3)	1.112	(1.011, 1.223)	
	14	CC		987.6	(779.1, 1251.8)	1.044	(0.931, 1.172)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	CC	69	1027.0	(802.1, 1315.0)			21.6
	7	Rolapitant + CC		1088.1	(858.5, 1379.2)	1.059	(0.927, 1.210)	
	14	CC		1048.2	(828.7, 1325.9)	1.021	(0.889, 1.172)	
Analyte = 5-OH-Omeprazole								
C_{max} (ng/mL)	1	CC	99	320.6	(272.7, 376.9)			24.6
	7	Rolapitant + CC		320.3	(281.4, 364.6)	0.999	(0.902, 1.106)	
	14	CC		352.9	(313.5, 397.2)	1.101	(0.989, 1.225)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	CC	99	939.7	(848.3, 1040.8)			12.7
	7	Rolapitant + CC		924.3	(851.0, 1003.9)	0.984	(0.936, 1.034)	
	14	CC		958.6	(882.8, 1041.0)	1.020	(0.959, 1.086)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	CC	93	969.4	(874.6, 1074.5)			11.6
	7	Rolapitant + CC		932.4	(855.1, 1016.7)	0.962	(0.913, 1.013)	
	14	CC		968.0	(891.7, 1050.8)	0.999	(0.946, 1.054)	

Statistical analysis of the effect of rolapitant and its active metabolite on the Tmax of omeprazole and 5-hydroxyomeprazole using non-parametric analysis is shown below.

Analyte	Parameter[a]	Between-Treatment Comparison	N[b]	Hodges-Lehmann Estimate Median Difference[c]	90% CI for Estimate of Median Difference[d]
Omeprazole	t_{max} (h)	Day 7 (Rolapitant + CC) vs. Day 1 (CC)	32	-0.017	(-0.625, 0.483)
		Day 14 (CC) vs. Day 1 (CC)	31	0.467	(-0.033, 0.750)
5-hydroxy-omeprazole	t_{max} (h)	Day 7 (Rolapitant + CC) vs. Day 1 (CC)	32	-0.058	(-0.650, 0.483)
		Day 14 (CC) vs. Day 1 (CC)	31	0.258	(-0.050, 0.742)

Conclusions:

- Co-administration of rolapitant IV with the Cooperstown cocktail (containing 40 mg omeprazole) had no effect on the systemic exposure of omeprazole (90% CIs for the raios of geometric means of AUC0-last and AUC0-inf on Day 7 and Day 14 were all within the 0.80 to 1.25 range) or on tmax.
- A marginal increase in omeprazole Cmax following rolapitant IV administration was noted (14% and 15% on Days 7 and 14, respectively; with 90% CI for the ratio of geometric means were 0.994 to 1.301 and 0.986 to 1.336, respectively). However, this increase is unlikely to be clinically significant.

Reviewer's comment: Concurred.

Warfarin (CYP2C9)

S-warfarin concentration-time profiles are shown below.

Figure 9. Mean (SD) S-Warfarin Plasma Concentration-Time Profile

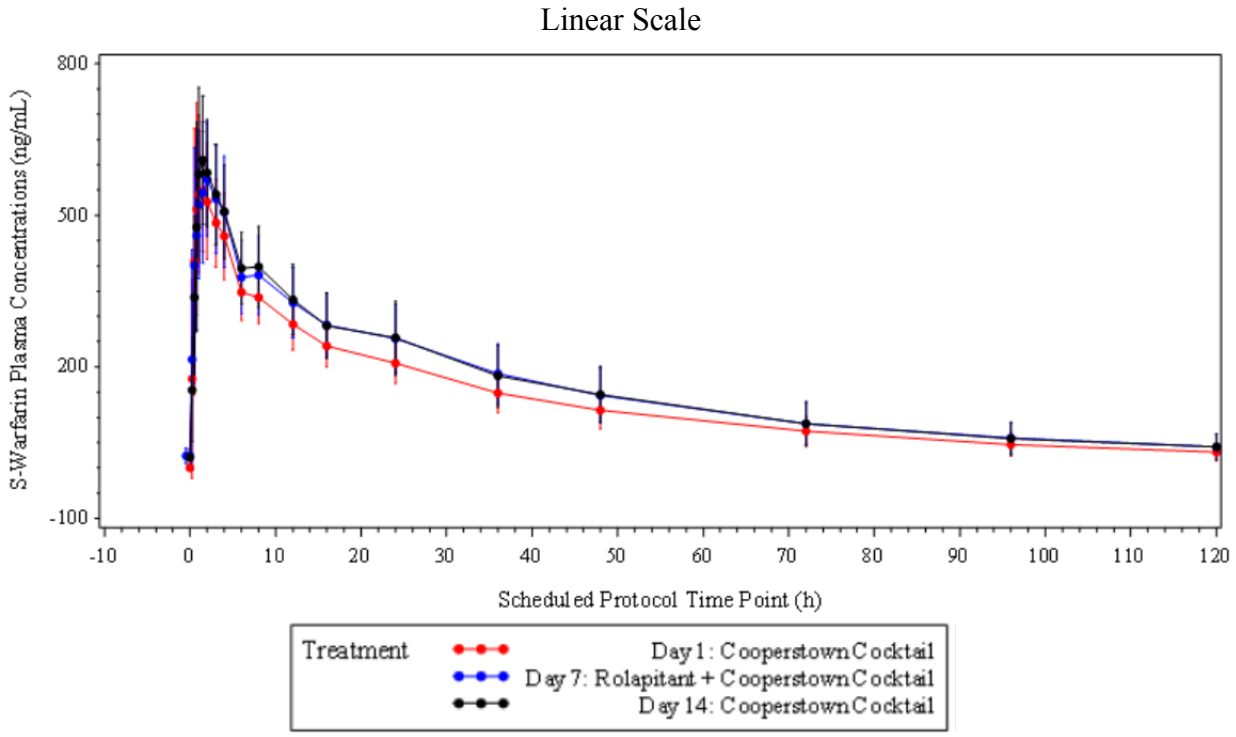
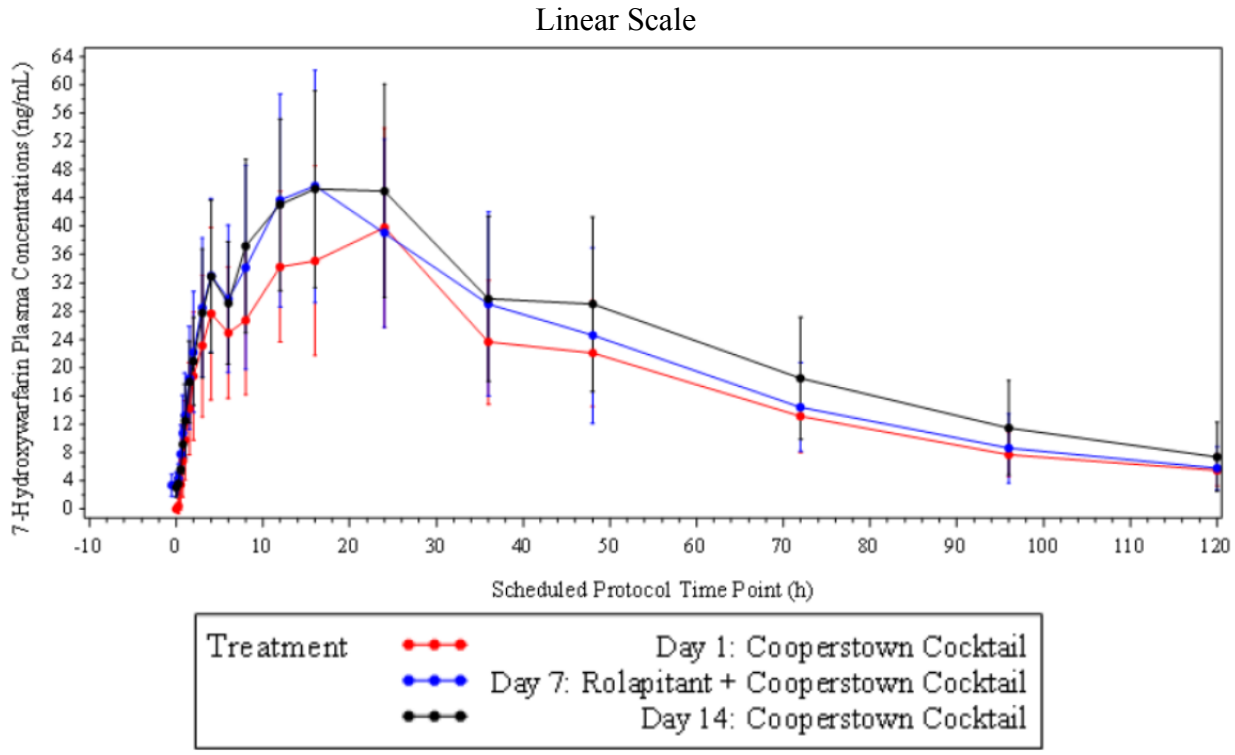


Figure 10. Mean (SD) 7-Hydroxyowarfarin Plasma Concentration-Time Profile



Descriptive Summary of the PK parameters of S-Warfarin and its metabolite estimated by non-compartmental analysis is shown below.

Treatment	Day	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
Analyte = S-Warfarin							
Cooperstown Cocktail	1	n	36	36	36	36	36
		Mean	648.11	1.24	37.63	15641.97	17474.25
		SD	139.759	0.778	8.144	3663.264	4754.561
		Median	656.00	1.00	36.62	14798.01	16341.52
		Min, Max	387.0, 972.0	0.5, 4.0	23.7, 52.7	8602.7, 22589.6	9085.0, 27314.3
		%CV	21.6	62.8	21.6	23.4	27.2
		Geometric Mean	633.10	1.05	36.77	15221.17	16863.95
Rolapitant IV + Cooperstown Cocktail	7	n	32	32	32	32	32
		Mean	655.88	1.72	39.73	18607.49	21182.69
		SD	129.333	1.064	7.352	5513.976	7252.858
		Median	649.00	1.53	39.74	17520.16	18902.05
		Min, Max	406.0, 986.0	0.3, 4.0	25.9, 52.9	9760.9, 29832.7	10121.5, 37005.9
		%CV	19.7	61.8	18.5	29.6	34.2
		Geometric Mean	643.21	1.38	39.03	17829.52	20039.41
Cooperstown Cocktail	14	n	31	31	31	31	31
		Mean	659.26	1.54	39.83	18732.22	21405.23
		SD	123.008	0.826	10.632	5669.753	7809.023
		Median	675.00	1.50	38.44	17098.67	18029.11
		Min, Max	420.0, 894.0	0.8, 4.0	25.1, 66.1	9911.0, 32193.5	10749.4, 41824.9
		%CV	18.7	53.6	26.7	30.3	36.5
		Geometric Mean	647.59	1.39	38.54	17960.64	20204.6
Analyte = 7-OH-Warfarin							
Cooperstown Cocktail	1	n	36	36	32	36	32
		Mean	44.06	19.65	36.28	2173.79	2479.12
		SD	13.793	6.399	15.268	600.785	660.779
		Median	44.8	24.00	31.08	2024.05	2236.00
		Min, Max	23.5, 74.0	4.0, 24.1	20.7, 101.0	1243.3, 4215.0	1310.3, 4738.3
		%CV	31.3	32.6	42.1	27.6	26.7
		Geometric Mean	42.00	18.07	34.15	2101.65	2403.12
Rolapitant IV + Cooperstown Cocktail	7	n	32	32	29	32	29
		Mean	49.99	17.64	33.15	2490.79	2776.39
		SD	16.889	6.618	6.843	851.746	943.826
		Median	47.70	16.02	32.47	2540.93	2798.62
		Min, Max	26.9, 92.6	8.0, 35.9	23.2, 54.2	1166.7, 5794.6	1432.3, 6413.0
		%CV	33.8	37.5	20.6	34.2	34.0
		Geometric Mean	47.36	16.62	32.52	2364.28	2644.01
Cooperstown Cocktail	14	n	31	31	30	31	30
		Mean	53.06	18.07	38.27	2820.29	3308.09
		SD	12.675	6.201	16.159	884.935	1403.986
		Median	49.30	16.02	34.50	2651.79	3011.75
		Min, Max	27.5, 81.9	4.0, 24.1	22.1, 99.4	1395.7, 5915.4	1614.4, 8538.5
		%CV	23.9	34.3	42.2	31.4	42.4
		Geometric Mean	51.59	16.71	35.94	2705.27	3101.98

Statistical analysis of the effect of rolapitant and its active metabolite on the systemic exposures of S-warfarin and 7-hydroxywarfarin is shown below.

Parameter	Day	Treatment	N[a]	Geometric LSM	Geometric LS Means 95% CI	Treatment Ratio[b]	90% CI for Ratio	Within Subject CV(%)[c]
Analyte = S-Warfarin								
C_{max} (ng/mL)	1	CC	99	633.1	(587.2, 682.5)			14.0
	7	Rolapitant + CC		649.1	(604.0, 697.5)	1.025	(0.964, 1.091)	
	14	CC		651.4	(607.7, 698.3)	1.029	(0.970, 1.091)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	CC	99	15221.2	(14036.6, 16505.7)			6.4
	7	Rolapitant + CC		17806.5	(16171.2, 19607.1)	1.170	(1.137, 1.203)	
	14	CC		1154.0	(16491.1, 19984.6)	1.193	(1.154, 1.233)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	CC	99	16864.0	(15386.4, 18483.4)			7.1
	7	Rolapitant + CC		19888.1	(17829.4, 22184.5)	1.179	(1.147, 1.213)	
	14	CC		20366.0	(18208.1, 22779.6)	1.208	(1.163, 1.254)	
Analyte = 7-OH-Warfarin								
C_{max} (ng/mL)	1	CC	99	42.0	(37.7, 46.7)			15.3
	7	Rolapitant + CC		48.6	(43.3, 54.7)	1.158	(1.083, 1.238)	
	14	CC		52.1	(47.7, 56.9)	1.241	(1.170, 1.315)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	CC	99	2101.6	(1924.9, 2294.7)			15.4
	7	Rolapitant + CC		2396.6	(2138.7, 2685.6)	1.140	(1.067, 1.219)	
	14	CC		2701.7	(2437.0, 2995.1)	1.286	(1.203, 1.374)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	CC	91	2387.6	(2186.8, 2606.9)			17.2
	7	Rolapitant + CC		2698.4	(2418.1, 3011.1)	1.130	(1.055, 1.211)	
	14	CC		3086.3	(2718.5, 3504.0)	1.293	(1.177, 1.419)	

Statistical analysis of the effect of rolapitant and its active metabolite on the Tmax of warfarin and 7-hydroxywarfarin using non-parametric analysis is shown below.

Analyte	Parameter[a]	Between-Treatment Comparison	N[b]	Hodges-Lehmann Estimate Median Difference[c]	90% CI for Estimate of Median Difference[d]
S-Warfarin	t_{max} (h)	Day 7 (Rolapitant + CC) vs. Day 1 (CC)	32	0.396	(-0.008, 0.625)
		Day 14 (CC) vs. Day 1 (CC)	31	0.242	(-0.017, 0.500)
7-hydroxy-warfarin	t_{max} (h)	Day 7 (Rolapitant + CC) vs. Day 1 (CC)	32	-3.908	(-4.025, 0.025)
		Day 14 (CC) vs. Day 1 (CC)	31	-0.033	(-4.000, 0.025)

Conclusions:

- Co-administration of rolapitant IV with the Cooperstown cocktail (containing 10 mg S-warfarin + 10 mg vitamin K) had no effect on Day 7 and Day 14 S-warfarin systemic exposure (90% CIs for Cmax and AUC0-last geometric LSM ratios were within the 0.80-1.25 range; Day 14 AUC0-inf upper 90% CI limit = 1.254) or on tmax.
- Co-administration of rolapitant IV with the Cooperstown cocktail (containing 10 mg S-warfarin + 10 mg vitamin K) had no effect on Day 7 7-hydroxywarfarin Cmax, AUC0-last, and AUC0-inf (90% CIs for geometric ratios of Cmax, AUC0-last, and AUC0-inf LSMs were all within the 0.80 to 1.25 range).
- On Day 14, increases of 24%, 29%, and 29% were observed for 7-hydroxywarfarin Cmax, AUC0- last, and AUC0-inf parameters, however, these changes are not likely to be clinically significant.

Reviewer's comments: The reviewer disagrees with the sponsor's conclusion.

The AUC0-inf of warfarin on Day 7 and Day 14 were increased by 18% and 21%, respectively. The 90%CI for the ratios was also shifted upwards and did not contain 1. Similar trend was observed on AUC0-last. In addition, Cmax, AUC0-inf and AUC0-last of 7-hydroxywarfarin were also elevated on Day 7 and continued to be elevated on Day 14. In fact, the increase in exposures to 7-hydroxywarfarin on Day 14 was more than that on Day 7.

In the original NDA for oral rolapitant, the sponsor conducted an in vivo DDI study using tolbutamide (CYP2C9 substrate) and found no interaction.

No INR was measured in this study. However, based upon the magnitude of changes in exposures to warfarin, the reviewer recommends monitoring INR when warfarin is co-administered with rolapitant.

Caffeine (CYP1A2)

Caffeine concentration-time profiles are shown below.

Figure 11. Mean (SD) Caffeine Plasma Concentration-Time Profile

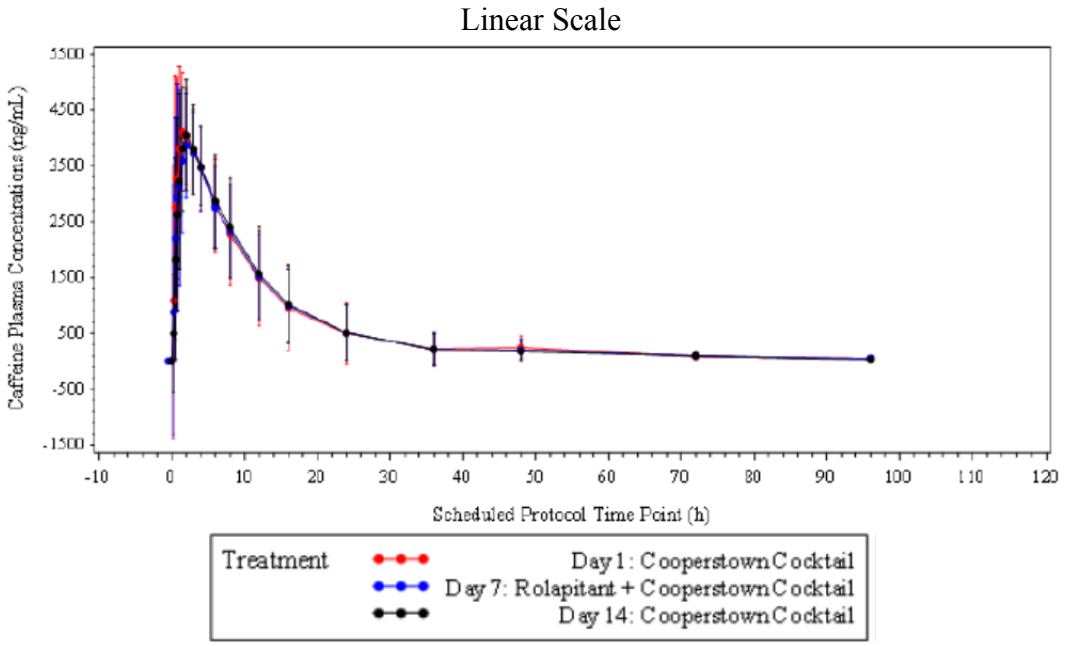
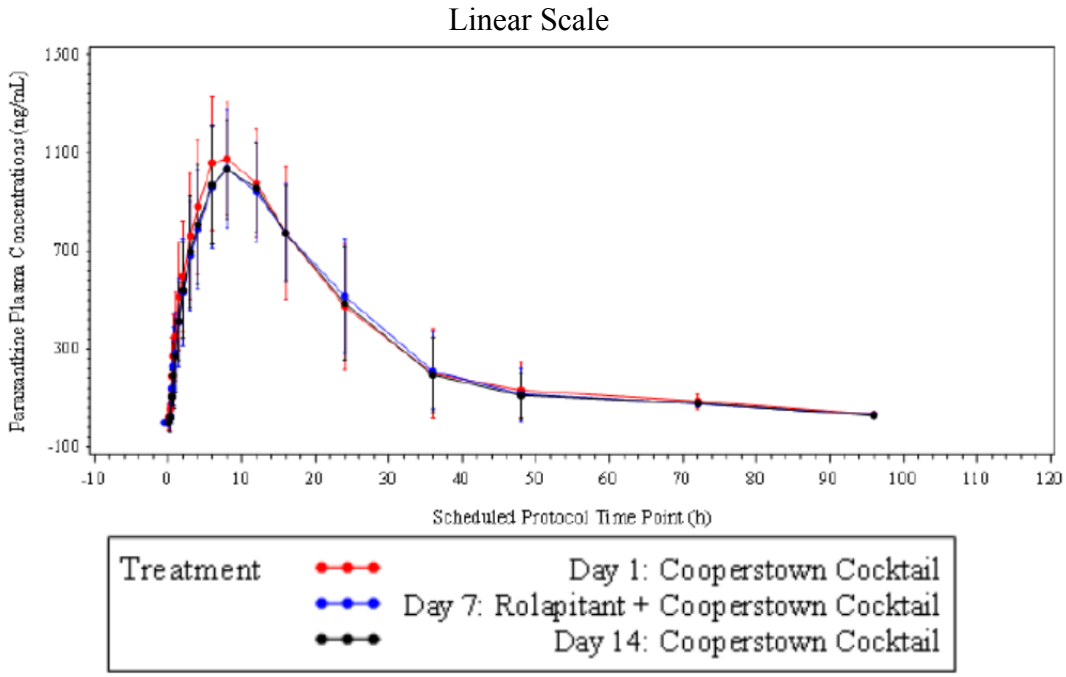


Figure 12. Mean (SD) Paraxanthine Plasma Concentration-Time Profile



Descriptive Summary of the PK parameters of caffeine and its metabolite estimated by non-compartmental analysis is shown below.

Treatment	Day	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
Analyte = Caffeine							
Cooperstown Cocktail	1	n	36	36	36	36	36
		Mean	5135.28	1.41	6.01	48009.29	48557.45
		SD	1537.119	0.985	2.771	25596.65	25797.67
		Median	5050.00	1.50	5.03	40099.48	40418.14
		Min, Max	2900.0, 10000.0	0.3, 4.0	2.7, 14.1	20748.2, 134923.9	20892.9, 136136.6
		%CV	29.9	69.8	46.1	53.3	53.1
		Geometric Mean	4936.50	1.10	5.53	43087.89	43611.74
Rolapitant IV + Cooperstown Cocktail	7	n	32	32	32	32	32
		Mean	4925.31	1.58	6.35	48150.26	48706.86
		SD	1376.869	1.053	2.759	23742.11	23979.31
		Median	4485.00	1.50	5.61	41224.49	41774.99
		Min, Max	3450.0, 9260.0	0.3, 4.0	3.1, 14.7	21882.5, 132839.1	22074.8, 134195.5
		%CV	28.0	66.5	43.5	49.3	49.2
		Geometric Mean	4766.32	1.22	5.91	44020.54	44544.88
Cooperstown Cocktail	14	n	31	31	31	31	31
		Mean	4499.35	1.63	6.26	48767.98	49305.98
		SD	855.570	0.912	2.712	24324.09	24499.71
		Median	4470.00	1.50	5.37	41962.92	42365.02
		Min, Max	3250.0, 6490.0	0.5, 4.0	3.1, 13.4	22721.2, 123078.4	23092.3, 124571.8
		%CV	19.0	56.0	43.3	49.9	49.7
		Geometric Mean	4421.97	1.40	5.84	44397.26	44932.11
Analyte = Paraxanthine							
Cooperstown Cocktail	1	n	36	36	36	36	36
		Mean	1159.94	8.60	7.58	24090.80	24803.37
		SD	215.701	2.917	3.213	7516.630	7731.122
		Median	1140.00	8.00	6.30	22810.62	23359.37
		Min, Max	712.0, 1630.0	6.0, 16.0	3.6, 17.1	13046.0, 44046.5	14349.8, 45037.8
		%CV	18.6	33.9	42.4	31.2	31.2
		Geometric Mean	1139.60	8.20	7.07	23052.41	23745.28
Rolapitant IV + Cooperstown Cocktail	7	n	32	32	32	32	32
		Mean	1093.44	9.65	7.86	23903.47	24661.48
		SD	210.236	4.428	3.247	6392.207	6599.700
		Median	1110.00	8.00	6.95	23414.22	23876.42
		Min, Max	686.0, 1620.0	6.0, 24.1	4.2, 17.2	13636.6, 41678.0	14494.5, 43298.2
		%CV	19.2	45.9	41.3	26.7	26.8
		Geometric Mean	1073.90	8.99	7.37	23119.61	23858.97
Cooperstown Cocktail	14	n	31	31	31	31	31
		Mean	1093.45	9.55	7.69	23335.59	24096.25
		SD	180.668	4.087	2.822	6061.864	6303.347
		Median	1090.00	8.00	6.79	22985.79	23650.86
		Min, Max	693.0, 1510.0	6.0, 24.0	4.4, 15.7	13815.3, 40193.0	14881.9, 41687.3
		%CV	16.5	42.8	36.7	26.0	26.2
		Geometric Mean	1078.51	8.90	7.30	22611.63	23348.47

Statistical analysis of the effect of rolapitant and its active metabolite on the systemic exposures of caffeine and paraxanthine is shown below.

Parameter	Day	Treatment	N[a]	Geometric LS Mean	Geometric LS Means 95% CI	Treatment Ratio[b]	90% CI for Ratio	Within Subject CV(%)[c]
Analyte = Caffeine								
C_{max} (ng/mL)	1	CC	99	4936.5	(4489.5, 5428.1)			16.7
	7	Rolapitant + CC		4796.5	(4391.3, 5239.1)	0.972	(0.902, 1.047)	
	14	CC		4437.0	(4152.9, 4740.6)	0.899	(0.841, 0.961)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	CC	99	43087.9	(37010.3, 50163.5)			9.8
	7	Rolapitant + CC		43589.8	(38095.3, 49876.8)	1.012	(0.970, 1.055)	
	14	CC		44510.3	(38759.8, 51113.8)	1.033	(0.987, 1.082)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	CC	99	43611.7	(37480.2, 50746.4)			9.9
	7	Rolapitant + CC		44129.0	(38581.9, 50473.6)	1.012	(0.970, 1.056)	
	14	CC		45056.6	(39276.4, 51687.5)	1.033	(0.986, 1.082)	
Analyte = Paraxanthine								
C_{max} (ng/mL)	1	CC	99	1139.6	(1067.1, 1217.0)			6.4
	7	Rolapitant + CC		1096.0	(1024.2, 1172.8)	0.962	(0.935, 0.990)	
	14	CC		1099.2	(1036.2, 1166.1)	0.965	(0.938, 0.992)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	CC	99	23052.4	(20843.5, 25495.4)			7.0
	7	Rolapitant + CC		23013.3	(21077.0, 25127.4)	0.998	(0.966, 1.031)	
	14	CC		22918.0	(20924.7, 25101.1)	0.994	(0.966, 1.023)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	CC	99	23745.3	(21487.7, 26240.0)			6.9
	7	Rolapitant + CC		23742.6	(21751.0, 25916.7)	1.000	(0.969, 1.031)	
	14	CC		23666.9	(21599.2, 25932.6)	0.997	(0.969, 1.025)	

Statistical analysis of the effect of rolapitant and its active metabolite on the Tmax of caffeine and paraxanthine using non-parametric analysis is shown below.

Analyte	Parameter[a]	Between-Treatment Comparison	N[b]	Hodges-Lehmann Estimate Median Difference[c]	90% CI for Estimate of Median Difference[d]
Caffeine	t_{max} (h)	Day 7 (Rolapitant + CC) vs. Day 1 (CC)	32	0.008	(-0.258, 0.492)
		Day 14 (CC) vs. Day 1 (CC)	31	0.112	(-0.242, 0.375)
Paraxanthine	t_{max} (h)	Day 7 (Rolapitant + CC) vs. Day 1 (CC)	32	0.075	(0.017, 1.017)
		Day 14 (CC) vs. Day 1 (CC)	31	0.108	(0.000, 2.000)

Conclusions:

Co-administration of rolapitant IV with the Cooperstown cocktail (containing 200 mg caffeine) had no effect on caffeine or paraxanthine systemic exposure.

Reviewer's comments: The reviewer concurs with the conclusion.

Dextromethorphan (CYP2D6)

Dextromethorphan (DMX) concentration-time profiles are shown below.

Figure 13. Mean (SD) Dextromethorphan Plasma Concentration-Time Profile

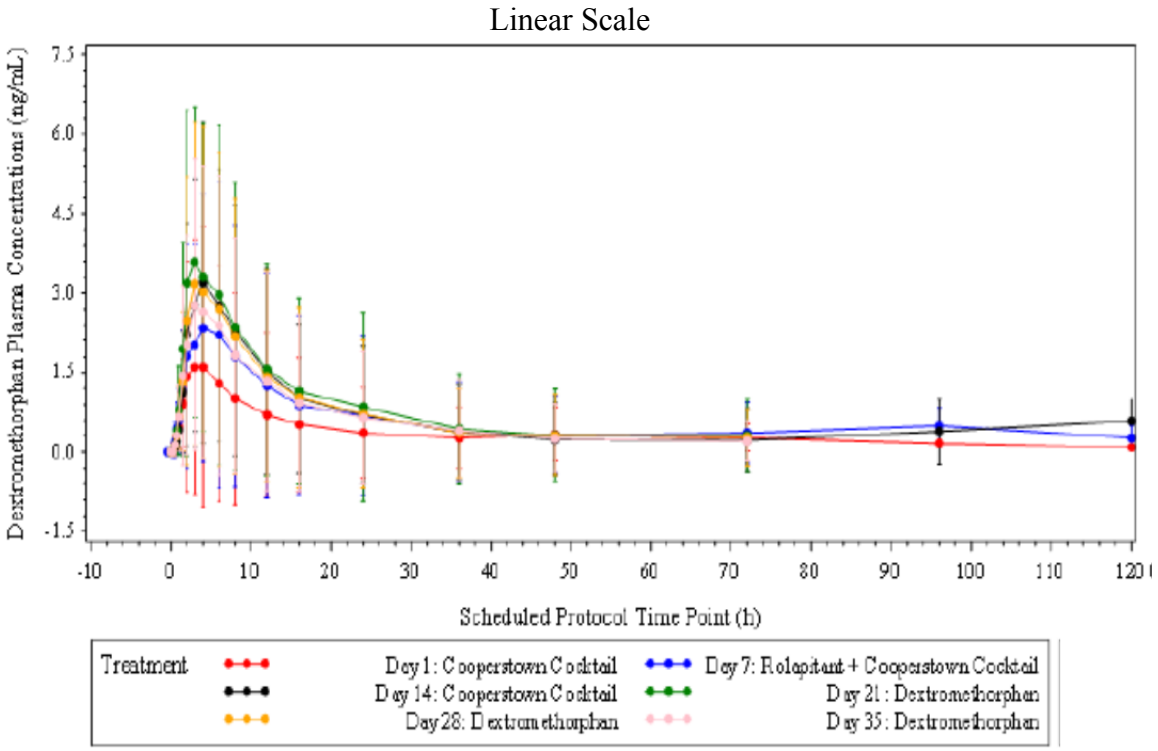
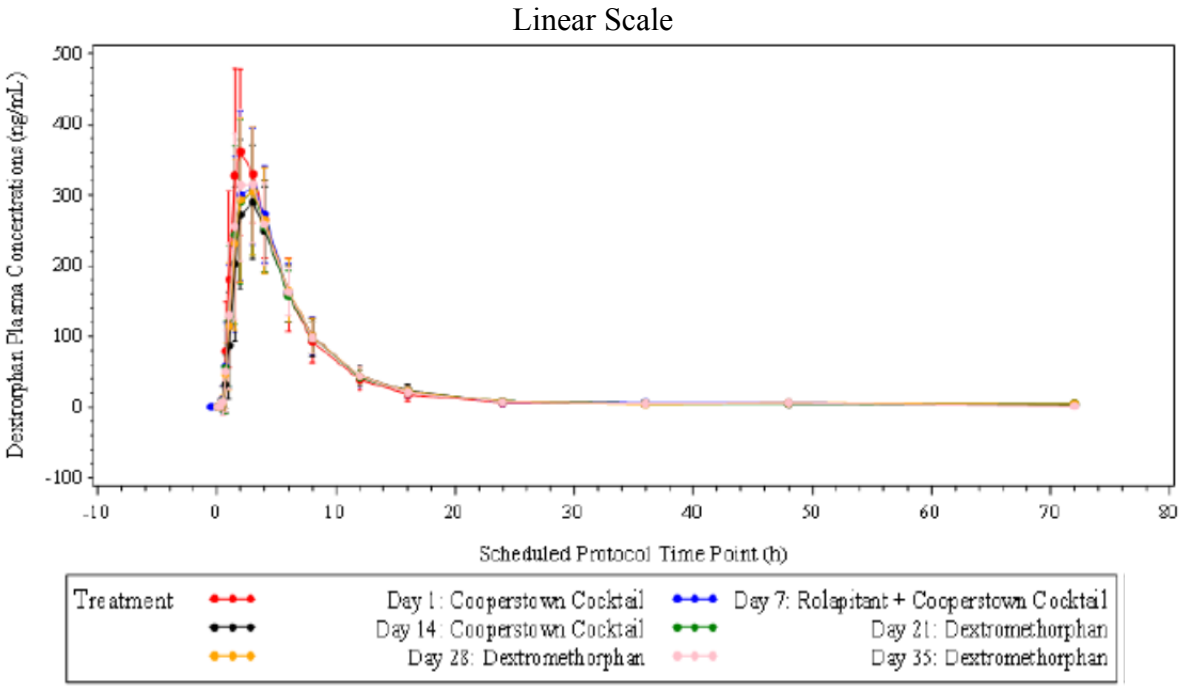


Figure 14. Mean (SD) Dextrorphan Plasma Concentration-Time Profile



Descriptive Summary of the PK parameters of DMX and its metabolite estimated by non-compartmental analysis is shown below.

Treatment	Day	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
Analyte = Dextromethorphan							
Cooperstown Cocktail	1	n	36	36	33	36	33
		Mean	1.91	2.94	8.30	23.49	25.85
		SD	2.744	2.589	2.949	51.559	54.049
		Median	1.02	2.03	7.82	7.08	8.98
		Min, Max	0.2, 12.2	0.8, 15.9	4.6, 19.8	1.2, 237.7	1.4, 241.0
		%CV	143.5	88.1	35.5	219.4	209.1
		Geometric Mean	1.09	2.40	7.90	8.72	10.08
Rolapitant IV + Cooperstown Cocktail	7	n	32	32	32	32	32
		Mean	2.85	3.05	10.21	43.10	44.33
		SD	3.024	1.319	4.012	80.715	83.185
		Median	1.90	3.01	9.54	16.82	17.28
		Min, Max	0.5, 12.6	0.8, 6.0	4.6, 26.2	2.9, 391.9	3.2, 408.0
		%CV	106.1	43.3	39.3	187.3	187.6
		Geometric Mean	1.90	2.74	9.69	19.16	20.09
Cooperstown Cocktail	14	n	31	31	31	31	31
		Mean	3.48	3.54	10.05	50.33	51.68
		SD	3.040	1.285	3.821	78.693	82.382
		Median	2.34	4.00	9.71	26.25	26.73
		Min, Max	0.6, 13.2	1.5, 6.1	5.5, 27.0	3.9, 437.1	4.2, 460.0
		%CV	87.3	36.3	38.0	156.4	159.4
		Geometric Mean	2.48	3.31	9.54	27.27	28.22
Dextromethorphan	21	n	32	32	31	32	31
		Mean	4.36	2.94	10.30	55.96	61.56
		SD	3.919	1.115	3.933	85.369	100.751
		Median	2.94	3.00	9.98	31.87	32.81
		Min, Max	0.5, 15.1	1.5, 6.2	6.1, 27.9	3.0, 444.5	3.3, 534.1
		%CV	90.0	37.9	38.2	152.6	163.7
		Geometric Mean	2.97	2.77	9.81	29.38	32.28
	28	n	32	32	31	32	31
		Mean	3.73	3.27	9.53	48.58	52.61
		SD	3.609	1.212	3.069	74.399	83.256
		Median	2.31	3.00	9.37	20.85	23.39
		Min, Max	0.4, 13.1	1.5, 6.0	4.9, 22.5	2.9, 373.1	4.0, 424.3
		%CV	96.8	37.0	32.2	153.2	158.3
		Geometric Mean	2.41	3.08	9.16	24.77	27.53
	35	n	31	31	31	31	31
		Mean	3.22	3.08	9.58	43.10	44.92
		SD	3.114	1.447	2.592	70.006	74.767
		Median	1.90	3.00	9.40	16.80	17.58
		Min, Max	0.5, 13.0	0.8, 6.0	4.7, 18.0	3.1, 343.7	3.4, 372.6
		%CV	96.7	47.0	27.1	162.4	166.5
		Geometric Mean	2.12	2.77	9.25	20.78	21.83

Treatment	Day	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{1/2}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
Analyte = Dextrorphan							
Cooperstown Cocktail	1	n	36	36	35	36	35
		Mean	397.36	2.27	4.24	2099.15	2142.24
		SD	97.180	0.877	2.044	368.918	367.264
		Median	411.50	2.00	3.76	2058.23	2084.18
		Min, Max	144.0, 556.0	1.5, 4.3	2.4, 12.9	1303.6, 2959.8	1338.2, 2982.4
		%CV	24.5	38.7	48.2	17.6	17.1
		Geometric Mean	382.90	2.13	3.94	2067.31	2111.24
Rolapitant IV + Cooperstown Cocktail	7	n	32	32	32	32	32
		Mean	343.47	2.78	5.36	2069.16	2110.24
		SD	92.033	0.929	3.847	341.515	334.622
		Median	356.50	2.98	4.38	2099.66	2132.79
		Min, Max	88.1, 510.0	1.5, 6.0	2.8, 25.0	1393.3, 2859.4	1527.5, 2903.1
		%CV	26.8	33.4	71.7	16.5	15.9
		Geometric Mean	326.57	2.65	4.83	2041.02	2084.01
Cooperstown Cocktail	14	n	31	31	31	31	31
		Mean	315.06	2.69	5.69	1980.78	2021.85
		SD	88.374	0.758	3.703	335.997	332.481
		Median	310.00	2.97	4.59	1969.52	2005.38
		Min, Max	72.9, 470.0	1.5, 4.0	3.0, 24.1	1298.6, 2601.1	1435.4, 2655.7
		%CV	28.0	28.2	65.0	17.0	16.4
		Geometric Mean	299.54	2.59	5.16	1952.57	1995.16
Dextromethorphan	21	n	32	32	32	32	32
		Mean	330.35	2.61	5.90	2042.48	2085.79
		SD	104.434	0.748	4.166	341.074	329.552
		Median	337.00	2.98	4.41	2106.55	2149.13
		Min, Max	67.1, 493.0	1.5, 4.0	3.1, 26.1	1252.3, 2573.4	1380.0, 2610.1
		%CV	31.6	28.7	70.6	16.7	15.8
		Geometric Mean	308.79	2.50	5.24	2011.85	2058.34
	28	n	32	32	32	32	32
		Mean	338.27	2.66	5.87	2060.41	2100.40
		SD	98.953	0.813	4.680	349.971	337.453
		Median	344.50	2.51	4.51	2141.86	2166.26
		Min, Max	74.5, 489.0	1.5, 4.1	3.2, 29.3	1308.2, 2615.3	1459.4, 2642.5
		%CV	29.3	30.5	79.8	17.0	16.1
		Geometric Mean	318.93	2.55	5.11	2028.99	2072.30
	35	n	31	31	31	31	31
		Mean	343.06	2.46	5.29	2071.54	2106.31
		SD	100.241	0.697	3.205	300.908	292.537
		Median	354.00	2.05	4.29	2130.43	2173.62
		Min, Max	85.0, 523.0	1.5, 4.0	3.0, 19.9	1403.9, 2589.0	1502.3, 2631.2
		%CV	29.2	28.3	60.6	14.5	13.9
		Geometric Mean	323.90	2.37	4.79	2048.95	2085.61

Statistical analysis of the effect of rolapitant and its active metabolite on the systemic exposures of DMX and its metabolite is shown below.

Parameter	Day	Treatment	N[a]	Geometric LS Mean	Geometric LS Means 95% CI	Treatment Ratio[b]	90% CI for Ratio	Within Subject CV(%)[c]
Analyte = Dextromethorphan								
C_{max} (ng/mL)	1	CC	194	1.1	(0.8, 1.5)			33.8
	7	Rolapitant + CC		1.9	(1.4, 2.6)	1.748	(1.520, 2.010)	
	14	CC		2.6	(1.9, 3.6)	2.419	(2.029, 2.883)	
	21	DM		3.0	(2.2, 4.1)	2.741	(2.209, 3.401)	
	28	DM		2.4	(1.7, 3.4)	2.226	(1.831, 2.706)	
	35	DM		2.1	(1.6, 3.0)	1.962	(1.618, 2.379)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	CC	194	8.7	(5.7, 13.2)			31.1
	7	Rolapitant + CC		19.1	(12.8, 28.6)	2.191	(1.914, 2.508)	
	14	CC		29.4	(19.7, 43.7)	3.368	(2.817, 4.027)	
	21	DM		29.3	(19.8, 43.5)	3.361	(2.739, 4.125)	
	28	DM		24.7	(16.6, 36.7)	2.834	(2.336, 3.439)	
	35	DM		20.8	(14.0, 31.0)	2.387	(1.990, 2.864)	
$AUC_{0\text{-inf}}$ (ng•h/mL)	1	CC	189	9.5	(6.3, 14.2)			30.0
	7	Rolapitant + CC		20.0	(13.5, 29.7)	2.115	(1.848, 2.421)	
	14	CC		30.4	(20.5, 44.9)	3.206	(2.692, 3.818)	
	21	DM		30.6	(20.7, 45.2)	3.232	(2.647, 3.947)	
	28	DM		26.1	(17.8, 38.3)	2.756	(2.270, 3.347)	
	35	DM		21.8	(14.8, 32.3)	2.307	(1.922, 2.769)	
Analyte = Dextrorphan								
C_{max} (ng/mL)	1	CC	194	382.9	(346.3, 423.3)			10.4
	7	Rolapitant + CC		333.5	(295.9, 375.9)	0.871	(0.836, 0.907)	
	14	CC		296.5	(259.7, 338.5)	0.774	(0.733, 0.819)	
	21	DM		316.1	(275.1, 363.2)	0.826	(0.779, 0.875)	
	28	DM		325.9	(286.1, 371.2)	0.851	(0.805, 0.900)	
	35	DM		333.3	(293.5, 378.5)	0.870	(0.823, 0.921)	
$AUC_{0\text{-last}}$ (ng•h/mL)	1	CC	194	2067.3	(1946.0, 2196.2)			7.9
	7	Rolapitant + CC		2049.7	(1932.9, 2173.5)	0.991	(0.961, 1.023)	
	14	CC		1947.2	(1831.7, 2069.9)	0.942	(0.909, 0.976)	
	21	DM		2018.3	(1892.5, 2152.4)	0.976	(0.929, 1.026)	
	28	DM		2035.6	(1908.4, 2171.2)	0.985	(0.938, 1.034)	
	35	DM		2059.0	(1951.1, 2172.9)	0.996	(0.950, 1.044)	

Statistical analysis of the effect of rolapitant and its active metabolite on the Tmax of DMX and dextrophan using non-parametric analysis is shown below.

Parameter	Day	Treatment	N[a]	Geometric LS Mean	Geometric LS Means 95% CI	Treatment Ratio[b]	90% CI for Ratio	Within Subject CV(%)[c]
$AUC_{0\text{-}inf}$ (ng•h/mL)	1	CC	193	2098.7	(1976.5, 2228.5)			7.7
	7	Rolapitant + CC		2092.0	(1978.3, 2212.4)	0.997	(0.967, 1.028)	
	14	CC		1991.0	(1878.2, 2110.6)	0.949	(0.916, 0.983)	
	21	DM		2064.0	(1943.8, 2191.6)	0.983	(0.937, 1.032)	
	28	DM		2078.1	(1956.9, 2207.0)	0.990	(0.944, 1.038)	
	35	DM		2094.8	(1990.5, 2204.5)	0.998	(0.952, 1.046)	

Conclusions:

- Co-administration of rolapitant IV with the Cooperstown cocktail (containing 30 mg dextromethorphan) on Day 7 resulted in a 2.2- and 2.1-fold increase in dextromethorphan AUC0- last and AUC0-inf, respectively, and in a 1.7-fold increase in Cmax.
- When the Cooperstown cocktail was administered alone on Day 14 (7 days after rolapitant IV administration), dextromethorphan AUC0-last, AUC0-inf, and Cmax increased 3.4-, 3.2-, and 2.4-fold, respectively, compared with Cooperstown cocktail administration alone on Day 1.
- Following rolapitant IV co-administration on Day 7, dextromethorphan systemic exposure was highest on Day 21 (3.4, 3.2-, and 2.7-fold increase in AUC0-last, AUC0-inf, and Cmax geometric LSMs relative to baseline), and gradually decreased, but remained high through the last day of PK sampling (2.4-, 2.3-, and 2.0-fold increase on Day 35 AUC0-last, AUC0-inf, and Cmax geometric LSMs relative to baseline).
- Dextrorphan systemic exposure (AUC) remained similar to baseline on all days (Days 7, 14, 21, 28, and 35), but a mean Cmax decrease of 23% and 17% was noted on Day 14 and Day 21, respectively.
- In general, dextromethorphan and dextrorphan tmax were similar when dextromethorphan was administered alone or with rolapitant IV. At certain time points, however, a slight delay in dextromethorphan and dextrorphan tmax (median estimate < 1 hour) were noted when the Cooperstown cocktail/dextromethorphan was administered following infusion with rolapitant IV relative to Cooperstown cocktail administration alone.
- Statistical analysis by genotype status (extensive and intermediate metabolizer) showed a similar effect of rolapitant IV co-administration on dextromethorphan PK parameter data in each subgroup, although dextromethorphan PK exposure was lower in extensive metabolizer compared to the data in intermediate metabolizer.

Reviewer's comment: The duration of CYP2D6 inhibition following single dose of rolapitant IV was at least four weeks with the peak inhibition occurring on Day 7 and Day 14 after rolapitant administration. By Day 28 following rolapitant administration, the degree of CYP2D6 inhibition is similar to that on Day 1.

The prolonged inhibition does not appear to be caused by the active metabolite as the IC_{50} of CYP2D6 inhibition by SCH is > 10 uM. The ratio of Cmax/Ki is 0.06 assuming the IC_{50} is 10 uM with Ki of 5 uM ($Ki=IC_{50}/2$). Rolapitant does inhibit CYP2D6 by competitive inhibition. However, the Tmax of rolapitant IV is 30 minute. Thus, the time course of CYP2D6 inhibition, i.e., peak inhibition occurring on Day 7 and Day 14 after dosing does not appear to be due to rolapitant.

There were 11 other metabolites found in mass balance study that were not detectable in plasma but detected urine or feces. Refer to Clin Pharm Review of the NDA for oral rolapitant. Because these metabolites were not detectable in the plasma, it is difficult to determine whether any of these metabolites contributed to the in vivo CYP2D6 inhibition.

The impact of this result on the product labeling, including the oral rolapitant product will need to be addressed. The concerns are two-fold:

a) when the disallowed concomitant medications (prohibited or avoided) may be resumed in patients following a single dose of rolapitant.

b) Rolapitant is currently allowed to be given repeatedly at an interval no less than every two weeks. This repeated dosing may result in additive inhibitory effect on CYP2D6. Whether CYP2D6 substrates should be allowed in the repeated dosing scenario needs to be addressed. If they are not allowed, when they may be resumed also needs to be addressed.

This part of the study was to evaluate the duration of CYP2D6 inhibition. The sponsor proposes to use this information to fulfill the PMC requirement for the oral rolapitant NDA:

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

4.2.2. Pivotal BA/BE Study: PR-11-5016-C

Reviewer's comment: Because the IV product used in this study was manufactured at a site which failed to meet the process inspection, the sponsor is required to conduct another relative BA/BE study using the final-to-marketed IV product manufactured at (b) (4) *a site proposed by the sponsor during the review cycle. The results presented here from the pivotal study (PR-11-5016-C) cannot be used to support the approval. The data presented here are for information only.*

Title: An Open-label, Randomized, Pivotal, Bioequivalence Study of Oral And Intravenous Rolapitant.

Study Design: open-label, randomized, single-dose, single-center, parallel-group bioequivalence study of rolapitant oral and rolapitant IV in healthy male and female subjects.

Treatment Groups

Treatment	Drug Name	Formulation	Strength	Dose	Dosing Conditions	Route
A	Rolapitant	Capsule	50 mg	4 × 50 mg	Fasting	Oral
B	Rolapitant	Sterile solution for IV administration	2 mg/mL	185 mg	Fasting	IV

IV = intravenous

Product information

The lot number for the capsules used in the study was PD12053. It is manufactured at (b) (4)

The lot number for the IV solution was 22901.001. It is manufactured at (b) (4)

PK sampling

Blood samples for PK analysis were taken before oral dosing/start of infusion (predose) and at 0.25 0.5, 0.75, 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 after oral dosing/start of infusion.

Pharmacokinetic Results

Demographics

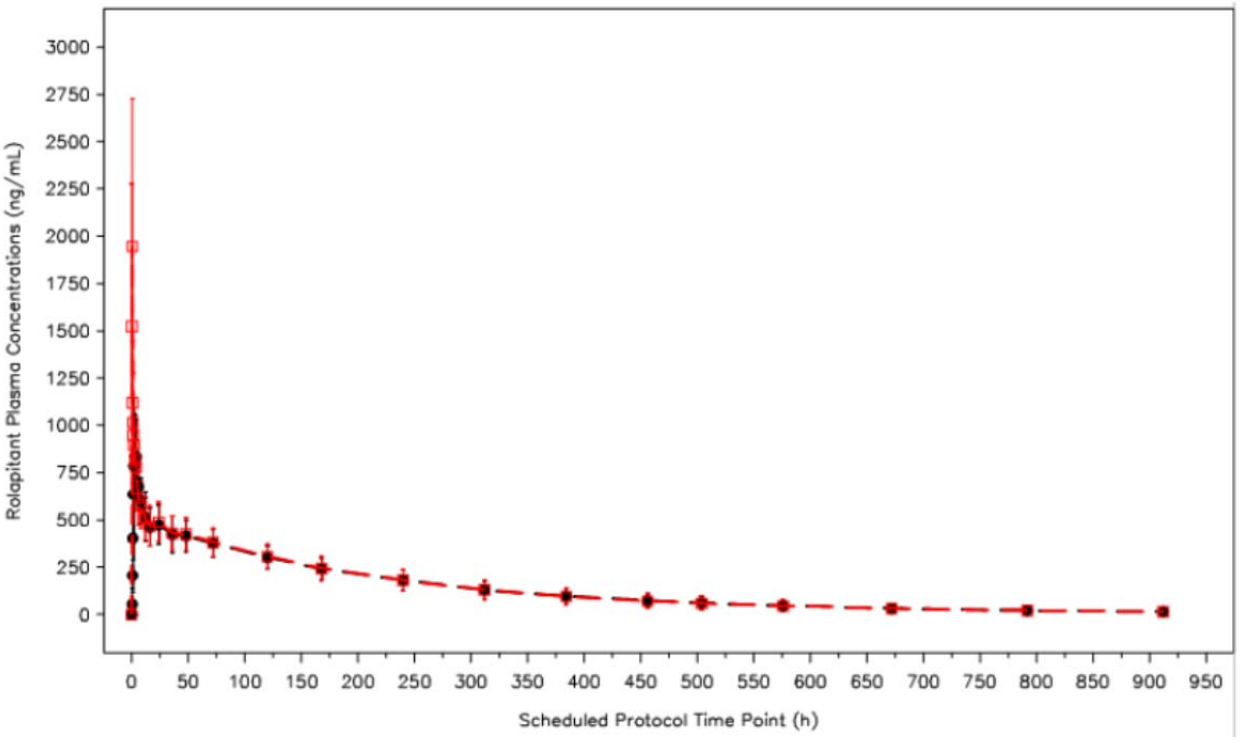
Characteristic	Treatment A 200 mg rolapitant oral N = 67	Treatment B 185 mg rolapitant IV N = 71
Gender - n (%)		
Male	42 (62.7)	44 (62.0)
Female	25 (37.3)	27 (38.0)
Age (y)		
Mean (SD)	38.2 (8.5)	40.1 (8.6)
Race - n (%)		
White	28 (41.8)	23 (32.4)
American Indian/Alaska Native	3 (4.5)	0
Asian	1 (1.5)	1 (1.4)
Black/African American	35 (52.2)	47 (66.2)
Ethnicity		
Hispanic/Latino	20 (29.9)	13 (18.3)
Non-Hispanic/Latino	47 (70.1)	58 (81.7)
Weight (kg)		
Mean (SD)	78.49 (11.57)	77.86 (13.22)
Height (cm)		
Mean (SD)	172.6 (9.3)	172.8 (10.9)
BMI (kg/m²)		
Mean (SD)	26.26 (2.57)	25.99 (3.10)

Summary of PK Parameters

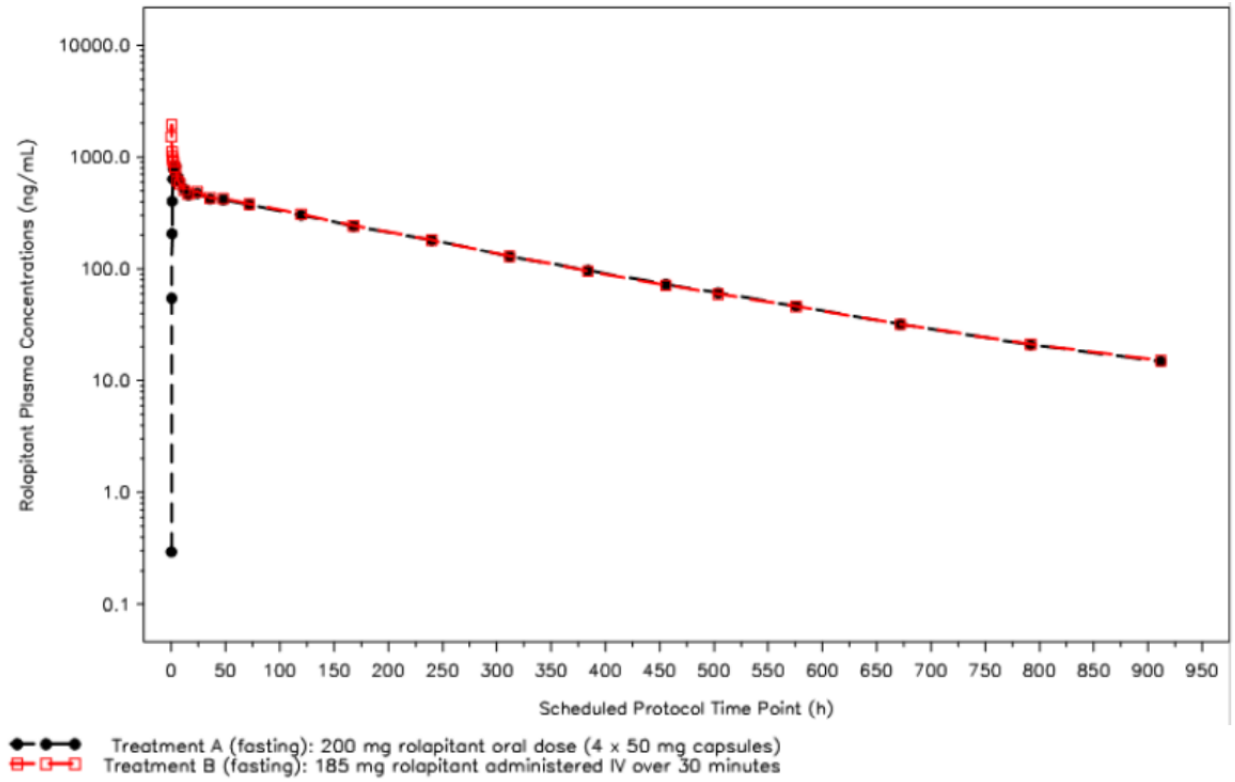
The mean concentration-time profiles of rolapitant are shown below.

Figure 15. Mean Rolapitant Plasma Concentration-Time Profile

Linear Scale

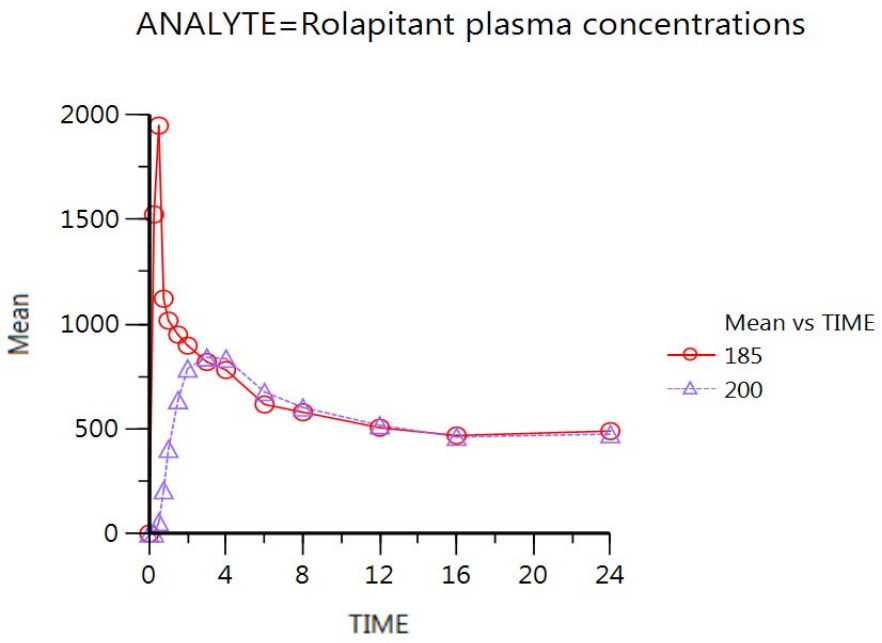


Semi-Log Scale



The mean concentration-time profile of rolapitant in the first 24 hours is shown below.

Figure 16. Mean Rolapitant Plasma Concentration-Time Profile – First 24 hours

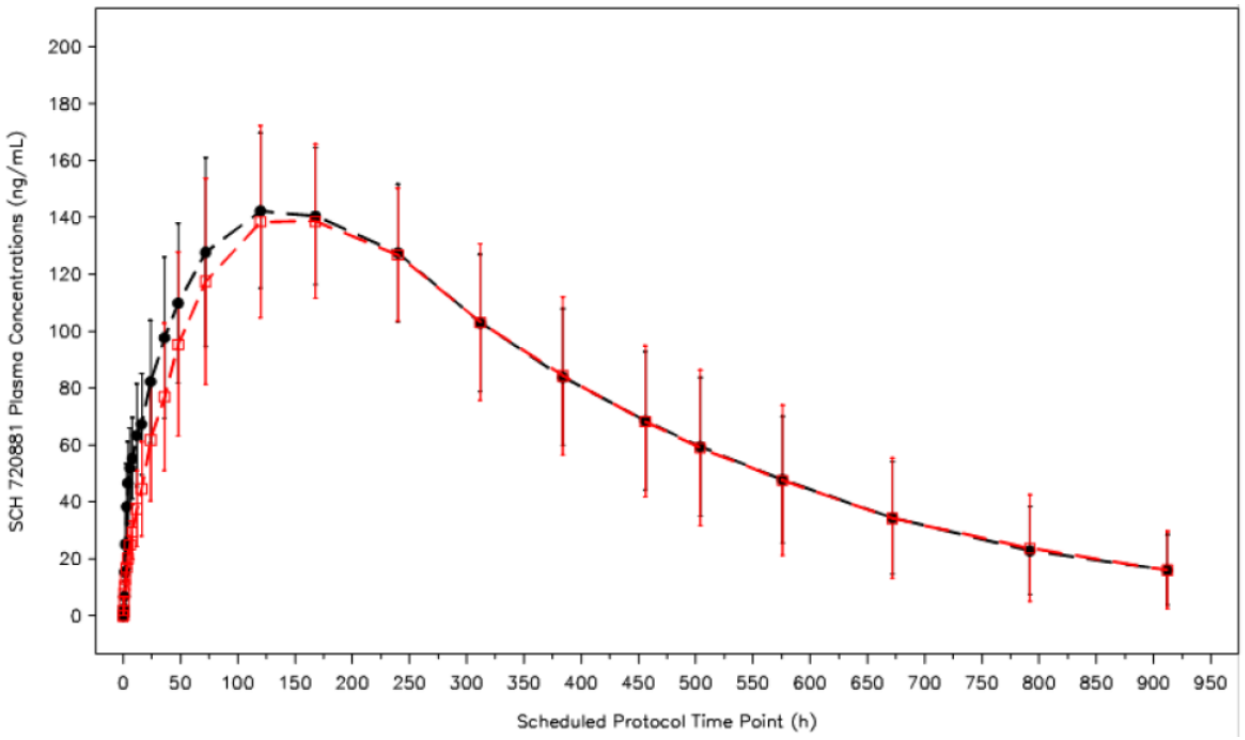


Red line represents IV administration, Blue line represents oral administration
Plot created by the reviewer

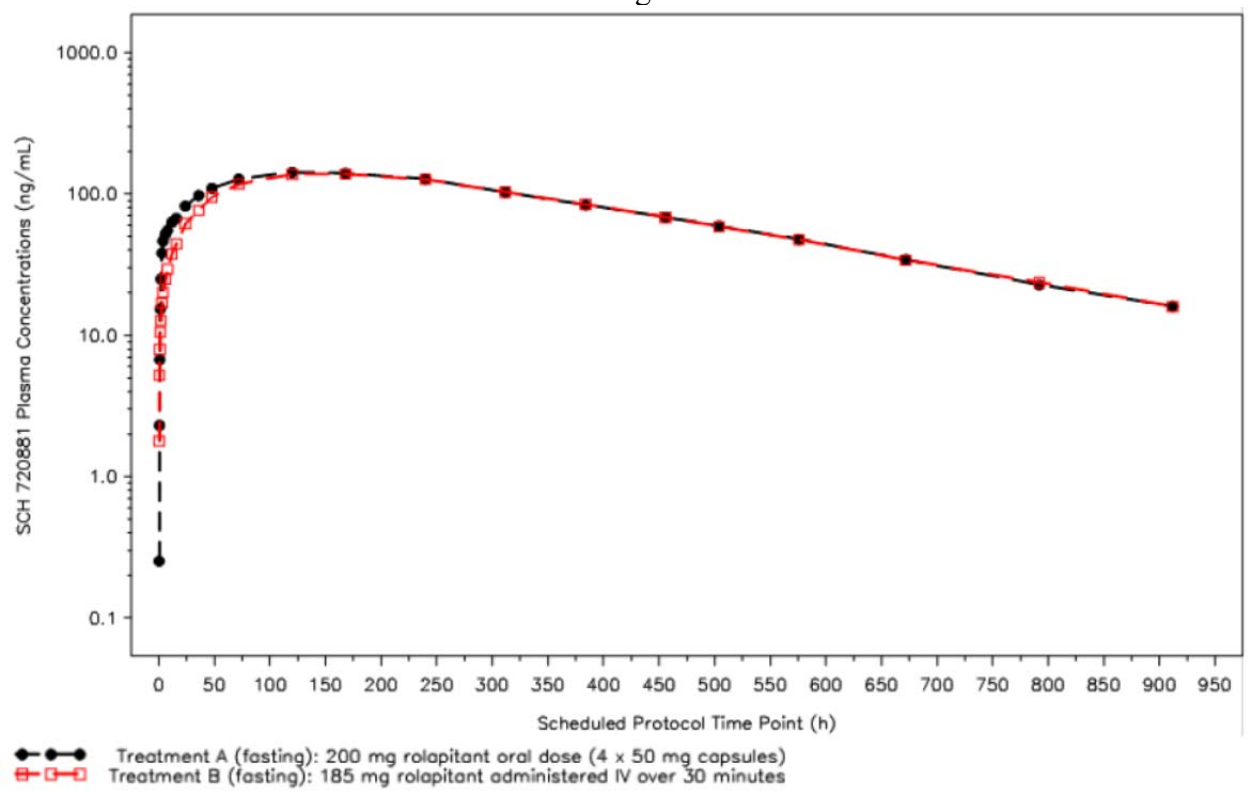
The mean concentration-time profile of the active metabolite is shown below.

Figure 17. Mean Active Metabolite SCH720881 Plasma Concentration-Time Profile

Linear Scale



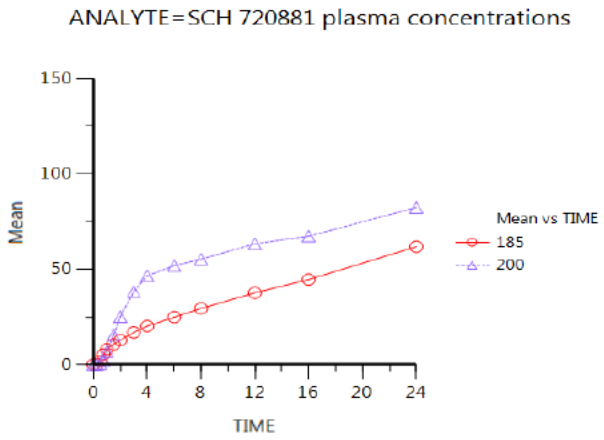
Semi-Log Scale



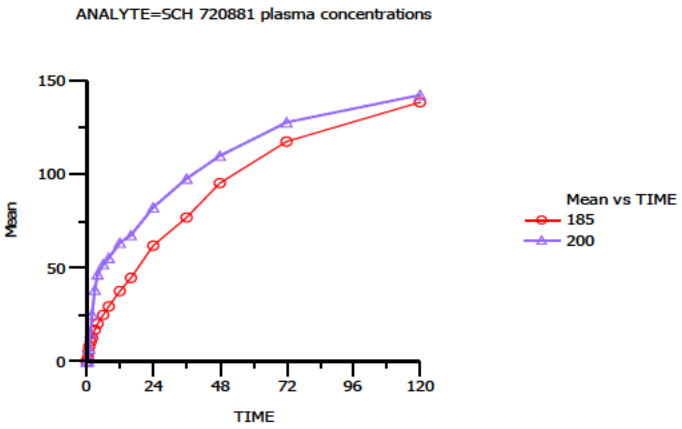
The mean concentration-time profiles for various partial AUC of the active metabolite are shown below.

Figure 18. Mean Metabolite Plasma Concentration-Time Profile – 24 hours and 120 hours

First 24 hours



First 120 hours



Red line represents IV administration, Blue line represents oral administration
Plot created by the reviewer

Descriptive summary of rolapitant PK parameters is shown below.

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	λ_z (1/h)	AUC_{0-t} (ng•h/mL)	AUC_{0-120} (ng•h/mL)	$AUC_{0-\infty}$ (ng•h/mL)
A[a]	N	62	62	62	62	62	62	62
	Mean	991.8	2.979	167.158	0.00451	118251.966	49189.337	122340.759
	SD	230.46	1.3578	48.7797	0.001362	29874.9196	8873.9400	33701.1690
	Median	964.0	2.980	161.267	0.00430	112961.795	48174.283	115995.795
	Min	649	1.45	84.67	0.0025	57396.40	34826.66	57710.12
	Max	1710	8.00	282.34	0.0082	219983.07	78935.46	243778.70
	%CV	23.2	45.6	29.2	30.2	25.3	18.0	27.5
	Geometric Mean	967.7	2.728	160.342	0.00432	114646.482	48444.093	118019.416
B[b]	N	61	61	61	61	61	61	61
	Mean	1986.1	0.554	160.950	0.00480	119982.888	51145.494	124016.737
	SD	773.81	0.4107	53.0205	0.001704	31479.3779	9405.1439	35564.4396
	Median	1910.0	0.500	152.427	0.00455	112730.860	50480.979	115778.870
	Min	654	0.23	64.70	0.0021	70035.76	32831.52	70502.49
	Max	4330	3.00	336.30	0.0107	202040.64	70530.98	217543.91
	%CV	39.0	74.2	32.9	35.5	26.2	18.4	28.7
	Geometric Mean	1841.3	0.489	152.703	0.00454	116127.168	50300.843	119373.900

Descriptive summary of active metabolite PK parameters is shown below.

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	λ_z (1/h)	AUC_{0-t} (ng•h/mL)	AUC_{0-120} (ng•h/mL)	$AUC_{0-\infty}$ (ng•h/mL)
A[a]	N	62	62	61	61	62	62	61
	Mean	150.8	151.341	196.175	0.00389	66333.427	13053.520	71708.400
	SD	28.03	56.7466	63.2356	0.001187	13992.5199	3009.1880	18520.8115
	Median	155.5	120.020	179.217	0.00387	65703.967	12353.387	69809.282
	Min	104	71.97	98.60	0.0021	38307.95	7932.05	38687.58
	Max	238	311.95	336.60	0.0070	108124.12	22138.81	128546.92
	%CV	18.6	37.5	32.2	30.5	21.1	23.1	25.8
	Geometric Mean	148.4	141.084	186.798	0.00371	64876.926	12738.604	69433.194
B[b]	N	61	61	59	59	61	61	59
	Mean	148.5	170.736	182.479	0.00416	64418.198	11431.397	68570.396
	SD	30.99	64.5546	57.6712	0.001263	15191.3383	3309.8581	19190.9028
	Median	145.0	167.980	167.663	0.00413	61534.196	11046.640	64135.416
	Min	101	47.98	80.80	0.0020	39755.70	5732.88	40060.27
	Max	238	384.00	353.19	0.0086	103802.92	20707.55	117022.25
	%CV	20.9	37.8	31.6	30.4	23.6	29.0	28.0
	Geometric Mean	145.5	158.550	174.237	0.00398	62753.374	10984.768	66171.904

Bioequivalence analysis for the systemic exposure to rolapitant is shown below.

Parameter	Treatment	N	n	Geometric LS Mean	Geometric LS Means 95% CI	Ratio (Test/ Reference)	90% CI for Ratio of Geometric LS Means
C_{max} (ng/mL)	A (reference)	123	62	967.69	(892.27, 1049.48)	1.90	(1.73, 2.10)
	B (test)		61	1841.28	(1696.66, 1998.23)		
AUC_{0-t} (ng•h/mL)	A (reference)	123	62	114646.48	(107548.64, 122212.76)	1.01	(0.94, 1.09)
	B (test)		61	116127.17	(108880.83, 123855.77)		
$AUC_{0-\infty}$ (ng•h/mL)	A (reference)	123	62	118019.42	(110189.17, 126406.09)	1.01	(0.93, 1.10)
	B (test)		61	119373.90	(111391.34, 127928.50)		
AUC_{0-120} (ng•h/mL)	A (reference)	123	62	48444.09	(46305.65, 50681.30)	1.04	(0.98, 1.10)
	B (test)		61	50300.84	(48062.72, 52643.19)		

Abbreviations: AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last measurable time point; AUC_{0-120} = area under the plasma concentration-time curve from time 0 to 120 hours, $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = observed maximum plasma concentration; LS = least-squares; N =total number of observations; n = number of observations

Bioequivalence analysis for the systemic exposure to the active metabolite is shown below.

Parameter	Treatment	N	n	Geometric LS Mean	Geometric LS Means 95% CI	Ratio (Test/ Reference)	90% CI for Ratio of Geometric LS Means
C_{max} (ng/mL)	A (reference)	123	62	148.36	(141.38, 155.68)	0.98	(0.93, 1.04)
	B (test)		61	145.55	(138.65, 152.79)		
AUC_{0-t} (ng•h/mL)	A (reference)	123	62	64876.93	(61359.30, 68596.21)	0.97	(0.91, 1.03)
	B (test)		61	62753.37	(59323.89, 66381.12)		
$AUC_{0-\infty}$ (ng•h/mL)	A (reference)	120	61	69433.19	(64990.95, 74179.07)	0.95	(0.88, 1.03)
	B (test)		59	66171.90	(61869.52, 70773.47)		
AUC_{0-120} (ng•h/mL)	A (reference)	123	62	12738.60	(11950.53, 13578.65)	0.86	(0.80, 0.93)
	B (test)		61	10984.77	(10299.82, 11715.27)		

Abbreviations: AUC_{0-t} = area under the plasma concentration-time curve from time 0 to the last measurable time point; AUC_{0-120} = area under the plasma concentration-time curve from time 0 to 120 hours, $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time 0 extrapolated to infinity; CI = confidence interval; C_{max} = observed maximum plasma concentration; LS = least-squares

Conclusions

Rolapitant 185 mg IV infusion (Treatment B) met bioequivalence and thus is bioequivalent to 200 mg rolapitant oral (Treatment A; 4 × 50 mg capsules) with 90% CIs of the ratio of mean geometric LSM of rolapitantAUC_{0-t} and $AUC_{0-\infty}$ of rolapitant contained within 0.80 to 1.25.

Reviewer's comment: The Cmax of rolapitant following IV administration is much higher than the reference product. Refer to Medical Officer's review of this NDA for the safety concern due to higher Cmax.

4.2.3. Single and Multiple Ascending Dose Study: PR-11-5012-C

Title: A Phase 1 Single Ascending and Multiple Ascending Dose Assessment of the Safety, Tolerability and Pharmacokinetics of Intravenous Rolapitant in Healthy Volunteers

Study Design: open–label study of rolapitant administered as an IV infusion over 30 or 45 minutes to healthy male and female subjects. Part 1 consisted of a SAD portion and Part 2 was a MAD portion. The parts were independent of each other; however, Part 2 was not initiated until Part 1 was completed.

Treatment Groups:

SAD: 20, 50, 100, 150, 185 and 200 mg infused over 30 minutes, 200 mg infused over 45 minutes.

MAD: 20, 40, and 60 mg infused over 30 minutes daily for 10 days.

PK sampling:

Part 1 SAD

Blood samples were collected before start of infusion (0 hours) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 120, 168, 240, 312, 384, 456 and 504 hours from the start of infusion. Additional blood samples were to be collected before infusion (0 hours) and at 3 and 6 hours from the start of the infusion for qualitative assessment of rolapitant metabolites from subjects receiving the 50, 100 and 200 mg dose levels.

Urine was also collected cumulatively for qualitative metabolite assessment before the start of the infusion, from start of the infusion to 3 hours and 3 to 6 hours from the start of the infusion (1 sample collection per window) on Day 1.

Reviewer's comment: the concentration of the parent drug and the active metabolite in the urine are low with many samples having concentrations < BLQ. This is consistent with the findings that rolapitant is eliminated primarily through the hepatic/biliary route for the oral product. Thus, urinary concentrations of parent and the active metabolite were not presented in this review.

Part 2 MAD

Blood samples were collected before start of infusion (0 hours) and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 hours from the start of infusion on Day 1 and Day 10 and 36, 48, 72, 120, 168 and 288 hours from the start of infusion on Day 10 only. In addition, PK blood samples for trough levels were to be collected before infusion on Days 3, 5 and 7. Additional blood samples were collected before infusion (0 hours) and at 3 and 6 hours from the start of infusion on Days 1 and 10 for qualitative assessment of rolapitant metabolites from subjects receiving the 40 and 60 mg dose levels.

Urine was also collected cumulatively for qualitative metabolite assessment before the start of infusion, from start of the infusion to 3 hours and 3 to 6 hours from the start of the infusion (1 sample per collection window) on Days 1 and 10 for the 40 and 60 mg dose levels.

Reviewer's comment: the concentration of the parent drug and the active metabolite in the urine are low with many samples having concentrations < BLQ. This is consistent with the findings that rolapitant is eliminated primarily through the hepatic/biliary route in the oral product. Thus, urinary concentrations of parent and the active metabolite were not presented in this review.

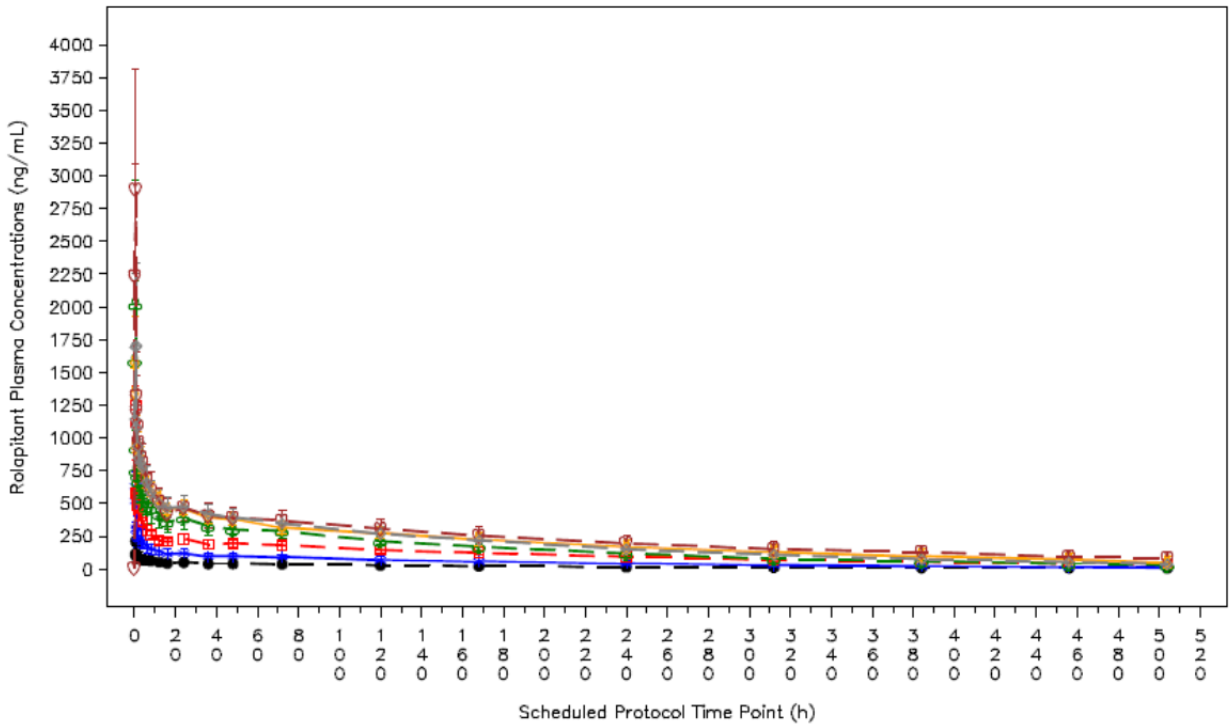
Results:

Part 1 SAD

The concentration-time profiles following each dose are shown below.

Figure 19. Mean (SD) Rolapitant Plasma Concentration - Time Profiles

Linear Scale



Semi-Log Scale

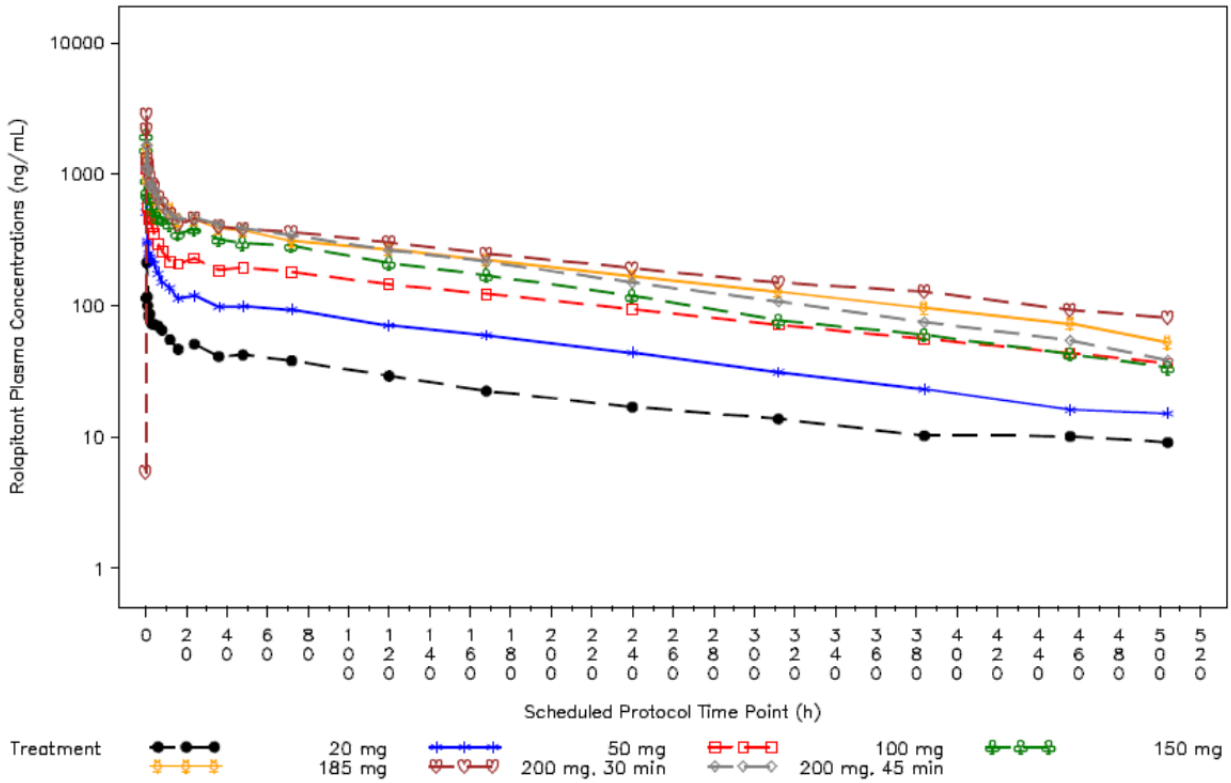


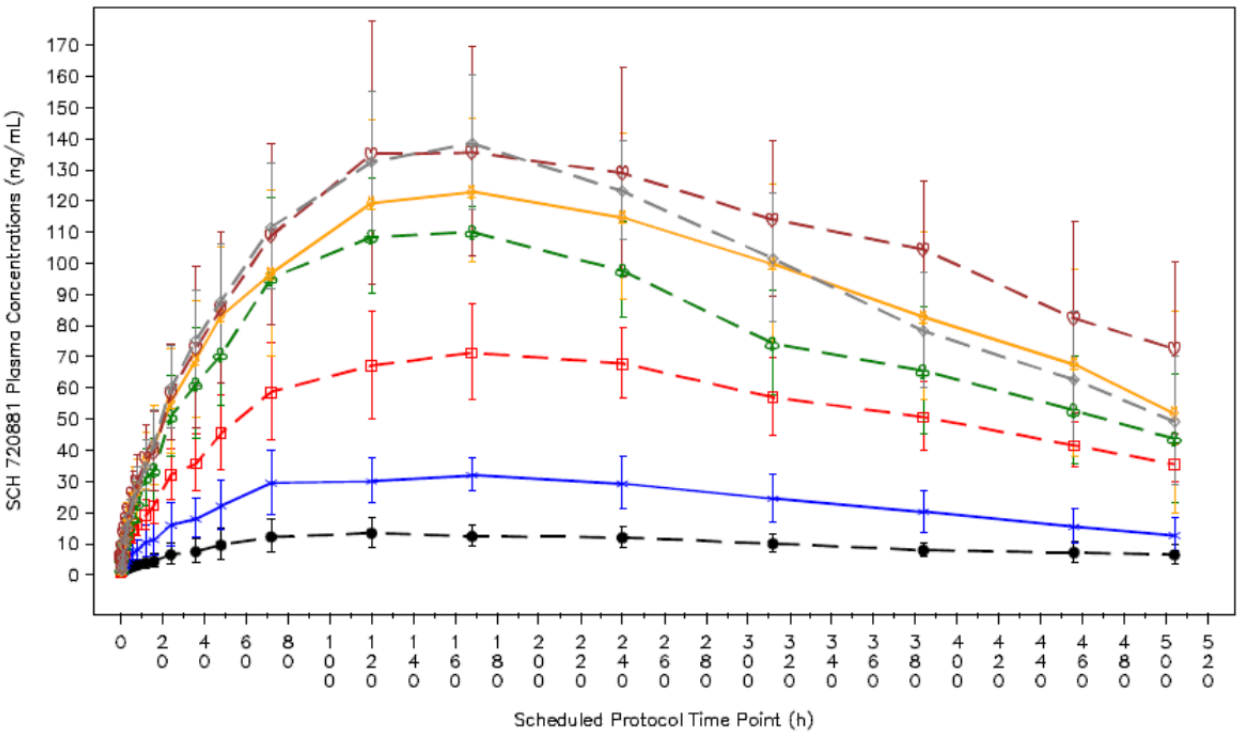
Table 3. Summary of Plasma Rolapitant Pharmacokinetic Parameters

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	λ_z (1/h)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-}24}$ (ng.h/mL)	$AUC_{0\text{-}120}$ (ng.h/mL)	$AUC_{0\text{-inf}}$ (ng.h/mL)	CL (L/h)	V_d (L)
20 mg	n	6	6	6	6	6	6	6	6	6	6
	Mean	251.8	0.500	205.273	0.00461	10921.560	1562.920	5227.000	14032.647	1.568	398.223
	SD	52.61	0.0000	113.3975	0.002944	1911.9436	340.8761	875.4821	4613.9826	0.5238	120.3382
	Median	250.5	0.500	202.600	0.00353	11182.860	1439.870	5068.285	13374.005	1.540	430.535
	Min	193	0.50	73.13	0.0019	8343.26	1216.79	4060.64	8589.08	1.03	245.66
	Max	313	0.50	375.32	0.0095	13496.83	2083.57	6523.25	19474.65	2.33	556.08
	%CV	20.9	0.0	55.2	63.9	17.5	21.8	16.7	32.9	33.4	30.2
	Geometric Mean	247.2	0.500	177.138	0.00391	10778.176	1533.746	5166.427	13389.864	1.496	381.715
50 mg	n	6	6	6	6	6	6	6	6	6	6
	Mean	642.2	0.458	144.393	0.00524	26302.978	3862.372	12654.633	29428.493	1.907	369.560
	SD	282.51	0.1021	45.4454	0.001744	8429.2449	1053.2498	3131.0056	10531.8252	0.7429	95.8578
	Median	704.5	0.500	146.030	0.00480	24184.965	4050.520	12682.515	26482.345	1.885	377.590
	Min	191	0.25	86.20	0.0033	15117.60	2531.46	9274.04	15573.26	1.19	239.22
	Max	995	0.50	212.48	0.0080	36749.72	4980.93	15909.74	42056.19	3.21	502.74
	%CV	44.0	22.3	31.5	33.3	32.0	27.3	24.7	35.8	39.0	25.9
	Geometric Mean	570.3	0.445	138.310	0.00501	25149.630	3735.193	12326.285	27813.556	1.796	358.710
100 mg	n	6	6	6	6	6	6	6	6	6	6
	Mean	1256.7	0.417	201.065	0.00359	54702.430	6935.385	24194.837	65718.300	1.545	447.053
	SD	287.03	0.1291	44.1095	0.000765	7440.5816	814.4919	3717.9456	9478.7805	0.2052	111.5582
	Median	1355.0	0.500	190.855	0.00366	55071.455	6941.335	24480.780	62063.715	1.610	415.560
	Min	770	0.25	151.28	0.0027	45170.75	5973.13	19627.54	56831.97	1.24	343.39
	Max	1550	0.50	256.25	0.0046	63922.38	8353.35	29677.77	80702.91	1.76	630.19
	%CV	22.8	31.0	21.9	21.3	13.6	11.7	15.4	14.4	13.3	25.0
	Geometric Mean	1224.8	0.397	197.107	0.00352	54274.308	6897.094	23956.774	65178.112	1.533	436.296
150 mg	n	6	6	6	6	6	6	6	6	6	6
	Mean	2045.3	0.463	137.727	0.00547	75981.288	11366.357	38620.965	83904.548	1.855	350.810
	SD	907.15	0.0898	45.1982	0.001650	12085.0743	2695.1806	6471.4652	18567.4313	0.3724	61.2773
	Median	2275.0	0.500	124.720	0.00561	75236.730	12805.375	39637.720	83029.975	1.805	333.740
	Min	862	0.28	91.65	0.0034	61007.13	7234.94	30945.75	62293.70	1.28	296.19
	Max	2930	0.50	205.66	0.0076	96552.22	13532.37	48295.46	117529.27	2.41	459.06
	%CV	44.4	19.4	32.8	30.1	15.9	23.7	16.8	22.1	20.1	17.5

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	λ_z (1/h)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-}24}$ (ng.h/mL)	$AUC_{0\text{-}120}$ (ng.h/mL)	$AUC_{0\text{-inf}}$ (ng.h/mL)	CL (L/h)	V_d (L)
	Geometric Mean	1843.0	0.454	131.896	0.00525	75211.881	11060.433	38168.673	82328.017	1.822	346.697
185 mg	n	7	7	7	7	7	7	7	7	7	7
	Mean	1653.7	0.447	189.819	0.00478	104752.363	14284.887	46610.866	123288.357	1.650	392.347
	SD	624.37	0.1351	101.4688	0.002688	23432.0506	1667.6916	5857.8996	40174.4323	0.5490	116.4819
	Median	1530.0	0.520	159.130	0.00436	110169.770	14110.530	46227.480	124265.490	1.490	352.920
	Min	746	0.25	81.49	0.0019	72032.89	11923.07	39174.46	73010.73	1.05	240.82
	Max	2690	0.55	357.32	0.0085	135721.88	16127.11	56010.30	176075.27	2.53	542.74
	%CV	37.8	30.2	53.5	56.3	22.4	11.7	12.6	32.6	33.3	29.7
	Geometric Mean	1546.2	0.425	166.401	0.00417	102420.755	14199.228	46299.104	117628.330	1.573	377.565
200 mg 30 min	n	11	11	11	11	11	11	11	11	11	11
	Mean	2915.5	0.493	193.010	0.00410	114459.968	15010.867	50559.716	141505.765	1.580	400.215
	SD	878.97	0.0241	66.7432	0.001734	27813.0025	2821.5858	9857.3668	47468.4039	0.5954	83.3457
	Median	3210.0	0.500	180.700	0.00384	119823.070	15073.800	50036.720	128664.120	1.550	424.410
	Min	1640	0.42	90.26	0.0022	64486.86	11843.52	39845.96	66355.46	0.90	211.26
	Max	4600	0.50	309.46	0.0077	164596.52	21300.07	71245.61	222534.91	3.01	507.68
	%CV	30.1	4.9	34.6	42.3	24.3	18.8	19.5	33.5	37.7	20.8
	Geometric Mean	2788.4	0.492	181.560	0.00382	111169.016	14784.956	49749.387	134089.375	1.491	390.688
200 mg 45 min	n	12	12	12	12	12	12	12	12	12	12
	Mean	1857.5	0.650	146.226	0.00502	98033.305	14426.306	48473.833	107030.527	1.936	398.579
	SD	568.97	0.1320	34.9701	0.001305	16426.0411	2189.1929	7358.2019	20052.4411	0.4045	88.4147
	Median	1830.0	0.750	154.630	0.00449	103231.030	14652.615	48952.780	110949.035	1.800	390.570
	Min	1180	0.48	90.79	0.0035	66659.17	8933.50	31904.88	74148.44	1.45	272.59
	Max	3130	0.77	199.45	0.0076	119096.12	17328.79	59109.59	137751.33	2.70	595.89
	%CV	30.6	20.3	23.9	26.0	16.8	15.2	15.2	18.7	20.9	22.2
	Geometric Mean	1784.5	0.637	142.203	0.00488	96649.707	14247.896	47910.512	105197.483	1.900	390.038

Figure 20. Mean (SD) SCH720881 Plasma Concentration - Time Profiles

Linear Scale



Semi-Log Scale

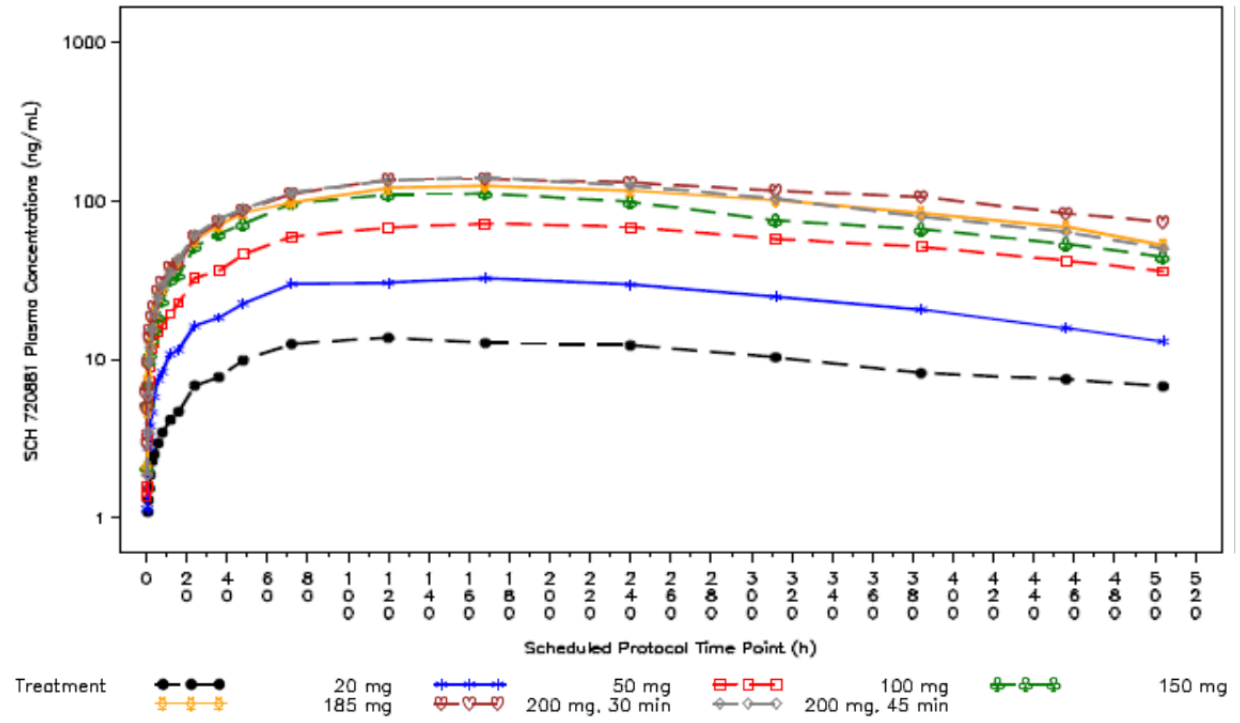


Table 4. Summary of Plasma Active Metabolite (SCH 720881) Pharmacokinetic Parameters

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	λ_z (1/h)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-}24}$ (ng.h/mL)	$AUC_{0\text{-}120}$ (ng.h/mL)	$AUC_{0\text{-inf}}$ (ng.h/mL)
20 mg	n	6	6	3	3	6	6	6	3
	Mean	14.9	187.873	205.440	0.00408	5069.495	95.298	1182.835	6752.347
	SD	3.89	130.9248	115.8833	0.001932	958.5801	44.9190	504.8770	1911.4668
	Median	14.6	143.680	162.230	0.00427	5234.295	90.055	1153.940	7210.110
	Min	9	72.03	117.37	0.0021	3602.33	35.92	462.35	4653.56
	Max	20	384.03	336.72	0.0059	6199.03	161.71	1854.19	8393.37
	%CV	26.1	69.7	56.4	47.4	18.9	47.1	42.7	28.3
	Geometric Mean	14.4	152.285	185.774	0.00373	4988.408	85.626	1078.529	6554.726
50 mg	n	6	6	6	6	6	6	6	6
	Mean	35.4	159.652	191.312	0.00399	12005.268	235.213	2748.253	15789.737
	SD	8.34	75.0340	51.6274	0.001665	2650.8078	99.4386	858.1196	4139.6610
	Median	35.8	167.695	206.110	0.00340	12175.485	221.770	2746.390	15199.445
	Min	25	71.98	94.71	0.0030	8407.63	139.13	1771.63	9843.18
	Max	48	239.58	228.37	0.0073	14564.91	411.00	4265.54	20824.72
	%CV	23.6	47.0	27.0	41.7	22.1	42.3	31.2	26.2
	Geometric Mean	34.6	142.435	183.602	0.00378	11749.754	219.581	2645.124	15314.273
100 mg	n	6	6	6	6	6	6	6	6
	Mean	73.9	147.830	271.092	0.00279	27580.700	466.668	5662.097	41485.612
	SD	15.30	58.2171	91.6261	0.000855	5090.6272	119.5860	1403.5827	4364.0936
	Median	68.3	143.465	248.320	0.00280	26496.965	453.870	5695.085	40488.250
	Min	55	71.98	169.66	0.0016	21486.02	302.55	4056.49	37335.69
	Max	97	241.18	430.13	0.0041	36923.26	605.63	7816.29	47619.72
	%CV	20.7	39.4	33.8	30.7	18.5	25.6	24.8	10.5
	Geometric Mean	72.6	138.075	259.328	0.00267	27218.851	453.338	5519.679	41298.004
150 mg	n	6	6	5	5	6	6	6	5
	Mean	118.0	135.770	229.780	0.00371	39573.277	691.345	9060.028	58234.514
	SD	14.05	38.9310	129.8811	0.001629	4876.4849	188.4321	2046.1352	23606.8778
	Median	117.0	143.320	182.000	0.00381	39850.300	717.325	9187.000	51878.620
	Min	99	72.00	127.19	0.0016	33680.98	373.73	6159.95	37264.23
	Max	137	168.30	441.82	0.0055	46796.92	927.20	11692.80	98171.93
	%CV	11.9	28.7	56.5	43.9	12.3	27.3	22.6	40.5

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	λ_z (1/h)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-24}}$ (ng.h/mL)	$AUC_{0\text{-120}}$ (ng.h/mL)	$AUC_{0\text{-inf}}$ (ng.h/mL)
	Geometric Mean	117.2	130.227	205.319	0.00338	39323.951	665.956	8857.554	55031.266
185 mg	n	7	7	6	6	7	7	7	6
	Mean	130.3	209.381	234.995	0.00379	49653.189	816.276	9841.217	70075.557
	SD	24.77	116.6569	110.4635	0.002205	8914.6748	244.4459	2512.0199	25653.3561
	Median	131.0	170.330	253.735	0.00279	49811.140	751.020	9885.560	64687.460
	Min	98	119.13	98.58	0.0019	38394.56	482.18	5845.19	41524.35
	Max	163	456.88	359.36	0.0070	62687.53	1233.07	13535.39	115050.89
	%CV	19.0	55.7	47.0	58.3	18.0	29.9	25.5	36.6
	Geometric Mean	128.2	188.977	209.414	0.00331	48970.393	785.778	9544.844	66518.555
200 mg 30 min	n	11	11	8	8	11	11	11	8
	Mean	145.8	190.223	290.363	0.00309	53475.887	840.780	10761.612	80726.279
	SD	41.07	67.5369	171.5546	0.001537	10996.2461	224.2958	3023.3648	26978.4675
	Median	134.0	167.320	247.985	0.00280	49954.050	777.430	10115.460	79817.155
	Min	107	119.22	121.38	0.0011	40553.61	592.18	7652.21	46144.04
	Max	251	311.13	621.19	0.0057	72854.61	1323.78	18658.65	130342.44
	%CV	28.2	35.5	59.1	49.7	20.6	26.7	28.1	33.4
	Geometric Mean	141.5	180.753	253.246	0.00274	52488.723	816.966	10446.422	76938.778
200 mg 45 min	n	12	12	11	11	12	12	12	11
	Mean	144.1	161.899	228.875	0.00350	51090.554	832.844	10908.694	68820.424
	SD	20.89	59.5445	96.9398	0.001367	7469.4949	186.9048	1915.5378	19187.5116
	Median	149.0	166.825	221.740	0.00313	49653.390	810.265	10847.155	65122.010
	Min	102	119.32	109.83	0.0015	38036.50	511.88	7390.10	52483.27
	Max	181	335.17	453.07	0.0063	65864.46	1180.38	13453.38	110377.70
	%CV	14.5	36.8	42.4	39.0	14.6	22.4	17.6	27.9
	Geometric Mean	142.6	154.652	212.444	0.00326	50597.873	812.762	10743.378	66771.138

Part 2 MAD – Day 1

Table 5. Summary of Plasma Rolapitant Pharmacokinetic Parameters – Multiple Ascending Dose – Day 1

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-}24}$ (ng.h/mL)
20 mg	n	6	6	6	6
	Mean	261.2	0.500	1847.648	1856.553
	SD	51.08	0.2739	415.5634	419.6767
	Median	275.0	0.500	1814.960	1825.950
	Min	162	0.25	1419.64	1422.45
	Max	304	1.00	2532.11	2544.94
	%CV	19.6	54.8	22.5	22.6
	Geometric Mean	256.0	0.445	1810.550	1818.819
40 mg	n	6	6	6	6
	Mean	619.5	0.425	3309.330	3321.487
	SD	125.15	0.1361	523.3282	516.0803
	Median	612.0	0.500	3279.985	3297.495
	Min	457	0.25	2646.59	2666.19
	Max	757	0.53	4167.44	4163.21
	%CV	20.2	32.0	15.8	15.5
	Geometric Mean	608.8	0.403	3275.780	3288.914
60 mg	n	6	6	6	6
	Mean	682.7	0.958	4247.155	4267.530
	SD	296.31	1.0298	470.8733	474.3508
	Median	716.0	0.500	4327.040	4345.420
	Min	296	0.25	3620.16	3638.31
	Max	1020	3.00	4793.47	4818.85
	%CV	43.4	107.5	11.1	11.1
	Geometric Mean	620.5	0.674	4224.919	4245.084

Table 6. Summary of Plasma SCH720881 Pharmacokinetic Parameters – Multiple Ascending Dose – Day 1

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-last}}$ (ng.h/mL)
20 mg	n	6	6	6
	Mean	17.3	23.883	139.663
	SD	7.55	0.0450	44.7098
	Median	18.9	23.860	148.055
	Min	4	23.85	64.84
	Max	24	23.95	184.44
	%CV	43.7	0.2	32.0
	Geometric Mean	15.2	23.883	132.181
40 mg	n	6	6	6
	Mean	13.4	23.862	186.272
	SD	6.43	0.0935	77.8278
	Median	11.7	23.860	177.570
	Min	7	23.77	84.27
	Max	24	24.03	308.26
	%CV	47.9	0.4	41.8
	Geometric Mean	12.3	23.862	172.151
60 mg	n	6	6	6
	Mean	12.9	23.833	187.740
	SD	5.30	0.0082	88.7936
	Median	14.0	23.830	200.235
	Min	6	23.83	81.73
	Max	20	23.85	325.41
	%CV	41.2	0.0	47.3
	Geometric Mean	11.8	23.833	168.976

Reviewer's comment: The AUClast of the active metabolite in the above table represents AUC0-24hr.

Conclusions - SAD

- Mean rolapitant Cmax, AUC0-24, AUC0-120, AUC0-last, and AUC0-inf increased in a dose proportional manner across the 20 to 200 mg dose range.
- The mean rolapitant t½ ranged from 138 to 205 hours across the 20 to 200 mg dose range.
- Single dose mean rolapitant total body CL and Vd were consistent across the 20 to 200 mg dose range(mean CL 1.55 to 1.94 L/h and mean Vd 351 to 447 L).
- Single dose SCH 720881 Cmax was approximately 5% to 8% that of rolapitant and median tmax ranged from 143 to 170 hours post rolapitant infusion.

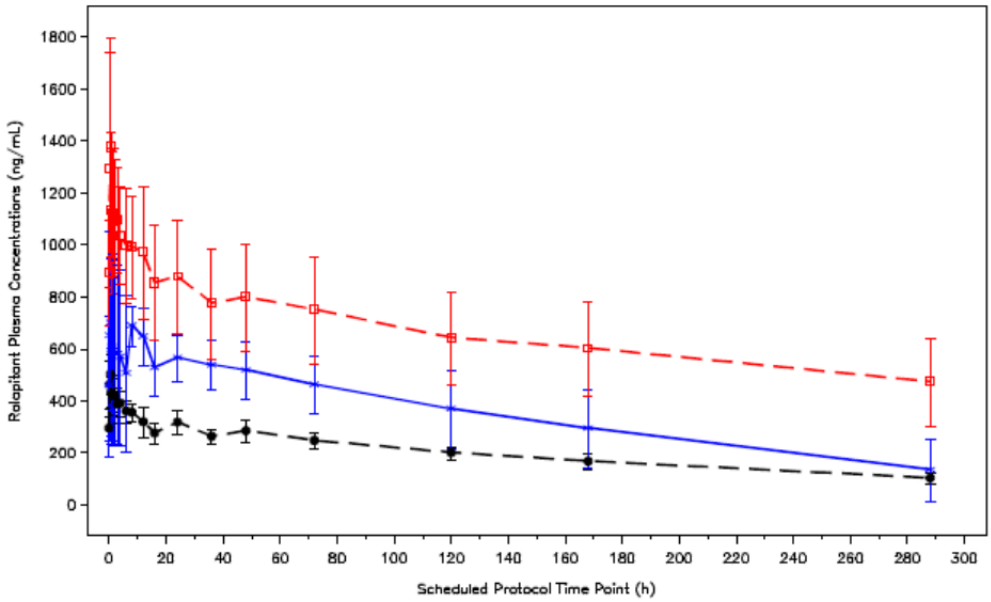
- Mean SCH 720881 t½ ranged from 191 to 290 hours across the 20 to 200 mg single dose.

Part 2 MAD – Day 10

Rolapitant concentration-time profiles are shown below.

Figure 21. Mean (SD) Rolapitant Plasma Concentration - Time Profiles – Day 10

Linear Scale



Semi-Log Scale

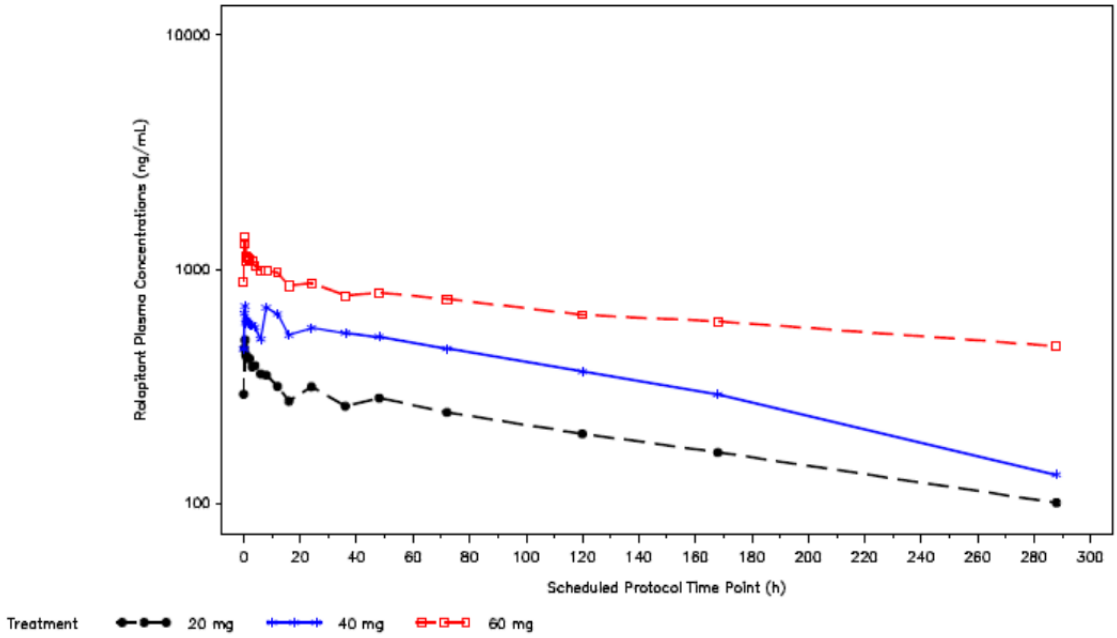


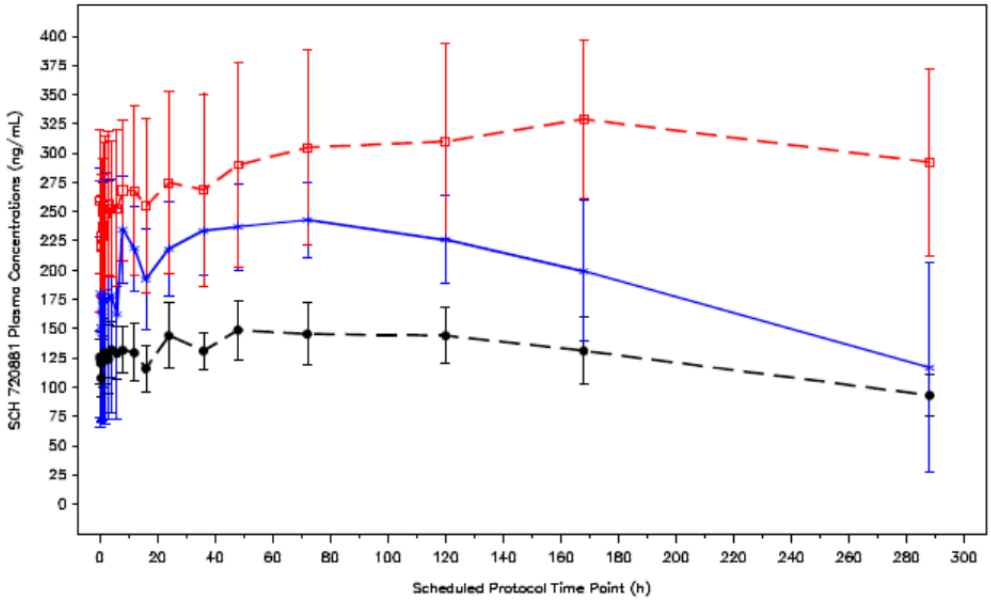
Table 7. Summary of Plasma Rolapitant Pharmacokinetic Parameters – Multiple Ascending Doses – Day 10

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	λ_z (1/h)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-}24}$ (ng.h/mL)	$AUC_{0\text{-}120}$ (ng.h/mL)	$AUC_{0\text{-inf}}$ (ng.h/mL)
20 mg	n	6	6	6	6	6	6	6	6
	Mean	513.8	0.432	176.135	0.00407	56148.937	7987.945	31640.355	82415.782
	SD	86.43	0.1430	32.9696	0.000863	6489.1743	1078.1812	3409.5837	13411.3602
	Median	492.0	0.500	177.020	0.00392	54954.225	7825.540	31181.055	79585.700
	Min	401	0.25	122.04	0.0031	49978.62	6970.57	28171.29	66625.25
	Max	635	0.57	225.18	0.0057	67684.59	9567.94	35954.87	100561.54
	%CV	16.8	33.1	18.7	21.2	11.6	13.5	10.8	16.3
	Geometric Mean	507.8	0.408	173.391	0.00400	55853.307	7928.597	31488.456	81518.615
40 mg	n	6	6	5	5	6	6	6	5
	Mean	943.7	0.550	137.556	0.00596	103330.985	15242.870	59652.455	136307.556
	SD	125.67	0.2445	56.6707	0.002903	33432.8652	1966.1621	12517.8237	62825.4981
	Median	925.0	0.510	136.750	0.00507	99665.235	14954.140	57421.915	119921.590
	Min	796	0.25	66.10	0.0035	60151.73	12707.45	45508.73	63184.42
	Max	1120	1.00	195.93	0.0105	145445.61	18212.00	76353.36	208356.50
	%CV	13.3	44.4	41.2	48.7	32.4	12.9	21.0	46.1
	Geometric Mean	936.8	0.508	127.146	0.00545	98635.213	15138.637	58578.154	124069.478
60 mg	n	6	6	2	2	6	6	6	2
	Mean	1410.2	1.003	231.110	0.00308	188217.240	22954.273	94097.955	254362.175
	SD	404.67	0.7557	52.2128	0.000693	52911.2246	5274.6046	24296.4204	73004.4972
	Median	1425.0	1.010	231.110	0.00308	172723.060	21363.110	88026.820	254362.175
	Min	911	0.25	194.19	0.0026	131301.68	17586.36	71959.88	202740.20
	Max	1870	2.00	268.03	0.0036	283596.55	32687.14	140653.30	305984.15
	%CV	28.7	75.3	22.6	22.5	28.1	23.0	25.8	28.7
	Geometric Mean	1359.6	0.726	228.142	0.00304	182673.297	22504.419	91867.380	249068.841

The major metabolite, SCH 720881 concentration-time profiles are shown below.

Figure 22. Mean (SD) SCH 720881 Plasma Concentration - Time Profiles – Day 10

Linear Scale



Semi-Log Scale

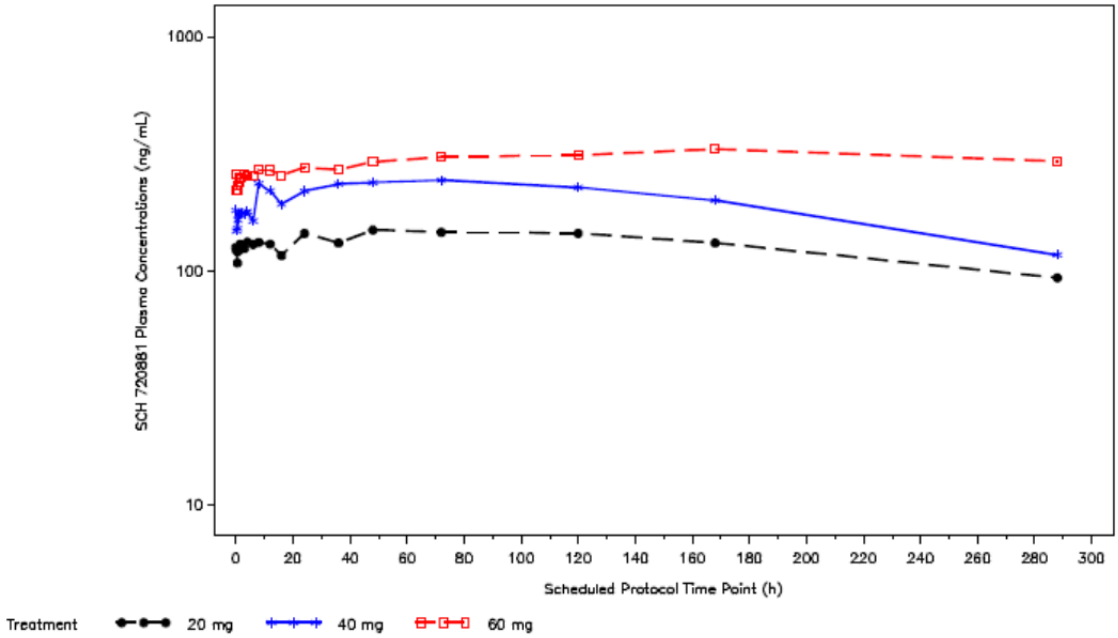


Table 8. Summary of Plasma SCH 720881 Pharmacokinetic Parameters – Multiple Ascending Dose – Day 10

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	λ_z (1/h)	$AUC_{0\text{-last}}$ (ng.h/mL)	$AUC_{0\text{-}24}$ (ng.h/mL)	$AUC_{0\text{-}120}$ (ng.h/mL)	$AUC_{0\text{-inf}}$ (ng.h/mL)
20 mg	n	6	6	3	3	6	6	6	3
	Mean	159.2	95.885	239.067	0.00308	36823.752	3068.028	16852.392	64359.023
	SD	27.32	66.0875	65.6563	0.001005	5733.2567	517.8297	2526.5127	8956.9726
	Median	160.5	95.755	273.790	0.00253	34895.060	3024.250	16721.420	68703.170
	Min	125	24.00	163.34	0.0025	33005.07	2523.23	13826.15	54058.38
	Max	189	168.07	280.07	0.0042	48112.39	3660.14	20051.74	70315.52
	%CV	17.2	68.9	27.5	32.6	15.6	16.9	15.0	13.9
	Geometric Mean	157.2	72.034	232.234	0.00298	36495.685	3031.669	16694.270	63919.053
40 mg	n	6	6	3	3	6	6	6	3
	Mean	266.8	81.217	188.920	0.00462	59051.205	5123.950	27642.547	79758.520
	SD	40.33	69.0168	109.0337	0.002613	10707.5998	908.3427	3382.1585	22973.3496
	Median	281.5	96.360	165.680	0.00418	56543.495	5086.775	29141.505	80378.970
	Min	215	0.00	93.38	0.0023	48532.65	3948.10	23336.33	56481.23
	Max	306	169.43	307.70	0.0074	73913.26	6509.51	31247.41	102415.36
	%CV	15.1	85.0	57.7	56.6	18.1	17.7	12.2	28.8
	Geometric Mean	264.1	55.773	168.222	0.00412	58267.865	5057.357	27462.156	77470.655
60 mg	n	6	6	1	1	6	6	6	1
	Mean	336.7	160.540	313.560	0.00221	87435.582	6238.487	34727.080	200824.340
	SD	68.65	78.5796			20315.3325	1623.8705	9531.9647	
	Median	321.5	168.270	313.560	0.00221	86122.565	6522.090	35522.805	200824.340
	Min	249	48.00	313.56	0.0022	66137.74	3975.48	22814.77	200824.34
	Max	455	288.53	313.56	0.0022	123634.39	8178.29	47953.30	200824.34
	%CV	20.4	48.9			23.2	26.0	27.4	
	Geometric Mean	331.1	141.461	313.560	0.00221	85627.113	6047.383	33594.250	200824.340

Conclusions - MAD

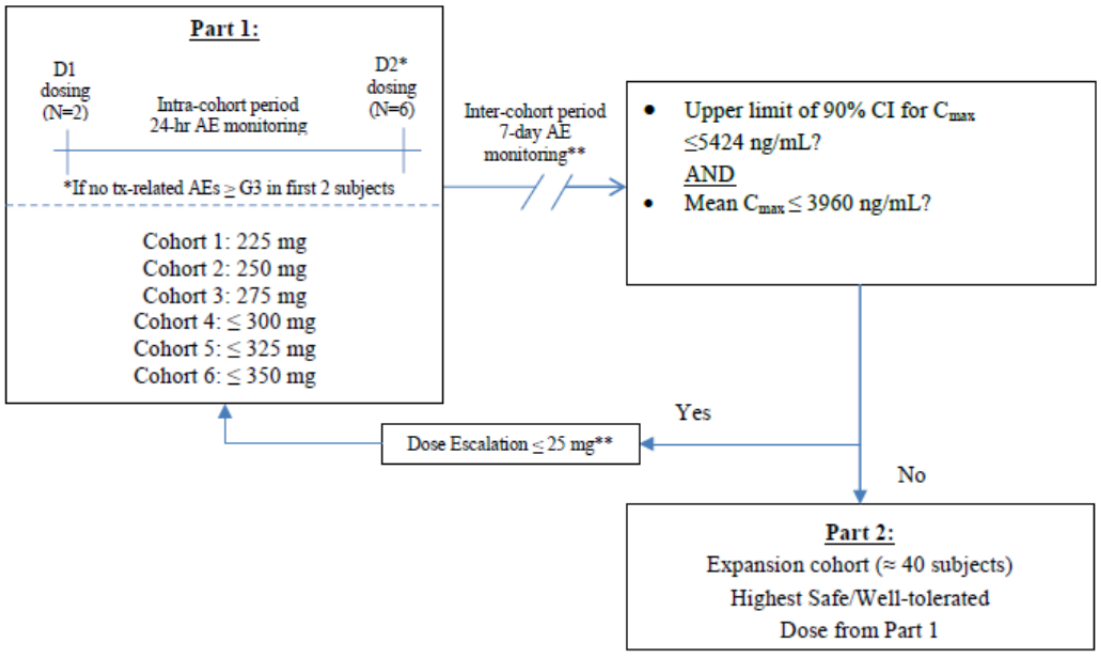
- Mean rolapitant Cmax, AUC0-24, AUC0-120, AUC0-last, and AUC0-inf increased in a dose proportional manner across the 20, 40 and 60 mg QD doses.
- Mean rolapitant Cmax following multiple doses (Day 10) was approximately 1.5- to 2.1 fold higher than for single dose (Day 1).
- Mean rolapitant t½ estimated after multiple daily doses ranged from 138 to 231 hours for the 20, 40 and 60 mg doses and was comparable to t½ estimated following single dose (Part 1 SAD).
- Mean SCH 720881 t½ estimated after multiple daily doses ranged from 189 to 314 hours for the 20, 40 and 60 mg doses and was also comparable to t½ estimated following single dose.

Reviewer's comment: It should be noted that rolapitant and its metabolite did not reach steady-state with 10-day dosing. It is expected to take ~5 weeks to reach steady-state based upon their terminal t1/2.

4.2.4. Single Ascending Dose Study: PR-11-5022-C

Title: A Phase 1, 2-Part, Single Ascending Dose Assessment of the Safety, Tolerability, and Pharmacokinetics of Rolapitant Intravenous in Healthy Volunteers

Study Design: This was a 2-part, open-label, SAD study of rolapitant IV administered as a 30-minute infusion to identify the maximum tolerated dose for safety.



Treatment groups:

Part 1		Part 2
Cohort	**Dose**	**Dose**
1	225 mg rolapitant IV	≤ 350 mg rolapitant IV (The highest safe and well tolerated dose in healthy adults in Part 1 was used in Part 2)
2	250 mg rolapitant IV	
3	275 mg rolapitant IV	
4[a]	≤ 300 mg rolapitant IV	
5[a]	≤ 325 mg rolapitant IV	
6[a]	≤ 350 mg rolapitant IV	

[a] After Cohort 3, the dose was determined by pre-specified safety and PK data with a dose increment not to exceed 25 mg.

Based on review of safety and PK data, the highest dose used in Part 1 of the study was 300 mg, and the actual dose used in Part 2 was 300 mg.

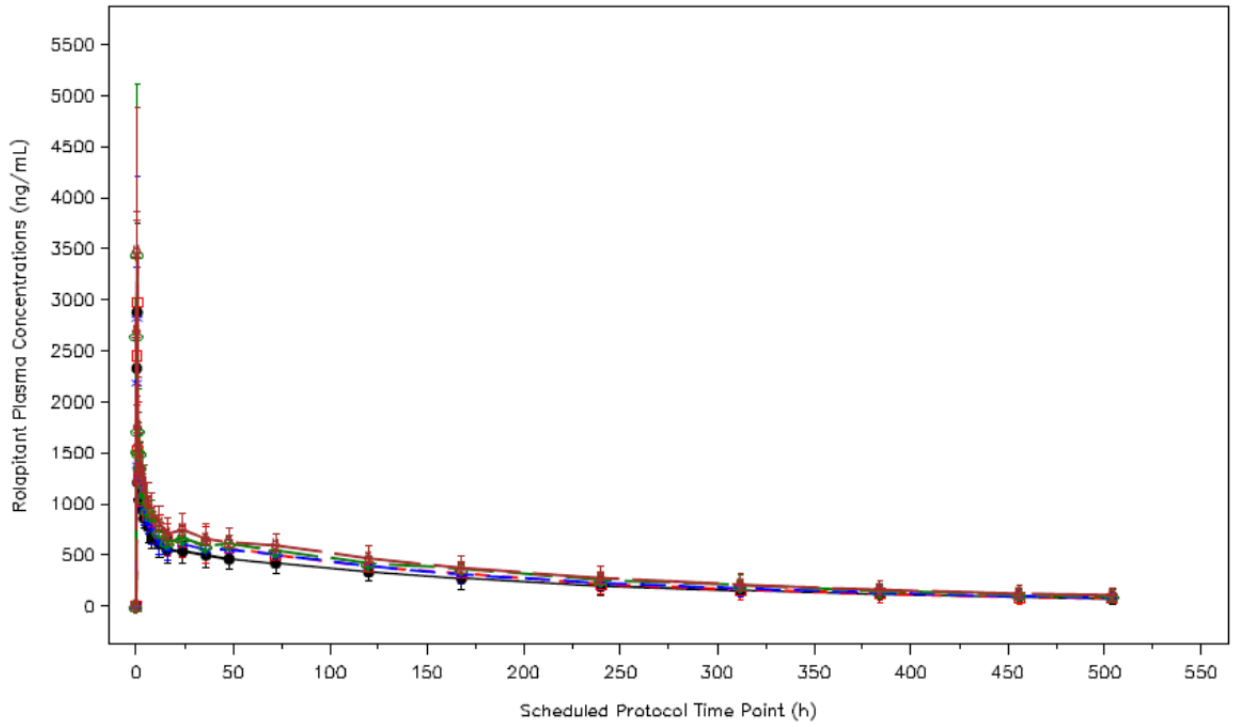
PK samples: predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 72, 120, 168, 240, 312, 384, 456, and 504 hours postdose.

Results

The concentration-time profiles following each dose were shown below.

Figure 23. Mean (SD) Rolapitant Plasma Concentration - Time Profiles

Linear Scale



Semi-Log Scale

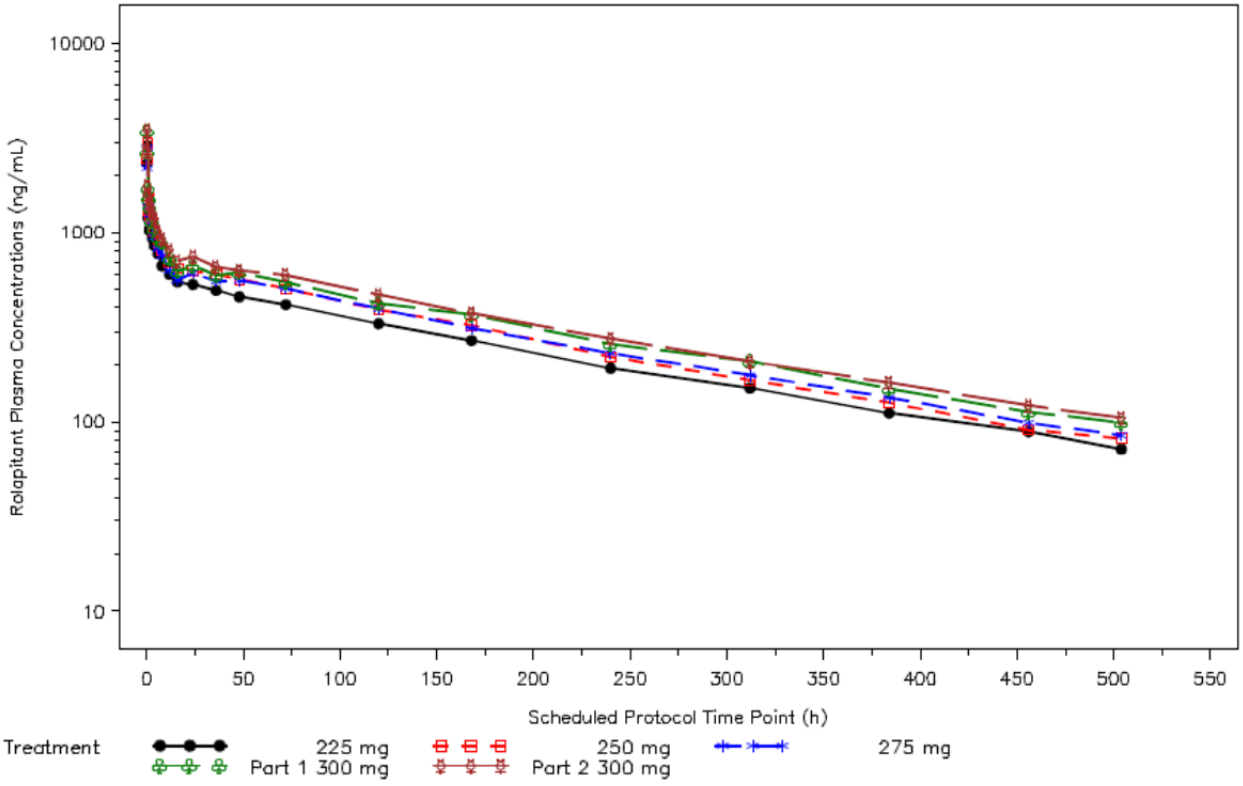


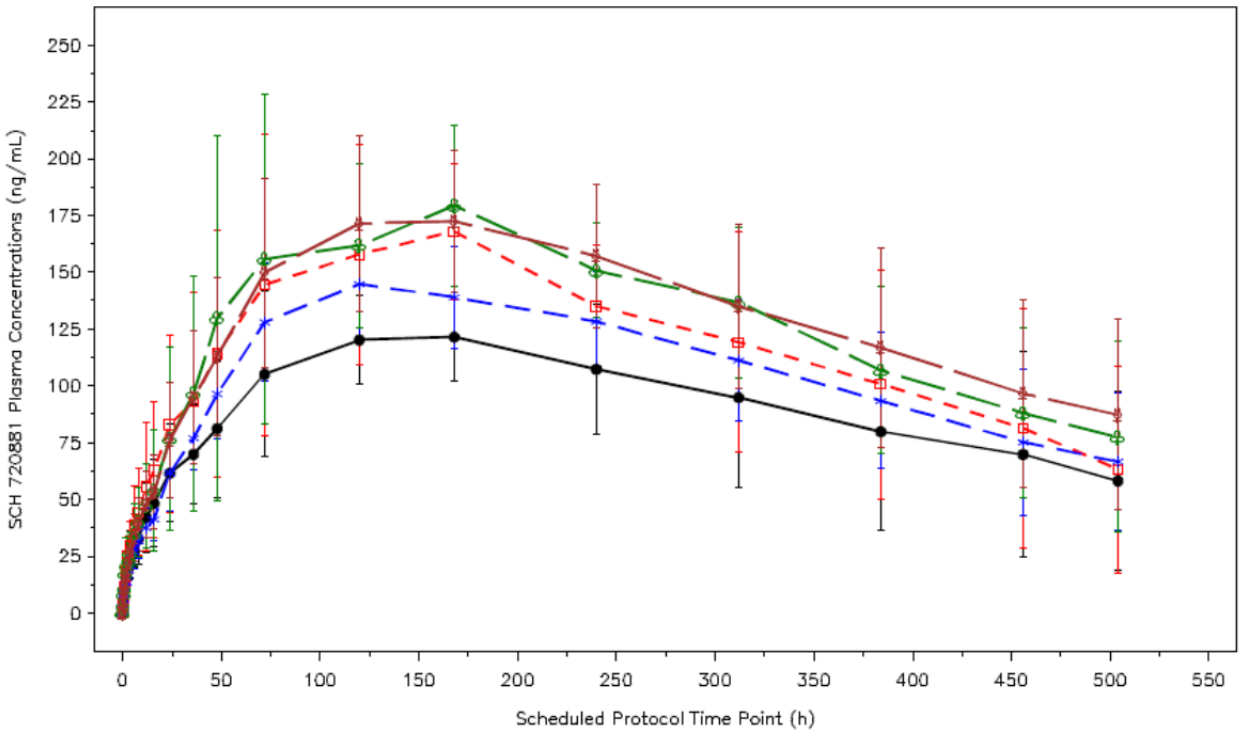
Table 9. Summary of Plasma Rolapitant Pharmacokinetic Parameters

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-24}}$ (ng•h/mL)	$AUC_{0\text{-120}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)	CL (L/h)	V_d (L)
Part 1 225 mg	N	8	8	7	8	8	8	7	7	7
	Mean	2972.5	0.438	150.451	120842.102	16904.960	57088.476	129207.560	1.963	373.854
	SD	767.40	0.1157	64.2869	38586.7803	2343.7550	9939.2119	47142.2662	0.7300	88.1834
	Median	2905.0	0.500	146.288	119428.212	17630.152	57663.472	139353.610	1.615	339.317
	Min	2120	0.25	67.12	73484.58	13187.25	42618.29	73898.05	1.13	294.82
	Max	4070	0.50	230.10	176036.58	19353.00	70018.10	199328.08	3.04	535.99
	%CV	25.8	26.5	42.7	31.9	13.9	17.4	36.5	37.2	23.6
	Geometric Mean	2886.9	0.420	137.187	115430.332	16754.110	56302.056	121756.266	1.848	365.746
Part 1 250 mg	N	8	8	8	8	8	8	8	8	8
	Mean	3051.3	0.478	135.493	140864.599	19823.665	68436.546	159568.742	1.708	293.939
	SD	678.64	0.0936	72.8607	32978.7430	3713.8294	11970.6898	47927.2149	0.5510	108.8331
	Median	2910.0	0.500	126.606	136206.198	19069.317	65220.548	160911.391	1.559	295.451
	Min	2290	0.25	44.17	94515.48	16136.65	57837.69	95277.63	1.11	130.81
	Max	4100	0.55	223.13	181554.89	28359.31	95706.06	225712.92	2.62	467.18
	%CV	22.2	19.6	53.8	23.4	18.7	17.5	30.0	32.3	37.0
	Geometric Mean	2989.1	0.466	116.515	137400.878	19562.438	67644.384	152987.612	1.634	274.688
Part 1 275 mg	N	8	8	6	8	8	8	6	6	6
	Mean	2857.5	0.628	140.653	140917.368	18337.270	66187.916	141738.669	2.034	403.054
	SD	1350.89	0.3526	30.7654	33877.8352	2015.4449	9917.6292	32220.0942	0.5030	82.5616
	Median	3100.0	0.500	131.245	137705.945	18170.596	64885.172	143188.068	1.921	402.367
	Min	1050	0.50	110.10	93762.97	15751.78	54981.27	96082.13	1.49	260.05
	Max	4410	1.50	182.58	196795.25	22580.35	87877.86	184174.82	2.86	506.73
	%CV	47.3	56.2	21.9	24.0	11.0	15.0	22.7	24.7	20.5
	Geometric Mean	2523.1	0.576	137.955	137367.982	18245.693	65598.761	138536.499	1.985	395.076

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-24}}$ (ng•h/mL)	$AUC_{0\text{-120}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)	CL (L/h)	V_d (L)
Part 1 300 mg	N	7	7	6	7	7	7	6	6	6
	Mean	3702.9	0.651	155.405	157091.546	20881.875	72642.469	171517.635	1.834	384.158
	SD	1428.03	0.6159	53.8735	29245.7418	2208.5903	4913.1120	40457.0014	0.4437	65.5755
	Median	3530.0	0.500	153.333	155256.034	21416.765	72899.217	177585.412	1.691	396.416
	Min	1840	0.25	76.72	119428.25	17862.73	67614.85	120745.44	1.28	275.01
	Max	5800	2.02	227.00	199972.08	23000.54	78824.41	233754.82	2.48	466.69
	%CV	38.6	94.5	34.7	18.6	10.6	6.8	23.6	24.2	17.1
	Geometric Mean	3453.3	0.506	146.722	154748.322	20777.489	72500.566	167514.813	1.791	379.087
Part 2 300 mg	N	55	55	46	55	55	55	46	46	46
	Mean	3540.4	0.480	153.322	167333.246	22555.544	78835.853	184211.883	1.795	367.096
	SD	1350.87	0.1724	57.8206	47081.6797	4110.7211	15276.1351	60958.5261	0.5580	99.4061
	Median	3540.0	0.500	159.447	157300.471	22099.521	78178.241	172739.893	1.737	363.417
	Min	1130	0.25	70.54	84283.09	14705.94	50608.48	86596.16	0.88	173.89
	Max	6800	1.53	384.59	293324.03	31915.85	122004.12	341937.13	3.46	617.58
	%CV	38.2	35.9	37.7	28.1	18.2	19.4	33.1	31.1	27.1
	Geometric Mean	3264.7	0.458	143.335	161296.358	22180.885	77422.511	175284.834	1.711	353.908
Parts 1 +2 300 mg	N	62	62	52	62	62	62	52	52	52
	Mean	3558.7	0.500	153.562	166176.925	22366.582	78136.600	182747.163	1.799	369.065
	SD	1348.59	0.2581	56.8762	45355.4621	3965.3315	14589.7332	58787.8427	0.5424	95.7649
	Median	3535.0	0.500	158.858	157217.076	22037.078	75757.319	173382.906	1.730	368.224
	Min	1130	0.25	70.54	84283.09	14705.94	50608.48	86596.16	0.88	173.89
	Max	6800	2.02	384.59	293324.03	31915.85	122004.12	341937.13	3.46	617.58
	%CV	37.9	51.6	37.0	27.3	17.7	18.7	32.2	30.1	25.9
	Geometric Mean	3285.4	0.463	143.722	160543.402	22017.805	76850.481	174370.209	1.720	356.725

Figure 24. Mean (SD) SCH720881 Plasma Concentration - Time Profiles

Linear Scale



Semi-Log Scale

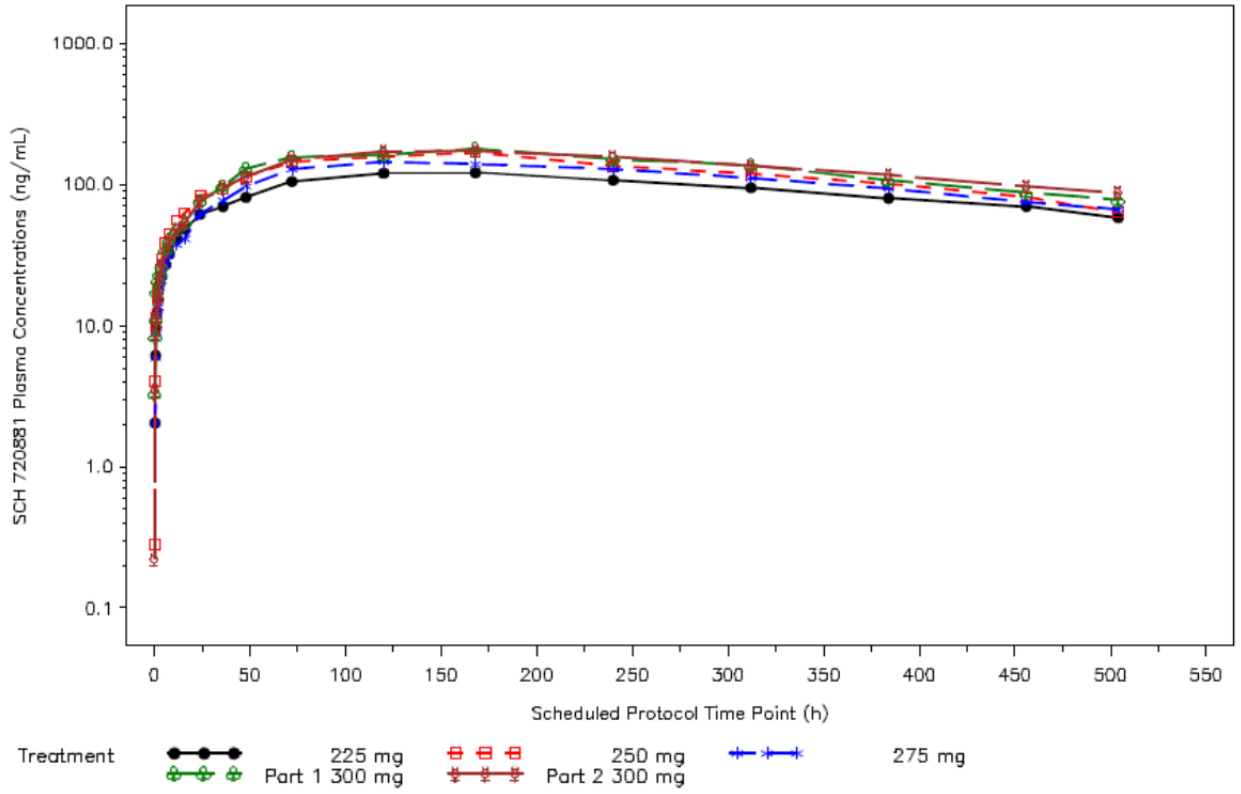


Table 10. Summary of Plasma Active Metabolite (SCH 720881) Pharmacokinetic Parameters

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-24}}$ (ng•h/mL)	$AUC_{0\text{-120}}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
Part 1 225 mg	N	8	8	3	8	8	8	3
	Mean	135.1	189.084	118.058	46319.805	931.491	10253.798	39647.549
	SD	25.91	98.5774	30.0770	11477.9969	322.5605	2928.2817	5549.7763
	Median	142.5	167.920	110.236	43556.709	785.352	9258.789	40925.882
	Min	103	72.02	92.67	32483.27	660.86	7293.68	33570.15
	Max	175	384.52	151.27	62924.89	1475.80	15214.61	44446.62
	%CV	19.2	52.1	25.5	24.8	34.6	28.6	14.0
	Geometric	132.9	168.285	115.611	45116.293	890.325	9920.598	39378.877
Part 1 250 mg	N	8	8	4	8	8	8	4
	Mean	181.5	179.655	101.753	59685.564	1238.356	13901.405	62429.989
	SD	50.16	91.4928	31.2076	9921.2878	574.6210	5858.0376	10613.2999
	Median	168.5	167.350	102.850	58003.041	956.170	11497.692	58792.809
	Min	137	71.93	64.18	50937.35	877.98	9627.67	54152.16
	Max	290	312.20	137.13	81356.65	2451.77	26863.91	77982.18
	%CV	27.6	50.9	30.7	16.6	46.4	42.1	17.0
	Geometric	176.3	158.399	97.930	59041.805	1150.955	13092.516	61808.471
Part 1 275 mg	N	8	8	3	8	8	8	3
	Mean	154.3	168.075	139.099	53773.246	862.514	11969.620	58398.885
	SD	16.36	96.0743	13.8121	6385.6486	204.0038	2095.2969	13215.2494
	Median	155.5	144.025	138.597	55351.683	869.677	12223.406	54766.518
	Min	127	71.93	125.54	42474.47	552.04	8552.93	47379.68
	Max	180	312.30	153.15	62752.87	1110.77	14937.48	73050.46
	%CV	10.6	57.2	9.9	11.9	23.7	17.5	22.6
	Geometric	153.5	145.938	138.642	53426.408	840.021	11798.792	57443.831

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	$t_{½}$ (h)	$AUC_{0\text{-last}}$ (ng•h/mL)	$AUC_{0\text{-}24}$ (ng•h/mL)	$AUC_{0\text{-}120}$ (ng•h/mL)	$AUC_{0\text{-inf}}$ (ng•h/mL)
Part 1 300 mg	N	7	7	2	7	7	7	2
	Mean	191.4	185.183	117.046	63947.168	1104.619	14526.145	68680.533
	SD	59.17	74.0963	30.4709	8079.0315	499.1078	6125.0375	7982.2933
	Median	170.0	168.650	117.046	64842.741	947.767	13044.265	68680.533
	Min	145	72.10	95.50	53478.74	684.41	10196.96	63036.20
	Max	316	311.65	138.59	74252.47	2202.96	28006.55	74324.87
	%CV	30.9	40.0	26.0	12.6	45.2	42.2	11.6
	Geometric Mean	185.1	171.196	115.046	63500.582	1035.331	13727.913	68448.208
Part 2 300 mg	N	55	55	14	55	55	55	14
	Mean	189.3	174.376	126.426	65290.050	1087.181	14229.260	62731.794
	SD	36.35	87.0765	17.8582	11988.7628	333.1105	3662.8779	10571.0600
	Median	187.0	167.120	124.821	65276.744	1018.480	14231.472	64297.396
	Min	113	71.90	98.35	38642.62	508.04	7712.35	43058.51
	Max	292	503.68	161.18	97039.85	1954.86	23018.08	80738.47
	%CV	19.2	49.9	14.1	18.4	30.6	25.7	16.9
	Geometric Mean	185.9	156.328	125.276	64176.132	1037.526	13772.413	61837.406
Parts 1 + 2 300 mg	N	62	62	16	62	62	62	16
	Mean	189.5	175.596	125.254	65138.434	1089.150	14262.779	63475.386
	SD	38.92	85.2299	18.6697	11568.9423	350.3750	3946.6613	10257.8755
	Median	187.0	167.215	124.821	65059.743	1009.007	14032.761	64297.396
	Min	113	71.90	95.50	38642.62	508.04	7712.35	43058.51
	Max	316	503.68	161.18	97039.85	2202.96	28006.55	80738.47
	%CV	20.5	48.5	14.9	17.8	32.2	27.7	16.2
	Geometric Mean	185.8	157.940	123.949	64099.502	1037.278	13767.382	62627.506

Conclusions:

- Mean rolapitant AUC0-24, AUC0-120, AUC0-last, and AUC0-inf increased in a dose proportional manner across the 225 to 300 mg dose range in Part 1 and Part 2 after a single dose.
- Mean rolapitant Cmax appeared to increase in a dose proportional manner across the 225 to 300 mg dose range, with slightly higher variability observed at 275 mg (47% in CV%).
- The variability of rolapitant (%CV) was low to moderate for Cmax and AUC parameters and was consistent with results observed in previous oral dose studies of rolapitant.
- Across Part 1 and Part 2, the mean rolapitant t½ ranged from 135 hours to 155 hours.
- Single dose mean rolapitant total body CL and Vd were consistent across the 225 to 300 mg dose range in Part 1 and Part 2 (mean CL ranged from 1.7 L/h to 2.0 L/h; mean Vd ranged from 294 L to 403 L.
- The mean SCH 720881 Cmax after a single dose of rolapitant IV was similar across the 2 parts of the study—approximately 4.5% to 6% that of rolapitant in Part 1 and 5.4% in Part 2. Across Part 1 and Part 2, the median SCH 720881 tmax ranged from 144 hours to 169 hours.

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/s/

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