CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209776Orig1s000

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:	NDA 209776
Supporting document/s:	SD# 0001
Applicant's letter date:	12/29/2016
CDER stamp date:	12/29/2016
Product:	TRADENAME (meropenem plus vaborbactam)
Indication:	(b) (4)
Applicant:	Rempex Pharmaceuticals
Review Division:	Division of Anti-infective Products
Reviewer:	James S. Wild, Ph.D.
Supervisor/Team Leader:	Terry Miller, Ph.D.
Division Director:	Sumathi Nambiar, M.D.
Project Manager:	Jane Dean, R.N., M.S.N.

Template Version: September 1, 2010

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 209776 are owned by Rempex Pharmaceuticals or are data for which Rempex Pharmaceuticals has obtained a written right of reference. Any information or data necessary for approval of NDA 209776 that Rempex Pharmaceuticals 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 209776.

TABLE OF CONTENTS

Table of Tables

Table of Figures

No table of figures entries found.

1 Executive Summary

1.1 Introduction

Meropenem is a broad spectrum (gram-positive, gram-negative and anaerobic bacteria) carbapenem antibiotic that has been marketed as an intravenous product in the United States since 1996 initially under the tradename Merrem®. It is currently approved for the treatment of complicated skin and skin structure infections and complicated intra-abdominal infections in adults and pediatric patients 3 months of age and older. In addition Merrem® is approved for the treatment of bacterial meningitis in pediatric patients 3 months of age and older.

Vaborbactam (RPX7009) is a novel β-lactamase inhibitor that is expected to restore the activity of carbapenems against resistant bacteria.

1.2 Brief Discussion of Nonclinical Findings

A vaborbactam-associated finding with potential clinical relevance was a low incidence of malformations in the rabbit embryo-fetal study. In the mid-dose (300 mg/kg/day) fetuses, malformations included intraventricular septal defects in two different litters, one supernumerary lung lobe in another fetus in another litter and three fused right lung lobes in another fetus in a fourth litter. In the high-dose group (1000 mg/kg/day), supernumerary lung lobes occurred in two fetuses in two litters. The relevance of these findings to humans in unknown, but the malformations are considered related to RPX7009 administration and will be listed on the product label. In this study, dams administered RPX7009 did not lose weight or demonstrate maternal toxicity, and fetal weight loss did not occur. The NOAEL values for maternal toxicity and fetal malformations were considered to be 1000 and 100 mg/kg/day respectively which are equivalent to approximately 5 times and 0.3 times respectively the maximum recommended human dose based on plasma AUC exposure comparisons and approximately 70 times and 6 times respectively the maximum recommended human dose based on plasma C_{max} exposure comparisons. The clinical relevance of the malformations is uncertain. Vaborbactam C_{max} values may have influenced malformations in the rabbit study, and the recommended 3-hour infusion time for clinical administration of vaborbactam is associated with much lower plasma C_{max} values than the 30-minute infusions in rabbits.

In the rat embryo-fetal study, 1/280 low-dose (100 mg/kg/day) fetuses was born with anencephaly and in the mid-dose group (300 mg/kg/day) 1/293 fetuses was born with hydrocephaly. Anencephaly is a rare malformation, but a single incidence in an absence of similar malformations in the high-dose group is not considered sufficient to demonstrate a relationship to RPX7009 administration. As in the rabbit embryo-fetal study, RPX7009 was not associated with maternal toxicity in pregnant rats including reduced maternal weights nor was it associated with fetal toxicity in the form of fetal weight loss. Toxicokinetics were not measured in this study, thus plasma AUC and C_{max} comparisons are not possible. The NOAEL values for maternal and fetal toxicity were

considered to be 1000 mg/kg/day which are equivalent to approximately 1.6 times the maximum recommended human dose based on surface area comparisons.

In general toxicology studies, vaborbactam (RPX7009) was not associated with significant toxicities in 28-day repeated-dose toxicology studies in rats and dogs at daily doses as high as 1000 mg/kg/day (respectively approximately equal to or 3 times the maximum recommended human dose in patients based on plasma AUC exposure) when administered alone or in combination with meropenem. A similar lack of toxicity occurred in in a 28-day toxicology study in juvenile rats with the same NOAEL of 1000 mg/kg/day. Also in a single-dose pharmacokinetic study conducted with juvenile rats, plasma exposures to both meropenem and vaborbactam were reduced compared to plasma exposures in adult rats suggesting more rapid metabolism in juvenile rats and limited potential for unexpectedly high exposures associated with administration of adult doses in pediatric patients.

Vaborbactam was not associated with genotoxicity in a full battery of testing including an *in vitro* Ames test, chromosome aberration test in human lymphocytes and *in vivo* micronucleus test in mice.

In developmental and reproductive toxicity studies other than the embryo-fetal studies, vaborbactam at the high dose of 1000 mg/kg/day in all studies, did not negatively affect male or female fertility, and had no effects on first or second generation offspring in rats in a pre-postnatal study.

In clinical use, meropenem has been associated with seizures and other adverse CNS events (potential for neuromotor impairment) occurring most commonly in patients with CNS disorders. The most common adverse reactions listed on the Merrem® label occurring in 2% or less of patients are: headache, nausea, constipation, diarrhea, anemia, vomiting and rash. Other serious adverse events for meropenem as listed on the Merrem® label are: hypersensitivity reactions and thrombocytopenia. In combination toxicology studies in rats and dogs meropenem did not produce significant toxicities when administered alone or in combination with vaborbactam for 28 days.

Meropenem was not genotoxic in a full battery of *in vitro* (Ames test, Chinese hamster ovary HGPRT assay, human lymphocyte cytogenic assay) and *in vivo* (mouse micronucleus assay) assays.

According to the Merrem® product label, in fertility studies in rats with a high dose of 1000 mg/kg/day (approximately 1.6 times the highest recommended human dose in patients based on body-surface area comparison) and in Cynomolgus monkeys with a high dose of 360 mg/kg/day (approximately equal to 1.2 times the highest recommended human dose in patients based on body-surface area comparison), meropenem did not impair fertility. In the same studies meropenem was not associated with malformations, but produced slight changes in fetal body weights in rats at doses of 250 mg/kg/day and above. In studies described in a literature report (Kawamura *et al.*,

1992), meropenem did not impair male and female fertility, produce malformations, or produce developmental toxicity in Segment I, II, and III studies in rats.

In pharmacokinetic studies, both meropenem and vaborbactam have been shown to widely distribute in body tissues with short plasma $t_{1/2}$ values on the order of 1 hour or less. Both meropenem and vaborbactam are primarily excreted in urine. However, in the 1-month combination toxicology studies in rats and dogs, systemic AUC exposures for vaborbactam and meropenem were not substantially altered when administered concomitantly, and neither agent as well as the hydrolyzed metabolite of meropenem was observed to accumulate with repeated dosing.

The nonclinical pharmacokinetic and toxicity data for vaborbactam and meropenem do not indicate a potential for general toxicity in the clinic above what is expected for treatment with meropenem alone. From a Pharmacology/Toxicology perspective, TRADENAME (meropenem plus vaborbactam) is approvable for the proposed indication. However, the fetal malformation results for vaborbactam in rabbits suggest physicians should describe the risk of fetal-malformations to pregnant women.

1.3 Recommendations

1.3.1 Approvability

The meropenem/vaborbactam product (TRADENAME) is approvable from a Pharmacology/Toxicology perspective.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Reviewers Recommended language for Section 8.1 Pregnancy

8.1 Pregnancy

Risk Summary

(b) (4)

(b) (4)

Based on animal findings, advise pregnant women of potential risks to a fetus. There are insufficient human data to establish whether there is a drug-associated risk of major birth defects or miscarriages with TRADENAME, meropenem, or vaborbactam in pregnant women.

Malformations (supernumerary lung lobes, interventricular septal defect) were observed in offspring from pregnant rabbits administered intravenous vaborbactam during the period of organogenesis at doses approximately equivalent to or above the maximum recommended human dose based on plasma AUC comparison. The clinical relevance of the malformations is uncertain. No similar malformations or fetal toxicity were observed in offspring from pregnant rats administered intravenous vaborbactam during organogenesis or from late pregnancy and through lactation at a dose equivalent to approximately 1.6 times the maximum recommended human dose based on body surface area comparison *[see Data]*.

No fetal toxicity or malformations were observed in pregnant rats and cynomolgus macaques administered intravenous meropenem during organogenesis at doses up to 1.6 and 1.2 times the maximum recommended human dose based on body surface area comparison, respectively. In rats administered intravenous meropenem in late pregnancy and during the lactation period, there were no adverse effects on offspring at doses equivalent to approximately 1.6 times the maximum recommended human dose based on body surface area comparison *[see Data]*.

The background risk of major birth defects and miscarriage for the indicated population is unknown. 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

Meropenem

(b) (4)

Reproductive studies have been performed with meropenem in rats at doses of up to 1000 mg/kg/day and in cynomolgus monkeys at doses of up to 360 mg/kg/day (on the

basis of body surface area comparisons, approximately 1.6 times and 1.2 times higher, respectively, the maximum recommended human dose of 2 grams every 8 hours). These studies revealed no evidence of harm to the fetus due to meropenem, although there were slight changes in fetal body weight at doses of 250 mg/kg/day (equivalent to approximately 0.4 times the maximum recommended human dose of 2 grams every 8 hours based on body surface area comparison) and above in rats. In a published study[1], meropenem administered to pregnant rats from Gestation Day 6 to Gestation Day 17, was associated with mild maternal weight loss at all doses, but did not produce malformations or fetal toxicity. The no-observed-adverse-effect-level (NOAEL) for fetal toxicity in this study was considered to be the high dose of 750 mg/kg/day (equivalent to approximately 1.2 times the highest recommended human dose based on body surface area comparison).

In a pre-postnatal study in rats described in the published literature[1], intravenous meropenem was administered to dams from Gestation Day 17 until Postpartum Day 21. There were no adverse effects in the dams and no adverse effects in the first generation offspring (including developmental, behavioral, and functional assessments and reproductive parameters) except that female offspring exhibited lowered body weights which continued during gestation and nursing of the second generation offspring. Second generation offspring showed no meropenem-related effects. The NOAEL value was considered to be 1000 mg/kg/day (approximately 1.6 times the highest recommended clinical dose based on body surface area comparisons).

(b) (4)

Vaborbactam

In a rat embryo-fetal toxicology study, intravenous administration of vaborbactam during Gestation Days 6-17 showed no evidence of maternal or embryofetal toxicity at doses up to 1000 mg/kg, which is equivalent to approximately 1.6 times the maximum human dose based on body surface area comparisons. In the rabbit, intravenous administration of vaborbactam during Gestation Days 7–19 at doses up to 1000 mg/kg/day

(approximately 5 times the maximum recommended human dose based on AUC exposure comparison) was not associated with maternal toxicity or fetal weight loss. A low incidence of malformations occurred in the 300 mg/kg/day mid-dose group (two fetuses from different litters with interventricular septal defects, one fetus with a fused right lung lobe and one fetus with a supernumerary lung lobe), and in the 1000 mg/kg/day high-dose group (two fetuses from different litters with supernumerary lobes). The NOAEL for fetal toxicity was considered to be 100 mg/kg/day which is equivalent to 0.3 times the maximum recommended human dose based on plasma AUC exposure comparisons and 6-times the maximum recommended human dose based on maximum plasma concentration (C_{max}) comparisons. The clinical relevance of the malformations is uncertain. Vaborbactam C_{max} values may have influenced malformations in the rabbit study, and the recommended 3-hour infusion time for clinical administration of vaborbactam is associated with lower C_{max} values than the 30-minute infusions in rabbits.

In a pre and postnatal study in rats, vaborbactam administered intravenously to pregnant dams from Gestation Day 6 to Lactation Day 20 caused no adverse effects on the dams, or in first and second generation offspring. The NOAEL was considered to be 1000 mg/kg/day (equivalent to approximately 1.6 times the maximum recommended human dose based on body surface area comparison).

8.2 Lactation

(b) (4)

Meropenem has been reported to be excreted in human milk. It is unknown whether vaborbactam is excreted in human milk. No information is available on the effects of meropenem and vaborbactam on the breast-fed child or on milk production.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TRADENAME and any potential adverse effects on the breast-fed child from TRADENAME or from the underlying maternal condition.

Reviewer's Recommended Language for Section 13

13 Nonclinical Toxicology

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

(b) (4)

Carcinogenesis

Long-term carcinogenicity studies have not been performed with TRADENAME, meropenem, or vaborbactam.

Mutagenesis

Meropenem

Genetic toxicity studies were performed with meropenem using the bacterial reverse mutation test, the Chinese hamster ovary HGPRT assay, cultured human lymphocytes cytogenic assay, and the mouse micronucleus test. There was no evidence of mutation potential found in any of these tests.

Vaborbactam

Genetic toxicity studies were performed with vaborbactam using the bacterial reverse mutation test, chromosomal aberration test and the mouse micronucleus test. There was no evidence of mutagenic potential found in any of these tests.

Impairment of Fertility

Meropenem

Reproductive studies were performed with meropenem in male and female rats at doses up to 1000 mg/kg/day with no evidence of impaired fertility (approximately equivalent to 1.6 times the maximum recommended human dose based on body surface area comparison).

In a reproductive study in cynomolgus monkeys at doses of meropenem up to 360 mg/kg/day (on the basis of body surface area comparison, approximately equivalent to 1.2 times the maximum recommended human dose no reproductive toxicity was seen.

Vaborbactam

Vaborbactam had no adverse effect on fertility in male and female rats at doses up to 1000 mg/kg/day, which is equivalent to approximately 1.6 times the maximum recommended human dose based on body surface area comparison.

1. Kawamura S, Russell AW, Freeman SJ, and Siddall, RA: Reproductive and Developmental Toxicity of Meropenem in Rats. Chemotherapy, 40:S238-250 (1992).

2 Drug Information

2.1 Drug

CAS Registry Number (Optional)
Meropenem: none

RPX7009: 1360457-46-0

Generic Name
Meropenem: meropenem

RPX7009: vaborbactam

Code Name
Meropenem: 330772

Vaborbactam: RPX7009, REBO-07

Chemical Name
Meropenem: (4R,5S,6S)-3-[[(3S,5S)-5-(Dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid trihydrate

Vaborbactam: (3R,6S)-2-hydroxy-3-[[2-(2-thienyl)acetyl]amino]-1,2-oxaborinane-6-acetic acid

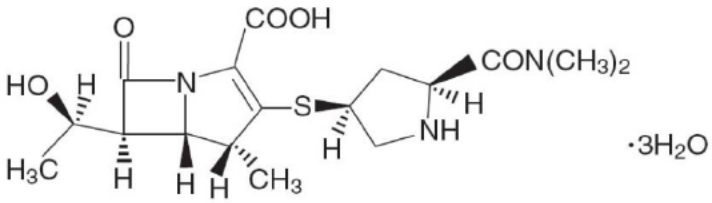
Molecular Formula/Molecular Weight

Meropenem: $C_{17}H_{25}N_3O_5S \cdot 3H_2O$/437.52 grams

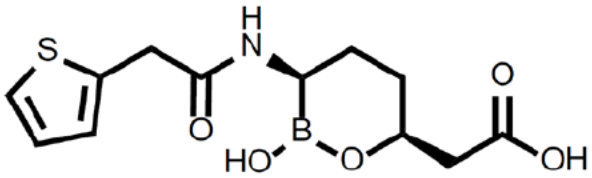
Vaborbactam: $C_{12}H_{16}BNO_5S$/297.14 grams

Structure or Biochemical Description

Meropenem



RPX7009



Pharmacologic Class

Meropenem: Penem Antimicrobial

Vaborbactam: Beta-lactamase Inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND (b) (4)

2.3 Drug Formulation

Table 1: Drug Product Formulation (Sponsor's Table)

Component	Reference to Standard	Function	Labeled Content Per Vial*
Meropenem Trihydrate	USP, Ph.Eur., Sterile	Active Ingredient	1140 mg**
Vaborbactam	In-house, Sterile	Active Ingredient	1000 mg
Sodium Carbonate	NF, Ph.Eur, Sterile	(b) (4)	575 mg
(b) (4)			

Ph. Eur. = European Pharmacopeia; USP = United States Pharmacopeia, NF = National Formulary

* There is a (b) (4)% overfill per vial (b) (4) mg of each meropenem and vaborbactam) to allow for delivery of the labeled content.

** Meropenem drug substance is provided as trihydrate. 1140 mg of meropenem trihydrate is equivalent to 1000 mg of meropenem anhydrous. With (b) (4)% overfill, (b) (4) mg of meropenem anhydrous is equivalent to (b) (4) mg of meropenem trihydrate.

2.4 Comments on Novel Excipients

There are no novel excipients. The (b) (4) excipient, sodium carbonate, has been used in previously approved intravenous products at higher concentrations than the amount (575 mg, 21.2%) included in each vial of the intravenous combination of meropenem

trihydrate and vaborbactam. In a previously approved powder for injection, sodium carbonate has been used in unit amounts up to 63%.

2.5 Comments on Impurities/Degradants of Concern

Vaborbactam (RPX7009) Drug Substance Impurities

The RPX7009 impurities and degradants and their specifications are shown in Table 2. The qualifying studies informing the impurity/degradant specifications are shown in Table 3 and the impurity/degradant NOAELs in each of the qualifying toxicity studies are described below.

Table 2: Release and Retest Specification for (b) (4) Vaborbactam Drug Substance. (Sponsor's Table)

Tests	Method	Acceptance Criteria
Appearance	Visual	White to off-white solid
Identification (IR)[a]	USP <197A>; Ph.Eur.2.2.24	Conforms
Identification[a]	HPLC (UV)	Conforms
Assay	HPLC (UV)	(b) (4) %, w/w
Related Substances (%w/w) (b) (4) Unspecified single impurities (b) (4) Total related substances	HPLC (UV)	NMT (b) (4) % NMT % NMT % NMT % NMT % NMT % NMT % NMT %
Residual Solvent[a] (b) (4)	GC-FID	NMT (b) (4) ppm
Water Content (% w/w)	USP <921>; Ph.Eur.2.5.32 Oven Method	NMT (b) (4)%
Specific Optical Rotation[a] 15 mg/mL in acetonitrile/water:1/4; 25°C	USP<781>; Ph.Eur.2.2.7	(b) (4)
Particle Size Distribution (µm)[a] d10 d90	USP<429>; Ph. Eur. 2.9.38	Report
Bulk Density (g/mL)[a] Untapped Tapped	USP<616>; Ph. Eur. 2.9.34	Report
(b) (4)		
Bacterial Endotoxins (kinetic-chromogenic limulus amoebocyte lysate method)	USP <85>, Ph.Eur.2.6.14 method D	NMT (b) (4) EU/mg

NMT = not more than
[a] Test conducted at release only

Table 3: Specification and Qualified levels of RPX7009 Impurities and Degradants. (Sponsor's Table)

Related Substances	Origin	Specification (%w/w)	Level Qualified (%w/w)	Toxicology Report No.
(b) (4)	Process impurity, degradant	NMT (b) (4)	(b) (4)	(b) (4) 1011-0762
	Degradant	NMT		1013-1352
	Degradant	NMT		1013-1352
	Degradant	NMT		1013-1352
	Process impurity	NMT		n/a
	Process impurity	NMT		(b) (4) 1012-0042
Single unspecified impurities	n/a	NMT 0.05	n/a	n/a

n/a = not applicable

(b) (4) This process impurity is not qualified in a toxicology study. Therefore its specification is limited to the NMT 0.05% which is the limit specified for unidentified single impurities by ICH Q3(R2).

(b) (4) This process impurity in the RPX7009 drug substance appears as a (b) (4)% impurity in the RPX7009 batch # 1207MP702 which was administered intravenously for 28 days to dogs in Study No.: (b) (4) 1012-0042. The RPX7009 high dose (1000 mg/kg/day) was the NOAEL in male and female dogs. The impurity NOAEL is (b) (4) times 1000 mg/kg/day = (b) (4) mg/kg/day which for dogs converts to a human equivalent dose (HED) of (b) (4) mg/kg/day. This value times the average weight of a human (60 kg) results in an impurity HED of (b) (4) mg/day which is (b) (4)% of the RPX7009 therapeutic dose of 6000 mg/day. The Sponsor has identified the qualification level for (b) (4) as (b) (4)% in the RPX7009 drug substance, and the specification level is established at a lower level of not more than (NMT) (b) (4)% of the active RPX7009.

All of the other RPX7009 impurities and degradants shown in Table 2 and Table 3 are qualified as described in the Drug Product Impurities and Degradants section below.

Potential Genotoxic Impurities in RPX7009

The Sponsor states (in section 3.2.S.3.2.4 of the NDA application) that all (b) (4) as well as all organic impurities were subjected to *in silico* assessment of genotoxic potential using two QSAR methodologies, Derek-Nexus and Leadscope. Some impurities tested positive for genotoxicity in the *in silico* assessments and were subsequently tested further in an Ames assay and/or controlled at the maximum acceptable limit (120 mcg/day; (b) (4) ppm of the daily 6 g RPX7009 clinical dose) recommended in the ICH M7 Guidance for drugs dosed for 1 month or less. Significantly, none of the RPX7009 impurities considered to be potentially genotoxic are expected to appear in the final RPX7009 drug substance and each is either purged or controlled an intermediate stage (Table 4).

Table 4: Potentially Genotoxic (b) (4) Impurities in RPX7009. (Sponsor's Table)

Impurity	*In silico* results	Ames results	Control Strategy
(b) (4)	positive	negative	(b) (4)
	positive	Not tested	
	positive	Negative	
	positive	positive	
	positive	Not tested	
	Known to be a probable carcinogen to humans		

Meropenem Drug Substance Impurities and Degradants

The specifications for the meropenem drug substance impurities, (b) (4) also referred to as meropenem Impurity A and B respectively (Table 5), are qualified as described in the Drug Product Impurities and Degradants section.

Residual Solvents

The only residual solvent is (b) (4) in the RPX7009 and meropenem drug substances. In the RPX7009 drug substance, the (b) (4) specification is (b) (4) ppm which is the recommended limit for (b) (4) residual solvents in ICH Q3C Tables and List. In the meropenem drug substance, the (b) (4) specification is lower, (b) (4)% or (b) (4) ppm.

Drug Product Impurities and Degradants

The specifications for the organic impurity/degradants in the meropenem–vaborbactam drug product are shown in Table 5. For each identified impurity, the specifications are below the levels qualified in specific toxicology studies as summarized below.

Table 5: Drug Product Specification and Qualification Level. (Sponsor's Table)

Related Substance (% w/w)	Specification	Qualification Level	Toxicology Study Report
Imp. A Meropenem	NMT (b) (4)	(b) (4) %	(b) (4) 1015-0201
Imp. B Meropenem	NMT	%	
(b) (4)	NMT	%	
	NMT	%	
	NMT	%	(b) (4) 1011-0762
	NMT	%	(b) (4) 1013-1352
	NMT	%	
	NMT	%	
Single, Unspecified Impurities (b) (4)	NMT	NA	NA
Total Impurities	NMT (b) (4) %	NA	NA

Meropenem Impurity A: This impurity appears as an average (b) (4) % impurity in the meropenem high-dose solution prepared from meropenem batch # 33077100704 which was administered intravenously to rats for 28 days in Study No.: (b) (4) 1015-0201. The meropenem high dose (500 mg/kg/day) was the NOAEL in male and female rats. The impurity NOAEL in males is (b) (4) times 500 mg/kg/day = (b) (4) mg/kg/day which for rats converts to a human equivalent dose (HED) of (b) (4) mg/kg/day. This value times the average weight of a human (60 kg) results in an impurity HED of (b) (4) mg/day which is (b) (4) % of the meropenem therapeutic dose of 6000 mg/day. The Sponsor has identified the qualification level for meropenem Impurity A as (b) (4) % and the specification level is established at a lower level of NMT (b) (4) % of the active meropenem.

Meropenem Impurity B: This impurity appears as an average (b) (4) % impurity in the meropenem high-dose solution prepared from meropenem batch # 33077100704 which was administered intravenously to rats for 28 days in Study No.: (b) (4) 1015-0201. The meropenem high dose (500 mg/kg/day) was the NOAEL in male and female rats. The impurity NOAEL in males is (b) (4) times 500 mg/kg/day = (b) (4) mg/kg/day which for rats converts to an HED of (b) (4) mg/kg/day. This value times the average weight of a human (60 kg) results in an impurity HED of (b) (4) mg/day which is (b) (4) % of the meropenem therapeutic dose of 6000 mg/day. The Sponsor has identified the qualification level for meropenem Impurity B as (b) (4) % and the specification level is established at a lower level of NMT (b) (4) % of the active meropenem.

(b) (4) This impurity which occurs (b) (4) appears as an average (b) (4) % impurity in the meropenem high-dose solution prepared from meropenem batch # 33077100704 which was administered intravenously for 28 days to rats in Study No.: (b) (4) 1015-0201. The meropenem high dose (500 mg/kg/day) was the NOAEL. The impurity NOAEL is (b) (4) times 500 mg/kg/day = (b) (4) mg/kg/day which for rats converts to an HED of (b) (4) mg/kg/day. This value times the average weight of a human (60 kg) results in an impurity HED of (b) (4)

mg/day which is (b) (4)% of the meropenem therapeutic dose of 6000 mg/day. The Sponsor has identified the qualification level for (b) (4) as (b) (4)% and the specification level is established at a lower level of NMT (b) (4)% of the active meropenem.

(b) (4) This impurity which occurs when (b) (4) appears as an average (b) (4)% impurity in the meropenem high-dose solution prepared from meropenem batch # 33077100704 which was administered intravenously for 28 days to rats in Study No.: (b) (4) 1015-0201. The meropenem high dose (500 mg/kg/day) was the NOAEL. The impurity NOAEL in males is (b) (4) times 500 mg/kg/day = (b) (4) mg/kg/day which for rats converts to an HED of (b) (4) mg/kg/day. This value times the average weight of a human (60 kg) results in an impurity HED o (b) (4) mg/day which is (b) (4)% of the meropenem therapeutic dose of 6000 mg/day. The Sponsor has identified the qualification level for (b) (4) as (b) (4)% and the specification level is established at a lower level of NMT (b) (4)% of the active meropenem.

(b) (4) This degradation product of RPX7009 appears as a (b) (4)% impurity in the RPX7009 batch # 1306MP701 which was administered intravenously for 28 days to dogs in Study No.: (b) (4) 1013-1352. The RPX7009 high dose (1000 mg/kg/day) was the NOAEL in male and female dogs. The impurity NOAEL in males is (b) (4) times 1000 mg/kg/day = (b) (4)mg/kg/day which for dogs converts to an HED of (b) (4) (b) (4) mg/kg/day. This value times the average weight of a human (60 kg) results in an impurity HED o (b) (4) mg/day which is (b) (4)% of the RPX7009 therapeutic dose of 6000 mg/day. The Sponsor has identified the qualification level for (b) (4) as (b) (4)% in the drug product, and the specification level is established at a lower level of NMT (b) (4)% of the active RPX7009.

(b) (4) This process impurity and degradation product of RPX7009 appears as a (b) (4)% impurity* (RRT (b) (4): see reviewer comment) in the RPX7009 batch # 1107427005-A which was administered intravenously for 14 days to dogs in Study No.: (b) (4) 1011-0762. The RPX7009 high dose (300 mg/kg/day) was the NOAEL in male and female dogs. The impurity NOAEL in males is (b) (4) times 300 mg/kg/day = (b) (4) mg/kg/day which for dogs converts to an HED of (b) (4) mg/kg/day. This value times the average weight of a human (60 kg) results in an impurity HED of (b) (4) mg/day which is (b) (4)% of the RPX7009 therapeutic dose of 6000 mg/day. The Sponsor has identified the qualification level for (b) (4) as (b) (4)% and the specification level is established at a lower level of NMT (b) (4)% of the active RPX7009.

***Reviewer Comment:** In response to an information request, clarification was provided by the Sponsor to confirm that the impurity with the RRT of (b) (4) listed in the Certificate of Analysis for the RPX7009 batch # 1107427005-A is in fact (b) (4)*

(b) (4) This degradation product of RPX7009 appears as a (b) (4)% impurity in the RPX7009 batch # 1306MP701 which was administered intravenously for 28 days to dogs in Study No.: (b) (4) 1013-1352. The RPX7009 high dose (1000 mg/kg/day) was the NOAEL in male and female dogs. The impurity NOAEL in males is (b) (4)

times 1000 mg/kg/day = (b) (4) mg/kg/day which for dogs converts to an HED of (b) (4) mg/kg/day. This value times the average weight of a human (60 kg) results in an impurity HED of (b) (4) mg/day which is (b) (4)% of the RPX7009 therapeutic dose of 6000 mg/day. The Sponsor has identified the qualification level for (b) (4) as (b) (4)% and the specification level is established at a lower level of NMT (b) (4)% of the active RPX7009.

(b) (4): This degradation product of RPX7009 appears as a (b) (4)% impurity in the RPX7009 batch # 1306MP701 which was administered intravenously for 28 days to dogs in Study No.: (b) (4) 1013-1352 (reviewed in Section 6.2). The RPX7009 high dose (1000 mg/kg/day) was the NOAEL in male and female dogs. The impurity NOAEL in males is (b) (4) times 1000 mg/kg/day = (b) (4) mg/kg/day which for dogs converts to an HED of (b) (4) mg/kg/day. This value times the average weight of a human (60 kg) results in an impurity HED of (b) (4) mg/day which is (b) (4) % of the RPX7009 therapeutic dose of 6000 mg/day. The Sponsor has identified the qualification level for (b) (4) as (b) (4)% and the specification level is established at a lower level of NMT (b) (4)% of the active RPX7009.

Elemental Impurities

The elemental impurities present in the meropenem-vaborbactam drug product will be controlled according to the recommendations stipulated in the ICH Q3D Guidance. The list measured elements included those recommended for parental drug products in Table 5.1 of the ICH Q3D Guidance as well as elements added during manufacture of the RPX7009 or meropenem drug substances (Table 6). The acceptance limits (permitted daily exposure, PDE) for each elemental impurity are those recommended in Table A.2.1 for parental drug products in ICH Q3D. The target limits are based on the PDE values and the daily drug product dose which the Sponsor identifies as (b) (4) grams for the total drug product mass per day.

Table 6: Elemental Impurities in the Meropenem-Vaborbactam Drug Product. (Sponsor's Table)

Target Element	Class	Parenteral PDE (µg/day)	Target Limits NMT (µg/g)	Intentionally Added?
(b) (4)				

2.6 Proposed Clinical Population and Dosing Regimen

Clinical Population: The patient population is male and female patients 18 years and older with creatinine clearance (CrCl) ≥ 40 ml/min. In patients with renal impairment the dose is adjusted as shown in the table below.

Table 7: Dosage Instructions for Patients with Renal Impairment. (Sponsor's Table)

(b) (4)

Dosing regimen: TRADENAME is intended to be administered in a dose of 4 grams (meropenem 2 g and vaborbactam 2 g) administered every 8 hours by intravenous infusion over a period of 3 hours.

2.7 Regulatory Background

Meropenem was first approved in 1996 (NDA 50706) as an IV formulation MERREM®. Subsequently meropenem has been approved in multiple generic formulations for IV administration. Vaborbactam (RPX7009) is a new medical entity that was submitted in IND (b) (4) and in the current NDA.

3 Studies Submitted

3.1 Studies Reviewed

Secondary Pharmacology

1. Combination Screen Data Report – Mpex Pharmaceuticals Inc. (Study No.: AA99075).
2. Effect of RPX-7009 on Enzymatic Activity of Mammalian Serine Proteases (Study No.: RPX-13-7009-6)

Safety Pharmacology

1. Effect of Biapenem and MP7009 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells (Study No.: 120116.SFN).
2. PatchXpress hERG Inhibition Assay (Study No.: AB01646).
3. RPX7009: A Neurological Assessment in Male Sprague-Dawley Rats using a Functional Observational Battery following a Single Intravenous Infusion (Study No.: 1011-0771).
4. RPX7009: A Cardiovascular Safety Pharmacology Study using Radiotelemetry in Conscious Male Beagle Dogs following Intravenous Infusion (Study No.: 1011-0792).
5. RPX7009: A Respiratory Safety Pharmacology Study in Conscious Male Sprague-Dawley Rats Following a Single Intravenous Infusion (Study No.: 1011-0781).

Pharmacokinetics

Absorption

1. Pharmacokinetics of RPX7009 Following a Single Intraperitoneal dose in Swiss-Webster mice (Study No.: SR-12-067).
2. Pharmacokinetics of RPX7009 Following a Single Intravenous Infusion in Male Cynomolgus Monkeys (Study No.: SR12-065).
3. Pharmacokinetics of RPX7009 Following a Single Intravenous Infusion in Male Beagle Dogs (Study No.: SR12-066).
4. Pharmacokinetics of Meropenem/RPX7009 Following a Single Intraperitoneal Dose in Neutropenic Swiss-Webster Mice (Study No.: SR13-224).
5. Pharmacokinetics of Meropenem/RPX7009 Alone or in Combination Following a Single Intravenous Infusion Dose in Sprague-Dawley Rats (Study No.: SR13-225).
6. Pharmacokinetics of Meropenem/RPX7009 Alone or in Combination Following Single Intravenous Infusions in Female Beagle Dogs (Study No.: SR13-226).

Distribution

1. Serum Protein Binding of RPX7009 in Human, Rat, Dog, Mouse, and Monkey Serum (Study No.: SR12-105).

2. ^{14}C-RPX7009: A Single Intravenous Infusion Pharmacokinetic, Quantitative Tissue Distribution, Excretion and Mass Balance Radioactivity Study in Sprague-Dawley Rats. ([redacted] (b) (4) Study No.: 1014-0181)

Metabolism

1. *In Vitro* Drug Metabolism Report: Metabolic Stability of RPX7009 in Liver Microsomes from Sprague-Dawley Rat, Beagle Dog, and Human (Study No.: MC12R-0011).
2. *In Vitro* Drug Metabolism Report: Lack of Metabolism of RPX7009 in Rat, Dog, and Human Hepatocytes (Study No.: MC12M-0003).
3. DMPK Report: Determination of the Inhibition Potential (IC_{50}) of RPX7009 with CYP450 Enzymes (Study No.: MC12R-0012).
4. DMPK Report: Determination of the Inhibition Constant (K_i) of RPX7009 with CYP2B6 and CYP2D6 (Study No.: MC12M-0019).
5. *In Vitro* Drug Metabolism Report: Determination of the Potential of RPX7009 to Induce the Expression of CYP1A2, CYP2B6, CYP3A4 using Human Hepatocytes (Study No.: MC12R-0013).

Excretion

1. Pharmacokinetics of RPX7009 Following a Single Intravenous Infusion in Sprague-Dawley Rats (Study Nos.: SR12-064).

General Pharmacology

Repeated-dose Toxicology

1. RPX7009: A 14-day Intravenous Infusion Toxicity Study in Sprague-Dawley Rats (Study No.: 1011-1221).
2. RPX7009: A 14-day Intravenous Infusion Toxicity Study in Beagle Dogs (Study No.: 1011-0762).
3. RPX7009/Meropenem: A 28-Day Intravenous Infusion Toxicity Study With a 28-Day Recovery Period in Sprague-Dawley Rats (Study No.: 1013-1341).
4. RPX7009/Meropenem: A 28-Day Intravenous Infusion Toxicity Study with a 28-Day Recovery Period in Beagle Dogs (Study No.: 1-13-1352).

Genetic Toxicology

1. Bacterial Mutagenicity Test – Ames Assay (Using Five Salmonella Strains) (Study No.: 148782).
2. RPX7009 Ames Test (Study No.: 74455).
3. RPX7009: *In Vitro* Mammalian Chromosome Aberration Test Performed with Human Lymphocytes (Study No.:74458).
4. RPX7009: Mouse Micronucleus Test (Study No.: 74457).

Reproductive and Developmental Toxicology

1. RPX7009: An Intravenous Fertility Study in Male Sprague-Dawley Rats (Study No.; 1014-0941)

2. RPX7009: An Intravenous Fertility Study in Female Sprague-Dawley Rats (Study No.: 1011-1711)
3. RPX7009: An Intravenous Embryo-Fetal Developmental Toxicity Study in New Zealand Rabbits (Study No.: 1011-1744)
4. RPX7009: An Intravenous Embryo-Fetal Developmental Toxicity Study in Sprague-Dawley Rats (Study No.: 1011-1721).
5. RPX7009: A Pre and Post-Natal Intravenous Study in Female Sprague-Dawley Rats (Study No.: 1013-0351).

Special Toxicology

1. Assessment of Phototoxic Potential: UV-VIS Spectra of RPX7009 Drug Product (Study No.: CHEM-14-010)

Juvenile Studies

1. RPX7009/Meropenem: A Single Dose Intravenous Infusion Toxicokinetic Study in Juvenile Sprague-Dawley Rats (Study No.: 2015-0211).
2. RPX7009/Meropenem: A 28-Day Intravenous Infusion Toxicity Study with a 28-Day Recovery Period in Juvenile Sprague-Dawley Rats (Study No.: 1015-0431).

Impurity Toxicity Testing

1. RPX7009/Meropenem: A 28-Day Intravenous Infusion Toxicity Study with Added Impurities ([redacted](b) (4)) and a 28-Day Recovery Period in Sprague-Dawley Rats (Study No.: 1015-0201).

3.2 Studies Not Reviewed

1. Validation of High Performance Liquid Chromatographic Mass Spectrometric Detection Method for the Determination of RPX7009 in Sprague Dawley Rat Plasma (Study No.: 0011-0800).
2. Validation of High Performance Liquid Chromatographic Mass Spectrometric Detection Method for the Determination of RPX7009 in Beagle Dog Plasma (Study No.: 0011-0810).
3. Validation of the Analytical Method for the Determination of RPX7009 in 0.9% Sodium Chloride for Injection USP (Study No.: 0011-1140).
4. Validation of High Performance Liquid Chromatographic Mass Spectrometric Detection Method for the Determination of RPX7009 in New Zealand Rabbit Plasma (Study No.: 0012-0750).
5. Validation of the Analytical Methods for the Determination of RPX7009, Biapenem, and Hydrolyzed Biapenem in 0.9% Sodium Chloride for Injection USP and in HEPES-Buffered Physiological Saline (Study No.: 0012-0050).
6. Validation of High Performance Liquid Chromatographic Mass Spectrometric Detection Method for the Determination of RPX7009 in Beagle Dog Plasma (K_2EDTA) (Study No.: 0012-0060).
7. Validation of the Analytical Method for the Determination of RPX7009, Meropenem, and Hydrolyzed Meropenem in 0.9% Sodium Chloride for Injection USP (Study No.: 0013-0980).

8. Partial Validation of a High Performance Liquid Chromatographic Mass Spectrometric Detection Method for the Determination of RPX7009 in Beagle Dog Plasma (K_2EDTA) (Study No.: 0013-0990).
9. Validation of High Performance Liquid Chromatographic Mass Spectrometric Detection Method for the Determination of Meropenem and Metabolite (Hydrolyzed Meropenem) in Beagle Dog Plasma (K_2EDTA) (Study No.: 0013-1000).
10. Validation of High Performance Liquid Chromatographic Mass Spectrometric Detection Method for the Determination of RPX7009 in Sprague Dawley Rat Plasma (K_2EDTA) (Study No.: 0013-1010).
11. Validation of High Performance Liquid Chromatographic Mass Spectrometric Detection Method for the Determination of Meropenem and Metabolite (Hydrolyzed Meropenem) in Sprague-Dawley Rat Plasma (K_2EDTA) (Study No.: 0013-1020).
12. Validation of the Analytical Method for the Determination of Carbavance (Meropenem and RPX7009), and Detection of Associated Impurities and Degradation Products in Saline (Study No.: 0015-0220).
13. Assessment of RPX2003 and RPX7009 as Potential Inhibitors of Human P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 and BSEP-mediated Transport. (Study No.: OPT-2012-081).
14. Assessment of RPX2003 and RPX7009 as Potential Substrates of Human OAT1, OAT3, and OCT2 Mediated Transport (Study No.: OPT-2012-082).
15. Assessment of RPX7009 as a Substrate of Human P-gp and BCRP mediated Transport (Study No.: OPT-2014-100).
16. RPX7009 and Biapenem: A 28-Day Intravenous Infusion Toxicity Study with a 28-Day Recovery Period in Beagle Dogs (Study No.: 1012-0042).
17. Acute Intravenous Toxicity of a Single Dose of RPX7009 in Swiss-Webster Mice (Study No.: AT10-184).
18. Acute Intravenous Toxicity of a Single Dose of RPX7009 in Sprague-Dawley Rats (Study No.: MTD11-099).
19. RPX7009: a 14-day Intravenous Injection Toxicity Study in Sprague Dawley Rats (Study No.: 1011-0751).
20. 7-Day Repeat Dose Toxicity of RPX7009 in Sprague-Dawley Rats (Study No.: SAT10-219)
21. RPX800007: Bacterial Reverse Mutation Test (Study No.: 41304 MMO).
22. RPX800026: Bacterial Reverse Mutation Test for RPX800026 (Study No.: 42501 MMO).
23. RPX7009 and Biapenem: A 28-Day Intravenous Infusion Toxicity Study with a 28-Day Recovery Period in Beagle Dogs (Study No.: 1012-0042).
24. RPX7009: An Intravenous Range-Finding Embryo-Fetal Developmental Toxicity Study in Sprague-Dawley Rats (Study No.: 2011-1701).
25. RPX7009: An Intravenous Range-Finding Embryo-Fetal Developmental Toxicity Study in New Zealand Rabbits (Study No.: 2011-1734).

3.3 Previous Reviews Referenced

4 Pharmacology

4.1 Primary Pharmacology

The review of primary pharmacology data was performed by the microbiology reviewer, Dr. Kerian Grande Roche.

4.2 Secondary Pharmacology

Study Title: Combination Screen Data Report. (Study No.: 1142702).

Methods
RPX7009 (code name MP 007009-03) was tested in a series of assays for its ability to inhibit or stimulate the activity of different enzymes or radioligand binding to different receptors. The test concentration of RPX7009 was 50 mcM and a total of 171 enzymes and receptors were examined. Significant responses were considered to be ≥ 50% inhibition or stimulation.

Results
RPX7009 did not produce a ≥ 50% inhibition or stimulation of the activity of any of the tested enzymes or radioligand binding to any of the tested receptors.

Study Title: Effect of RPX7009 on Enzymatic Activity of Mammalian Serine Proteases. (Study No.: RPX-13-7009-6)

Methods
RPX7009 was tested at concentrations of 15, 30, 60,125, 250, 500, and 1000 mcM for its ability to inhibit the activity of 11 different mammalian serine proteases (trypsin, chymotrypsin, plasmin, thrombin, elastase, urokinase, tissue plasminogen activator, chymase, dipeptidyl peptidase 7, neutrophil elastase, cathepsin A). Two known inhibitors of serine peptidases, leupeptin and 2-aminoethyl benzenesulfonyl fluoride hydrochloride (AEBSF) were also tested as controls.

Results
RPX7009 at concentrations up to 1000 mcM did not affect the activity of any of the test enzymes. In contrast both of the control inhibitors, leupeptin and AEBSF produced concentration-dependent inhibition of all of the enzymes.

4.3 Safety Pharmacology

According to the product label for Merem IV®, meropenem has been associated with seizures and other CNS disorders (delirium and paresthesias). In a published review of safety results for 6000 patients treated with meropenem (Linden, 2007), the incidence of seizures considered to be related to meropenem treatment was considered to be 0.07%. Meropenem has not been reported to alter other safety pharmacology endpoints, including cardiovascular effects.

Several original safety pharmacology studies were conducted with RPX7009 in support of this NDA application, and the studies are reviewed below.

1. **Effect of Biapenem and MP7009 on Cloned hERG Potassium Channels Expressed in Human Embryonic Kidney Cells** (Study No.: 120116.SFN).

Methods
This GLP-compliant study included a quality assurance statement with the study report. Human HEK293 cells were stably transfected with hERG cDNA, and hERG potassium channel currents were evaluated using patch-clamp techniques when the cells were incubated with vehicle (HEPES-buffered physiological saline, pH 7.4), 10 and 300 mcM concentrations of biapenem, MP7009 (another name for RPX7009), a reference compound (500 nM E-4031), or a positive control compound (60 nM terfenadine). The vehicle control and each concentration of biapenem and RPX7009 were tested in three cells and the positive control was tested in 2 cells. Each recording ended with a final application of a supramaximal concentration of E-4031.

Results
The vehicle control produced a 1.3 ± 1.1% (Mean ± SEM) inhibition of hERG potassium channel currents. Biapenem inhibited hERG current by 1.2 ± 0.5% at a 10 mcM concentration and 0.9 ± 0.3% at a 300 mcM concentration. Thus no significant differences were seen from the vehicle control at either concentration. Similarly MP7009 inhibited hERG potassium currents by 1.7 ± 0.6% at 10 mcM and 1.5 ± 0.9% at 300 mcM, thus producing inhibition similar to the vehicle control. In contrast, 60 nM terfenadine, the positive control agent inhibited hERG potassium current by 79.1 ± 4.4% confirming the sensitivity of the test system to hERG inhibition. These results suggest that high 300 mcM concentrations of both biapenem and MP7009 have little effect on hERG potassium channel currents.

2. **PatchXpress hERG Inhibition Assay** (Study No.: AB01646).

Methods
In this non-GLP study, MP7009 (RPX7009) at concentrations of 1.00, 3.16, 10.00, 31.6, and 100 mcM was tested for inhibition of the hERG potassium channel using a PatchXpress automated electrophysiology instrument in voltage-clamped HEK293 cells stably transfected with the human hERG gene. Three cells were tested for each RPX7009 concentration as well as for a vehicle control preparation and a positive control, 10 mcM cisapride that was tested to confirm the sensitivity of the system.

Results
RPX7009 produced a dose-dependent inhibition of hERG postassium channel currents with a maximal inhibition of approximately 15% at a concentration of 100 mcM compared to the vehicle control (Table 8). The results indicate that RPX7009 IC_{50} for hERG inhibition was greater than 100 mcM. The positive control results were not reported.

Table 8: The Percent Inhibition of hERG Potassium Channels by RPX7009 at Concentrations of ≥ 100 mcM. (Sponsor's Table)

Cone [microM]	N=	%Control					
		Mean	StdDev	SEM	Rep 1	Rep2	Rep3
1.00	3	99.08	1.59	0.92	100.05	97.24	99.94
3.16	3	95.41	2.74	1.58	94.68	93.10	98.43
10.00	3	92.15	0.71	0.41	91.40	92.80	92.27
31.60	3	87.71	3.67	2.12	83.49	90.18	89.44
100.00	3	85.39	3.54	2.04	81.63	88.66	85.89

3. **RPX7009: A Neurological Assessment in Male Sprague-Dawley Rats Using a Functional Observational Battery Following a Single Intravenous Infusion** (Study No.: 1011-0771).

Methods

This GLP-compliant study including a quality assurance statement was initiated on August 17, 2011 by (b) (4). Male Sprague-Dawley rats (10/group) were administered a single 15 minute intravenous infusion of RPX7009 at doses of 0, 100, 300, and 1000 mg/kg. Qualitative and quantitative functional observational battery (FOB) evaluations were performed four times: before dosing, and 5 minutes, 2 hours, and 24 hours after dosing. The FOB included open field, manupulative, physiological, and neuromuscular evaluations.

Results

No animals died prematurely during the study. Based on comparison to predose assessments and control animal assessments, RPX-7009 did not produce any relevant effects on any of the FOB parameters.

4. **RPX7009: A Cardiovascular Safety Pharmacology Study Using Radiotelemetry in Conscious Male Beagle Dogs Following Intravenous Infusion** (Study No.: 1011-0792).

Methods

This GLP-compliant study including a quality assurance statement was initiated on August 31, 2011 by (b) (4). Beagle dogs were administered a single 15 minute intravenous infusion of vehicle (0.9% saline) or RPX7009 in doses of 30, 100, and 300 mg/kg. Four animals were dosed according to a Latin Square design with at least a 3 day washout period between doses. For each animal, electrocardiograms were obtained by telemetry (measurement of PQ, PR, QRS, QT, RR intervals, and calculation of QTcF and QTcV), and heart rate, blood pressure (mean, systolic and diastolic pressure), and body temperature were monitored. Cardiovascular measurements were measured continuously from 60 minutes before dosing, until approximately 24 hours after dosing. Animals were also assessed for mortality and clinical signs.

Results

The results did not indicate any biologically significant treatment- or dose-related effects of RPX7009 on any of the measured cardiovascular parameters.

5. **RPX7009: A Respiratory Safety Pharmacology Study in Conscious Male Sprague-Dawley Rats Following a Single Intravenous Infusion** (Study No.: 1011-0781).

Methods
This GLP-compliant study including a quality assurance statement was initiated on August 22, 2011 by (b) (4). Male Sprague-Dawley rats (8/group) were administered single 15-minute infusions of vehicle (0.9% sodium chloride) or RPX7009 doses of 100, 300, or 1000 mg/kg. Respiratory function was evaluated using whole body plethysmography four times: before dosing for one hour, 5-125 minutes after dosing, and 3.5 to 4.5 and 24-25 hours after dosing. The respiratory parameters, tidal volume, minute volume, and respiratory rate were measured and reported in 5 minute averages. In addition, the animals were assessed for mortality and clinical signs.

Results
No mortality and no RPX7009-related adverse clinical signs occurred in the study. The pre-dose respiratory analysis did not indicate substantial differences between groups. Analysis of post-dose respiratory results indicated that RPX7009 treatment did not affect any of the respiratory parameters compared to baseline or control values.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Analytical Methods
A number of study reports that describe validated HPLC and MS methods for measuring RPX7009 and meropenem and metabolites in plasma from dogs, rabbits, and rats and in dosing solutions were submitted. These studies are not reviewed in this document.

Meropenem

Absorption
The pharmacokinetic parameters for meropenem in association with meropenem–vaborbactam (2 g each) administration in patients are shown below (Table 9). In combination administration studies with RPX-7009 in patients, plasma meropenem AUC exposures generally did not increase with repeated dosing and were similar with and without concomitant RPX7009 administration.

Table 9: Population Pharmacokinetic Parameters [(b) (4)] Mean [(b) (4)] of Meropenem and Vaborbactam Following Administration of TRADENAME (meropenem 2 g and vaborbactam 2 g) by 3-hour Infusion in Patients. (Sponsor's Table from the TRADENAME Draft Label)

Parameter	Meropenem	Vaborbactam
C_{max} (µg/mL)	57.3 (b) (4)	71.3 (b) (4)
AUC_{0-24}, Day 1 (µg•h/mL)	637 (b) (4)	821 (b) (4)
$AUC_{0-24,\ steady-state}$ (µg•h/mL)	650 (b) (4)	835 (b) (4)
CL (L/h)	10.5 (b) (4)	7.95 (b) (4)
[redacted] (b) (4)		
$t_{1/2}$, β (h)	2.30 (b) (4)	2.25 (b) (4)

Distribution

According to the Merrem® product label, the plasma-protein binding of meropenem is approximately 2%. The current TRADEAME product label lists the steady-state volume of distribution for meropenem as 20.2 L which is consistent with distribution beyond the vascular space. Tissue distribution select human tissues is reported on the Merrem® product label and shown below in Table 10.

Table 10: Meropenem Concentrations in Selected Human Tissues (Highest Concentration Reported) (Table from the Merrem® Label)

Tissue	Intravenous. Dose (gram)	Number of Samples	Mean [µg/mL or mcg/(gram)]1	Range [µg/mL or mcg/(gram)]
Endometrium	0.5	7	4.2	1.7–10.2
Myometrium	0.5	15	3.8	0.4–8.1
Ovary	0.5	8	2.8	0.8–4.8
Cervix	0.5	2	7	5.4–8.5
Fallopian tube	0.5	9	1.7	0.3-3.4
Skin	0.5	22	3.3	0.5–12.6
Interstitial fluid[2]	0.5	9	5.5	3.2-8.6
Skin	1	10	5.3	1.3–16.7
Interstitial fluid[2]	1	5	26.3	20.9–37.4
Colon	1	2	2.6	2.5–2.7
Bile	1	7	14.6 (3 hours)	4–25.7
Gall bladder	1	1	—	3.9
Peritoneal fluid	1	9	30.2	7.4–54.6
Lung	1	2	4.8 (2 hours)	1.4–8.2
Bronchial mucosa	1	7	4.5	1.3–11.1
Muscle	1	2	6.1 (2 hours)	5.3–6.9
Fascia	1	9	8.8	1.5–20
Heart valves	1	7	9.7	6.4–12.1
Myocardium	1	10	15.5	5.2–25.5
CSF (inflamed)	20 mg/kg[3] 40 mg/kg[4]	8 5	1.1 (2 hours) 3.3 (3 hours)	0.2-2.8 0.9-6.5
CSF (uninflamed)	1	4	0.2 (2 hours)	0.1–0.3

1. at 1 hour unless otherwise noted
2. obtained from blister fluid
3. in pediatric patients of age 5 months to 8 years
4. in pediatric patients of age 1 month to 15 years

Metabolism
The single metabolite for meropenem, meropenem open lactam, occurs through hydrolysis and is microbiologically inactive.

Excretion
According to the Merrem® product label, approximately 70% of the meropenem dose is excreted unchanged in urine within 12 hours with a further 28% recovered in urine as the open lactam meropenem metabolite.

RPX7009

Multiple new pharmacokinetic studies were conducted for RPX7009 in support of this NDA application and the reports are summarized below.

Absorption

1. **Pharmacokinetics of RPX7009 Following a Single Intraperitoneal Dose in Swiss-Webster Mice** (Study No.: SR-12-067).

Methods
In three pharmacokinetic studies, RPX7009 was administered to Swiss Webster mice in intraperitoneal doses of 5, 15, and 50 mg/kg. Groups of three mice were sacrificed and blood collected at 0.08, 0.16, 0.25, 0.33, 0.5, 0.75, 1.0, 2.0, 3.0, and 4.0 hours after dosing. Plasma concentrations of RPX7009 were measured using a HPLC-MS method.

Results
Plasma C_{max} and AUC values for RPX7009 increased in a roughly dose-linear manner. The estimated half-life of RPX7009 in mice was short, on the order of 10-15 minutes. Plasma clearance remained relatively unchanged for all doses as did the volume of distribution which was large indicating widespread RPX7009 distribution beyond the vascular compartment (Table 11).

Table 11: Plasma Pharmacokinetics of RPX7009 in Mice.

Study No.	Dose (mg/kg)	Cl (L/hr/kg)	AUC (hr x mg/kg)	C_{max} (mg.L)	$t_{1/2}$ (hr)	V_{SS} (L/kg)
PK10-208	5	1.6	3.1	8.3	0.16	0.38
PK10-209	15	1.8	8.3	19.5	0.20	0.50
PK10-210	50	1.6	31.4	67.1	0.25	0.60

2. **Pharmacokinetics of RPX7009 Following a Single Intravenous Infusion in Male Cynomolgus Monkeys** (Study Nos.: SR12-065).

Methods
Male Cynomolgus monkeys (N = 3/dose) received a single intravenous infusion (30 minute infusion) of 2, 6, or 20 mg/kg RPX7009. Blood samples were collected at 0.25, 0.5, 0.58, 0.6, 0.75, 1, 1.5, 2, 3, 4, 6, 8 and 24 hours after the end of infusion. Samples

were processed to serum and stored frozen at -80°C before thawing and analysis. Serum concentrations were estimated based on a RPX7009 standard curve in monkey plasma and HPLC-MS analysis.

Results
Serum C_{max} and AUC values increased in a roughly dose-linear fashion (Table 12). The clearance and steady state volume of distribution (Vss) values remained roughly the same at all three doses. The mean $t_{1/2}$ value for the high-dose group was substantially higher than the mean $t_{1/2}$ for the lower dose groups (approximately 30 minutes for both groups). However, the $t_{1/2}$ variability was also much greater in the high-dose group, and this variability does not allow clear conclusions regarding the effect, if any, of RPX7009 dose on serum $t_{1/2}$. However, the plasma RPX7009 $t_{1/2}$ also increased with dose in a dog pharmacokinetic study (Study No.: 2012-0032) suggesting clearance pathways for RPX7009 may become saturated at sufficiently high doses in some species.

Table 12: RPX7009 Plasma PK Parameters (Mean ± SD) in Cynomolgus Monkeys

Dose	Clearance (L/hr/kg)	AUC (hr x mg/kg)	C_{max} (mg/L)	$T_{1/2}$ (h)	V_{ss} (L/kg)
2	0.51 ± 0.07	3.96 ± 0.51	5.35 ± 0.28	0.57 ± 0.03	0.26 ± 0.01
6	0.50 ± 0.08	12.19 ± 1.89	17.04 ± 1.68	0.55 ± 0.12	0.24 ± 0.01
20	0.48 ± 0.03	41.84 ± 2.53	54.89 ± 3.32	1.89 ± 1.73	0.26 ± 0.03

3. **Pharmacokinetics of RPX7009 Following a Single Intravenous Infusion in Male Beagle Dogs.** (Study No.: SR12-066)

Methods
This non-GLP study was conducted by Rempex Pharmaceuticals in San Diego, California in 2012. Male Beagle dogs (n = 3/dose) received a single intravenous infusion (30 minutes) of 2, 6, or 20 mg/kg RPX7009. Blood samples were collected at 0.25, 0.5, 0.58, 0.6, 0.75, 1, 1.5, 2, 3, 4, 6, 8, and 24 hours after the end of dosing. Blood samples were processed to serum and stored at -80°C until analysis using a HPLC-MS technique.

Results
Serum C_{max} and AUC values increased in a roughly dose-linear manner across the dose range. The steady state volume of distribution (Vss) remained static across the dose range. Serum $t_{1/2}$ was increased for the 20 mg/kg dose suggesting possible saturation of clearance pathways, but the high standard deviation is indicative of variable results among the 3 test animals at this dose (Table 13).

Table 13: RPX7009 Pharmacokinetic Parameters in Beagle Dogs. (Sponsor's Table)

Dose (mg/kg)	PK Parameters				
	Cl (L/hr/kg)	AUC (hr*mg/L)	C_{max} (mg/L)	$T_{1/2}$ (h)	V_{ss} (L/kg)
2	0.33 ± 0.03	6.13 ± 0.65	6.49 ± 0.31	0.66 ± 0.06	0.25 ± 0.02
6	0.33 ± 0.04	18.39 ± 2.36	19.56 ± 1.42	0.71 ± 0.09	0.26 ± 0.01
20	0.27 ± 0.02	73.64 ± 5.38	66.79 ± 6.16	1.53 ± 0.73	0.27 ± 0.03

4. **Pharmacokinetics of Meropenem/RPX7009 Following a Single Intraperitoneal Dose in Neutropenic Swiss-Webster Mice. (**Study No. SR13-224)

Methods

This group of seven related studies (each study employed one dose of meropenem or RPX7009 or of the combination) was conducted by Rempex Pharmaceuticals in San Diego California in 2013. Female Swiss-Webster mice were administered single intraperitoneal doses of 30, 100, and 300 mg/kg meropenem in combination with 50 mg/kg RPX7009 (Table 14). Groups of 3 mice/timepoint were sacrificed at 0.08, 0.25, 0.30, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0, and 24 hours after dosing, and blood samples were collected and processed to plasma. Samples were stored at -80°C until measurement of plasma RPX7009 and meropenem using a HPLC-MS technique.

Table 14: Study Design for Study Report No.: SR13-224. (Sponsor's Table)

Compounds	TimePoints (hr)	Number of Mice per Timepoint	Route of Administration
Meropenem 300 mpk (+ RPX7009 50 mpk)	0.08, 0.25, 0.30, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0,24	3	Intraperitoneal
Meropenem 100 mpk (+ RPX7009 50 mpk)	0.08, 0.25, 0.30, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0,24	3	Intraperitoneal
Meropenem 300 mpk (+ RPX7009 50 mpk)	0.08, 0.25, 0.30, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0,24	3	Intraperitoneal
Meropenem 30 mpk	0.08, 0.25, 0.30, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0,24	3	Intraperitoneal
Meropenem 100 mpk	0.08, 0.25, 0.30, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0,24	3	Intraperitoneal
Meropenem 300 mpk	0.08, 0.25, 0.30, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0,24	3	Intraperitoneal
RPX7009 50 mpk	0.08, 0.25, 0.30, 0.50, 0.75, 1.0, 1.5, 2.0, 3.0, 6.0,24	3	Intraperitoneal

Results

The plasma AUC and clearance (CL) values for RPX7009 did not substantially change when single Intravenous doses of 50 mg/kg RPX7009 were administered with 30, 100, or 300 mg/kg meropenem compared to RPX7009 administered alone (Table 15). Plasma RPX7009 C_{max} values tended to decrease with increasing concomitant doses of meropenem. Plasma $t_{1/2}$ values did not vary substantially or change in a meropenem-dose dependent manner.

Table 15: Plasma Pharmacokinetic Parameters of RPX7009 Alone or in Combination with Three Different Doses of Meropenem in Neutropenic Swiss-Webster Mice. (Sponsor's Table)

Compound	Study Number	Dose (mg/kg)	AUC (hr*mg/l)	CL (l/hr/kg)	Cmax (mg/ml)	T1/2 (hr)
RPX7009(+Meropenem)	PK13-155	50 (+300)	30.15	1.66	44.62	0.05
RPX7009 (+Meropenem)	PK13-139	50 (+100)	27.74	1.80	53.16	0.19
RPX7009 (+Meropenem)	PK13-156	50 (+30)	30.07	1.66	56.26	0.05
RPX7009	PK11-206	50	29.24	1.71	62.45	0.18

Plasma AUC values for meropenem increased in a roughly dose-linear manner with meropenem dose, but did not substantially change when administered with concomitant 50 mg/kg doses of RPX7009 (Table 16). Plasma C_{max} values were also not appreciably influenced by concomitant administration with RPX7009. Plasma $t_{1/2}$ values increased with meropenem dose but were not changed by concomitant administration with RPX7009.

Table 16: Plasma Pharmacokinetic Parameters of Meropenem when Administered Alone or in Combination with 50 mg/kg Meropenem in Neutropenic Swiss-Webster Mice. (Sponsor's Table)

Compound	Study Number	Dose (mg/kg)	AUC (hr*mg/l)	CL (l/hr/kg)	Cmax (mg/ml)	T1/2 (hr)
Meropenem (+ RPX7009)	PK13-155	300 (+50)	130.85	2.29	260.44	0.26
Meropenem	PK13-180	300	153.03	1.96	244.51	0.32
Meropenem (+ RPX7009)	PK13-139	100 (+50)	49.19	2.03	138.00	0.21
Meropenem	PK13-158	100	45.15	2.21	106.00	0.20
Meropenem (+ RPX7009)	PP13-156	30 (+50)	20.00	1.47	63.57	0.04
Meropenem	PK13-157	30	15.97	1.88	52.06	0.03

5. **Pharmacokinetics of Meropenem/RPX7009 Alone or in Combination Following a Single Intravenous Infusion Dose in Sprague-Dawley Rats.** (Study No.: SR13-225)

Methods

This group of seven related studies (each study employed one dose of meropenem or RPX7009 or of the combination) was conducted by Rempex Pharmaceuticals in San Diego California in 2013. Male Sprague-Dawley rats were administered single intravenous infusions over 30 minutes of meropenem (30, 100, 300 mg/kg) alone or in

combination with 300 mg/kg RPX7009. Blood samples were collected from groups of 3 rats per timepoint at 0.5, 1, 1.5, 1.58, 1.67, 1.75, 2, 3, 4, 6, and 24 hours after the end of infusion then processed to plasma. Samples were stored at -80°C until measurement of plasma RPX7009 and meropenem using a HPLC-MS techniques.

Table 17: Study Design for Study Report No.: SR13-225. (Sponsor's Table)

Compounds	Dose (mg/kg)	Plasma Collection Time Points (hr)	Number of Animal per Timepoint	Length of Infusion (hr)	Route of Administration
Meropenem + RPX7009	30 +300	0.5, 1, 1.5, 1.58, 1.67, 1.75, 2, 3, 4, 6, 24	3	1.5	Intravenous Infusion
Meropenem + RPX7009	100 +300				
Meropenem + RPX7009	300 +300				
Meropenem Alone	30, 100, 300				
RPX7009	300				

Results

The plasma AUC values for RPX7009 were slightly increased when single Intravenous doses of 100 mg/kg RPX7009 was administered with 30, 100, or 300 mg/kg meropenem compared to RPX7009 administered alone (Table 18). Plasma RPX7009 C_{max} values tended to increase and plasma clearance (Cl) values tended to decreased with concomitant doses of meropenem, but not in a meropenem dose-dependent manner. Plasma $t_{1/2}$ values also decreased with concomitant meropenem dosing.

Table 18: Plasma Pharmacokinetic Parameters of RPX7009 Alone or in Combination with Three Different Doses of Meropenem in Rats. (Sponsor's Table)

Compound	Study Number	Dose(mg/kg)	AUC (hr*mg/l)	Cl (l/hr/kg)	Cmax (mg/ml)	t1/2 (hr)
RPX7009 (+Meropenem)	PK13-086	300 (+30)	188.9	1.61	328.56	1.49
RPX7009 (+Meropenem)	PK13-087	300 (+100)	202.04	1.5	339.99	1.51
RPX7009 (+Meropenem)	PK13-088	300 (+300)	187.01	1.62	326.66	0.88
RPX7009	PK11-229	300	151.46	2.02	239.11	2.02

Plasma AUC values for meropenem increased in a roughly dose-linear manner with meropenem dose, but did not substantially change when administered with concomitant 50 mg/kg doses of RPX7009 (Table 19). Plasma C_{max} values were also not substantially or consistently influenced by concomitant administration with RPX7009. Neither the meropenem dose nor concomitant administration with RPX7009 consistently altered plasma $t_{1/2}$ values, and clearance (Cl) were similar for all dosing conditions.

Table 19: Plasma Pharmacokinetic Parameters of Three Doses of Meropenem Alone or in Combination with 300 mg/kg of RPX7009 in Rats. (Sponsor's Table)

Compound	Study Number	Dose(mg/kg)	AUC (hr*mg/l)	CL (l/hr/kg)	Cmax (mg/ml)	t1/2 (hr)
Meropenem (+ RPX7009)	PK13-83	30	11.41	2.91	22.71	0.07
Meropenem	PK13-086	30 (+300)	10.30	2.92	20.50	0.06
Meropenem (+ RPX7009)	PK13-84	100	36.02	2.8	71.49	0.07
Meropenem	PK13-087	100 (+300)	31.32	3.25	61.97	0.21
Meropenem (+ RPX7009)	PK13-85	300	79.45	3.8	157.28	0.54
Meropenem	PK13-088	300 (+300)	98.7	3.05	196.14	0.2

6. **Pharmacokinetics of Meropenem and RPX7009 Alone and in Combination Following Single Intravenous Infusions in Female Beagle Dogs.** (Study No.: SR13-226)

Methods

This non-GLP study was conducted in [redacted] (b) (4) in April 2013 by [redacted] (b) (4). Female Beagle dogs (3/group) were administered low and high doses of meropenem and RPX7009 as single agents and in combination (Table 20).

Table 20: Study Design for Study No.: 2013-0972. (Sponsor's Table)

Administration Group	Dose Level (mg/kg)	Dose Conc. (mg/mL)	Infusion Rate (mL/kg/hr)[a]	Number of Females Dogs
1.RPX7009-Low Dose	300	15	40	3
2.RPX7009-High Dose	1000	50		3
3.Meropenem-Low dose	150	7.5		3
4.Meropenem-High Dose	500	25		3
5.RPX7009/Meropenem-Low dose	300/150*	15/7.5*		3
6.RPX7009/ Meropenem -High Dose	1000/500*	50/25*		3

*Dose level for each test item, RPX7009/Meropenem, respectively.

[a] Administered as a 30-minute infusion (dose volume of 20 mL/kg/day)

Results

The plasma C_{max} and AUC values for both meropenem and RPX7009 increased in a roughly dose-proportional manner (Table 21 and Table 22) Pharmacokinetic values were very similar for meropenem, meropenem open-lactam, and RPX7009 in association with the single-agent and combination administrations.

Table 21: Meropenem Pharmacokinetic Parameters Including Meropenem Open-Lactam Plasma AUC Values. (Sponsor's Table)

Parameter	Meropenem 150 mg/kg	Meropenem 150 mg/kg (Plus RPX7009 300 mg/kg)	Meropenem 500 mg/kg	Meropenem 500 mg/kg (Plus RPX7009 1000 mg/kg)
N	3	3	3	3
Half-Life (hr)	0.5±0.1	0.5±0.1	0.6±0.0	0.7±0.0
Cmax (mg/L)	401.0±52.6	421.3±11.8	1456.5±106.7	1296.2±156.8
AUC (0-inf) (hr*mg/L)	443.6±38.1	475.9±34.3	1687.4±93.5	1750.6±140.9
AUC(0-Tlast) (hr*mg/L)	441.3±38.0	472.8±35.9	1685.2±93.0	1746.6±139.6
AUC (0-inf)/Dose	2.96	2.81	3.37	3.50
Clearance (L/hr)	0.3±0.0	0.3±0.0	0.3±0.0	0.3±0.0
Vss (L)	0.3±0.0	0.3±0.0	0.3±0.0	0.3±0.0
Meropenem Open-Lactam AUC(0-Tlast) (hr*mg/L)	44.5±12.1	45.2±3.4	146.4±1.3	194.5±16.4

Table 22: RPX7009 Pharmacokinetic Parameters. (Sponsor's Table)

Parameter	RPX7009 300 mg/kg	RPX7009 300 mg/kg (Plus Meropenem 150 mg/kg)	RPX7009 1000 mg/kg	RPX7009 1000 mg/kg (Plus Meropenem 500 mg/kg)
N	3	3	3	3
Half-Life (hr)	0.7±0.1	0.8±0.1	1.4±0.2	1.0±0.2
Cmax (mg/L)	791.5±198.6	768.7±32.6	2323.8±235.0	2400.9±279.5
AUC (0-inf) (hr*mg/L)	1088.8±293.8	1094.4±72.0	3681.8±335.7	3704.8±320.3
AUC(0-Tlast) (hr*mg/L)	1083.0±290.7	1088.1±69.5	3672.2±334.2	3965.7±328.2
AUC (0-inf)/Dose	3.63	3.65	3.68	3.70
Clearance (L/hr)	0.3±0.1	0.3±0.0	0.3±0.0	0.3±0.0
Vss (L)	0.3±0.1	0.3±0.0	0.4±0.0	0.3±0.0

Distribution

1. **Serum Protein Binding of RPX7009 in Human, Rat, Dog, Mouse, and Monkey Serum** (Study No.: SR12-105).

Methods

Serum protein binding of RPX-7009 in human, rat, dog, mouse, and monkey serum was measured using LC-MS and ultrafiltration methods. RPX7009 concentrations of 1, 5, 15, and 50 mcg/ml were tested in duplicate.

Results
The serum protein-binding results are summarized in Table 23. RPX7009 serum-protein binding varied to an extent between species, but was generally similar at the different RPX7009 concentrations. The greatest percent of RPX7009 protein binding occurred in human serum (29-37%), followed by rat and monkey with the least percent serum protein binding in mice and dogs. In every species, a relatively small percentage of total RPX7009 bound serum proteins suggesting that much of the administered dose of RPX7009 would be expected to remain as free compound in circulation.

Table 23: Serum Protein Binding of RPX7009 in Human, Rat, Mouse, Monkey, and Dog Serum. (Sponsor's Table)

RPX7009 Concentration (ug/mL)	Human Protein Binding (% bound)	Rat Protein Binding (% bound)	Mouse Protein Binding (% bound)	Monkey Protein Binding (% bound)	Dog Protein Binding (% bound)
1	37	27	7	11	8
5	30	10	8	10	3
15	29	12	4	10	0
50	36	17	4	17	13

2. **^{14}C-RPX7009: A Single Intravenous Infusion Pharmacokinetic, Quantitative Tissue Distribution, Excretion and Mass Balance Radioactivity Study in Sprague-Dawley Rats**. ([redacted](b) (4) Study No.: 1014-0181)

Methods
This GLP-compliant study was conducted in Quebec Canada in April 2014. Male and Female Sprague Dawley rats were administered vehicle (0.9% sodium chloride for injection) or 100 mg/kg ^{14}C-RPX7009.

A number of samples including blood and plasma samples, selected tissues, organs, and carcasses were collected for quantitative tissue distribution and pharmacokinetic evaluations. Samples were collected at the following targeted time points: At the end of the infusion period (30 minutes), and at 0.25, 0.5, 1, 1.5, 3.5, 5.5, 11.5, 23.5, 47.5, 71.5, and 95.5 hours following the end of the infusion period. In addition, urine, feces and cage washes were collected. Urine was collected pre-dose (approximately 24 hours prior to dosing), and at 0-8 hours, 8-16 hours, 16-24 hours, 24-48 hours, 48-72 hours, and 72-96 hours post-start of infusion. Feces was collected pre-dose (approximately 24 hours prior to dosing), and at 0-24 hours, 24-48 hours, 48-72 hours, and 72-96 hours post-start of infusion. Cage washes were collected pre-dose and at approximately 48 hours and 96 hours post-start of infusion.

The mean dose received by the treated animals was 96.2 and 98.0 mg equiv/kg for males and females, respectively (targeted dose level was 100 mg/kg and 20 mcCi/animal) and the mean radioactivity level was 20.5 and 19.1 mcCi/animal for males and females. The mean values of the radioactivity content in the pre-dose and post-

dose dosing formulation aliquots were within acceptable ranges (± 15% of targeted dpm counts).

Radioactivity content was determined by liquid scintillation spectrometry and converted to mass mcg equiv/g on the basis of the specific activity (0.6850 and 0.7658 for males and females, respectively) of the ^{14}C-RPX7009 dose formulation. The fraction of total drug-derived radioactivity of the administered dose was also determined in matrices where possible. In blood, plasma, tissues, organs and carcasses, drug-derived radioactivity data (mcg equiv/g) concentration-time data were used to determine the pharmacokinetic parameters. For Group 2 (Mass Balance) animals, the selected intervals and cumulative amount of total drug-derived radioactivity excreted in urines and feces, cage washes and carcasses (sum of all tissues/organs collected) up to 96 hours post-start of infusion were calculated and expressed as percentage of dose.

Results

The highest concentrations of ^{14}C-RPX7009-derived radioactivity in blood and plasma were observed at the end of the infusion period and declined thereafter with measureable quantities generally absent 6 hours after the end of dosing (Table 24 and Table 25). Higher concentrations occurred in plasma relative to blood, and results were similar for both sexes.

Table 24: Radioactivity Pharmacokinetic Parameters in Blood and Plasma in Male Rats. (Sponsor's Table)

Dose Level (mg/kg/day)	Matrix	t½ (hr)	T_{max} (hr)	C_{max} (µg equiv./g)	T_{last} (hr)	$AUC_{(last)}$ (hr*µg equiv./g)	$AUC_{(0\text{-}96h)}$ (hr*µg equiv./g)	$AUC_{(0-\infty)}$ (hr*µg equiv./g)	V_z (g/kg)	Cl (g/hr/kg)	MRT (hr)
100	Blood	1.706	0.500	34.41	6.000	34.13	36.23	35.86	6864.33	2788.93	1.321
	Plasma	NR [b]	0.500	81.74	6.000	62.19	63.09	NR [b]	NR [b]	NR [b]	NR [b]

Table 25: Radioactivity Pharmacokinetic Parameters in Blood and Plasma in Female Rats. (Sponsor's Table)

Dose Level (mg/kg/day)	Matrix	t½ (hr)	T_{max} (hr)	C_{max} (µg equiv./g)	T_{last} (hr)	$AUC_{(last)}$ (hr*µg equiv./g)	$AUC_{(0\text{-}96h)}$ (hr*µg equiv./g)	$AUC_{(0-\infty)}$ (hr*µg equiv./g)	V_z (g/kg)	Cl (g/hr/kg)	MRT (hr)
100	Blood	1.891	0.500	35.92	6.000	33.33	35.49	35.29	7730.92	2833.54	1.438
	Plasma	6.759	0.500	81.68	24.000	58.88	59.54	59.41	16411.29	1683.09	1.437

For both genders, at the end of the infusion period, the radioactivity was widely distributed among tissues, however with low mean drug-derived concentrations (Table 26 and Table 27). The highest mean tissue concentration of radioactivity was found in the kidneys, prostate, urinary bladder, seminal vesicles and liver and the lowest in the spinal cord and brain, consistent with the urinary system being the main route of excretion. For all evaluated tissues, the highest concentrations of radioactivity was measured at the end of the infusion period (0.5 hr) or 15 minutes post-end of infusion with the exception of the stomach contents and the small and large intestines and their contents which were influenced by gastrointestinal transit time. At 12 hours after infusion, measureable quantities of radioactivity were absent in most tissues.

Table 26: Mean Concentration of Radioactivity in Tissues Collected in the First 12 Hours in Male Rats. (Sponsor's Table)

Matrix	(µg equiv/g)															
	Nominal Timepoints post Start of Infusion (hr)															
	0.5		0.75		1		1.5		2		4		6		12	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
Blood	34.41	1.14	29.31	NC	12.34	2.35	4.40	0.43	3.14	0.46	1.22	0.34	0.70	0.14	0.00	0.00
Plasma	81.74	2.74	67.01	NC	23.33	5.18	4.52	0.68	2.20	0.54	0.36	0.05	0.30	0.02	0.00	0.00
Adipose Tissue	8.43	0.87	6.16	NC	3.00	1.00	1.32	0.79	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	12.51	0.43	12.88	NC	5.57	0.98	1.69	0.30	1.07	0.26	0.00	0.00	0.00	0.00	0.00	0.00
Bone	11.17	2.72	8.11	NC	4.71	0.39	2.25	0.22	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Bone Marrow	10.88	0.55	12.71	NC	5.92	0.77	2.53	0.68	2.37	0.50	0.82	0.17	0.54	0.13	0.05	0.08
Brain	1.66	0.19	1.57	NC	0.56	0.51	0.40	0.07	0.27	0.06	0.11	0.03	0.00	0.00	0.00	0.00
Cartilage	26.75	1.42	23.12	NC	12.01	2.92	3.73	0.40	2.38	0.36	0.46	0.04	0.00	NC	0.00	0.00
Carcass	24.77	2.14	19.35	NC	9.68	2.63	4.34	1.62	1.91	0.29	0.73	0.10	0.71	0.23	0.39	0.16
Epididymides	23.97	2.52	22.26	NC	8.19	0.83	3.28	1.74	1.44	0.07	0.00	0.00	0.00	0.00	0.00	0.00
Eyes	9.82	0.64	11.92	NC	7.92	1.84	2.13	0.55	1.54	0.35	0.36	0.03	0.30	0.18	0.00	0.00
Stomach	19.03	1.60	13.93	NC	7.56	2.82	2.05	0.50	1.41	0.37	0.00	0.00	0.00	0.00	0.40	0.69
Stomach Content	0.39	0.67	1.06	NC	3.07	4.49	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.16	2.01
Small Intestines	29.78	4.90	28.70	NC	41.25	15.41	34.08	5.39	19.57	16.09	2.92	0.59	1.96	0.96	0.33	0.57
Small Intestines Content	27.01	1.99	30.14	NC	54.50	20.89	56.18	7.72	45.20	39.25	8.26	2.09	4.38	2.03	1.25	0.55
Large Intestines	14.91	4.35	9.47	NC	5.88	1.95	3.92	3.77	9.07	13.44	13.90	7.81	18.33	9.52	11.56	6.77
Large Intestines Content	1.06	0.34	0.44	NC	0.24	0.41	0.17	0.30	19.77	34.25	57.86	4.68	57.72	11.87	38.67	23.77
Harderian Glands	10.65	1.55	9.25	NC	5.16	1.25	2.57	0.27	2.23	0.34	1.55	0.14	1.36	0.04	0.70	0.64
Heart	15.24	0.34	14.51	NC	5.36	1.03	0.88	0.77	0.57	0.51	0.00	0.00	0.00	0.00	0.00	0.00
Kidneys	391.12	19.87	652.27	NC	164.95	53.49	44.62	29.08	18.24	7.84	3.45	0.33	2.78	0.36	1.56	0.23
Liver	179.94	28.89	176.12	NC	89.04	9.17	19.25	0.61	10.63	3.63	1.12	0.11	0.00	0.00	0.00	0.00
Lungs with bronchi	28.18	2.18	29.69	NC	12.36	2.18	5.22	0.54	3.93	0.32	1.44	0.38	0.84	0.10	0.00	0.00
Lymph Nodes (Mesenteric)	21.02	1.78	15.16	NC	8.23	1.78	3.27	0.69	1.78	0.30	0.80	0.18	0.00	0.00	0.00	0.00
Pancreas	32.11	12.06	18.69	NC	7.39	1.52	4.65	4.26	0.76	0.67	0.00	0.00	0.00	0.00	0.00	0.00
Pituitary	16.36	1.17	13.44	NC	6.54	0.88	2.80	0.60	1.32	1.15	0.00	0.00	0.00	0.00	0.00	0.00
Prostate	281.18	378.25	139.42	NC	33.86	8.16	69.02	103.01	8.03	7.86	1.11	1.14	0.62	1.07	0.00	0.00
Salivary Glands	20.17	2.78	14.98	NC	6.35	1.04	2.16	0.27	1.53	0.17	0.00	0.00	0.00	0.00	0.00	0.00
Seminal Vesicles	198.18	289.33	25.09	NC	9.82	5.45	40.38	62.12	4.81	4.52	0.00	0.00	0.46	0.80	0.00	0.00
Skeletal Muscle	7.62	0.61	7.67	NC	3.86	1.57	0.29	0.51	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Skin	37.58	1.05	35.04	NC	11.77	2.94	3.59	0.94	2.15	NC	0.00	0.00	0.00	0.00	0.00	0.00
Spinal Cord (Cervical)	1.97	0.19	1.57	NC	1.25	0.45	0.37	0.04	0.21	0.03	0.09	0.09	0.00	0.00	0.00	0.00
Spleen	9.04	5.40	10.44	NC	5.56	0.73	3.99	1.19	2.68	0.46	1.23	0.22	0.29	0.51	0.00	0.00
Testes	13.91	1.36	12.85	NC	4.94	1.14	1.43	0.13	0.86	0.11	0.00	0.00	0.00	0.00	0.00	0.00
Thymus	12.25	1.99	12.59	NC	5.56	0.73	1.98	0.11	0.92	0.90	0.00	0.00	0.00	0.00	0.00	0.00
Thyroids with Parathyroids	25.02	1.42	28.98	NC	13.95	6.73	2.64	0.86	2.22	0.91	0.00	0.00	0.00	0.00	0.00	0.00
Urinary Bladder	224.80	188.64	409.87	NC	47.34	31.31	263.51	387.73	22.92	16.50	1.87	0.90	0.96	0.34	0.83	0.33

Table 27: Mean Concentration of Radioactivity in Tissues Collected in the First 12 Hours in Female Rats. (Sponsor's Table)

Matrix	(µg equiv/g) Nominal Timepoints post Start of Infusion (hr)															
	0.5		0.75		1		1.5		2		4		6		12	
	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
Blood	35.92	3.11	22.24	5.03	10.92	2.93	5.62	0.84	3.12	0.23	1.38	0.21	0.72	0.06	0.00	0.00
Plasma	81.68	7.25	47.73	13.19	18.36	5.97	6.01	1.41	1.57	0.06	0.48	0.05	0.31	0.03	0.22	0.04
Adipose Tissue	11.73	0.55	5.73	0.92	4.08	2.73	3.93	5.82	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Adrenals	13.15	1.14	8.40	1.70	4.64	1.36	3.74	2.74	1.03	0.13	0.33	0.01	0.00	0.00	0.00	0.00
Bone	9.19	2.65	6.49	1.39	3.04	0.63	2.34	0.25	0.81	0.72	0.00	0.00	0.00	0.00	0.00	0.00
Bone Marrow	13.78	1.74	8.38	1.34	5.48	1.28	3.94	0.33	2.22	0.08	1.01	0.05	0.40	0.04	0.00	0.00
Brain	1.68	0.20	1.35	0.43	0.48	0.42	0.26	0.45	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Cartilage	23.50	3.97	17.44	4.24	10.35	3.75	6.34	0.11	2.70	0.29	0.77	0.17	0.13	0.22	0.00	0.00
Carcass	25.28	3.70	15.53	1.68	8.21	1.82	5.50	4.25	1.54	0.49	0.98	0.21	0.76	0.39	0.55	0.09
Eyes	13.58	7.01	8.08	2.18	4.88	0.87	3.55	0.85	1.24	0.21	0.40	0.05	0.16	0.02	0.00	0.00
Stomach	22.17	3.84	9.90	1.72	6.36	0.44	3.32	1.59	1.00	0.09	0.26	0.45	0.00	0.00	0.00	0.00
Stomach Content	0.00	0.00	0.00	0.00	2.17	2.85	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Small Intestines	23.38	3.79	34.30	8.28	35.03	12.56	28.01	5.12	29.21	7.84	4.14	3.51	1.05	1.05	0.60	0.52
Small Intestines Content	18.73	2.67	26.19	4.24	52.94	16.42	42.81	9.43	54.28	4.52	10.18	9.74	2.10	1.96	1.00	0.12
Large Intestines	37.67	34.34	9.72	2.10	4.30	1.28	11.68	15.77	1.03	0.13	14.31	6.12	9.63	1.42	4.51	2.30
Large Intestines Content	1.42	1.46	0.00	0.00	0.00	0.00	1.19	2.05	0.00	0.00	30.21	5.31	46.88	1.25	23.76	7.83
Harderian Glands	11.77	1.91	8.09	1.98	3.43	0.86	2.78	0.13	1.63	0.14	1.05	0.16	0.47	0.41	0.25	0.43
Heart	17.03	1.84	9.58	3.09	4.57	1.10	2.06	0.32	0.86	0.06	0.00	0.00	0.00	0.00	0.00	0.00
Kidneys	422.00	118.43	183.32	66.38	89.70	27.24	45.91	20.27	10.05	1.54	3.29	0.60	2.39	0.48	1.67	0.08
Liver	148.71	32.53	92.78	14.41	53.69	16.58	22.76	8.01	5.94	0.45	1.13	0.33	0.00	0.00	0.00	0.00
Lungs with bronchi	29.54	1.94	21.64	3.63	13.08	4.06	7.06	0.67	4.13	0.21	1.71	0.18	0.64	0.55	0.00	0.00
Lymph Nodes (Mesenteric)	28.54	18.82	12.15	2.22	7.59	2.77	3.92	0.92	1.85	0.21	0.95	0.06	0.60	0.10	0.24	0.01
Ovaries	25.65	4.19	21.09	3.92	8.92	3.04	4.02	0.60	1.60	0.08	0.58	0.08	0.26	0.03	0.06	0.11
Pancreas	21.49	1.46	14.03	4.23	5.89	1.67	3.23	1.54	1.02	0.04	0.00	0.00	0.00	0.00	0.00	0.00
Pituitary	23.48	4.17	14.67	3.67	6.23	1.31	4.24	0.22	2.45	0.15	0.00	0.00	0.00	0.00	0.00	0.00
Salivary Glands	20.46	4.36	12.27	1.86	5.95	1.77	2.81	0.45	1.22	0.06	0.00	0.00	0.00	0.00	0.00	0.00
Skeletal Muscle	13.40	8.23	5.32	1.10	3.41	0.87	7.24	8.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
Skin	40.41	5.32	29.16	4.97	13.38	4.73	4.87	1.42	1.62	0.27	0.00	0.00	0.00	0.00	0.00	0.00
Spinal Cord (Cervical)	3.28	1.16	1.67	0.33	0.91	0.45	0.58	0.26	0.22	0.02	0.00	0.00	0.00	0.00	0.00	0.00
Spleen	12.14	0.73	8.51	1.43	5.16	1.50	4.22	0.09	2.80	0.30	1.31	0.05	0.25	0.43	0.00	0.00
Thymus	12.32	0.94	9.05	1.46	5.15	1.29	2.61	0.19	0.99	0.07	0.00	0.00	0.00	0.00	0.00	0.00
Thyroids with Parathyroids	17.33	3.98	10.83	1.71	6.27	1.41	3.67	1.42	1.73	0.45	0.00	0.00	0.00	0.00	0.00	0.00
Urinary Bladder	384.70	218.57	84.98	57.43	47.36	22.04	68.52	101.07	3.53	0.28	1.87	0.90	0.78	0.39	0.33	0.05
Uterus	41.22	14.86	27.63	5.38	16.18	7.74	15.50	18.88	1.87	0.26	0.57	0.50	0.00	0.00	0.00	0.00

The highest percentage of the dose within the available tissues was in the carcass, liver, skin, kidneys, skeletal muscle, and the content of the small and large intestines,ranging from 20% to 4% at approximately T_{max} (Table 28). The percentage of dose recovered in all other tissues and GI tract content accounted for less than 1.2% each.

Table 28: Tissues containing The Highest Percentage of Radioactivity. (Sponsor's Table)

	Males		Females	
Tissues	Maximum %	Minimum %	Maximum %	Minimum %
Carcass	19.7	0.13	20.0	0.14
Liver	8.5	0.00	6.2	0.00
Skin	6.9	0.00	7.4	0.00
Large Intestines Content	6.9	0.02	6.6	0.00
Small Intestines Content	5.9	0.00	6.3	0.00
Kidneys	5.1	0.00	3.6	0.01
Skeletal Muscle	3.55	0.00	6.23	0.00

The majority of the drug-derived radioactivity was excreted in the urine within the first 8 hours post-start of infusion (82% and 72% in males and females, respectively) with a mean total recovery (for both genders) over 96 hours after infusion of 81% in urine, 7% in feces and <1.0% (negligible) in carcasses and cage washes. These results are consistent with the low concentrations of drug-derived radioactivity in tissues and its rapid elimination from the tissues. In addition to excretion in urine, a very small fraction of the received dose excreted by the biliary route with subsequent fecal elimination. Male to female C_{max} and AUC ratios showed no evidence of gender difference in the absorption, distribution, and excretion pattern of ^{14}C-RPX7009.

Metabolism

1. ***In Vitro* Drug Metabolism Report. Metabolic Stability of RPX7009 in Liver Microsomes from Sprague-Dawley Rat, Beagle Dog, and Human** (Study No.: MC12R-0011).

Methods
In this non-GLP study, 1.0 mcM RPX7009 was incubated for 15, 30, and 60 minutes with liver microsomes from Sprague-Dawley rats, Beagle dogs, and humans before termination of the reactions and analysis of metabolites with LC/MS/MS. Two positive control substances, testosterone and desipramine were tested in parallel incubations to confirm the metabolic ability of the microsome preparations.

Results
In incubations with microsomes from all three species, 1 mcM RPX7009 was shown to be very stable and undergo little or no metabolism.

2. ***In Vitro* Drug Metabolism Report. Lack of Metabolism of RPX7009 in Rat, Dog, and Human Hepatocytes** (Study No.: MC12M-0003).

Methods
In this non-GLP study, 10.0 mcM RPX7009 was incubated with rat, dog, and human hepatocytes for 0, 30, 60 and 120 minutes. Incubation samples were analyzed for metabolites with HPLC in conjunction with time-of-flight mass spectrometry. In addition, two positive controls, testosterone and desipramine, were incubated with hepatocytes from all species to confirm metabolic activity.

Results
RPX7009 (10 mcM) appeared to be very stable in incubations with hepatocytes from rat, dog, and humans for up to 120 minutes, and potential metabolites were not detected. In contrast both testosterone and desipramine, the positive control agents, were substantially metabolized in a time-dependent manner.

3. **DMPK Report: Determination of the Inhibition Potential (IC_{50}) of RPX7009 with CYP450 Enzymes** (Study No.: MC12R-0012).

Methods
In this non-GLP study, eight concentrations (0.0457, 0.137, 0.412, 1.23, 3.70, 11.1, 33.3, and 100 mcM) of RPX7009 were incubated with human liver microsomes for 0 and 30 minutes at 37°C before adding industry-accepted, isozyme-specific CYP450 substrates. Seven CYP450 isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4) were monitored for inhibition. In addition, incubation samples were assessed with LC/MS/MS for metabolites. For each assay, control incubations with isozyme specific inhibitory controls were performed. The direct inhibitory effects of RPX7009 were examined in the assays where the CYP450 substrates were added immediately after the start of incubation, and time-dependent inhibitory effects were examined in assays where RPX7009 was incubated with liver microsomes for 30 minutes before adding CYP450 substrates.

Results
As summarized in Table 29, in the direct inhibition assay without pre-incubation of RPX7009 with microsomes, CYP2B6 and CYP2D6 were apparently inhibited by RPX7009 but the other CYP450 isozymes were not, even at the highest RPX7009 concentration (100 mcM). Regarding the CYP2B6 and CYP2D6 inhibition, the Sponsor indicated that the results of a subsequent study (Study No.: MC12M-0019 reviewed below) suggested the apparent inhibition was an artifact specific to the experimental methodology.

In the time-dependent inhibition assay, CYP1A2 and CYPP3A4 were slightly inhibited with IC_{50s} estimated to be > 50 mcM, and the rest of the CYP450 isozymes (excluding purportedly artifactual results for CYP2B6 and CYP2D6) were weakly inhibited by RPX7009 with IC_{50} values ≥ 100 mcM. For all of the CYP450 isozymes, the IC_{50} for RPX7009 inhibition was expected to greatly exceed plasma therapeutic concentrations.

Table 29: Direct and Time-Dependent Inhibition of Specific CYP450 Isozyme Activity by RPX7009. (Based on Information from a Table in the Study Report)

Isozyme	IC_{50} (mcM)			
	Direct Effects (No Pre-Incubation)		Time-Dependent Effects (With Pre-Incubation)	
	RPX2003	Positive Control	RPX2003	Positive Control
CYP1A2	NI	12	>50	0.87
CYP2B6	a	0.042	a	0.022
CYP2C8	NI	12	>100	2.0
CYP2C9	NI	0.72	NI	≈0.02
CYP2C19	NI	11	≈100	6.9
CYP2D6	a	0.097	a	≈0.03
CYP3A4-M	NI	0.12	>50	<0.02
CYP3A4-T	NI	4.3	>50	<0.05

NI = No inhibition was observed
a = probable artifact
M = mibefradil for the positive inhibition control

T = testosterone for the positive inhibition control

4. **DMPK report: Determination of the Inhibition Constant (K_i) of RPX7009 with CYP2B6 and CYP2D6** (Study No.: MC12M-0019).

Methods
The purpose of this non-GLP study was to further clarify the *in vitro* inhibitory potential of RPX7009 for the CYP2B6 and CYP2D6 isozymes. In order to assess the inhibitory constant (K_i) of RPX7009 for CYP2B6, seven RPX7009 concentrations (0, 1.23, 3.70, 11.1, 33.3, 100, and 300 mcM) were incubated with pooled human liver microsomes for 15 minutes at 37°C. Similarly the K_i for inhibition of CYP2D6 was assessed in experiments using six concentrations (0, 3.70, 11.1, 33.3, 100, and 300 mcM) of RPX7009 incubated with pooled human liver microsomes. Control incubations were performed for each assay with appropriate positive inhibitory controls (thioTEPA for CYP2B6 and quinidine for CYP2D6). All assays were conducted with three different concentrations of probe substrates (bupropion for CYP2B6 and dextromethorphan for CYP2D6) at about 1/3, 1, and 3 times the K_m. In addition, an LC/MS/MS analysis of incubation samples was employed to detect any metabolites.

Results
The K_i values for RPX7009 were estimated to be >600 mcM and ≈200 mcM for CYP2B6 and CYP2D6 respectively.

5. ***In Vitro* Drug Metabolism Report: Determination of the Potential of RPX7009 to Induce the Expression of CYP1A2, CYP2B6, and CYP3A4 using Human Hepatocytes** (Study No.: MC12R-0013).

Methods
In this non-GLP study which was performed at (b) (4) beginning on February 20, 2012 and ending on March 13, 2012, plated, cryopreserved human hepatocytes were incubated with 20 mcg/ml, 100 mcg/ml and 1 mg/ml concentrations of RPX7009 for 48 hours. Positive control substances were employed in parallel incubations with the same hepatocytes to establish positive induction responses for each isozyme. Positive control inducers for the specific isozymes were omeprazole, phenobarbital, and rifampin for CYP1A2, CYP2B6, and CYP3A4 respectively. Following the induction exposures of RPX7009 or positive controls, activities for the three CYP isozymes were determined by incubating the cells with specific substrates (phenacetin for CYP1A2, bupropion for CYP2B6 and testosterone for CYP3A4) and measuring the metabolite products (acetaminophen for CYP1A2, hydroxybupropion for CYP2B6 and hydroxytestosterone for CYP3A4).

Results
Activities for CYP1A2, CYP2B6, and CYP3A4 increased 9.45 – 14.2 fold, 5.16 – 11.9 fold, and 6.42 – 33.2 fold relative to vehicle control incubations after exposure to the specific positive-control inducer substances. The highest concentration of RPX7009 (1 mg/ml) induced up to 12.3%, 15.9% and 2.60% of the positive control response for

CYP1A2, CYP2B6, and CYP3A4 respectively (Table 30). Based on the FDA Guidance: "Guidelines for Industry: Drug Interaction Studies-Study Design, Data Analysis and Implications for Dosing and Labeling," enzyme induction ≥ 40% of the positive control response is considered to be significant enzyme induction. Based on this criteria, RPX7009 did not significantly induce CYP1A2, CYP2B6, and CYP3A4 isozymes in human hepatocyte cultures.

Table 30: The Ability of RPX7009 to Acutely Induce CYP1A2, CYP2B6, or CYP3A4 Enzyme Activity in Human Hepatocytes.

Isozyme	Donor	Mean Percent of Positive Control		
		20 mcg/ml	100 mcg/ml	1000 mcg/ml
CYP1A2	LMP	-0.0 %	-0.6 %	6.0 %
	CDP	-0.4 %	1.6 %	6.7 %
	EJW	-2.6 %	-2.5 %	12.3 %
CYP2B6	LMP	2.7 %	2.3 %	15.9 %
	HCl-15	3.9 %	5.4 %	5.0 %
	HCl-18	4.3 %	2.1 %	4.2 %
CYP3A4	LMP	0.0 %	-0.1 %	2.6 %
	HCl-15	2.6 %	2.5 %	-1.9 %
	HCl-18	2.4 %	1.1 %	1.3 %

Reviewer Comment: *While the induction assay described above adequately assesses the acute induction potential of RPX7009 for the specified CYP450 isozymes, it does not address chronic effects. Conceivably, RPX7009 could stimulate a chronic exposure effect, eg increased isozyme activity or protein expression following repeated exposure.*

Excretion

1. **Pharmacokinetics of RPX7009 Following a Single Intravenous Infusion in Sprague-Dawley Rats.** (Study Report No.: SR12-064; Study Nos.: PK10-183 and PK10-218)

Methods

Two non-GLP studies were conducted by Rempex Pharmaceuticals in San Diego California in 2012. In the studies, male Sprague-Dawley rats were place in regular or metabolic cages and administered 20 (Study No.: PK10-183; n = 8) or 50 (Study No.: PK10-218; n =3) mg/kg RPX7009 by intravenous infusion over a period of 30 minutes. Blood samples were collected at multiple time points (0.16, 0.33, 0.5, 0.58, 0.66, 0.75, 1, 2, 3, and 8 hours) after dosing and processed to plasma. In addition, urine and feces were collected on ice from rats administered 50 mg/kg RPX7009 at 0-2, 2-4, 4-6, 6-8, and 8-24 hours after infusion, then stored at -80°C until analysis for RPX7009 content. RPX-7009 concentrations in plasma, urine, and feces were determined using a HPLC-MS technique.

Results

As shown in Table 31, plasma C_{max} and AUC values increased in a roughly dose-dependent manner. In addition, plasma clearance (Cl) remained constant irrespective of dose and the steady-state volume of distribution (VSS) increased with the higher dose.

Table 31: Pharmacokinetics (Mean ± SD) of a Single Infusion of RPX7009 at Doses of 20 and 50 mg/kg in Sprague Dawley Rats.

Dose (mg/kg)	AUC (mg x h/L)	C_{max} (mg/L)	V_{ss} (L/kg)	Cl (L/hr/kg)
20	11.38 ± 0.35	19.25 ± 0.71	0.55 ± 0.03	1.76 ± 0.05
50	29.11 ± 4.69	47.11 ± 6.93	0.81 ± 0.19	1.75 ± 0. 26

Following administration of 50 mg/kg RPX7009, 90% of the dose was recovered unchanged in urine and 6.6% in feces over 24 hours.

5.2 Toxicokinetics

(If not included in toxicity studies)

6 General Toxicology

6.1 Single-Dose Toxicity

The single-dose studies that were submitted included data for only one animal per study. Because of the limited nature of the data, reviews of the studies are not included in this document.

6.2 Repeat-Dose Toxicity

Two repeated-dose toxicology studies for RPX7009, 14-day intravenous dose studies in rats and dogs, were fully reviewed in conjunction with IND (b) (4) Summary findings for these studies are shown below.

1. **Study Title: RPX7009: A 14-Day Intravenous Toxicity Study in Sprague-Dawley Rats.** (Study No.: 1011-1221)

Key Study Findings

Repeated-daily dosing of RPX7009 for 14 days did not appear to cause any toxicity and the NOAEL was considered to be the highest dose, 1000 mg/kg/day.

Methods

In this GLP-compliant study, Male and female Sprague Dawley rats received daily intravenous infusions of vehicle (0.9% sodium chloride) or RPX7009 in doses of 100, 300, or 1000 mg/kg/day for 14 days followed by euthanasia on Day 15 (Table 32). Observations and measurements included: mortality, clinical signs, body weights, food consumption, ophthalmoscopy, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, histopathology, and toxicokinetics.

Table 32: Study Design for Study No.: 1011-1221. (Sponsor's Table)

Treatment Group	Dose Level (mg/kg/day)	Dose Conc. (mg/mL)	Dose Volume (mL/kg)	Infusion Rate (mL/kg/hour)	Number of Animals			
					Main		TK	
					M	F	M	F
1. Control*	0	0	10	40	10	10	3	3
2. RPX7009	100	10			10	10	9	9
3. RPX7009	300	30			10	10	9	9
4. RPX7009	1000	100			10	10	9	9

* Group 1, animals received the control item, saline alone.
M: male; F: female; TK: toxicokinetic

Results

RPX7009-related toxicity was not observed for any of the measurements. The only significant finding that was attributed to RPX7009 administration was increased serum phosphorus (+9-10%) in the mid- and high-dose males. This finding was not considered to be toxicologically relevant because the increased phosphorus levels were still within the range of historical controls, there were no histopathology correlates, and serum phosphorus was not increased in females. The NOAEL value was considered to be the high dose of 1000 mg/kg/day.

The toxicokinetic parameters for both Days 1 and 14 followed similar patterns, and gender differences were not apparent for any parameter (Table 33). On both Days 1 and 14, plasma C_{max} and AUC increased in a roughly dose-proportional fashion. The results indicate that RPX7009 did not accumulate in plasma with repeated dosing. Plasma half-life (ranging from 0.21 to 0.45 hours) and mean residence times (ranging from 0.12 to 0.28 hours) were short suggesting RPX7009 clears rapidly from plasma. Mean clearance on Day 1 decreased with increasing dose, suggesting saturation of excretion pathways with higher doses. Similarly, volume of distribution decreased at higher doses suggesting tissue saturation.

Table 33: Toxicokinetic Parameter Summary for Study No.: 1011-1221.

Parameter	Group 2		Group 3		Group 4	
	Male	Female	Male	Female	Male	Female
Day 1						
C_{max} (mcg/ml)	231	217	735	758	2595	2565
T_{max} (hr)	0.00	0.00	0.00	0.00	0.00	0.00
AUC_{all} (hr x mcg/ml)	64	51	239	219	1037	857
$t_{1/2}$ (h)	0.42	0.33	0.26	0.31	0.40	0.45
Cl (ml/hr/kg)	1596	1974	1262	1382	967	1170
V_z (ml/kg)	966	941	478	625	554	762
MRT (hr)	0.25	0.15	0.21	0.17	0.28	0.26
Day 14						
C_{max} (mcg/ml)	249	217	791	701	2581	2481
T_{max} (hr)	0.00	0.00	0.00	0.00	0.00	0.00
AUC_{all} (hr •	62	57	245	207	1052	899

mcg/ml)						
$t_{1/2}$ (h)	0.25	0.21	0.28	0.25	NR	NR
Cl (ml/hr/kg)	1656	1775	1234	1457	NR	NR
V_z (ml/kg)	608	536	504	522	NR	NR
MRT (hr)	0.14	0.12	0.19	0.14	NR	NR

2. **Study Title: RPX7009: A 14-Day Intravenous Infusion Toxicity Study in Beagle Dogs** (Study No.: 1011-0762)

Key Study Findings

RPX7009 administered daily by intravenous infusion for 14 days to Beagle dogs did not produce notable toxicity. The NOAEL for this study was considered to be the highest dose, 300 mg/kg/day.

Methods

In this GLP-compliant study, Beagle dogs were administered 15-minute infusions of vehicle control (0.9% sodium chloride) or 0, 30, 100, and 300 mg/kg/day RPX7009 for 14 days then euthanized on Day 15 (Table 34). Measurements and observations included: mortality, clinical signs, body weight, food consumption, ophthalmoscopy, ECG, hematology, clinical chemistry, urinalysis, gross pathology, organ weights, histopathology, and toxicokinetics.

Table 34: Study Design for Study No.: 1011-0762. (Sponsor's Table)

Dosing Group	Dose Level (mg/kg/day)	Dose Conc. (mg/mL)	Dose Rate** (mL/kg/hr)	Number of Animals	
				Males	Females
1. Control*	0	0	20	4	4
2. RPX7009	30	6		4	4
3. RPX7009	100	20		4	4
4. RPX7009	300	60		4	4

* Group 1 animals received the control item, saline, alone.
** Dose volume of 5mL/kg, administered over 15 minutes.

Results

RPX7009 did not alter any of the endpoint measurements and no toxicity findings were considered related to RPX7009 administration. The NOAEL value was considered to be the high dose of 300 mg/kg/day.

In toxicokinetic measurements, RPX7009 was not detected in samples from the saline control group. On both collection days, the maximum plasma concentrations occurred at the end of the 15-minute infusion for both genders. Notably the plasma exposure (AUC) did not increase with repeated dosing indicating that RPX7009 did not accumulate in plasma. Consistent with results from single-dose pharmacokinetic studies in dogs and monkeys, the plasma $t_{1/2}$ increased at the high-dose suggesting a dose-dependent saturation of clearance pathways (Table 35).

Table 35: Toxicokinetic Parameter Summary for Days 1 and 14 for Study No.: 1011-0762.

Parameter	Group 2		Group 3		Group 4	
	Male	Female	Male	Female	Male	Female
Day 1						
C_{max} (mcg/ml)	109 ± 9	99 ± 12	353 ± 65	461 ± 40	1286 ± 53	1104 ± 220
T_{max} (hr)	0.00	0.00	0.00	0.00	0.00	0.00
AUC_{all} (hr x mcg/ml)	101 ± 8	94 ± 16	349 ± 23	332 ± 51	1107 ± 194	1060 ± 155
$t_{1/2}$ (h)	0.73 ± 03	0.64 ± 0.03	1.04 ± 0.09	0.73 ± 0.15	1.49 ± 0.33	1.79 ± 0.16
Cl (ml/hr/kg)	304 ± 22	353 ± 35	287 ± 20	310 ± 49	277 ± 46	271 ± 35
V_z (ml/kg)	321 ± 26	326 ± 28	433 ± 65	321 ± 20	591 ± 165	704 ± 151
MRT (hr)	0.84 ± 0.07	0.74 ± 0.03	0.98 ± 0.09	0.76 ± 0.10	0.91 ± 0.12	0.87 ± 0.07
Day 14						
C_{max} (mcg/ml)	93 ± 3	113 ± 18	372 ± 127	425 ± 55	1090 ± 306	1158 ± 363
T_{max} (hr)	0.00	0.00	0.00	0.00	0.00	0.00
AUC_{all} (hr x mcg/ml)	84 ± 6	71 ± 11	293 ± 46	294 ± 45	949 ± 122	922 ± 219
$t_{1/2}$ (h)	0.71 ± 0.04	0.64 ± 0.03	1.07 ± 0.02	0.78 ± 0.14	1.82 ± 0.07	1.57 ± 0.47
Cl (ml/hr/kg)	363 ± 24	434 ± 75	348 ± 56	351 ± 57	319 ± 39	328 ± 91
V_z (ml/kg)	370 ± 22	402 ± 66	541 ± 99	392 ± 54	840 ± 123	703 ± 100
MRT (hr)	0.76 ± 0.04	0.65 ± 0.05	0.83 ± 0.04	0.76 ± 0.06	0.88 ± 0.09	0.80 ± 0.20

Study title: RPX7009/Meropenem: A 28-day Intravenous Infusion Toxicity Study with a 28-day Recovery Period in Sprague Dawley Rats.

Study no.: (b) (4) # 1013-1341
Study report location: Electronic transmission
Conducting laboratory and location: (b) (4)
Date of study initiation: July, 2013
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: RPX7009 (RPX): Lot # 1306MP701, purity of 97.5%.
Meropenem (MP): batch # 3641305001, purity of 80.3%.

Reviewer Comment: *The purity of the batch of meropenem used in this study is lower than optimal.*

Key Study Findings

RPX7009 and meropenem administered alone or in combination by intravenous infusion for 28 days did not produce significant toxicity in rats. Also neither compound substantially affected the pharmacokinetics of the other when administered together.

Both compounds exhibited slightly increased exposure after 28 days of dosing compared to Day 1 values. The NOAEL values for RPX7009 and meropenem were considered to be 1000 mg/kg/day and 300 mg/kg/day respectively.

Methods

Doses:	See Table 36.
Frequency of dosing:	Once daily for 28 consecutive days
Route of administration:	Intravenous via catheter, over 30 minutes
Dose volume:	20 mL/kg/day, infused at 40 mL/kg/hr
Formulation/Vehicle:	0.9% sodium chloride
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	10/sex/dose
Age:	9-10 weeks at study initiation.
Weight:	M: 309-451 g; F: 209-321 g
Satellite groups:	Recovery: 5/sex/dose, TK: 3/sex/dose control, 9/sex/dose drug
Unique study design:	Combination RPX and MP were combined in a single container prior to administration.
Deviation from study protocol:	Multiple protocol deviations were noted. However, none was considered to have altered the results or compromised the integrity of the study.

Table 36: Study Design for Study No.: 1013-1341. (Sponsor's Table)

Administration Group	Dose Level (mg/kg/day)	Dose Conc. (mg/mL)	Infusion Rate (mL/kg/hr)[a]	Number of Animals					
				Main		Rec		TK	
				M	F	M	F	M	F
1.Control/Vehicle #	0	0	40	10	10	5	5	3	3
2.RPX7009-Low Dose	300	15		10	10	5	5	9	9
3.RPX7009-High Dose	1000	50		10	10	5	5	9	9
4.Meropenem-Low dose	100	5		10	10	5	5	9	9
5.Meropenem-High Dose	300	15		10	10	5	5	9	9
6.RPX7009/Meropenem-Low dose	300/100 *	15/5 *		10	10	5	5	9	9
7.RPX7009/ Meropenem - High Dose	1000/300 *	50/ 15 *		10	10	5	5	9	9

#Group 1 animals received the reference item 0.9% sodium chloride for injection, USP (saline) alone.
*Dose level or concentration for each test item, RPX7009/Meropenem, respectively.
[a] Administered as a 30-minute infusion (dose volume of 20 mL/kg/day)
M: Male F: Female Rec: Recovery TK: Toxicokinetic

Observations and Results

Table 37: Schedule of Observations for Study No.: 1013-1341

Observations	Schedule
Mortality	Animals were checked for mortality daily during all phases of the study.
Clinical Signs	Clinical signs were monitored twice daily during all phases of the

<table>
<tr><td></td><td>study. Also detailed clinical signs were performed on surviving animals prior to assignment, during the week prior to initiation of dosing and weekly thereafter.</td></tr>
<tr><td>Body Weights</td><td>Body weights were recorded on all surviving animals prior to group assignment, during the week prior to initiation of dosing, and weekly thereafter including the day before initiation of dosing and the day before necropsy.</td></tr>
<tr><td>Food Consumption</td><td>Individual food consumption was measured on surviving animals once weekly throughout the study starting one week prior to the start of dosing.</td></tr>
<tr><td>Ophthalmology</td><td>Ophthalmology parameters were assessed once in the pre-dose period and once in the last week of dosing</td></tr>
<tr><td>Clinical Pathology</td><td>Blood samples were collected for hematology, coagulation, and clinical chemistry analysis prior to the scheduled necropsy on Day 28. Urine was collected overnight the night before necropsy.</td></tr>
<tr><td>Toxicokinetics</td><td>Blood samples were collected from toxicokinetic animals (3 animals/gender/group/timepoint) on Days 1 and 28 as summarized in the table below.
<table>
<tr><td colspan="2">No. of rats / gender / time point / group</td><td>Pre-dose</td><td colspan="8">Toxicokinetic time points post EOI (end-of-infusion)</td></tr>
<tr><td></td><td></td><td></td><td>0 min*</td><td>15 min</td><td>30 min</td><td>1 h</td><td>1.5 h</td><td>3.5 h</td><td>5.5 h</td><td>11.5 h</td></tr>
<tr><td>Group 1</td><td>3</td><td>√</td><td>√</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="3">Groups 2-7</td><td>3 (Subset 1)</td><td>√</td><td></td><td></td><td>√</td><td></td><td></td><td>√</td><td></td><td></td></tr>
<tr><td>3 (Subset 2)</td><td></td><td>√</td><td></td><td></td><td>√</td><td></td><td></td><td>√</td><td></td></tr>
<tr><td>3 (Subset 3)</td><td></td><td></td><td>√</td><td></td><td></td><td>√</td><td></td><td></td><td>√</td></tr>
</table>
*within 0 and 2 minutes prior to the end of infusion</td></tr>
<tr><td>Necropsy</td><td>Main Study animals were euthanized and necropsied on Day 29 and Recovery animals were euthanized and necropsied on Day 57.</td></tr>
</table>

Mortality and Clinical Signs

One Group 5 female was euthanized on Day 18, and one Group 3 female died while on study. The former was related to a wound at the catheter site, while the latter was possibly associated with atropine administration for the eye exam. There were no other remarkable clinical signs in theses females. Clinical signs in all treated rats did not differ remarkably from the incidence in controls.

Body Weights

There were no statistically significant differences in body weights between groups.

Feed Consumption

There were no remarkable differences in food consumption between groups.

Ophthalmoscopy

A Board-certified veterinary ophthalmologist examined the eyes of all surviving animals including funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations.

There were no treatment-related effects on the eyes.

Hematology and Coagulation

The battery of hematology and coagulation parameters that were evaluated is shown in Table 78.

The percent neutrophils were significantly decreased (decreased approximately 50%) and percent lymphocytes were significantly increased (increased approximately 12%) on Day 29 compared to control values. Also, the absolute number of white blood cells and lymphocytes at the end of the treatment period were non-significantly increased in the Group 7 females (approximately 45% and 60% increased respectively compared to control values).

There were no significant treatment-related differences for any of the hematology parameters at the end of the Recovery period in males. In females, the percent lymphocytes were significantly increased in Groups 4, 5, and 7 and the percent neutrophils were significantly decreased in Groups 5 and 7. Each of the affected groups was treated with meropenem during dosing, suggesting the effects were mediated by meropenem.

There were no changes in coagulation parameters with treatment or after Recovery.

Clinical Chemistry

The serum chemistry parameters that were measured are listed in Table 80.

Total bilirubin was significantly increased in Group 7 females at the end of the Recovery period. There were no other remarkable changes in serum chemistry values for females or males at the end of treatment or recovery.

Urinalysis

The measured urinalysis parameters are listed in Table 79.

There were no treatment-related changes.

Organ Weights

The organs that were weighed are listed in Table 81

No absolute or relative organ weights were altered by treatment in the Main or Recovery Studies.

Gross Pathology

There were no remarkable observations with treatment as compared to controls. The most frequently described changes were at the injection site (beige material around the catheter tip or intima), but there were no discernible dose-dependent patterns. Injection-site material was still noted at the end of the Recovery period.

Histopathology

Adequate Battery: Yes. The panel of tissues and organs that were examined for histopathology are listed in Table 81.

Peer Review: No

Histological Findings
There were a number of observations at the infusion site (vascular intimal proliferation and/or thrombosis and vascular/perivascular inflammation), but these showed no relationship with dose and occurred with about the same incidence and severity in all groups.

The injection-site reactions were still evident in all groups at the end of the Recovery period. There were no other remarkable dose-dependent findings at the end of treatment or at recovery.

In the early-death 1000 mg/kg animal, dark discoloration of the pituitary and thymus were noted. In the 300 mg/kg early-death female, infusion-site beige and red material and enlarged lymph nodes were observed.

Toxicokinetics

The pharmacokinetic parameters for RPX7009 did not differ significantly between genders on Days 1 and 28, or with the addition of meropenem (Table 38). Meropenem plasma pharmacokinetics followed a similar pattern, and RPX7009 did not affect the pharmacokinetics of meropenem (Table 39). Plasma exposures to the inactive metabolite of meropenem, hydrolyzed meropenem, were greater than for meropenem indicating rapid conversion of meropenem to its hydrolyzed form (Table 40). The plasma $t_{1/2}$ values for hydrolyzed meropenem and RPX7009 were short averaging less than half an hour. Plasma C_{max} and AUC values for RPX7009, meropenem, and hydrolyzed meropenem were slightly (0-20%) increased on Day 28 compared to Day 1.

Table 38: Mean RPX7009 Toxicokinetic Parameters in the 28-Day Toxicology Study in Rats, Study No.: 1013-1341. (Sponsor's Table)

		Group 2 (300 mg/kg/day)		Group 3 (1000 mg/kg/day)		Group 6 (300 mg/kg/day)		Group 7 (1000 mg/kg/day)	
	Gender	M	F	M	F	M	F	M	F
	Day 1								
C_{max}	(µg/mL)	478.86	419.08	2026.73	1892.02	464.97	425.23	2087.59	1752.02
C_{last}	(µg/mL)	14.98	4.61	2.37	22.13	6.77	4.29	0.79	1.13
T_{max}	(hr)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
T_{last}	(hr)	2.00	2.00	4.00	2.00	2.00	2.00	4.00	4.00
$AUC_{(last)}$	(hr*µg/mL)	287.48	224.82	1305.92	1059.70	279.30	238.36	1289.56	1063.55
$AUC_{(0-12)}$	(hr*µg/mL)	302.46	229.43	1308.29	1081.83	286.07	242.65	1290.35	1064.67
$AUC_{(0-\infty)}$	(hr*µg/mL)	294.45	226.46	1307.49	1068.71	281.71	239.94	1289.97	1064.15
t½	(hr)	0.32	0.25	0.46	0.28	0.25	0.26	0.36	0.37
V_z	(mL/kg)	473.99	470.48	505.24	380.74	378.26	461.52	400.67	506.05
Cl	(mL/hr/kg)	1018.85	1324.76	764.83	935.71	1064.93	1250.30	775.21	939.72
MRT	(hr)	0.47	0.39	0.48	0.40	0.43	0.40	0.46	0.45

Table 38 continued

		Group 2 (300 mg/kg/day)		Group 3 (1000 mg/kg/day)		Group 6 (300 mg/kg/day)		Group 7 (1000 mg/kg/day)	
	Gender	M	F	M	F	M	F	M	F
	Day 28								
C_{max}	(µg/mL)	554.92	453.28	2374.50	2285.37	461.85	526.00	1872.09	2095.04
C_{last}	(µg/mL)	8.85	2.65	2.49	1.47	7.92	4.39	1.71	0.69
T_{max}	(hr)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
T_{last}	(hr)	2.00	2.00	4.00	4.00	2.00	2.00	4.00	4.00
$AUC_{(last)}$	(hr*µg/mL)	336.61	259.64	1524.16	1228.32	294.33	295.45	1295.14	1195.11
$AUC_{(0-12)}$	(hr*µg/mL)	345.46	262.29	1526.64	1229.79	302.25	299.84	1296.85	1195.80
$AUC_{(0-\infty)}$	(hr*µg/mL)	339.82	260.43	1525.70	NR	297.12	296.91	1296.16	1195.49
t½	(hr)	0.25	0.21	0.43	NR	0.24	0.23	0.41	0.39
V_z	(mL/kg)	320.25	346.28	408.49	NR	356.21	335.39	460.07	465.97
Cl	(mL/hr/kg)	882.83	1151.93	655.43	NR	1009.68	1010.41	771.51	836.48
MRT	(hr)	0.44	0.41	0.49	NR	0.46	0.40	0.50	0.41

Table 39: Mean Toxicokinetic Parameters for Meropenem in the 28-Day Toxicology Study in Rats, Study No.: 1013-1341. (Sponsor's Table)

		Group 4 (100 mg/kg/day)		Group 5 (300 mg/kg/day)		Group 6 (100 mg/kg/day)		Group 7 (300 mg/kg/day)	
	Gender	M	F	M	F	M	F	M	F
	Day 1								
C_{max}	(µg/mL)	44.78	59.42	142.94	166.95	43.97	53.07	158.31	129.57
C_{last}	(µg/mL)	2.88	3.41	0.37	3.84	0.47	1.24	0.35	0.37
T_{max}	(hr)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
T_{last}	(hr)	0.75	0.75	1.50	1.00	1.00	1.00	2.00	2.00
$AUC_{(last)}$	(hr*µg/mL)	17.15	22.71	56.86	65.64	17.25	20.88	62.55	53.46
$AUC_{(0-12)}$	(hr*µg/mL)	17.51 [a]	23.14 [a]	56.95	66.60	17.37	21.19	62.89	53.83
$AUC_{(0-\infty)}$	(hr*µg/mL)	NR	NR	56.95	NR	NR	NR	NR	NR
t½	(hr)	NR	NR	0.16	NR	NR	NR	NR	NR
V_z	(mL/kg)	NR	NR	1243.80	NR	NR	NR	NR	NR
Cl	(mL/hr/kg)	NR	NR	5267.92	NR	NR	NR	NR	NR
MRT	(hr)	NR	NR	0.27	NR	NR	NR	NR	NR
	Day 28								
C_{max}	(µg/mL)	75.51	63.81	201.65	189.73	61.74	58.80	164.26	184.68
C_{last}	(µg/mL)	3.22	0.34	0.75	4.18	0.66	0.36	0.33	2.87
T_{max}	(hr)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
T_{last}	(hr)	0.75	1.00	1.50	1.00	1.00	1.00	1.50	1.00
$AUC_{(last)}$	(hr*µg/mL)	28.72	24.68	79.22	73.72	24.22	22.94	65.37	71.93
$AUC_{(0-12)}$	(hr*µg/mL)	29.12 [a]	24.76	79.41	74.77	24.39	23.03	65.45	72.65
$AUC_{(0-\infty)}$	(hr*µg/mL)	NR	NR	NR [b]	NR	NR	NR	65.44	NR
t½	(hr)	NR	NR	NR [b]	NR	NR	NR	0.15	NR
V_z	(mL/kg)	NR	NR	NR [b]	NR	NR	NR	1004.55	NR
Cl	(mL/hr/kg)	NR	NR	NR [b]	NR	NR	NR	4584.26	NR
MRT	(hr)	NR	NR	NR [b]	NR	NR	NR	0.27	NR

a: Determined with 2 non-zero concentrations only.
b: Not Reported due to Non-qualifying parameter (R^2 adjusted > 0.9000)

Table 40: Mean Toxicokinetic Parameters for Hydrolyzed Meropenem in the 28-Day Toxicology Study in Rats, Study No.: 1013-1341. (Sponsor's Table)

		Group 4 (100 mg/kg/day)		Group 5 (300 mg/kg/day)		Group 6 (100 mg/kg/day)		Group 7 (300 mg/kg/day)	
	Gender	M	F	M	F	M	F	M	F
	Day 1								
C_{max}	(µg/mL)	110.63	94.48	341.49	272.43	113.86	118.49	385.35	277.00
C_{last}	(µg/mL)	0.34	4.63	0.37	0.97	0.71	0.20	0.19	0.18
T_{max}	(hr)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
T_{last}	(hr)	4.00	2.00	6.00	4.00	4.00	4.00	6.00	6.00
$AUC_{(last)}$	(hr*µg/mL)	87.21	63.13	266.39	212.98	99.58	79.44	299.64	217.20
$AUC_{(0-12)}$	(hr*µg/mL)	87.55	67.76	267.48	213.95	100.30	79.64	300.21	217.75
$AUC_{(0-\infty)}$	(hr*µg/mL)	87.43	65.90	NR [b]	213.71	100.18	79.56	299.80	217.37
t½	(hr)	0.45	0.41	NR [b]	0.52	0.58	0.42	0.59	0.67
	Day 28								
C_{max}	(µg/mL)	142.94	128.21	373.84	331.23	155.28	140.36	324.11	350.77
C_{last}	(µg/mL)	6.99	2.52	0.34	0.71	0.19	3.59	0.54	0.55
T_{max}	(hr)	0.50	0.50	0.50	0.50	0.50	0.50	0.50	0.50
T_{last}	(hr)	2.00	2.00	6.00	4.00	4.00	2.00	6.00	4.00
$AUC_{(last)}$	(hr*µg/mL)	103.41	81.75	299.87	230.81	122.47	93.40	290.50	235.20
$AUC_{(0-12)}$	(hr*µg/mL)	110.41	84.27	300.88	231.52	122.65	96.99	292.11	235.75
$AUC_{(0-\infty)}$	(hr*µg/mL)	107.05	82.78	300.21	231.32	122.56	94.93	NR [b]	235.57
t½	(hr)	0.36	0.28	0.71	0.50	0.36	0.30	NR [b]	0.47

b: Not Reported due to Non-qualifying parameter (R^2 adjusted > 0.9000)

Dosing Solution Analysis: All dosing concentrations at Days 0 and 28 were within approximately 6% of the targeted dose.

Study title: RPX7009/meropenem: A 28-day Intravenous Infusion Toxicity Study with a 28-day Recovery Period in Beagle Dogs.

Study no.:	1013-1352
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	July 16, 2013
GLP compliance:	Yes, final submitted 3/28/14
QA statement:	Yes; no significant differences between draft and final noted.
Drug, lot #, and % purity:	RPX7009, lot # 1306MP701, purity of 97.5%; meropenem: batch # 3641305001, purity of 80.3% pure.

Key Study Findings

RPX7009 and meropenem administered alone or in combination by intravenous infusion for 28 days did not produce substantial toxicity in dogs.

- In Main-Study males in all groups scrotal reddening was observed, and severity increased in a meropenem dose-dependent manner. In 2/3 males receiving the high-dose of meropenem, scrotal ulcers were observed. For the high-dose meropenem groups, scrotal reddening persisted in the recovery period.
- WBC and cholesterol were significantly increased in males and females receiving high-dose meropenem alone or in combination with RPX7009. WBC absolute numbers persisted after the recovery period, but serum cholesterol values were similar to control values after the recovery period.
- Injection-site reactions (dark red areas of the subcutis near the injection site) were observed in all groups including vehicle control animals in the Main Study. Injection-site reactions were greatly reduced after the recovery period.
- Neither compound substantially affected the pharmacokinetics of the other when administered together. Both compounds exhibited slightly increased exposure after 28 days of dosing compared to Day 1 values.
- The NOAEL values for RPX7009 and meropenem were considered to be 1000 mg/kg/day and 500 mg/kg/day respectively.

Methods

Doses	See Table 41.
Frequency of dosing:	Daily for 28 consecutive days.
Route of administration:	Intravenous, via saphenous and or cephalic vein using an infusion pump
Dose volume:	20 ml/kg/day at a rate of 40 ml/kg/hr.
Formulation/Vehicle:	0.9% NaCl
Species/Strain:	Beagle dogs
Number/Sex/Group:	3/sex/dose
Age:	6.1 to 6.7 months
Weight:	7.6 to 9.6 kg in males, 6.2 to 8.4 in females
Satellite groups:	Recovery: 2/sex/dose
Unique study design:	Both meropenem and RPX7009 were mixed in the same container prior to administration. Beagle dogs (3/sex/group) were administered daily intravenous doses of meropenem and RPX7009 alone and in combination for 28 days. On Day 29 Main Study animals were euthanized and examined. After a 28-day recovery period, Recovery Study animals were euthanized on Day 56 and examined.
Deviation from study protocol:	Multiple study protocol deviations were noted. However, none was considered to have altered the results or compromised the integrity of the study.

Table 41: Study Design of Study No.: 1013-1352. (Sponsor's Table)

Administration Group	Dose Level (mg/kg/day)	Dose Conc. (mg/mL)	Infusion Rate (mL/kg/hr)[a]	Number of Animals			
				Main		Recovery	
				M	F	M	F
1. Control/Vehicle*	0	0	40	3	3	2	2
2. RPX7009-Low Dose	300	15		3	3	2	2
3. RPX7009-High Dose	1000	50		3	3	2	2
4. Meropenem-Low dose	150	7.5		3	3	2	2
5. Meropenem-High Dose	500	25		3	3	2	2
6. RPX7009/ Meropenem -Low dose	300/150**	15/7.5**		3	3	2	2
7. RPX7009/ Meropenem -High Dose	1000/500**	50/25**		3	3	2	2

*Group 1 animals received the reference item 0.9% sodium chloride for injection, USP (saline) alone.
**Dose level or concentration for each test item, RPX7009/Meropenem, respectively.
M: male; F: female
[a]Administered as a daily 30-minute infusion (dose volume of 20 mL/kg/day)

Observations and Results

Observations	Schedule
Mortality	Animals were checked for mortality daily during all phases of the study.
Clinical Signs	Clinical signs were monitored twice daily during all phses of the study. Also detailed clinical signs were performed on surviving animals prior to assignment, during the week prior to initiation of dosing and weekly thereafter.
Body Weights	Body weights were recorded on all surviving animals prior to group assignment, during the week prior to initiation of dosing, and weekly thereafter including the day before initiation of dosing and the day before necropsy.
Food Consumption	Individual food consumption was measured on surviving animals once daily throughout the study starting one week prior to the start of dosing.
Ophthalmology	Ophthalmology parameters were assessed once in the pre-dose period and once in the last week of dosing
Electrocardiogram (ECG)	ECG measurements were obtained for all animals once during the pre-treatment period, once during the last week of dosing, and once at the end of the Recovery Period.
Clinical Pathology	Blood samples were collected for hematology, coagulation, and clinical chemistry analysis prior to the scheduled necropsy on Day 28. Urine was collected overnight the night before necropsy.
Toxicokinetics	Blood samples were collected from all animals on Days 1 and 28 at the following timepoints: pre-dose, immediately prior to the end of the infusion, and at 5, 15, and 30 minutes and at 1, 1.5, 3.5, 5.5. and 11.5 hours after the end of infusion.
Necropsy	Main Study animals were euthanized and necropsied on Day 29 and Recovery animals were euthanized and necropsied on

	Day 57.

Mortality and Clinical Signs

All dogs survived to scheduled sacrifice. Scrotal skin reddening in males was noted in all dose groups with meropenem dose-dependent increases in severity. In the meropenem high-dose groups, scrotal reddening persisted at the end of the recovery period.

Body Weights

There were no toxicologically relevant changes in body weight with treatment.

Feed Consumption

There were minimal effects on food consumption with dose and gender.

Ophthalmoscopy

There were no significant effects with treatment.

ECG

There were no effects of treatment with meropenem, RPX7009 or the combination on heart rate or QT intervals.

Hematology

The hematology and coagulation parameters that were examined in this study are listed in Table 78.

In general, there were no statistically significant changes in hematologic or coagulation parameters with treatment. Due to inter-animal variability, the WBC increases in males and females in the high-dose meropenem and to a lesser extent the high-dose meropenem and RPX7009 group may not be relevant. In the males treated with high-dose meropenem alone, the WBC number showed a non-statistically significant increase of approximately 40%. This was reflected in increases in neutrophils, lymphocytes, monocytes, and eosinophils. The male high-dose combination group also showed a 15% increase in WBC absolute numbers. Similar results were noted in females. Absolute WBC numbers were still elevated at the end of the recovery period.

Clinical Chemistry

The measured serum chemistry parameters are shown in Table 80.

With the exception of a cholesterol increase of 23% in the high-dose meropenem alone group and a 37% increase in the high-dose combination group in females at the end of dosing, there were no dose-dependent changes with treatment. There were no significant changes at the end of recovery.

Urinalysis

The measured urinalysis parameters are listed in Table 79.

There were no remarkable urinalysis changes with treatment.

Gross Pathology

All dogs, males and females including controls, had dark red areas of the subcutis near the infusion site which did not appear to be more severe with any treatment. One 500 mg/kg meropenem male dog had a bilateral adhesion at the head of the epididymis. Visible skin wounds in the scrotum were observed in 2/3 males receiving 500 mg/kg meropenem and 1/3 males receiving 500 mg/kg meropenem/1000 mg/kg RPX7009. The scrotal ulcers may have been related to administration of high-dose meropenem. One 1000 mg/kg RPX7009 male had several dark red foci at the pyloric junction. In the females, dark areas of the colon, rectum and stomach were observed, although there was generally no relationship to dose or treatment.

Scrotal ulcers did not occur in recovery males receiving high-dose meropenem (either alone or in combination with RPX7009). The injection-site reactions occurring in all Main Study animals were greatly reduced after the recovery period.

Organ Weights

The organs that were weighed for this study are shown in Table 81.

No organ weight changes were observed that were considered related to treatment during the Main Study or during the recovery period.

Histopathology

Adequate Battery: Yes. The battery of tissues and organs examined for histopathology are listed in Table 81.

Peer Review
No

Histological Findings
In Main Study animals, scrotal ulceration (initially identified as gross pathology) was observed in the 2/3 males administered 500 mg/kg/day meropenem and 1/3 males administered 500 mg/kg meropenem/1000 mg/kg RPX7009. In the affected animals, the scrotal ulcers were associated with substantial inflammation that extended into the epididymides with associated secondary hypo/aspermia in the testes and aspermia/oligospermia in the epididymides. However, bilateral epididymidal aspermia/oligospermia was also observed in 1/3 control males. Other findings occurred in all groups in both males and females including infusion-site histopathology (mainly hemorrhage and inflammation), lung inflammation and granulomas, and pituitary cysts.

In the two high-dose recovery males, scrotal ulceration was not observed. Other findings occurred in all groups.

Special Evaluation

None

Toxicokinetics

The pharmacokinetic parameters for RPX7009 did not differ significantly between genders on Days 1 and 28, or with the addition of meropenem (Table 42 and Table 43). Meropenem plasma pharmacokinetics followed a similar pattern, and RPX7009 did not affect the pharmacokinetics of meropenem (Table 44 and Table 45). Plasma C_{max} and AUC values increased in a roughly dose-dependent manner for both compounds. Plasma exposures to the inactive metabolite of meropenem, hydrolyzed meropenem, were much lower than for meropenem indicating much less conversion of meropenem to its hydrolyzed form compared to rats (Table 46 and Table 47). The plasma $t_{1/2}$ values for RPX7009, meropenem, and hydrolyzed meropenem averaged approximately 0.7, 0.6 and 1 hour respectively. Plasma C_{max} and AUV values for RPX7009, meropenem, and hydrolyzed meropenem were similar on Day 28 compared to Day 1.

Table 42: Plasma C_{max} and AUC Values for RPX7009 after 1 Day of Dosing in Dogs. (Sponsor's Table)

Gender	Group Number	Dose Level		C_{max}		$AUC_{(0-12)}$	
		Value (mg/kg/day)	Fold Increase	Value (µg/mL)	Fold Increase	Value (hr*µg/mL)	Fold Increase
M	2	300	1.00	776.79	1.00	954.26	1.00
	3	1000	3.33	2714.50	3.49	3265.47	3.42
		Overall	3.33		3.49		3.42
		DP Factor			1.05		1.03
	6	300	1.00	731.77	1.00	958.20	1.00
	7	1000	3.33	2699.64	3.69	3289.79	3.43
		Overall	3.33		3.69		3.43
		DP Factor			1.11		1.03
F	2	300	1.00	788.64	1.00	946.09	1.00
	3	1000	3.33	2838.68	3.60	3356.88	3.55
		Overall	3.33		3.60		3.55
		DP Factor			1.08		1.06
	6	300	1.00	776.18	1.00	916.78	1.00
	7	1000	3.33	2679.74	3.45	3282.89	3.58
		Overall	3.33		3.45		3.58
		DP Factor			1.04		1.07

Table 43: Plasma C_{max} and AUC Values for RPX7009 after 28 Days of Dosing in Dogs. (Sponsor's Table)

Gender	Group Number	Dose Level		C_{max}		$AUC_{(0-12)}$	
		Value (mg/kg/day)	Fold Increase	Value (µg/mL)	Fold Increase	Value (hr*µg/mL)	Fold Increase
M	2	300	1.00	803.58	1.00	979.60	1.00
	3	1000	3.33	2519.20	3.13	3235.87	3.30
		Overall	3.33		3.13		3.30
		DP Factor			0.94		0.99
	6	300	1.00	748.20	1.00	920.52	1.00
	7	1000	3.33	2386.95	3.19	2964.41	3.22
		Overall	3.33		3.19		3.22
		DP Factor			0.96		0.97
F	2	300	1.00	769.87	1.00	1027.86	1.00
	3	1000	3.33	2550.46	3.31	3212.00	3.12
		Overall	3.33		3.31		3.12
		DP Factor			0.99		0.94
	6	300	1.00	732.96	1.00	883.61	1.00
	7	1000	3.33	2902.63	3.96	3112.23	3.52
		Overall	3.33		3.96		3.52
		DP Factor			1.19		1.06

Table 44: Plasma C_{max} and AUC Values for Meropenem after 1 Day of Dosing in Dogs. (Sponsor's Table)

Gender	Group Number	Dose Level		C_{max}		$AUC_{(0-12)}$	
		Value (mg/kg/day)	Fold Increase	Value (µg/mL)	Fold Increase	Value (hr*µg/mL)	Fold Increase
M	4	150	1.00	355.07	1.00	369.53	1.00
	5	500	3.33	1204.62	3.39	1276.61	3.45
		Overall	3.33		3.39		3.45
		DP Factor			1.02		1.04
	6	150	1.00	382.92	1.00	403.88	1.00
	7	500	3.33	1140.78	2.98	1245.55	3.08
		Overall	3.33		2.98		3.08
		DP Factor			0.89		0.93
F	4	150	1.00	328.42	1.00	326.80	1.00
	5	500	3.33	1177.98	3.59	1211.65	3.71
		Overall	3.33		3.59		3.71
		DP Factor			1.08		1.11
	6	150	1.00	376.21	1.00	365.75	1.00
	7	500	3.33	1204.87	3.20	1276.82	3.49
		Overall	3.33		3.20		3.49
		DP Factor			0.96		1.05

Table 45: Plasma C_{max} and AUC Values for Meropenem after 28 Days of Dosing in Dogs. (Sponsor's Table)

Gender	Group Number	Dose Level		C_{max}		$AUC_{(0-12)}$	
		Value (mg/kg/day)	Fold Increase	Value (µg/mL)	Fold Increase	Value (hr*µg/mL)	Fold Increase
M	4	150	1.00	410.81	1.00	368.29	1.00
	5	500	3.33	1114.12	2.71	1086.33	2.95
		Overall	3.33		2.71		2.95
		DP Factor			0.81		0.88
	6	150	1.00	343.75	1.00	360.72	1.00
	7	500	3.33	1095.29	3.19	1106.45	3.07
		Overall	3.33		3.19		3.07
		DP Factor			0.96		0.92
F	4	150	1.00	346.46	1.00	308.24	1.00
	5	500	3.33	1198.29	3.46	993.98	3.22
		Overall	3.33		3.46		3.22
		DP Factor			1.04		0.97
	6	150	1.00	343.97	1.00	333.99	1.00
	7	500	3.33	1267.93	3.69	1132.32	3.39
		Overall	3.33		3.69		3.39
		DP Factor			1.11		1.02

Table 46: Plasma C_{max} and AUC Values for Hydrolyzed Meropenem after 1 Day of Dosing in Dogs. (Sponsor's Table)

Gender	Group Number	Dose Level		C_{max}		$AUC_{(0-12)}$	
		Value (mg/kg)	Fold Increase	Value (µg/mL)	Fold Increase	Value (hr*µg/mL)	Fold Increase
M	4	150	1.00	12.09	1.00	27.78	1.00
	5	500	3.33	45.02	3.72	97.24	3.50
		Overall	3.33		3.72		3.50
		DP Factor			1.12		1.05
	6	150	1.00	15.64	1.00	33.61	1.00
	7	500	3.33	53.59	3.43	106.43	3.17
		Overall	3.33		3.43		3.17
		DP Factor			1.03		0.95
F	4	150	1.00	13.53	1.00	27.86	1.00
	5	500	3.33	47.93	3.54	102.38	3.67
		Overall	3.33		3.54		3.67
		DP Factor			1.06		1.10
	6	150	1.00	15.73	1.00	31.40	1.00
	7	500	3.33	59.59	3.79	124.72	3.97
		Overall	3.33		3.79		3.97
		DP Factor			1.14		1.19

Table 47: Plasma C_{max} and AUC Values for Hydrolyzed Meropenem after 28 Days of Dosing in Dogs. (Sponsor's Table)

Gender	Group Number	Dose Level		C_{max}		$AUC_{(0-12)}$	
		Value (mg/kg)	Fold Increase	Value (µg/mL)	Fold Increase	Value (hr*µg/mL)	Fold Increase
M	4	150	1.00	13.68	1.00	27.33	1.00
	5	500	3.33	46.93	3.43	90.33	3.31
		Overall	3.33		3.43		3.31
		DP Factor			1.03		0.99
	6	150	1.00	15.69	1.00	31.54	1.00
	7	500	3.33	56.03	3.57	100.79	3.20
		Overall	3.33		3.57		3.20
		DP Factor			1.07		0.96
F	4	150	1.00	14.53	1.00	25.54	1.00
	5	500	3.33	48.04	3.31	83.38	3.26
		Overall	3.33		3.31		3.26
		DP Factor			0.99		0.98
	6	150	1.00	17.12	1.00	30.25	1.00
	7	500	3.33	62.75	3.67	107.89	3.57
		Overall	3.33		3.67		3.57
		DP Factor			1.10		1.07

Dosing Solution Analysis: Meropenem or RPX7009 above the lower limit of quantification was not detected in the control samples. The RPX7009 actual concentrations in all the dosing solutions were within 10% of the nominal concentrations.

Study title: RPX7009/Meropenem: A 28-Day Intravenous Infusion Toxicity Study With Added Impurities ((b) (4) (b) (4) and (b) (4) and a 28-Day Recovery Period in Sprague-Dawley Rats.

Study no.: (b) (4) Study No.: 1015-0201.

Study report location: Electronic transmission

Conducting laboratory and location: (b) (4)

Date of study initiation: April 17, 2015

GLP compliance: No

QA statement: No

Drug, lot #, and % purity: RPX7009, Lot No.: LTRE7A2004, purity of 100.2.
meropenem, Lot No.: 33077100704, purity not reported, potency of 75.9%.
(b) (4) Lot No.: 15-AA2059, purity of 98.66.

[redacted] Lot No.: 15-AA2215, purity of 80.42%.
[redacted] Lot No.: 15-AA2216, purity of 76.03%.

Key Study Findings

RPX7009 and meropenem administered alone or in combination by intravenous infusion for 28 days did not produce significant toxicity in rats. The enriched impurities in dosing solutions ([redacted] and [redacted] did not appear to produce enhanced toxicity, or alter the toxicokinetics of meropenem or RPX7009. The NOAEL values for RPX7009 and meropenem were considered to be 1000 mg/kg/day and 500 mg/kg/day respectively.

Methods

Doses:	See Table 48.
Frequency of dosing:	Once per day
Route of administration:	Intravenous infusion (30 minutes)
Dose volume:	20 ml/kg, 40 ml/kg/hour
Formulation/Vehicle:	0.9% Sodium Chloride for Injection, USP
Species/Strain:	Sprague-Dawley [Crl:CD(SD)IGS] rats
Number/Sex/Group:	Main Study: 10/sex/group
Age:	9-10 weeks at the onset of dosing
Weight:	At the onset of dosing: males: 271-375 g; and females: 212-289 g.
Satellite groups:	Recovery: 5/sex/group; Toxicokinetics: 3/sex/group for vehicle control animals and 9/sex/group for the treatment groups.
Unique study design:	Sprague Dawley rats were administered RPX7009 and meropenem alone and in combination by intravenous infusion for 28 days. In addition, several impurities were enriched in the dosing solutions including: [redacted] (final concentration of [redacted]% of the RPX7009 concentration), [redacted] [redacted]% of the RPX7009 concentration), and [redacted] added at [redacted]% of the RPX7009 concentration).
Deviation from study protocol:	Multiple deviations from the study protocol were noted. However, none was considered to have altered the study results or compromised the study integrity.

Table 48: Study Design for Study No.: 1015-0201. (Sponsor's Table)

Administration Group	Dose Level (mg/kg)	Dose Conc. (mg/mL)[b]	Infusion Rate (mL/kg/hr)[a]	Number of Animals					
				Main		Recovery		TK	
				M	F	M	F	M	F
1.Control [#]	0	0	40	10	10	5	5	3	3
2. RPX7009/Meropenem-Low dose	100/50 *	5/2.5*		10	10	5	5	9	9
3.RPX7009/Meropenem -Mid dose	300/150 *	15/7.5 *		10	10	5	5	9	9
4.RPX7009/ Meropenem -High Dose	1000/500 *	50/ 25 *		10	10	5	5	9	9

#Group 1 animals received the reference item/vehicle 0.9% sodium chloride for injection, USP (saline) alone.
*Dose level or concentration for each test item, RPX7009/Meropenem, respectively.
[a]Administered as a 30-minute infusion (dose volume of 20 mL/kg/day)
[b]The impurities (b) (4) were added at a final concentration of (b) (4)% of the final RPX7009 concentration, the impurity (b) (4) was added at (b) (4)% of the final RPX7009 concentration.
M: Male, F: Female, TK: Toxicokinetic

Observations and Results

Observations	Schedule
Mortality	Animals were checked for mortality daily during all phases of the study.
Clinical Signs	Clinical signs were monitored twice daily during all phses of trhe study. Also detailed clinical signs were performed on surviving animals prior to assignment, during the week prior to initiation of dosing and weekly thereafter.
Body Weights	Body weights were recorded on all surviving animals prior to group assignment, during the week prior to initiation of dosing, and weekly thereafter including the day before initiation of dosing and the day before necropsy. On the day of the scheduled necropsy, a fasted body weight was recorded for calculation of relative organ weight.
Food Consumption	Individual food consumption was measured on surviving animals once weekly throughout the study starting one week prior to the start of dosing.
Ophthalmology	Ophthalmology parameters were assessed once in the pre-dose period and once in the last week of dosing
Clinical Pathology	Blood samples were collected for hematology, coagulation, and clinical chemistry analysis prior to the scheduled necropsy on Day 28. Urine was collected by cystocentesis at necropsy for some animals.
Toxicokinetics	Blood samples were collected from toxicokinetic animals (3 animals/gender/group/timepoint) on Days 1 and 28 as summarized in the table below.

<table>
<tr><td></td><td>
<table>
<tr><th colspan="2" rowspan="2">No. of rats / gender / time point / group</th><th rowspan="2">Pre-dose</th><th colspan="8">Toxicokinetic time points post EOI (end-of-infusion)</th></tr>
<tr><th>0 min*</th><th>15 min</th><th>30 min</th><th>1 h</th><th>1.5 h</th><th>3.5 h</th><th>5.5 h</th><th>11.5 h</th></tr>
<tr><td>Group 1</td><td>3</td><td>√</td><td>√</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="3">Groups 2-7</td><td>3 (Subset 1)</td><td>√</td><td></td><td></td><td>√</td><td></td><td></td><td>√</td><td></td><td></td></tr>
<tr><td>3 (Subset 2)</td><td></td><td>√</td><td></td><td></td><td>√</td><td></td><td></td><td>√</td><td></td></tr>
<tr><td>3 (Subset 3)</td><td></td><td></td><td>√</td><td></td><td></td><td>√</td><td></td><td></td><td>√</td></tr>
</table>
*within 0 and 2 minutes prior to the end of infusion
</td></tr>
<tr><td>Necropsy</td><td>Main Study animals were euthanized and necropsied on Day 29 and Recovery animals were euthanized and necropsied on Day 57.</td></tr>
</table>

Mortality

No animals died during the study

Clinical Signs

There were no treatment-related clinical signs observed during the Main Study or the Recovery Study.

Body Weights

There were no treatment-related changes in body weights relative to control values during the Main or Recovery Studies.

Feed Consumption

Food consumption was similar for all the groups.

Ophthalmoscopy

No ophthalmoscopy-changes related to treatment were noted in the Main Study.

ECG: Not performed

Hematology

The measured hematology and coagulation parameters are listed in Table 78.

Hematology and coagulation parameters were not changed by any of the treatments in the Main study and no differences between control and treatment values were apparent in the Recovery Study.

Clinical Chemistry

The measured serum chemistry parameters are shown in Table 80.

Serum chemistry parameters were generally similar in all the groups in the Main Study and the Recovery Study.

Urinalysis

The measured urinalysis parameters are shown in Table 79.

No variations in urinalysis results were related to treatments

Gross Pathology

No treatment-related gross pathology was noted for Main or Recovery Study animals.

Organ Weights

The list of organs that were weighed is shown in Table 81.

No treatment-related changes in organ weights were observed in Main or Recovery Study animals.

Histopathology

Adequate Battery: Yes. The panel of tissues and organs examined for histopathology are shown in Table 81.

Peer Review

No

Histological Findings

No treatment related histopathology findings were observed. Injection-site reactions including chronic organizing thrombosis and intima proliferation were noted in most treatment groups including controls. The injection-site reactions did not substantially reverse during the recovery period. In the lung, mixed cell infiltrates, hemorrhage, and foreign body granuloma were observed, but the highest incidence was in vehicle control animals in the Main Study, and the histopathology almost entirely reversed during the recovery period.

Special Evaluation

None

Toxicokinetics

Each blood sample was collected by jugular venipuncture then processed to plasma. Plasma RPX7009, meropenem, and hydrolyzed meropenem were measured using validated LC/MS/MS assays.

Neither RPX7009 nor meropenem were detected in plasma samples from control animals except for a very low concentration (2.02 mcg/ml) in one control animal. Plasma AUC values increased in a greater than dose-dependent manner for RPX7009, but values were similar for males and females (Table 49). Also Day 1 and Day 28 values for plasma C_{max} and AUC values were similar for RPX7009 indicating a lack of plasma accumulation with repeated dosing. For both sexes, the volume of distribution (Vz) and

mean residence time (MRT) for RPX7009 were lower following repeated dosing on Day 28 compared to Day 1 (Table 50).The total body clearance (Cl) was generally comparable between both days for the high dose, but with an inverse relationship for dose on Day 28. Plasma $t_{1/2}$ values were highest on Day 1 (approximately 30-60 minutes) then lower on Day 28 (approximately 12–26 minutes), with the greatest $t_{1/2}$ value on Day 28 occurring with the high dose. This pattern is consistent with clearance saturation occurring with the higher RPX7009 doses.

The toxicokinetic parameters for meropenem were similar for both sexes and on both Day 1 and Day 28 indicating an absence of plasma accumulation (Table 51). The apparent terminal elimination phase was determined only for Group 4 males on Day 28, and the plasma Cl, Vz, MRT, and $t_{1/2}$ values in that group were: 3459 ml/hr/kg, 869 ml/kg, 16 minutes, and 10 minutes respectively. Plasma meropenem increased in a roughly dose-proportional manner but plasma concentrations were low on both Days 1 and 28 consistent with rapid metabolism to hydrolyzed meropenem.

Hydrolyzed meropenem formed quickly in plasma with a T_{max} of 30 minutes for all treatment groups (Table 52). The plasma C_{max} and AUC values for hydrolyzed meropenem increased in a roughly dose-proportional manner and was similar on Days 1 and 28 indicating a lack of plasma accumulation. Values were also similar for males and females. The molar ratios of hydrolyzed meropenem to parent meropenem were generally consistent ranging from 3.3 to 5.4. The results are consistent with rapid and extensive metabolism of meropenem to hydrolyzed meropenem.

Table 49: Mean Toxicokinetic Parameters for RPX7009 on Day 1 and Day 28.
(Sponsor's Table)

	RPX7009/Meropenem	Group 2 (100/50 mg/kg)		Group 3 (300/150 mg/kg)		Group 4 (1000/500 mg/kg)	
	Sex	M	F	M	F	M	F
	Day 1						
C_{max}	(µg/mL)	115	104	385	336	1633	1534
T_{max} [a]	(min)	30	30	30	30	30	30
$AUC_{(0-12)}$	(hr*µg/mL)	69	58	243	235	1115	1005
	Day 28						
C_{max}	(µg/mL)	96	130	388	382	1756	1403
T_{max} [a]	(min)	30	30	30	30	30	30
$AUC_{(0-12)}$	(hr*µg/mL)	62	67	247	230	1125	919

a: Relative to the start of the 30 minutes infusion;

Table 50: Clearance (Cl), Retention Time (MRT) and Estimated Half-Life ($t_{1/2}$) Values in Plasma and Volume of Distribution (Vz) for RPX7009 on Days 1 and 28.

Dose Level	Day	Vz (ml/kg)		Cl (ml/hr/kg)		MRT (hr)		$t_{1/2}$ (hr)	
		Male	Female	Male	Female	Male	Female	Male	Female
100	1	NR	NR	NR	NR	NR	NR	NR	NR
300		NR	NR	NR	NR	NR	NR	NR	NR
1000		640	1369	897	968	0.528	0.661	0.494	0.959
100	28	616	431	1640	1491	0.456	0.361	0.260	0.200
300		473	386	1234	1315	0.445	0.422	0.266	0.203
1000		432	607	889	1088	0.500	0.463	0.337	0.386

Table 51: Mean Toxicokinetic Parameters on Day 1 and Day 28 for Meropenem. (Sponsor's Table)

	RPX7009/Meropenem	Group 2 (100/50 mg/kg)		Group 3 (300/150 mg/kg)		Group 4 (1000/500 mg/kg)	
	Sex	M	F	M	F	M	F
	Day 1						
C_{max}	(µg/mL)	24	26	60	57	259	207
T_{max} [a]	(min)	30	30	30	30	30	30
$AUC_{(0-12)}$	(hr*µg/mL)	13	10	32	36	111	113
	Day 28						
C_{max}	(µg/mL)	26	34	84	69	366	194
T_{max} [a]	(min)	30	30	30	30	30	30
$AUC_{(0-12)}$	(hr*µg/mL)	10 [b]	13 [b]	33	28	145	79

a: Relative to the start of the 30 minutes infusion;
b. Information purposes only since determined with less than three non-zero concentrations.

Table 52: Mean Toxicokinetic Parameters on Days 1 and 28 for Hydrolyzed Meropenem. (Sponsor's Table)

	RPX7009/Meropenem	Group 2 (100/50 mg/kg)		Group 3 (300/150 mg/kg)		Group 4 (1000/500 mg/kg)	
	Sex	M	F	M	F	M	F
	Day 1						
C_{max}	(µg/mL)	71	59	204	169	623	555
T_{max} [a]	(min)	30	30	30	30	30	30
$AUC_{(0-12)}$	(hr*µg/mL)	56	46	173	142	527	435
	Day 28						
C_{max}	(µg/mL)	54	62	178	168	552	506
T_{max} [a]	(min)	30	30	30	30	30	30
$AUC_{(0-12)}$	(hr*µg/mL)	56	45	157	121	491	391

a: Relative to the start of the 30 minutes infusion;

Dosing Solution Analysis

The dosing formulations were prepared daily and maintained in refrigerated conditions and protected from light until use. Dosing formulation samples were collected on Days 1 and 28 and examined for actual RPX7009 and meropenem concentrations as well as impurities and degradation products (b) (4) Validated HPLC assays were used for analysis of RPX7009, meropenem, (b) (4) and other impurities and degradants.

The vehicle control solution was shown to not contain RPX7009 or meropenem. All of the analyzed representative samples of the dosing formulations were reported to be within the acceptance criteria of ± 10.0% of the nominal concentrations of RPX7009 and meropenem. The concentrations of impurities and degradation products were similar in the Day 1 (Table 53) and Day 28 (Table 54).

Table 53: Concentration of RPX7009 and Meropenem and the % Area of the Impurities and the Degradation Products in Dosing Formulations on Day 1. (Sponsor Table)

Treatment Group	Dose Conc. (mg/mL)	Collection Date [a]	Estimated Conc. (mg/mL)		% Area (b) (4)
			RPX7009	Meropenem	
1. Control	0	14-May-2015	BLQ	BLQ	
2. RPX7009/ Meropenem	5 2.5		4.64	2.30	
3. RPX7009/ Meropenem	15 7.5		14.58	7.31	
4. RPX7009/ Meropenem	50 25		49.28	23.90	
1. Control	0	15-May-2015	BLQ	BLQ	
2. RPX7009/ Meropenem	5 2.5		4.98	2.51	
3. RPX7009/ Meropenem	15 7.5		14.76	7.45	
4. RPX7009/ Meropenem	50 25		50.06	24.60	

[a] Collected for each Day 1 replicate

*%Area values reported relative to Meropenem peak area.
** %Area values reported relative to RPX7009 peak area.

BLQ: Below Limit of Quantitation
ND: Not Detected

Table 54: Concentration of RPX7009 and Meropenem and the % Area of the Impurities and the Degradation Products in Dosing Formulations on Day 28. (Sponsor Table)

Treatment Group	Dose Conc. (mg/mL)	Collection [a] Date	Estimated Conc. (mg/mL)		% Area
			RPX7009	Meropenem	(b) (4)
1. Control	0	10-Jun-2015	BLQ	BLQ	
2. RPX7009/ Meropenem	5 2.5		4.72	2.52	
3. RPX7009/ Meropenem	15 7.5		14.49	7.72	
4. RPX7009/ Meropenem	50 25		48.50	25.07	
1. Control	0	11-Jun-2015	BLQ	BLQ	
2. RPX7009/ Meropenem	5 2.5		4.85	2.54	
3. RPX7009/ Meropenem	15 7.5		14.25	7.50	
4. RPX7009/ Meropenem	50 25		47.95	25.48	

[a] Collected for each Day 28 replicate

*%Area values reported relative to Meropenem peak area.
** %Area values reported relative to RPX7009 peak area.
BLQ: Below Limit of Quantitation
ND: Not Detected

7 Genetic Toxicology

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

Study title: Bacterial Mutagenicity Test – Ames Assay (Using 5 Salmonella Strains)

Study no.:	148782
Study report location:	Electronic transmission
Conducting laboratory and location:	(b) (4)
Date of study initiation:	Not identified, The study completion date was 2/3/11
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	MP7009 (RPX7009), lot # and purity were not identified.

Key Study Findings

RPX7009 (MP7009) was not mutagenic in Ames assays with 5 *Salmonella typhimurium* test strains with and without S9 activation.

Methods

Strains: *Salmonella typhimurium* strains (TA97a,

	TA98, TA100, TA102, and TA1535)
Concentrations in definitive study:	0.05, 0.159, 0.501, 1.582, and 5 mg/plate
Basis of concentration selection:	Based on cytotoxicity results from a range-finding study
Negative control:	saline
Positive control:	The positive controls were as shown in Table 55.
Formulation/Vehicle:	saline
Incubation & sampling time:	Plates were incubated 48-72 hours at 37°

Table 55: Positive Control Agents for Study No.: 148782 (Sponsor's Table)

CONTROL	STRAIN	METABOLIC ACTIVATION	CONCENTRATION	LOT NUMBER
ICR-191 Acridine	TA97a	No	1.0 µg/plate	TDSG3966
2-nitrofluorene	TA98	No	10.0 µg/plate	TDSG3967
Sodium azide	TA100 and TA1535	No	1.5 µg/plate	TDSG4168
Cumene	TA102	No	200 µg/plate	TDSG3924
2-aminoanthracene	all strains (except TA1535)	Yes	10.0 µg/plate	TDSG3945
2-aminoanthracene	TA1535	Yes	1.6 µg/plate	TDSG3946

Study Validity

The following study validity criteria were met:

1. The negative control reversion rates for each test strain were within acceptable ranges based on laboratory historical data.
2. The appropriate positive control agents produced a 2-fold or greater increase in reversion rates for all test strains.

Results

A positive result for any strain was considered to be at least a 2-fold increase in the number of revertant colonies per plate over the negative-control values. None of the tested RPX7009 concentrations produced a precipitate or altered the bacterial background lawns indicating an absence of cytotoxicity. Also, for all of the test strains with or without S9 activation, none of the tested RPX7009 concentrations produced a 2-fold or greater increase in the number of revertant colonies compared to concurrent negative-control plates. In contrast, all of the positive-control agents produced at least 3-fold increases in the number of revertants compared to negative-control conditions.

Study title: RPX7009: Ames Test

Study no.:	74455
Study report location:	Electronic transmission
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	October 26, 2011
GLP compliance:	Yes
QA statement:	Yes

Drug, lot #, and % purity:	RPX7009, lot # 1108427005B, purity 99.76%.

Key Study Findings

RPX7009 was negative for mutagenicity in an Ames assay.

Methods

Strains:	*Salmonella typhimurium* strains: TA 102, TA 100, TA 98, TA 1537, TA 1535
Concentrations in definitive study:	50, 160, 500, 1600, and 5000 mcg/plate in the presence and absence of S9 mix.
Basis of concentration selection:	The concentrations used in the main study were based on the results of a preliminary toxicity test.
Negative control:	0.9% NaCl
Positive control:	Without S9 activation: Cumene hydroperoxide for TA 102, sodium azide for TA 100 and TA 1535, 2-nitrofluorene for TA 98, and 9-aminoacridine hydrochloride for TA 1537. With S9 activation: 2-aminoanthracene (2-AA) for TA 100, TA 98, TA 1537, TA 1535, and TA 102.
Formulation/Vehicle:	0.9% NaCl
Incubation & sampling time:	For each test, the plates were incubated for three days at 37°C followed by counting of the number of revertant colonies.

Study Validity

The following validation criteria were met:
1. Negative and positive control data were consistent with the historical control data.
2. The positive control data showed marked increases over the concurrent negative control values.
3. The evaluation of the data was not restricted by loss of plates through contamination or otherwise.

Results

Even at the highest concentration, RPX7009 was not toxic to any of the strains of test bacteria. No reductions in the growth of the background lawn or non-revertant bacteria or marked reductions in the number of revertant colonies were observed.

No RPX-7009-related increases in revertant colonies in any of the tester strains with and without S9 activation were considered to be biologically relevant. In contrast, each of the positive control agents produced large increases in the number of revertant colonies.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: RPX7009: In Vitro Mammalian Chromosome Aberration Test Performed With Human Lymphocytes

Study no.:	74458
Study report location:	Electronic transmission
Conducting laboratory and location:	[redacted] (b) (4)
Date of study initiation:	October 25, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MP7009 (same as RPX7009), lot # 1108427005B, purity of 99.76%

Key Study Findings

RPX7009 did not cause chromosomal aberrations when incubated *in vitro* with cultured human lymphocytes.

Methods

Cell Lines:	Primary human lymphocytes obtained from healthy, non-smoking volunteers
Concentrations in definitive study:	First test: 39.1, 78.1, 156, 313, 625, 1250, 2500, and 5000 mcg/ml. First test repeat with S9 activation: 625, 1250, 2500, and 5000 mcg/ml. Second test: 156, 313, 625, 1250, 2500, and 5000 mcg/ml.
Basis of concentration selection:	Used a range of concentrations up to the maximum required concentration.
Negative control:	0.9% NaCl
Positive control:	Daunomycin in the absence of S9 activation, cyclophosphamide in the presence of S9 mix.
Formulation/Vehicle:	0.9% NaCl
Incubation & sampling time:	First test and repeat first test: with and without S9 activation, cultures were incubated for three hours with control or test articles, then rinsed and incubated for a further 15 hours until harvest. Second test: cultures without S9 activation were treated for 18 hours until harvest, and cultures with S9 mix were treated for 3 hours, then rinsed and incubated for a further 15 hours until harvest. For all cultures, demecolcine was added to each culture for the last two hours before

harvest.

Study Validity

The following validation criteria were met for this study.

1. The frequency of cells with structural chromosome aberration in the vehicle controls was consistent with historical data. The frequency was ≤ 5%.
2. The frequency of cells with structural chromosome aberrations in the positive controls was significantly higher than that of the vehicle controls.

Results

Metaphase cells were examined for chromosome or chromatid gaps, breaks, or exchanges. No biologically significant increases in the frequency of metaphases with chromosomal aberrations were observed in cultures treated with RPX7009 in the presence of S9 activation in either the first or second test. A small, significant increase was observed for the lowest concentration of RPX7009 (39.1 mcg/ml) that was selected for metaphase analysis in the absence of S9 activation in the first test, but it was not considered biologically significant because it did not occur at higher RPX7009 doses in both tests, it was not repeatable in the second test, and in the first test, it only occurred in one of the duplicate cultures (8% aberrant metaphases in one culture, but 0% in the other duplicate culture).

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

Study title: RPX7009: Mouse Micronucleus Test

Study no:	74457
Study report location:	Electronic transmission
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 18, 2011
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	MP7009 (same as RPX7009), Lot # 1108427005B, purity of 99.76%

Table 56: Study Design for Study No.: 74457.

Group	Treatment	Animal Number	Euthanasia Time
Group 1	Negative Control: Vehicle	5 males	24 hours
		5 males	48 hours
Group 2	2000 mg/kg RPX7009	5 males	24 hours
Group 3	Positive Control: Cyclophosphamide (20 mg/kg)	5 males	24 hours

Key Study Findings

RPX7009 did not demonstrate any genotoxic activity in a mouse micronucleus test.

Methods

Doses in definitive study:	2000 mg/kg
Frequency of dosing:	Single dose
Route of administration:	Intravenous infusion
Dose volume:	20 ml/kg
Formulation/Vehicle:	0.9% NaCl
Species/Strain:	BomTac:NMRI mice
Number/Sex/Group:	5 males per time point/group
Satellite groups:	none
Basis of dose selection:	The single dose for the Main Study was chosen based on the results of a preliminary toxicology study.
Negative control:	0.9% NaCl
Positive control:	20 mg/kg cyclophosphamide

Study Validity

The following study validation criteria were met:

1. The frequencies of micronucleated polychromatic erythrocytres for the negative control and positive control mice were within acceptable ranges and compatible with historical control data.
2. The increases in the positive control values over the negative control values were large and significant, demonstrating the sensitivity of the assay.

Results

No significant effect on the frequency of polychromatic erythrocytes (PCE) was observed for the RPX7009 treatment or positive control group compared to the negative control group. No biologically or significant increases in the frequency of micronucleated PCE were seen in the group of mice treated with RPX7009 compared to the vehicle control group.

7.4 Other Genetic Toxicity Studies

None

8 Carcinogenicity

No carcinogenicity studies were included with the NDA 209766 application.

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: RPX7009: An Intravenous Fertility Study in Male Sprague-Dawley Rats

Study no.:	(b) (4) # 1014-0941
Study report location:	Electronic transmission
Conducting laboratory and location:	(b) (4)

	(b) (4)
Date of study initiation:	May 26, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPX7009, Batch # 1311MP702, purity of 100.2 %.

Key Study Findings

Intravenous administration of RPX7009 to male rats before and during mating did not significantly alter fertility parameters, reproductive organ weights, or sperm counts, motility, and morphology.

Methods

Doses:	0, 100, 300, and 1000 mg/kg/day
Frequency of dosing:	Once per day
Dose volume:	10 ml/kg
Route of administration:	Intravenous infusion at a rate of 40 ml/kg/hour
Formulation/Vehicle:	0.9% Sodium Chloride for Injection
Species/Strain:	Sprague-Dawley rats
Number/Sex/Group:	25 males per group (25 females per group were not dosed)
Satellite groups:	None
Study design:	Male Sprague-Dawley rats were administered single daily doses of RPX7009 (100, 300, 1000 mg/kg/day) or vehicle (0.9% sodium chloride for injection) for 28 days prior to mating, and during 14 days mating until the day prior to necropsy (total of 42 days).
Deviation from study protocol:	Multiple protocol deviations were noted. However, none of the deviations was considered to have altered the results or compromised the integrity of the study.

Observations and Results

Mortality

No RPX7009-related mortalities were observed during the study. One vehicle control animal died on Study Day 71.

Clinical Signs

No RPX7009-related clinical signs were observed.

Body Weight

No RPX7009-related adverse effects on body weight were observed.

Feed Consumption

No RPX7009-related adverse effects on feed consumption were observed.

Toxicokinetics: Not performed

Dosing Solution Analysis

No RPX7009 was measurable (values were below the lower limit of quantification) in the vehicle control dosing solutions. All of the actual concentrations of the RPX7009 dosing solutions were within ± 10% of the nominal concentrations.

Necropsy

Males were examined for internal and external gross pathology. For each male, absolute and relative (to body weight) organ weights for epididymides, prostate and testes were obtained with paired organs weighed separately. The following male tissues were preserved and fixed for histological examination: abnormalities, epididymis, prostate, seminal vesicles, and right testes.

No gross pathology, absolute or relative organ weight changes or histopathology findings were attributed to RPX7009 dosing.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Fertility measurements included: mean day to mating, mating index, fertility index, and conception rate. In addition, epididymidal sperm were evaluated for counts, percent motility, and morphology.

There were no RPX7009-related effects on the mean day to mating, mating index, or fertility index for males. The mean spermatozoa counts, motility, and sperm with abnormal morphology were unaffected by RPX7009. One high-dose male demonstrated sperm with no motility and approximately 90% less spermatozoa than the mean value for the high-dose group as well as a high percentage (82.5%) of abnormal sperm.

Study title: RPX7009: An Intravenous Fertility Study in Female Sprague-Dawley Rats

Study no.:	(b) (4) # 1011-1711
Study report location:	Electronic transmission
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 25, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPX7009, Lot # SHB-018-080B, purity of 99.83%; Lot # SHB-018-080A, purity of 99.86%; Lot # 410209-2, purity of

99.35%.

Key Study Findings

RPX7009 administered by intravenous infusion to female rats before, during, and after mating did not alter any fertility parameters, estrous cycles, or ovary weights.

Methods

Doses:	0, 100, 300, and 1000 mg/kg/day.
Frequency of dosing:	Once per day
Dose volume:	10 ml/kg
Route of administration:	Intravenous infusion at a rate of 40 ml/kg/hour
Formulation/Vehicle:	0.9% Sodium Chloride for Injection
Species/Strain:	Sprague-Dawley Rats
Number/Sex/Group:	25 females per group.
Satellite groups:	None
Study design:	Female rats received once daily intravenous doses of RPX7009 (100, 300, and 1000 mg/kg/day) or vehicle (0.9% sodium chloride for injection) beginning 14 days prior to mating, during mating, and up to Day 7 of gestation inclusive. Female rats were assessed for body weights, food consumption, clinical observations, estrous cycles, and caesarian section parameters (number and distribution of corpora lutea, implantation sites, live and dead embryos, and resorptions.
Deviation from study protocol:	Multiple study protocol deviations were noted, but none was considered to have altered the study results or to have compromised the study integrity.

Observations and Results

Mortality

One low-dose female was found dead on Day 15 after the first night of placement with a male for mating. The death was not considered to be related to treatment with RPX7009.

Clinical Signs

No clinical signs were considered to be related to RPX7009 administration.

Body Weight

No RPX7009-related losses in body weight were observed during the premating and gestation periods.

Feed Consumption

No RPX7009-related changes in food consumption were observed during the premating and gestation periods.

Estrous Cycle

The number of estrous cycles over 10 days and the average cycle length was not significantly altered by treatment with RPX7009.

Toxicokinetics: Not performed

Dosing Solution Analysis

All of the dosing formulation samples had actual concentrations that were within the acceptance criteria of ± 10% of nominal values. The vehicle control samples did not have measureable amounts of RPX7009, all values were below the limit of quantification.

Estrous Cycle

The estrous cycles of females treated with RPX7009 were comparable to vehicle control values during the pretreatment and dosing periods.

Necropsy

Each animal was examined for external and internal gross pathology. The ovaries of each female sacrificed on GD13 were dissected free of fat and weighed. The following tissues were retained and fixed: animal identification, mammary glands (cervical and inguinal), ovaries, uterus (horns, body, and cervix), vagina, and any abnormal findings.

There were no abnormal macroscopic findings considered related to treatment with RPX7009. Also absolute ovary weights were not altered by treatment with RPX7009. In the absence of gross pathology findings, no histopathology evaluations were performed.

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Treatment with RPX7009 did not alter the following fertility parameters: number of mating females, mean days to mating, number of pregnant females, mating index, fertility index, or conception rate. Uterine findings, including mean group values for the number of corpora lutea, implantation sites, live embryos, dead embryos, resorptions, and pre and post-implantation losses were also not altered by treatment with RPX7009. One mid-dose female had total resorptions.

Study title: Reproductive and Developmental Toxicity in Meropenem in Rats. (Segment I Fertility Studies in Male and Female Rats)

Study no.:	Literature Manuscript: Kawamura *et al.*: Reproductive and developmental toxicity of meropenem in rats. Chemotherapy, 40:S238-250 (1992).
Study report location:	Global Submit Review, NDA 209776
Conducting laboratory and location:	Sumitomo Chemical Co., Ltd., Environmental Health Science Laboratory, 1-98 Kasugade-naka, 3-chome, Konohana-ku, Osaka 554, Japan.
Date of study initiation:	Not identified
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Meropenem, Batch Nos.: U-203 (ADM49414/87) and U-204 ((ADM49414/88) from Sumitomo Pharmaceuticals, purity not identified.

Key Study Findings

- None of the meropenem dose groups exhibited impaired mating, fertility, copulation index, or fertility index for male rats.
- Meropenem did not impair female mating, fertility, copulation index, or fertility index and there were no abnormalities in the estrus cycle.
- Caesarean section data revealed no differences between treatment groups and the control group with regard to the number of corpora lutea, number of implants and live fetuses and number of pre- and post-implantation losses.
- The NOAEL dose for male and female fertility was considered to be the high meropenem dose of 1000 mg/kg/day.

Methods

Doses:	0, 240, 500, and 1000 mg/kg/day
Frequency of dosing:	Once per day via tail vein
Dose volume:	Not identified
Route of administration:	intravenous
Formulation/Vehicle:	Meropenem was mixed in a 1:1 molar ratio with sodium carbonate then dissolved in distilled water to a stock solution concentration of 200 mg/ml and used within 2 hours of preparation.
Species/Strain:	Alpk:ApfSD (Wistar) rats
Number/Sex/Group:	22/sex/group
Satellite groups:	none
Study design:	Male rats were dosed daily for 11 weeks before mating and during the two week mating period then euthanized and necropsied (thoracoabdominal organs were examined).

	Female rats were dosed for 2 weeks before mating, during the two week mating period, and until gestation day (GD) 7. Mated females were euthanized on GD 20 and caesarean sections were performed, the thoracoabdominal organs were examined and pregnancy status was determined. In pregnant females, the numbers of corpora lutea, implants, live fetuses and dead conceptuses were tabulated.
Deviation from study protocol:	Not reported in the manuscript.

Observations and Results

Mortality

One high-dose (1000 mg/kg/day) male died during restraint with dosing and one high-dose female was euthanized due to tail ulceration.

Clinical Signs

Males and females in all meropenem treatment groups had either soft stool or diarrhea. Urine staining was more common in males in the mid- and high-dose groups. Tail damage occurred due to dosing in all groups was observed.

Body Weight

High-dose males had reduced body-weight gain compared to vehicle control animals throughout the period prior to mating. High-dose females had reduced body-weight gain prior to mating, but not during pregnancy.

Feed Consumption

Decreased food consumption was observed in high-dose males throughout the dosing period and in females in all meropenem treatment groups during the first week of dosing.

Toxicokinetics: Not performed

Dosing Solution Analysis

Not reported other than to report that dosing solutions had previously been shown to be stable for at least 2 hours.

Necropsy

Fertility Parameters (Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.)

Males: None of the meropenem dose groups exhibited impaired mating, fertility, copulation index, or fertility index.

Females: Meropenem did not impair female mating, fertility, copulation index, or fertility index and there were no abnormalities in the estrus cycle.

Caesarean section data revealed no differences between treatment groups and the control group with regard to the number of corpora lutea, number of implants and live fetuses, and number of pre- and post-implantation losses (Table 57).

Additionally, fetal body weights were not decreased in meropenem-treatment groups; in the high-dose group, fetal weights were significantly increased compared to control values. There was no effect on mean placental weight, amniotic fluid weight, empty uterus weights and no difference in fetal sex ratios in any of the meropenem groups (Table 57). The significant decrease in placental Index values (the ratio of placental weights to fetal weights) in the mid- and high-dose groups was a reflection of higher fetal weights in these groups.

Table 57: Caesarean Section Data for the Segment I Study with Meropenem.
(Manuscript Table)

9.2 Embryonic Fetal Development

Study title: An Intravenous Embryo-Fetal Development Toxicity Study in Sprague-Dawley Rats

Study no.:	(b) (4) Study No.: 1011-1721
Study report location:	Electronic transmission
Conducting laboratory and location:	(b) (4)

	(b) (4)
Date of study initiation:	May 1, 2012
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPX7009, Lot # SHB-001-178, purity of 99.66

Key Study Findings

RPX7009 administered at doses as high as 1000 mg/kg/day by intravenous infusion to pregnant rats did not alter caesarian section data. One fetus in the low-dose RPX7009 group was born with anencephaly and one fetus in the mid-dose group was born with hydrocephaly. Anencephaly is very rare, but a single incidence (1/280 fetal incidence of 0.36% and 1/21 litter incidence of 4.8%) in the absence of similar malformations in the mid- and high-dose groups is not considered sufficient to clearly demonstrate a relationship to RPX7009 administration. The maternal NOAEL and the NOAEL for fetal toxicity for this study is considered to be the high-dose of 1000 mg/kg/day.

Methods

Doses:	0, 100, 300, and 1000 mg/kg/day
Frequency of dosing:	Once per day
Dose volume:	10 ml/kg
Route of administration:	Intravenous
Formulation/Vehicle:	0.9% sodium chloride for injection
Species/Strain:	Sprague-Dawley rats
Number/Sex/Group:	22 females/group
Satellite groups:	none
Study design:	RPX7009 (IV doses of 100, 300, and 1000 mg/kg/day) or vehicle (0.9% sodium chloride for injection) was administered daily from GD 6 to GD 17 inclusive via a surgically implanted femoral catheter. On Gestation Day (GD) 21 dams were euthanized, given a gross pathology examination, and the uterine contents were examined. Fetuses were weighed and examined externally. Half of the fetuses in each litter were examined for internal malformations with heads removed and placed in Bouin's fluid for examination by the technique of Wilson. The other half of the fetuses were processed for skeletal examination.
Deviation from study protocol:	Multiple study protocol deviations were noted, but none was considered to have altered the study results or to have compromised the study integrity.

Observations and Results

Mortality

No RPX7009-related mortalities were observed.

Clinical Signs

No RPX7009-related clinical signs were observed.

Body Weight

There were no RPX7009-related effects on body weights, body weight changes, or corrected body weights for pregnant females.

Feed Consumption

No RPX7009-related changes in food consumption were reported.

Toxicokinetics: Not performed

Dosing Solution Analysis

The actual concentrations of the RPX7009 dosing solutions were all within the acceptance criteria, ± 10.0% of the nominal value. The vehicle control samples did not contain RPX7009 concentrations above the limit of quantification.

Necropsy

No gross pathology findings associated with RPX7009 administration were reported.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

No RPX7009-related effects were observed for gravid uterus weights, the number of corpora lutea, the number of implantation sites, live fetuses, sex ratio, total resorptions or pre- or post-implantation losses.

Offspring (Malformations, Variations, etc.)

Fetal weights were not altered by maternal treatment with RPX7009. Also no external or skeletal malformations were considered related to RPX7009 administration (Table 59) and skeletal variations (Table 60) were not increased in the RPX7009 groups. However, one fetus in the low-dose RPX7009 group (100 mg/kg/day) was born with anencephaly and one mid-dose (300 mg/kg/day) fetus was born with hydrocephaly (Table 58). Anencephaly is a rare malformation, but a single incidence in the low-dose group is not considered to be sufficient to clearly demonstrate a relationship to RPX7009 administration.

Table 58: Major Malformations in the Rat Embryo-fetal Study

Dose Group	Litters/fetuses[a]	Malformations
Major Visceral Malformations[b]		

Vehicle control	1/1	Thyroid missing
RPX7009 low-dose (100 mg/kg/day)	1/1	Anencephaly
RPX7009 mid-dose (300 mg/kg/day)	1/1	Hydrocephaly

[a] The total litters/fetuses examined for each group were: Vehicle Control: 22/281; RPX7009 low dose: 21/280; RPX7009 mid-dose: 21/293; RPX7009 high dose: 21/285.
[b] All of the major malformations occurred in different litters.

Table 59: Minor External, Visceral, and Skeletal Malformations for the Rat Embryo-fetal Study.

Dose Group	Litters/fetuses			
	Group 1	Group 2	Group 3	Group 4
Heart				
Hemorrhagic vesicle	0/0	0/0	0/0	1/1
Ureter				
Dilated	1/1	1/2	1/1	0/0
Skull				
Frontal bone (incomplete ossification)	1/1	0/0	0/0	1/1
Exoccipital bones (irregular ossification)	0/0	0/0	0/0	1/1
Hyoid bone (incomplete ossification)	14/27	11/23	10/29	17/44
Hyoid bone (unossified)	0/0	3/6	0/0	0/0
Interparietal bone (incomplete ossification)	13/30	10/24	12/36	11/32
Nasal bones (incomplete ossification)	0/0	1/1	0/0	0/0
Parietal bones (incomplete ossification)	8/13	4/5	7/9	3/5
Supraoccipital bone (incomplete ossification)	1/1	2/2	1/1	4/7
Pelvic Girdle				
Ilium bone: incomplete ossification	8/19	11/23	11/22	7/12
Pubis bone: incomplete ossification	1/1	0/0	0/0	2/3
Ribs				
Absent	0/0	0/0	0/0	1/1
Rudimentary on 7th vervical vertebra	0/0	0/0	0/0	2/2
Incomplete ossification	1/1	0/0	2/2	4/5
Nodule	1/2	0/0	1/1	0/0
Wavy	1/1	0/0	0/0	0/0
Ossification center on 7th cervical vertebrae	0/0	0/0	1/1	0/0
Vertebral Column				
Ossification center on 1st lumbar vertebra	10/16	5/11	9/24	9/15
Cervical vertebrae: arches irregular ossification	10/16	9/12	12/17	4/7
Cervical vertebrae: arches incomplete ossification	0/0	0/0	1/1	0/0
Lumbar vertebrae: arches incomplete ossification	1/1	1/1	1/2	0/0
Lumbar vertebrae: centrum semi-bipartite	0/0	1/1	0/0	0/0
Thoracic Vertebrae				
Thoracic vertebrae: arches incomplete ossification	0/0	0/0	1/1	0/0
Thoracic vertebrae: absent	0/0	0/0	0/0	1/1
Sternebrae and Xiphisternum				
Sternebrae 5th: absent	0/0	0/0	0/0	1/1

Forelimbs				
Humerus: incomplete ossification	8/12	12/18	13/21	10/18
Hindlimbs				
Femur: incomplete ossification	19/55	19/53	19/59	17/48
Fibula: incomplete ossification	0/0	0/0	0/0	0/0
Tibia: incomplete ossification	2/2	0/0	2/5	2/2
Group 1: Vehicle Control; Group 2: RPX7009 low dose; Group 3: RPX7009 mid-dose; Group 4: RPX7009 high dose.				

Table 60: Incidence of Skeletal Variations in the Rat Embryo-Fetal Study.
(Sponsor's Table)

GROUP 1: Control (0 mg/kg/day)
GROUP 2: RPX7009 (100 mg/kg/day)
GROUP 3: RPX7009 (300 mg/kg/day)
GROUP 4: RPX7009 (1000 mg/kg/day)

FINDING		GROUP 1	GROUP 2	GROUP 3	GROUP 4
		% AFFECTED	% AFFECTED	% AFFECTED	% AFFECTED
THORACIC CENTRUM VARIANTS	MEAN	44.8	38.5	45.2	48.3
	SD	27.96	22.34	21.16	24.32
	N	22	21	22	21
STERNEBRAL VARIANTS (1-4)	MEAN	0.0	0.0	0.7	1.0
	SD	0.00	0.00	3.05	4.36
	N	22	21	22	21
STERNEBRAL VARIANTS (5-6)	MEAN	28.0	31.2	28.7	29.5
	SD	21.70	26.55	24.38	22.51
	N	22	21	22	21

Study title: An Intravenous Embryo-Fetal Development Toxicity Study in New Zealand Rabbits.

Study no.: (b) (4)
Study report location: Electronic transmission
Conducting laboratory and location: (b) (4)
Date of study initiation: August 17, 2012
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: RPX7009, Lot No.: P232-159-2, purity of 98.59%.

Key Study Findings

Fetal weights for male and females and combined fetal weights were not reduced for any of the RPX7009 dose groups compared to vehicle-control values. However, two females in the low-dose RPX7009 group and one in the mid-dose group had total resorptions. In addition, two mid-dose fetuses from different litters exhibited malformations including intraventricular septal defect, supernumerary lung lobes, and fused lung lobes. Supernumerary lung lobes also occurred in two fetuses in two litters in the high-dose RPX7009 group. Because these malformations did not occur in the vehicle-control group and occurred at a higher incidence than in the historical control database, their incidence is considered to be possibly related to RPX7009 administration. The maternal NOAEL for this study is considered to be 1000 mg/kg/day and the NOAEL for fetal toxicity is considered to be the low-dose of 100 mg/kg/day.

Methods

Doses:	0, 100, 300, and 1000 mg/kg/day
Frequency of dosing:	Once per day
Dose volume:	10 ml/kg
Route of administration:	IV infusion for 15 minutes/day
Formulation/Vehicle:	0.9% sodium chloride for injection USP
Species/Strain:	New Zealand White rabbits
Number/Sex/Group:	22 female rabbits/group in the Main Study.
Satellite groups:	Toxicokinetic animals: 2 vehicle control females and 4 females each from all the RPX7009 treatment groups.
Study design:	Pregnant female New Zealand White rabbits were administered IV RPX7009 (0, 100, 300, and 1000 mg/kg/day) in daily 15 minute infusions from Gestation Days (GD) 7 to 19 inclusive. Surviving animals were euthanized on GD 29 and necropsied.
Deviation from study protocol:	Multiple study protocol deviations occurred in this study, but none was considered to have altered the results or compromised the study integrity.

Table 61: Study Design for the Rabbit Embryo-Fetal Study. (Sponsor's Table)

Treatment Group	Dose Level (mg/kg/day)	Dose Conc. (mg/mL)	Dose Volume (mL/kg)**	Infusion rate (mL/kg/hour)	Number of pregnant Females	
					Main	Toxicokinetics
1. Control *	0	0	10	40	22	2
2. RPX7009	100	10			22	4
3. RPX7009	300	30			22	4
4. RPX7009	1000	100			22	4

* Group 1, animals received the control item alone.
** administered over a 15-minute period.

Observations and Results

Mortality

One female in the low-dose (100 mg/kg/day) RPX7009 group was euthanized due to deteriorating condition on GD 10. This death was not considered related to RPX7009 administration.

Clinical Signs

No clinical signs considered related to RPX7009 administration were observed.

Body Weight

No RPX7009-related changes in body weight, body weight changes, or corrected body weights of pregnant females were noted.

Feed Consumption

Treatment with RPX7009 did not alter food consumption in pregnant females.

Toxicokinetics

Plasma RPX7009 concentrations were measured using a validated LCMS technique. The RPX7009 plasma C_{max} and AUC values increased in a roughly dose-dependent manner on GD 7 and GD 19 (Table 62). Mean values for both the plasma C_{max} and AUC values increased on GD 19 compared to GD 7, particularly for high-dose animals, suggesting some accumulation with repeated dosing. This finding may be related to dose-dependent reductions in clearance (Cl) and reduced clearance values for all doses on GD 19 compared to GD 7. The estimated volume of distribution (Vz) also dramatically increased approximately 5-fold on both measurement days for the high dose compared to the lower doses. This pattern suggests differential distribution, including increased tissue accumulation with the higher dose administration which may be related to saturation of clearance pathways. Consistent with the dose-dependent reductions in clearance, the plasma $t_{1/2}$ values increased on the order of 5-fold with the high dose compared to the plasma $t_{1/2}$ values associated with the lower doses.

Table 62; RPX7009 Pharmacokinetic Parameters in the Rabbit Embryo-Fetal Study. (Sponsor's Table)

		Group 2 (100 mg/kg/day)	Group 3 (300 mg/kg/day)	Group 4 (1000 mg/kg/day)
GD 7				
C_{max}	(µg/mL)	421	1381	3862
T_{max}[a]	(hr)	0.25	0.25	0.25
$AUC_{(All)}$	(hr*µg/mL)	223	868	3490
$AUC_{(0-\infty)}$	(hr*µg/mL)	221	819	3494
t½	(hr)	0.30	0.39	2.87
Cl	(mL/hr/kg)	457	366	289
V_z	(mL/kg)	195	204	1191
MRT	(hr)	0.39	0.49	0.71
GD 19				
C_{max}	(µg/mL)	431	1420	4967
T_{max}[a]	(hr)	0.25	0.25	0.25
$AUC_{(All)}$	(hr*µg/mL)	261	926	4435
$AUC_{(0-\infty)}$	(hr*µg/mL)	260	919	4444
t½	(hr)	0.42	0.42*	2.24
Cl	(mL/hr/kg)	384	326*	244
V_z	(mL/kg)	235	196*	831
MRT	(hr)	0.47	0.52*	0.89

*Values obtained from a single animal
a: Median is presented for T_{max}

Dosing Solution Analysis

The actual RPX7009 concentrations of all the RPX7009 dosing solutions were within the acceptance criteria, ± 10% of the nominal concentrations, and control samples did not contain RPX7009 at concentrations exceeding the lower limit of quantification.

Necropsy

None of the gross pathology findings were considered to be related to RPX7009 administration.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Two females in the low-dose RPX7009 group and one in the mid-dose group had total resorptions. RPX7009 administration at all doses did not alter the mean number of corpora lutea, implantation sites, live or dead fetuses, sex ratio, total resorptions, pre- or post-implantation losses, and gravid uterus weight compared to vehicle control values. Placental weights were not reduced for any of the RPX7009 dose groups compared to vehicle control values.

Offspring (Malformations, Variations, etc.)

Fetal weights for male and females and combined fetal weights were not reduced for any of the RPX7009 dose groups compared to vehicle control values.

Major External, Visceral and Skeletal Malformations: Few major malformations were observed, and with one exception individual malformations occurred in only one fetus in one litter (Table 63). In the mid-dose group one fetus had a fused lung (3 fused lung lobes) and another fetus in a different litter had a supernumerary lung while two different fetuses in two different litters had interventricular septal defects. In the high-dose RPX7009 group, two fetuses in two different litters exhibited supernumerary lobes. The supernumerary lung lobes in the high dose group are considered to be possibly related to RPX7009 administration because the same anomaly did not occur in the vehicle control group, their incidence (2/170 fetuses = 1.2%; 2/21 litters = 9.5%) increased with dose, there were two incidences, and the incidence in the high-dose group was higher than in the appropriate historical control (litter incidence of 0.0%). In the mid-dose group, the incidence of interventricular septal defect was considered to a malformation possibly related to RPX-7009 administration because it occurred twice in the same group in different litters and with a higher incidence (2/169 fetuses = 1.2%; 2/18 litters = 11.1%) than in the appropriate historical control (litter incidence range of 0.0 to 0.66%). Similarly the fusing of 3 right lung lobes in one fetus and supernumerary lung lobes in another fetus in another litter (0.59% fetal incidence and litter incidence of 5.6% for each malformation) in the mid-dose group occurred at a higher incidence than in the appropriate historical control (litter incidence of 0.0% for each malformation)

No major skeletal malformations were reported in any group. Minor visceral and skeletal malformations occurred with a similar incidence in all groups (Table 64) as did skeletal variations (Table 65).

Table 63: Major External and Visceral Fetal Malformations in the Rabbit Embryo-Fetal Study.

Dose Group	Litters/fetuses[a]	Malformations
Major External Malformations[b]		
RPX7009 low-dose (100 mg/kg/day)	Dam 2512/Fetus #6	omphalocele
RPX7009 mid-dose (300 mg/kg/day)	Dam 3513/Fetus #2	Short tail
Major Visceral Malformations[c]		
RPX7009 mid-dose (300 mg/kg/day)	Dam 3507/Fetus #2	Fused 3 right lung lobes
	Dam 3513/Fetus #2	Dilated ascending aorta and interventricular septum defect.
	Dam 3518/Fetus #3	Supernumerary lung lobe
	Dam 3521/Fetus #8	Multiple malformations in the heart (interventricular septal defect, right papillary muscles, and semi lunar and tricuspid valves absent)
RPX7009 high-dose (1000 mg/kg/day)	Dam 4514/Fetus #4 Dam 4516/Fetus #2	Supernumerary lung lobe

[a] The total litters/fetuses examined for each group were: Vehicle Control: 21/181; RPX7009 low dose: 16/154; RPX7009 mid-dose: 18/169; RPX7009 high dose: 21/170.
[b] All of the major external malformations occurred in different litters.
[c] All of the major visceral malformations occurred in different litters.

Minor External, Visceral and Skeletal Malformations: Most of the malformations that the Sponsor categorized as minor occurred at low incidence and with similar incidences in each group. The most common minor malformations (occurring in more than one animal) are shown in Table 64 below.

Table 64: Minor Visceral and Skeletal Malformations

Dose Group	Litters/fetuses			
	Group 1	Group 2	Group 3	Group 4
Heart				
Minor vessel abnormality	3/3	0/0	0/0	2/2
Large ventricular chamber	0/0	0/0	2/2	0/0
Small ventricular chamber	0/0	0/0	2/2	0/0
Lung				
Accessory lobe absent	1/1	0/0	2/2	1/1
Small accessory lobe	0/0	2/3	1/1	0/0
Split accessory lobe	2/2	0/0	0/0	0/0
Ureter				
Retrocaval	0/0	0/0	3/3	0/0
Liver				
Supernumerary lobe	3/4	2/4	1/1	0/0
Dark discoloration	2/3	2/2	1/1	1/1
Cysts	2/2	1/1	1/1	1/2
Spleen				
Discolored	0/0	1/1	2/2	0/0
Skull				
Frontal bone: incomplete ossification	4/4	3/3	4/4	2/2
Hyoid bone: incomplete ossification	1/2	2/3	2/3	1/1
Interparietal bone: incomplete ossification	0/0	1/2	3/3	0/0
Nasal bones: incomplete ossification	1/1	0/0	1/1	0/0
Parietal bones: incomplete ossification	2/2	1/1	1/1	0/0
Supraoccipital bone: incomplete ossification	0/0	1/1	1/1	0/0
Pelvic Girdle				
Pubis bone: incomplete ossification	1/3	4/4	3/7	0/0
Ribs				
Rudimentary ribs	6/6	1/2	2/2	2/2
Abnormal ossification	4/4	2/2	1/2	7/8
Vertebral Column				
Incomplete ossification: caudal vertebrae	0/0	1/1	3/3	0/0
Misaligned: caudal vertebrae	7/8	8/9	6/9	5/5

Incomplete ossification: cervical vertebrae	1/2	1/1	0/0	0/0
Semi-bipartite: thoracic vertabrae	8/19	6/17	11/19	13/15
Sternebrae and Xiphisternum				
Fused sternabra	2/2	3/3	2/2	3/3
Limbs				
Reduced count of metacarpals or phalanges	1/1	2/3	1/1	0/0
Reduced count: Polex	1/1	2/2	1/1	0/0
Group 1: Vehicle Control; Group 2: RPX7009 low dose; Group 3: RPX7009 mid-dose; Group 4: RPX7009 high dose.				

Skeletal Variations: Skeletal variations in the ribs and sternabrae occurred at similar incidences in all groups (Table 65).

Table 65: The Relative Incidence of Skeletal Variations in the Rabbit Embryo-fetal Study. (Sponsor's Table)

GROUP 1: Control (0 mg/kg/day)
GROUP 2: RPX7009 (100 mg/kg/day)
GROUP 3: RPX7009 (300 mg/kg/day)
GROUP 4: RPX7009 (1000 mg/kg/day)

FINDING		GROUP 1	GROUP 2	GROUP 3	GROUP 4
		% AFFECTED	% AFFECTED	% AFFECTED	% AFFECTED
RIBS VARIANTS	MEAN	19.8	34.5	30.7	26.3
	SD	23.52	30.51	28.40	21.02
	N	21	16	18	21
STERNEBRAL VARIANTS (1-4)	MEAN	0.5	1.2	0.0	0.0
	SD	2.42	3.27	0.00	0.00
	N	21	16	18	21
STERNEBRAL VARIANTS (5-6)	MEAN	69.2	57.4	68.6	62.9
	SD	30.79	27.63	24.12	26.05
	N	21	16	18	21

Study title: Reproductive and Developmental Toxicity of Meropenem in Rats. (Segment II Embryo-Fetal Study)

Study no.:	Literature Manuscript: Kawamura et al.: Reproductive and developmental toxicity of meropenem in rats. Chemotherapy, 40:S238-250 (1992).
Study report location:	Global Submit Review (NDA 209776)
Conducting laboratory and location:	Sumitomo Chemical Co., Ltd., Environmental Health Science Laboratory, 1-98 Kasugade-naka, 3-chome, Konohana-ku, Osaka 554, Japan.
Date of study initiation:	Not identified

GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Meropenem, Batch Nos.: U-203 (ADM49414/87) and U-204 ((ADM49414/88) from Sumitomo Pharmaceuticals, purity not identified.

Key Study Findings

- Uterine examination on GD 20 of pregnant rats revealed no difference between meropenem treatment and control groups for the number of corpora lutea, implants, live fetuses, and pre- and post-implantation losses.
- Meropenem-related fetal weight loss was not considered to have occurred.
- The single instance of micrognathia in a high-dose fetus was not considered to be clearly indicative of a teratogenic effect. Similarly the incidence of dumbbell-shaped centrum in the high-dose group (17.5%) was reportedly within the historical control range (5.3% to 21.4%) and therefore not considered to be related to meropenem administration.
- The NOAEL value for fetal toxicity was considered to be the high dose of 750 mg/kg/day.

Methods

Doses:	0, 240, 500, and 750 mg/kg/day
Frequency of dosing:	Once per day via tail vein
Dose volume:	Not identified
Route of administration:	intravenous
Formulation/Vehicle:	Meropenem was mixed in a 1:1 molar ratio with sodium carbonate then dissolved in distilled water to a stock solution concentration of 200 mg/ml and used within 2 hours of preparation.
Species/Strain:	Alpk:ApfSD (Wistar) rats
Number/Sex/Group:	36 mated females per group
Satellite groups:	none
Study design:	Pregnant females about 10 weeks old were accepted into the study on Gestation Day (GD) 0 then dosed with meropenem from GD 6 to GD 17. About 20 dams/group were euthanized on GD 20, and underwent caesarean section. Uterine contents were examined and the skeletons and viscera of live fetuses were examined. The remaining dams (approximately 12) were allowed to give birth naturally and their condition was observed during pregnancy and at delivery. Dams with live pups were allowed to nurse their offspring until postpartum day (PPD) 21 when dams were euthanized, necropsied and the number of implantation sites in the dams

	were determined, and the live birth rate was calculated.
Deviation from study protocol:	Not reported in the manuscript

Observations and Results

Mortality

One vehicle control animal was sacrificed on GD 13 due to tail damage. One control dam and one high-dose dam were sacrificed before PPD 21 because of loss of whole litters from each animal.

Clinical Signs

Tail damage related to the tail-vein dosing was observed in all groups.

Body Weight

Body weight gain in all dams in the meropenem treatment groups was slightly lower than control values during the gestation period, but body weight and body weight gain were unaffected during lactation.

Feed Consumption

Food consumption was low in all groups during the administration period.

Toxicokinetics

Fifteen minutes after the administration of the high-dose on GD15, the mean plasma concentration of meropenem in dams was 144 ± 13.7 mcg/ml and the mean concentration in fetuses was 4.6 ± 0.6 mcg/g (approximately 3% of maternal plasma concentrations). These results confirm placental transmission. Plasma toxicokinetic parameters were not calculated.

Dosing Solution Analysis

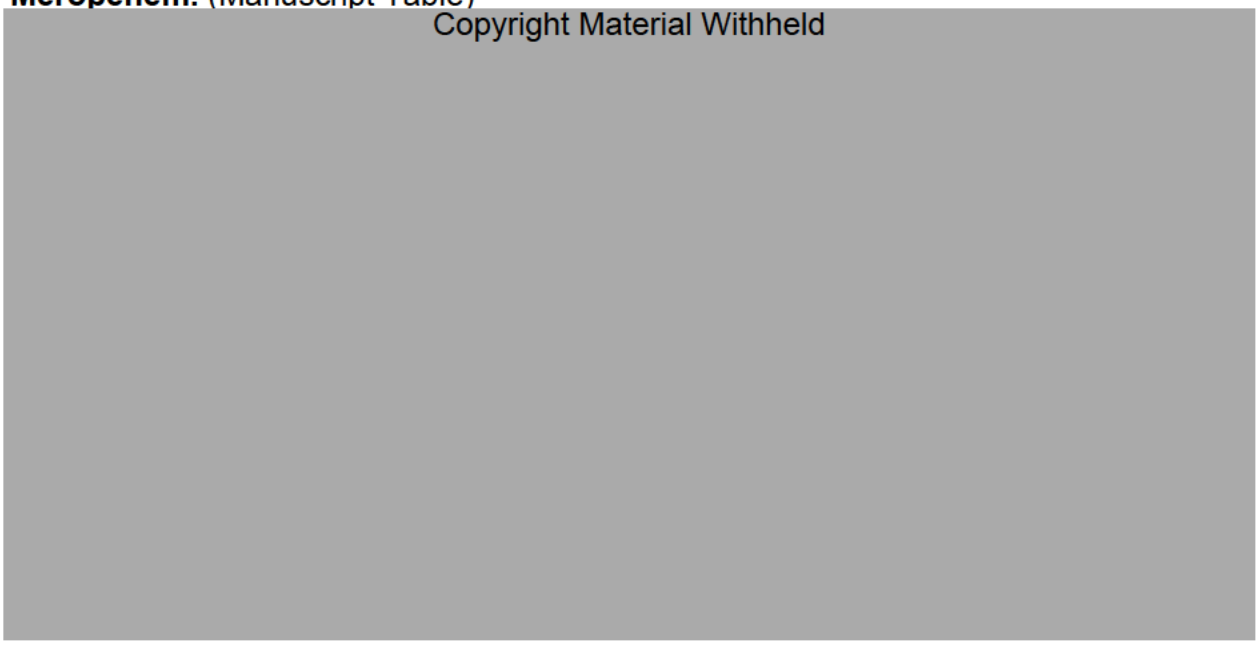
Not described except to note that in a previous analysis the dosing solution had been shown to be stable for at least two hours.

Necropsy

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

Uterine examination on GD 20 revealed no difference between treatment and control groups for the number of corpora lutea, implants, live fetuses, and pre- and post-implantation losses (Table 66). Fetal weights in the mid-dose group was significantly lower than control values, but because the weight difference was small (approximately 4%) and significant weight loss did not occur in the high-dose group, the fetal weight loss in the mid-dose group was not considered related to meropenem administration.

Table 66: Caesarean Section Data for the Rat Embryo-Fetal Study with Meropenem. (Manuscript Table)



Offspring (Malformations, Variations, etc.)

The external, visceral, and skeletal malformations are summarized in (Table 67). Most of the malformations occurred at a similar incidence in all groups. The malformations that occurred only in a meropenem-treatment group or at a significantly higher incidence in a meropenem treatment group were micrognathia (1 fetus in the high-dose meropenem group) and dumbbell-shaped centrum (significantly higher incidence in the high-dose group). The single instance of micrognathia was not considered to be clearly indicative of a teratogenic effect. Similarly the incidence of dumbbell-shaped centrum in the high-dose group (17.5%) was reportedly within the historical control range (5.3% to 21.4%) and therefore not considered to be related to meropenem administration.

\

Table 67: Fetal External, Visceral, and Skeletal Malformations in the Rat Embryo-Fetal Study with Meropenem. (Manuscript Table)

9.3 Prenatal and Postnatal Development

Study title: RPX7009: A Pre and Post-Natal Intravenous Study in Female Sprague-Dawley Rats

Study no.:	1013-0351
Study report location:	Electronic transmission
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 18, 2014
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPX7009, Lot No.: 1306MP701, purity of 97.5%.

Key Study Findings

The administration of RPX7009 at doses of 100, 300, and 1000 mg/kg/day to pregnant rats by intravenous infusion from Gestation Day 6 to Post-Partum Day 20 did not produce adverse effects for the F_0, F_1, or F_2 generations.

- The reproductive performance of the F_0 generation was not adversely affected compared to vehicle control dams.
- The viability development (including sensory, behavioral and functional assessments and reproductive ability of the F_1 generation was not adversely affected.
- The F_2 generation was not adversely affected for viability on Post-Partum Day 4, body weights or sex ratio.

Methods

Doses:	0, 100, 300, 1000 mg/kg/day
Frequency of dosing:	Once per day
Dose volume:	10 ml/kg infused at a dose rate of 40 ml/kg/hour.
Route of administration:	intravenous
Formulation/Vehicle:	0.9% sodium chloride
Species/Strain:	Sprague-Dawley rats
Number/Sex/Group:	22 females per group
Satellite groups:	none
Study design:	F_0: RPX7009 was administered by intravenous infusion from Gestation Day (GD) 6 to Post-Partum Day (PPD) 20 inclusive to pregnant rats. Infusions were performed via a surgically implanted femoral catheter. Dams were assessed for clinical signs, body weights, food consumption, parturition day, litter size, and external sex determination of F_1 offspring. F_1: On PPD 4, litters for each F_0 dam were reduced to 8 pups/litter (4 males and 4 female pups where possible) and the remaining unselected pups were euthanized. The selected pups underwent physical, reflexology, and sensory development assessments. The selected F_1 pups were weaned on PPD 21 and separated from dams at which time 1 pup/sex/litter were selected for mating and estrous cycle assessments (females only) and 1 pup/sex/litter was chosen to continue F_1 assessments and undergo learning and memory assessments. All F_1 males selected for mating were terminated at the end of the assessment period and underwent necropsy examination. F_1 females that mated and littered were euthanized on PPD 4 to PPD 6, then necropsied and examined for corpora lutea counts and implantation sites. At the same time, F_2 pups were euthanized and examined for internal and

	external gross pathology. The F_1 males and females that were used for the learning and memory tests were euthanized on PPD 98.
Deviation from study protocol:	Multiple deviations from the study protocol were noted. However, none of the deviations were considered to have altered the results or compromised the integrity of the study.

Observations and Results

F_0 Dams

Survival:	No F_0 dams were found dead or euthanized prematurely due to RPX7009 administration. However 2 vehicle-control, 3 low-dose, 2 mid-dose, and 2 high-dose dams were euthanized prior to PPD 21 due to cannibalism of their litters, failure to produce sufficient milk, or due to a skin wound.
Clinical signs:	No RPX7009-related clinical signs were observed.
Body weight:	No RPX7009-related changes in body weight were observed during gestation or lactation.
Feed consumption:	No RPX7009-related changes in food consumption were observed during gestation or lactation.
Uterine content:	No RPX7009-related effects on pre and post-implantation loss, live birth index, sex ratio, and numbers of live or dead pups were observed.
Necropsy observation:	No RPX7009-related gross pathology findings were observed.
Toxicokinetics:	Not performed
Dosing Solution Analysis	RPX7009 was below the limit of quantification in the vehicle control dosing solution. In the RPX7009 dosing solutions, the nominal concentrations were within ± 10.0% of the actual concentrations which was within the acceptance criteria.
Other:	No RPX7009-related effects on maternal performance including gestation index, gestation length, or duration of parturition were observed. Similarly litter size at parturition, or at weaning on PPD 21 and pup viability (pre- and post-culling) were unaffected by dosing with RPX7009.

F_1 Generation

Survival:	No F_1 generation pups male or female were found dead or prematurely euthanized due to the effects of RXP7009 administration.
Clinical signs:	No clinical signs were considered related to RPX7009 administration in F_1 pups from birth to weaning.
Body weight:	There were no RPX7009-related effects on body weight and body weight changes for F_1 male or F_1 female pups

	from PPD 1 to weaning at PPD 21, for females and males from PPD 28 to GD 20 and PPD 28 to 98.
Feed consumption:	No RPX7009-related effects on food consumption for F_1 males and females were noted from PPD 28 to placement for mating. Also food consumption was not changed during gestation and up to PPD 98 for females.
Physical development:	Physical and developmental assessments included the timing of pinna unfolding, eye opening, preputial separation, tooth eruption, and vaginal opening as well as righting reflex, negative geotaxis, pupillary closure on PPD 21, timing of auricular startle response, and visual placing response on PPD 21. None of the tested physical and developmental indices were affected by RPX7009 administration. Eye opening occurred significantly earlier for mid- and high-dose females, high-dose males, and total (male and female) mid- and high-dose animals compared to control values, but this finding was not considered to be toxicologically relevant.
Neurological assessment:	Learning and memory of the animals were evaluated by assessing selected animals (1/sex/group) on PPD 23-25 for passive avoidance, on PPD 55-60 for motor activity (figure 8 maze), and on PPD 61-68 for learning and memory in an E-shaped water maze. None of the maternal RPX7009 doses altered the results for passive activity, motor activity, or learning by water maze compared to control values.
Reproduction:	There were no RPX7009-related effects on maternal performance including estrous cycle, gestation index, gestation length, duration of parturition, pre and post-implantation loss live birth index, litter size, and numbers of live, dead, or malformed pups. Also RPX7009 did not affect the mean day of mating, mating indices, or fertility indices compared to control values.
Other:	none

F_2 Generation

Survival:	A total of 34 F_2 pups from 29 litters were found dead or euthanized from birth to PPD 4 including 5 control pups in (5 litters), 7 (6) low-dose pups, 11 (8) mid-dose pups and 11 (10) high-dose pups. The primary cause of death was food deprivation (lack of milk in stomach) in all groups. The viability index for F_2 pups on PPD 4 was not changed in the RPX7009 groups compared to the vehicle control group.
Body weight:	No RPX7009-related changes in body weight or body weight changes were noted in F_2 pups on PPD 0 and 4.
External evaluation:	Clinical observations were not specific to or increased in incidence in the RPX7009 groups.
Male/Female ratio:	F_2 pup sex ratio was not changed in the RPX7009 groups on either PPD 0 or 4.
Other:	None

Study title: Reproductive and Developmental Toxicity in Meropenem in Rats. (Segment III Pre-postnatal Study)

Study no.:	Literature Manuscript: Kawamura *et al.*: Reproductive and developmental toxicity of meropenem in rats. Chemotherapy, 40:S238-250 (1992).
Study report location:	Global Submit Review (NDA 209776)
Conducting laboratory and location:	Sumitomo Chemical Co., Ltd., Environmental Health Science Laboratory, 1-98 Kasugade-naka, 3-chome, Konohana-ku, Osaka 554, Japan.
Date of study initiation:	Not identified
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	Meropenem, Batch Nos.: U-203 (ADM49414/87) and U-204 (ADM49414/88) from Sumitomo Pharmaceuticals, purity not identified.

Key Study Findings

- In F_0 dams, meropenem doses up to 1000 mg/kg/day had no effect with regard to the mean gestation period, viability index and lactation index up to PPD 21. Also no effect on the number of mothers with whole litters lost or at least one pup dead, the ratio of males, and mean fetal body weight.
- Mean body weight in F_1 females in the high-dose group was low throughout maturation, but in F_1 males it was not decreased compared to control values.

- In F_1 offspring, meropenem produced no clear developmental changes in morphological differentiation, innate reflexes, sensorimotor function and hearing.
- The reproductive capacity test of F_1 animals was not impaired in any group.
- Uterine examination of F_1 females revealed no difference from control values for: the number of corpora lutea, number of implants, number of live F_2 fetuses, and number of pre- and post-implantation losses were reported.
- No differences occurred in mean F_2 fetal weight, proportion of male fetuses or the mean weights of the placenta, amniotic fluid, and of the empty uterus.

Methods

Doses:	0, 240, 500, and 1000 mg/kg/day
Frequency of dosing:	Once per day via tail vein
Dose volume:	Not identified
Route of administration:	intravenous
Formulation/Vehicle:	Meropenem was mixed in a 1:1 molar ratio with sodium carbonate then dissolved in distilled water to a stock solution concentration of 200 mg/ml and used within 2 hours of preparation.
Species/Strain:	Alpk:ApfSD (Wistar) rats
Number/Sex/Group:	22/sex/group
Satellite groups:	none
Study design:	Pregnant females about 10 weeks old were accepted into the study on Gestation Day (GD) 0 then dosed with meropenem from GD 17 to Post-Partum Day (PPD) 21. The condition of the dams during delivery and lactation was observed for the Segment II dams. Pups were examined for postpartum growth, function and development, and reproductive capacity including observation of F_2 fetuses. On PPD 35, 22 F_1 males and females from each group were selected and mated. All pregnant females were sacrificed on the 20th day of their gestation and the uterine contents examined.
Deviation from study protocol:	Not discussed in the manuscript

Observations and Results

F_0 Dams

Survival:	Two low-dose dams died during the dosing procedure.
Clinical signs:	Mainly tail damage associated with the dosing procedure.
Body weight:	None of the meropenem groups exhibited reduced body weights or body weight gains during the gestation period.
Feed consumption:	Food consumption was significantly lower in the

	meropenem-treatment groups during the gestation period, but there was no effect during the lactation period.
Uterine content:	Not performed for F_0 dams
Necropsy observation:	Not reported
Toxicokinetics:	Not performed.
Dosing Solution Analysis	Not reported
Other:	Compared to the control group, meropenem had no effect on any of the treatment groups with regard to the mean gestation period, viability index and lactation index up to PPD 21. Also no effect on the number of mothers with whole litters lost or at least one pup dead, ratio of males, and mean fetal body weight was observed.

Table 68: Litter Survival Parameters in the Rat Segment III Study with Meropenem
(Manuscript Table)

Copyright Material Withheld

F_1 Generation

Survival:	One dam in the vehicle control group and one dam in the mid-dose group aborted their litters.
Clinical signs:	Not reported
Body weight:	Mean body weight in females in the high-dose group was low throughout maturation, but in males it was not decreased compared to control values.
Feed consumption:	Not reported

Physical and neurological development:	Meropenem produced no clear developmental changes in morphological differentiation, innate reflexes, sensorimotor function, and hearing. The changes that were observed did not occur in a dose-responsive manner. Negative geotaxis was seen in a significantly large number of pups in the low-dose group, but not in the mid- and high-dose groups. Low-dose females also demonstrated a transient increase in activity inside the maze in a figure-8 maze test on PPD 35 and in high-dose males on PPD 77. The startle reaction was mildly elevated in mid-dose females.
Reproduction:	The reproductive capacity test of F_1 animals was not impaired in any group.
Other:	Uterine Examination of F_1 Females: no difference from control values for: the number of corpora lutea, number of implants, number of live fetuses, and number of pre- and post-implantation losses were reported. Also no differences occurred in mean F_2 fetal weight, proportion of male fetuses or the mean weights of the placenta, amniotic fluid, and of the empty uterus.

F_2 Generation

Survival:	F_2 live fetuses were similar in all groups
Body weight:	Fetal weights were similar in all groups
External evaluation:	Reportedly, macroscopic observation of the F_2 fetuses found no abnormalities related to administration.
Male/Female ratio:	The proportion of male fetuses was similar in all groups.
Other:	none

10 Special Toxicology Studies

1. Assessment of Phototoxic Potential: IV-VIS Spectra of PRX7009 Drug Product

Methods

The molar extinction coefficient (MEC) for RPX7009 was determined when dissolved in methanol and water at a concentration of 0.1 mg/ml. The UV spectra of the dissolved solutions was determined between the light wavelengths of 290 and 700 nm. The RPX7009 drug product (batch No.: CL3-402) used in a Phase 1 clinical trial was tested.

Results

In water, RPX7009 drug product produced a MEC of 60 L/mol • cm, and a MEC of 22 L/mol • cm in methanol (Table 69). These MECs are significantly lower than the threshold of 1000 L/mol • cm recommended in the ICH S10 Guidance. Based on these results, the RPX7009 drug product is not considered to be sufficiently photoreactive as to cause phototoxicity.

Table 69: MECs for RPX7009 Drug Product in Water and Methanol. (Sponsor's Table)

Solvent	Concentration (g/L)	λ_{max} (nm)	Absorbance	MEC (L mol^{-1} cm^{-1})
Water	0.1072	292	0.0202	60
Methanol	0.1016	292	0.0070	22

2. **RPX7009/Meropenem: A Single Dose Intravenous Infusion Toxicokinetic Study in Juvenile Sprague-Dawley Rats.** Study No.: 2015-0211

Methods

This non-GLP-compliant study was conducted by (b) (4) Juvenile Sprague-Dawley rats (age 24 days old at the start of the study) received single 30-minute intravenous infusions of RPX7009 and meropenem administered alone and in combination as shown in Table 70. Blood samples were collected for toxicokinetic analysis pre-dose and at 1, 2, 4, 8, 12, and 24 hours after dosing.

Table 70: Study Design for Study No.: 2015-0211. (Sponsor's Table)

Treatment Group	Dose Level (mg/kg/day)	Dose Conc. (mg/mL)	Dose Rate (mL/kg/hr)[a]	Number of Males
1. Meropenem (low dose)	50	2.5	40	40
2. Meropenem (mid dose)	150	7.5		40
3. Meropenem (high dose)	500	25		40
4. RPX7009 (low dose)	100	5		40
5. RPX7009 (mid dose)	300	15		40
6. RPX7009 (high dose)	1000	50		40
7. RPX7009/Meropenem (low dose)	100/50*	5/2.5*		40
8. RPX7009/Meropenem (mid dose)	300/150*	15/7.5*		40
9. RPX7009/Meropenem (high dose)	1000/500*	50/25*		40

[a]Administered as a 30-minute infusion (dose volume of 20 mL/kg/day)
*Dose level or concentration for each test item, RPX7009/Meropenem, respectively.

Results

Quantifiable levels of RPX7009 or meropenem were not detected in pre-dose samples from any group. Plasma C_{max} and AUC values for RPX7009 (Table 71), meropenem (Table 72), and hydrolyzed meropenem (Table 73) were similar when RPX7009 and meropenem were administered alone or together. RPX7009 and meropenem plasma C_{max} and AUC values were half as much or lower than comparable Day 1 values for the same doses of RPX7009 or meropenem administered to adult male rats in Study No.: 1013-1341. These results indicate that juvenile animals are able to metabolize and process both RPX7009 and meropenem as well as or better than adult animals and suggest that unexpectedly higher exposures with possibly associated toxicities will not occur in juvenile animals.

RPX7009 clearance (Cl) decreased with dose suggesting saturation of clearance pathways. Both the plasma C_{max} and AUC values increased in a more than dose-dependent manner for RPX7009. For meropenem and hydrolyzed meropenem, C_{max} and AUC values increased in a roughly dose-dependent manner. As in adult rats, meropenem was rapidly metabolized to its inactive metabolite, hydrolyzed meropenen in male juvenile rats. Hydrolyzed meropenem was also rapidly metabolized with plasma $t_{1/2}$ values of 13 to 52 minutes.

Table 71: Mean Toxicokinetic Parameters for RPX7009 after a Single Intravenous Infusion of RPX7009 alone or in Combination with Meropenem in Male Juvenile Rats. (Sponsor's Table)

		Group 4 (100 mg/kg)	Group 5 (300 mg/kg)	Group 6 (1000 mg/kg)	Group 7 (100 mg/kg)[b]	Group 8 (300 mg/kg)[b]	Group 9 (1000 mg/kg)[b]
C_{max}	(µg/mL)	35	160	729	38	138	631
T_{max}[a]	(min)	35	35	35	35	35	35
$AUC_{(0-12)}$	(hr*µg/mL)	19	85	413	19	78	349
$AUC_{(0-\infty)}$	(hr*µg/mL)	18[c]	85	411	18[c]	78	346
t½	(min)	7.9[c]	8.4	10	7.0[c]	9.6	12
V_z	(mL/kg)	1038[c]	715	614	910[c]	900	842
Cl	(mL/hr/kg)	5444[c]	3530	2435	5438[c]	3830	2886
MRT	(min)	25[c]	25	26	23[c]	26	26

a: adjusted with length of infusion (30 min);
b: administered in combination with Meropenem;
c: regression line includes C_{max}, presented for information purposes only.

Table 72: Mean Toxicokinetic Parameters for Meropenem after a Single Intravenous Infusion of RPX7009 alone or in Combination with Meropenem in Male Juvenile Rats. (Sponsor's Table)

		Group 1 (50 mg/kg)	Group 2 (150 mg/kg)	Group 3 (500 mg/kg)	Group 7 (50 mg/kg)[b]	Group 8 (150 mg/kg)[b]	Group 9 (500 mg/kg)[b]
C_{max}	(µg/mL)	5	21	63	6	25	71
T_{max}[a]	(min)	35	35	35	35	35	35
$AUC_{(0-12)}$	(hr*µg/mL)	-	-	25	-	10	29
$AUC_{(0-\infty)}$	(hr*µg/mL)	-	-	25[c]	-	10[c]	29[c]
t½	(min)	-	-	4[c]	-	4[c]	0.07[c]
V_z	(mL/kg)	-	-	2053[c]	-	1304[c]	1698[c]
Cl	(mL/hr/kg)	-	-	19802[c]	-	14667[c]	17328[c]
MRT	(min)	-	-	21[c]	-	21[c]	21[c]

a: adjusted with length of infusion (30 min);
b: administered in combination with RPX7009;
c: regression line includes C_{max}, presented for information purposes only.

Table 73: Mean Toxicokinetic Parameters for Hydrolyzed Meropenem after a Single Intravenous Infusion of RPX7009 alone or in Combination with Meropenem in Male Juvenile Rats. (Sponsor's Table)

		Group 1 (50 mg/kg)	Group 2 (150 mg/kg)	Group 3 (500 mg/kg)	Group 7 (50 mg/kg)[b]	Group 8 (150 mg/kg)[b]	Group 9 (500 mg/kg)[b]
C_{max}	(µg/mL)	26	81	242	23	80	303
T_{max}[a]	(min)	35	35	35	35	35	35
$AUC_{(0-12)}$	(hr*µg/mL)	19	53	167	17	60	197
$AUC_{(0-\infty)}$	(hr*µg/mL)	19	52	166	17	-	197
t½	(min)	13	14	32	13	-	52

a: adjusted with length of infusion (30 min);
b: Meropenem administered in combination with RPX7009.

Reviewer Comment: *A deficiency in this study was that it did not include female juvenile rats and thus sex differences were not evaluated. Also because multiple doses of the RPX7009 and meropenem were not administered, the toxicokinetic effects of repeated dosing were not examined.*

Study title: RPX7009/Meropenem: A 28-Day Intravenous Infusion Toxicity Study with a 28-Day Recovery Period in Juvenile Sprague-Dawley Rats.

Study no.:	Study No.: 1015-0431
Study report location:	Electronic transmission
Conducting laboratory and location:	(b) (4)
Date of study initiation:	June 8, 2015
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPX7009, Lot # LTRE7A2004, purity of 100.2% meropenem, Lot # 33077100704, potency of 75.9%; purity not reported.

Key Study Findings

Meropenem and RPX7009 administered separately or together did not produce appreciable toxicity with repeated dosing in juvenile rats. The NOAEL values were considered to be the high doses of 500 mg/kg/day meropenem and 1000 mg/kg/day RPX7009.

Methods

Doses:	See Table 74.
Frequency of dosing:	Once per day
Route of administration:	Intravenous 30 minute infusion
Dose volume:	40 ml/kg/hr
Formulation/Vehicle:	0.9% sodium chloride for Injection
Species/Strain:	Sprague-Dawley rats

Number/Sex/Group:	15/sex/group for Main Study animals and
Age:	At the onset of dosing, animals were 24 days post-partum
Weight:	Males: 49-92 grams; Females: 43-83 grams
Satellite groups:	10/sex/group for Recovery Study animals
Unique study design:	Male and female juvenile rats were administered meropenem and/or RPX7009 according to the schedule shown in Table 74. Main Study and Recovery animals were dosed for 28 days beginning on Post-Partum Day (PPD) 24 and ending on PPD 52. Main Study animals were euthanized on Day 29 and Recovery animals were euthanized 28 days later on Day 52 (PPD 80).
Deviation from study protocol:	Multiple study deviations were noted. However, none was considered to have altered the study results or compromised the study integrity.

Table 74: Study Design for Study No.: 1015-0431. (Sponsor's Table)

Administration Group	Dose Level (mg/kg/day)	Dose Conc. (mg/mL)	Infusion Rate (mL/kg/hr)[a]	Number of Animals			
				Main		Recovery	
				M	F	M	F
1.Control #	0	0	40	15	15	10	10
2.Meropenem (low dose)	50	2.5		15	15	10	10
3.Meropenem (high dose)	500	25		15	15	10	10
4.RPX7009 (low dose)	100	5		15	15	10	10
5.RPX7009 (high dose)	1000	50		15	15	10	10
6.RPX7009/Meropenem (low dose)	100/50*	5/2.5*		15	15	10	10
7.RPX7009/ Meropenem (high dose)	1000/500*	50/25*		15	15	10	10

#Group 1 animals received the reference item 0.9% sodium chloride for injection, USP (saline) alone.
[a]Administered as a 30-minute infusion (dose volume of 20 mL/kg/day)
*Dose level or concentration for each test item, RPX7009/Meropenem, respectively.
M: Male; F: Female

Observations and Results

Observations	Schedule
Mortality	Animals were checked for mortality daily during all phases of the study.
Clinical Signs	Clinical signs were monitored twice daily during all phases of the study. Also detailed clinical signs were performed weekly on surviving animals starting on PPD 23 and ending on the day of necropsy.
Body Weights	Body weights were recorded on all surviving animals prior to surgery (PPD 20), on the day prior to initiation of dosing (PPD 23), then weekly thereafter until the day before necropsy. On the

	day of necropsy, a fasted body weight was recorded for calculation of the relative organ weight.
Tibia length	Tibial length was recorded for all surviving animals (excluding dams) on the day prior to initiation of dosing (PPD 23) then weekly until the day of necropsy.
Food Consumption	Individual food consumption was measured on surviving animals post-weaning (PPD 21) then once weekly except on day of food deprivation throughout the study following the start of dosing. Baseline food consumption was obtained for three days prior to the initiation of dosing.
Ophthalmology	Ophthalmology parameters were assessed once in the pre-dose period and once in the last week of dosing.
Functional Observational Battery (FOB)	FOB measurements were performed on all Recovery animals during the pretreatment period, and on all surviving Recovery animals following completion of the final 28th dose (PPD 51) and once during the last week of recovery.
Clinical Pathology	Blood samples were collected for hematology, coagulation, and clinical chemistry analysis prior to the scheduled necropsy on Day 29 (PPD 52). Urine was collected overnight the night before necropsy.
Necropsy	Main Study animals were euthanized and necropsied on Day 29 (PPD 52) and Recovery animals were euthanized and necropsied four weeks later on PPD 80.

Mortality

One Group 6 male was found dead on PPD 49 (3 days before the scheduled necropsy). The cause of death was not determined, however, right atrium dilation possibly associated with heart failure was observed. In addition one Group 7 Recovery male was euthanized on post-partum Day 75 due to a wound with discharge. Neither death was considered to be associated with test-article administration.

Clinical Signs

No clinical signs were considered to be related to meropenem or RPX7009 administration.

Body Weights

Administration of meropenem or RPX7009 alone or in combination was not associated with body weight changes compared to vehicle control values.

Tibia Length

No changes in tibia length or tibia length changes were associated with the administration of meropenem or RPX7009 either alone or in combination during the Main Study or the Recovery Period.

Feed Consumption

Administration of meropenem or RPX7009 alone or in combination was not associated with changes in food consumption compared to vehicle control values.

Ophthalmoscopy

Funduscopic (indirect ophthalmoscopy) and biomicroscopic (slit lamp) examinations were performed by a board-certified veterinary ophthalmologist.

Functional Observation Battery (FOB)

FOB measurements included a full panel of open-field, manipulative, and neuromuscular evaluations.

There were no qualitative or quantitative changes in FOB measurements attributed to dosing with meropenem or RPX7009 either alone or in combination. All of the responses fell within normal ranges for rats.

ECG: Not performed

Hematology

The list of measured hematology parameters are shown in Table 78.

Few hematology parameters were significantly different than control values, but the changes were considered to be incidental due to inconsistent dose-responsiveness, small magnitude of change, and lack of consistency between sexes. On PPD 52 (Day 29), plasma APTT values were reduced 10-14% in males receiving high-dose meropenem and low-dose RPX7009, however APTT values were not affected by high-dose RPX7009 or in any female dose groups. Male APTT values were similar to control values by the end of the recovery period.

Clinical Chemistry

The serum chemistry parameters that were measured are listed in Table 80.

None of the measured serum chemistry parameters were considered to be altered by the treatments with meropenem and/or RPX7009 in Main Study animals or in Recovery animals. Incidental significant differences in parameter values did not occur in both sexes or in a consistent dose-dependent manner.

Urinalysis

The urinalysis parameters that were measured are shown in (Table 79).

None of the urinalysis parameters were significantly altered by meropenem and/or RPX7009.

Gross Pathology

Gross pathology associated with infusion-site reactions occurred at a low incidence (2-6 animals/sex/group) in all of the groups including the vehicle-control group. Findings appeared as clear, red, or beige material adherent to the intima of the vein or catheter or raised or dark areas at the infusion site.

Organ Weights

The organs that were weighed for this study are listed in (Table 81).

No significant organ weight changes occurred in response to meropenem or RPX7009 administration in combination or alone during the Main and Recovery periods.

Histopathology

Adequate Battery: Yes; the list of tissues and organs prepared for histology are listed in Table 81).

Peer Review: No

Histological Findings
The primary histopathology findings were occasional infusion-site reactions which occurred at a low incidence (2-6 animals/sex/group) in all groups. In conjunction with the gross pathology findings, histopathology findings included thrombosis, granulomas or mural inflammation at infusion sites. The infusion-site reactions persisted through the recovery period.

Special Evaluation: None

Toxicokinetics: Not performed

Dosing Solution Analysis

Meropenem and RPX7009 were confirmed to not be present in the vehicle control solutions above the lower limit of detection. The actual concentrations of meropenem and RPX7009 were shown to be within the ± 10% acceptance criteria of the nominal concentrations.

11 Integrated Summary and Safety Evaluation

A vaborbactam-associated finding with potential clinical relevance was a low incidence of malformations in the rabbit embryo-fetal study. In mid-dose (300 mg/kg/day) fetuses, malformations included interventricular septal defects in two different litters, one supernumerary lung lobe in another fetus in another litter and a three fused right lung lobes in another fetus in a fourth litter. In the high-dose group (1000 mg/kg/day), supernumerary lung lobes occurred in two fetuses in two litters. Because these malformations did not occur in the vehicle-control group and occurred at a higher incidence than in the historical control database for the originating colony of rabbits, their incidence is considered to be possibly related to RPX7009 administration, and the malformations will be listed on the product label. In the same study, dams administered

RPX7009 did not lose weight or demonstrate maternal toxicity and fetal weights were also not reduced. The NOAEL value for maternal toxicity was considered to be 1000 mg/kg/day which is equivalent to approximately 5 times and 70 times the maximum recommended human dose based on AUC and C_{max} exposure comparisons respectively. Based on the low incidence of malformations in the mid- and high-dose groups and an absence of maternal toxicity, the NOAEL for fetal toxicity was considered to be 100 mg/kg/day which is equivalent to much less than the maximum recommended human dose based on AUC exposure comparison and approximately 6 times the maximum recommended human dose based on C_{max} exposure comparison (Table 75). The clinical relevance of the malformations is uncertain. Vaborbactam C_{max} values may have influenced malformations in the rabbit study, and the recommended 3-hour infusion time for clinical administration of vaborbactam is associated with much lower C_{max} values than the 30-minute infusions in rabbits.

In the rat embryo-fetal study, 1/280 low-dose (100 mg/kg/day) fetuses was born with anencephaly and in the mid-dose group (300 mg/kg/day) 1/293 fetuses was born with hydrocephaly. Anencephaly is a rare malformation, but a single incidence in the absence of similar malformations in high-dose group is not considered sufficient to clearly demonstrate a relationship to RPX7009 administration. As in the rabbit embryo-fetal study, RPX7009 was not associated with maternal toxicity in pregnant rats or fetal weight loss. The NOAEL values for maternal and fetal toxicity were considered to be the high dose of 1000 mg/kg/day. In the absence of concurrent toxicokinetic measurements including plasma AUC and C_{max} values in the rat embryo-fetal study, safety margin determinations are based on body surface area comparisons and calculation of human equivalent doses (HED). The HED values for maternal and fetal toxicity in the rat embryo-fetal study are approximately equivalent to 1.6 times the maximum recommended human dose (Table 76).

Other than the low incidence of malformations in the rabbit embryo-fetal study, vaborbactam in multiple repeated-dose toxicology studies was not associated with significant toxicities even with high doses providing AUC exposures equal to or in excess of the exposures expected in patients. Vaborbactam (RPX7009) was not associated with significant toxicities in 28-day repeated-dose toxicology studies in rats and dogs at daily doses as high as 1000 mg/kg/day (respectively approximately equal to or 3 times the maximum recommended human dose in patients based on plasma AUC exposure) when administered alone or in combination with meropenem. A similar lack of toxicity occurred in in a 28-day toxicology study in juvenile rats with the same NOAEL of 1000 mg/kg/day. Also, in a single-dose pharmacokinetic study conducted with juvenile rats, plasma exposures to both meropenem and vaborbactam were reduced compared to plasma exposures in adult rats suggesting more rapid metabolism in juvenile rats and limited potential for unexpectedly high exposures associated with administration of adult doses in pediatric patients.

Vaborbactam was not associated with genotoxicity in a full battery of testing (*in vitro* Ames test, chromosome aberration test in human lymphocytes and *in vivo* micronucleus test in mice). Because neither the duration of clinical dosing with vaborbactam nor

clinical exposure will exceed 6 months, nonclinical carcinogenicity studies are not recommended.

In Segment I and Segment III developmental and reproductive toxicity studies, intravenous vaborbactam at the high dose of 1000 mg/kg/day in all studies did not produce adverse effects. In the male fertility study, vaborbactam did not significantly alter mean fertility parameter outcomes, male reproductive organ weights, or sperm counts, motility or morphology. Similarly in the female fertility study, vaborbactam was not associated with altered fertility parameter outcomes, duration of estrous cycles, or ovary weights. In the pre-postnatal study in rats, the reproductive performance of the F_0 generation was not adversely affected compared to vehicle control dams, and the viability, development (including sensory, behavioral and functional assessments) and reproductive ability of the F_1 generation was not adversely affected. Finally, the F_2 generation was not adversely affected for viability on post-partum day 4, body weights or sex ratio. The vaborbactam NOAEL values in the Segment I and Segment III studies are equivalent to approximately 1.6 times the maximum recommended clinical dose based on body surface area comparison (Table 76).

Table 75: Safety Margins for Clinical Vaborbactam Administration Based on Comparative AUC and C_{max} Values in the Embryo-Fetal Study in Rabbits.

Study	NOAEL (mg/kg/day)		Male		Female		Safety Margin based on Plasma AUC [c]	Safety Margin on Plasma C_{max} [d]
			AUC [a]	C_{max} [b]	AUC [a] (mcg • hr/ml)	C_{max} [b] (mcg/hr)		
Embryo-fetal in Rabbits	Maternal	1000	----	----	4444	4967	5.3	≈ 70
	Fetal	100	260	431	260	431	0.31	≈ 6.0

[a] Gestation Day (GD) 19 plasma $AUC_{(0-\infty)}$ data from Study No.: 1011-1744 in rabbits.
[b] Gestation Day (GD) 19 plasma C_{max} data from Study No.: 1011-1744 in rabbits.
[c] The vaborbactam AUC associated with a 2 gram TID dose in patients is 835 mcg • hr/ml.
[d] The vaborbactam C_{max} associated with a 2 gram TID dose in patients is 71.3 mcg • hr/ml.

Table 76: Safety Margins for Clinical Vaborbactam Administration Based on HED Values in the Reproductive and Developmental Toxicology Studies in Rats.

Study	NOAEL (mg/kg/day)		HED [a]		Safety Margin based on HED [b]
			Male	Female	
Male Fertility in Rats	1000		161.3	----	≈ 1.6
Female Fertility in Rats			----	161.3	≈ 1.6
Embryo-fetal in Rats	Maternal	1000	----	161.3	≈ 1.6
	Fetal	1000	161.3	161.3	≈ 1.6
Pre-postnatal in Rats	1000		161.3	161.3	≈ 1.6

[a] The conversion factor for derivation of the human equivalent dose (HED) based on whole body surface area comparisons is divide the NOAEL by 6.2 for rats and 3.1 for rabbits.
[b] The maximum daily clinical dose of vaborbactam is 2 grams TID which for an average 60 kg human is equal to 100 mg/day.

Meropenem has been marketed in the United States since 1996 initially under the tradename Merrem®. In clinical use, meropenem has been associated with seizures and other adverse CNS events (potential for neuromotor impairment) occurring most commonly in patients with CNS disorders. The most common adverse reactions listed on the Merrem® label occurring in 2% or less of patients are: headache, nausea, constipation, diarrhea, anemia, vomiting and rash. Other serious adverse events for meropenem as listed on the Merrem® label are: hypersensitivity reactions and thrombocytopenia. In combination toxicology studies in rats and dogs meropenem did not produce significant toxicities, and the NOAEL for each study was the high dose of 500 mg/kg/day when administered alone or in combination with vaborbactam for 28 days.

As described on the Merrem® product label, meropenem was not genotoxic in a full battery of *in vitro* (Ames test, Chinese hamster ovary HGPRT assay, human lymphocyte cytogenic assay) and *in vivo* (mouse micronucleus assay) assays. Nonclinical carcinogenicity studies for meropenem have not been performed. However, like vaborbactam, the duration of clinical dosing or exposure for meropenem is not expected to exceed 6 months and therefore carcinogenicity studies are not recommended.

According to the Merrem® product label, meropenem in fertility studies with a high dose of 1000 mg/kg/day in rats and 360 mg/kg/day in Cynomolgus monkeys did not impair fertility. These doses are approximately equivalent to 1.6 and 1.2 times respectively the maximum recommended human dose based on body surface area comparison. In the same studies, meropenem was not associated with malformations, but produced slight changes in fetal body weights in rats at doses of 250 mg/kg/day and above.

In addition to the Segment I and II study information included on the Merrem® product label, a full panel of Segment I, II, and III studies with meropenem in rats has been described in a literature report (Kawamura *et al.*, 1992). This paper reports that in the male/female fertility study, the high-dose (1000 mg/kg/day) of meropenem suppressed weight gain and food consumption in males prior to mating and also in females prior to mating but not during pregnancy. However, male and female mating and fertility and female estrus cycles were not affected by meropenem administration. Similarly, female caesarean section data (number of corpora lutea, number of implants and live fetuses, number of pre- and postimplantation loss, fetal sex ratio) were not affected by dosing with up to 1000 mg/kg/day meropenem. In the Segment II study, maternal body weights were reduced, but meropenem at a high dose of 750 mg/kg/day did not alter caesarean section data or fetal weights, and meropenem was not associated with fetal malformations. In the Segment III study, meropenem at doses up to 1000 mg/kg/day did not affect maternal body weight or mean gestation period, fetal viability index, lactation index, ratio of male F_1 offspring, or mean fetal body weight at birth. Also, indicators of neonatal development in F_1 offspring (morphological differentiation, innate reflexes, sensorimotor function and hearing) were not altered by maternal meropenem exposure. Caesarean-section data for F_1 dams and the fetal weights and sex ratios of F_2 offspring were similar in all groups. The NOAEL values were considered to be the high meropenem doses in all of the studies, 1000 mg/kg/day in the Segment I and III studies,

and 750 mg/kg/day in the Segment II studies which are equivalent to approximately 1.6 and 1.2 times the maximum recommended human dose based on whole body surface area comparisons (Table 77).

Table 77: Safety Margins for Meropenem Based on NOAEL and Human Equivalent Dose (HED) values in the Reproductive and Developmental Toxicology Studies Described in Kawamura *et al.*, 1992.

Study	NOAEL (mg/kg/day)		HED [b] (mg/kg/day)	Safety Margin [c]
Male Fertility in Rats	1000		161.3	≈ 1.6
Female Fertility in Rats			161.3	≈ 1.6
Embryo-fetal in Rats	Maternal	750 [a]	121.0	≈ 1.2
	Fetal	750	121.0	≈ 1.2
Pre-postnatal in Rats	1000		161.3	≈ 1.6

[a] Maternal body weight gain was reportedly slightly low in all meropenem-dose groups during the gestation period, but body weight and the amount of body weight gain was unaffected during gestation.
[b] The conversion factor for calculating the rat HED based on comparison of the whole-body surface areas of rats and humans is divide the rat NOAEL by 6.2.
[c] The maximum recommended human dose of meropenem is 6 grams/day (2 grams TID) which for an average 60 kg human is equal to 100 mg/kg/day.

In pharmacokinetic studies, both meropenem (based on information from the Merem® label) and vaborbactam have been shown to widely distribute in body tissues with short plasma $t_{1/2}$ values on the order of 1 hour or less. Both meropenem and vaborbactam are primarily excreted in urine. However, in the 1-month combination toxicology studies in rats and dogs, systemic AUC exposures for vaborbactam and meropenem were not substantially altered when administered concomitantly, and neither agent as well as the hydrolyzed metabolite of meropenem was observed to accumulate with repeated dosing.

All of the drug substance and drug product impurities for meropenem and vaborbactam were qualified in nonclinical toxicology studies at higher levels than their designated specifications or the specifications are restricted to the ICH Q3(R2) limit for unspecified impurities. Some impurities tested positive for genotoxicity in the *in silico* assessments and were subsequently tested further in an Ames assay and/or controlled at the maximum acceptable limit (120 mcg/day; (b) (4) ppm of the daily 6 g RPX7009 clinical dose) recommended in the ICH M7 Guidance for drugs dosed for 1 month or less. Significantly, none of the RPX7009 impurities considered to be potentially genotoxic are expected to appear in the final RPX7009 drug substance. The elemental impurities present in the meropenem-vaborbactam drug product will be controlled according to the recommendations stipulated in the ICH Q3D Guidance and the residual solvents are specified at the limits recommended in the ICH Q3C Tables and List.

The nonclinical pharmacokinetic and toxicity data for vaborbactam and meropenem do not indicate a potential for general toxicity in the clinic above what is expected for treatment with meropenem alone. From a Pharmacology/Toxicology perspective,

TRADENAME (meropenem plus vaborbactam) is approvable for the proposed indication. However, the fetal malformation results for vaborbactam in the rabbit Segment II study suggest physicians should advice female patients about the risks to pregnancy.

REFERENCES

1. Linden P: Safety profile of meropenem: an updated review of over 6,000 patients treated with meropenem. Drug Saf, 30:657-668 (2007).

2. Kawamura S, Russell AW, Freeman SJ, and Siddall, RA: Reproductive and Developmental Toxicity of Meropenem in Rats. Chemotherapy, 40:S238-250 (1992).

12 Appendix/Attachments

Table 78: Hematology Parameters

Study No.	1011-1221	1011-0762	1013-1341	1013-1352	1015-0201	1015-0431
Species	**Rat**	**Dog**	**Rat**	**Dog**	**Rat**	**Rat**
Cell morphology	X	X	X	X	X	X
Hemoglobin concentration	X	X	X	X	X	X
Hemaglobin distribution width	X	X	X	X	X	X
Hematocrit	X	X	X	X	X	X
Erythrocyte count	X	X	X	X	X	X
Platelet count	X	X	X	X	X	X
Plateletcrit / thrombocrit	X	X	X	X	X	X
Mean platelet volume						
Mean corpuscular volume	X	X	X	X	X	X
Mean corpuscular hemoglobin	X	X	X	X	X	X
Mean corpuscular hemoglobin concentration	X	X	X	X	X	X
Red cell distribution width	X	X	X	X	X	X
Total leukocyte count	X	X	X	X	X	X
Reticulocyte count	X	X	X	X	X	X
Reticulocyte hemoglobin content						
Differential leukocyte count (Absolute and relative neutrophil, lymphocyte, monocyte, eosinophil, basophil counts)	X	X	X	X	X	X
Blood smear for cell morphology (if necessary for interpretation)						
Activated partial	X	X	X	X	X	X

thromboplastin time (APTT)						
Prothrombin time (PT)	X	X	X	X	X	X
Fibrinogen						

Table 79: Urinalysis Parameters

Study No.	**1011-1221**	**1011-0762**	**1013-1341**	**1013-1352**	**1015-0201**	**1015-0431**
Species	**Rat**	**Dog**	**Rat**	**Dog**	**Rat**	**Rat**
Bilirubin	X	X	X	X	X	X
Blood	X	X	X	X	X	X
Color and Appearance	X	X	X	X	X	X
Glucose	X	X	X	X	X	X
Ketones	X	X	X	X	X	X
Microscopic Analysis	X	X	X	X	X	X
pH	X	X	X	X	X	X
Protein	X	X	X	X	X	X
Specific Gravity	X	X	X	X	X	X
Urobilinogen	X	X	X	X	X	X
Volume	X	X	X	X	X	X

Table 80: Serum Chemistry Parameters

Study No.	**1011-1221**	**1011-0762**	**1013-1341**	**1013-1352**	**1015-0201**	**1015-0431**
Species	**Rat**	**Dog**	**Rat**	**Dog**	**Rat**	**Rat**
Aspartate aminotransferase	X	X	X	X	X	X
Alanine aminotransferase	X	X	X	X	X	X
Alkaline phosphatase	X	X	X	X	X	X
Blood urea nitrogen						
Urea	X	X	X	X	X	X
Creatinine	X	X	X	X	X	X
Creatine kinase						
Glucose	X	X	X	X	X	X
Cholesterol	X	X	X	X	X	X
Triglycerides	X	X	X	X	X	X
Total protein	X	X	X	X	X	X
Albumin	X	X	X	X	X	X
Total bilirubin	X	X	X	X	X	X
Sodium	X	X	X	X	X	X
Sorbitol dehydrogenase						
Potassium	X	X	X	X	X	X
Chloride	X	X	X	X	X	X
Calcium	X	X	X	X	X	X
Inorganic phosphorus	X	X	X	X	X	X
Gamma-glutamyl transferase						
Glutamate dehydrogenase						

Globulin	X	X	X	X	X	X
Albumin/globulin ratio	X	X	X	X	X	X

Table 81: Panel of Organs and Tissues that were Weighed or Examined for Histopathology

Study #	1011-1221	1011-0762	1013-1341	1013-1352	1015-0201	1015-0431
Species	**Rat**	**Dog**	**Rat**	**Dog**	**Rat**	**Rat**
Adrenals	X*	X*	X*	X*	X*	X*
Aorta	X	X	X	X	X	X
Bone Marrow smear						
Bone (sternum, and/or femur and/or rib)	X	X	X	X	X	X
Brain	X*	X*	X, *	X, *	X, *	X, *
Bronchi						
Cecum	X	X	X	X	X	X
Cervix						
Colon	X	X	X	X	X	X
Conjunctiva						
Duodenum	X	X	X	X	X	X
Epididymides	X	X	X	X	X	X
Esophagus	X	X	X	X	X	X
Eye	X	X	X	X	X	X
External ear						
Fallopian tube						
Gall bladder		X		X		
Gross lesions	X	X	X	X	X	X
Harderian gland						
Heart	X*	X*	X, *	X, *	X, *	X, *
Hypophysis						
Ileum	X	X	X	X	X	X
Infusion site	X	X	X	X	X	X
Jejunum	X	X	X	X	X	X
Joint, tibiofemoral						
Kidneys	X*	X*	X, *	X, *	X, *	X, *
Lachrimal gland						
Larynx						
Liver	X*	X*	X, *	X, *	X, *	X, *
Lungs	X	X	X	X	X	X
Lymph nodes, inguinal						
Lymph nodes, mediastinal						
Lymph nodes	X	X	X	X	X	X

mandibular						
Lymph nodes, mesenteric,	X	X	X	X	X	X
Mammary Gland						
Muscle (biceps, femoris)						
Nasal cavity						
Nasal turbinates						
Optic nerves	X	X	X	X	X	X
Ovaries	X*	X*	X, *	X, *	X, *	X, *
Oviduct						
Pancreas	X	X	X	X	X	X
Parathyroid	X*	X*	X, *	X, *	X, *	X, *
Peripheral nerve						
Peyer's patches						
Pharynx						
Pituitary	X*	X*	X, *	X, *	X, *	X, *
Prostate	X*	X*	X, *	X, *	X, *	X, *
Rectum			X	X	X	X
Salivary gland	X	X	X	X	X	X
Sciatic nerve	X	X	X	X	X	X
Seminal vesicles	X	X				
Skeletal muscle	X	X	X	X	X	X
Skin	X	X	X	X	X	X
Spinal cord	X	X	X	X	X	X
Spleen	X*	X*	X, *	X, *	X, *	X, *
Sternum	X	X	X	X	X	X
Stomach	X	X	X	X	X	X
Testes	X*	X*	X, *	X, *	X, *	X, *
Thymus	X*	X*	X, *	X, *	X, *	X, *
Thyroid	X*	X*	X, *	X, *	X, *	X, *
Tongue	X	X	X	X	X	X
Tonsils						
Trachea	X	X	X	X	X	X
Ureter						
Urinary bladder	X	X	X	X	X	X
Uterus	X*	X*	X, *	X, *	X, *	X, *
Vagina	X	X	X	X	X	X
Vertebra, Lumbar						
Zymbal gland						

X, histopathology performed

*, organ weight obtained

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

/s/

JAMES S WILD
07/14/2017

TERRY J MILLER
07/14/2017