CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208399Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208399
Supporting document/s:	042
Applicant's letter date:	4/25/2017
CDER stamp date:	4/25/2017
Product:	Varubi® (rolapitant) (Injectable Emulsion for Intravenous Use)
Indication:	Prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy
Applicant:	Tesaro, Inc.
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Tamal Chakraborti, PhD
Supervisor:	Sushanta Chakder, PhD
Division Director:	Donna Griebel, MD
Project Manager:	Mary Chung, PharmD

TABLE OF CONTENTS

Executive Summary

Introduction

Rolapitant is a substance P/Neurokinin 1 (NK1) receptor antagonist. An oral version (Varubi® tablets) of rolapitant was approved on September 01, 2015. This application is for an intravenous (IV) version [Varubi® IV (rolapitant) injectable emulsion, for intravenous use] of rolapitant. Varubi injectable emulsion is indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. The recommended dosage is 166.5 mg administered as an IV infusion over 30 minutes within 2 hours prior to the initiation of chemotherapy on Day 1.

The original NDA was submitted on March 11, 2016. This resubmission is a complete response to the deficiencies outlined in the Division's Complete Response (CR) letter dated January 11, 2017.

Brief Discussion of Nonclinical Findings

The Applicant did not submit any nonclinical study report in this submission. Nonclinical studies have been conducted with rolapitant to support approval of rolapitant tablets and rolapitant injectable emulsion under NDA 206500 and NDA 208399, respectively. Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD and pharmacology review of NDA 208399 dated November 28, 2016 by Tamal Chakraborti, PhD.

Recommendations

Approvability

There are no nonclinical approvability issues.

Additional Non Clinical Recommendations

None

Labeling

Nonclinical sections of the proposed draft labeling of VARUBI® conforms to the content and format of labeling for human prescription drug and biological products under 21CFR201.57. However, the following revisions are recommended.

8.1 Pregnancy

Applicant's Version:

8.1 Pregnancy

Risk Summary

The limited data with VARUBI use in pregnant women are insufficient to inform a drug associated risk of birth defects or miscarriage. In animal reproduction studies, there were no adverse developmental effects observed with oral administration of rolapitant hydrochloride in rats and rabbits during the period of organogenesis at doses up to 1.3 times and 2.9-times, respectively, the maximum recommended human dose (MRHD) *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

The potential embryo-fetal toxicity of rolapitant hydrochloride was assessed in pregnant rats administered oral doses equivalent to up to 22.5 mg/kg per day rolapitant throughout organogenesis. Rats administered doses equivalent to 13.5 or 22.5 mg/kg per day rolapitant exhibited evidence of maternal toxicity including decreased body weight gain and/or body weight loss and a concomitant decrease in food consumption during the first week of dosing. (b) (4) (b) (4) were observed at doses equivalent to up to 22.5 mg/kg per day rolapitant (approximately 1.3 times the recommended intravenous human dose on a body surface area basis). In rabbits administered rolapitant (b) (4) throughout the period of organogenesis, oral doses equivalent to up to 27 mg/kg per day rolapitant (approximately 3 times the recommended intravenous human dose on a body surface area basis) were without effects on the developing fetus.

The pre- and postnatal developmental effects of rolapitant hydrochloride were assessed in rats administered oral doses equivalent to 2.25, 9 or 22.5 mg/kg per day rolapitant during the periods of organogenesis and lactation. Maternal toxicity was evident based on mortality/moribund condition, decreased body weight and food consumption, total litter loss, prolonged parturition, decreased length of gestation, and increased number of unaccounted for implantation sites at a dose equivalent to 22.5 mg/kg per day (approximately 1.3 times the recommended intravenous human dose on a body surface area basis). Effects on offspring at this dose included decreased postnatal survival, and decreased body weights and body weight gain, and may be related to the maternal toxicity observed. At a maternal dose equivalent to 9 mg/kg per day rolapitant (approximately 0.5 times the recommended intravenous human dose on a body surface area basis), there was a decrease in memory in female pups in a maze test and a decrease in pup body weight.

Evaluation: The Applicant's proposed version appears to be acceptable. However, the following revisions (rolapitant hydrochloride to rolapitant) were made.

Recommended Version:

8.1. Pregnancy

Data

Animal Data

The potential embryo-fetal toxicity of rolapitant was assessed in pregnant rats administered oral doses up to 22.5 mg/kg per day throughout the period of organogenesis. Rats administered doses of 13.5 or 22.5 mg/kg per day rolapitant exhibited evidence of maternal toxicity including decreased body weight gain and/or body weight loss and a concomitant decrease in food consumption during the first week of dosing. No adverse embryo-fetal developmental effects were observed at doses up to 22.5 mg/kg per day rolapitant (approximately 1.3 times the recommended intravenous human dose on a body surface area basis). In rabbits administered rolapitant throughout the period of organogenesis, oral doses up to 27 mg/kg per day (approximately 3 times the recommended intravenous human dose on a body surface area basis) were without effects on the developing fetus.

The pre- and postnatal developmental effects of rolapitant were assessed in rats administered oral doses of 2.25, 9 or 22.5 mg/kg per day during the periods of organogenesis and lactation. Maternal toxicity was evident based on mortality/moribund condition, decreased body weight and food consumption, total litter loss, prolonged parturition, decreased length of gestation, and increased number of unaccounted for implantation sites at a dose of 22.5 mg/kg per day (approximately 1.3 times the recommended intravenous human dose on a body surface area basis). Effects on offspring at this dose included decreased postnatal survival, and decreased body weights and body weight gain, and may be related to the maternal toxicity observed. At a maternal dose of 9 mg/kg per day rolapitant (approximately 0.5 times the recommended intravenous human dose on a body surface area basis), there was a decrease in memory in female pups in a maze test and a decrease in pup body weight.

8.2 Lactation

Applicant's Version:

8.2 Lactation

Risk Summary

There are no data on the presence of rolapitant in human milk, the effects of rolapitant in the breastfed infant, or the effects of rolapitant on milk production. Rolapitant (b) (4) administered orally to lactating female rats was present in milk *[see Data]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VARUBI and any potential adverse effects on the breastfed infant from VARUBI or from the underlying maternal condition or the use of concomitant chemotherapy.

Data

Radioactivity from labeled [^{14}C] rolapitant hydrochloride was transferred into milk of lactating rats following a single oral dose equivalent to 22.5 mg/kg rolapitant, and the maximum radioactivity in milk was observed at 12 hours post-dose. The mean milk/plasma radioactivity concentration ratios in dams at 1 to 48 hours post-dose ranged from 1.24 to 3.25. Based on average daily consumption of milk (2 mL/day) and the maximum milk radioactivity determined, pup exposure is expected to be 0.32% of the orally administered dose.

Evaluation: The Applicant's proposed version appears to be acceptable. However, the following revisions (rolapitant hydrochloride to rolapitant) are made.

Recommended Version:

8.2 Lactation

Data

Radioactivity from labeled [^{14}C] rolapitant was transferred into milk of lactating rats following a single oral dose of 22.5 mg/kg, and the maximum radioactivity in milk was observed at 12 hours post-dose. The mean milk/plasma radioactivity concentration ratios in dams at 1 to 48 hours post-dose ranged from 1.24 to 3.25. Based on average daily consumption of milk (2 mL/day) and the maximum milk radioactivity determined, pup exposure is expected to be 0.32% of the orally administered dose.

8.4 Pediatric Use

Applicant's Version:

8.4 Pediatric Use

Safety and efficacy of VARUBI have not been established in pediatric patients.

Evaluation: The results of the oral juvenile animal toxicology study in rats are incorporated.

Recommended Version:

8.4 Pediatric Use

Juvenile Animal Toxicity Data

In an oral juvenile toxicity study in rats (b) (4) rolapitant (b) (4) dose (b) (4) of 11.3, 22.5 and 45 mg/kg/day from postnatal Day 7 through PND 70 (equivalent human age of newborn to 16 years), (b) (4) a delay in the attainment of balanopreputial separation in males and acceleration of the attainment of vaginal patency in females at 22.5 and 45 mg/kg/day (approximately 1.3 and 2.6 times, respectively, the recommended intravenous human dose on a body surface area basis). Treated males and females were mated following a 2-week wash-out period after the last dose. (b) (4) (approximately 1.3 and 2.6 times, respectively, the recommended intravenous human dose on a body surface area basis). There were lower mean numbers of implantation sites, corpora lutea, and mean number of viable embryos at these doses when compared to control.

13. Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Applicant's Version:

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
Carcinogenic potential of rolapitant (b) (4) was assessed in 2-year carcinogenicity studies in CD-1 mice and Sprague-Dawley rats. In mice, there were no drug-related neoplastic findings at doses equivalent to up to 135 mg/kg per day rolapitant (approximately 3.9 times the recommended intravenous human dose on a body surface area basis). In rats, there were no drug-related neoplastic findings at doses equivalent to up to 90 mg/kg per day rolapitant (approximately 5.2 times the recommended intravenous human dose on a body surface area basis).

Mutagenesis
Rolapitant (b) (4) was not genotoxic in an Ames test, a human peripheral blood lymphocyte chromosome aberration test, and a mouse micronucleus test.

Impairment of Fertility
In a fertility and early embryonic development study in female rats, rolapitant (b) (4) at an oral dose equivalent to 9 mg/kg per day (approximately 0.5 times the recommended intravenous human dose on a body surface area basis) caused a transient decrease in maternal body weight gain and increases in the incidence of pre- and post-implantation loss. At a dose equivalent to 4.5 mg/kg per day (approximately 0.2 times the recommended intravenous human dose on a body surface area basis), there were slight decreases in the number of corpora lutea and implantation sites. Rolapitant (b) (4) did not affect the fertility or general reproductive performance of male rats at doses equivalent to up to 90 mg/kg per day rolapitant (approximately 5.2 times the recommended intravenous human dose on a body surface area basis).

Evaluation: The Applicant's proposed version appears to be acceptable. However, the following revisions (b) (4) to rolapitant) were made.

Recommended Version:

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis
The carcinogenic potential of rolapitant was assessed in 2-year carcinogenicity studies in CD-1 mice and Sprague-Dawley rats. In mice, there were no drug-related neoplastic findings at doses up to 135 mg/kg per day (approximately 3.9 times the recommended intravenous human dose on a body surface area basis). In rats, there were no drug-related neoplastic findings at doses up to 90 mg/kg per day (approximately 5.2 times the recommended intravenous human dose on a body surface area basis).

Mutagenesis
Rolapitant was not genotoxic in an Ames test, a human peripheral blood lymphocyte chromosome aberration test, and a mouse micronucleus test.

Impairment of Fertility
In a fertility and early embryonic development study in female rats, rolapitant at an oral dose of 9 mg/kg per day (approximately 0.5 times the recommended intravenous human dose on a body surface area basis) caused a transient decrease in maternal body weight gain and increases in the incidence of pre- and post-implantation loss. At a rolapitant dose of 4.5 mg/kg per day (approximately 0.3 times the recommended intravenous human dose on a body surface area basis), there were slight decreases in the number of corpora lutea and implantation sites. Rolapitant did not affect the fertility or general reproductive performance of male rats at doses up to 90 mg/kg per day (approximately 5.2 times the recommended intravenous human dose on a body surface area basis).

Regulatory Background

- Original NDA was submitted on March 11, 2016
- Complete Response (CR) letter was issued on January 11, 2017
- End of review meeting was held on March 22, 2017 to discuss the Applicant's plan to address the deficiencies identified in the above CR letter.

Studies Submitted

Studies Reviewed

The Applicant did not submit any nonclinical study report in this submission.

Studies Not Reviewed

N/A

Previous Reviews Referenced

- Pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD
- Pharmacology review of NDA 208399 dated November 28, 2016 by Tamal Chakraborti, PhD
- Pharmacology review of IND 72,754 dated December 20, 2016 by Tamal Chakraborti, PhD
- Pharmacology review of IND 72,754 dated August 23, 2017 by Tamal Chakraborti, PhD

Integrated Summary and Safety Evaluation

The Applicant did not submit any nonclinical study report in this submission. Nonclinical studies have been conducted with rolapitant to support approval of rolapitant tablets and

rolapitant injectable emulsion under NDA 206500 and NDA 208399, respectively. A Complete Response letter was issued on January 11, 2017. However, no nonclinical safety issues were identified in the initial submission. In the current review, some labeling changes are recommended. In addition, a recommendation to add the findings of the oral juvenile rat toxicity study was also made in Section 8.4 of the label.

Appendix/Attachments

None

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

/s/

TAMAL K CHAKRABORTI
09/14/2017

SUSHANTA K CHAKDER
09/14/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	208399
Supporting document/s:	001
Applicant's letter date:	3/11/2016
CDER stamp date:	3/11/2016
Product:	Rolapitant hydrochloride (Varubi®, Injectable Emulsion for Intravenous Use)
Indication:	Prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy
Applicant:	Tesaro, Inc.
Review Division:	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Reviewer:	Tamal Chakraborti, PhD
Supervisor:	Sushanta Chakder, PhD
Division Director:	Donna Griebel, MD
Project Manager:	Mary Chung, PharmD

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 208399 are owned by Tesaro, Inc. or are data for which Tesaro, Inc. has obtained a written right of reference. Any information or data necessary for approval of NDA 208399 that Tesaro, Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 208399.

TABLE OF CONTENTS

1 Executive Summary

1.1 Introduction

Rolapitant is a substance P/Neurokinin 1 (NK1) receptor antagonist. An oral version (tablets, Varubi®) of rolapitant was approved on September 01, 2015. This application is for an intravenous (IV) version [Varubi® IV (rolapitant) injectable emulsion, for intravenous use] of rolapitant. Varubi injectable emulsion is indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. The recommended dosage is 166.5 mg administered as an IV infusion over 30 minutes within 2 hours prior to the initiation of chemotherapy on Day 1.

1.2 Brief Discussion of Nonclinical Findings

Nonclinical studies have been conducted with rolapitant to support approval of rolapitant tablets under NDA 206500. Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

Toxicology studies in two species (rat and cynomolgus monkey) were conducted up to 13 weeks treatment duration by the IV route to support the IV rolapitant formulation. The Central Nervous System (CNS) appeared to be the primary target organ in both species. Treatment related clinical signs included convulsions and tremors, which were consistent with the findings of the oral toxicology studies. However, there were no rolapitant related histopathological findings in the brain in the above IV toxicology studies in both species. Vehicle related effects (clinical pathology changes and histopathology changes in the adrenal gland and liver) were observed in the IV toxicology studies. Histopathological findings in the adrenal gland (diffuse vacuolation of the adrenal cortex and brown pigmentation of adrenal glands) and liver (Kupffer cells) appeared to be related to the vehicle. In addition, infusion site reactions were observed, which included abscess formation and/or inflammation.

1.3 Recommendations

1.3.1 Approvability

There are no nonclinical approvability issues.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Nonclinical sections of the proposed draft labeling of VARUBI® conforms to the content and format of labeling for human prescription drug and biological products under 21CFR201.57. However, the following revisions are recommended.

8.1 Pregnancy

Applicant's Version:

8.1. Pregnancy

Risk Summary

There are no available data on VARUBI use in pregnant women to inform any drug-associated risks. In animal reproduction studies, there were no (b) (4) effects observed with oral administration of rolapitant (b) (4) in rats and rabbits during the period of organogenesis at doses up to (b) (4) times and 2.9 times, respectively, the maximum recommended human dose (MRHD) *[see Data]*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

The potential embryo-fetal toxicity of rolapitant hydrochloride was assessed in pregnant rats administered oral doses equivalent to up to 22.5 mg/kg per day rolapitant (b) (4) throughout organogenesis. Rats administered doses equivalent to 13.5 or 22.5 mg/kg per day rolapitant (b) (4) exhibited evidence of maternal toxicity including decreased body weight gain and/or body weight loss and a concomitant decrease in food consumption during the first week of dosing. No (b) (4) effects were observed at doses equivalent to up to 22.5 mg/kg per day rolapitant (b) (4) approximately (b) (4) times the recommended human dose on a body surface area basis). In rabbits administered rolapitant hydrochloride throughout the period of organogenesis, oral doses equivalent to up to 27 mg/kg per day (b) (4) (approximately (b) (4) times the recommended human dose on a body surface area basis) were without effects on the developing fetus.

The pre- and postnatal developmental effects of rolapitant (b) (4) were assessed in rats administered oral doses equivalent to 2.25, 9 or 22.5 mg/kg per day rolapitant (b) (4) during the periods of organogenesis and lactation. Maternal toxicity was evident based on mortality/moribund condition, decreased body weight and food consumption, total litter loss, prolonged parturition, decreased length of gestation, and increased number of unaccounted for implantation sites at a dose equivalent to 22.5 mg/kg per day (b) (4) (approximately (b) (4) times the recommended human dose on a body surface area basis). Effects on offspring at this dose included decreased postnatal survival, and decreased body weights and body weight gain, and may be related to the maternal toxicity observed. At a maternal dose equivalent to 9 mg/kg per day rolapitant (b) (4) (approximately 0.5 times the recommended human dose on a body surface area basis), there was a decrease in memory in female pups in a maze test and a decrease in pup body weight.

(b) (4) The Applicant's proposed version appears to be acceptable. However, human dose multiples values were revised based on the recommended intravenous human dose of 166.5 mg (~167 mg/day or approximately 2.8 mg/kg/day) of Varubi.

Recommended Version:

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Data

Animal Data

The potential embryo-fetal developmental toxicity of rolapitant hydrochloride was assessed in pregnant rats administered oral doses equivalent to up to 22.5 mg/kg per day rolapitant throughout organogenesis. Rats administered 13.5 or 22.5 mg/kg per day rolapitant exhibited evidence of maternal toxicity including decreased body weight gain and/or body weight loss and a concomitant decrease in food consumption during the first week of dosing. (b) (4) were observed at doses up to 22.5 mg/kg per day rolapitant (approximately 1.3 times the recommended intravenous human dose of 166.5 mg on a body surface area basis). In rabbits administered rolapitant throughout the period of organogenesis, oral doses up to 27 mg/kg per day (approximately 3 times the recommended intravenous human dose of 166.5 mg on a body surface area basis) were without effects on the developing fetus.

The pre- and postnatal developmental effects of rolapitant were assessed in rats administered oral doses of 2.25, 9 or 22.5 mg/kg per day during the periods of organogenesis and lactation. Maternal toxicity was evident based on mortality/moribund condition, decreased body weight and food consumption, total litter loss, prolonged parturition, decreased length of gestation, and increased number of unaccounted for implantation sites at a dose of 22.5 mg/kg per day (approximately 1.3 times the recommended intravenous human dose of 166.5 mg on a body surface area basis). Effects on offspring at this dose included decreased postnatal survival, and decreased body weights and body weight gain, and may be related to the maternal toxicity observed. At a maternal dose of 9 mg/kg per day rolapitant (approximately 0.5 times the recommended human dose of 166.5 mg on a body surface area basis), there was a decrease in memory in female pups in a maze test and a decrease in pup body weight.

8.2 Lactation

Applicant's Version:

8.2. Lactation

Risk Summary

There are no data on the presence of rolapitant in human milk, the effects of rolapitant in the breastfed infant, or the effects of rolapitant on milk production. Rolapitant (b) (4) administered orally to lactating female rats was present in milk [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VARUBI and any potential adverse effects on the breastfed infant from VARUBI or from the underlying maternal condition or the use of concomitant chemotherapy.

Data

Radioactivity from labeled [^{14}C] rolapitant hydrochloride was transferred into milk of lactating rats following a single oral dose equivalent to 22.5 mg/kg rolapitan (b) (4) and the maximum radioactivity in milk was observed at 12 hours post-dose. The mean milk/plasma radioactivity concentration ratios in dams at 1 to 48 hours post-dose ranged from 1.24 to 3.25. Based on average daily consumption of milk (2 mL/day) and the maximum milk radioactivity determined, pup exposure is expected to be 0.32% of the orally administered dose.

Evaluation: The Applicant's proposed version appears to be acceptable.

Recommended Version: None

13. Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Applicant's Version:

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic potential of rolapitant (b) (4) was assessed in 2-year carcinogenicity studies in CD-1 mice and Sprague-Dawley rats. In mice, there were no drug-related neoplastic findings at doses (b) (4) (b) (4) up to 135 mg/kg per day (b) (4) (approximately (b) (4) times the recommended human dose on a body surface area basis). In rats, there were no drug-related neoplastic findings at doses equivalent to up to 90 mg/kg per day rolapitant free base (approximately (b) (4) times the recommended human dose on a body surface area basis).

Rolapitant hydrochloride was not genotoxic in an Ames test, a human peripheral blood lymphocyte chromosome aberration test, and a mouse micronucleus test.

In a fertility and early embryonic development study in female rats, rolapitant hydrochloride at an oral dose equivalent to 9 mg/kg per day (b) (4) (approximately 0.5 times the recommended human dose on a body surface area basis) caused a transient decrease in maternal body weight gain and increases in the incidence of pre- and post-implantation loss. At a dose equivalent to 4.5 mg/kg per day (b) (4) (approximately 0.2 times the recommended human dose on a body surface area basis), there were slight decreases in the number of corpora lutea and implantation sites. Rolapitant hydrochloride did not affect the fertility or general reproductive performance of male rats at doses equivalent to up to 90 mg/kg per day rolapitant (b) (4) (approximately 4.9 times the recommended human dose on a body surface area basis).

Evaluation: The Applicant's proposed version appears to be acceptable. However, human dose multiple values were revised based on the recommended intravenous human dose of 166.5 mg (~167 mg/day or approximately 2.8 mg/kg/day) of Varubi.

Recommended Version:

13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic potential of rolapitant was assessed in 2-year oral carcinogenicity studies in CD-1 mice and Sprague-Dawley rats. In mice, there were no drug-related neoplastic findings at doses up to 135 mg/kg per day rolapitant (approximately 3.9 times the recommended intravenous human dose of 166.5 mg on a body surface area basis). In rats, there were no drug-related neoplastic findings at doses up to 90 mg/kg per day rolapitant (approximately 5.2 times the recommended intravenous human dose of 166.5 mg on a body surface area basis).

Rolapitant hydrochloride was not genotoxic in an Ames test, a human peripheral blood lymphocyte chromosome aberration test, and a mouse micronucleus test.

In a fertility and early embryonic development study in female rats, rolapitant at an oral dose of 9 mg/kg per day (approximately 0.5 times the recommended intravenous human dose of 166.5 mg on a body surface area basis) caused a transient decrease in maternal body weight gain and increases in the incidence of pre- and post-implantation loss. At a dose of 4.5 mg/kg per day (approximately 0.2 times the recommended intravenous human dose of 166.5 mg on a body surface area basis), there were slight decreases in the number of corpora lutea and implantation sites. Rolapitant did not affect the fertility or general reproductive performance of male rats at doses up to 90 mg/kg per day (approximately 5.2 times the recommended intravenous human dose of 166.5 mg on a body surface area basis).

2 Drug Information

2.1 Drug

CAS Registry Number:

Rolapitant (b) (4) (USAN rolapitant): 552292-08-7
Rolapitant hydrochloride (b) (4) (USAN rolapitant hydrochloride): 914462-92-3

Generic Name: Rolapitant hydrochloride

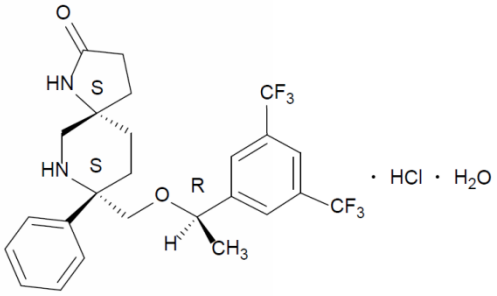
Code Name: SCH 619734 hydrochloride (b) (4) or 17TR68M Rolapitant

Chemical Name: (5S,8S)-8-[[(1R)-1-[3,5 Bis(trifluoromethyl)phenyl]ethoxy]methyl]-8-phenyl-1,7-diazaspiro[4.5]decan-2-one hydrochloride (b) (4)

Molecular Formula/Molecular Weight:

Rolapitant (b) (4) (USAN rolapitant): $C_{25}H_{26}F_6N_2O_2$/500.49
Rolapitant hydrochloride (b) (4) (USAN rolapitant hydrochloride): $C_{25}H_{29}ClF_6N_2O_3$ or $C_{25}H_{26}F_6N_2O_2.HCl.H_2O$/554.96

Structure: The following figure (from page 1 of Section 3.2.S.1 of the submission) shows the structure of rolapitant hydrochloride.



Rolapitant hydrochloride

Pharmacologic Class: Substance P/Neurokinin 1 (NK1) receptor antagonist

2.2 Relevant INDs, NDAs, and DMFs

- IND 72754 (Rolapitant Oral, Tesaro, Inc.)
- IND 117307 (Rolapitant, IV, Tesaro, Inc.)
- NDA 206500 (Rolapitant, Oral, Tesaro, Inc.)

2.3 Drug Formulation

Rolapitant (Varubi) injectable emulsion for IV infusion is a sterile formulation containing 166.5 mg rolapitant (equivalent to 185 mg of rolapitant hydrochloride) and the following inactive ingredients: polyoxyl 15 hydroxystearate (44 mg/mL), medium chain triglycerides (11 mg/mL), soybean oil (6.[(b)(4)] 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 pH. Varubi injectable emulsion is supplied as a sterile, translucent white homogenous emulsion in a stoppered vial. Each vial delivers 166.5 mg/92.5 mL (1.8 mg/mL) rolapitant. The following table (from page 1 of Section 2.3.P of the submission) shows the composition of the drug product (DP).

Table 1: Composition of Rolapitant Injectable Emulsion

Ingredient	Trade Name/ Common Name	Function	Compendial Grade	Concentration (g/100 mL)	Amount per Unit (g)[a]
Rolapitant hydrochloride[b]	(b) (4)				
Polyoxyl 15 Hydroxy-stearate					
Medium Chain Triglycerides (b) (4)					
Soybean oil					
Sodium Chloride					
Dibasic Sodium Phosphate Anhydrous					
Hydrochloric acid					
Sodium hydroxide					
Water for Injection					

(b) (4)

2.4 Comments on Novel Excipients

Polyoxyl 15 Hydroxystearate ((b) (4)

When calculated per dose, animals were administered (b) (4) fold more polyoxyl-15-hydroxystearate than the above intended clinical dose. When the calculations included the frequency of administration (daily in animals vs. not more than once every other week in humans),

the dose multiples relative to human were (b) (4)-fold in rats and monkeys, respectively, as shown in the table below (from page 80 of Section 2.6.6 of the submission).

Table 40: Dose Multiples of Polyoxyl-15-Hydroxystearate in Humans (166.5 mg/dose rolapitant base), Based on Rat and Monkey IV Studies (volume in vehicle control group of 3-month studies)

Study	Placebo Vol. (mL/kg)	Dose	Dose Multiples Based on Body Weight for humans	
		(mg/kg)	Multiples based on daily dose	Multiples based on intended clinical use[a]
14-day and 3-month IV rat (QD)	10	440	(b) (4)	
14-day IV monkey (QD)	10	440		
1- and 3-month IV monkey (QD)	7.5	330		
Human Use (Q2W)	(b) (4)			

[a] A factor of 14 is being applied to calculate multiples due to the shortest interval between intended human clinical use (Q2W).

Based on the above, the presence of polyoxyl 15 hydroxystearate at (b) (4)% in the drug product is qualified in toxicology studies and is acceptable.

Medium-Chain Triglycerides (b) (4) of MCT per dose.

In the course of the intravenous toxicity studies, (b) (4) was administered as part of the vehicle control in separate groups from the saline control groups. In 14-day repeat dose studies, doses of (b) (4) up to 220 mg/kg/day in rats and 110 mg/kg/day in monkeys caused no significant vehicle related toxicity. These were the highest doses administered in these studies. In subchronic studies, vehicle was administered daily at dose volumes of up to 10 mL/kg (110 mg/kg/day (b) (4) in rats and 7.5 mL/kg (82.5 mg/kg/day (b) (4) in monkeys for up to 3 months without adverse effects. In comparison, the recommended intravenous infusion volume of rolapitant is 92.5 mL per patient (1.3 mL/kg in a 70 kg patient). This equates to (b) (4) mg of (b) (4) per dose and (b) (4) mg/kg/dose for a 70 kg patient. In humans, rolapitant will not be administered more frequently than every other week. Due to rapid elimination of rolapitant in the preclinical safety species, daily dosing was used in toxicology studies to achieve adequate exposure. When adjusted for a human-equivalent two-week dosing period, rats and monkeys were respectively exposed to 1540 mg/kg (110 mg/kg/day x 14 day) and 1155 mg/kg (82.5 mg/kg/day x 14 day)

(b) (4) per 2 week period with no adverse findings. At these NOAEL doses of (b) (4) in both species, the exposure is approximately (b) (4)-fold (rats) and (b) (4)-fold (monkeys) higher than in humans, therefore providing adequate exposure margins from data collected in GLP studies as shown in the following table (from page 5 of SDN 009 dated June 13, 2016 .)

Table 1: Dose Multiples of (b) (4) in Humans (166.5 mg/dose rolapitant base), Based on Rat and Monkey IV Studies (volume in vehicle control group of 3-month studies)

Study	Placebo Vol. (mL/kg)	Dose (mg/kg)	Dose Multiples Based on Body Weight for humans	
			Multiples based on daily dose	Multiples based on intended clinical use[a]
14-day and 3-month IV rat (QD)	10	110	(b) (4)	
14-day IV monkey (QD)	10	110		
1- and 3-month IV monkey (QD)	7.5	82.5		
Human Use (Q2W)	(b) (4)			

[a]A factor of 14 is being applied to calculate multiples due to the shortest interval between intended human clinical use (Q2W).

Based on the above, the presence of (b) (4)% in the drug product is qualified in toxicology studies and is acceptable.

2.5 Comments on Impurities/Degradants of Concern

The highest levels of total impurities reported in the 10 batches produced by the commercial route (Process (b) (4) are shown in the table (from page 3 of 3.2.S.3 of the submission) below.

Table 1: Summary of Highest Levels of Total Impurities in Commercial Process

(b) (4)

(b) (4)

No single impurity was above the ICH qualification threshold of 0.15% for doses ≤ 2 g per day in any of the 10 drug substance batches as shown in the above table. The specifications for the drug substance are shown in the table (from page 1 and 2 of Section 3.2.S.4 of the submission) below.

Table 1: Specifications for Rolapitant Hydrochloride

Test	Type	Analytical Method	Acceptance Criteria
Description	Visual	AA.TG018	White to off-white powder
(b) (4)			
(b) (4)			

Table 1: Specifications for Rolapitant Hydrochloride (Continued)

Test	Type	Analytical Method	Acceptance Criteria
(b) (4)			(b) (4)

The specifications of impurities met the ICH Q3A qualification threshold for drug substances with a maximum daily dose ≤ 2 g per day. Therefore, the above specifications for drug substance impurities are acceptable.

Potential Genotoxic Impurity (PGI): The Applicant has conducted assessment of PGI for the rolapitant hydrochloride (b) (4) drug substance (DS) per the ICH M7 guidance using two Quantitative Structure Activity Relationship (QSAR) screens (DEREK and Leadscope). Any identified PGIs including mutagenic impurities were controlled to below the Threshold of Toxicological Concern (TTC) in the final Active Pharmaceutical Ingredient (API). The TTC for total PGIs was calculated to be (b) (4) ppm (b) (4) ppm/0.185 = (b) (4) ppm equivalent to an exposure of (b) (4) µg per day) based on a maximum life time exposure of no more than 30 doses and the recommended dose of 185 mg per dose (as hydrochloride (b) (4), or 166.5mg as (b) (4)). Per the ICH M7 guidance, maximum allowable daily intake of an individual genotoxic impurity is (b) (4) µg per day for the treatment duration of ≤1 month. The structure, origin, and control strategy for the three identified PGIs are shown in the table below (from page 18 of Section 3.2.S.3 of the submission).

Table 3: Summary of Identified PGIs in API Synthesis Starting from the RSM, and Proposed Control Strategy

Category	Name	Structure	Step of Origin	Proposed Control Strategy
(b) (4)	(b) (4)			

All three PGIs were controlled to levels below the TTC. Batch analysis data confirmed that the levels of the potential (b) (4) were below (b) (4) ppm, which is significantly below the TTC. The following table (from page 20 of Section 3.2.S.3 of the submission) shows the batch analysis data for (b) (4) (b) (4) levels in the API.

Table 5: Batch Analysis Data on (b) (4) (b) (4) Levels in API

Test	Tentative Limits	Batch Number
		(b) (4)

Residual Solvents: A total of (b) (4) organic solvents (b) (4) were used in the synthesis of rolapitant hydrochloride. Residual levels of these solvents were monitored in the drug substance. The residual solvent levels for all batches were within ICH Q3C limits and are acceptable. The origin of each solvent and the highest levels observed in batches produced were shown in the table (from page 22 of Section 3.2.S.3 of the submission) below.

Table 7: Summary of Residual Organic Solvents in Registration Process

Name	Class	Manufacturing Step	Method of Monitor	Highs Level Observed
(b) (4)				

(b) (4)

Heavy Metals: The proposed specification for heavy metals in the drug substance is Not More Than (NMT) (b) (4) ppm (b) (4) %).

(b) (4) e used as (b) (4) e.g. (b) (4) and (b) (4). The levels of (b) (4) in drug substance batches were < (b) (4) ppm (b) (4) and ≤ (b) (4) ppm (b) (4)), respectively. Based on the recommended daily dose of 185 mg of rolapitant hydrochloride, the exposure to (b) (4) would be approximately (b) (4) µg per day, respectively, which are well below the parenteral PDE for (b) (4) ((b) (4) µg per day) per the ICH Q3D guidance and are acceptable.

Based on the recommended daily dose of 185 mg of rolapitant hydrochloride, the exposure to heavy metals including (b) (4) and (b) (4)

from the drug product would be approximately (b) (4) µg per day, which exceeds the parenteral PDE for (b) (4) (b) (4) µg per day) and (b) (4) (b) (4) µg per day) per the ICH Q3D guidance. Thus, the proposed specification for heavy metals at NMT (b) (4) ppm was not considered acceptable. The Applicant was asked (letter dated May 24, 2016) to reduce the specification limit for heavy metals so that the daily exposure of (b) (4) and (b) (4) is ≤ (b) (4) µg per day, respectively. The Applicant agreed (SDN 009 dated June 13, 2016) to reduce the specification limit for heavy metals in the drug substance to NMT (b) (4) ppm. At (b) (4) ppm ((b) (4) %) limit and based on a proposed daily dose of 185 mg of rolapitant hydrochloride, the exposure to (b) (4) and (b) (4) would be approximately (b) (4) µg per day, which is well below the parenteral PDE for (b) (4) and (b) (4) of (b) (4) µg per day and ≤ (b) (4) µg per day, respectively. The Applicant stated (SDN 009 dated June 13, 2016) that the heavy metals specification (in Section 3.2.S.4.1 of the NDA) for rolapitant hydrochloride (b) (4) drug substance will be changed and the revised specifications will be submitted to the Agency in the first Annual Report. The Applicant's revised specification for heavy metals at NMT (b) (4) ppm is acceptable.

Container Closure System (CCS)

The Container Closure System (CCS) is composed of a (b) (4) The following table (from page 5 of Section 3.2.P.7, SDN 025) shows the details of the components of the CCS.

Table 1: Details of Packaging Components, Including Suppliers

Component	Materials of Construction	Type III DMF	Manufacturer
(b) (4)			

Extractables/Leachables (E/L)

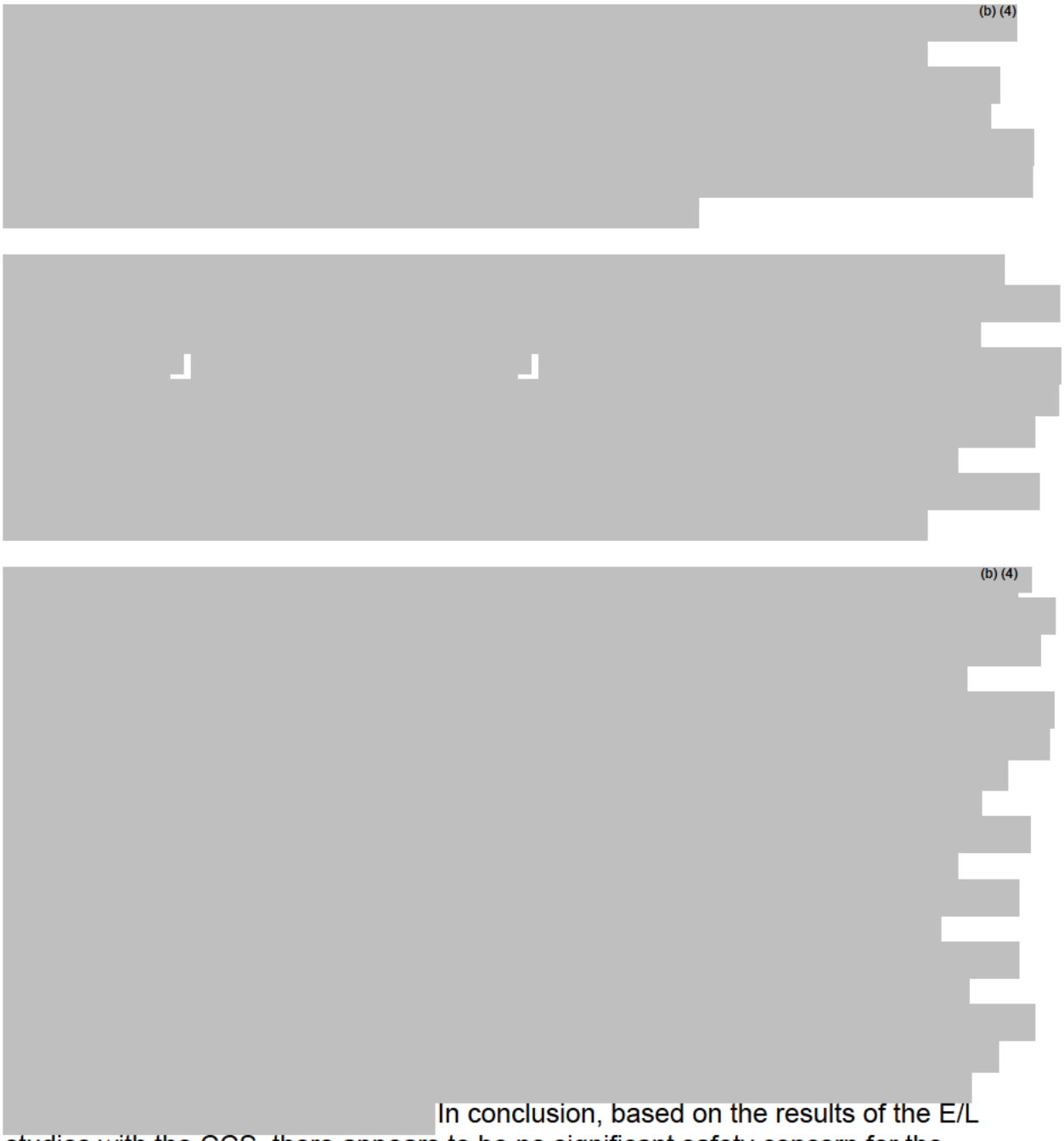
Initially, the Applicant proposed to use the CCS containing (b) (4) However, the stopper remained the same. It is to be noted here that Extractables/Leachables (E/L) studies were conducted with the (b) (4) stopper. The Applicant did not conduct E/L studies with the (b) (4) was considered inert and is considered suitable for parenteral drug products. For the leachables testing, the drug product was supplied in a (b) (4) with a (b) (4) with (b) (4) and (b) (4). The E/L program for the CCS consisted of the following three segments.

- (b) (4)

- (b) (4)
-

(b) (4)

Therefore, the above estimated daily exposure to (b) (4) does not appear to raise significant safety concern."



In conclusion, based on the results of the E/L studies with the CCS, there appears to be no significant safety concern for the extractables/leachables from the CCS for Varubi® (rolapitant) injectable emulsion.

2.6 Proposed Clinical Population and Dosing Regimen

Varubi is indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. The recommended dosage is 166.5 mg administered as an intravenous infusion over 30 minutes within 2 hours prior to the initiation of chemotherapy on Day 1.

2.7 Regulatory Background

- Type B meeting was held on April 5, 2010 to discuss the phase 3 development program.
- Type C End of Phase (EOP) 2 follow-up meeting was held on July 5, 2011 to discuss revised clinical development program.
- Type B EOP2 meeting was held on January 28, 2013 to discuss the Chemistry, Manufacturing, and Controls (CMC) strategy of rolapitant.
- Type B Pre-NDA meeting was held on July 2, 2014.
- Type B Pre-NDA meeting was held on July 2, 2014.
- Type B Pre-NDA meeting to discuss the clinical and nonclinical content for the planned NDA for rolapitant injection.

3 Studies Submitted

3.1 Studies Reviewed

The Applicant has submitted all study reports, which were also submitted under NDA 206500 for rolapitant oral tablet. Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

The following study reports are reviewed here.

STUDY TITLE	REPORT NO./Submission No.	PAGE
PHARMACOKINETICS		24
Protein Binding Study for SCH 720881	DM27583	24
TOXICOLOGY		24
Repeat-Dose		24
Rat		24
7-Day, Intravenous, Dose Range Finding (DRF)	14-3882	34
14-Day, Intravenous, DRF	14-3875	34
6-Week, Intravenous	(b) (4)-276501/SDN 016	24
13-Week, Intravenous	15-3889	32
13-Week, Intravenous	15-3893	33
Monkey		45
28-Day, Intravenous	2013-012	45
13-Week, Intravenous	2013-015	54

3.2 Studies Not Reviewed

The following study reports were not reviewed.

(b) (4)

(b) (4)

3.3 Previous Reviews Referenced

- Pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD
- Pharmacology review of IND 117,307 dated August 14, 2013 by Tamal Chakraborti, PhD
- Pharmacology review of IND 72754 dated July 2, 2015 by Tracy L. Behrsing, PhD
- Pharmacology review of IND 72,754 dated May 9, 2012 by Tamal Chakraborti, PhD
- Pharmacology review of IND 72,754 dated December 5, 2012 by Tamal Chakraborti, PhD
- Pharmacology review of IND 72,754 dated November 24, 2010 by Tamal Chakraborti, PhD
- Pharmacology review of IND 72,754 dated March 10, 2006 by Ke Zhang, PhD
- Pharmacology review of IND 72,754 dated December 29, 2005 by Ke Zhang, PhD

4 Pharmacology

4.1 Primary Pharmacology

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

4.2 Secondary Pharmacology

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

4.3 Safety Pharmacology

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

5.2 Toxicokinetics

Protein Binding Study for SCH 720881 (DM27583)

Methods: In this study, the stability of ^{3}H-SCH 720881 (metabolite of rolapitant) in the plasma and ultrafiltrate (UF) from the mouse, rat, rabbit, dog, monkey, and human was evaluated using High Pressure Liquid Chromatography (HPLC). Specific binding of ^{3}H-SCH 720881 to human plasma proteins was measured as a function of time. ^{3}H-SCH 720881 was incubated at a concentration of 0.2 µg/mL at 37^{0}C for up to 30 hours.

Results: Under the conditions of the study, ^{3}H-SCH 720881 was stable in the plasma and UF from all six species up to 30 hours at 37^{0}C. In the human plasma, protein binding ranged from 99.5-100%. Data for other species was not provided in the report.

6 General Toxicology

6.1 Single-Dose Toxicity

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

6.2 Repeat-Dose Toxicity

Study title: 6-Week Intravenous Infusion Toxicity and Toxicokinetic Study in Sprague Dawley Rats with a 6-Week Recovery Period

Study no.:	(b) (4) -276501
Study report location:	EDR SDN 016, Section 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 5, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Rolapitant, Lot no. 22903.003, 101%

Key Study Findings:

- There two deaths in males (vehicle control and 20 mg/kg) and two deaths in females (vehicle control and 20 mg/kg). These deaths were not considered treatment related.
- There were no significant treatment related clinical signs or effects on body weight.
- In males, higher Alkaline Phosphatase (ALP) and Alanine Aminotransferase (ALT) levels were observed at 20 mg/kg. Relation to the treatment was unknown

in the absence of dose response (as only one dose group was tested in this study), lack of histopathological correlates and values (ALP) were within the historical control range.

- There were no significant treatment related gross necropsy findings
- Histopathological changes were observed in the lung (subacute inflammation, edema, and hemorrhage), infusion site (intimal thickening, intravascular thrombosis, medial hypertrophy, subacute inflammation of the vessel walls, and perivascular hemorrhage), testes (hypospermatogenesis in one of the testes and unilateral hypospermia in the epididymis), and liver (mild periportal vacuolation of hepatocytes in one male at 20 mg/kg, another 20 mg/kg/dose group male had a locally extensive chronic infarct of a liver lobe characterized by hemorrhage and fibrosis with little remaining hepatic parenchyma). The relation to the treatment was unknown in the absence of dose response (only one dose was tested in this study) and these were also observed in control animals.
- The NOAEL could not be determined as only one dose was tested in this study.

Methods: In a 90-day intravenous (IV) study in rats (Study No. 15-3893), daily IV administration via femoral cannulas resulted in a vehicle related increase in infection. The current study was designed to test the hypothesis that a less frequent dosing regimen would reduce and/or eliminate infection.	
Doses:	0 (saline), 0 (vehicle), 20 mg/kg
Frequency of dosing:	Once biweekly (4 total doses; Days 0, 14, 28, and 42)
Route of administration:	IV infusion (30-minute)
Dose volume:	10 mL/kg
Formulation/Vehicle:	4.4% Solutol® HS15, 1.1% Medium-Chain Triglycerides (MCT), and 0.66% soybean oil in 20 mM Phosphate-Buffered Saline (PBS) pH 7.5.
Species/Strain:	Sprague Dawley (SD) rats
Number/Sex/Group:	10-25/sex/group
Age:	Males and females were 10-12 weeks old.
Weight:	All males and females weighed more than 220 g at the initiation of the treatment.
Satellite groups:	Toxicokinetic (TK)
Unique study design:	Shown in the table below
Deviation from study protocol:	Protocol deviations did not negatively impact the quality or integrity of the data or the outcome of the study results.

The study design is shown below (from page 32 of the report).

Toxicology Groups

Group Number	Treatment	Dose Level (mg/kg/dose)	Dose Volume (mL/kg)	Number of Animals [a]	
				Males	Females
1	Saline	0	10	20	20
2	Vehicle (Placebo)	0	10	25	25
3	Rolapitant	20	10	25	25

Toxicokinetic Groups

Group Number	Treatment	Dose Level (mg/kg/dose)	Dose Volume (mL/kg)	Number of Animals [b]	
				Males	Females
2A	Vehicle (Placebo)	0	10	3	3
3A	Rolapitant	20	10	6	6

[a] = 20 animals/sex/group were euthanized on the day following the last dose administration; the remaining 4-5 animals/sex in Groups 2 and 3 were assigned to the recovery period and surviving animals were euthanized following a 43-day nondosing (recovery) period.

[b] = All animals were euthanized and discarded following the final blood collection.

Basis of Dose Selection: The 20 mg/kg dose was considered as the highest tolerated dose in a 90-day IV study in rats (Study No. 15-3893). As stated above, in the above 90-day study, daily IV administration via femoral cannulas resulted in a vehicle-related increase in infection. This study was designed to test the hypothesis that a less frequent dosing regimen would reduce and/or elimination infection.

Observations and Results:

Mortality: All animals were observed twice daily for mortality and moribundity.

There were no deaths attributed to administration of the test article or vehicle (placebo). There were 2 early deaths in males (one animal in the vehicle control group and one animal at 20 mg/kg). Animal number 8287 (20 mg/kg, male) was euthanized due to an exposed catheter on Day 8. Microscopic findings for this animal included unorganized intravascular thrombus in the right ventricle and mild hemorrhage in the lung. The reason for euthanasia was unrelated to test article administration. Animal no. 8206 (vehicle control, male) was found dead on Day 14. The cause of death was undetermined. The animal had a small intravascular unorganized thrombus in the right ventricle and medial hypertrophy of vessel walls in the lungs. The changes in the lungs in both males were considered related to, and consequences of, IV infusion.

There were 2 early deaths in females. Animal no. 8365 (vehicle control, female) was found dead on Day 15 with an undetermined cause of death. There was mild subacute

inflammation of the lung, but this finding was not of a severity to be the cause of death. Animal no. 8348 (20 mg/kg, female) was assigned as a recovery animal, and was euthanized due to an exposed port on Day 78. The animal had minimal subacute inflammation of the lung, a well-delineated focus of necrotizing inflammation at the infusion site, and decreased numbers of corpora lutea in the ovary (consistent with senescence). The reason for euthanasia was unrelated to test article administration.

Clinical Signs: Clinical signs were observed prior to infusion and at approximately 45 minutes following the end of infusion. There were no significant treatment related clinical signs.

Body Weights: Body weights were recorded on a weekly basis.

The mean initial (Week 0) and final (Week 6) body weights of saline control males were 321 and 490 g, respectively. The mean initial (Week 0) and final (Week 6) body weights of vehicle control males were 325 and 500 g, respectively. The mean initial (Week 0) and final (Week 6) body weights of saline control females were 265 and 490 g, respectively. The mean initial (Week 0) and final (Week 6) body weights of vehicle control females were 324 and 332 g, respectively. There were no significant treatment related effects on body weight.

Feed Consumption: Food consumptions were recorded on a weekly basis.

The mean initial (Week 0-1) and final (Week 5-6) food consumption of saline control males were 27 and 22 g/animal/day, respectively. The mean initial (Week 0-1) and final (Week 5-6) food consumption of vehicle control males were 20 and 20 g/animal/day, respectively. The mean initial (Week 0-1) and final (Week 5-6) food consumption of saline control females were 21 and 22 g/animal/day, respectively. The mean initial (Week 0-1) and final (Week 5-6) food consumption of vehicle control females were 21 and 22 g/animal/day, respectively. There were no significant treatment related effects on food consumption.

Ophthalmoscopy: Ophthalmoscopy was performed during acclimation (Week -1/-2) and Week 5. There were no significant treatment related ophthalmoscopic findings.

Electrocardiography (ECG): Not performed

Hematology: Hematology was conducted at Weeks 6 and 12. There were no significant treatment related hematology findings.

Clinical Chemistry: Clinical chemistry was conducted at Weeks 6 and 12.

In males, there were higher group mean values for serum ALP (20.5% higher than controls; mean 141 U/L vs. 117-118 U/L for controls) and serum ALT (36.4% higher than control; mean 60 U/L vs. 44-45 U/L for controls) values at 20 mg/kg compared to both controls. The higher ALT value was outside of the (b) (4) historical control

range for the study means, but the ALP value was within the (b) (4) historical control range for the study means. There were no significant treatment related histopathological correlates. One animal (male no. 8270, 20 mg/kg) with an incidental partially infarcted liver lobe had the highest individual ALP value (195 U/L), and this isolated finding partly contributed to a higher group mean ALP. Relation to the treatment was unknown in the absence of dose response (as only one dose group was tested in this study), lack of histopathological correlates and values (ALP) were within the historical control range.

Urinalysis: Urinalysis was conducted at Weeks 6 and 12. There were no significant treatment related urinary findings.

Gross Pathology: Gross pathology was conducted at necropsy. There were no significant treatment related gross pathology findings at primary or recovery necropsies.

Organ Weights: The following (from page 40 of the report) organs were weighed from all animals at the scheduled necropsies.

Adrenals	Pituitary
Brain	Prostate with seminal vesicles
Epididymides	Spleen
Heart	Testes
Kidneys	Thymus
Liver	Thyroid with parathyroids [a]
Ovaries with oviducts	Uterus

[a] = Weighed after fixation.

There were no significant treatment related effects on organ weights at primary or recovery necropsies.

Histopathology: Microscopic examination was performed on all tissues as listed in the table below (from page 39 of the report) from all animals at the primary necropsy.

Adrenals (2)
Aorta
Bone with marrow
  Femur
  Sternum
Bone marrow smear
  (from femur) [a]
Brain (7 levels) [b]
Cervix
Epididymides (2) [c]
Eyes with optic nerve (2) [d]
Gastrointestinal tract
  Esophagus
  Stomach
  Duodenum
  Jejunum
  Ileum
  Cecum
  Colon
  Rectum
Heart
Infusion site
Kidneys (2)
Larynx
Liver (sections of 2 lobes)
Lungs (including bronchi, fixed
  by inflation with fixative)
Lymph nodes
  Axillary (2)
  Mandibular (2)
  Mesenteric
Ovaries (2) with oviducts [e]
Pancreas
Peripheral nerve (sciatic)
Peyer's patches
Pharynx
Pituitary
Prostate
Salivary glands (mandibular [2])
Seminal vesicles (2)
Skeletal muscle (rectus femoris)
Skin with mammary gland [f]
Spinal cord (cervical, thoracic, lumbar)
Spleen
Testes (2) [c]
Thymus
Thyroid (with parathyroids [2]) [e]
Tongue
Trachea
Urinary bladder
Uterus
Vagina
Gross lesions (when possible)

[a] = Bone marrow smears were obtained at the scheduled necropsies and from the animals euthanized *in extremis*, but not placed in formalin; slides were not examined.
[b] = Histologic trimming of the brain was performed per WIL Research SOPs such that 7 cross (coronal) sections of the brain were taken.
[c] = Fixed in modified Davidson's solution
[d] = Fixed in Davidson's solution
[e] = Oviducts and parathyroids were examined if in plane of section and in all cases where a gross lesion of the organ was present.
[f] = For females; a corresponding section of skin was taken from the same anatomic area in males.

Adequate Battery: Yes

Peer Review: There were no significant treatment related microscopic findings at the primary necropsy, thus the pathology peer review was not performed per protocol amendment 3.

Histological Findings: There were no significant test article related microscopic findings at the primary or recovery necropsies. Incidental findings or those findings attributed to experimental manipulations are discussed below.

Lungs: In the lungs of all control and treated groups, there was subacute inflammation, edema, and hemorrhage, which were each considered to be a result of saline-based infusion. Saline or saline-based vehicle infusion has been associated with periarterial infiltrations of eosinophils and with medial hypertrophy of pulmonary vessels in the lungs of rats (Morton, D, et al., 1997, Histologic Lesions Associated with Intravenous Infusions of Large Volumes of Isotonic Saline Solution in Rats for 30 Days, Toxicol Pathol, 25(4): 390-394). There was no toxicologically relevant difference in severity or incidence of these findings between the saline control (Group 1), vehicle control (Group 2), or 20 mg/kg (Group 3) groups.

Infusion Site (femoral vein): There was vascular intimal thickening, intravascular thrombosis, medial hypertrophy, subacute inflammation of the vessel walls, and perivascular hemorrhage at the infusion site. The incidence and severity of these changes were similar between all groups, and were expected tissue reactions to placement of an infusion catheter. There was no significant test article related difference in the degree of such tissue reaction.

Infusion Site (Tail): In the animals with an infusion site in the tail, there was a low incidence and low severity of hemorrhage and subacute inflammation. These findings were within the expected range of tissue reaction to placement of a catheter.

Testes/Epididymides: In 4 male animals (nos. 8217 [saline control], 8290 [saline control], 8271 [vehicle control], and 8251 [20 mg/kg]), there was unilateral hypospermatogenesis in one of the testes and unilateral hypospermia in the epididymis. The seminiferous tubules were lined only by Sertoli cells, with nearly complete absence of spermatogenic epithelium. The epididymis was generally void of spermatozoa and occasionally contained cellular debris. In each of the affected animals, the contralateral testis and epididymis were normal. The cause for the unilateral cessation of spermatogenesis was unknown. However, this was also observed in the control animals. In the absence of a dose response and occurrences in control animals, these findings were not considered to be related to the test article.

Liver: One 20 mg/kg/dose group male (no. 8209) had mild periportal vacuolation of hepatocytes. This change was characterized by a mixture of micro and macrovesicles, and was not associated with alteration in the serum chemistry or the liver weight for that particular animal. The change was considered incidental and unrelated to test article. Another 20 mg/kg/dose group male (no. 8270) had a locally extensive chronic infarct of a liver lobe characterized by hemorrhage and fibrosis with little remaining hepatic parenchyma. The other liver parenchyma was normal. The infarct was considered a spurious finding likely secondary to torsion of the liver lobe. This was correlated in part to a high serum ALP level in this animal, which contributed to the high group mean serum ALP in the 20 mg/kg males. Torsion of a liver lobe was considered a sporadic finding in rats (Jones, T.C., 1967, Pathology of the Liver in Rats and Mice, In Pathology of Laboratory Rats and Mice, Cotchin, E.; Roe, F.J., Eds.; Oxford and Edinburgh, Blackwell Scientific Publications: Philadelphia, PA, p 16;

Thoolen, B, et al., 2010, Proliferative and Nonproliferative Lesions of the Rat and Mouse Hepatobiliary System, Toxicol Pathol, 38 (7 Supplement), 5S-81S).

Special Evaluation: None

Toxicokinetics: Blood samples for toxicokinetics were collected from 3 animals/sex/time point from Group 2A animals at 1 and 4 hours after the start of infusion and from Group 3A animals at 30 minutes and 1, 2, 4, 8, and 24 hours after the start of infusion on study days 0 and 42.

Exposure (AUC_{last}) in females was approximately 2-fold higher when compared to males on both days (Day 0 and 42). C_{max} in males and females was similar on both days. For SCH 720881 (metabolite of rolapitant), AUC_{last} in females was approximately 11 to 15-fold lower when compared to males on both days. C_{max} for the metabolite in females was approximately 9-fold lower when compared to males on both days. Exposure to rolapitant and SCH 720881 was similar on both days. Exposure to SCH 720881 was lower when compared to rolapitant. Metabolite to parent ratios ranged from 0.00593 (0.593%) to 0.0068 (0.680%) in females and 0.157 (15.7%) to 0.183 (18.3%) in males. Exposure data and differences in metabolite to parent ratios indicated that male rats metabolized rolapitant to SCH 720881 at a higher level when compared to females. For rolapitant, terminal half-life ($t_{1/2}$) ranged from 7.14 to 8.01 hours in males and from 25.1 to 29.3 hours in females. For SCH 720881, $t_{1/2}$ ranged from 19.0 to 22.5 hours in males and the half-life was not calculable in females. The following (from page 51 of the report) table shows the TK parameters.

Text Table 1. Summary of Toxicokinetic Parameters

Dosage	AUC_{last} (ng•hr/mL)		C_{max} (ng/mL)		T_{max} (hr)	
	Day 0	Day 42	Day 0	Day 42	Day 0	Day 42
			Rolapitant			
Males						
20 mg/kg Rolapitant	34,400	37,900	9430	8180	0.5	0.5
Females						
20 mg/kg Rolapitant	72,700	76,500	12,200	9630	0.5	0.5
			SCH 720881			
Males						
20 mg/kg Rolapitant	6280	5960	350	387	2	1
Females						
20 mg/kg Rolapitant	431	521	39	43.8	24	24

Dosing Solution Analysis: Dosing solution analysis report was not included in the study report.

Study title: 13-Week Intravenous Infusion Toxicity Study in Rats with a 6-Week Recovery Period

Study no.:	15-3889
Study report location:	EDR SDN 001, Section 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Not provided
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Rolapitant HCl monohydrate. Lot # and purity data were not provided.

This study was originally designed to examine the toxicity and toxicokinetics of rolapitant when administered daily to rats, via a 30-minute intravenous (IV) infusion, for 13 weeks and to evaluate recovery during a 6-week treatment-free recovery period. The original study design is shown below (from page 8 of the report).

		Daily Doses[a]			Number of Animals									
					Total on Study		Toxicity Study						TK Study[b] Days 1, 30 and 90	
							Total		Terminal Necropsy		Recovery Necropsy			
Group	Compound	Dose (mg/kg/dose)	Volume (mL/kg)	Conc. (mg/mL)	M	F	M	F	M	F	M	F	M	F
1	Saline	0	10	0.0	13	13	10	10	10	10	0	0	3	3
2	Placebo	0	10	0.0	18	18	15	15	10	10	5	5	3	3
3	Rolapitant	10	5	2.0	16	16	10	10	10	10	0	0	6	6
4	Rolapitant	20	10	2.0	16	16	10	10	10	10	0	0	6	6
5	Rolapitant	40	10	4.0	21	21	15	15	10	10	5	5	6	6

[a]Doses represent rolapitant HCL monohydrate.
[b]Toxicokinetic samples were collected on Days 1, 30 and 90.

Due to numerous unscheduled deaths (from Day 14 through 27) throughout the saline control, placebo control and test article treated groups; this study was terminated early, with treatment duration of ~26 to 29 days. Many of the unscheduled decedents had large masses and/or thickened areas/swelling externally and internally at the location of the catheter vein, tip or insertion site. Necropsy findings included abnormal material and thickening of the skin, catheter tip, and catheter vein, causing inflammation and abscess. Additionally, in many animals, the catheter was not present in the anticipated location in the vena cava, or was outside of the vena cava. Preliminary results indicated that the observations may be associated with the misplacement of the catheters. The Applicant stated “In our professional experience and judgment, the study was not going to achieve the original goal of three-month dose duration with interpretable results. The study was therefore discontinued to investigate and address potential formulation and/or catheter-related issues.” The Sponsor did not provide the details of the methods and results of this study.

Study title: 13-Week Intravenous Infusion Toxicity Study in Rats

Study no.:	15-3893
Study report location:	EDR SDN 001, Section 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 22, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Rolapitant HCl monohydrate, Lot No. 22901.001, 100.3%

Key Study Findings:

- There were mortalities in all groups including the saline and vehicle (placebo) treated animals (number of unscheduled sacrifices or deaths/total number in group = 3/26, 13/36, 12/32, 9/32, and 15/42 for saline, placebo, and 10, 20, and 40 mg/kg/day, respectively).
- Treatment related clinical signs included convulsions at 40 mg/kg/day.
- Infusion site reactions included abscess formation, bacteremia and/or inflammation, which were observed across all groups including the saline and placebo control. However, the incidence and severity was higher in the placebo control and rolapitant groups when compared to the saline control group.
- Test article related clinical pathology changes included minimal to marked increases in AST and ALT at $\geq$20 mg/kg/day in unscheduled decedents. AST and ALT increases were considered to be test article related due to the greater magnitude and increased incidences observed in Group 4 animals.
- Placebo-related clinical chemistry changes in unscheduled decedents included increased ALP, AST, ALT, bilirubin, urea nitrogen, and creatinine and increased ALP in animals surviving to termination.
- Placebo-related hematology changes included decreases in red cell mass with or without increases in reticulocytes and Red Cell Distribution Width (RDW), and increases in total White Blood Cell (WBC), neutrophils, monocytes, and/or lymphocytes.
- Increases in liver weights were observed in males at 20 mg/kg/day and in both sexes at 40 mg/kg/day.
- There were no significant test article related macroscopic or microscopic findings. Placebo related histopathological changes were observed in the liver (pigment deposition within macrophages and granulomatous inflammation).
- The NOAEL could not be determined as treatment related changes were observed at all doses.

Methods:	
Doses:	0 (saline), 0 (vehicle), 10, 20, and 40 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Intravenous (IV) infusion (30-minute)
Dose volume:	5 mL/kg
Formulation/Vehicle:	4.4% Solutol® HS15, 1.1% mid-chain triglycerides (MCT), and 0.66% soybean oil in 20 mM phosphate-buffered saline (PBS) pH 7.5.
Species/Strain:	Sprague Dawley (SD) rats
Number/Sex/Group:	10/sex/group
Age:	Animals were approximately 77 days old at the initiation of the treatment
Weight:	Males: 228 to 375 g; Females: 204 to 289 g
Satellite groups:	Toxicokinetic (TK)
Unique study design:	Shown in the table below
Deviation from study protocol:	Protocol deviations were not considered to have compromised the validity or integrity of the study.

The study design is shown below (from page 19 of the report).

Group	Treatment	Dose (mg/kg/day)[a]	Number of animals					
			Toxicity study					
			Main study		Recovery phase[b]		Satellite study[c]	
			Male	Female	Male	Female	Male	Female
1	Saline	0	10	10	0	0	3	3
2	Placebo	0	10	10	5	5	3	3
3	Rolapitant	10	10	10	0	0	6	6
4	Rolapitant	20	10	10	0	0	6	6
5	Rolapitant	40	10	10	5	5	6	6

[a]Doses represent rolapitant HCL monohydrate.
[b]Animals for the recovery phase were sacrificed at termination of dosing.
[c]Toxicokinetic samples were collected on Days 1, 30 and 93.
The first day of dosing was defined as Day 1 of the study.

Basis of Dose Selection: The dose selection was based on the results of a 14-day IV toxicity study (SN 07395, pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD) and 14-day IV Dose Range-Finding (DRF) study (Study No. 14-3875) in rats. In addition, a 7-day IV DRF study (Study No. 14-3882, non-GLP) at 30, 40, 50, and 60 mg/kg/day was also conducted to help the dose selection for the current study.

In the 7-day IV (30-minute infusion) DRF study in rats, animals (n = 6/sex/dose) were treated with rolapitant HCl monohydrate at 0 [4.4% polyoxyl 15 hydroxystearate (Solutol HS 15, 1.1% MCT and 0.66% soybean oil in PBS buffer, pH 7.5), 30, 40, 50, and 60

mg/kg/day. Clinical signs observed at Day 1 at 60 mg/kg/day in both sexes included convulsions, splayed limbs, tremors and prostration. On Day 2, the 60 mg/kg/day dose group was terminated and the animals were euthanized for humane reasons. In addition, there were adverse clinical signs observed at 50 mg/kg/day in both sexes on Day 1, which persisted through the end of treatment. These clinical signs at 50 mg/kg/day included splayed limbs, decreased activity, increased sensitivity, abnormally cold to touch, tremors, pale, piloerection, hunched, and irregular/rapid/slow breathing. No significant clinical signs were observed at 30 or 40 mg/kg/day. Treatment related clinical pathology findings in decedent rats included increases in WBC, including neutrophils and monocytes, and increases in AST and chloride, and decreases in glucose. Macroscopic evaluations in 1 of 6 males at 60 mg/kg/day included red, firm mass on the accessory lobe of the liver and pale, green areas on the left lobe of the liver in 1 of 6 females at 60 mg/kg/day.

In the 14-day IV (30-minute infusion) study (Study No. 14-3875) in rats, the intended doses were 0 (saline), 0 [vehicle: 4.4% polyoxyl 15 hydroxystearate (Solutol HS 15), 1.1% MCT and 0.66% refined soybean oil in PBS, pH 7.5), 10, 20, and 40 mg/kg/day. However, during the initial week of treatment, it was noted that only half of the intended dose level was being administered (5, 10, and 20 mg/kg/day). As the initial dose levels and volumes were incorrect (half the intended dose), the study was discontinued after either 6 days (TK), 7 days (tox: females), or 8 days (tox: males) of treatment, and a drug wash-out period of 7-9 days was performed, in order to restart the study with the correct dose levels and dose volumes for all groups. The study was restarted at 10, 20 and 40 mg/kg/day. The following table (from page 8 of the report shows the study design).

					Number of Animals									
					Total on Study		Toxicity Study Total		Toxicity Study Terminal Necropsy		Toxicity Study Recovery Necropsy		TK Study[b] Days 1, 30 and 90	
Group	Compound	Dose (mg/kg/dose)	Daily Doses[a] Volume (mL/kg/~~hour~~)	Conc. (mg/mL)	M	F	M	F	M	F	M	F	M	F
1	Saline	0	10	0.0	13	13	10	10	10	10	0	0	3	3
2	Placebo	0	10	0.0	18	18	15	15	10	10	5	5	3	3
~~3~~[c]	~~Rolapitant~~	~~10~~	~~5~~	~~2.0~~	~~16~~	~~16~~	~~10~~	~~10~~	~~10~~	~~10~~	~~0~~	~~0~~	~~6~~	~~6~~
4	Rolapitant	~~20~~ **10**	~~10~~ **5**	2.0	16	16	10	10	10	10	0	0	6	6
5	Rolapitant	~~40~~ **20**	10	~~4.0~~ **2.0**	~~21~~ **16**	~~21~~ **16**	~~15~~ **10**	~~15~~ **10**	10	10	~~5~~	~~5~~	6	6
7[c]	**Rolapitant**	~~5~~ **40**	~~5~~ **10**	~~2.0~~ **4.0**	~~16~~ **21**	~~16~~ **21**	~~10~~ **15**	~~10~~ **15**	10	10	~~0~~ **5**	~~0~~ **5**	6	6

[a] Doses represent rolapitant HCL monohydrate.
[b] Toxicokinetic samples were collected on Day 1 of Treatment Phase 1 and Day 1 and 14 of Treatment Phase 2.
[c] Group 3 animals originally received only 5 mg/kg/day and when the study was restarted, they became the high dose. They were re-labelled as "Group 7" so as not to cause any confusion with ascending dose level by group. In addition, spare study animals (naïve) were added to this group as recovery animals, as were present in Group 5, to determine reversibility of test article-related effects in the high dose.
Note: Group 6 in the electronic data system was spare animals; therefore it could not be used as a treated dose level.

It is to be noted here that this study was originally designed for 13 weeks of treatment with a 6-week recovery period. However, subsequent to the restart of the study, the decision was made to terminate treatment after 14 days at the new dose levels rather than continue with 13 weeks followed by a recovery, providing more information for

dose selection/refinement for the 3-month pivotal rat toxicity study. The Applicant decided that the study would be difficult to interpret due to the acclimation to the test article at a lower dose level, and the overall integrity of the study could be questioned. The sponsor did not provide details of the methods and results of this study. Treatment related clinical signs during Week 1 in both sexes at 40 mg/kg/day included convulsion, decreased activity, partially-closed and/or prominent eyes, flattened posture, irregular breathing, and excessive chewing. These findings generally resolved at Week 2, with decreased activity, the most consistent finding at Week 2. Additionally at 40 mg/kg/day, in Week 1, there was decreased body weight gain in both sexes. Treatment related decreases in body weight gain were observed in females at 5 and 40 mg/kg/day (-10% of mean saline control on Day 14). There were decreases in food consumption in both sexes in the second treatment phase at 5 and 40 mg/kg/day (-27 and -29%, respectively of mean saline control values in Week 1), however, food consumption increased in these animals to -10 and -20% of mean saline control values by the end of 14 days of treatment. Macroscopic evaluations were performed on the two unscheduled decedents at 5 and 40 mg/kg/day [Animal Nos. 7035 (toxicity male) and No. 7562 (TK female)] and macroscopic findings in these animals included masses at the catheter insertion site and scrotum, and edema and thickening in the catheter vein and insertion site, respectively. There was no scheduled histopathology.

Based on the results of the above studies, the high dose for the current study was selected as 40 mg/kg/day. Mid dose (20 mg/kg/day) was half of the high dose, and low dose (10 mg/kg/day) was half of the mid-dose.

Observations and Results:

Mortality: All animals were observed twice daily for mortality.

There were a total of 52 unscheduled decedents. Primary cause of morbidity or mortality was bacterial infection, marked to severe abscesses and/or inflammation of the catheterized vein with or without systemic spread to other organs such as liver and/or kidneys. In addition, five animals were euthanized due to convulsions. Three of those 5 animals were in the 40 mg/kg/day dose group, and 2 of 3 animals were sacrificed for humane reasons on Day 2 and 4. One animal at 10 mg/kg/day also had convulsions on Day 61 and was found to have an abscess at necropsy. On Day 40, one placebo animal also had convulsion. At necropsy, adrenal glands, mediastinal lymph node, and spleen were found to be enlarged in this placebo treated animal. The following table (from page 53 of the report) shows the mortalities.

Text Table 3.3-1 Major factor(s) contributing to deaths in unscheduled decedents in rats given saline, placebo or rolapitant via intravenous infusion for up to 13 weeks

Group/Sex		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Rolapitant mg/kg/day		0	0	10	20	40	0	0	10	20	40
No. of animals	Main	0	7	4	2	4	3	4	4	3	6
	TK	0	0	2[a]	2	4[a]	0	2[a]	2[a]	2	1
Total UDs		0	7	6	4	8	3	6	6	5	7
Bacterial infection		-	6	5	4	6	-	4	3	5	4
Vascular lesions		-	-	-	-	-	2	-	1	-	2
Kidney lesions		-	1	-	-	-	-	-	-	-	-
Liver lesions		-	-	-	-	1	-	-	-	-	-
Lymphoma		-	-	-	-	-	-	-	1	-	-
Catheter-related (loss of patency)		-	-	-	-	-	1	1	-	-	-
Undetermined		-	-	-	-	-	-	-	-	-	1

[a] 1 rat/group(Animal Nos. 3044, 5069, 2548, 3551) had gross findings only, no tissues were saved

Clinical Signs: Clinical signs were observed twice daily.

Convulsions were observed at 0 (placebo/vehicle), 10, and 40 mg/kg/day in animal nos. 5561, 5563, 2548, 5059, and 3040 (Days of deaths/sacrifice: 2, 4, 40, 52, and 61, respectively). Other clinical observations in the early decedents in placebo (vehicle) and rolapitant treated males and females generally included distended abdomen/swollen areas, impaired locomotion/irregular gait, dark abdominal/inguinal areas, masses/firm areas, vocalization upon touch, decreased activity, thinness, hunched or flattened posture, ulcerated skin, and/or labored/irregular/rapid breathing, indicative of poor clinical condition.

Body Weights: Body weights were recorded on a weekly basis.

Mean initial (Week 1) and final (Week 13) body weights of saline control (Group 1) males were 351 and 537 g, respectively. The mean initial (Week 1) and final (Week 13) body weights of placebo vehicle control (Group 2) males were 354 and 548 g, respectively. The mean initial (Week 1) and final (Week 13) body weights of saline control (Group 1) females were 239 and 296 g, respectively. The mean initial (Week 1) and final (Week 13) body weights of vehicle control females (Group 2) were 249 and 299 g, respectively. There were no significant treatment related effects on body weights.

Feed Consumption: Food consumptions were recorded on a weekly basis.

Mean initial (Week 1) and final (Week 13) food consumptions of saline control (Group 1) males were 25 and 27 g/animal/day, respectively. Mean initial (Week 1) and final (Week 13) food consumptions of placebo vehicle control (Group 2) males were 24 and 27 g/animal/day, respectively. Mean initial (Week 1) and final (Week 13) food consumptions of saline control (Group 1) females were 18 and 20 g/animal/day, respectively. Mean initial (Week 1) and final (Week 13) food consumptions of vehicle

control (Group 2) females were 19 and 19 g/animal/day, respectively. There were no significant treatment related effects on food consumption.

Ophthalmoscopy: Ophthalmoscopy was performed at the pretest and at the end of the dosing. There were no significant treatment related ophthalmoscopy findings.

Electrocardiography (ECG): Not performed

Hematology: Hematology was conducted at end of dosing.

Unscheduled Decedents: Treatment related hematology changes in unscheduled decedents included decreases in RBC mass (hemoglobin, hematocrit and RBC) with or without increases in reticulocytes and Red cell Distribution Width (RDW), and increases in total WBC, neutrophils, monocytes, and/or lymphocytes. Changes were observed in Groups 2-5 with no consistent dose related trends, and were considered to be related to placebo. The following table (from page 56 of the report) shows the hematology changes.

Text Table 3.8.1-1. Hematology changes (versus Group 1) in unscheduled decedent rats

Sex	Males[b]				Females[a]			
Group	2	3	4	5	2	3	4	5
Dose (mg/kg/day)	0Pl	10	20	40	0Pl	10	20	40
HGB	-	dec	dec	dec	-22%	-8.8%	-35%	-25%
HCT	-	dec	dec	dec	-20%	-6.5%	-31%	-22%
RBC	-	dec	dec	dec	-21%	-12%	-30%	-23%
Reticulocytes	inc	-	Inc	-	-	98%	-	-
RDW	inc	inc	inc	inc	-	22%	26%	-
WBC	inc	inc	-	-	-	45%	2.0X	66%
Neutrophils	inc	inc	-	-	58%	26%	2.4X	85%
Lymphocytes	inc	inc	-	-	-	-	-	-
Monocytes	inc	inc	inc	inc	-	2.3X	2.1X	78%

HGB: Hemoglobin; HCT: Hematocrit; RBC: red blood cells; RDW: red cell distribution width; WBC: total white blood cells; inc: generally increased as compared with normal values; dec: generally decreased as compared with normal values; Pl: Placebo.
[a]: Decreases and increases <2X expressed as percent change versus saline control. Increases ≥2X expressed as fold change versus saline control.
[b] :There were no Group 1 Unscheduled Decedent males for comparison.
- : no change

Scheduled Sacrifice: There were no significant treatment related hematology changes in animals surviving to their scheduled termination.

Clinical Chemistry: Clinical chemistry was conducted at the end of dosing.

Unscheduled Decedents: Most notable change included a slight to moderate increase in ALP in both sexes administered placebo (Group 2) and at ≥10 mg/kg (Groups 3 to 5). In addition, there were minimal to marked increases in AST and ALT in Group 2 and 5 males and Group 4 and 5 females, minimal increases in bilirubin (Group 2 males and Group 4 females), urea nitrogen (Group 2 and 4 females) and creatinine

(Group 2 females). Most changes were considered vehicle related, with the exception of increases in AST and ALT, which were considered to be related to the test article. The following table (from page 57 of the report) shows the clinical chemistry changes in decedent animals.

Text Table 3.8.3-1. Placebo- or test article-related clinical chemistry changes (vs. Group 1) in unscheduled decedent rats

Sex	Males[b]				Females[a]			
Group	2	3	4	5	2	3	4	5
Dose (mg/kg/day)	0Pl	10	20	40	0Pl	10	20	40
AST	inc	-	-	inc	-	-	17X	4.8X
ALT	inc	-	-	inc	-	-	7.8X	2.2X
ALKP	inc	inc	inc	inc	3.6X	+90%	4.1X	3.0X
BUN	-	-	-	-	2.7X	-	2.1X	-

Sex	Males[b]				Females[a]			
Group	2	3	4	5	2	3	4	5
Dose (mg/kg/day)	0Pl	10	20	40	0Pl	10	20	40
Creatinine	-	-	-	-	3.0X	-	-	-
Total Bilirubin	inc	-	-	-	-	-	inc	-

Pl: placebo; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALKP: alkaline phosphatase; BUN: blood urea nitrogen; inc: generally increased as compared with normal values.
[a] : Decreases and increases <2X expressed as percent change versus saline control. Increases ≥2X expressed as fold change versus saline control.
[b] : There were no Group 1 Unscheduled Decedent males for comparison.
- : no change

Scheduled Sacrifice: Clinical chemistry changes were limited to increases in ALP in males and females in Groups 2, 3, 4 and 5. These ALP increases were considered to be vehicle related.

Urinalysis: Urine was collected overnight (approximately 16 hours) from animals housed in metabolism cages. Time of collection was not mentioned. There were no significant treatment related urinary changes.

Gross Pathology: Gross pathology was conducted at necropsy. There were no significant treatment related gross pathology findings.

Organ Weights: The following (from page 32-34 of the report) organs were weighed from all animals at the scheduled necropsies.

Text Table 2.6.5-1: Tissues weighed, preserved and examined microscopically

ORGAN NAME	WEIGHED	PRESERVED	EXAMINED MICROSCOPICALLY (GROUP 1, 2 and 5)[a]
adrenal glands	X	X	X
aorta (thoracic)		X	X
bone marrow smear (femur)		X	
bone (sternum, femur with joint)		X	X
bone marrow (sternum, femur)		X	X[b]
brain (medulla, pons, cerebrum and cerebellum)	X	X	X
epididymides	X	X	X
esophagus		X	X
eyes		X	X
Harderian gland		X	X
heart	X	X	X

ORGAN NAME	WEIGHED	PRESERVED	EXAMINED MICROSCOPICALLY (GROUP 1, 2 and 5)[a]
infusion site[c]		X	X
kidneys	X	X	X
lacrimal glands		X	X
large intestine (cecum, colon, rectum)		X	X
liver	X	X	X
lungs (with mainstem bronchi)		X	X
lymph nodes (axillary, mesenteric)		X	X
mammary gland (inguinal)		X	X[d]
nerve (sciatic)		X	X
optic nerve		X	
ovaries	X	X	X
pancreas		X	X
pituitary gland	X[e]	X	X
prostate gland	X[f]	X	X
salivary glands (mandibular)		X	X
seminal vesicles	X[f]	X	X
skeletal muscle (*rectus femoris*)		X	X
skin and subcutis (dorsal – base of tail)		X	X
small intestine (duodenum, ileum, jejunum, Peyer's patches\GALT)		X	X[d]
spinal cord (cervical, thoracic, lumbar)		X	X
spleen	X	X	X
stomach		X	X
testes	X	X	X
thymus	X	X	X
thyroid/parathyroid glands	X[e]	X	X[e]
tongue		X	
trachea		X	X
urinary bladder		X	X
uterus (body/horns) with cervix	X	X	X
vagina		X	X

ORGAN NAME	WEIGHED	PRESERVED	EXAMINED MICROSCOPICALLY (GROUP 1, 2 and 5)a
Zymbal's gland		X	
tissues with macroscopic findings including tissue masses		X	X

[a]These tissues were also examined for animals in Groups 3-4 which died prior to study termination
[b]Qualitative examination (no differential count).
[c]Infusion site includes insertion site, catheter with vein, vein 1 cm from catheter tip (TS), and vein at catheter tip (LS).
[d]Mammary gland for males and GALT were evaluated only if present in routine sections.
[e]Weight taken post-fixation.
[f]Prostate and seminal vesicles were weighed together.
[g]Evaluation of one was sufficient if one of pair is missing.

Dose-related increase in liver weights in males at 20 mg/kg/day and in males and females at 40 mg/kg/day were observed, however, there were no histopathological correlates. The following table (from page 59 of the report) shows the liver weight changes.

Text Table 3.9-1. Rolapitant-related organ weight changes (% difference relative to controls) in rats treated for up to 13 weeks

Group/sex Rolapitant (mg/kg/day)	2M placebo	3M 10	4M 20	5M 40	2F placebo	3F 10	4F 20	5F 40
Liver								
Absolute weight (%)	2.23	9.04	26.83[a]	20.02[a]	8.44	0.81	8.17	22.73[a]

[a]Statistically significant difference between mean values for test article-treated and saline control groups.

Kidney, prostate/seminal vesicle and adrenal gland weights were increased when compared to the saline control group (Group 1). These differences were considered secondary to abscesses and inflammation at the infusion sites. Higher mean kidney weights were associated with abscess/inflammation in 1 of 8 males at 20 mg/kg/day, and 3 of 11 males and 1 of 9 females at 40 mg/kg/day. Lower mean weights for prostate/seminal vesicles in 40 mg/kg/day group males and increased mean weights for adrenal glands in 40 mg/kg/day group females were also associated with abscesses and inflammation. Decreased pituitary gland weight in rolapitant treated females lacked a histologic correlate and was not considered rolapitant related.

Histopathology: Microscopic examination was performed on all tissues as listed in the above table from all animals at the primary necropsy.

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Histopathological changes were observed in the liver (pigment in macrophages, granulomatous inflammation) when compared to saline

control. Granulomatous inflammation consisted of generalized Kupffer cell hypertrophy and hyperplasia and randomly scattered granulomas composed of macrophages, with lesser numbers of lymphocytes, plasma cells, and/or occasional necrotic hepatocytes. These finds were considered vehicle (placebo) related findings as these were also observed in placebo treated rats except for granulomatous inflammation in males. The following table (from page 60 of the report) shows the liver findings.

Text Table 3.10.2-1 Incidence of Placebo-related lesions in the liver of rats examined microscopically at the end of up to 13 weeks of dosing

Group/Sex	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Rolapitant mg/kg/day	0	placebo	10	20	40	0	placebo	10	20	40
Total # of animals	13	11	10	12	13	10	12	10	11	14
Pigment, macrophages	0	9	3	11	9	0	10	1	8	9
Inflammation, granulomatous	0	0	2	4	1	0	2	1	1	1

In addition, procedure and placebo related histopathological changes were observed at the infusion sites (abscess formation with or without bacterial infection and inflammation). The incidence and severity of the changes were greater in the placebo-treated groups with no consistent relationship to rolapitant. The following table (from page 61 of the report) shows the infusion site changes.

Text Table 3.10.2-2 Incidence of procedure and/or placebo-related lesions in rats examined microscopically at the end of up to 13 weeks of dosing

Group/Sex		1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
	Total	13	11	10	12	13	10	12	10	11	14
Rolapitant mg/kg/day		0	0	10	20	40	0	0	10	20	40
Abscess at Infusion Vein at Catheter tip		3	4	2	2	3	5	5	4	1	2
Kidney Pyelonephritis		0	1	2	1	1	0	3	3	1	0
Liver Abscesses		0	1	0	1	0	0	0	1	0	1

Secondary Findings: Findings considered secondary to infusion site abscess formation and/or inflammation were observed in the lungs, kidneys, spleen, adrenal glands, thymus, and bone marrow in saline control, placebo vehicle, and rolapitant treated groups. Lung findings included pulmonary arterial thromboembolism, perivascular and interstitial inflammation, bronchial/bronchiolar mucus cell hyperplasia, aggregates of alveolar macrophages, alveolar hemorrhage, and the presence of perivascular foreign body granulomas. Similar findings have been reported in infusion studies in rats (Morton, D. et al., 1997, Histologic Lesions Associated with Intravenous Infusions of Large Volumes of Isotonic Saline Solution in Rats for 30 Days, Journal of Toxicol Pathol, 25: 390-394). Kidney findings included pyelonephritis, an infectious inflammatory condition that was present in both sexes in all groups except saline controls.

Special Evaluation: None

Toxicokinetics: On Days 1 and 30, blood samples were obtained for TK analyses from 3 animals/sex/time point from Groups 1 and 2 at 1 and 4 hours postdose and from Groups 3-5 at 30 minutes, 1, 2, 4, 8 and 24 hours postdose.

Rolapitant: On Day 1, C_{max} values of rolapitant increased more than dose proportionately over the dose range 10 to 40 mg/kg/day. However, on Day 30, C_{max} values increased less than the dose proportionately. Systemic exposure (AUC_{0-24h}) to rolapitant increased approximately proportionately with increasing dose over the dose range 10 to 40 mg/kg/day on Day 1, but slightly less than the proportionately on Day 30. C_{max} values of rolapitant in female rats were similar to those in males on Day 1; however, AUC_{0-24}h values were 1.1 to 1.6-fold higher than those in males. On Day 30, both C_{max} and AUC_{0-24h} values in females were similar to those in males. After repeated doses (Day 30), C_{max} and AUC_{0-24h} values for rolapitant were generally similar to those values after a single dose (Day 1) at 10 and 20 mg/kg/day; however, at 40 mg/kg/day, these values were lower. The accumulation ratios, based on AUC_{0-24h} values, were generally close to 1 at 10 and 20 mg/kg/day. In general, the results indicated little or no accumulation of rolapitant following repeated dosing. Toxicokinetic parameters for rolapitant are shown in the following (from page 51 of the report) table.

Rolapitant

Dose level (mg/kg/day)	C_{max} (ng/mL)				AUC_{0-24} (ng.h/mL)			
	Day 1		Day 30		Day 1		Day 30	
	Males	Females	Males	Females	Males	Females	Males	Females
10	2780	2490	3390	3630	22800	35800	37400	35600
20	8060	7910	6790	7970	47300	71300	59800	75600
40	21300	17700	10700	11100	116000	131000	89900	74200

Dose level (mg/kg/day)	Dose level ratio	C_{max} ratio				AUC_{0-24} ratio			
		Day 1		Day 30		Day 1		Day 30	
		Males	Females	Males	Females	Males	Females	Males	Females
10	1	1	1	1	1	1	1	1	1
20	2.0	2.9	3.2	2.0	2.2	2.1	2.0	1.6	2.1
40	4.0	7.7	7.1	3.2	3.1	5.1	3.7	2.4	2.1

SCH720881 (Metabolite): On Day 1, C_{max} values for SCH720881 increased approximately proportionately with increasing dose over the dose range 10 to 40 mg/kg/day; however, on Day 30, C_{max} values increased by less than the proportionately. AUC_{0-24h} values for SCH720881 increased approximately dose proportionately over the dose range 10 to 40 mg/kg/day on Day 1, however, on Day 30, the AUC_{0-24h} values increased less than the dose proportionately. C_{max} and AUC_{0-24h} values for SCH720881 were about 88% lower on Day 1 and about 69% lower on Day 30 than those in males. After repeated doses (Day 30), C_{max} and AUC_{0-24h} values for SCH720881 were generally similar to those values after a single dose (Day 1) in males, however, they were higher than the values after a single dose in females. In males, the accumulation

ratios, based on AUC_{0-24h} values, were lower than 1 indicating little or no accumulation of SCH720881 after repeated dosing of rolapitant. In females, however, the accumulation ratios were greater than 1 indicating accumulation of SCH720881 following repeated dosing. The following table (from page 52 of the report) shows the TK parameters for SCH 720881.

SCH720881

Dose level (mg/kg/day)	C_{max} (ng/mL)				AUC_{0-24} (ng.h/mL)			
	Day 1		Day 30		Day 1		Day 30	
	Males	Females	Males	Females	Males	Females	Males	Females
10	187	19.6	240	78.7	3370	222	4470	1240
20	328	51.8	564	161	6860	509	8430	2110
40	557	104	460	151	11500	1150	6010	2320

Dose level (mg/kg/day)	Dose level ratio	C_{max} ratio				AUC_{0-24} ratio			
		Day 1		Day 30		Day 1		Day 30	
		Males	Females	Males	Females	Males	Females	Males	Females
10	1	1	1	1	1	1	1	1	1
20	2.0	1.8	2.6	2.4	2.0	2.0	2.3	1.9	1.7
40	4.0	3.0	5.3	1.9	1.9	3.4	5.2	1.3	1.9

Dosing Solution Analysis: Dosing solution analysis report was not included in the study report.

Study title: 28-Day Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 28-Day Recovery Period

Study no.:	2013-012
Study report location:	EDR, Section 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	January 3, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Rolapitant solution, Lot no. 13(b) (4)0314-047 (101.3%), 13(b) (4)0314-078 (99.7%)

Key Study Findings:

- There were no mortalities or significant treatment related clinical signs.
- There were no significant treatment related effects on body weights, organ weight, and clinical pathology parameters.
- There was no significant treatment related gross or histopathology findings. Some of the histopathology findings (decreased diffuse vacuolation of the adrenal gland cortex and brown pigmentation) appeared to be related to the vehicle.

- The NOAEL was considered as 15 mg/kg/day.

Methods:	
Doses:	0 (saline), 0 (vehicle), 3, 10 and 15 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Intravenous (IV) infusion (30-minute)
Dose volume:	7.5 mL/kg
Formulation/Vehicle:	4.4% Solutol® HS15, 1.1% Medium-Chain Triglycerides (MCT), and 0.66% soybean oil in 20 mM Phosphate-Buffered Saline (PBS), pH 7.5
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	4-6/sex/group
Age:	2 year and 4 months to 3 years and 10 months
Weight:	Male: 2.55 to 3.32 kg; Female: 2.43 to 3.41 kg
Satellite groups:	Toxicokinetic (TK)
Unique study design:	Shown in the table below
Deviation from study protocol:	Protocol deviations did not affect the quality or integrity of the study.

The study design is shown below (from page 10 of the report).

Group Assignments

Group Number	Duration (minutes)	Dose Level (mg/kg)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Animals[c]	
					Male	Female
1[a]	30	0	7.5	0	4	4
2[b]	30	0	7.5	0	6	6
3	30	3	1.5	2	4	4
4	30	10	5	2	4	4
5	45	15	7.5	2	6	6

[a]Saline Control
[b]Vehicle Control
[c]Four animals/sex/group were necropsied on Day 29 and the remaining animals were maintained for a 28-day recovery period.

Basis of Dose Selection: The dose levels were selected based on the results of a 14-day IV infusion study in cynomolgus monkeys (Study Number 2013-009, please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing). In this study, rolapitant was administered once daily by IV infusion at 3 and 10 mg/kg/day for 30 minutes, and at 15 and 20 mg/kg/day for 45 minutes, respectively. There was no mortality. Dose was reduced from 20 mg/kg/day to 15 mg/kg/day due to adverse clinical signs (decreased activity, convulsions, lateral recumbency, partially and/or completely

closed eyelids, and shallow breathing, dilated pupils, salivation, and ataxia immediately after treatment). There were no significant treatment related histopathology findings. Based on this, the high dose of 15 mg/kg/day was selected for the current study, the low dose of 3 mg/kg/day was expected to have no adverse effects, and the mid dose of 10 mg/kg/day was selected to demonstrate dose-response.

Observations and Results:

Mortality: Animals were observed twice daily for mortality and moribundity. There were no mortalities.

Clinical Signs: Clinical signs were observed prior to infusion and at approximately 45 minutes and 4 hours postdose. There were no significant treatment related or vehicle related clinical signs.

Body Weights: Body weights were recorded on a weekly basis.

Mean initial (Week 0) and final (Day 26) body weights of saline control males were 2.9 and 3.0 kg, respectively. Mean initial (Week 0) and final (Day 26) body weights of vehicle control males were 2.8 and 2.9 kg, respectively. Mean initial (Week 0) and final (Day 26) body weights of saline control females were 2.8 and 2.7 kg, respectively. Mean initial (Week 0) and final (Day 26) body weights of vehicle control females were 2.9 and 2.9 kg, respectively. There were no significant treatment related effects on body weights.

Feed Consumption: Food consumptions were recorded qualitatively on a daily basis. Quantitative food consumption data were not provided.

Ophthalmoscopy: Ophthalmoscopy was performed at pretest and prior to scheduled necropsy. There were no significant treatment related ophthalmoscopic findings.

Electrocardiography (ECG): ECG was performed at pretest, predose and 30 minutes postdose on Days 1 and 28, and prior to the recovery necropsy. Sinus tachycardia (an average heart rate > 270 beats/min) was observed in 4 animals in the vehicle control group. All instances of sinus tachycardia occurred in the vehicle control group (1 instance) or at pretest (3 instances) or recovery (1 instance) intervals. There were no significant rolapitant related ECG findings.

Hematology: Hematology was conducted at pretest and prior to the terminal and recovery necropsy. At the terminal collection, mild reductions in red cell mass (erythrocytes, hemoglobin and hematocrit; up to -19%) and minimal to mild increases in absolute reticulocytes (up to +139%) were observed in all groups (including saline and vehicle controls), relative to pretest values in both sexes. These effects were considered secondary to procedure related blood loss (blood collections, etc.), and were considered unrelated to the test article or vehicle. Overall, there were no significant meaningful treatment related effects on hematology parameters.

Clinical Chemistry: Clinical chemistry was conducted at pretest and prior to the terminal and recovery necropsy.

Mild to moderate decreases in cholesterol was observed in both sexes in the vehicle control (up to -50%), and at 3 (up to -26%), 10 (up to -45%) and 15 mg/kg/day (up to -44%), relative to pretest values. Reductions in cholesterol were considered vehicle related, and were fully recovered by the end of the recovery period in both sexes receiving the vehicle alone and at 15 mg/kg/day. Based on their low magnitude and lack of dose response and full recovery, reductions in cholesterol were not considered adverse.

With the exception of females at 15 mg/kg/day, elevations in AST and ALT were approximately +3-fold and +2-fold, respectively, relative to pretest values. The magnitude of the increase in AST in females at 15 mg/kg/day (+6.1-fold vs pretest value) was largely attributed to one female (animal no. 5501), where AST was increased by 23.4-fold, relative to the individual pretest value, and approximately 8-fold, relative to the mean saline control. With the exception of animal number 5501, increases in AST and ALT were of generally similar magnitudes across all groups. The increase in AST in animal number 5501 was not considered test article related due to the sporadic nature of the change and lack of histopathological correlate. Overall, there were no significant meaningful test article related effects on clinical chemistry parameters.

Urinalysis: Urine samples were collected for at least 16 hours (time of collection was not mentioned). There were no significant treatment related urinary effects.

Gross Pathology: Gross pathology was conducted at necropsy. Brown adrenal glands were observed in two terminal males at 15 mg/kg/day, one terminal female vehicle control, and one terminal female at 10 mg/kg/day. Microscopic correlate was decreased diffuse cortical vacuolation. Brown adrenal glands were considered related to the vehicle and not test article related, as this was seen in the vehicle control group. There were no other significant test article related gross pathology findings at primary or recovery necropsies.

Organ Weights: The following (from page 865 of the report) organs were weighed from all animals at the scheduled necropsies.

- Adrenal (2)*
- Aorta
- Bone with marrow [femur]
- Bone with marrow [rib]
- Bone with marrow [sternum]
- Bone marrow smear [2 collected][a]
- Brain [cerebrum, midbrain, cerebellum, medulla/pons]*
- Epididymis (2)
- Eye including optic nerve (2)
- Gallbladder
- GALT [gut associated lymphoid tissue]
- Gastrointestinal tract:
  - esophagus
  - stomach [cardia, fundus, and pylorus]
  - duodenum
  - jejunum
  - ileum
  - cecum
  - colon
  - rectum
- Gonads:
  - ovary (2)* with oviduct (2)
  - testis (2)*
- Gross lesions
- Heart*
- Infusion site, last
- Joint tibiofemoral
- Kidney (2)*
- Larynx
- Liver [3 sections collected; 2 examined]*
- Lung with bronchi [collected whole; 2 sections examined]
- Lymph nodes: mandibular [2 collected; 1 examined] and mesenteric
- Mammary gland [process females only]
- Pancreas
- Pituitary*
- Prostate* and seminal vesicle (2)
- Salivary gland, mandibular [2 collected; 1 examined][b]*
- Salivary gland, parotid [2 collected; 1 examined]
- Salivary gland, sublingual [2 collected; 1 examined]
- Sciatic nerve
- Skeletal muscle, rectus femoris
- Skin
- Spinal cord [cervical, thoracic, and lumbar]
- Spleen*
- Thymus*
- Thyroid/parathyroid (2)*
- Tongue
- Trachea
- Ureter (2)
- Urinary bladder
- Uterus/Cervix
- Vagina

[a]Bone marrow smears were collected at the scheduled necropsies and held.
[b]Only the right mandibular salivary gland was weighed.

(2) Paired organ
*Weighed organ

There were no significant treatment related effects on organ weights at primary or recovery necropsies.

Histopathology: Microscopic examination was performed on all tissues as listed in the above table from all animals at the primary and recovery necropsy.

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Decreased diffuse vacuolation of the adrenal cortex was observed in the vehicle control, 3 (male only), 10, and 15 mg/kg/day terminal male and female monkeys. The cytoplasm of cortical cells in the zona fasicularis stained more eosinophilic and lacked the normal microvesicular appearance. This change correlated

with the gross finding of brown adrenal glands. Adrenal glands with normal appearing microvesicular cortices were seen in recovery vehicle control and 15 mg/kg males and females and indicated reversibility of the decreased vacuolation change. This was considered most likely vehicle related, as this was observed in the vehicle control group and lack of dose response. Besides the findings of the cytoplasm in the zona fasicularis, no other histopathology changes were observed in the adrenal glands. The following tables (from page 912-913 of the report) show the incidences of adrenal gland findings in males.

(b) (4) Research Study Number 2013-012
Rolapitant: A 28-Day Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 28-Day Recovery Period

Summary of Microscopic Observations - MALE
Terminal

Tissue / Observation	Severity	Saline Control (30 minute)	Vehicle Control (30 minute)	3 mg/kg (30 minute)	10 mg/kg (30 minute)
Number of Animals Examined		4	4	4	4
adrenal glands		(4)	(4)	(4)	(4)
mineralization	- minimal	0	0	1	0
vacuolation, decreased, diffuse cortical		0	4	1	4
	- mild	0	1	0	0
	- moderate	0	0	1	0
	- severe	0	3	0	4
within normal limits		4	0	2	0
aorta		(4)	(4)	(4)	(4)
within normal limits		4	4	4	4
bone marrow, femur		(4)	(4)	(4)	(4)
within normal limits		4	4	4	4
bone marrow, rib		(4)	(4)	(4)	(4)
within normal limits		4	4	4	4
bone marrow, sternum		(4)	(4)	(4)	(4)
within normal limits		4	4	4	4

( ) - Number observed

(b) (4) Research Study Number 2013-012
Rolapitant: A 28-Day Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 28-Day Recovery Period

Summary of Microscopic Observations - MALE
Terminal

Tissue Observation	Severity	15 mg/kg (45 minute)
Number of Animals Examined		4
adrenal glands		(4)
mineralization	- minimal	0
vacuolation, decreased, diffuse cortical		4
	- mild	0
	- moderate	0
	- severe	4
within normal limits		0
aorta		(4)
within normal limits		4
bone marrow, femur		(4)
within normal limits		4
bone marrow, rib		(4)
within normal limits		4
bone marrow, sternum		(4)
within normal limits		4

( ) - Number observed

The following tables (from page 930-931 of the report) show the incidences of adrenal gland findings in females.

(b) (4) Research Study Number 2013-012
Rolapitant: A 28-Day Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 28-Day Recovery Period

Summary of Microscopic Observations - FEMALE
Terminal

Tissue Observation	Severity	Saline Control (30 minute)	Vehicle Control (30 minute)	3 mg/kg (30 minute)	10 mg/kg (30 minute)
Number of Animals Examined		4	4	4	4
adrenal glands		(4)	(4)	(4)	(4)
mineralization	- minimal	0	1	0	0
vacuolation, decreased, diffuse cortical		0	4	0	4
	- mild	0	0	0	1
	- moderate	0	1	0	3
	- severe	0	3	0	0
within normal limits		4	0	4	0
aorta		(4)	(4)	(4)	(4)
within normal limits		4	4	4	4
bone marrow, femur		(4)	(4)	(4)	(4)
within normal limits		4	4	4	4
bone marrow, rib		(4)	(4)	(4)	(4)
within normal limits		4	4	4	4
bone marrow, sternum		(4)	(4)	(4)	(4)
within normal limits		4	4	4	4

( ) - Number observed

(b) (4) Research Study Number 2013-012
Rolapitant: A 28-Day Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 28-Day Recovery Period

Summary of Microscopic Observations - FEMALE
Terminal

Tissue Observation	Severity	15 mg/kg (45 minute)
Number of Animals Examined		4
adrenal glands		(4)
mineralization	- minimal	0
vacuolation, decreased, diffuse cortical		4
	- mild	0
	- moderate	4
	- severe	0
within normal limits		0
aorta		(4)
within normal limits		4
bone marrow, femur		(4)
within normal limits		4
bone marrow, rib		(4)
within normal limits		4
bone marrow, sternum		(4)
within normal limits		4

( ) - Number observed

Increased pigment (brown, granular, and minimally refractile under polarized light) within Kupffer cells of the liver was observed in the vehicle control (4 of 4 animals), 10 (3 of 4 males), and 15 mg/kg/day terminal males (4 of 4 animals) and females (3 of 4 animals) and in the vehicle control (2 of 2 males and 2 of 2 females) and 15 mg/kg/day recovery males (2 of 2 animals) and females (2 of 2 animals). Further staining with special stains indicated that the pigment was most likely Solutol, a pegylated fatty acid present in the vehicle, and/or its product. This pigment was similar in the livers of vehicle control groups and groups treated with the test article and therefore considered to be vehicle related and not test article related. Pigment in the liver Kupffer cells persisted after the 28 day recovery period. Overall, there were no significant test article related histopathology findings at primary or recovery necropsies. The following tables show the histopathology findings in the liver in the terminal necropsy.

Male:

Tissue Findings	Severity	Saline	Vehicle	3 mg/kg/d	10 mg/kg/d	15 mg/kg/d
N		4	4	4	4	4
Liver						
Pigment, increased Kupffer cell	Minimal	0	4	0	3	4

Female:

Tissue Findings	Severity	Saline	Vehicle	3 mg/kg/d	10 mg/kg/d	15 mg/kg/d
N		4	4	4	4	4
Liver						
Pigment, increased Kupffer cell	Minimal	0	2	0	0	3

Special Evaluation: None

Toxicokinetics: Blood samples were collected from all animals at predose, within 2 minutes prior to the end of infusion (30 or 45 minutes following the start of infusion), 1, 3, 6, 8, and 24 hours postdose on Days 1 and 28.

There were no apparent sex difference in mean systemic exposure to rolapitant and SCH 720881 (metabolite). Mean systemic exposure ($AUC_{0\text{-}24hr}$) to rolapitant and SCH 720881 increased with increasing dose in an approximately dose proportional manner across the dose range. Following repeated administration, mean systemic exposure ($AUC_{0\text{-}24hr}$) to rolapitant did not appear to change. Following repeated administration, mean systemic exposure ($AUC_{0\text{-}24hr}$) to SCH 720881 appeared greater than that on Day 1. Systemic exposure ($AUC_{0\text{-}24hr}$) to SCH 720881 was lower than systemic exposure to rolapitant. The Metabolite:Parent (M/P) ratios did not appear to change with increasing dose, and appeared to increase following repeated administration. Mean TK parameters are shown in the following table (from page 760 of the report).

Table 1: Mean (±SD) and CV% Rolapitant Toxicokinetic Parameters on Days 1 and 28 Following Intravenous Infusion Administration of 3, 10, and 15 mg/kg Rolapitant to Cynomolgus Monkeys (Males and Females Combined)

Analyte	Dose (mg/kg)	Day	Statistic	Cmax (ng/mL)	Cmax/Dose (kg*ng/mL/mg)	Tmax (hr)[a]	AUC0-24hr (hr*ng/mL)	AUC0-24hr/Dose (hr*kg*ng/mL/mg)	R[b]
ROLAPITANT	3	1	N	8	8	8	8	8	NA
			Mean	1470	490	0.50 (0.5 - 0.5)	11300	3780	NA
			SD	309	103	NA	2270	756	NA
			CV%	21.0	21.0	NA	20.0	20.0	NA
		28	N[c]	8	8	8	8	8	8
			Mean[c]	1750	584	0.50 (0.5 - 1)	11800	3930	1.03
			SD[c]	550	183	NA	3600	1200	0.145
			CV%[c]	31.4	31.4	NA	30.5	30.5	14.2
	10	1	N	8	8	8	8	8	8
			Mean	3060	1020	0.50 (0.5 - 1)	12500	4150	1.09
			SD	3400	1130	NA	3710	1240	0.173
			CV%	111	111	NA	29.8	29.8	15.9
		28	N	8	8	8	8	8	NA
			Mean	6700	670	0.50 (0.5 - 0.5)	44400	4440	NA
			SD	2170	217	NA	11000	1100	NA
			CV%	32.4	32.4	NA	24.7	24.7	NA
			N	8	8	8	8	8	8
			Mean	4270	427	0.50 (0.5 - 0.5)	32400	3240	0.737
			SD	913	91.3	NA	7990	799	0.105
			CV%	21.4	21.4	NA	24.6	24.6	14.2

NA – Not applicable
a: Median (minimum – maximum)
b: $R = AUC_{0\text{-}24hr\ Day\ 28}/AUC_{0\text{-}24\ Day\ 1}$
c: The 0.5 hr timepoint for animal number 3001 was excluded

Dosing Solution Analysis: Dosing solution analysis report was not included in the study report.

Study title: 13-Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 6-Week Recovery Period

Study no.:	2013-015
Study report location:	EDR, Section 4.2.3.2
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 17, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Rolapitant IV 2 mg/mL, Lot No. 22901.001, 99.9-100.7%

Key Study Findings:

- There was no mortality.
- Treatment related clinical signs at 15 mg/kg/day included convulsions, tremor and decreased activity.
- There were no significant test article related effects on body weight, ophthalmic evaluations, and there were no significant meaningful differences were observed in clinical pathology parameters.
- There was no significant test article related macroscopic or microscopic changes.
- Histopathological changes were considered to be due to the vehicle and were not considered adverse as they recovered at the end of the 6-week recovery period.
- The NOAEL was considered as 10 mg/kg/day.

Methods:	
Doses:	0 (saline), 0 (vehicle), 3, 10 and 15 mg/kg/day
Frequency of dosing:	Once daily
Route of administration:	Intravenous (IV) infusion (30-minute)
Dose volume:	1.5-7.5 mL/kg
Formulation/Vehicle:	4.4% Solutol® HS15, 1.1% mid-chain triglycerides (MCT), and 0.66% soybean oil in 20 mM phosphate-buffered saline (PBS) pH 7.5.
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	4-6/sex/group
Age:	3 years to 5 years 10 months of age
Weight:	Male: 3.20 to 6.25 kg; Female: 3.05 to 4.80 kg
Satellite groups:	None
Unique study design:	Shown in the table below
Deviation from study protocol:	Protocol deviations did not affect the quality or integrity of the study.

The study design is shown below (from page 10 and 49 of the report).

Group Assignments

Group Number	Dose Level (mg/kg)	Dose Volume (mL/kg)	Dose Concentration (mg/mL)	Number of Animals[c]	
				Male	Female
1	0[a]	7.5	0	4	4
2	0[b]	7.5	0	6	6
3	3	1.5	2	4	4
4	10	5.0	2	4	4
5	15	7.5	2	6	6[d]

[a]Saline Control
[b]Placebo Control
[c]Two animals/sex in Groups 2 and 5 were maintained until the recovery necropsy on Day 134. Remaining animals were submitted for terminal necropsy on Day 92.
[d]Beginning on Day 55, one female (animal number 5502) was dosed at a reduced dose level of 12.5 mg/kg and at a dose volume of 6.25 mL/kg.

Group	Number of Animals		Animal Number	
	Males	Females	Males	Females
1	4	4	1001-1004	1501-1504
2	6	6	2001-2006	2501-2506
3	4	4	3001-3004	3501-3504
4	4	4	4001-4004	4501-4504
5	6	6	5001-5006	5501-5506

Beginning on Day 11, one female at 15 mg/kg/day (animal number 5502) had the infusion duration extended to 90 minutes and beginning on Day 55, the dose level for this animal was reduced to 12.5 mg/kg/day at a rate of 6.25 mL/kg. This animal was a Group 5 animal but was reported separately on tables at a dose level of 15/12.5 mg/kg/day. Beginning on January 11, 2015, the infusion duration for all remaining males and females at 15 mg/kg/day was extended to 45 minutes.

Basis of Dose Selection: The dose levels were selected based on the results of a 14-day IV infusion study (Study Number 2013-009, refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD) and the 28-day study (Study Number 2013-012, reviewed above) in cynomolgus monkeys.

In the 14-day study (Study Number 2013-009), rolapitant was administered once daily by IV infusion at 3 and 10 mg/kg/day for 30 minutes, and at 15 and 20 mg/kg/day for 45 minutes, respectively. There was no mortality. Dose was reduced from 20 mg/kg/day to 15 mg/kg/day due to adverse clinical signs (decreased activity, convulsions, lateral recumbency, partially and/or completely closed eyelids, and shallow breathing, dilated pupils, salivation, and ataxia immediately postdose). There were no significant treatment related histopathology findings. Based on this, a high dose of 15 mg/kg/day was selected for the current study, the low dose of 3 mg/kg/day was expected to have no adverse effects, and the mid dose of 10 mg/kg/day was selected to demonstrate dose-response.

Observations and Results:

Mortality: All animals were observed twice daily for mortality and moribundity. There were no mortalities.

Clinical Signs: Clinical signs were observed prior to infusion and at approximately 45 minutes and 4 hours postdose. Treatment related clinical signs at 15 mg/kg/day included convulsions, tremors, and decreased activity.

Convulsion/Tremor: At 15 mg/kg/day on Day 4, two high dose male animals (# 5001 and 5002) had convulsions at 45 minute postdose, which were resolved by 4 hour postdose. Tremors were observed for animal # 5003 (high dose male) on Days 21-23; animal # 5503 (high dose female) on Days 8, 19, and 44; animal # 5505 (high dose female) on Day 2; animal # 5502 (high dose female) on Days 15, 20-22, 25-27, 32, 33, 48, 49, 52; and animal # 5506 (high dose female) on Day 8. These observations were considered test article related.

Decreased Activity: Animal # 4503 (female, 10 mg/kg) exhibited decreased activity on Days 78 and 79; animal # 5502 (female, 15 mg/kg) on Days 23, 25, 35, and 39; and animal # 5504 (female, 15 mg/kg) on Days 25, 26, 27, and 28 and control animal # 1002 (male) on Day 51 and placebo animal # 2503 (female) on Day 34. Even though a control animal showed this sign, the frequency and number of animal affected in the treated groups showed a test article related trend.

Body Weights: Body weights were recorded on a weekly basis.

Mean initial (Week -1) and final (Week 13) body weights of saline control males were 4.9 and 4.9 kg, respectively. Mean initial (Week -1) and final (Week 13) body weights of vehicle control males were 4.8 and 5.1 kg, respectively. Mean initial (Week -1) and final (Week 13) body weights of saline control females were 3.6 and 3.8 kg, respectively. Mean initial (Week -1) and final (Week 13) body weights of vehicle control females were 3.7 and 3.8 kg, respectively. There were no significant treatment related effects on body weight.

Feed Consumption: Food consumptions were recorded qualitatively on a daily basis. Quantitative food consumption data were not provided.

Ophthalmoscopy: Ophthalmoscopy was performed at pretest and prior to scheduled necropsy. Persistent hyaloid and atrophy of the optic nerve were observed at pretest for animal number 3003 (3 mg/kg, male) and animal number 5001 (15 mg/kg, male), respectively, and were not considered to be test article related. There was an apparent lack of dose response. Per the ophthalmologist's report, these observations were representative of pathology that would be expected for this group of animals considering age, sex and strain. There were no obvious trends in pathology that would suggest that these findings were test article related. There were no other significant treatment related ophthalmoscopic findings.

Electrocardiography (ECG): ECG was performed at pretest, and at predose and 30 minutes postdose on Days 1 and 91, and prior to the recovery necropsy. Females at 15 mg/kg/day showed mild slowing of the heart rate (lengthening of RR interval; 309.94 msec vs. 272.65 msec in saline control) compared to saline control. This finding was likely considered test article related, but was not considered adverse based on the small magnitude of the change. The following tables (from pages 438 and 439 of the report) show the heart rates.

(b) (4)Research Study Number 2013-015
Rolapitant: A 13-Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 6-Week Recovery Period

Summary of Heart Rate, beats/minute - MALE

	0 mg/kg (Saline Control)			0 mg/kg (Placebo Control)			3 mg/kg			10 mg/kg			15 mg/kg		
Study Interval	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N
Pretest	223.07	23.754	4	220.94	13.348	6	230.93	13.901	4	240.75	27.122	4	224.10	33.030	6
Day 1 predose	212.47	19.072	4	225.19	15.886	6	221.73	11.909	4	236.50	32.688	4	220.40	30.012	6
Day 1 postdose	210.31	33.680	4	218.04	12.914	6	213.66	13.825	4	233.16	18.175	4	220.25	27.578	6
Terminal predose	220.06	12.022	4	223.66	6.993	6	212.29	11.325	4	233.63	26.741	4	207.93	25.981	6
Terminal postdose	214.50	11.924	4	223.96	25.572	6	217.32	10.960	4	230.08	15.761	4	199.14	17.027	6

(b) (4) Research Study Number 2013-015
Rolapitant: A 13-Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 6-Week Recovery Period

Summary of Heart Rate, beats/minute - FEMALE

Study Interval	0 mg/kg (Saline Control) Mean	SD	N	0 mg/kg (Placebo Control) Mean	SD	N	3 mg/kg Mean	SD	N	10 mg/kg Mean	SD	N	15 mg/kg Mean	SD	N
Pretest	239.72	9.974	4	228.82	22.453	6	248.11	3.215	4	224.40	19.574	4	241.98	20.554	5
Day 1 predose	234.04	15.682	4	231.08	16.124	6	244.72	6.658	4	239.99	13.516	4	236.08	16.098	5
Day 1 postdose	224.52	11.572	4	224.47	18.150	6	237.39	12.437	4	228.18	6.356	4	218.50	17.202	5
Terminal predose	229.36	15.668	4	221.13	17.187	6	222.26	19.146	4	222.49	32.875	4	219.88	12.685	5
Terminal postdose	220.30	8.162	4	218.16	15.204	6	228.60	9.583	4	225.47	11.982	4	193.91[a]	8.892	5

The QT interval was longer than placebo control in males at the terminal postdose interval at 15 mg/kg/day (180.07 msec vs. 162.24 msec in placebo control). As a difference from saline was not noted and absolute values for saline control and the 15 mg/kg/day group were comparable, the difference from placebo control was not considered test article related. The following tables (from pages 446-447 of the report) show the QT intervals.

(b) (4) Research Study Number 2013-015
Rolapitant: A 13-Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 6-Week Recovery Period

Summary of QT Interval, msec - MALE

Study Interval	0 mg/kg (Saline Control) Mean	SD	N	0 mg/kg (Placebo Control) Mean	SD	N	3 mg/kg Mean	SD	N	10 mg/kg Mean	SD	N	15 mg/kg Mean	SD	N
Pretest	166.50	11.322	4	158.29	6.820	6	158.90	4.267	4	158.09	15.644	4	162.91	12.808	6
Day 1 predose	173.72	5.830	4	160.75	7.193	6	165.17	5.796	4	166.55	20.095	4	167.61	8.628	6
Day 1 postdose	183.77	17.020	4	161.29	8.208	6	167.49	5.726	4	166.93	16.296	4	169.78	11.923	6
Terminal predose	172.41	11.574	4	165.85	8.772	6	172.79	10.607	4	166.32	12.147	4	171.20	6.490	6
Terminal postdose	176.39	5.782	4	162.24	6.016	6	170.86	4.220	4	172.02	16.611	4	180.07[c]	5.196	6

(b) (4) Research Study Number 2013-015
Rolapitant: A 13-Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 6-Week Recovery Period

Summary of QT Interval, msec - FEMALE

Study Interval	0 mg/kg (Saline Control) Mean	SD	N	0 mg/kg (Placebo Control) Mean	SD	N	3 mg/kg Mean	SD	N	10 mg/kg Mean	SD	N	15 mg/kg Mean	SD	N
Pretest	165.80	16.072	4	161.19	6.132	6	160.90	2.355	4	167.33	8.458	4	158.87	6.485	5
Day 1 predose	169.78	13.905	4	161.19	12.510	6	161.96	5.314	4	158.90	4.456	4	159.97	3.259	5
Day 1 postdose	168.00	13.217	4	158.93	4.848	5	160.57	5.040	4	160.64	2.819	4	166.14	5.987	5
Terminal predose	172.32	14.914	4	166.77	9.658	6	175.22	6.694	4	165.56	13.950	4	168.18	5.603	5
Terminal postdose	178.80	16.241	4	172.75	14.949	6	170.24	4.680	4	165.62	6.083	4	179.38	7.409	5

There was no other significant treatment related ECG changes.

Hematology: Hematology was conducted at pretest and prior to the terminal and recovery necropsy. There were no significant meaningful treatment related effects.

Clinical Chemistry: Clinical chemistry was conducted at pretest and prior to the terminal and recovery necropsy. Mild to moderate decreases in cholesterol concentration were observed in both sexes administered the vehicle (up to -41%), 3 (up to -28%), 10 (up to

-42%) and 15 mg/kg/day (up to -41%) of rolapitant, and in the female at 12.5/15 mg/kg/day (-24%), relative to pretest values. Reductions in cholesterol concentration were considered vehicle-related, and fully resolved by the end of the recovery period. Based on their low magnitude and recovery, reductions in cholesterol were not considered adverse. Minimal to mild decreases in albumin concentration (up to -11%) with concomitant minimal to mild increases in globulin concentration (up to +15%) were observed in both sexes administered the vehicle and at 10 and 15 mg/kg/day of rolapitant, relative to pretest values. These were considered likely vehicle related and were recovered by the end of the recovery period. There were no other significant meaningful treatment related effects on clinical chemistry parameters.

Urinalysis: Urine samples were collected for at least 16 hours (time of collection was not mentioned). There were no significant treatment related urinary changes.

Gross Pathology: Gross pathology was conducted at necropsy. There were no significant treatment related gross macroscopic changes.

Organ Weights: The following (from page 1116 of the report) organs were weighed from all animals from all dose groups at the scheduled necropsies.

- Adrenal (2)*
- Aorta
- Bone with marrow [femur]
- Bone with marrow [rib]
- Bone with marrow [sternum]
- Bone marrow smear [2 collected][a]
- Brain [cerebrum, midbrain, cerebellum, medulla/pons]*
- Epididymis (2)
- Eye including optic nerve (2)
- Gallbladder
- GALT [gut associated lymphoid tissue]
- Gastrointestinal tract:
  - esophagus
  - stomach [cardia, fundus, and pylorus]
  - duodenum
  - jejunum
  - ileum
  - cecum
  - colon
  - rectum
- Gonads:
  - ovary (2)* with oviduct (2)
  - testis (2)*
- Gross lesions
- Heart*
- Infusion site [1 cm distal/proximal to catheter tip and at catheter tip]
- Joint tibiofemoral
- Kidney (2)*
- Larynx
- Liver [3 sections collected; 2 examined]*
- Lung with bronchi [collected whole; 2 sections examined]
- Lymph nodes: mandibular [2 collected; 1 examined] and mesenteric
- Mammary gland [process females only]
- Pancreas
- Pituitary*
- Prostate* and seminal vesicle (2)
- Salivary gland, mandibular [2 collected; 1 examined]
- Salivary gland, parotid [2 collected; 1 examined]
- Salivary gland, sublingual [2 collected; 1 examined]
- Sciatic nerve
- Skeletal muscle, rectus femoris
- Skin
- Spinal cord [cervical, thoracic, and lumbar]
- Spleen*
- Thymus*
- Thyroid/parathyroid (2)*
- Tongue
- Trachea
- Ureter (2)
- Urinary bladder
- Uterus/Cervix
- Vagina

[a]Bone marrow smears were collected at the scheduled necropsies and held.

(2) Paired organ
*Weighed organ

There were no significant treatment related effects on organ weights at primary or recovery necropsies.

Histopathology: Microscopic examination was performed on all tissues as listed in the table above from all animals from all groups at the primary and recovery necropsy (Group 2 and 5).

Adequate Battery: Yes

Peer Review: Yes

Histological Findings: Microscopic changes associated with the terminal placebo control and rolapitant groups included decreased vacuolation of the adrenal gland cortex,

pigment within liver Kupffer cells, mandibular and/or mesenteric lymph node macrophages, spleen macrophages, and bone marrow macrophages (females only), and hepatocellular hypertrophy (males only). These changes were considered to be vehicle-related, and were not considered adverse as they recovered at the end of the 6-week recovery period and lack of cellular degeneration/necrosis in any organs listed in the above table. Histopathological changes are shown in the following table (from page 28 of the report).

Table A: Placebo-related Microscopic Observations - Terminal										
Dose level: mg/kg	0[a]		0[b]		3		10		15	
Sex	M	F	M	F	M	F	M	F	M	F
Number Examined	4	4	4	4	4	4	4	4	4	4
Adrenal glands										
Vacuolation, decreased, diffuse cortical	0	0	4	4	2	0	4	4	4	4
-mild	0	0	0	0	0	0	0	2	0	0
-moderate	0	0	0	0	1	0	0	2	0	0
-severe	0	0	4	4	1	0	4	0	4	4
Liver										
Hypertrophy, hepatocellular, panlobular										
-minimal	0	0	2	0	0	0	0	0	4	0
Pigment, increased Kupffer cell	0	0	4	4	3	1	4	2	4	4
-minimal	0	0	0	0	3	1	2	0	1	2
-mild	0	0	4	4	0	0	2	2	3	2
Lymph node, mandibular										
Pigment, increased macrophage	0	0	3	4	0	1	3	3	4	3
-minimal	0	0	2	4	0	1	3	3	4	2
-mild	0	0	1	0	0	0	0	0	0	1
Lymph node, mesenteric										
Pigment, increased macrophage										
-minimal	0	0	2	0	0	0	0	0	0	1
Spleen										
Pigment, increased macrophage	1	0	3	2	0	0	2	3	2	2
-minimal	1	0	2	0	0	0	2	3	2	2
-mild	0	0	1	2	0	0	0	0	0	0
Bone marrow, femur										
Macrophages, pigmented										
-minimal	0	0	0	3	0	0	0	0	0	1
Bone marrow, rib										
Macrophages, pigmented	0	1	0	4	0	0	0	0	0	2
-minimal	0	1	0	3	0	0	0	0	0	2
-mild	0	0	0	1	0	0	0	0	0	0
Bone marrow, sternum										
Macrophages, pigmented										
-minimal	0	1	0	4	0	0	0	0	0	3

M - Male

F - Female

[a]Saline Control

[b]Placebo Control

Microscopic changes observed in the recovery placebo control and rolapitant treated groups (decreased vacuolation of the adrenal gland cortex, pigment within liver Kupffer cells, mandibular and/or mesenteric lymph node macrophages, spleen macrophages, and bone marrow macrophages) showed almost complete reversibility after a 6-week recovery period. Hepatocellular hypertrophy of the liver was not present and was considered to be completely reversible after a 6-week recovery period. These changes

were considered to be related to the vehicle as these changes were seen in the vehicle control animals. Histopathological findings in the recovery animals are shown in the following table (from page 29 of the report).

Table B: Placebo-related Microscopic Observations - Recovery					
Dose level: mg/kg	0[a]		15		15/12.5
Sex	M	F	M	F	F
Number Examined	2	2	2	1	1
Adrenal glands					
Vacuolation, decreased, diffuse cortical					
-moderate	1	0	0	0	0
Liver					
Pigment, increased, Kupffer cells	2	2	2	1	1
-minimal	0	0	0	1	1
-mild	2	2	2	0	0
Lymph node, mandibular					
Pigment, increased macrophage	2	2	2	1	1
-minimal	0	2	2	1	1
-mild	2	0	0	0	0
Lymph node, mesenteric					
Pigment, increased macrophage					
-minimal	1	1	0	0	0
Spleen					
Pigment, increased macrophage					
-minimal	2	2	2	1	1
Bone marrow, femur					
Macrophages, pigmented					
-minimal	2	1	0	0	1
Bone marrow, rib					
Macrophages, pigmented					
-minimal	2	1	0	0	1
Bone marrow, sternum					
Macrophages, pigmented					
-minimal	2	1	0	0	1
M - Male F - Female	[a]Placebo Control				

Overall, there were no significant test article related microscopic changes in terminal or recovery animals.

Special Evaluation: None

Toxicokinetics: Blood samples were collected from all animals at predose, 30 min, 1, 3, 6, 8, and 24 hours postdose on Days 1 and 91.

Mean systemic exposure ($AUC_{0\text{-}24hr}$) to rolapitant increased with increasing dose in an approximately dose proportional manner across the dose range on Days 1 and 91. Mean systemic exposure ($AUC_{0\text{-}24hr}$) to SCH 720881 (metabolite) increased with increasing dose in an approximately dose proportional manner across the dose range on Day 1. On Day 91, mean systemic exposure to SCH 720881 increased with increasing dose in an approximately less than dose proportional manner across the dose range, while mean systemic exposure to rolapitant did not appear to change. Following repeated administration, mean systemic exposure to SCH 720881 appeared to be greater than mean systemic exposure to SCH 720881 on Day 1 and systemic exposure to SCH 720881 was lower than systemic exposure to rolapitant. Mean TK parameters for rolapitant and SCH 720881 are shown in the tables below (from page 1041-1042 of the report).

(b) (4) Research Study Number 2013-015
Rolapitant: A 13-Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 6-Week Recovery Period

Table 1: Mean (±SD) and CV% Rolapitant Toxicokinetic Parameters on Days 1 and 91 Following Intravenous Infusion Administration of 3, 10, and 15 mg/kg Rolapitant to Cynomolgus Monkeys (Males and Females Combined)

Analyte	Dose (mg/kg)	Day	Statistic	C_{max} (ng/mL)	C_{max}/Dose (kg*ng/mL/mg)	T_{max} (hr)[a]	T_{last} (hr)[a]	$AUC_{0\text{-}24hr}$ (hr*ng/mL)	$AUC_{0\text{-}24hr}$/Dose (hr*kg*ng/mL/mg)	R[b]
ROLAPITANT	3	1	N	8	8	8	8	8	8	NA
			Mean	1710	569	0.5(0.5 - 0.5)	24(24 - 24)	14300	4760	NA
			SD	366	122	NA	NA	2560	855	NA
			CV%	21.4	21.4	NA	NA	18.0	18.0	NA
ROLAPITANT	3	91	N	8	8	8	8	8	8	8
			Mean	1900	635	0.5(0.5 - 1)	24(24 - 24)	17200	5730	1.20
			SD	562	187	NA	NA	6750	2250	0.357
			CV%	29.5	29.5	NA	NA	39.3	39.3	29.9
ROLAPITANT	10	1	N	8	8	8	8	8	8	NA
			Mean	6640	664	0.5(0.5 - 0.5)	24(24 - 24)	44600	4460	NA
			SD	1770	177	NA	NA	8380	838	NA
			CV%	26.7	26.7	NA	NA	18.8	18.8	NA
ROLAPITANT	10	91	N	8	8	8	8	8	8	8
			Mean	6500	650	0.5(0.5 - 1)	24(24 - 24)	46400	4640	1.07
			SD	2360	236	NA	NA	12600	1260	0.392
			CV%	36.3	36.3	NA	NA	27.1	27.1	36.5
ROLAPITANT	15	1	N	12	12	12	12	12	12	NA
			Mean	13200	877	0.5(0.5 - 0.5)	24(24 - 24)	73300	4890	NA
			SD	4990	333	NA	NA	13900	930	NA
			CV%	38.0	38.0	NA	NA	19.0	19.0	NA
ROLAPITANT	15	91	N	11	11	11	11	11	11	10
			Mean	11500	768	0.75(0.75 - 0.75)	24(24 - 24)	64400	4290	0.875
			SD	3190	213	NA	NA	15200	1020	0.115
			CV%	27.7	27.7	NA	NA	23.7	23.7	13.1

NA – Not applicable
a: Median (minimum – maximum)
b: $R = AUC_{0\text{-}24hr\ Day\ 91}/AUC_{0\text{-}24\ Day\ 1}$

(b) (4) Research Study Number 2013-015
Rolapitant: A 13-Week Intravenous Infusion Toxicity Study in Cynomolgus Monkeys with a 6-Week Recovery Period

Table 2: Mean (±SD) and CV% SCH 720881 Toxicokinetic Parameters on Days 1 and 91 Following Intravenous Infusion Administration of 3, 10, and 15 mg/kg Rolapitant to Cynomolgus Monkeys (Males and Females Combined)

Analyte	Dose (mg/kg)	Day	Statistic	C_{max} (ng/mL)	C_{max}/Dose (kg*ng/mL/mg)	T_{max} (hr)[a]	T_{last} (hr)[a]	$AUC_{0\text{-}24hr}$ (hr*ng/mL)	$AUC_{0\text{-}24hr}$/Dose (hr*kg*ng/mL/mg)	R[b]	M:P[c]
SCH 720881	3	1	N	8	8	8	8	8	8	NA	8
			Mean	51.8	17.3	24(8 - 24)	24(24 - 24)	840	280	NA	0.0594
			SD	23.9	7.97	NA	NA	288	96.0	NA	0.0171
			CV%	46.1	46.1	NA	NA	34.3	34.3	NA	28.8
SCH 720881	3	91	N	8	8	8	8	8	8	8	8
			Mean	104	34.8	6(0.5 - 8)	24(24 - 24)	2130	710	2.88	0.121
			SD	57.9	19.3	NA	NA	1100	367	2.17	0.0145
			CV%	55.5	55.5	NA	NA	51.7	51.7	75.5	12.1
SCH 720881	10	1	N	8	8	8	8	8	8	NA	8
			Mean	156	15.6	24(24 - 24)	24(24 - 24)	2560	256	NA	0.0579
			SD	27.1	2.71	NA	NA	521	52.1	NA	0.00771
			CV%	17.3	17.3	NA	NA	20.3	20.3	NA	13.3
SCH 720881	10	91	N	8	8	8	8	8	8	8	8
			Mean	266	26.6	0.5(0.5 - 6)	24(24 - 24)	5100	510	2.07	0.109
			SD	77.5	7.75	NA	NA	1760	176	0.893	0.00864
			CV%	29.2	29.2	NA	NA	34.5	34.5	43.1	7.94
SCH 720881	15	1	N	12	12	12	12	12	12	NA	12
			Mean	190	12.7	24(8 - 24)	24(24 - 24)	3300	220	NA	0.0463
			SD	32.4	2.16	NA	NA	382	25.4	NA	0.00984
			CV%	17.1	17.1	NA	NA	11.6	11.6	NA	21.2
SCH 720881	15	91	N	11	11	11	11	11	11	10	11
			Mean	330	22.0	1(0.75 - 3)	24(24 - 24)	5410	361	1.68	0.0846
			SD	75.3	5.02	NA	NA	1270	84.9	0.435	0.00762
			CV%	22.8	22.8	NA	NA	23.5	23.5	25.9	9.01

NA – Not applicable
a: Median (minimum – maximum), median value only reported if actual collection interval
b: $R = AUC_{0\text{-}24hr\ Day\ 28}/AUC_{0\text{-}24\ Day\ 1}$
c: $M:P = AUC_{0\text{-}24hr\ SCH\ 720881}/AUC_{0\text{-}24hr\ Rolapitant}$

Dosing Solution Analysis: Dosing solution analysis report was not included in the study report.

7 Genetic Toxicology

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

7.2 *In Vitro* Assays in Mammalian Cells

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

7.4 Other Genetic Toxicity Studies

N/A

8 Carcinogenicity

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

9.2 Embryonic Fetal Development

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

9.3 Prenatal and Postnatal Development

Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD.

10 Special Toxicology Studies

N/A

11 Integrated Summary and Safety Evaluation

The Applicant has conducted 13-week intravenous (infusion) toxicity studies in rats and 28-day and 13-week intravenous (infusion) toxicity studies in cynomolgus monkeys to support the intravenous rolapitant formulation. The Central Nervous System (CNS) appeared to be the primary target organ. Treatment related convulsions and tremors were observed in these studies. Vehicle related effects (clinical pathology and histopathology changes in the liver) were also observed in these studies. In addition, infusion site reactions were observed, which included abscess formation and/or inflammation. The NOAEL could not be determined for the 13-week rat study due to mortality observed at all placebo and rolapitant dose levels. The NOAEL in the 13-week study in cynomolgus monkeys was 10 mg/kg/day. Some of the histopathological findings (diffuse vacuolation of the adrenal cortex and brown pigmentation of adrenal glands and Kupffer cells in the liver) in monkey studies appeared to be related to the vehicle. Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD for other nonclinical studies with rolapitant including reproductive toxicity, genotoxicity, and carcinogenicity.

The recommended dosage of Varubi (rolapitant) injectable emulsion for intravenous use is 166.5 mg (~3 mg/kg or 0.214 mg/kg/day) of rolapitant administered every 14 days. The NOAEL of 10 mg/kg/day identified in the 13-week intravenous toxicity study in cynomolgus monkeys offer adequate (approximately 15-fold based on body surface

area) margin of safety for the proposed dose of 166.5 mg of rolapitant administered every 14 days or 0.214 mg/kg/day. The following table (from page 20 of Section 2.4 of the submission) shows the exposure multiples for rolapitant and its metabolite at the NOAEL in animals and humans. Overall, from a nonclinical standpoint, there are no approvability issues.

Table 1: Estimated Exposure Multiples for Rolapitant at the NOAEL in Animals *vs.* the Single 185 mg IV Dose in Humans.

Species	Study Duration/ Route	Study Number	NOAEL (mg/kg/day)	Steady State Mean Rolapitant Values at NOAEL			Exposure Multiple at the NOAEL	
				C_{max} (µg/mL)	$AUC_{0\text{-}24hr}$ (µg·hr/mL)	AUC Projected[a]	C_{max}	AUC Projected
Mouse	3-M oral	SN 03665	M≥150 F = 75	13.50 7.06	128.0 69.5	2,,688 1,459.5	6.8 3.6	21.6 11.7
Rat	3-M IV	SN 15-3893	M=20 F=20	6.79 7.97	59.8 75.6	1,255.8 1,587.6	3.4 4.0	10.2 12.8
Rat	6-M oral	SN 03115	M=100 F=100	5.53 5.90	79.7 72.0	1,673.7 1,512.0	2.8 3.0	13.5 12.2
Monkey	3-M IV	SN 2013-015	M/F=10	6.50	46.40	974.4	3.3	7.8
Monkey	9-M oral	SN 03663	≥30	4.33	70.1	1,472.1	2.2	11.9
Human	Single-dose IV	PR-11-5016-C	185 mg total	1.986	124.016[b]			

[a] AUC Projected is $AUC_{0\text{-}24hr}$ multiplied by 21
[b] $AUC_{0\text{-}\infty}$ from the single 185 mg IV dose

12 Appendix/Attachments

None

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/s/

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11/28/2016

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11/28/2016