CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201023

PHARMACOLOGY REVIEW(S)

MEMORANDUM

Jevtana (Cabazitaxel)

Date: June 14, 2010
To: File for NDA 201023
From: John K. Leighton, PhD, DABT
Associate Director for Pharmacology/Toxicology
Office of Oncology Drug Products

I have examined pharmacology/toxicology supporting review and labeling provided by Drs. Khasar and Helms and supervisory memorandum provided by Dr. Verbois. I concur with their conclusions that Jevtana may be approved for the proposed indication and that no additional pharmacology/toxicology studies are needed.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

JOHN K LEIGHTON
06/14/2010

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:	201,023
Supporting document/s:	0000
Applicant's letter date:	December 18, 2009
CDER stamp date:	03/31/2010
Product:	Cabazitaxel (XRP6258)
Indication:	Metastatic prostate cancer
Applicant:	Sanofi Aventis SPA
Review Division:	Division of Drug Oncology Products
Reviewer:	Whitney S. Helms, Ph.D.
Supervisor/Team Leader:	Hans Rosenfeldt, Ph.D. acting for S. Leigh Verbois, Ph.D.
Division Director:	Robert L. Justice, M.D., M.S.
Project Manager:	Christy L. Cottrell

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6 pages of Pharmacology has been withheld in full immediately following this page as B4 CCI/TS

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

WHITNEY S HELMS
06/14/2010

HANS M ROSENFELDT
06/14/2010

MEMORANDUM

Date: June 3, 2010
From: S. Leigh Verbois, Ph.D.
Supervisory Pharmacologist
Division of Drug Oncology Products
To: File for NDA #201,023
Cabazitaxel (JEVTANA)
Re: Approvability of Pharmacology and Toxicology

Non-clinical studies that investigated the pharmacology and toxicology of cabazitaxel provided to support NDA 201,023 for the treatment of patients with metastatic prostate cancer were reviewed in detail by Whitney S. Helms, Ph.D., and G. Sachia Khasar, Ph.D. The supporting information included studies of intravenously administered cabazitaxel that investigated the drug's pharmacology, pharmacokinetics and ADME, safety pharmacology, general toxicology (rat and dog), genetic toxicity (*in vivo* and *in vitro*), and reproductive toxicity in both rats and rabbits. The studies cited in the review consist primarily of original research conducted by the applicant.

The pharmacology studies submitted to the NDA demonstrate that cabazitaxel is a taxane which binds tubulin, promotes microtubule polymerization and prevents disassembly. Based on this, the pharmacological classification of cabazitaxel is a microtubule inhibitor, like other taxanes which have similar mechanisms of action. Drug induced toxicity, including gastrointestinal toxicity, bone marrow toxicity, and neuronal toxicity were observed non-clinically. These findings are not unexpected and were well characterized.

Cabazitaxel increased micronuclei in rats, and increased numerical aberrations with or without metabolic activation in an *in vitro* test in human lymphocytes. No induction of structural aberrations was observed in human lymphocytes. Additionally cabazitaxel was negative in the Ames test. The positive *in vivo* genotoxicity findings are consistent with the pharmacological activity of the compound (inhibition of tubulin depolymerization).

Like other taxanes, cabazitaxel is a highly toxic to the developing embryo or fetus causing embryolethality, pre and post implantation loss, fetal death and decreased fetal weight at a doses approximately 0.02-0.06 times the Cmax in cancer patients at the recommended human dose of 25 mg/m^2. Teratogenesis was not detected however minor variations, (i.e. delays in skeletal ossifications) at doses 0.02x the maximum recommended human dose were observed. In the rabbit study abject maternal toxicity without fetal or embryonic toxicity was observed. Although these studies utilized doses that there far below the clinical dose maternal toxicity or development toxicity was observed in each study. Because the potential benefit from the use of the JEVTANA in pregnant women in this patient population may outweigh the potential risk to the developing fetus, Pregnancy Category D is recommended for this patient population.

Numerous issues chemistry and manufacturing issues were identified during the review of JEVTANA which impacted the pharmacology and toxicology review of JEVTANA. These are discussed in detail in the primary review and include the potential propensity of the drug product to form a precipitate, and impurity and residual solvent qualification. The sponsor has adequately qualified impurites either through non-clinical studies or through provided information. With regard to precipitate formation, although the lung is the most sensitive organ for precipitate induced toxicity and wheezing was noted in the rat in chronic study, precipitate was not noted in the study and nor was there histopathological evidence of pulmonary toxicity associated with wheezing. Although this is a theorectical concern there is not data to indicate that precipition occurred in the drug product in non-clinical studies.

Recommendations: I concur with Drs. Helms's and Khasar's conclusion that pharmacology and toxicology data support the approval of NDA 201,023 for JEVTANA. There are no outstanding nonclinical issues related to the approval of JEVTANA for the proposed indication.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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/s/

SANDI L VERBOIS
06/03/2010

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:	201,023
Supporting document/s:	0000
Applicant's letter date:	December 18, 2009
CDER stamp date:	03/31/2010
Product:	Cabazitaxel (XRP6258)
Indication:	Metastatic prostate cancer
Applicant:	Sanofi Aventis SPA
Review Division:	Division of Drug Oncology Products
Reviewer:	G. Sachia Khasar, Ph.D. Whitney S. Helms, Ph.D.
Supervisor/Team Leader:	S. Leigh Verbois, Ph.D.
Division Director:	Robert L. Justice, M.D., M.S.
Project Manager:	Christy L. Cottrell

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1 Executive Summary

1.1 Recommendations

1.1.1 Approvability

Recommended for approval. The non-clinical studies with cabazitaxel support the safety of its use in hormone refractory metastatic prostate cancer.

1.1.2 Additional Non Clinical Recommendations

None

1.1.3 Labeling

See labeling for recommendations. Separate labeling review will be provided.

1.2 Brief Discussion of Nonclinical Findings

Cabazitaxel is a microtubule inhibitor derived from the taxane, docetaxel. Like other taxanes, cabazitaxel acts by binding tubulin and promoting microtubule polymerization and preventing disassembly. In *in vitro* assays, the effects of cabazitaxel on microtubule assembly and stabilization were comparable to the effects docetaxel and more pronounced than the effects of paclitaxel at similar concentrations. Cabazitaxel also showed *in vitro* activity against a panel of tumor cell lines that were paclitaxel or docetaxel resistant with IC_{50}s that were as much as 10-fold lower than those of docetaxel. A panel of murine and human tumor cell lines with resistance to other cytotoxic agents also had some sensitivity to cabazitaxel at physiologically relevant concentrations.

In vivo studies were conducted to examine the potential activity of cabazitaxel against a variety of tumor types in tumor implant models. Treatment with cabazitaxel led to delayed tumor progression compared to untreated controls in nude mice implanted with several different human gastric, prostate, colon, lung, pancreatic, kidney, and head and neck tumors. With 4/9 lines tested in this model (including a colon, a head and neck, a pancreatic, and a prostate line) tumor free survival was recorded. When treatment with cabazitaxel was compared directly to treatment with docetaxel in these lines, cabazitaxel had similar or improved activity. In a human docetaxel-resistant breast tumor model, cabazitaxel treatment of implanted SCID mice resulted in a significant delay in tumor growth compared to either docetaxel or ixabepilone. In a final set of *in vivo* experiments 2 glioblastoma lines were implanted either subcutaneously or intracranially into nude mice. After tumors were established mice were treated with

docetaxel, cabazitaxel, or 2 other clinical candidates. Cabazitaxel showed similar activity to docetaxel in the subcutaneous models and enhanced activity in the intracranial models. Taken together, the *in vivo* studies suggest that cabazitaxel may have activity similar or superior to docetaxel in a variety of clinical therapeutic settings.

Exposure to cabazitaxel is dose-dependent; the drug appears to distribute rapidly into tissues and crosses both the blood-brain and placental barriers. Metabolism of cabazitaxel is NADPH-dependent with 3 major metabolites detected in rat, dog, and human liver microsomes (RPR123142, RPR112698 and RP56976 (docetaxel)). Human metabolism of the drug appeared to be faster than that of dogs or rats as the rate of disappearance of the parent drug in liver microsomes from each species was highest in human and lowest in rats. Total plasma clearance was rapid in all species tested but tended to decrease with increasing dose in dogs. The *in vitro* plasma protein binding was similar between species with ≤ 10% of the drug being free; percent of free drug was highest in humans and lowest in dogs. Cabazitaxel (10 μM) induced CYP3A in primary cultures of rat hepatocytes, however, this induction it is not believed to be clinically relevant as the *in vitro* concentration at which induction was observed was significantly higher (~16 fold) than the physiologically relevant concentrations. Excretion of the drug is primarily in the feces though small amounts were detectable in urine and in breast milk.

Both *in vivo* and *in vitro* safety pharmacology studies were performed to assess the effects of RPR 116258 on the CNS, cardiovascular system, and renal and GI function. While there was some variation in dosing among the studies due to dose concentration errors, male Sprague-Dawley rats were treated by IV injection with 5% glucose, vehicle, or 3, 9, or 15 mg/m^2 single doses of RPR 116258. In a single dose cardiovascular study performed in anesthetized Beagle dogs, there were clear effects of the vehicle alone or RPR116258 on respiration rate, heart rate, and blood pressure. Decreased heart rate in the treated animals compared to a glucose only control correlated with prolongation of ECG parameters, and reduced cardiac output and stroke volume. There was an increase in respiration rate beginning approximately 5 minutes after the start of dosing and lasting through the dosing period of 1 hour and into the recovery period. By the 2 hour post-dose time-point breathing had almost returned to the baseline rate. Changes in heart rate were less prolonged, beginning approximately 15 minutes after the beginning of dosing, but persisted during the entire dosing period. Approximately 15 to 30 minutes after dosing, heart rate was recovering. Changes in cardiovascular parameters were similar between vehicle and RPR 116258 suggesting that the effects were due to the PS80 based vehicle, a finding that has been established in other products using this vehicle; however, there was a small increase (~13% above baseline) in QTc in RPR 116258 treated dogs that was not seen in the vehicle only treated animals. In the renal study there was a significant dose-dependent decrease in urinary potassium. These decreases exceeded those seen in the positive control group. There were similar decreases in the amount of urinary chloride levels, though these changes did not reach statistical significance or the degree of the change seen in the positive control. Thus, while there was no clear evidence of renal damage caused by administration of a single dose of RPR 116258 at the 24 hour time-point, there was some effect on urinary electrolyte levels. No significant drug-related effects were noted in the CNS or GI studies.

In order to better characterize cabazitaxel-induced toxicities,the sponsor performed chronic toxicity studies in both rats and dogs. Male and female Sprague Dawley rats were administered 0, 1, 5 and 20/10 mg/kg (0, 6, 30, 120/60 mg/m^2) of cabazitaxel IV over 1 hour every 3 weeks for 6 months (10 cycles). Male and female Beagle dogs were administered 0, 0.1, 0.25, or 0.5 mg/kg (0, 2, 5, 10 mg/m^2) of cabazitaxel IV over 1 hour every 3 weeks for 9 months (13 cycles). Batches of cabazitaxel used in these chronic toxicity studies included levels of synthesis impurities significantly higher than the specified limits and were used to qualify impurity levels in the clinical lots. Two known impurities of the drug product that were not added in excess to the nonclinical batches were (b) (4) and (b) (4); however the level of (b) (4) a characterized genotoxic compound, is acceptable based on ICH Q3A guidelines, given that the patient population has a very limited life expectancy. Although (b) (4) is part of the drug product, the daily exposure is (b) (4) lower than a daily intake of ≤50 mg allowed in ICH Q3C for (b) (4) as (b) (4) residual solvent. Additionally, impurities (b) (4) eluted as a single peak that cannot be fully resolved in the specifications. The specifications for this peak are set at (b) (4) and the sponsor has qualified it to (b) (4) (b) (4) (b) (4) in non-clinical studies with the claim that both impurities are represented equally. Despite this claim, there is a chance that one of these impurities could have represented 100% of the peak in the nonclinical studies; however, because the specification is set so close to the ICH Q3A qualification threshold of 0.15% and because the likelihood that the peak represented in the non-clinical batch consists of 100% of a single impurity is low, no additional investigation is warranted.

Decreased motor activity and tremors were observed in cabazitaxel-treated dogs at doses ≥ 2 mg/m^2. In addition, histopathological findings of sciatic nerve degeneration, axon fragmentation and dorsal root swelling were seen in both acute single dose and repeat-dose studies in mice and rats. These findings are consistent with the peripheral and sensory neuropathies observed in the clinic. In addition, there was evidence of skeletal muscle myofiber degeneration in rats which appears to correlate with musculoskeletal and connective tissue disorders in the clinic.

The bone marrow is a major target of cabazitaxel related toxicity. There were findings of decreased bone marrow cellularity at all doses in the rat and in the high dose group of the dog. These histologic changes in bone marrow correlated with hematologic decreases in neutrophils, reticulocytes, lymphocytes, platelets and overall WBCs and are reflective of the hematological adverse events seen clinically. Similary, clinically noted gastrointestinal tract disturbances, manifested as diarrhea, nausea, and vomiting, appear to correlate with the cytotoxicity of cabazitaxel on the GI tract in mice, rats and dogs. In dogs GI toxicity was evidenced by clinical signs of liquid feces and vomiting and histopathologically by regeneration/degeneration of glands, shortening or atrophy of villi and inflammation, at doses ≥2 mg/m^2, <1/10 the clinical dose.

Pyelonephritis and kidney necrosis contributed to the deaths of 3/13 male rats before schedule but without corresponding clinical chemistry findings in the rat chronic toxicity study. The histopathological findings in the kidney in early death animals along with decreased urinary volume at late time-points during the dosing and recovery phases at all dose levels and a significant decrease in urinary potassium levels in the

dedicated safety pharmacology study suggest that the kidney is an important target of cabazitaxel toxicity. The reports of kidney failure in the clinic bare a resemblance to the non-clinical cases of pyelonephritis. Wheezing and noisy breathing were observed in rats during the 10 cycle study. Although these observations could suggest airway obstruction due to possible drug precipitate, there are no histopathological findings to support this idea. The wheezing and noisy breathing are more likely a result of airway inflammation due to a compromised immune system. Additionally, in dogs there were changes in respiration which correlated with findings of inflammation in the lungs at all dose levels. Finally, liver fibrosis and necrosis were seen in rats and dogs at doses ≥5 mg/m^2. As cabazitaxel is metabolized in the liver, exposure and hence toxicity may be enhanced in patients with liver disease.

Reproductive toxicology studies were performed in both rats and rabbits to assess the effects of the drug on fertility and embryofetal development. Neither male nor female fertility was affected by the drug in the dedicated fertility studies, though the doses used in these studies resulted in exposures significantly below those at the recommended human dose. In the rat chronic toxicity studies there were decreases in the organ weights of the testes, prostate, epididymides, ovaries, and uterus accompanied by histopathological findings suggesting that the reproductive organs were targets. At doses ≥ 6 mg/m^2 (~0.2-0.35X the human clinical dose based on AUC) there were rare findings (1/10 M) of oligospermia in the epididymis, degeneration/regeneration in the seminal vesicle, and seminiferous tubule atrophy in the testis. At 30 mg/m^2, approximately the clinical dose based on AUC, the frequency and severity of these findings increased and at the high dose level of 120/60 mg/m^2 they were seen in all animals. Doses ≥ 30 mg/m^2 resulted drug-related in mortality in the chronic rat study, however, clinically supportive care is given to mitigate many cabazitaxel-related toxicities in humans, suggesting that the potential for an effect of cabazitaxel on male fertility at the clinically recommended dose may exist. Similary, in females dosed with ≥ 6 mg/m^2 there were findings of necrosis in the corpora lutea. Despite the absence of an effect on the ability of female rats to become pregnant when dosed with cabazitaxel, there was an embryotoxic effect with an increase in resorptions at the 1.2 mg/m^2 dose level that resulted in a resorption index of approximately 28%.

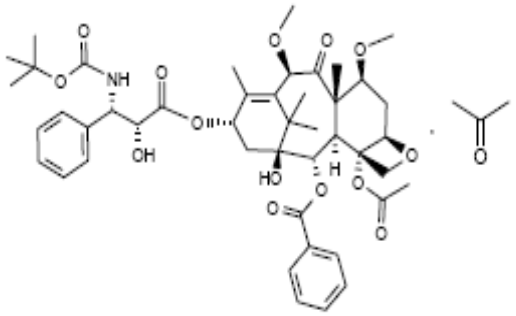
The results of rat embyrofetal development studies showed that cabazitaxel is both fetotoxic and abortifacient. At doses ≥ 0.96 mg/m^2 (~0.06 X the human clinical exposure based on Cmax) there were dose-dependent increases in post implantation loss (~40% and 72% in the 0.96 and 1.5 mg/m^2 dose groups respectively). There were dose-dependent decreases in fetal birth weight at doses ≥ 0.48 mg/m^2 (~ 0.02 X the human clinical exposure based on Cmax). along with mild increases in incidences of skeletal variations and incomplete ossifications. In rabbits there was significant maternal toxicity including death at doses > 0.24 mg/m^2. Despite this toxicity, there was no effect seen in rabbits on pregnancy parameters including pre- or post-implantation loss, though the highest dose given to pregnant rabbits resulted in a level of exposure that was ~ 0.015 times the low end of the human exposure range based on Cmax. At doses ≥ 0.24 mg/m^2 (a dose resulting in exposures below the level of quantitation) there were mild decreases in fetal birth weight. In addition, at the 0.36 mg/m^2 dose level there was an increased incidence of membranous skull variations (although the increases were within the range of historical control data). The animal studies suggest that

administration of cabazitaxel to pregnant women may pose a risk for fetal toxicity. Pregnancy category D is recommended.

2 Drug Information

2.1 Drug

CAS Registry Number:	183133-96-2 (as solvent free form)
Generic Name:	Cabazitaxel
Code Name:	RPR116258A (RPR116258, acetone solvate) XRP6258 (project code)
Chemical Name:	(2α,5β,7β,10β,13α)-4-(acetyloxy)-13-({(2R,3S)-3-[(tertbutoxycarbonyl)amino]-2-hydroxy-3-phenylpropanoyl}oxy)-1-hydroxy-7,10-dimethoxy-9-oxo-5,20-epoxytax-11-en-2-yl benzoate-propan-2-one (1:1)
Molecular Formula/Molecular Weight:	$C_{45}H_{57}NO_{14}$,C_3H_6O/ 894 (for acetone solvate) 835.9 (for the solvent free)
Structure:	



Pharmacologic class:	Microtubule inhibitor
Relevant INDs/NDAs/DMFs	IND # 56,999; DMF #s (b) (4)

2.3 Clinical Formulation

2.3.1 Drug Formulation

Cabazitaxel is available as a non-aqueous concentrate for solution for infusion at 60 mg/1.5 mL. It is supplied with a solvent vial containing (b) (4) of a 13% w/w aqueous solution of alcohol (USP), also referred to as ethanol (96 per cent) in Ph. Eur., for preparation of an intermediate premix at 10 mg/mL, prior to dilution with 0.9% sodium chloride solution or 5% dextrose solution in an infusion bag.

2.3.2 Comments on Novel Excipients

None

2.3.3 Comments on Impurities/Degradants of Concern

None

2.4 Proposed Clinical Population and Dosing Regimen

Patients with metastatic hormone refractory prostate cancer (HRPC) previously treated with docetaxel-based treatment.

cabazitaxel 25 mg/m² is administered IV (Day 1) over 1 hour every 3 weeks

2.5 Regulatory Background

- 04/1999, IND 56,999 activated
- 06/2006 End of Phase 2 meeting
- 09/2006 SPA agreement for EFC6193
- 11/2009 Fast Track designation for mHRPC patients
- 02/2010 PreNDA meeting
- 03/31/2010 NDA 201,023 submission

3 Studies Submitted

3.1 Studies Reviewed

Pharmacodynamics

Study #	Title
RPR/RD/DISC/BIOL/CR VA 973	RPR 116258: Effects on the polymerization-depo0lymerization of pure tubulin *In vitro*
RPR/RD/DISC/BIOL/CR VA 974	*In vitro* antiproliferative activity against sensitive and multidrug resistant murine and human tumor cell lines
SRI1999	*In vitro* cytotoxicity study of RPR 116258 in chemotherapeutic resistant tumor cell lines
IVT0056	RPR 116258: *In vitro* activity of 2 related metabolites RPR 112698 and RPR 123142 on the P388 cell line compared to RPR 116258

Study #	Title
RPR/RD/DISC/BIOL/CR VA 971	RPR 116258: *In vivo* evaluation in tumor bearing nice
RPR/RD/DISC/BIOL/CR VA 995	RPR 116258: *In vivo* evaluation in tumor bearing nice (additional data)
IVV0047	Response of sc GXF-209 human gastric tumor to treatment with docetaxel or RPR 116258A (Study AVE-31B).
IVV0047ext	Response of sc GXF-209 human gastric tumor to treatment with docetaxel or RPR 116258A - EXT (Study AVE-31B).
IVV0084	RPR 116258A: *In vivo* evaluation in comparison with docetaxel and ixabepilone in a human docetaxel-insensitive tumor model.
SRI1998	Evaluation of RP 56976, RPR 109881A, RPR 116258, and RPR 116258(L) for antitumor activity against sc and intracranially implanted human glioblastomas U251 and SF-295 in NCr-nu mice
990018-S-810/830	RPR 116258: *In vitro* receptor binding profile

Safety Pharmacology

Study #	Title
PAT0192	XRP6258: *In vitro* Effects on the Cloned hERG Channel Stably Expressed in CHO Cells.
DS/CRVA 98–092	RPR 116258: Effects in the Irwin Test in Male Rats After Intravenous Administration.
DS/CRVA 98–093	RPR 116258: Anti- and Proconvulsant Effects in Male Rats After Intravenous Administration
DS/CRVA 98–094	RPR 116258: Effects in a Tail Flick Test of Nociception in Male Rats After Intravenous Administration.
DS/CRVA 98–095	RPR 116258: Effects on Locomotor Activity in Male Rats After Intravenous Administration
DS/CRVA 98–098	RPR 116258: Effects on Renal Function in Saline-Loaded Male Rats After Intravenous Administration.
DS/CRVA 98–099	RPR 116258: Effects on the Gastrointestinal Transit of a Charcoal Meal in Male Rats After Intravenous Administration.
DS/CRVA 98–100	RPR 116258: Effects on Basal Tone and on Responses to various Spasmogens in the guinea Pig Isolated Ileum
DS/CRVA 98–101	RPR 116258: Effects on Respiration Rate and BodyTemperature in Male Rats After Intravenous Administration
DS/CRVA 98–102	RPR 116258: Effects on General Hemodynamics and Respiration Rate in Anesthetized Male Beagle Dogs After Intravenous Administration
DS/CRVA 98–103	RPR 116258: Effects on Hexobarbital Sleeping Time in Male Rats After Intravenous Administration
DS/CRVA 98–104	RPR 116258: *In Vitro* Effects on Action Potential Parameters in Sheep Isolated Purkinje Fibers.

Pharmacokinetics

Study #	Title
DMPK/FR2245	Determination of RPR 116258 and its metabolite RP56976, in plasma of tumor-bearing mice by LC/MS/MS following a single IV administration at 40 mg/kg
DMPK/FR 2307	Determination Of RPR 116258 In Mouse Plasma By LC/MS/MS
DOS1008	Method and validation of a LC/MS/MS assay for the quantitation of RPR 116258 in lithium-heparin mice plasma
DMPK/US-98-044	Method and validation of an automated LC/MS/MS assay for analysis of RPR 116258 in rat or rabbit plasma

Study #	Title
DOS1040	Validation of an LS/MS/MS assay for the simultaneous quantitation of RPR 116258 and RPR 123142 in heparinized rat plasma
DMPK/FR 2230	Determination of RPR 116258 and its metabolite RP 56976 In dog plasma by LC/MS/MS
DMPK/FR 2314	Improvement of the determination of RPR 116258 in dog plasma by LC/MS/MS
DOS1041	Validation of an LC/MS/MS assay for the simultaneous quantitation of RPR 116258 and RPR 123142 in heparinized dog plasma
DMPK/FR 2246	Determination of RPR 116258 and its metabolite RP 56976, in tumors of tumor-bearing mice by LC/MS/MS following a single IV administration at 40 mg/kg
DMPK/FR 2250	Determination of RPR 116258 and its metabolite RP 56976, in brains of tumor-bearing mice by LC/MS/MS following a single IV administration at 40 mg/kg
DMPK/FR 2256	Determination of RPR 116258 and its metabolite RP 56976, in liver of tumor-bearing mice by LC/MS/MS following a single IV administration at 40 mg/kg
DOS1319	Validation of an LC/MS/MS assay for the quantitation of XRP 6258 (RPR 116258) in rabbit plasma
SPP0254	Long-Term Stability Of XRP 6258 (RPR 116258) In Rabbit Plasma
DMPK/FR 2329	RPR 116258 - Intravenous Pharmacokinetic Study In CD2F1 Female Mice Following A 1-Hour Infusion
DMPK/FR 2281	Pharmacokinetics And Tissue Distribution In Mammary 16/C Tumor-Bearing Mice (C3H/HeN) After A Single, Intravenous Administration of 40 mg/kg (120 mg/m²)
ABS0529	Pharmacokinetics following a single 1-hour infusion of XRP 6258 at the dose of 2.5 mg/kg (15 mg/m²) to male Sprague Dawley rats
LPR0995	*In vitro* protein binding of [^{14}C]-XRP 6258 to mouse, rat, rabbit, dog and human plasma proteins
PKFAC 9901	*In Vitro* Blood Distribution Of RPR 116258
DMPK/FR 2263	14C-RPR 116258 - Radioactivity kinetics and excretion in the C3H/HeN mouse following a single, intravenous administration at 20 mg/kg (or 60 mg/m²).
DMPK/FR 2295	The pharmacokinetics and distribution, of 14C-RPR 116258 in the blood, plasma and brain of the mouse, following an intravenous infusion at 30 mg/m².
DMPK/FR 2251	^{14}C-RPR 116258 - Radioactivity kinetics in the male and female rats following a single, intravenous administration at 2.5 mg/kg
DMPK/FR 2285	The pharmacokinetics, distribution, and metabolism of ^{14}C-RPR 116258 in the blood, plasma and brain of the mouse, rat and dog following intravenous infusions of doses ranging from 15 to 90 mg/m^2.
DMPK/FR.2268	^{14}C-RPR 116258 - Distribution by whole-body autoradioluminography in male and female albino rats and male pigmented rats following a single, intravenous administration at 2.5 mg.kg-1 (15 mg.m-2)
PLT0080	Placental transfer of total radioactivity after intravenous administration of [14C]-XRP6258 at the dose of 0.08 mg/kg (0.48 mg/m2) to pregnant Sprague-Dawley rats
DMPK/FR 2270	^{3}H-RPR 116258 : *In vitro* metabolism in liver microsomes from mouse, rat, rabbit, dog, monkey and man
DMPK/FR 2310	^{14}C-RPR 116258- Metabolic profiles of ^{14}C-RPR 116258 in female mice following a single intravenous administration at 20 mg/kg or 60 mg/m^2
DMPK/FR 2306	^{14}C-RPR 116258- Metabolic profiles of ^{14}C-RPR 116258 in male and female rats following a single intravenous administration at 2.5 mg/kg
MET0741	*In vivo* metabolism of XRP 6258 following a 60-min single intravenous infusion of [^{14}C]-XRP6258 at 0.5 mg/kg to male dogs
MIS0099	*In vivo* inter-species comparison of XRP 6258 metabolism following a single intravenous infusion of [^{14}C]-XRP 6258 to mice, rats, dogs and human

Study #	Title
RPR/RD/SA/CRVA 00-439	RPR116258A : *In-Vitro* Cytochrome P450 Enzyme Induction Study In Primary Cultures Of Rat Hepatocytes
DMPK/FR. 2262	^{14}C-RPR 116258 - Radioactivity excretion in the male and female rats following a single, intravenous administration at 2.5 mg/kg
DMPK/FR 2252	^{14}C-RPR 116258 - Radioactivity excretion in the bile duct of canulated male rats following a single intravenous administration at 2.5 mg/kg
AEB0312	Excretion balance and pharmacokinetics of total radioactivity and XRP 6258 after a single 1-hour intravenous infusion of [^{14}C]-XRP 6258 at the dose of 0.5 mg/kg (10 mg/m²) to male beagle dogs
MIL0014	Milk excretion of total radioactivity after intravenous administration of [^{14}C]-XRP 6258 at the dose of 0.08 mg/kg (0.48 mg/m^2) to lactating female Sprague-Dawley rats

TOXICOLOGY

Repeat-dose studies

Study #	Title
TSK0038	XRP6258 – 10-Cycle Intravenous (1-hour infusion) Toxicity Study in Rats (each Cycle Consisting of a Single Injection Every 3 Weeks) Followed by an 8-Week Treatment-free Period.
TSK0037	XRP6258: 13-Cycle Intravenous Toxicity Study In Dogs (Consisting Of A Single Administration Every 3 Weeks) With 3-Day Observation And 8-Week Recovery Periods

Genotoxicity

Study #	Title
DS/CRVA 98–020	RPR 116258: Bacterial Reverse Mutation Test
HIS1883	XRP6258 (batch spiked with impurities) - Bacterial reverse mutation test (Ames test)
DS/CRVA 98–022	RPR 116258: *In Vitro* Chromosome Aberration Test In Cultured Human Peripheral Blood Lymphocytes
DS/CRVA 98–023	RPR 116258: Intravenous Bone Marrow Micronucleus Test In Rats
DS/CRVA 98–156	RPR 116258A (Batch P98041me): Bacterial Reverse Mutation Test

Reproductive and Developmental Toxicity

Study #	Title
SA/CRVA 99-264	RPR 116258A: Intravenous Male Fertility Study In Rats
SA/CRVA 00-069	RPR 116258A - Intravenous Female Fertility And Early Embryonic Developmental Toxicity Study In Rats
DS/CRVA 99–018	RPR 116258A: Intravenous Embryofetal Developmental Toxicity Study In Rats
SA/CRVA 99–019	RPR 116258A: Intravenous Embryofetal Developmental Toxicity Study In Rabbits
DS/CRVA 98–034	RPR 116258: 13–Day Intravenous Exploratory Toxicity Study In Female Rabbits
DS/CRVA 98–035	RPR 116258: Intravenous Range–Finding Toxicity Study In Pregnant Rabbits
DS/CRVA 98–036	RPR 116258: Intravenous Range–Finding Toxicity Study In Pregnant Rats

Reviewed under IND 56,999

Safety Pharmacology

DS/CRVA 98–026	RPR 116258: Local Intravenous, Paravenous or Intra–Arterial Tolerance Study In Male Rabbits
DS/CRVA 98–025	RPR 116258: *In Vitro* Compatibility and Hemolytic Potential With Human Plasma, Serum and Blood

Pharmacokinetics

DMPK/FR 2242	Pharmacokinetics in dogs after a single IV infusion at 0.25, 0.5 or 1 mg/kg

Single-dose studies

Study #	Title
DS/CRVA 97–114	RPR 116258: Single–Dose Intravenous Range–Finding Lethality Study In Mice With A 2–Week Observation Period
DS/CRVA 98–027	RPR 116258: Single–Dose Intravenous Lethality Study In Mice With A 4–Week Observation Period
DS/CRVA 98–157	RPR 116258A (Batch P98041ME): Single–Dose Intravenous Lethality Study In Mice With A 4–Week Observation Period
DS/CRVA 98–030	RPR 116258: Single–Dose Intravenous Neurotoxicity Study In Mice With 2–Week And 10–Week Observation Periods
DS/CRVA 99–029	RPR 116258A: Single–Dose Intravenous Neurotoxicity Study In Mice With Histopathological Evaluation On Days 5, 10, 15 And 28
DS/CRVA 98–028	RPR 116258: Single–Dose Intravenous Toxicity Study In Rats With A 4–Week Observation Period
DS/CRVA 97–115	RPR 116258: Single–Dose Intravenous Range–Finding Toxicity Study In Dogs With A 4–Week Observation Period
DS/CRVA 98–029	RPR 116258: Single–Dose Intravenous Toxicity Study In Dogs With An 8–Week Observation Period

Repeat-dose studies

DS/CRVA 98–031	RPR 116258: 5–Day Intravenous Lethality Study In Mice With A 4–Week Observation Period
DS/CRVA 98–032	RPR 116258: 5–Day Intravenous Toxicity Study In Rats With A 4–Week Observation Period
DS/CRVA 98–033	RPR 116258: 5–Day Intravenous Toxicity Study In Dogs With An 8–Week Observation Period
DS/CRVA 97–116	RPR 116258: 5–Day Intravenous Range–Finding Lethality Study In Mice With A 2–Week Observation Period
DS/CRVA 97–117	RPR 116258: 5–Day Intravenous Range–Finding Toxicity Study In Dogs With A 4–Week Observation Period

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3.3 Previous Reviews Referenced

IND 056,999

4 Pharmacology

4.1 Primary Pharmacology

Study title: RPR 116258: Effects on the Polymerization-Depolymerization of Pure Tubulin *In Vitro*

Study no.:	RPR/RD/DISC/BIOL/CRVA 973
Study report location:	EDR 4.2.1.1
Conducting laboratory and location:	Rhone-Poulenc Rorer Research & Development Alfortville, France
Date of study initiation:	November 1994
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	RPR 116258/ PHI 3665 Docetaxel (RP 56976)/ PRS 120 Paclitaxel (RP 48725)/ BEZ 5546

Methods

Purpose: To evaluate the effects of RPR 116258 on microtubule assembly/disassembly in comparison to known taxoids docetaxel and paclitaxel

Study design: Turbidity was measured in a spectrophotometer as an indication of microtubule formation. Increased turbidity correlates with increased microtubule presence.

Polymerization: Taxoids (0.1 to 1 µM in DMF) were added to 6 µM tubulin (supplemented with 6mM MgCl2 and 1 mM GTP). Polymerization was initiated by shifting the temperature from 2°C to 37°C. Turbidity was recorded. The concentration of taxoid at which decreased the lag time to polymerization by 50% (LT50) was determined.

Disassembly: Cold reversibility of 9µM tubulin (supplemented with 6mM MgCl2 and 1 mM GTP) polymerized at 37°C in the presence of taxoids (0.25 to 5µM) for 30 min. was evaluated by dropping the temperature and recording time until completed drop in turbidity. The IC_{50} (concentration at which depolymerization rates decreased by 50%) was determined.

Results:

The addition of RPR 116258 to tubulin resulted in decreased lag time during polymerization in a dose depedendent manner. Treatment of polymerized tubulin with RRP 116258 also resulted in stabilization of microtubules. The effects of RPR 116258 in these assays were comparable to docetaxel at the same concentrations and were

more pronounced than the effects of paclitaxel at the lowest conentrations examined. Thus, RPR 116258 has the same effects on tubulin polymerization and depolymerization as other taxoids.

Study title: RPR 116258: *In Vitro* Antiproliferative Activity Against Sensitive and Multidrug Resistant Murine and Human Tumor cell Lines

Study no.:	RPR/RD/DISC/BIOL/CRVA 973
Study report location:	EDR 4.2.1.1
Conducting laboratory and location:	Rhone Poulenc Rorer Research & Development Alfortville, France
Date of study initiation:	June 1995
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	RPR 116258/ HEB 697, LIE 1061, PHI 3665 Docetaxel (RP 56976)/ PRS 120

Methods

Purpose:
- To evaluate the cytotoxicity of RPR 116258 in a panel of murine and human parent cell lines or lines selected for drug resistance.
- To compare the cytotoxicity of RPR 116258 to docetaxel.

Study design: Cell lines in the exponential growth phase were added to 96 well plates with varying concentrations of RPR 116258 or docetaxel. Growth inhibition (IC_{50}) was determined

Results

Table 1: Cabazitaxel *In Vitro* Inhibition of Tumor Cell Lines

Cell line	IC_{50} (µg/mL)		Docetaxel/ RPR 116258
Murine	Docetaxel	RPR 116258	
P388 (murine leukemia)	0.065±0.003	0.034±0.03	1.91
P388/DOX*	3.3±0.23	0.34±0.03	8.82
P388	0.032±0.01	0.0108±0.0038	2.96
P388/VCR*	0.187±0.031	0.02±0.0025	9.35
P388	0.032±0.01	0.0108±0.0038	2.96
P388/TXT*	0.155±0.018	0.02±0.012	7.75
P388	0.057±0.001	0.031±0.012	1.84
P388/CPT5	0.6±0.05	0.15±0.012	4
Human			
HL60 (leukemia)	0.025±0.0029	0.0178±0.008	1.4
HL60/TAX (paclitaxel resistant)*	0.203±0.085	0.046±0.024	4.41
KB (epidermoid carcinoma)	0.034±0.017	0.029±0.021	1.17
KB VI (vinblastine resistant)*	2.0±0.1	0.223±0.011	8.97
Calc18 (breast adenocarcinoma)	0.0062±0.0014	0.0030±0.0018	2.07
Calc18/TXT (docetaxel resistant)*	0.141±0.031	0.0134±0.0032	10.5
CaCo-2 (colon carcinoma, docetaxel resistant)	0.108±0.017	0.022±0.003	4.91

*Expressed mdr1 mRNA (P-gp+)

A wide panel of cell lines showed similar sensitivity to RPR 116258 compared to docetaxel. In addition, RPR 116258 demonstrated significantly greater cytotoxicity than docetaxel in drug resistant cell lines, including docetaxel resistant cells. IC_{50} values calculated in the *in vitro* assay were all below Cmax for the therapeutic human range.

Study title: *In Vitro* Cytotoxicity Study of RPR 116258 in Chemotherapeutic Resistant Tumor Cell Lines

Study no.:	(b) (4) 1999
Study report location:	EDR 4.2.1.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	1 1999
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	RPR 116258/ BFC611 Doxorubicin/ NSC 123127

Methods

Concentrations:	0.03-1000 ng/mL
Purpose:	To determine concentrations at which RPR 116258 has some activity in inhibition of chemosensitive and chemoresistant cell lines.
Study design:	18 cell lines (chemoresistant and parent cells) were incubated with vehicle, media only, RPR 116258, or a doxorubicin positive control.

Results

(Excerpted from Sponsor)

Table 2: Cabazitaxel *In Vitro* Inhibition of Chemoresistant Cell Lines

IC_{50} (ng/mL)			
Cell Line (murine)	**Day 3**	**Day 4**	**Day 5**
L1210	7.62	7.92	14.04
L1210/ADR	75.38	78.48	90.10
L1210/ARA-C	6.05	7.79	8.81
L1210/CPA	7.89	7.28	7.51
L1210/DDPt	4.72	7.46	8.82
L1210/5-FU	ND	2.32	2.16
L1210/L-PAM	9.17	9.29	11.68
P388	5.80	6.52	7.24
P388/ACT-D	49.33	75.73	72.75
P388/MTX	5.60	6.93	6.89
P388/VCR	2.51	4.01	6.12
P388/VP-16	10.23	21.98	20.92
Cell Line (human)	**Day 3**	**Day 5**	**Day 7**
A549	2.92	13.78	11.46
A549/VP-16	2.18	2.82	4.89
LOX IMVI	2.92	2.74	2.06
LOX/VCR	2.80	4.14	2.78
MCF7	8.26	18.51	6.57
MCF7/ADR	5.84	16.34	10.50

ND Not determined due to limited growth of untreated cell controls.

IC_{50} values for a range of murine and human parent and chemoresistant cell lines fell between 2 and 90 ng/mL. IC_{50} values remained stable over the 5 (murine) or 7 (human) day test period with the biggest increases (when present) occurring between Day 3 and Day 5.

Study title: RPR 116258: *In Vitro* Activity of 2 Related Metabolites RPR 112698 and RPR 123142 on the P388 Cell Line Compared to RPR 116258

Study no.:	IVT0056
Study report location:	EDR 4.2.1.1
Conducting laboratory and location:	Sanofi-aventis research & development Vitry-sur-Seine Cedex, France
Date of study initiation:	July 3, 1998
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	RPR 116258/ PHI 3700/ 100% RPR 112698/ ALA 5299/ 100% RPR 123142/ PAZ 05086/ 100%

Methods

Concentrations:	0.0001-10 µg/mL
Purpose:	To determine the effects of RPR 116258 and two of its major metabolites (RPR 112698 and RPR 123142) on *in vitro* cell proliferation

Study design: The murine leukemia cell line P388 was incubated for 96 hours with RPR 116258 or its metabolites. IC_{50} was determined for all compounds tested.

Results

(Excerpted from Sponsor)

Table 3: Inhibition of P388 by Cabazitaxel and Its Metabolites

List of tested compounds	Number of individual experiments	Mean IC_{50}rel values (µg/ml)
RPR 116258	2	0.01656
RPR 112698	3	0.03357
RPR 123142	3	0.01938

RPR 116258 and its 2 metabolites RPR 112698 and RPR123142 inhibit the proliferation of P388 cells to a similar extent.

Study title: RPR 116258: *In Vivo* Evaluation in Tumor-Bearing Mice

Study no.: RPR/RD/DISC/BIOL/CRVA 971
Study report location: EDR 4.2.1.1
Conducting laboratory and location: Rhone-Poulenc Rorer Research & Development Alfortville, France
Date of study initiation: January 1995
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: RPR 116258/ HEB 697, LIE 809,LIE 1059,LIE 1061, PHI 3647, PHI 3665, PHI 3700 Docetaxel/ PRS 120, FCH 160/ 100%

Methods

Purpose: To examine the ability of RPR 116258 to decrease tumor burden of a panel of solid or hematologic tumors in a variety of mouse xenograft models

Study design: Solid tumors: Mice were implanted bi-laterally on Day 0 with early or late stage solid tumors. Treatment (IV injection) was started 3 to 17 days later depending on the type of tumor. Mice were weighed as a group 3-5 times weekly until a nadir was reached, 1-2 times weekly thereafter. Tumors were measured 2-3 times weekly with a caliper. Tumor weights were determined to calculate anti-tumor activity.

Hematologic tumors: Mice were implanted i.p. on Day 0 with 1 x 10^6 leukemia cells. Treatment was started on Day 1.

Results

Table 4: *In Vivo* Tumor Effects

Tumor Model Regimen	2X/3X weekly			3X Daily X 5		
	+ anti-tumor activity	Delay of tumor progress.	Tumor free survival	+ anti-tumor act.	Delay of tumor progress	Tumor free survival
Melanoma						
B16	x	x	nd			
B16/TXT (docetaxel resistant)	x	x	nd			
Colon						
C38 (adenocarc)	x	x	x			
C51 (mucinous adenocarc)	x	x	nd			
Pancreatic						
P03 (Grade II)	x	x	x			
P02 (Grade III)	x	x	nd			
Mammary						
MA16/C	x	x	nd	x	x	
MA17/A	x	x	x	x		
Human Mammary						
Calc18	x	x	x			
Calc18/TXT (docetaxel resistant)		x	nd			
Lung						
3LL	x	x	nd			
Leukemia						
P388	x	x	0			
P388/VCR (vincristine resistnant)						

*nd: data not shown

RPR 116258 demonstrated activity in all tested xenograft models with the exception of the vincristine resistant leukemia. While a variety of IV dosing regimens were tested, the daily and 3 times daily regimens were more toxic than the 2 to 3 times weekly regimens. RPR 116258 showed activity even in cell lines that were resistant to docetaxel.

Study title: RPR 116258A: *In Vivo* Evaluation in Tumor-Bearing Mice (additional data)

Study no.: RPR/RD/DISC/BIOL/CRVA 995
Study report location: EDR 4.2.1.1
Conducting laboratory and location: Rhone-Poulenc Rorer Research & Development Alfortville, France
Date of study initiation: September 1998
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: RPR 116258/ PHI 3700/ RPR 116258A/P98058ME/ 92.5% Docetaxel/ 9714320/ 100%

Methods

Study design: Swiss nude mice were bilaterally implanted with solid tumor cell lines by ip injection on Day 0. Treatment by IV injection (0.4 mL/dose) with

RPR 116258, RPR 116258A or docetaxel was started 8 to 24 days after tumor transplantation. Mice were weighed as a group 3-5 times weekly until a nadir was reached, 1-2 times weekly thereafter. Tumors were measured 2-3 times weekly with a caliper. Tumor weights were determined to calculate anti-tumor activity.

Results

Table 5: *In Vivo* Effects on Human Tumor Models

Human Tumor Model	HNTD (mg/kg)	# of doses	+ anti-tumor activity**	Delay of tumor progress	Tumor free survival
Colon					
HCT 116 (carcinoma)	12	3	+	+	+
HT-29 (adenocarcinoma)*	7.4	3	+	+	
HCT-8 (non-met adeno)*	14	2		+	
Lung					
NCI-H460 (large cell carc.)	12	2	+	+	
A549 (carc)*	12	3	+	+	
Head and Neck					
SR475 (carc)*	14	3	+	+	+
Pancreas					
MIA PaCa-2*	12	4	+	+	+
Kidney					
Caki-1 (clear cell carc)*	12	2	+	+	
Prostate					
DU 145 (non androgen sens. carc)	12	4	+	+	+

*docetaxel control included
** anti-tumor activity was considered + if complete or partial regressions were observed at HNTD

RPR 116258A delayed tumor progression and showed anti-tumor acitivity against a variety of human tumor xenografts. In the one tumor cell line that did not have any recorded regressions at the highest non-toxic dose, the HCT-8 colon adenocarcinoma, there was still evidence of a delay in tumor progression. 4/9 lines tested showed tumor free survival at the HNTD for RPR 116258A. In instances where the activity of RPR 116258A was compared to docetaxel, RPR 116258A showed anti-tumor activity at lower doses, but with similar or better numbers of regressions.

Study title: Responses of sc GXF-209 Human Gastric Tumor to Treatment with Docetaxel or RPR 116258A

Study no.: IVV0047 (sponsor)
AVE-31B (b) (4)
Study report location: EDR 4.2.1.1
Conducting laboratory and location: (b) (4)
Date of study initiation: September 7, 2005
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: RPR 116258A

Docetaxel

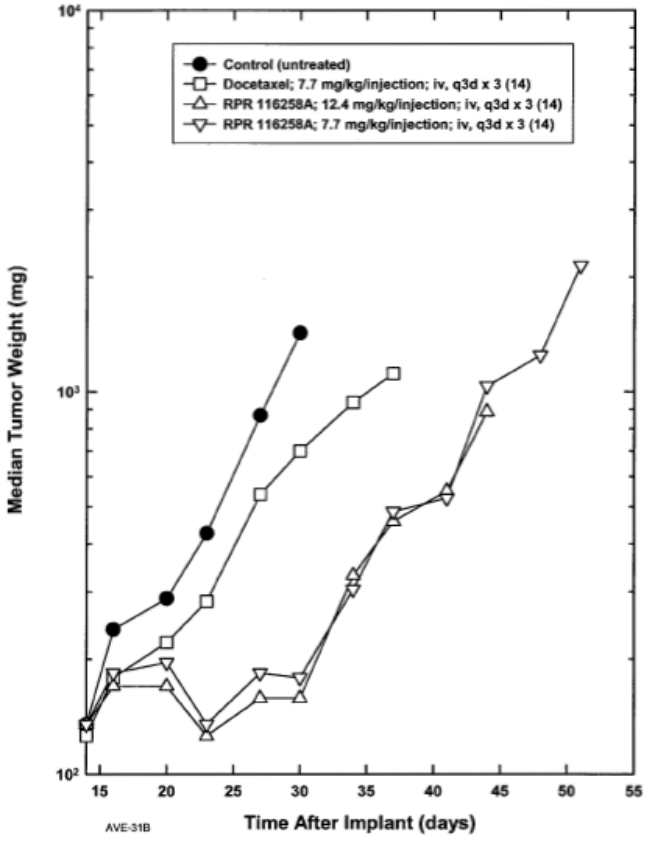
Methods

Doses:	0, 7.7, 12.4, 20, and 32.3 mg/kg RPR 116258A or Docetaxel
Frequency of dosing:	Once every 3 days for a total of 3 injections
Route of administration:	IV injection
Dose volume:	0.4 mL
Formulation/Vehicle:	5% EtOH, 5% Tween-80, 90% D5W (5% dextrose)
Species/Strain:	Nude mice
Number/Sex/Group:	8 females/group
Age:	~6 weeks
Study design:	30-40 mg fragments of the human gastric tumor GXF-209 were implanted subcutaneously into the right flank of nude mice and allowed to grow for 14 days to a weight of 126-135 mg before the beginning of treatment.

Results

(Excerpted from Sponsor)

Figure 1: Response of SC GXF-209 Gastric Tumor to Treatment with Docetaxel or RPR 116258A



Treatment with doses ≥ 12.4 mg/kg for docetaxel or 20 mg/kg for RPR 116258 resulted in at least 1/8 deaths in each treatment group. Treatment with the lower doses of RPR 116258 showed an increased delay of tumor growth compared to control or low dose docetaxel treated animals though there were no tumor free survivors. Thus, in this gastric tumor model RPR 116258 showed some mild tumor inhibition.

Study title: RPR 116258A: *In Vivo* Evaluation in Comparison with Docetaxel and Ixabepilone in a Human Docetaxel-Insensitive Tumor Model

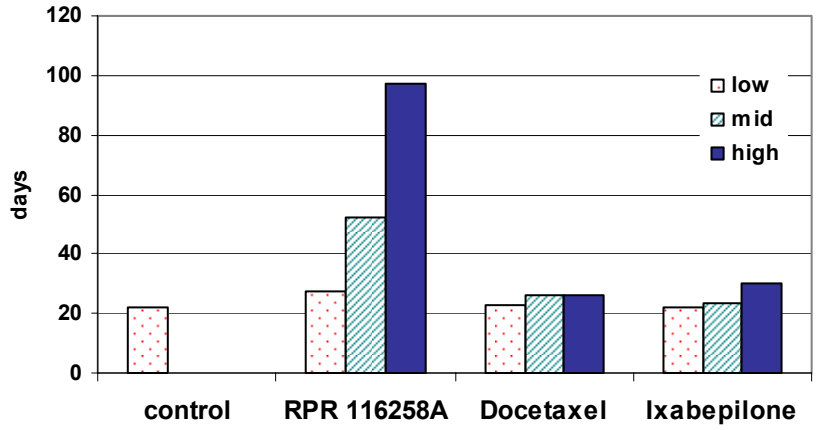
Study no.:	IVV0084
Study report location:	EDR 4.2.1.1
Conducting laboratory and location:	Sanofi-aventis Research & Development Vitry-sur-Seine Cedex, France
Date of study initiation:	December 26, 2007
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	RPR 116258A/ GRV1286, P99043S/ 93.8% Docetaxel/ 6057SS/ 99.7% Ixabepilone/ P-34029-157-1

Methods

Doses:	RPR 116258A, Docetaxel: 5.8, 9.3, 15, and 24.2 mg/kg Ixabepilone: 2.2, 3.6, 5.8, and 9.3 mg/kg
Frequency of dosing:	Days 13, 16, and 19
Route of administration:	IV
Dose volume:	0.4 mL
Formulation/Vehicle:	5% ethanol / 5% Polysorbate 80 / 90% glucose-5% in sterile water
Species/Strain:	SCID mice
Number/Sex/Group:	10 females control 5 females/group
Age:	8-10 wks.
Weight:	18.38-23.31g
Study design:	SCID mice were implanted subcutaneously with established docetaxel resistant UISO BCA-1 (Her-2 +) human breast carcinomas. Treatment with RPR 116258A, docetaxel, or ixabepilone began 13 days after tumor implantation when tumors had reached a weight of 66-79 mg.

Results

Figure 2: Time for Mean Tumor Weight to Reach 1000 mg



Low: 5.8 mg/kg RPR 116258A, Docetaxel 2.2 mg/kg Ixabepilone
Mid: 9.3 mg/kg RPR 116258A, Docetaxel 3.6 mg/kg Ixabepilone
High: 15 mg/kg RPR 116258A, Docetaxel 5.8 mg/kg Ixabepilone

The UISO BCA-1 was confirmed by flow cytometry to be Her-2+, but did not express high levels of P-gp. Despite the lack of P-gp expression, treatment of animals receiving xenografts of this breast cancer line with docetaxel showed that the tumor was in fact docetaxel resistant. Similarly, the tumor was not sensitive to treatment with ixabepilone. RPR 116258A treatment did, however, result in a significant dose-dependent delay in tumor growth at doses ≥9.3 mg/kg, suggesting that the drug may have an effect in docetaxel resistant tumors.

Study title: Evaluation of RP 56976, RPR 109881A, RPR 116258, and RPR 116258(L) for Antitumor Activity Against Subcutaneously and Intracranially Implanted Human Glioblastomas U251 and SF-295 in NCr-nu Mice

Study no.:	(b) (4)-1998
Study report location:	EDR 4.2.1.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	October 17, 1998
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	RP 56976/ 9714320 RPR 109881A/ P96079K RPR 116258/ BFC611 RPR 116258(L)/ GRV1228 BCNU/ LF080 L-4/ LLH84

Methods

Doses: 0, 15, 22, and 33 mg/kg (RP 56976, RPR 109881A)
0,13.4, 20, and 30 mg/kg (RPR 116258, RPR 116258 (L))
Frequency of dosing: Every 4 days for 3 doses: SF-295
Every 6 days for 3 doses: U251
Route of administration: IV
Dose volume: 0.4 mL
Formulation/Vehicle: 5% EtOH, 5%Tween-80, 90% D5W (5% dextrose)
Species/Strain: NCr-nu mice
Number/Sex/Group: 10/ dose/drug
Age: 6-8 wks
Weight: 21-26 g
Study design: A set of 4 experiments was performed. In RP-35 and RP-34 the U251 and SF-295 glioblastoma tumors were implanted subcutaneously in nude mice. In RP-36 and RP-38, the same tumors were implanted intracranially.

Tumor	Treatment Initiation	
	Subcutaneous	Intracranial
U251	Tumor weight:100-150 mg	4 days post-transplant
SF-295	1 day post-transplant	2 days post-transplant

Results

RPR 116258 showed activity against the U251 and SF-295 glioblastoma lines in both subcutaneous and intracranial transplantation models. While docetaxel (RP 56976) showed greater activity than RPR 116258 in the subcutaneous models, RPR 116258 had greater activity in the intracranial models (at doses that were not toxic).

Table 6: Effects on Subcutaneous or Intracranially Implanted Tumors

Subcutaneous SF-295

Drug	Dose (mg/kg)	Early Deaths	Tumor Free Survival	Days of Delay
Control	0		0/20	
RP 56976	15		4/9	34.5
	22		2/9	77
	33		7/9	>84.9
RPR 109881A	15		0/9	13.7
	22		1/9	22
	33		2/9	38.7
RPR 116258	13.4		0/9	18.9
	20		2/9	39.7
	30		1/9	67.5
RPR 116258(L)	13.4		1/9	28.4
	20		2/9	75.3
	30		2/9	65.3
BCNU (+ control)	12		0/9	5.3
	18		1/9	11.7
	27		4/9	>84.9

Subcutaneous U251

Drug	Dose (mg/kg)	Early Deaths	Tumor Free Survival	Days of Delay
Control	0		1/20	
RP 56976	15	1/10	7/10	>85.7
	22	1/10	7/10	>85.7
	33	1/10	9/10	>85.7
RPR 109881A	15	0/10	1/10	36.6
	22	2/10	0/10	41.8
	33	0/10	1/10	54.4
RPR 116258	13.4	0/10	6/10	>85.7
	20	0/10	3/10	81.2
	30	3/10	4/10	>85.7
RPR 116258(L)	13.4	2/10	5/10	>85.7
	20	2/10	6/10	>85.7
	30	1/10	9/10	>85.7
BCNU (+ control)	12	1/10	1/10	21.8
	18	0/10	2/10	48.1
	27	5/10	2/10	>85.7

Intracranial U251

Drug	Dose (mg/kg)	122-Day Survival	Avg. Day of Death	%ILS*
Control	0	1/20	34	
RP 56976	15	0/10	45	+32
	22	4/10	51.5	+51
	33	3/10	69	+102
RPR 109881A	15	2/10	49	+44
	22	1/10	52	+52
	33	4/10	66	+94
RPR 116258	13.4	3/10	83	+144
	20	4/10	103	+202
	30	5/10	94	+176
RPR 116258(L)	13.4	0/10	49	+44
	20	4/10	59	+73
	30	0/10	80	+135
BCNU (+ control)	12	0/10	51.5	+51
	18	7/10	104	+205
	27	10/10	--	

* % Increased Life Span

Intracranial SF-295

Drug	Dose (mg/kg)	68-Day Survival	Avg. Day of Death	%ILS*
Control	0	0/20	16	
RP 56976	15	1/10	21	+31
	22	0/10	22	+38
	33	0/10	27.5	+72
RPR 109881A	15	0/10	21	+31
	22	1/10	26	+63
	33	0/10	24	+50
RPR 116258	13.4	1/10	29	+81
	20	0/10	31	+94
	30	0/10	14.5	-9
RPR 116258(L)	13.4	0/10	21.5	+34
	20	0/10	22	+38
	30	0/10	20.5	+28
BCNU (+ control)	12	0/10	33	+106
	18	1/10	37	+131
	27	2/10	24	+50

4.2 Secondary Pharmacology

Study title: RPR 116258: *In Vitro* Receptor Binding Profile

Study no.: 990018-s-810/830-e
Study report location: EDR 4.2.1.2
Conducting laboratory and location: (b) (4)
Date of study initiation: April 27, 1997
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: RPR 116258/ PHI 3665/ 94.5%

Methods

Concentrations: 0, 1, 3, and 10 µM
Purpose: To determine the affinity of RPR 116258 for a panel of physiologically important receptors by measuring the ability of RPR 116258 to compete off radioligands to these receptors.
Study design: Membranes or cytosolic fractions were prepared from rat, guinea pig, or calf tissues. Specific binding was defined as the total amount of receptor binding that incubation with the cold reference compound could displace. Percent inhibition was calculated as the decrease of specific binding for each receptor.

Results

.At a concentration of 10 µM RPR 116258 inhibited binding at the dopamine uptake and σ receptors by 18 and 21% respectively. Inhibition of binding of other receptors was lower and not dose-dependent. RPR 116258 caused <25% inhibition of binding at any of the measured receptors.

(Excerpted from Sponsor)

Table 7: Affinities of RPR 116258 for the 25 Binding Sites Studied

Results (mean for 3 determinations) are given as a percentage of inhibition of radioligand specific binding.
IC_{50} is the concentration inhibiting by 50% the radioligand specific binding.

Binding site	% inhibition RPR 116258 (µM)			Reference compound		Laboratory book reference
	1	3	10	name	IC_{50} (nM)	
α_1-adrenoceptor	–	–	–	prazosin	0.35	XT 21.05.97
α_2-adrenoceptor	–	–	–	yohimbine	68.7	XT 16.05.97
β-adrenoceptor	–	–	–	atenolol	3,210	ST 16.05.97
Norepinephrine uptake	–	–	–	protriptyline	3.5	FMO 06.05.97
Benzodiazepine (central)	–	–	–	diazepam	15.8	FMO 21.05.97
D_2 dopamine	–	–	–	(+) butaclamol	20.3	ST 12.05.97
Dopamine uptake	–	–	21	nomifensine	92.0	ST 23.05.97
GABA uptake	–	–	–	nipecotic acid	6,340	LC 15.05.97
glycine (strychnine. sens.)	–	–	–	strychnine	9.2	LC 13.05.97
H_1 histamine	–	–	–	pyrilamine	1.5	NS 07.05.97
Muscarine	–	–	–	atropine	0.42	NL 16.05.97
Nicotine	–	–	–	nicotine	16.4	NL 14.05.97
Opiates	11	–	–	naloxone	3.5	FM 12.05.97
Phencyclidine	10	–	–	(+) MK-801	12.8	CB 15.05.97
5-HT_{1A} serotonin	–	–	–	8-OH-DPAT	3.9	NL 14.05.97
5-HT_2 serotonin	–	–	–	ketanserin	2.0	ST 20.05.97
5-HT uptake	–	–	–	zimelidine	117	FM 15.05.97
σ receptor	–	–	16	haloperidol	70.5	NS 05.05.97
glucocorticoid	–	–	–	dexamethasone	78.0	FM 12.05.97
estrogen	–	–	–	17β-estradiol	1.8	FM 13.05.97
progesterone	–	–	–	R5020	11.1	ST 28.05.97
testosterone	17	18	–	mibolerone	2.2	ST 05.05.97
Ca^{++} channel (verapamil site)	–	–	–	D600	34.5	NS 29.04.97
Na^+ channel (site 1)	–	–	–	tetrodotoxin	9.5	CB 06.05.97
Na^+ channel (site 2)	–	–	–	veratridine	3,840	XT 30.04.97

– : < 10% inhibition

4.3 Safety Pharmacology

<u>Neurological effects</u>:

Study title: RPR 116258: Effects in the Irwin Test in Male Rats After Intravenous Administration

Study no.:	RPR/RD/DS/CRVA 98-092
	(b) (4) RKT00101
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 11, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258/ BFC 611/ 96.5% Chlorpromazine HCl/ 94H1064/

Methods

Doses:	0, 0.5, 1.5, and 5 mg/kg RPR 116258 5% glucose only, 2 mg/kg Chlorpromazine HCl
Frequency of dosing:	Single dose
Route of administration:	IV injection (1 mL/min)
Dose volume:	5 mL/kg
Formulation/Vehicle:	RPR 116258 in PS80 and 13% EtOH diluted in 5% glucose in order to reach 2.5% PS80 and 0.975% EtOH Chlorpromazine HCl in sterile saline
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	6 males/group
Age:	7-9 weeks
Weight:	247-298 g
Study design:	Irwin test to detect effects on the gross behavioral and physiological states of rats
Deviation from study protocol:	

Results

Changes were apparent in the behavior of rats treated with chlorpromazine HCl, the positive control. There were no significant drug-related changes in rat behavior or physiology up to 6 hours after a single dose administration of RPR 116258 at doses up to 5 mg/kg (30 mg/m^2).

Study title: RPR 116258: Effects on Locomotor Activity in Male Rats After Intravenous Administration

Study no.:	RPR/RD/DS/CRVA 98-095
	(b) (4) RKT00104
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 11, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258/ BFC 611/ 96.5% Chlorpromazine HCl/ 94H1064/

Methods

Doses:	0, 0.5, 1.5, and 5* mg/kg RPR 116258 5% glucose only, 5 mg/kg Chlorpromazine HCl
Frequency of dosing:	Single dose
Route of administration:	IV injection (1 mL/min)
Dose volume:	5 mL/kg
Formulation/Vehicle:	RPR 116258 in PS80 and 13% EtOH diluted in 5% glucose in order to reach 2.5% PS80 and 0.975% EtOH Chlorpromazine HCl in sterile saline
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	8 males/group
Age:	7-9 weeks
Weight:	277-326 g
Study design:	Total, amubulatory, and rearing activity was measured continuously for 9 minutes at 30 and 90 minutes post-dosing in transparent observation cages with infrared beam activity meters
Deviation from study protocol:	*4/8 high dose group animals received only 4.4 mg/kg instead of 5 mg/kg due to solution errors

Results
(Excerpted from Sponsor)

Table 8: RPR 116258 Effects on Rat Activity

Group	Treatment	Total Locomotor Counts/min	Ambulatory Counts/min	Rearing Counts/min
E	5 ml/kg Vehicle	581 ± 78.7	427 ± 62.6	27.3 ± 2.9
C	Glucose (5%)	457 ± 63.3	321 ± 55.4	26.5 ± 5.0
A	0.5 mg/kg RPR116258	545 ± 58.5	372 ± 50.3	26.3 ± 2.8
F	1.5 mg/kg RPR116258	616 ± 110.2	411 ± 81.3	22.3 ± 4.4
D	5 mg/kg RPR116258	537 ± 66.6	375 ± 55.9	26.1 ± 3.6
B	5 mg/kg Chlorpromazine	5.5 ± 1.6***	2.4 ± 0.8***	0 ± 0***

Data are presented as mean ± s.e.m., n = 8.

Treatment of rats with 5 mg/kg chlorpromazine, the positive control, resulted in decreased locomotion and rearing activity consistent with its known pharmacologic activity. Treatment of rats with a single dose of up to 5 mg/kg (30 mg/m^2) RPR 116258 had no significant effect on locomotion or rearing.

Study title: RPR 116258: Anti- and Proconvulsant Effects in Male Rats After Intravenous Administration

Study no.:	RPR/RD/DS/CRVA 98-093 (b) (4) RKT00102
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 11, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258/ BFC 611/ 96.5% Sodium Phenobarbital/ 76HO292/ Amphetamine sulfate/ 46HI367/ Pentylenetetrazole/36H0813

Methods

Doses:	0, 0.5, 1.5, and 5 mg/kg RPR 116258 5% glucose Anticonvulsant test: 30 mg/kg sodium phenobarbital Proconvulsant test: 30 mg/kg amphetamine sulphate
Frequency of dosing:	Single dose
Route of administration:	IV injection (1 mL/min) RPR 116258 Oral sodium phenobarbital (in sterile saline) Oral amphetamine sulfate (in sterile saline)
Dose volume:	5 mL/kg
Formulation/Vehicle:	RPR 116258 in PS80 and 13% EtOH diluted in 5% glucose in order to reach 2.5% PS80 and 0.975% EtOH
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	16 males/group (8 in anti-, 8 in proconvulsant tests)
Age:	7-9 weeks
Weight:	252-352 g anticonvulsant 215-292 g proconvulsant
Study design:	Anticonvulsant: 30 min. post dosing rats received 65 mg/kg pentylenetetrazole (subcutaneous injection) Proconvulsant: 30 min. post dosing rats received 32.5 mg/kg pentylenetetrazole (subcutaneous injection) Following pentylenetetrazole injection animals were observed for 45 min. for the occurrence of generalized clonic seizures accompanied by loss of posture. A seizure was defined as a convulsive episode persisting for ≥ 2 seconds. Number of seizures and the presence/absence of tonic flexion/extension of the hindpaws was recorded.
Deviation from study protocol:	Rats in the anticonvulsant test high dose group received only 4.25 mg/kg RPR 116258

Results:

Anticonvulsant Test

(Excerpted from Sponsor)

Table 9: Anticonvulsant Test

Group	Treatment	Number of Animals Exhibiting a Seizure	Time to Onset of First Seizure (s)
H	5 ml/kg Vehicle	8/8	501 ± 82
G	Glucose (5%)	8/8	500 ± 59
L	0.5 mg/kg RPR 116258	8/8	526 ± 70
K	1.5 mg/kg RPR 116258	8/8	571 ± 96
I	4.25 mg/kg RPR 116258	8/8	408 ± 55
J	30 mg/kg sodium phenobarbital	1/8	1123 ***

Data are presented as mean ± s.e.m., n = 8 (except Group J where n = 1).

Proconvulsant Test

(Exceprted from Sponsor)

Table 10: Proconvulsant Test

Group	Treatment	Number of Animals Exhibiting a Seizure
B	5 ml/kg Vehicle	3/8
E	Glucose (5%)	2/8
C	0.5 mg/kg RPR 116258	1/8
D	1.5 mg/kg RPR 116258	3/8
A	5 mg/kg RPR 116258	3/8
F	30 mg/kg amphetamine sulphate	7/8

Administration of a single dose of RPR 116258 at doses up to 5 mg/kg had neither an anti- nor proconvulsant effect.

Study title: RPR 116258: Effects on Hexobarbital Sleeping Time in Male Rats After Intravenous Administration

Study no.:	RPR/RD/DS/CRVA 98-103 (b) (4) RKT00107
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 11, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258/ BFC 611/ 96.5% Hexobarbital Chlorpromazine HCl/ 94H1065

Methods

Doses:	0, 0.5, 1.7, and 5 mg/kg RPR 116258 5% glucose
Frequency of dosing:	Single dose
Route of administration:	IV injection (1 mL/min) RPR 116258
Dose volume:	5 mL/kg
Formulation/Vehicle:	RPR 116258 in PS80 and 13% EtOH diluted in 5% glucose in order to reach 2.5% PS80 and 0.975% EtOH
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	8 males/group
Age:	7-9 weeks
Weight:	267-323 g
Study design:	30 minutes after the end of dosing, animals were given a single IP injection of 125 mg/kg hexobarbital, which causes a loss of the righting reflex. Time to loss of right reflex was then noted. Time taken until regaining the righting reflex was noted and sleeping time was calculated.
Deviation from study protocol:	Animals in the mid dose group were supposed to be dosed at 1.5 mg/kg, however, concentration analysis showed that the actual concentration was 12% higher so animals were actually treated at 1.7 mg/kg

Results

(Excerpted from Sponsor)

Table 11: Effects on Sleep Time

Group	Treatment	Time to Loss of righting reflex (seconds)	Sleeping time (seconds)
F	5 ml/kg Vehicle	108 ± 8	1648 ± 44
B	Glucose (5%)	121 ± 14	1641 ± 91
A	0.5 mg/kg RPR 116258	128 ± 13	1647 ± 134
C	1.7 mg/kg RPR 116258	100 ± 1	1636 ± 153
E	5 mg/kg RPR 116258	105 ± 8	1728 ± 95
D	5 mg/kg Chlorpromazine	76 ± 17	3799 ± 404***

Data are presented as mean ± s.e.m., n = 8.

Chlorpromazine, the positive control substance, caused a mild decrease in the time to loss of righting reflex following administration of hexobarbital along with a significant (~2 fold) increase in sleep time. Treatment with RPR 116258 did not lead to significant changes in time to loss of righting reflex. At the 5 mg/kg dose level animals did have a minor increase in sleeping time (~5% increase, or ~1.5 minutes) compared to vehicle or glucose controls; however, as this increase was small, it did not appear to be a significant effect. There were individual animals at all RPR 116258 dose levels that had recorded sleep times of > 2000s, though no animals in the vehicle or glucose only control groups crossed the 2000s threshold. Thus, at doses up to 5 mg/kg, RPR 116258 had a mild effect on hexobarbital induced sleeping time, though the magnitude of this effect makes it of questionable toxicologic importance.

Study title: RPR 116258: Effects in a Tail Flick Test of Nociception in Male Rats After Intravenous Administration

Study no.:	RPR/RD/DS/CRVA 98-094 (b) (4) RKT00103
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 11, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258/ BFC 611/ 96.5% Morphine HCl/ 23906

Methods

Doses:	0, 0.5, 1.5, and 5 mg/kg RPR 116258 5% glucose 10 mg/kg Morphine HCl
Frequency of dosing:	Single dose
Route of administration:	IV injection (1 mL/min) RPR 116258
Dose volume:	5 mL/kg
Formulation/Vehicle:	RPR 116258 in PS80 and 13% EtOH diluted in 5% glucose in order to reach 2.5% PS80 and 0.975% EtOH
Species/Strain:	Sprague Dawley rats
Number/Sex/Group:	8 males/group
Age:	7-9 weeks
Weight:	249-283 g
Study design:	An infrared heat source was applied to the tail of male rats for ≤ 10 seconds. Time taken for the rat to deflect the tail and tail flick latency was noted. Time-points: -30, -20, -10, and 0 min pre-dose 10, 30, 60, 120, 180 min. post-dose
Deviation from study protocol:	

Results

(Excerpted from Sponsor)

Table 12: Tail Latency/Nociception Effects

		Tail Flick Latency (sec ± s.e.m.) at Time (min) Post Dose							
Group	Treatment	-20	-10	0	10	30	60	120	180
B	5 ml/kg Vehicle	3.0 ± 0.3	2.5 ± 0.2	1.3 ± 0.1	2.7 ± 0.3	2.9 ± 0.2	2.7 ± 0.1	2.8 ± 0.1	2.5 ± 0.2
C	Glucose (5%)	3.3 ± 0.1	2.8 ± 0.3	1.6 ± 0.1	2.4 ± 0.3	3.0 ± 0.2	3.3# ± 0.2	3.0 ± 0.3	3.0 ± 0.3
A	0.5 mg/kg RPR 116258	3.0 ± 0.2	2.6 ± 0.3	1.4 ± 0.2	3.7 ± 0.9	4.0 ± 0.6	3.7 ± 0.5	2.8 ± 0.2	2.7 ± 0.2
E	1.5 mg/kg RPR 116258	3.4 ± 0.2	3.3 ± 0.2	1.4 ± 0.1	3.0 ± 0.5	3.3 ± 0.5	3.7 ± 0.5	3.3 ± 0.4	3.2 ± 0.3
F	5 mg/kg RPR 116258	3.9 ± 0.4	3.0 ± 0.2	1.5 ± 0.1	2.6 ± 0.3	3.6 ± 0.2	3.9 ± 0.3	3.6 ± 0.3	3.8†† ± 0.4
D	10 mg/kg Morphine HCl	3.5 ± 0.4	3.8 ± 0.2	1.7 ± 0.2	10.0*** ± 0	10.0*** ± 0	10.0*** ± 0	9.9*** ± 0.1	8.3*** ± 1.0

Data are presented as mean ± s.e.m., n = 8.

The administration of morphine HCl as a positive control substance resulted in increased tail flick latency in a test of nociception in male rats. There were no

significant increases in tail flick latency demonstrated in rats administered ≤ 5 mg/kg RPR 116258 in the same study, suggesting that the drug does affect nociception.

Cardiovascular Effects

Study title: XRP6258: *In Vitro* Effects on the Cloned hERG Channel Stably Expressed in CHO Cells

Study no.:	PAT 0192
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	Sanofi-Aventis Research & Development Drug Safety Evaluation Rueil-Malmaison, France
Date of study initiation:	September 17, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	XRP6258 (RPR 116258A)/0326012 (20030144)/ 93.2%

Methods

Concentrations:	0, 1.1, 3, 10, and 30 µmol/L XPR6258 in DMSO
Study design:	Standard hERG assay Negative control: DMSO (vehicle) Positive control: cisapride monohydrate (0.1 µmol/L)

Results

Table 13: hERG Assay Inhibition

XPR6258 Concentration (µmol/L)	1.1	3	10	30	+ Cisapride monohydrate
Avg. % Inhibition	4.4%	6.6%	10.2%	15.1%	74.1%

No IC_{50} or IC_{25} was established for XRP6258 in the hERG assay. There was significant hERG inhibition was demonstrated in cells after treatment with the cisapride monohydrate positive control. XRP6258 perfusion did result in a mild increase (~10%) in inhibition at concentrations ≥ 10 µmol/L. This drug concentration was significantly greater than the Cmax concentration that has been observed in humans at the clinically recommended dose. Exposure to XRP6258 is, therefore, not predicted to result in QT prolongation.

Study title: RPR 116258: *In Vitro* Effects on Action Potential Parameters in Sheep Isolated Cardiac Purkinje Fibres

Study no.: RPR/RD/DS/CRVA 98-104
RKT00111
Study report location: EDR 4.2.1.3
Conducting laboratory and location: (b) (4)
Date of study initiation: April 9, 1998
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: RPR 116258/BFC 611/ 96.5%

Methods

Doses: 0, 1, 3, and 10 µM
Study design: Isolated Purkinje fibers (sheep) were electrically paced at 1 Hz.
APD30, APD60, APD90, Vmax, upstroke amplitude, and diastolic membrane potential were recorded.
dl-Sotalol HCl was used as a positive control.
Deviation from study protocol:

Results

(Excerpted from Sponsor)

Table 14: In Vitro Effects on Action Potential

	Treatment Group	
	Vehicle (n = 4)	RPR 116258 (n = 4)
APD_{30} (ms)	62.0 ± 15.5	67.3 ± 17.1
APD_{60} (ms)	220.8 ± 15.1	248.0 ± 29.6
APD_{90} (ms)	273.3 ± 11.5	292.3 ± 33.5
V_{max} (V/s)	590.5 ± 74.1	557.3 ± 39.9
Upstroke amplitude (mV)	116.3 ± 3.4	117.5 ± 2.1
Diastolic membrane potential (mV)	-89.3 ± 2.3	-87.3 ± 2.5

Table 15: *In Vitro* Effects on Action Potential-Difference from Pre-treatment Control

Concentration (µM)	1		3		10		*dl*-Sotalol	
	Vehicle	RPR	Vehicle	RPR	Vehicle	RPR	Vehicle	+
APD30 (ms)	+6.5±5.6	**-6.5±4.6**	+7.5±1.8	**-13.5±13.6**	-9.5±12.1	**-5.3±20.2**	-9.5	**+6.95**
APD60 (ms)	+4.5±6.2	**-6.5±7.8**	+10±5.9	**-11.5±10.7**	-15±10.7	**-16±18**	-15.05	**+40.25**
APD90 (ms)	2.8±5.5	**-5.5±7.9**	+9.3±6.8	**-8.5±9.7**	-5.3±8	**-11.3±13.8**	-5.3	**+68.95**
Vmax (V/s)	+5±14.6	**+7.3±10**	-23.8±17.4	**+21±15.8**	-75±36.8	**-8.3±5.8**	-28.5	**+59.03**
Upstroke Amp. (mV)	+1.0±0.4	**-1.8±1.1**	+1.0±0.6	**-0.3±0.6**	+1.0±3.3	**-2.3±2.6**	+0.95	**+1**
Diastolic Membrane Potential (mV)	+0.8±0.5	**+0.3±0.3**	-0.3±1.4	**-0.3±0.5**	0±1.1	**0±0.4**	+.02	**-4.2**

Changes in measured parameters were calculated as differences from pre-treatment controls. There were no significant dose-dependent increases in APD30, APD60, or APD90 after purkinje fiber perfusion with RPR 116258 at concentrations up to 10 µM despite increases of 40 to 69 ms in the positive control findings. The results of this assay do not predict a significant effect of RPR 116258 on QT prolongation.

Study title: RPR 116258: Effects on General Haemodynamics and Respiration Rate in Anaesthetized Male Beagle Dogs After Intravenous Administration

Study no.:	RPR/RD/DS/CRVA 98-102 RKT00110
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 19, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258/BFC 611/ 96.5%

Methods

Doses:	0 and 0.45 mg/kg RPR 116258 5% glucose solution
Frequency of dosing:	Single dose
Route of administration:	IV infusion (over 60 minutes)
Dose volume:	12mL/kg
Formulation/Vehicle:	RPR 116258 in PS80 and 13% EtOH diluted in 5% glucose in order to reach 2.5% PS80 and 0.975% EtOH
Species/Strain:	Beagle dogs
Number/Sex/Group:	4 males/group
Age:	25-36 weeks
Weight:	11.5-14 kg
Study design:	

Dogs were sedated with acetylpromazine and kept under general anaesthesia (pentobarbitone sodium) for the duration of the study. Devices were surgically implanted to detect the following parameters:

- Arterial blood pressure and heart rate
- Femoral arterial blood flow
- Femoral arterial blood conductance
- Left ventricular pressure
- Cardiac output
- Stroke volume
- Total peripheral resistance
- ECG
- Respiration parameters
- Arterial blood gases

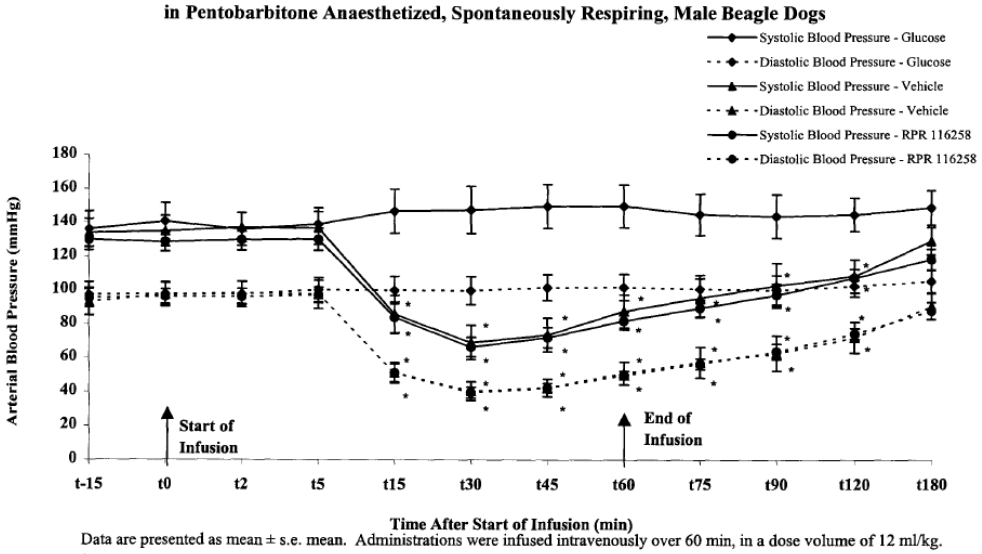
After the surgical implantation, dogs were stabilized for at least 30 minutes before baseline readings were taken. The 5% glucose solution, vehicle, or RPR 116258 were then injected over 60 minutes. The beginning of the injection was designated as t0. Data samples were recorded at -15, t0, +2*, +5, +15, +30, +45, +60, +75, +120, and +180 minutes.
*Cardiac output not recorded
Deviation from study protocol:

Results

There were changes in the blood pressure, heart rate, and ECG parameters in both RPR 116258 and vehicle treated animals compared to animals treated only with 5% glucose. Decreased blood pressure and heart rate in animals treated with vehicle or RPR 116258 were apparent from 15 minutes after the start of infusion until the end of infusion at 60 minutes. Following the end of infusion, both blood pressure and heart rate began to return to baseline measures. Decreased heart rate in vehicle or RPR 116258 treated animals correlated with increased time in ECG parameters (RR, PR, QRS, QT, and QTc). The increase in QT was apparent even in the heart rate corrected QTc. Increases in QTc were higher in RPR 116 258 than in vehicle treated animals with the largest differences seen between 45 and 75 minutes after the beginning of dosing and maxing at an average increase of 49 ms (~13%) above baseline.

(Excerpted from Sponsor)

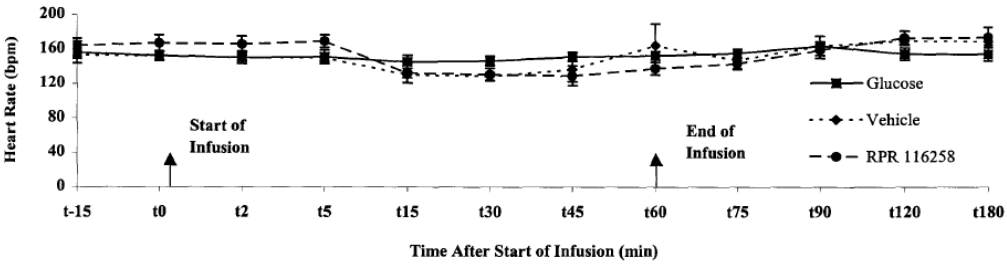
Figure 3: Beagle Dog Arterial Blood Pressure



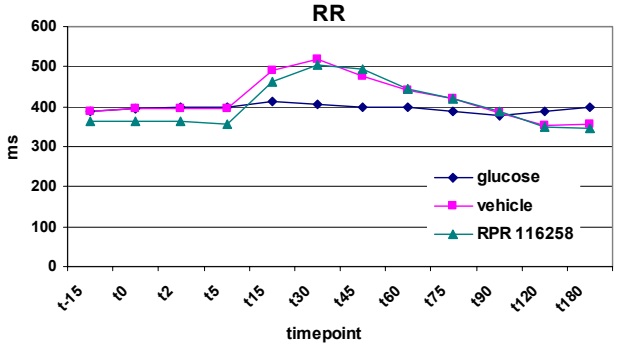
Data are presented as mean ± s.e. mean. Administrations were infused intravenously over 60 min, in a dose volume of 12 ml/kg.
*$P < 0.05$ compare to 5% glucose solution.

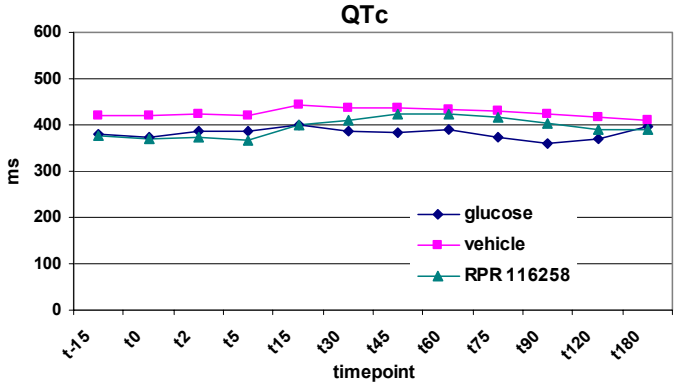
Figure 4: Beagle Dog Heart Rate, RR, QTc

The Effects of 5% Glucose Solution, Vehicle and 0.45 mg/kg RPR 116258 on Heart Rate in Pentobarbitone Anaesthetized, Spontaneously Respiring, Male Beagle Dogs



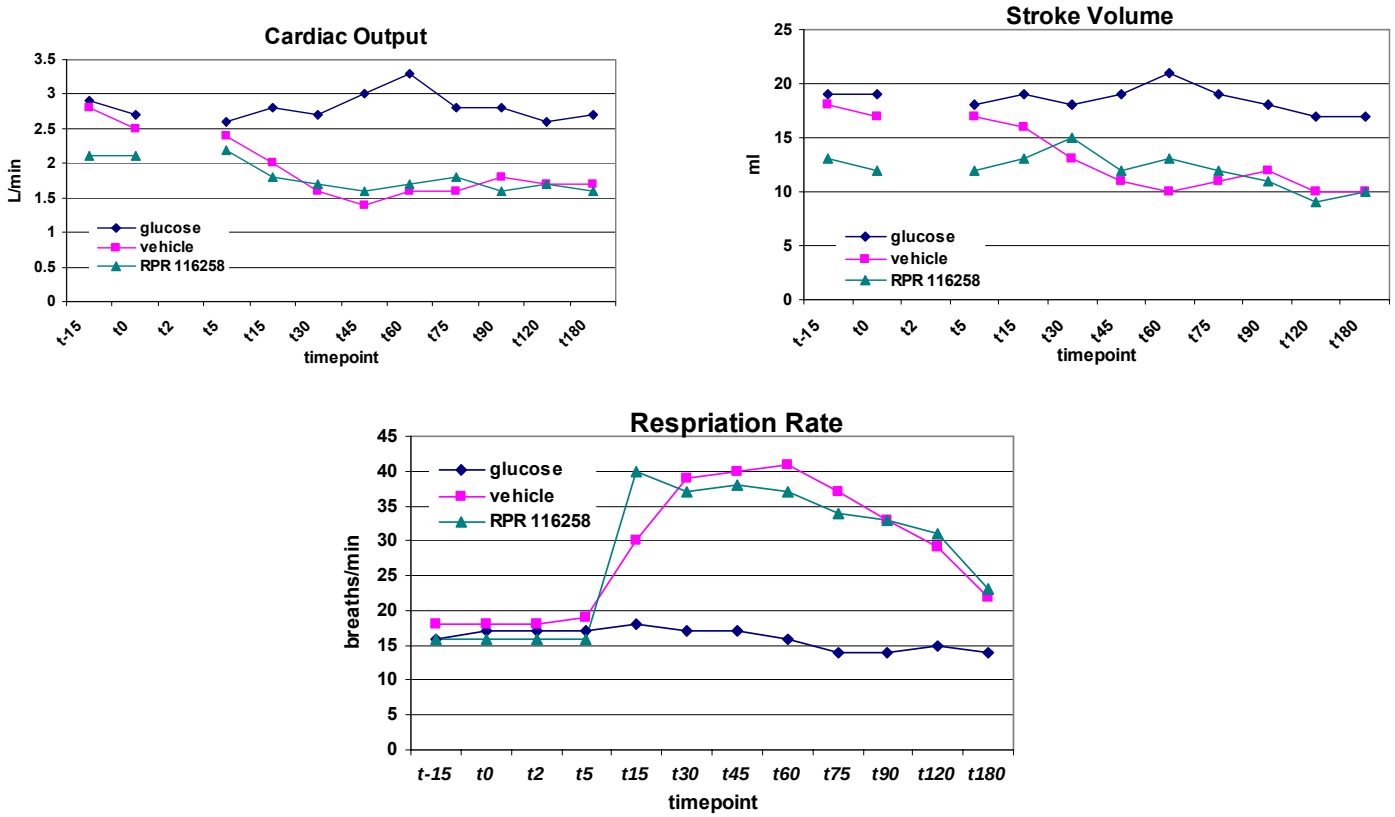
Data are presented as mean ± s.e. mean. Administrations were infused intravenously over 60 min, in a dose volume of 12 ml/kg





Decreases were also seen in left ventricle pressure, femoral flow and cardiac output for vehicle or RPR 116258 treated animals. Stroke volume was also decreased in vehicle treated animals. This decrease was not seen in the RPR 116258 treated dogs, though this difference may be due to a lower stroke volume at baseline in this group. In contrast to heart rate and blood pressure, respiration rate was increased compared to baseline in vehicle or RPR 116258 treated dogs. There were no significant changes in blood gas levels or pH in any of the treatment groups.

Figure 5: Beagle Dog Cardiac Output/Stroke Volume/Respiration Rate



Changes in hemodynamic parameters induced by treatment of anesthetized dogs appeared to be primarily related to the vehicle rather than specifically to the drug substance. There was a mild prolongation of QTc seen during treatment that may be related to RPR 116258. Changes typically became evident at 15 to 30 minutes after the beginning of dosing and were starting to reverse by 2 hours after the end of dosing.

Study title: RPR 116258: Effects on Respiration Rate and Body Temperature in Male Rats after Intravenous Administration

Study no.:	RPR/RD/DS/CRVA 98-101 RKT00108
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 11, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258/ BFC 611/ 96.5% Chlorpromazine HCl/ 94H1064

Methods

Doses:	0, 0.5, 1.5, and 5 mg/kg RPR 116258 5% glucose solution
Frequency of dosing:	Single dose
Route of administration:	IV infusion (1mL/min)
Dose volume:	5 mL/kg
Formulation/Vehicle:	RPR 116258 in PS80 and 13% EtOH diluted in 5% glucose in order to reach 2.5% PS80 and 0.975% EtOH
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	8 males/group
Age:	7-9 weeks
Weight:	243-287 g
Study design:	15 minutes after dosing animals were placed in a plethysmography chamber supplied with 0.5 L/min of air. Respiration rate was measured at 30 minutes post-dose, body temperature at 30 and 60 minutes post-dose
Deviation from study protocol:	1 animal in the low dose group (0.5 mg/kg) did not receive the full dose of the drug. Readings from this animal were included in the statistical analysis, but individual readings from the animal were not significantly different from readings from other animals in this group and did not appear to effect the interpretation of the study.

Results

(Excerpted from Sponsor)

Table 16: Effects on Respiration Rate

Effect of RPR 116258 and Chlorpromazine Hydrochloride on Respiration Rate and Body Temperature

Group Mean Data

Group	Treatment	Pre Dose Body Temp (°C)	Respiration Rate (breaths/min)	30 min Post Dose Body Temp (°C)	60 min Post Dose Body Temp (°C)
C	5 ml/kg Vehicle	38.1 ± 0.1	136.9 ± 6.3	38.2 ± 0.1	38.1 ± 0.1
B	Glucose (5%)	38.3 ± 0.1	127.9 ± 4.5	38.1 ± 0.1	38.0 ± 0.1
D	0.5 mg/kg RPR 116258	38.0 ± 0.1	125.3 ± 4.7	38.2 ± 0.1	38.2 ± 0.2
A	1.5 mg/kg RPR 116258	38.2 ± 0.1	141.0 ± 6.0	38.2 ± 0.1	38.2 ± 0.1
F	5 mg/kg RPR 116258	38.1 ± 0.1	129.8 ± 3.2	38.0 ± 0.1	38.1 ± 0.1
E	10 mg/kg Chlorpromazine	38.0 ± 0.1	96.4^{+++} ± 5.7	35.7^{+++} ± 0.2	34.7‡‡‡ ± 0.2

Data are presented as mean ± s.e.m., n = 8.

Though treatment with the positive control substance (chlorpromazine HCl) resulted in decreased respiration rate and body temperature in rats, there was no significant effect of RPR 116258 or the vehicle on these parameters after treatment with a single dose.

Renal

Study title: RPR 116258: Effects on Renal Function in Saline-Loaded Male Rats After Intravenous Administration

Study no.:	RPR/RD/DS/CRVA 98-098 RKT00105
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 12, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258/ BFC 611/ 96.5% Furosemide/ N166

Methods

Doses:	0, 0.415/0.5, 1.5, and 5 mg/kg RPR 116258 5% glucose solution
Frequency of dosing:	Single dose
Route of administration:	IV infusion (1mL/min)
Dose volume:	5 mL/kg
Formulation/Vehicle:	RPR 116258 in PS80 and 13% EtOH diluted in 5% glucose in order to reach 2.5% PS80 and 0.975% EtOH
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	8 males/group
Age:	7-9 weeks
Weight:	209-249 g
Study design:	Food was withheld the night before experimentation. Water was withheld on the day of testing for 3 hr. prior to oral volume loading with 25 mL/kg of sterile saline. 30 minutes after saline rats were treated and placed in individual metabolic cages. Urinalysis was performed on urine samples collected at 3, 6, and 24 hrs. post-dose. After the 6 hr. time-point, rats were allowed food and water *ad libitum*.
Deviation from study protocol:	4 animals in the low dose group received 0.415 mg/kg instead of 0.5 mg/kg due to solution error

Results

Table 17: Effects on Renal Function

Effects on Renal Function		Urine Vol (mL)	pH	Urinary Electrolytes		
Treatment Group	Post-Dose Time Period			Sodium (mmol/kg)	Potassium (mmol/kg)	Chloride (mmol/kg)
5% Glucose	0-3	1.9±0.2	6.3±0.2	1±0.13	0.43±0.07	0.97±0.12
	3-6	1.2±0.2	6.3±0.2	0.92±0.16	0.36±0.06	0.77±0.16
	6-24	4.9±0.4	6.6±0.3	2.74±0.29	39.8±6.33	6.2±0.41
Vehicle	0-3	2.3±0.2	6.3±0.2	1.08±0.12	0.39±0.07	0.95±0.13
	3-6	0.9±0.2	6.3±0.2	0.89±0.15	0.22±0.04	0.72±0.14
	6-24	5.3±0.3	7.3±0.3	3.2±0.25	33.17±2.51	6.62±0.39
0.415/0.5 mg/kg RPR 116258	0-3	2.5±0.2	6.5±0.3	1.36±0.13	0.45±0.06	1.26±0.11
	3-6	1±0.1	6.6±0.2	0.9±0.13	0.26±0.04	0.73±0.12
	6-24	5.3±0.3	7.1±0.4	3.21±0.58	29.28±4	6.66±0.42
1.5 mg/kg RPR 116258	0-3	3.3±0.3	6.5±0.2	1.59±0.24	0.63±0.06	1.45±0.18
	3-6	1.2±0.2	6.5±0.2	0.85±0.12	0.27±0.04	0.69±0.1
	6-24	5.8±0.6	7.4±0.3	3.47±0.28	16.64±1.32	5.8±0.4
5 mg/kg RPR 116258	0-3	2.5±0.3	7.1±0.1	1.4±0.18	0.53±0.05	1.23±0.12
	3-6	1.1±0.2	6.3±0.2	0.93±0.21	0.31±0.07	0.75±0.18
	6-24	6.2±0.8	6.8±0.3	3.09±0.31	15.49±1.57	5.29±0.32
5 mg/kg Furosemide	0-3	7.4±0.4	6.1±0.1	4.24±0.09	0.75±0.03	4.52±0.09
	3-6	0.3±0.1	5.5±0.5	0.33±0.07	0.14±0.04	0.21±0.05
	6-24	4.6±0.3	7±0.2	1.41±0.26	21.69±3.96	3.36±0.56

*Highlighted cells show a statistically significant (≥1.5 mg/kg), dose-dependent decrease

Treatment with the positive control substance, furosemide, resulted in large increases in urine volume and urinary electrolytes in male rats at the three hour time-point. By the 24 hour time-point, furosemide treated animals had decreases in urinary electrolytes as well as a slight decrease in urinary volume compared to glucose only animals. Treatment with RPR 116258 did not result early in large increases in urine volume; however, mild increases in urine electrolytes were noted in animals treated with ≥ 1.5 mg/kg RPR 116258 when compared to either the vehicle or glucose only at the three hour time-point. There were no significant differences between vehicle or glucose only groups and RPR 116258 treated groups at the 6 hour time-point. By the 24 hour time-point, there was a dose-dependent decrease in potassium seen in RPR-116258 treated animals compared to either glucose (~61% decrease in the high dose group) or vehicle (~53% decrease). No other significant changes were noted, although smaller decreases in chloride excretion were also noted at RPR 116258 doses of ≥ 1.5 mg/kg and are toxicologically relevant as similar decreases were seen in the positive control group. This study suggested that RPR 116258 was affecting electrolyte levels in animals, but did not demonstrate significant kidney toxicity in animals treated with up 5 mg/kg RPR 116258 at the 24 hour time-point.

Gastrointestinal

Study title: RPR 116258: *In Vitro* Effects on Basal Tone and on Responses to Various Spasmogens in the Guinea-Pig Isolated Ileum

Study no.:	RPR/RD/DS/CRVA 98-100 RKT00109
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 13, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258/ BFC 611/ 96.5% Acetylcholine chloride/ 57H2625 Histamine dihydrochloride/ 57H1172 5-hydroxytryptamine creatinine sulphate/ 26H032 Barium chloride dihydrate/ 126H3540

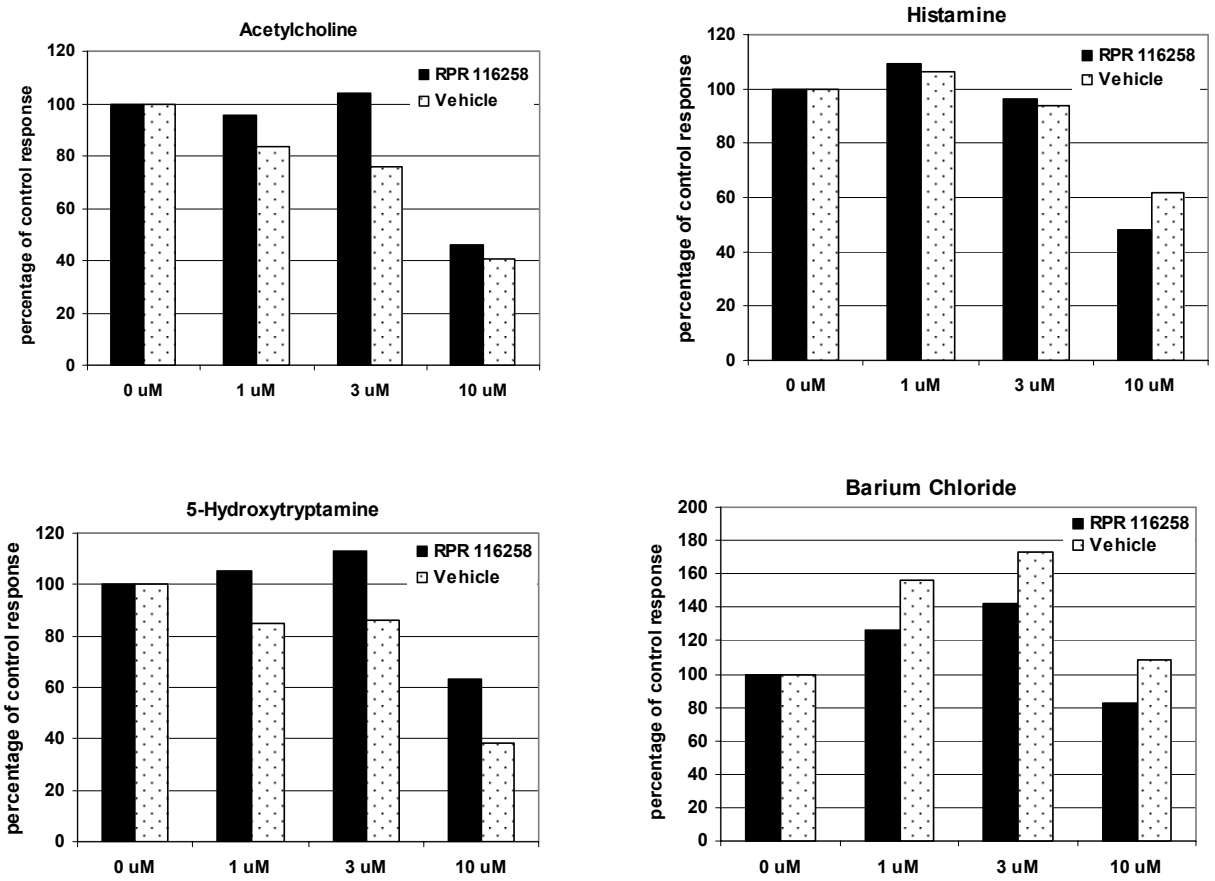
Methods

Doses:	0, 1, 3, and 10 µM RPR 116258
Formulation/Vehicle:	RPR 116258 in PS80 and 13% EtOH diluted in 5% glucose

Study design:
Ileums were taken from 4 euthanized guinea pigs, placed in Tyrode's solution, then cut into 2 cm segments. Intestinal contents were removed. One end of the tissue was impaled on a fixed pin in the organ bath, the other was attached through both sides of the intestinal wall with a thread. The free end of the thread was attached to an isometric force transducer. Each of the 4 spasmogens (acetylcholine chloride, histamine dihydrochloride, 5-hydroxytryptamine creatinine sulphate, and barium chloride dihydrate) was applied to 2 segments for 20s then washed out. This was repeated until stable and reproducible responses were obtained. Concentrations of spasmogen that produced 50-70% maximum contraction were determined. After allowing tissues to relax, RPR 116258 or vehicle were applied to the segments for 30 minutes. Effects on basal tone were recorded. Submaximal concentrations of spasmogens were applied the treated segments and responses recorded. After resting higher concentrations of RPR 116258 or vehicle were applied and the test was repeated.

Results

Table 18: Effects on Spasmogen Response



The application of vehicle alone at concentrations mimicking those seen with increasing amounts of RPR 116258 inhbited contractility in response to either acetylcholine or 5-hydroxytryptamine. When RPR 116258 was present, there was some increase in the response to either of these spasmogens compared to vehicle alone. Neither RPR 116258 or vehicle affected the spasmogenic response to histamine at concentrations ≤ 3 µM. Vehicle alone appeared to potentiate the response to barium chloride; RPR 116258 showed some inhibition of vehicle enhanced response to this compound. While there were some significant differences seen in effects on spasmogen activity between vehicle and RPR 116258, the overall effect of the drug on spasmogen activity was unremarkable.

Study title: RPR 116258: Effects on the Gastrointestinal Transit of a Charcoal Meal in Male Rats After Intravenous Administration

Study no.:	RPR/RD/DS/CRVA 98-099 RKT00106
Study report location:	EDR 4.2.1.3
Conducting laboratory and location:	(b) (4)
Date of study initiation:	March 11, 1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258/ BFC 611/ 96.5% Morphine hydrochloride / 23906

Methods

Doses:	0, 0.5, 1.5, and 5 mg/kg 5% glucose 10 mg/kg morphine hydrochloride
Frequency of dosing:	Single dose
Route of administration:	IV injection (1 mL/min)
Dose volume:	5 mL/kg
Formulation/Vehicle:	RPR 116258 in PS80 and 13% EtOH diluted in 5% glucose in order to reach 2.5% PS80 and 0.975% EtOH
Species/Strain:	Sprague Dawley rat
Number/Sex/Group:	8 males/group
Age:	7-9 weeks
Weight:	226-260 g
Study design:	30 minutes after dosing rats (starved the night before) were fed a 1 mL charcoal suspension (10g charcoal: 30 g flour: 60 mL water). 30 minutes after the charcoal, rats were sacrificed and the following parameters were examined • Distance that the charcoal had travelled along intestine from pyloric sphincter • Total intestinal length • Gastric emptying

Results

(Excerpted from Sponsor)

Table 19: Effects on GI Movement

Effect of RPR 116258 and Morphine Hydrochloride on Gastrointestinal Transit and Gastric Emptying

Group Mean Data

Treatment	% Distance travelled	Stomach weight (g)
5 ml/kg Vehicle	53.1 ± 2.0	2.8 ± 0.2
Glucose (5%)	54.8 ± 1.7	2.6 ± 0.2
0.5 mg/kg RPR 116258	49.6 ± 2.6	2.6 ± 0.1
1.5 mg/kg RPR 116258	51.6 ± 1.3	2.6 ± 0.1
5 mg/kg RPR 116258	54.9 ± 1.4	2.5 ± 0.1
10 mg/kg Morphine HCl	7.8 ± 3.6 ***	2.8 ± 0.1

While treatment with morphine HCl (the positive control) did inhibit gastric motility, there were no significant changes in gastric motility or gastric emptying seen in rats treated with RPR 116258 compared to either vehicle or 5% glucose.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

Absorption

Study Title: Pharmacokinetics following a single 1-hour infusion of XRP6258 at the dose of 2.5 mg/kg (15 mg/m²) to male Sprague Dawley rats
Study #: ABS0529
Drug, batch #/Purity: RPR 116258A, batch # 20080250 /purity %
Formulation: RPR 116258A was dissolved in PS80/ethanol/Glucose 5%

Table 20: Sampling schema

Rat Id.	Sampling time (h)											
	0.5	1*	1.08	1.25	1.5	2	4	6	8	10	24	48
101-102-103	X				X				X			
104-105-106		X				X				X		
107-108-109			X				X				X	
110-111-112				X				X				X

*: just before the end of infusion

(Exceprted from the sponsor's submission)

12 Sprague Dawley rats were divided into 4 subgroups of 3 rats each. Each rat was administered a single dose of cabazitaxel (2.5 mg/kg (15 mg/m^2)) by IV infusion for 1 hour. After the start of infusion, sampling carried out as shown in the Table 3. Cabazitaxel concentrations were determined in plasma samples, using a validated LC/MS/MS method.

One animal died at the end of the 1-hour infusion under isoflurane anesthesia. The cause of death was not determined. Hypothermia due to the 1-hour isoflurane anesthesia and piloerection were observed in all animals after the end of infusion for 20-30 minutes.

Table 21: Cabazitaxel plasma concentrations

Time (h)	0.50	1	1.08	1.25	1.50	2	4	6	8	10	24
Conc (ng/mL)	327	477	162	119	33.8	20.8	8.79	7.63	7.08	5.71	BLQ

Plasma concentrations of cabazitaxel are presented inTable 4. The maximum plasma concentration occurred at the end of the 1-hour intravenous infusion. After the end of infusion, plasma concentrations decreased rapidly up to 2 hours then a slower elimination of unchanged compound was observed.

Table 22: Plasma PK parameters of cabazitaxel in male rats

C_{max} (ng/mL)	t_{max} (1) (h)	AUC_{last} (ng.h/mL)	t_{last} (h)	AUC (ng.h/mL)	$AUC_{\%Ext_}$ (%)	CL ((L/(h.kg))	Vss (L/kg)	$t_{1/2z}$ (h)	time interval for $t_{1/2z}$ calculation
477	1	438	10	522	16.0	4.79	22.7	10.1	[4 - 10]

(1): end of infusion

(Excerpted from the sponsor's submission)

Cabazitaxel (2.5 mg/kg (15 mg/m^2)) was administered by IV infusion as a single dose over 1 hour.

Cabazitaxel volume of distribution at steady state was 22.7 L/kg. The systemic plasma clearance was 4.79 L/h.kg , representing 120% of the hepatic blood flow. The apparent terminal half-life was l0.1 hours (Table 5).

Cabazitaxel pharmacokinetics in dogs was previously submitted in IND 56,999 and reviewed by Margaret Brower, Ph.D. (See *Attachment 1* (DMPK/FR 2242)).

Distribution

Study Title: *In vitro* protein binding of [^{14}C]-XRP6258 to mouse, rat, rabbit, dog and human plasma proteins
Study #: LPR0995
Drug, batch #/Purity: [^{14}C]-XRP6258, batch # SYN2534 /purity 99.9 %
Specific activity: 2628 KBq/mg

Rat, dog and human data are reviewed.
Plasma proteins were obtained from male Sprague Dawley rats, male Beagle dogs and healthy human volunteers. Plasma samples were spiked to obtain concentrations of 50, 100, 1000, 5000, 10 000 and 50 000 ng/mL

The determination of equilibrium time was performed on frozen human plasma. Cabazitaxel concentration was 50 000 ng/mL and incubation times were 1, 2 and 3h.Non-specific adsorption was studied using dialysis conditions (plasma/buffer). No major degradation was observed in all plasma species including human up to 2h. At 3h a clear degradation was observed in all species including human. The percentage of cabazitaxel bound to plasma from rat, dog and human are presented in Table 6.

Table 23: Mean percentage of in vitro bound and free

Conc (ng/mL)	mean percentage values (n=3)					
	Rat (SD male)		Dog (Beagle, male)		Human (male)	
	Bound	Free	Bound	Free	Bound	Free
50	95.7	4.3	97.4	2.6	91.8	8.2
100	96.9	3.1	97.3	2.7	92.1	7.9
1000	95.3	4.7	97.3	2.7	93.0	7.0
5000	94.6	5.5	96.3	3.7	94.7	5.3
10000	96.1	3.9	97.0	3.0	90.1	9.9
50000	94.4	5.6	93.3	6.7	89.9	10.1

High binding was observed in all the species including human. The free fraction of cabazitaxel in human plasma>rat>dog (Table 6).

Study Title: The pharmacokinetics, distribution, and metabolism of ^{14}C-RPR 116258 in the blood, plasma and brain of the mouse, rat and dog following intravenous infusions of doses ranging from 15 to 90 mg/m^2.
Study #: DMPK/FR.2285
Drug, batch #/Purity: ^{14}C-RPR 116258, 3300-299/Purity: 97.7%
Specific activity: 1.99 GBq/mmol

To compare blood, plasma and brain exposures across species, one identical dose of 15 mg/m^2 was tested in Crl:CD®-(SD)BR female rats and female Beagle dogs. An additional dose was administered in rats (60 mg/m²).

Table 24: Dosing protocol

Species	Dose (mg/m2)	Dosing volume (mL/kg)	Duration of infusion
Female SD rats	15, 60	10	2.3 minutes
Female Beagle dogs	15	12	1 hour

Sampling: Blood and brain were collected in

- Rats at 0.03, 0.25, 1, 6, 24, 72 and 168 hours after dosing.
- Dogs at the end of infusion, 1, 6, and 24 hours after the end of infusion.

Blood and brain samples were collected from 2 rats at each sampling time over a period of 0-168h post-dosing and in one dog at sampling time during the first 24 hours after dosing. The total radioactivity of the different samples was determined by liquid spectrometry using a Beckman LS 6000 SC spectrometer equipped with an external standard system (number H). The pharmacokinetic parameters for rats and dogs are summarized inTable 25The Tmax for rats and dogs at all doses was 0.03 hour.

Table 25: Cmax and AUC

	Rat				Dog	
Dose (mg/m^2)	**15**		**60 (x4)**		**15**	
	Cmax	**AUC$_{0-168}$**	**Cmax**	**AUC$_{0-168}$**	**Cmax**	**AUC$_{0-24}$**
Blood	0.68	4.9	3.6	13.4	0.21	2.1
Plasma	0.55	1.6	4.3	11.0	0.18	0.54
Brain	0.09	3.9	0.49	39.1	0.03	0.48
Ventricle	2.7	155	14.0	487	4.2	49.5
Brain/Blood ratio	0.13	0.80	0.14	2.92	0.14	0.23
Brain/Plasma ratio	0.16	2.44	0.11	3.55	0.17	0.89

Cmax µg eq/mL or µg eq/g; AUC-[equivalent RPR 116258 µg.h/mL or µg.h/g] *AUC

Cabazitaxel rapidly penetrated the brain and was maximal within 2 minutes and declined very slowly, being detectable in rats at 168 hours and in dogs at 24 hours. The brain/plasma total radioactivity AUC ratio in rats increased with increasing dose indicating a higher brain penetration with increasing dose. Maximal blood and plasma concentrations were reached at the end of infusion and rapidly decreased up to 6 hours.

Study title: XRP6258: Placental Transfer of Total Radioactivity After Intravenous Administration of [14C]-XRP6258 at the Dose of 0.08 mg/kg (0.48 mg/m^2) to Pregnant Sprague-Dawley Rats

Study no.:	PLT0080
Study report location:	EDR 4.2.2.3
Conducting laboratory and location:	Sanofi-Aventis Research & Development Alfortville, France
Date of study initiation:	June 30, 2008
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	XRP6258/ SYN2151

Methods

Doses:	0.08 mg/kg
Frequency of dosing:	Single dose
Route of administration:	IV infusion (2 min.)
Dose volume:	5 mL/kg
Formulation/Vehicle:	Polysorbate 80/Ethanol/Glucose 5% (0.25/0.1/100)
Species/Strain:	Sprague-Dawley rat
Number/Sex/Group:	4 pregnant females/time-point
Age:	~11 weeks
Weight:	307-357 g
Study design:	8 pregnant rats were dosed with 14C labeled XRP6258 on Gestational Day 17 (GD17) and samples were taken/ autoradiography was performed at 0.5 and 24 hrs.

Results

(Excerpted from Sponsor)

Table 26: Placental Transfer

Table (5.1) 1 - Mean radioactivity dam tissues and fetal structures concentrations after 2-min intravenous infusion (0.08 mg/kg) of [^{14}C]-XRP6258 to the pregnant rat, on Day 17 of gestation.

Tissue/Fluid	Mean Conc. (ngEq./mL or ngEq./g) - n= 3			
	0.50h	24h	0.50h	24h
	Dam		Fetus	
Blood	76.8 ± 7.50	BLQ	BLQ	BLQ
Brain	BLQ	BLQ	BLQ	BLQ
Kidney	1000 ± 60.8	89.2 ± 6.62	-	-
Liver	469 ± 74.5	12.7 ± 1.01	BLQ	BLQ
Lung	1650 ± 40.4	45.7 ± 6.97	BLQ	BLQ
Myocardium	675 ± 32.6	24.8 ± 2.14	BLQ	BLQ
Ovary	858*	24.1 ± 2.38	-	-
Placenta	152 ± 0.577	BLQ	-	BLQ
Trophoblast	39.6 ± 5.03	12.2 ± 1.80	-	-
Mammary glands	45.5 ± 2.55	16.9 ± 1.01	-	-
Amnios	29.3 ± 0.379	16.1 ± 0.751	-	-
Dam plasma (LSC)	11.1	1.80	-	-
Whole fetus (LSC)	-	-	BLQ	BLQ
Fetal liver (LSC)	-	-	BLQ	3.27

LOQ(WBA): 11.8 ngEq./g LOQ(whole fetus, LSC): 1.73 ngEq./g

LOQ(plasma, LSC): 1.04 ngEq./mL

LOQ(fetal liver, LSC): 2.49 ngEq./g

*: n= 2 measurements (technical constraint)

The highest levels of radioactivity were seen in dams at the 0.5 hr. time-point. Organs with the highest levels of exposure were the lung, kidney, ovary, and liver. Radioactivity was also detectable in the placenta. By 24 hours after dose administration, levels of radioactivity had fallen significantly in all organs of the dams. Levels of radioactivity were undetectable in the fetus at 0.5 hours, but small amounts were detectable in the fetal liver at the 24 hour time-point. The low level of radioactivity measured in the fetal liver at 24 hours shows that XRP6258 is able to cross the placenta in pregnant rats.

Metabolism

Study Title: *In vitro* metabolism in liver microsomes from mouse, rat, rabbit, dog, monkey, and man
Study #: DMPK/FR/2270

The sponsor conducted studies with liver microsomes from male and female mouse, male and female rat, male rabbit, male dog and human livers.

The rat, dog and human data are reviewed.

Metabolic profiling was carried out with microsomes from pools of male or female rat (*Sprague-Dawley/CD*) livers and from individual male *Beagle* dog livers. Human livers were obtained from organ transplant donors (b) (4)

Protein contents and total cytochrome P450 were determined and the data are shown in the table below:

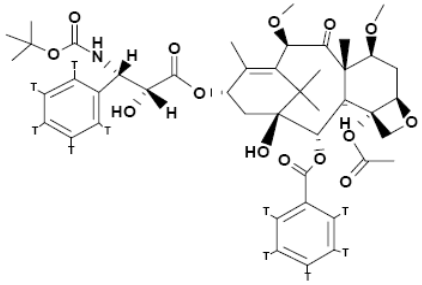
Table 27: Microsome P450 Content

SPECIES	REF	SEX	PROTEIN mg/mL	P450 nmol/mg
Rat	9601-R1-0	M	31.8	0.46
	9502-R2-0	F	19.3	0.86
Dog	9601-C1-0	M	17.1	0.42
Human	Pool 98 n°2	M+F	19.7	0.37

The structure of radiolabelled cabazitaxel (^{3}H-RPR 116258 (batch 129-067-0023)), used in the study is shown below:

(Excerpted from Sponsor)

Figure 6 : Structure of Radiolabelled Cabazitaxel



(T =^{3}H denotes the position of labeling)

^{3}H-RPR 116258 (batch 129-067-0023) was synthesized at the (b) (4) (b) (4) with a specific activity of 2.3 Ci/mmol (85.1 Gbq/mmol).

Incubation mixtures contained liver microsomes (2 mg microsomal protein per ml), NADPH (1 mM) and $MgCl_2$ (10 mM) in a potassium phosphate buffer (0.1M pH 7.4) at 37 °C in a shaking water bath under air oxygen. Reactions were started by the addition of cabazitaxel to obtain an initial concentrations of 1 µM and 1µCi per ml. Reactions were stopped by mixing one volume of the incubate with one volume of methanol. Incubations times were from 0.5 to 120 minutes. The samples were profiled for parent drug and metabolites by HPLC with radiochemical detection or mass spectrometry detection. Quantification of ^{3}H-RPR 116258 and radiolabeled metabolites was also perfomed.

Results

Cabazitaxel (RPR 116258) biotransformation rate was the highest in human liver microsomes (about 200 pmol/min/mg) and the lowest in the rat (about 20 pmol/min/mg). Incubation of cabazitaxel with liver microsomes from rat, dog, and man resulted in at least eighteen radiolabelled compounds that were identified as cabazitaxel metabolites, many of which were at low levels. The metabolites were formed in the presence of NADPH. The structures of the major metabolites were elucidated by ESI/LC/MS. Minor

metabolites M01, M02, M03, M04, M05, M07, M08, M09, M010, M011, M012 and M013 remained unidentified because the amounts of metabolites were insufficient for NMR analysis.

The main metabolic pathway included oxidative O-demethylation processes to yield the 10-O-demethyl (RPR 123142) and the 7-O-demethyl (RPR 112698) derivatives, subsequent O-demethylation to give the 7-10-O-demethyl RPR116258 (RP 56976,docetaxel) and successive oxidations of the tert-butyl group moiety of docetaxel leading to the formation of the alcohol derivative RPR 104952 and then formation of an unstable aldehyde which cyclizes to form a hydroxyoxazolidinone RPR111026. The metabolic reactions leading to the formation of RPR 111026 were not detected in rat liver microsomes. The proposed *in vitro* metabolic pathway of cabazitaxel is shown in the Figure 7 below:

(Excerpted from Sponsor)

Figure 7: Proposed in vitro metabolic pathway in liver microsomes

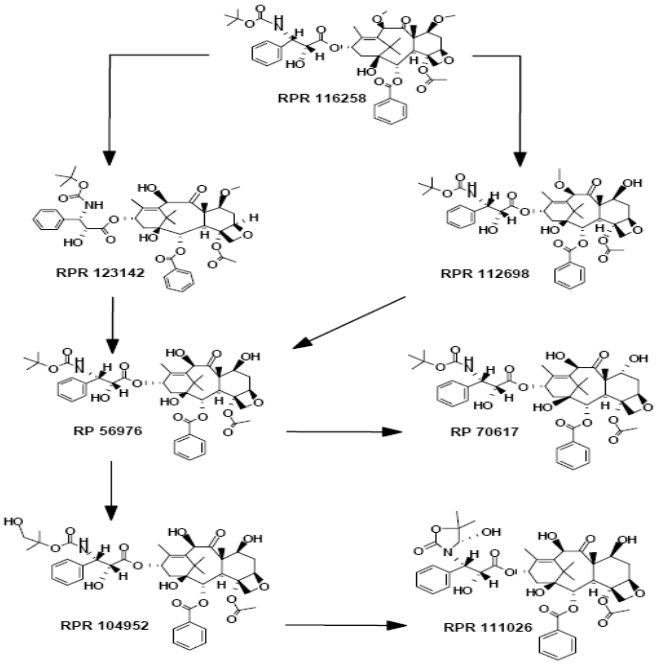


Table 28 below shows AUC values of the major metabolites and percentage of total metabolites. Table 3 (left panel) also shows that the recovery of radioactivity in the form of parent drug and its metabolites was virtually complete.

Table 28: AUC values of cabazitaxel and metabolites

RPR 116258 and metabolite AUCs, calculated over the incubation period (0.5-120 min) with liver micrsomes

	Male Rat	Female Rat	Dog	Man
M08	--	--	--	14.10
RPR104952	1.07	3.42	27.62	20.94
RPR111026	--	--	18.25	20.80
M02	--	--	--	5.92
M01	7.67	9.84	--	--
RP56976	2.30	1.92	28.09	16.71
RPR112698	5.57	12.61	13.52	13.74
RPR123142	8.56	5.39	2.71	3.23
RPR116258	94.39	84.72	31.57	14.51

Individual metabolite AUCs, calculated from period 0.5-120 min of incubation with liver microsomes and expressed as percentage of total metabolites AUC

	Male Rat	Female Rat	Dog	Man
M08	--	--	--	14.78
RPR104952	4.25	10.31	30.62	21.94
RPR111026	--	--	20.24	21.79
M02	--	--	--	6.20
M01	30.46	29.64	--	--
RP56976	9.15	5.79	31.15	17.51
RPR112698	22.11	38.02	14.99	14.40
RPR123142	34.04	16.25	3.00	3.38

Values in µM•min

RPR 116258 metabolism in dog liver microsomes was qualitatively the most similar to that in human liver microsomes.

Study Title: *In vivo* metabolism following a single intravenous infusion of [^{14}C]-XRP6258 to Sprague Dawley rats
Study #: DMPK/FR.2306-[MIS0099]
Drug, batch #/Purity: [^{14}C]-XRP6258, batch # 3351-039/purity 99.25%
^{14}C dose: 1.7 MBq/kg
Dose and route: 15 mg/m^2 by IV infusion (1-2 minutes)

Study Title: *In vivo* metabolism following a single intravenous infusion of [^{14}C]-XRP6258 to Beagle dogs
Study #: [FSRFU-MET0741-EN-E01]
Drug, batch #/Purity: [^{14}C]-XRP6258, batch # SYN2151 (X38007)/purity 99.25%
^{14}C dose: 1.2 MBq/kg
Dose and route: 10 mg/m^2 by IV infusion over 1 hour

Study Title: *In vivo* metabolism following a single intravenous infusion of [^{14}C]-XRP6258 to humans (3 males/1 female)
Study #: BEX6702
Drug, batch #/Purity: RPR 116258A, batch CL-12898 (CL-12707)/purity 99.25%
^{14}C dose: 1.85 MBq/kg
Dose and route: 25 mg/m^2 by IV infusion over 1 hour

Following the administration of cabazitaxel in rats dogs and humans, the unchanged drug was the main circulating compound in plasma from all species including human (≥70% of radioactivity AUC; Table 29).

Table 29: Plasma

Compound	Rat (0-24h)		Male Dog (0-48h)	Human (0-5/11h)
	Male	Female		
XRP6258	83.1 [1680]	80.7 [1223]	79.5 [177]	70.2 [268.5]
RPR123142 (10-O-demethyl on taxane)	0.6 [11]		4.4 [10]	3.6 [21.2]
M01 (tBu-hydroxy-XRP6258)	15.8 [319]	18.5 [281]		
RPR130523 (cleaved XRP6258)			6.7 [15]	
Total radioactivity	[2021]	[1516]	[223]	[409]

The main circulating metabolite in human corresponded to RPR123142, 10-O-demethyl-XRP6258, representing 3.6% of radioactivity AUC and 5.1% of cabazitaxel AUC. The pharmacologically active metabolites RPR112698 and RP56976 (docetaxel) were present in the *in vitro* study in human liver microsomes >10% (Table 3) but were not detected in human plasma after IV administration of cabazitaxel. RPR123142, was not detected the excreta (urine and feces) (Table 30). Due to the low concentrations of the pharmacologically active metabolites in human plasma and excreta, they were not considered relevant.

Table 30: Rat, Dog and Human Comparison of in vivo Metabolc Profile in Excreta

Compound (% of administered dose)	Rat (0-72h)		Male Dog (0-144h)	Human (0-168/240h)
	Male	Female		
XRP6258	0.1	0.1	0.1	2.3
M01b (oxazolidinedione-XRP6258)	4.3	5.1		
RPR112698 (7-O-demethyl on taxane)	0.9	0.6	13.5	2.4
RP56976: docetaxel (di-O-demethyl on taxane)	0.6	0.3	17.2	1.7
M01a**			0.4	2.5
M01 (tBu-hydroxy-XRP6258)	10.5	12.3		
M02c (hydroxyoxazolidine-XRP6258)	6.5	11.5		
M02d (oxazolidinedione-RPR112698)	2.1	3.9		2.6
M03c (hydroxyoxazolidine-RPR123142)	3.9	2.3		
RPR104943 (oxazolidinedione-docetaxel)			0.3	19.4
M06a (hydroxyoxazolidine-XRP6258)	10.5	11.7		
M07 (tBu-hydroxy-RPR112698)	5.0	4.4	2.6	4.4
RPR104952 (tBu-hydroxy-docetaxel)	3.8	2.4	27.0	6.9
M05 (hydroxyoxazolidine-RPR112698)	4.6	4.7	0.3	2.6
RPR111026 (hydroxyoxazolidine-docetaxel)	7.8	4.0	3.8	8.7
M08b (hydroxyoxazolidine-RPR112698)	4.2	4.2		1.5
RPR111059 (hydroxyoxazolidine-docetaxel)	6.4	3.8	2.3	6.7
M09b (hydroxyoxazolidine-hydroxy-docetaxel)				4.4
Total radioactivity	79.1	77.0	79.9	71.2

RPR123142 was also detected in the plasma of male dogs (4.4%) and in male rats (0.6%). Doses of 30 mg/m^2 in the 10-cycle toxicity study in rats and 10 mg/m^2 in the 13-cycle study in dogs give lower exposures of RPR123142 than in human at the therapeutic dose of 25 mg/m². However, RPR123142 was also the main circulating metabolite in female mice (16.5% of radioactivity AUC). The non-lethal dose in mouse study #CRVA/DS/98-157 (*IND 56,999 (1998) reviewed by Margaret Brower, Ph.D.)* was 60 mg/m^2, giving a higher exposure than the therapeutic dose.

Species	**RPR123142** (10-O-demethyl on taxane)	
	% AUC	mg/m^2
Male rat	0.6	0.18
Male Dog	4.4	0.44
Female mouse	16.5	9.9
Human	3.6	0.9

In rats, the main metabolite corresponded to M01, the t-butyl-hydroxy derivative of XRP6258 and was present in the plasma (15.8%, Table 5), excreta (>10%, Table 31) in he liver (>50%) and in the lungs (>26%, Table 7) of radioactivity AUC.

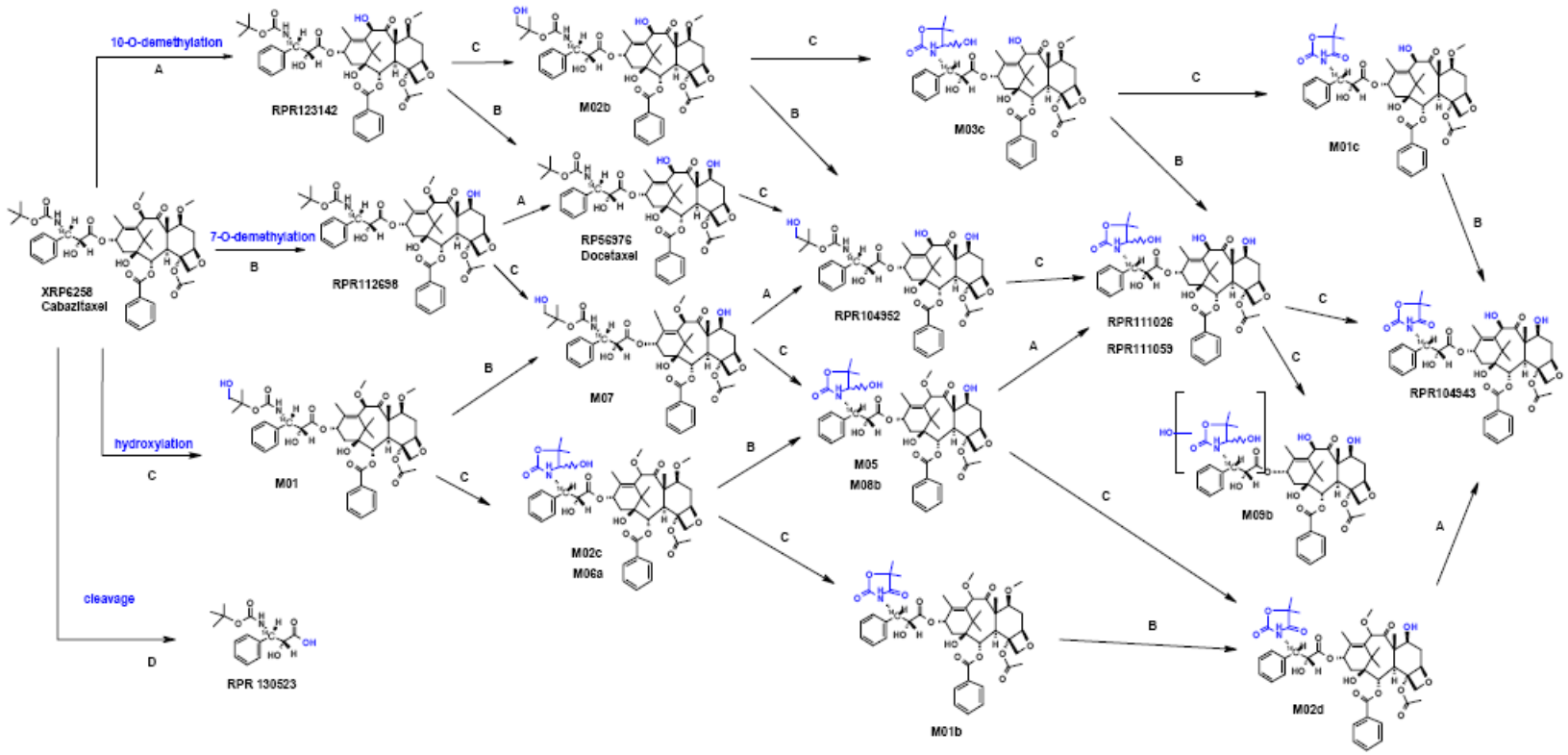
Table 31: XRP6258 and its metabolites in liver and lungs
% of radioactivity AUC [tissue to plasma AUC ratio]

Compound	**Liver**		**Lung**	
	Rat (0-24h)		**Rat (0-24h)**	
	Male	**Female**	**Male**	**Female**
XRP6258	22.5 [6.6]	26.5 [12.2]	71.6 [36.2]	69.6 [50.5]
RPR123142 (10-O-demethyl on taxane)	1.3 [57.3]	1.0 [-]	0.5 [40.1]	
RPR112698 (7-O-demethyl on taxane)	3.4 [-]	2.5 [-]		
RP56976: docetaxel (di-O-demethyl on taxane)	6.7 [-]	6.4 [-]		
M01 (tBu-hydroxy-XRP6258)	52.1 [80.4]	59.6 [120]	26.4 [70.4]	28.7 [90.7]
M02b (tBu-hydroxy-RPR123142)	6.7 [-]	2.5 [-]		
Total radioactivity	[24.3]	[37.2]	[42.0]	[58.6]

The proposed interspecies metabolic pathway is presented in Figure 8

(Excerpted from Sponsor)

Figure 8: Proposed metabolic pathway



Study Title: RPR 116258A: *In vitro* cytochrome P450 enzyme induction study in primary cultures of rat hepatocytes
Study #: SA/CRVA 00-439
Drug, batch #/Purity: RPR 116258A, batch WSD 3044/purity 99.3%
Formulation: RPR 116258A was dissolved in dimethylsufoxide (DMSO) to obtain stock solutions at 4.8, 24, 96 and 4000 µM. RPR116258A stock solutions were diluted in treatment medium (TM) containing 0.2% bovine serum albumin (BSA), 10 IU/ml penicillin, 10 µg/ml streptomycin, 1 µM hydrocortisone and 100 IU/l insulin) to obtain final concentrations of 0.012, 0.06, 0.24 and 10 µM (final concentration of 0.25% DMSO).
Negative control: The negative control consisted of TM containing 0.25% DMSO
Positive control: The positive controls consisted of Phenobarbital dissolved in TM at final concentration of 1 mM; Dexamethasone dissolved in TM containing 0.01% ethanol at final concentration of 1 µM; 3-Methylcholanthrene (3-MC) dissolved in TM containing 0.25% DMSO at final concentration of 5 µM.

Primary cultured rat hepatocytes isolated from livers of male Sprague Dawley Crl:CD (SD)IGS BR rats were exposed to cabazitaxel, the negative or the positive control for 72 hours. At the end of the 72-hour treatment, cultured hepatocytes were incubated with testosterone. The hydroxylated metabolites of testosterone (positions 2α, 2β, 6α, 15β, 7α, 15α, 6β, 16α, 16β and androstenedione) corresponding to different CYP-dependent activities were analyzed using HPLC. Cultured hepatocytes were then homogenized and S9 mix fractions were prepared and separated by SDS-polyacrylamide gel electrophoresis followed by Western immunoblotting using specific antibodies raised against rat CYP 1A1/2, 2B1/2, 3A, 2E1 and 4A. At 10 µM, western blot analysis was restricted to CYP 2B1/2 and 3A.

(Excerpted from sponsor)

Figure 9: Western blots of CYP 2B1/2 and CYP3A

(b) (4)

The results of these tests show that cabazitaxel 10 µM is an inducer of CYP3A in primary cultures of rat hepatocytes.

Excretion

Study Title: ^{14}C-RPR 116258 - Radioactivity excretion in the male and female rats following a single, intravenous administration at 2.5 mg/kg
Study #: DMPK/FR. 2262
Drug, batch and Purity: ^{14}C-RPR 116258
Specific activity: 1.99 GBq/mmol

^{14}C-RPR 116258 (2.5 mg/kg in 10 ml/kg) was administered to 4M/4F Sprague Dawley rats, intravenously. Rats were placed in individual glass metabolism cages. Urine and feces were separately collected in amber glass round-bottomed flasks at +4°C. Sampling was carried out at: 0-24, 24-48, 48-72, 72-96, and 96-168 hours after Dosing. Liver, kidneys, brain, stomach and intestinal tract (wall and contents), skin and carcass with remaining tissues were dissected from the animals used for excreta collection at 168 hours. The gastrointestinal tract and gastrointestinal contents were individually recovered for residual radioactivity assessment. The total radioactivity of the different samples was determined by liquid spectrometry using a Beckman LS 6000 SC spectrometer equipped with an external standard system (number H).

Table 32: Radioactivity elimination in male and female rats

Male rats

	0-24h	24h-48h	48h-168h	Total excreted
Urine	1.83 ± 0.21	0.69 ± 0.24	1.63 ± 1.07	4.14 ± 1.44
Feces	29.87 ± 26.76	36.74 ± 22.50	24.47 ± 3.03	91.08 ± 4.96
Expired air	NS	NS	-	-
Total excreted				**96.61 ± 3.72**

Female rats

	0-24h	24h-48h	48h-168h	Total excreted
Urine	1.48 ± 0.20	0.67 ± 0.28	1.50 ± 0.54	3.65 ± 0.94
Feces	36.48 ± 19.10	37.00 ± 23.42	26.53 ± 2.82	90.89 ± 2.29
Expired air	NS	NS	-	-
Total excreted				**96.08 ± 3.23**

(Excerpted from the sponsor's submission)

Rats were administered a single IV dose of ^{14}C-RPR 116258 (2.5 mg/kg (15 mg/m^2)). As seen in Table 7, radioactivity was excreted largely in feces within 168 hours, on average 91.08 ± 4.97 % of the dose for male rats and 90.89 ± 2.29 % for female rats. Approximately 4% of the radioacti8vity was excreted in the urine. Most of radioactivity excreted via fecal route came from biliary excretion, as demonstrated previously.

Study title: XRP6258: Milk Excretion of Total Radioactivity After Intravenous Administration of [14C]-XRP6258 at the Dose of 0.08 mg/kg (0.48 mg/m2) to Lactating Female Sprague-Dawley Rats

Study no.:	MIL0014
Study report location:	EDR 4.2.2.3
Conducting laboratory and location:	Sanofi-Aventis Research & Development Alfortville, France
Date of study initiation:	June 8, 2008
GLP compliance:	No
QA statement:	No
Drug, lot #, and % purity:	XRP6258/ SYN2151/ 99%

Methods

Doses:	0.08 mg/kg (0.48 mg/m^2), 0.2 MBq/kg
Frequency of dosing:	Single dose
Route of administration:	IV infusion (2 min.)
Dose volume:	5 mL/kg
Formulation/Vehicle:	Polysorbate 80/Ethanol/Glucose 5% (0.25/0.1/100)
Species/Strain:	Sprague-Dawley rat
Number/Sex/Group:	3 females/time-point; 4 pups/female
Age:	Dams: 10-11 weeks Pups: PND11
Weight:	Dams: 279-349 g
Study design:	Dams were treated on Day 11 of lactation. At 2, 6, and 24 hours post-dosing, 3 dams/timepoint and their 4 pups were sacrificed. Total radioactivity was measured in the blood and plasma of the dams, and in the blood, gastrointestinal tract, and carcass of the pups.

Results

Table 33: Cabazitaxel in Rat Breast Milk

Radioactivity Concentrations (ngEq./g or mL)			
Matrix	Time (h)		
	2h	6h	24h
DAMS (n=3)			
Plasma	4.34 ± 0.161	1.56 ± 0.245	1.25 ± 0.284
PUPS (n=4)			
Blood	BLQ	BLQ	BLQ
Stomach content	1.79 ± 1.56	5.77 ± 3.07	0.810 ± 1.40
Intestine content	BLQ	2.08 ± 0.432	10.3 ± 1.47
Carcass	BLQ	BLQ	BLQ

LOQ (plasma): 0.703 ngEq./mL
LOQ (blood): 1.89 ngEq./mL
LOQ (stomach cont.): 2.87 ngEq./g
LOQ (intestine cont.): 2.93 ngEq./g
LOQ (carcass): 0.205 ngEq./g

In dams, radioactivity was present at all sampling times but began declining after the 2 hour point. Radioactivity was detected in the stomach of pups by the 2 hour post-dose time point, increased by the 6 hour time-point and then declined. Intestinal radioactivity was measurable by the 6 hour time-point and then increased. The presence of radioactivity at measurable level in the GI tract of pups after single dose administration of the drug to mothers indicates that XPR6258 is excreted in breast milk. The sponsor calculates that approximately 1.5% of the total dose is excreted in the 24 hour time period.

6 General Toxicology

6.1 Single-Dose Toxicity

Acute single dose and repeat-dose toxicity studies were previously reviewed by Margaret Brower, Ph.D. *attachment #1*).

6.2 Repeat-Dose Toxicity

Study title: XRP6258 - 10-Cycle Intravenous (1-Hour Infusion) Toxicity Study In Rats (Each Cycle Consisting Of A Single Injection Every 3 Weeks) Followed By An 8-Week Treatment-Free Period.

Study no.:	TSK0038 / (b) (4) AA73745
Study report location:	4.2.3.2.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	May 15, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	P-33125-216-1 (batch no. 0326012 of XRP6258 enriched with 3.6 % of impurities), and 96.4% purity.

Key Study Findings

- 13M/11F at 20/10 mg/kg dose level died or were sacrificed due to severe toxicity
- 20 mg/kg was reduced to 10 mg/kg after cycle 1
- Administration of 10 mg/kg was stopped after the 4th cycle in males and 6th cycle in females
- Clinical signs included decreased activity, thin body, hunched gait, pilorection, paleness in both male and female rats at ≥5 mg/kg.
- Reduced WBC, platelets, reticulocytes, neutrophils lymphocytes, monocytes, basophils and LUC at ≥1 mg/kg
- Elevated glucose level at ≥1 mg/kg in male and female rats, elevated ALT at 5 mg/kg,
- Decreased bone marrow cellularity at all doses, decreased celluraity and necrosis in lymph nodes, Decreased lymphocytes in the spleen and thymus severe oligospermia, prostate inflammation and atrophy, myofiber degeneration in skeletal muscles, sciatic nerve degeneration at 20/10 mg/kg, severe cornea ulceration and lense fiber degeneration.

Methods

Doses:	0, 1, 5, 20/10 mg/kg (0, 6, 30, 120/60 mg/m^2)
Frequency of dosing:	Every 3 weeks
Route of administration:	Intravenous infusion
Dose volume:	5
Formulation/Vehicle:	Vial of 40 mg/mL stock solution of XRP6258 in pure polysorbate(PS) 80/ PS80, 0.25% (w/w) and ethanol 0.01% (w/w) in an aqueous solution of 5% (w/w) glucose
Species/Strain:	Sprague-Dawley Crl: CD rats
Number/Sex/Group:	10
Age:	~9 weeks
Weight:	Males, 323-388 g; Females, 184-252 g
Satellite groups:	Males, 338-387 g; Females, 191-245 g

Observations and Results

Mortality

Table 34: Mortality

Day	Animal Number	Sex	Dose Level mg/kg	Attribution
87	38	M	1	After blood sampling
144	34			Squamous cell carcinoma on ear
102	74	M	5	After blood sampling
142	88	F		Stomach full of fluid Death associated with changes in GI tract Abscesses in the liver
245*	87	F		Dead after blood sampling Hemorrhage in bronchi
4	91	M	20/10	Lymphoid and bone marrow depletion, septic thrombus at injection site Necrosis in kidneys, bacteria in kidneys and injection site, prostate inflammation Pyelonephritis
7	94			
9	105			
39	98			
46	97			
46	101			
66	92			
66	93			
66	95			
66	96			
66	99			
72*	102			
80*	100		20/10	
92	114	F		Lymphoid and bone marrow depletion
108	106			
108	107			
108	108			
108	109			
108	110			
108	111			
108	112			
108	113			
108	115			
126*	118			

*Died during treatment free days (#102, 9d; #100, 17d; #118, 21d & #87, 56d after the last treatment)

Clinical Signs

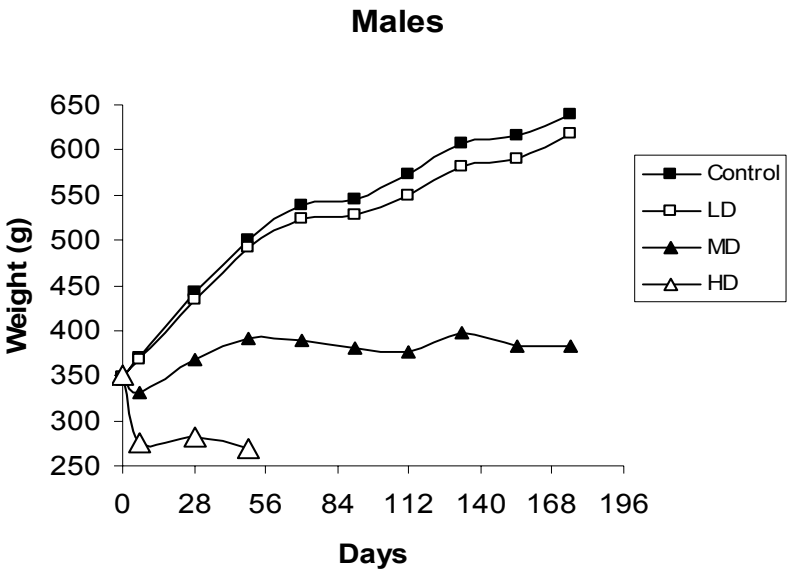
Table 35: Clinical signs

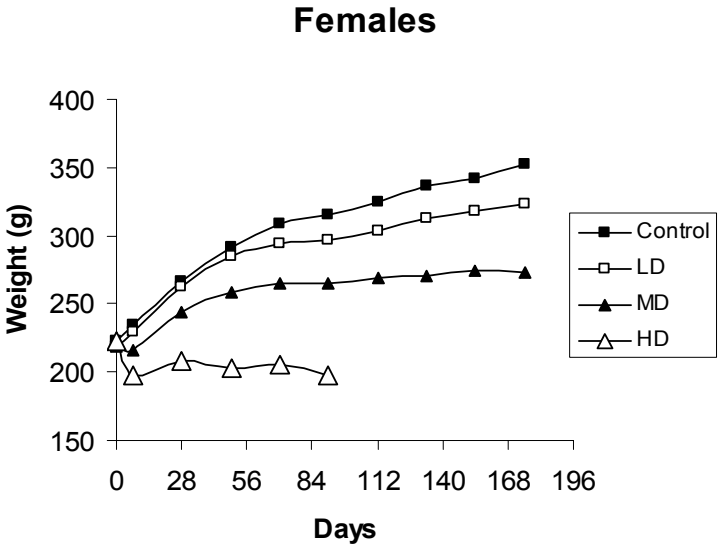
Sign	Dose	0	1 mg/kg	5 mg/kg	20/10 mg/kg
	M	**0**/10/*5*	**2**/**8**/*5*	**1**/9/*5*	**13**/0/*2*
	F	**0**/10/*5*	**0**/10/*5*	**2**/**9**/*4*	**11**/0/*4*
Preterminal/Terminal /*Recovery*					
Lacrimation	M	3	1	6	**4**
	F	--	--	1	**3**
Scabs	M	6	2	6	**1**
	F	5	4	**1**/6	**3**
Noisy breathing	M	1	--	**2**	**4**
	F	--	--	--	**--**
Agressive	M	1	--	--	**1**
	F	--	--	--	**2**
Broken tooth	M	--	--	**1**/2	**1**
	F	--	--	1	**1**
Sores	M	--	2	--	**1**
	F	--	--	2	**--**
Swelling	M	--	**1**/1	5	**3**
	F	--	--	1	**2**
Pale	M	--	**1**	**1**/8	**13**
	F	--	--	**1**/8	**5**
↓Activity	M	--	--	14	**13**
	F	--	--	--	**4**
Extensive hair loss	M	--	--	**1**/14	**--**
	F	--	--	**1**/14	**11**
Thin	M	--	--	4	**12**
	F	--	--	3	**11**
Hunched gait	M	--	--	5	**9**
	F	--	--	2	**7**
Unsteady gait	M	--	--	2	**6**
	F	--	--	--	**6**
Loss of whiskers	M	--	--	**1**/14	**12**
	F	--	--	**1**/12	**11**
Teeth short	M	--	--	14	**2**
	F	--	--	**1**/13	**11**
Pilorection	M	--	2	**1**/14	**13**
	F	--	--	3	**11**
Opacity of the eye	M	--	--	1	**2**
	F	--	--	1	**1**
Wheezing	M	--	--	--	**8**
	F	--	--	--	**6**
Cold to touch	M	--	--	--	**4**
	F	--	--	1	**--**
Tremors	M	--	--	--	**--**
	F	--	--	--	**1**

(Incidence); --: no finding

Body Weights

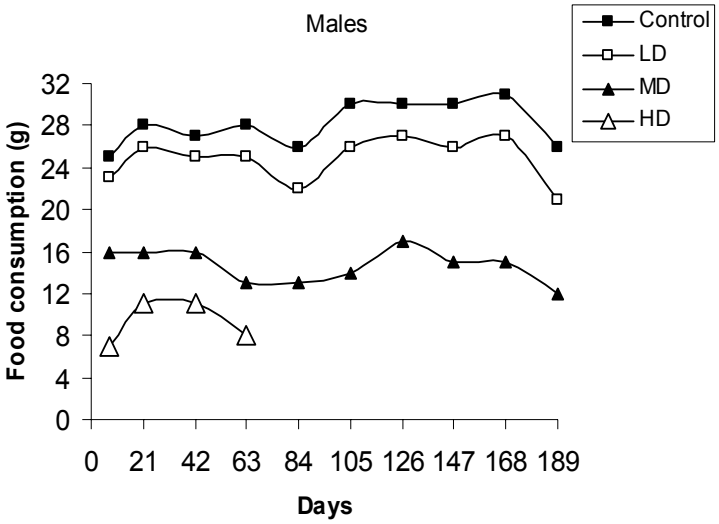
Figure 10: Male and Female rat weights

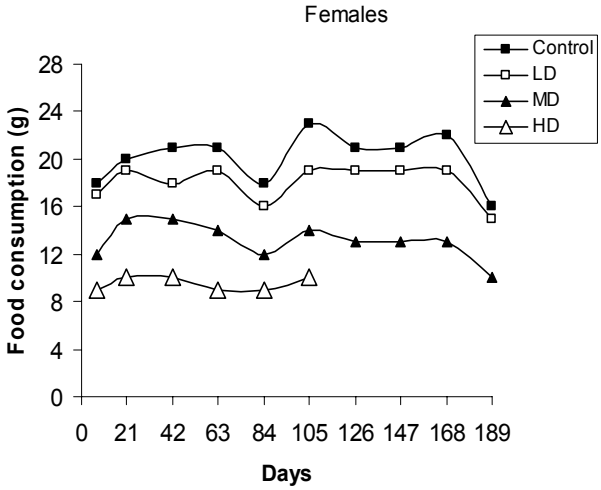




Feed Consumption

Figure 11: Male and Female Rat Food Consumption





Ophthalmoscopy: No significant findings.

ECG: Not done

Hematology

Table 36: Hematology

Parameter	Sex	Control			1 mg/kg			5 mg/kg			20/10 mg/kg	
	Day	3	87	192	3	87	192	3	87	192	3	87
Pre-terminal/Terminal/*Recovery (day 245)*												
Reticulocytes $x10^9$/L	M	313.4	252.8	213.2	↓91%	↓96%	↓95%	↓98%	↓97%	↓92%/↓ *25%*	↓77%	ND
	F	257.3	215.0	150.2	↓81%	↓88%	↓80%/ *↓23%*	↓98%	↓96%	↓96%/ *↓22%*	↓98%	↓96%
Platelets $x10^9$/L	M	1307	1305	1218	↓19%	↓33%	↓28%	↓45%	↓52%	↓47%	↓53%	ND
	F	1332	1265	1153	↓26%	↓24%	↓23%	↓45%	↓56%	↓58%/ *↓18%*	↓46%	↓55%
WBC $x10^6$/L	M	10.2	10.4	10.5	↓26%	↓36%	↓45%	↓51%	↓59%	↓69%/ *↓42%*	↓72%	ND
	F	8.77	7.24	6.65	--	↓24%	↓37%	↓52%	↓55%	↓63%/ *↓26%*	62%	62%
Neutrophils $x10^9$/L	M	1.29	1.58	2.10	↓51%	↓53%	↓58%	↓47%	↓31%	↓44%	↓47%	ND
	F	1.08	0.82	0.99	↓45%	↓36%	↓47%	↓70%	↓43%	↓45%	↓66%	↓35%
Lymphocytes $x10^9$/L	M	8.38	8.31	7.83	↓21%	↓30%	↓40%/ *↓21%*	↓50%	↓63%	↓75%/↓ *43%*	↓76%	ND
	F	7.24	6.04	5.28	--	↓21%	↓33%	↓51%	↓54%	↓65%/ *↓29%*	↓61%	↓64%
Monocytes $x10^6$/L	M	0.29	0.27	0.32	↓82%	↓84%	↓85%	↓86%	↓78%	↓84%/ *↓60%*	↓85%	ND
	F	0.22	0.17	0.21	↓50%	↓71%	↓72%	↓90%	↓84%	↓83%/ *↓31%*	↓86%	↓77%
Eosinophils $x10^9$/L	M	0.10	0.15	0.17	↓36%	↓57%	↓58%	↓73%	↓89%	↓82%/ *↓43%*	↓75%	ND
	F	0.16	0.11	0.13	↓39%	↓40%	↓60%	↓87%	↓93%	↓88%	↓91%	↓93%
Basophils $x10^9$/L	M	0.05	0.04	0.04	↓18%	↓25%	*↓44%*	↓38%	↓47%	↓67%/ *↓64%*	↓56%	ND
	F	0.03	0.03	0.02	↓27%	↓21%	↓30%	↓33%	↓34%	↓40%/ *↓50%*	↓48%	↓34%
LUC 10^9/L	M	0.05	0.08	0.04	↓28%	↓64%	↓55%	↓66%	↓86%	↓89%/ *↓38%*	↓79%	ND
	F	0.05	0.06	0.03	↓35%	↓36%	↓38%	↓75%	↓80%	↓90%/ *↓34%*	↓79%	↓87%

(% Change from control value); ND-not determined

Clinical Chemistry

Table 37: Clinical chemistry

Parameter	Sex	Control			1 mg/kg			5 mg/kg			20/10 mg/kg	
	Day	3	87	192	3	87	192	3	87	192	3	87
Pre-terminal/Terminal/*Recovery (day 245)*												
Glucose mmol/L	M	4.32	5.66	6.16	--	↑26%	↑32%	↑32%	↑36%	↑18%	↑67%	ND
	F	4.42	6.03	6.33	--	--	--	↑42%	↑39%	↑20%	↑53%	↑48%
Creatinine µmol/L	M	43.3	42.1	40.9	--	--	--	--	--	*↓23%*	--	ND
	F	45.3	49.1	49.7	--	--	--	--	--	--	--	↓22%
Tot. cholesterol mmol/L	M	1.53	1.68	2.07	--	↑30%	--	↑37%	↑61%	--	↑88%	ND
	F	2.14	2.45	2.67	--	--	--	--	--	↑28%	--	↑27%
Triglycerides mmol/L	M	0.76	0.86	1.26	--	--	--	--	↓52%	↓66%	--	ND
	F	0.57	0.53	0.62	--	--	↓27%	--	--	↓25%	↓35%	↓26%
ALP IU/L	M	502.4	218.9	184.2	--	--	--	--	↓28%	↓26%	↓23%	ND
	F	389.3	102.4	71.3	--	--	--	↓22%	--	--	↓34%	--
AST IU/L	M	139.9	149.9	171.6	--	--	--	--	--	↑45%	--	ND
	F	145.5	136.2	139.9	--	--	--	--	--	*↓25%*	--	↓29%
ALT IU/L	M	24.3	27.5	34/*85*	--	--	--	--	↑65%	↑266%/ *↓73%*	--	ND
	F	22.7	29.5	29.6	↓27%	--	--	--	↓32%	↑48%	--	↑38%

(% Change from control value); --: no significant change

Urinalysis

Table 38: Urinalysis

Dose →	Sex	0				1 mg/kg	5 mg/kg				20/10	
Parameter		3	87	192	245	--	3	87	192	245	3	245
Volume mL	M	11.45	16.35	18.29	21.02	--	--	↓19%	↓21%	↓34%	↓34%	ND
	F	6.63	11.64	11.27	8.40	--	--	↓28%	↓26%	↓20%	--	↓23%
Osmol mOsm/kg	M	586.0	540.9	517.5	554.2	--	--	--	--	--	↑74%	ND
	F	945.2	746.4	660.9	677.4	--	--	--	--	--		ND
pH	M	7.10	7.73	7.47	7.30	--	--	--	--	--	6.63	ND
	F	6.37	6.70	6.50	6.80	--	--	--	--	--		ND
Protein g/L	M	0.944	0.787	0.900	0.624	--	--	--	↓27%	↓27%	↑41%	ND
	F	0.317	0.234	0.222	0.190	--	--	↑43%	↑38%	--	--	↑38%

(% Change from control value); --: no significant change

Gross Pathology

Table 39: Gross pathology

Macroscopic Findings		Control		1 mg/kg		5 mg/kg		20/10 mg/kg	
		M	F	M	F	M	F	M	F
	Group Size:	**0**/10/*5*	**0**/10/*5*	**2**/8/*5*	**0**/10/*5*	**1**/9/*5*	**2**/9/*4*	**13**/0/*2*	**11**/0/*4*
	Grade	**Pre-terminal**/Terminal/*Recovery*							
Epididymides, small	Present	--	--	--	--	--	--	**8**	--
Kidneys, enlarged	Present	--	--	--	--	--	--	**2**/*2*	--
Liver, pale raised area	Present	--	--	--	--	--	--	**2**/*2*	**1**
Skin, alopecia	Present	--	--	--	--	--	--	**1**	**4**
Skin, ulcerated	Present					2			
Stomach, fluid, distended	Present	--	--	--	--	2	--	**1**	**2**
Testes, small	Present	--	--	--	--	--	--	**8**/*2*	**--**
Uterus, small	Present	--	--	--	--	--	--	--	**2**

(Incidence); --: no finding

Organ Weights

Table 40: Organ Weights

Organ	Sex	Control	1 mg/kg	5 mg/kg	20/10 mg/kg
Pre-terminal/Terminal/*Recovery*					
Adrenal gland	M	0.060	--	↓14%	↓27%/↓*25%*
	F	0.067	--	↓8%	↓*20%*
Epididymides	M	1.54	--	↓33%	↓64%/↓*60%*
Prost+Sem vesic		4.12	--	↓33%	↓38%/↓*52%*
Testes		3.75	--	↓18%	↓64%/↓*58%*
Heart	M	1.73/*1.89*	--	↓19%/↓*22%*	↓35%/↓*36%*
	F	1.11	--	↓13%	↓24%/↓*22%*
Kidneys	M	3.98	--	↓22%	↓42%/↓*29%*
	F	2.10	--	--	↓20%/↓*18%*
Liver	M	18.81/*20.07*	--	↓35%/↓*31%*	↓54%/↓*25%*
	F	9.75/*9.30*	--	↓8%/↓*6%*	↓31%//↓*29%*
Lungs	M	1.86/*2.07*	--	↓14%/↓*17%*	↓15%/↓*30%*
	F	1.46/*1.39*	--	--	↓15%/↓*16%*
Pituitary	M	0.013/*0.014*	--	↓20%/↓*21%*	↓86%/↓*29%*
	F	0.019/*0.024*	--	↓19%/↓*27%*	↓14%/↓*41%*
Spleen	M	0.916/*0.917*	--	↓35%/↓*30%*	↓47%/↓*34%*
	F	0.556	--	↓23%	↓26%

Organ	Sex	Control	1 mg/kg	5 mg/kg	20/10 mg/kg
Pre-terminal/Terminal/*Recovery*					
Thyroid	M	0.024	--	↓22%	↓42%/↓*18%*
	F	0.016/*0.018*	--	↓19%/↓*17%*	↓19%/↓*17%*
Ovaries	F	0.134/*0.133*	--	↓17%/↓*23%*	↓27%/↓*14%*

(% Change from Control)

Histopathology

Adequate Battery: Yes
Peer Review: Yes
Histological Findings

Table 41: Histological findings

Microscopic Findings		Control		1 mg/kg		5 mg/kg		20/10 mg/kg	
		M	F	M	F	M	F	M	F
	Group Size:	**0**/10/*5*	**0**/10/*5*	**2**/8/*5*	**0**/10/*5*	**1**/9/*5*	**2**/9/4	**13**/0/*2*	11/0/*4*
	Grade	**Pre-terminal**/Terminal/*Recovery*							
Adrenal glands Blood cyst	Min.	--	--	--	--	--	2	--	--
	Mod	--	--	--	--	--	2/*2*	--	**1**
	All	--	--	--	--	--	4/*2*	--	--
Bone Marrow Femur ↓Cellularity	Mild	--	--	1	--	4	1	*1*	**1**/*1*
	Mod	--	--	6	1	1/*2*	*2*	**1**	**1**
	Severe	--	--	2	8		**1**/10	**10**	**8**
	All	--	--	9	9	5/*2*	**1**/11	**11**/*1*	**10**/*1*
Bone Marrow Femur ↑myelopoiesis	Severe	--	--	1	1	--	--	*1*	--
Bone Marrow Sternum ↓Cellularity	Min.	--	--	--	6	--	--	--	--
	Mild	--	--	7	1	--	*1*	*1*	**1**/*1*
	Mod.	--	--	2/*3*	--	--		**1**	**1**
	Severe	--	--	--	--	9	**1**/10	**10**	**8**
	All	--	--	9/*3*	7	9	**1**/10/*1*	**11**/*1*	**10**/*1*
Brain, Abscess	Mod	--	--	--	--	--	1	--	--
GI Tract									
Regeneration/degeneration of glands	Min.	--	--	8	7	5	4/*2*	**8**	**6**
	Mild	--	--	--	--	4	6	**1**/*1*	--
	Mod.	--	--	--	--	--			--
	All	--	--	8	7	9	10/*2*	**9**/*1*	**6**
Shortening of villi	Min.	--	--	--	--	1	3	**2**	**6**
	Mild	--	--	--	--	4	5	**4**	**1**
	Mod.	--	--	--	--	3	1	**1**	**1**
	All	--	--	--	--	8	8	**7**	**8**
Inflammation	Min.	--	--	1	--	4	6	**2**	**6**
	Mild	--	--	--	--	3/*2*	--	**2**	**1**
	Mod	--	--	--	--	--	--	**4**	**1**
	All	--	--	1	--	7/*2*	6	**8**	**8**
Epididymides									
Oligospermia	Mild	--	--	--	--	--	--	1	--
	Mod	--	--	--	--	--	--	5	--
	Severe	--	--	*1*	--	--	--	**7**/*2*	--
	All	--	--	*1*	--	--	--	**13**/*2*	--

Microscopic Findings		Control		1 mg/kg		5 mg/kg		20/10 mg/kg	
		M	F	M	F	M	F	M	F
	Group Size:	**0**/10/*5*	**0**/10/*5*	**2**/8/*5*	**0**/10/*5*	**1**/9/*5*	**2**/9/4	**13**/0/*2*	11/0/*4*
	Grade	**Pre-terminal**/Terminal/*Recovery*							
Degenerative cells in epithelium	Min	--	--	--	--	1	--	**4**/*2*	--
	Mild	--	--	--	--	--	--	**6**	--
	Mod	--	--	--	--	--	--	**1**	--
	All	--	--	--	--	1	--	**11**/*2*	--
Irregular size nuclei in epithelium	Min	--	--	--	--	--	--	*2*	--
	Mild	--	--	--	--	9/*1*	--	**--**	--
	All	--	--	--	--	9/*1*	--	*2*	--
Nuclear Crowding	Min	--	--	--	--	2/*2*	--	**--**	--
	Mild	--	--	--	--	*1*	--	*2*	--
	All	--	--	--	--	2/*3*	--	*2*	--
Inflamm in intersitium w/exocytosis	Min	--	--	--	--	3/*2*	--	**11**/*2*	--
	Mild	--	--	--	--	--	--	**1**	--
	All	--	--	--	--	3/*2*	--	**12**/*2*	--
Sperm Granuloma	Mod	--	--	--	--	--	--	**1**	--
	All	--	--	--	--	--	--	**1**	--
Atrophy	Mild	--	--	--	--	--	--	**2**	--
	All	--	--	--	--	--	--	**2**	--
Eyes									
Acute inflamm.	Min	--	--	--	2	--	4	--	--
	Mod	--	--	--	--	--	1	--	--
	All	--	--	--	2	--	5	--	--
Lens fiber swelling/degeneration	Min	--	--	--	--	--	--	**9**/*2*	**7**/*4*
	Mild	--	--	--	--	--	--	1	**3**
	All	--	--	--	--	--	--	**10**/*2*	10/*4*
Cornea ulceration	Severe	--	--	--	--	--	1	**6**	**1**
Focal retinal atrophy	Min	--	--	--	--	--	3	**2**	-
	Mild	--	--	--	--	1	--	--	--
Heart									
Epicardial inflammation	Mild	--	--	--	--	1	--	--	--
Kidneys Pyelonephritis	Mild	--	--	--	--		--	**2**/*1*	--
	Severe	--	--	--	--		--	**1**	--
	All	--	--	--	--		--	**3**/*1*	--
Liver									
Subacute abscess	Severe	--	--				1	--	--
Hepatocellular necrosis	Min	--	--	2	3	2	1	**1**	--
	Mild	--	--	--	1	2	1	**--**	--
	All	--	--	2	4	4	2	**--**	--
Chronic abscess	Mild	--	--	--	--	--	--	**1**	**1**
	Mod	--	--	--	--	--	--	**2**	**--**
	All	--	--	--	--	--	--	**3**	**1**
Lungs		--	--	--	--	--	--	**--**	**--**
Abscess	Mod	--	--	--	--	--	--	**--**	**1**
Alveolar edema	Mild	--	--	--	--	--	--	**1**	**1**
	Mod	--	--	--	--	--	--	**1**	--

Microscopic Findings		Control		1 mg/kg		5 mg/kg		20/10 mg/kg	
		M	F	M	F	M	F	M	F
	Group Size:	**0**/10/*5*	**0**/10/*5*	**2**/8/*5*	**0**/10/*5*	**1**/9/*5*	**2**/9/4	**13**/0/*2*	11/0/*4*
	Grade	**Pre-terminal**/Terminal/*Recovery*							
Mamm. gland									
Atrophy	Mod	--	--	--	--	--	--	**3**/*1*	1/*1*
	Severe	--	--	--	--	--	2	-	-
Loss of adipose tissue	Mild	--	--	--	--	--	--	**3**	**2**
	Mod	--	--	--	--	--	--	**4**	**1**
	Severe	--	--	--	--	--	1	**1**/*1*	**1**/*1*
	All	--	--	--	--	--	--	**8**/*1*	**4**/*1*
		--	--	--	--	--	1	--	--
Mandib LN									
Decreased cellularity	Min	--	--	1	--	*5*	*3*	**2**/*1*	--
	Mild	--	--	--	--	4	10/*1*	**3**	**4**
	Mod	--	--	--	--	2	--	**3**	**2**/*1*
	Severe	--	--	--	--	--	1	**4**/*1*	**4**
	All	--	--	1	--	11	11/*1*	**12**/*3*	**10**/*1*
Mesent. LN									
Decreased cellularity	Min.	--	--	--	--	--	6	--	**3**
	Mild	--	--	--	--	11	2/*3*	**8**	**4**
	Severe	--	--	--	--	--	1	**3**/*1*	**2**/*1*
	All	--	--	--	--	11	9	**11**/*1*	**9**/*1*
Single cell necrosis	Min	--	--	1	--	8	5	**6**	**7**
	Mild	--	--		--	--	1	**1**	--
	All	--	--	1	--	8	6	**7**	**7**
Nasal cavities									
Ameloblast atrophy	Mod	--	--	--	--	2/*1*	3/*1*	**4**	**9**
	Severe	--	--	--	--	9/*3*	8/*3*	**3**	**1**
	All	--	--	--	--	11/*4*	11/*4*	**7**	**10**
Tooth root Inflammation	Mild	--	--	--	1	3/*2*	*1*	**1**	**1**
	Mod.	--	--	1	--	2/*1*	1	--	--
	Severe	--	--	--	--	--	1	--	**2**
	All	--	--	1	1	5/*3*	2	**1**	**3**
Ovaries Corpora lutea Necrosis	Min	--	--	--	--	--	4	-	**2**
	Mild	--	--	--	2	--	2	--	--
	All	--	--	--	2	--	6	--	--
Peyer's patches Germinal centers absent	--	--	--	3	--	5	--	--	--
Prostate									
Atrophy	Min.	--	--	--	--	--	--	*2*	--
	Mod	--	--	--	--	--	--	**2**	--
	Severe	--	--	--	--	--	--	**1**/*1*	--
	All	--	--	--	--	--	--	**3**/*3*	--
Inflammation	Mild	--	--	--	--	--	--	**2**/*2*	--
	Mod	--	--	--	--	--	--	**3**	--
	Severe	--	--	--	--	--	--	**5**	--
	All	--	--	--	--	--	--	**10**/*2*	--
Degen/Regen	Min.	--	--	--	--	--	--	**3**/*2*	--
	All	--	--	--	--	--	--	**3**/*2*	--

Microscopic Findings		Control		1 mg/kg		5 mg/kg		20/10 mg/kg	
		M	F	M	F	M	F	M	F
	Group Size:	**0**/10/*5*	**0**/10/*5*	**2**/8/*5*	**0**/10/*5*	**1**/9/*5*	**2**/9/4	**13**/0/*2*	11/0/*4*
	Grade	**Pre-terminal**/Terminal/*Recovery*							
Stratified Epith w/nuclear crowding	Min.	--	--	--	--	--	--	**1**	--
	Mild	--	--	--	--	--	--	**1**/*1*	--
	All	--	--	--	--	--	--	**2**/*1*	--
Absess formation	Present	--	--	--	--	--	--	*1*	--
Edema	Mod	--	--	--	--	--	--	*1*	--
	All	--	--	--	--	--	--	*1*	--
Sciatic nerve, fiber degeneration	Min	--	--	--	--	--	--	**3**	**7**
	Mild	--	--	--	--	--	--	**6**	**2**
	Mod	--	--	--	--	--	--	**1**	**-**
	All	--	--	--	--	--	--	**10**	**9**
Seminal veiscle									
Degeneration/regeneration	Min	--	--	1/*2*	--	4/*1*	--	**4**/*1*	--
	Mild	--	--	--	--	3	--	**4**	--
	Mod	--	--	--	--	--	--	**1**/*1*	--
	All	--	--	1/*2*	--	7/*1*	--	**9**/*2*	--
Inflammation	Min.	--	--	--	--	--	--	**2**	--
	Mild	*1*	--	--	--	--	--	**2**/*1*	--
	Mod.	--	--	--	--	--	--	*1*	--
	All	*1*	--	--	--	--	--	**4**/*2*	--
Coag.Gland, Inflamm.	Min.	--	--	--	--	--	--	**1**	--
	Mild	--	--	--	--	--	--	**1**/*2*	--
	Mod.	--	--	--	--	--	--	**3**	--
	Severe	--	--	--	--	--	--	**1**	--
	All	--	--	--	--	--	--	**6**/*2*	--
Coag.Gland, degen/regen	Min.	--	--	--	--	--	--	**2**	--
	Mild	--	--	--	--	--	--	**1**	--
	All	--	--	--	--	--	--	**3**	--
Coag. Gland, stratified epithelium	Mild	--	--	--	--	--	--	**4**	--
	All	--	--	--	--	--	--	**4**	--
Skeletal muscle									
Myofiber atrophy	Mild	--	--	--	--	7/*2*	1/*1*	**3**/*2*	**4**/*2*
	Mod	--	--	--	--	1		**2**	**1**
	All	--	--	--	--	8/*2*	1/*1*	**5**/*2*	**5**/*2*
Spleen									
Decreased lymphocytes	Min	--	--	3	1	4	4	**3**	**5**
	Mild	--	--	--	--	6	3	**2**	**1**/*1*
	Mod	--	--	--	--	1	--	**1**/*1*	--
	Severe	--	--	--	--		1	**3**/*1*	**2**
	All	--	--	3	1	11	8	**9**/*2*	**8**/*1*
Testes									
Seminiferous tubular atrophy	Min	--	--	--	--	1	--	**--**	--
	Mod	--	--	--	--	--	--	**1**	--
	Severe	--	--	*1*	--	--	--	**12**/*2*	--
	All	--	--	*1*	--	1	--	**13**/*2*	--
Focal Atrophy	Min	1	--	*1*	--	1/*1*	--	**--**	--
	All	1	--	*1*	--	1/*1*	--	**--**	--

Microscopic Findings		Control		1 mg/kg		5 mg/kg		20/10 mg/kg	
		M	F	M	F	M	F	M	F
	Group Size:	**0**/10/*5*	**0**/10/*5*	**2**/8/*5*	**0**/10/*5*	**1**/9/*5*	**2**/9/4	**13**/0/*2*	11/0/*4*
	Grade	**Pre-terminal**/Terminal/*Recovery*							
Multi-nuc cells	Min	--	--	--	--	1	--	--	--
	All	--	--	--	--	1	--	--	--
Vacuolation	Min	--	--	--	--	1/*1*	--	--	--
	All	--	--	--	--	1/*1*	--	--	--
Interstitial Fluid	Mild	--	--	--	--	--	--	**1**	--
	Mod	--	--	--	--	--	--	**3**	--
	All	--	--	--	--	--	--	**4**	--
Sperm Granuloma	Mild	--	--	--	--	--	--	**1**	--
	All	--	--	--	--	--	--	**1**	--
Thymus									
Decreased lymphocytes	Mod	--	--	--	--	1	6	**1**/*1*	**2**
	Severe	--	--	--	--	7/*3*	2	**11**/*1*	**8**/*1*
	All	--	--	--	--	8/*3*	8	**12**/*2*	**10**/*1*
Uterus									
Glandular atrophy	Min	--	--	--	--	--	**3**	--	
	Mild	--	--	--	--	--	**4**	--	**1**
	Mod	--	--	--	--	--	**2**	--	**3**
	Severe	--	--	--	--	--	**1**	--	**4**/*1*
	All	--	--	--	--	--	**10**	--	**8**/*1*
Urinary bladder, Glandular atrophy	Mod	--	--	--	--	--	--	--	*1*
	Severe	--	--	--	--	--	--	--	*2*
	All	--	--	--	--	--	--	--	*3*

Special Evaluation: None

Toxicokinetics

Table 42: cabazitaxel toxicokinetics in male and female SD rats

Dose	Sex	Cmax (ng/mL)			AUC $_{0-25}$ (ng.h/mL)		
Cycle →		1	5	10	1	5	10
1	M	61.3	46.5	65.8	165	199	240
	F	16.3	35.8	47.2	91.7	138	129
5	M	771	771	665	1160	1180	1030
	F	476	516	531	772	749	760
20/10	M	5650	ND	ND	10500	ND	ND
	F	4950	1320	ND	8390	1880	ND

ND-Not determined

Note: The 20 mg/kg dose of cabazitaxel was reduced to 10 mg/kg after cycle 1 due to severe toxicity. Treatment at 10 mg/kg was stopped after the 4th cycle in male and 6th cycle in female rats.

Study title: XRP6258:13-cycle intravenous toxicity study in dogs (consisting of a single administration every 3 weeks) with 3-day observation and 8-week recovery periods

Study no.:	TSK0037
Study report location:	4.2.3.2.1
Conducting laboratory and location:	Sanofi-Aventis Recherche & Développement, Groupe sanofi-aventis 1 avenue Pierre Brossolette 91835 Chilly-Mazarin – Cedex, France
Date of study initiation:	June 02, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	XRP6258, P-33125-216-1 (Batch No. 0326012 of XRP6258 enriched with 3.6% of synthetic impurities), and 96.9% purity.

Key Study Findings

- Clinical signs included decreased motor activity, tremors, vocalization, liquid feces reddened skin
- 3 days after each dosing cycle there were decreases in platelets, lymphocytes and neutrophils, WBC and basophils.
- Histopathological findings were in the GI tract, deccreased cellurity of bone marrow in the sternum, inflammatory cells in the lungs and increased epididymal vacuolation
- Polysorbate 80 may have effect on food consumption in dogs

Methods

Doses:	0.1, 0.25, 0.5 mg/kg (0, 2, 5, 10 mg/m^2)
Frequency of dosing:	Every 3 weeks
Route of administration:	Intravenous infusion
Dose volume:	5 mL/kg
Formulation/Vehicle:	Vial of 40 mg/mL stock solution of XRP6258 in pure polysorbate 80/PS80, 0.25% (w/w) and ethanol 0.01% (w/w) in an aqueous solution of 5% (w/w) glucose
Species/Strain:	Beagle Dogs
Number/Sex/Group:	5
Age:	14-15 months
Weight:	Males, 5.9-9.3 kg; Females, 5.2-7.5 kg
Satellite groups:	All

Observations and Results

Mortality

There were no unscheduled deaths during this study.

Clinical Signs

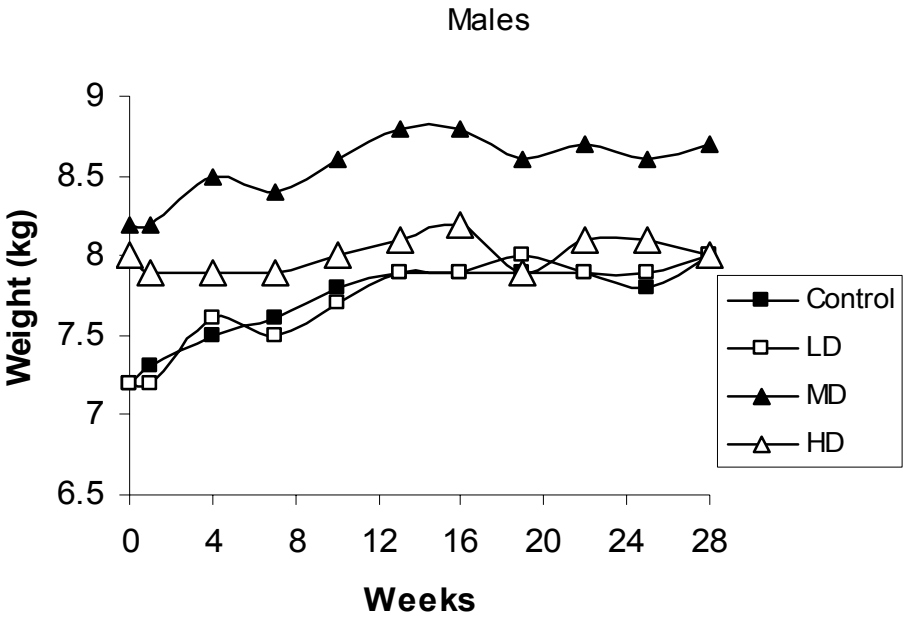
Table 43: Clinical Signs

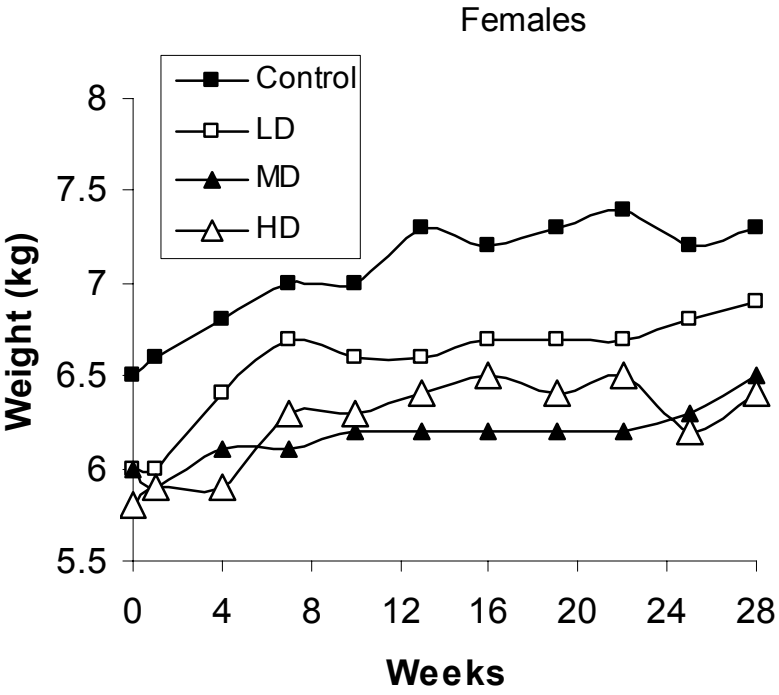
Sign	Dose	0	0.1 mg/kg	0.25 mg/kg	0.5 mg/kg
	M	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*
	F	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*
Preterminal/Terminal /*Recovery*					
Agitation, extreme or moderate	M	2	3	5	4
	F	2	5	5	5
Liquid feces	M	--	--	--	1
	F		--	1	1
↓Motor activity	M	--	--	1	1
	F	--	--	--	--
Nodule, hind limb	M	--	--	4	2
	F	2	--	3	2
↑Respiratory rate	M	1	2	2	2
	F	--	--	1	1
Salivation	M	--	--	--	1
	F	--	1	1	--
Skin reddened, whole body	M	--	1	1	--
	F	1	1	--	3
Swelling, both hindpaws	M	--	--	1	1
	F	--	--	--	1
Tremors	M	--	2	1	
	F	--	3	3	1
Vomiting, extreme	M	--	--	--	1
	F	--	--	--	--
Vocalization	M	4	3	5	5
	F	1	3	3	4

--: no findings

Body Weights

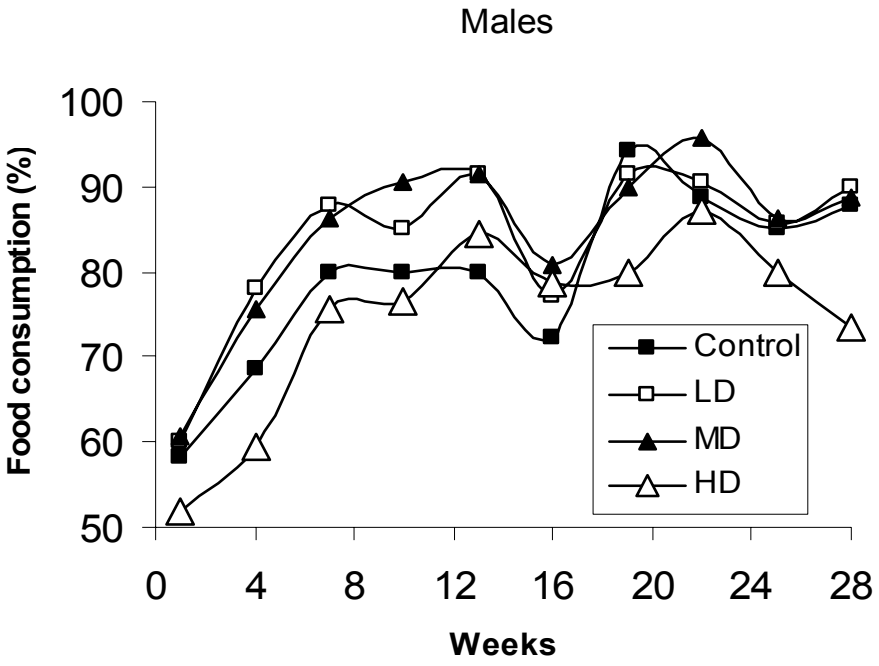
Figure 12: Male and Female body weights

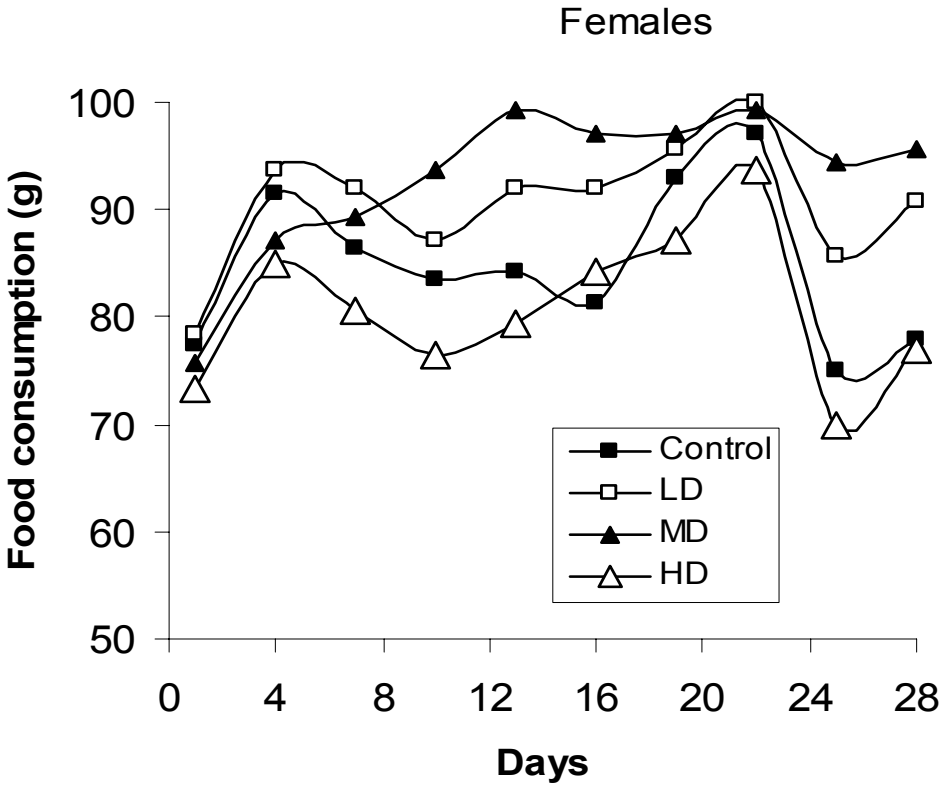




Feed Consumption

Figure 13: Male and Female food consumption





Ophthalmoscopy: No significant findings.

ECG

Table 44: Heart rate and QTcv

Dose		Heart Rate Beats/min			QTcv ms		
Day of infusion →		1	106	253	1	106	253
0	M	183.2	187.2	192.6	233.0	230.0	236.2
	F	171.4	165.6	179.2	240.4	238.0	229.2
0.1 mg/kg	M	↓20%	↓24%	↓25%	↑10.6	--	--
	F	↓16%	--	--	--	--	--
0.25 mg/kg	M	↓20%	↓28%	↓28%	↑17.0	--	--
	F	↓17%	--	--	--	--	--
0.5 mg/kg	M	↓12%	↓28%	↓19%	↑18.4	↑7.6	--
	F	↓13%	--	--	--	--	--

(Heart Rate: % Change from control value; QTcv: Change from control value, ms).
QTcv = corrected QT using Van de Water formula (QTcv = QT - 87 * (RR interval - 1).

Hematology

Table 45: Hematology

Parameter	Sex	Control			0.1 mg/kg			0.25 mg/kg			0.5 mg/kg		
	Day	4	109	256	4	109	256	4	109	256	4	109	256
Pre-erminal/Terminal/*Recovery (day 309)*													
Reticulocytes $x10^{12}/L$	M	0.051	0.051	0.038	--	--	--	↓20%	↓18%	--	↓75%	↓78%	↓76%/ *↓38%*
	F	0.061	0.054	0.054	--	--	--	--	--	--	↓71%	↓69%	↓75%/ *↓57%*
Platelets $x10^{9}/L$	M	312	338	340	--	--	--	--	--	--	31%	17%	--
	F	420.4	434.4	424.4	--	--	--	--	--	--	↓51%	↓34%	↓41%
WBC $x10^{9}/L$	M	8.67	8.59	7.91	--	--	--	--	↑31%	--	--	--	--
	F	10.19	9.95	9.13	--	--	--	--	--	--	↓40%	↓31%	↓39%
Neutrophils $x10^{9}/L$	M	4.99	4.96	4.78	--	--	--	--	--	--	--	--	--
	F	6.41	6.47	5.87	--	--	--	--	--	--	↓40%	↓37%	↓41%
Lymphocytes $x10^{9}/L$	M	2.47	2.63	2.43	--	--	--	--	--	--	↓45%	↓43%	↓41%
	F	2.56	2.59	2.54	--	--	--	--	--	--	↓38%	↓27%	↓38%
Monocytes $x10^{9}/L$	M	0.43	0.38	0.30	--	--	--	--	↑45%	↑97%	--	↑29%	↑64%
	F	0.36	0.35	0.32	--	--	--	--	--	--	--	--	--
Eosinophils $x10^{9}/L$	M	0.61	0.44	0.27	--	--	--	--	--	--	↓49%	↓25%	--
	F	0.76	0.40	0.27	--	--	--	↓53%	--	--	↓61%	--	↓59%
Basophils $x10^{9}/L$	M	0.11	0.11	0.07	--	--	--	↓27%	↓36%	--	↓77%	↓64%	↓49%
	F	0.07	0.08	0.08	--	--	--	--	--	--	↓50%	↓28%	↓51%/ *↓37%*
LUC $10^{12}/L$	M	0.07	0.07	0.05	--	--	--	--	--	--	--	--	--
	F	0.04	0.06	0.05	--	--	--	--	↓41%	↓26%	--	--	--

(% Change from control value); --: no significant change)

Clinical Chemistry

Table 46: Clinical Chemistry

Parameter	Sex	Control			0.1 mg/kg			0.25 mg/kg			0.5 mg/kg		
	Day	4	109	256	4	109	256	4	109	256	4	109	256
Pre-erminal/Terminal/*Recovery (day 309)*													
AST IU/L	M	27.0	28.8	28.2	--	--	--	--	--	--	--	↑53%	↑65%
	F	26.8	26.0	30.0	--	--	--	--	--	--	--	--	↑25%
ALT IU/L	M	35.8	36.8	41.2	--	--	--	--	--	--	--	--	--
	F	35.2	34.8	40.0/ *39.0*	--	--	--	↓30%	--	--	↓26%	↓27%	↓26%/ *↓35%*
ALP IU/L	M	243.2	295.5	562.4	--	--	--	--	--	--	--	--	--
	F	270.6	261.0/ *290.1*	239.8	--	--	--	↑51%	↑114%	↑106%/ *↑28%*	--	--	--
Total Cholesterol mmol/L	M	3.09	3.21	3.18	--	--	--	--	--	--	--	--	--
	F	3.47	3.99	3.87/ *3.38*	--	--	--	--	--	--	--	--	*↑79%*
Triglycerides mmol/L	M	0.37	0.40	0.37	--	--	--	--	--	--	--	--	--
	F	0.47	0.47	0.51/ *0.61*	--	--	--	--	--	--	--	--	*↑68%*

(% Change from control value); --: no significant change

Urinalysis

Table 47: Urinalysis

Parameter	**Sex**	**Control**			**0.1 mg/kg**			**0.25 mg/kg**			**0.5 mg/kg**		
	Day	**4**	**109**	**256**	**4**	**109**	**256**	**4**	**109**	**256**	**4**	**109**	**256**
Pre-erminal/Terminal/*Recovery (day 309)*													
Urinary volume mL	M	109.2	124.2	72.7	--	--	--	--	--	--	--	--	--
	F	146.8	148.2	144.1	--	--	*↓24%*	--	--	↓39%/ *↓73%*		↓34%	↓44%/ *↓36%*
Osmolarity mOsm	M	152.2	188.2	119.1	--	--	--	--	--	--	--	--	--
	F	169.7	173.3	158.6			*↓26%*			*↓57%*			↓42%/ *↓32%*

(% Change from control value)

Gross Pathology

Table 48: Gross Pathology

Macroscopic Findings		Control		0.1 mg/kg		0.25 mg/kg		0.5 mg/kg	
		M	F	M	F	M	F	M	F
	Group Size:	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*
	Grade	**Preterminal**/Terminal/*Recovery*							
Heart, Focus/area, red	Present	--	--	--	--	2	--	--	--
Intestine, colon Focus/area, red	Present	--	--	--	--	--	*1*	1	2
Kidneys, anomaly	Present	--	--	--	--	1	--	--	--
Lungs, Focus/area, red	Present	--	--	--	--	--	1	2	--
Focus/area, white	Present	--	--	--	1	--	1	--	*1*
Stomach, Focus/area, red	Present	--	--	--	--	--	--	2	2
Thyroid gland, cyst	Present	--	--	--	--	1	--	--	--
Uterus, small	Present	--	--	--	1	--	--	--	--

(Incidence); --: no finding

Organ Weights

Table 49: Organ weight

Organ	Sex	Control	0.1 mg/kg	0.25 mg/kg	0.5 mg/kg
Pre-terminal/Terminal/*Recovery*					
Adrenal gland	M	1.09	--	↑28.2%	--
	F	1.39	--	--	--
Epididymides	M	2.66	↑26.3%	↑32.3%	↑14.3%
Testes		10.84	↑13.4%	↑37.1%	↑13.3%
Kidneys	M	33.61	↑19.1%	↑27.4%	↑9.7%
	F	33.58	↓13.3%	↓10.0%	↓12.9%
Liver	M	220.0	--	↑15.4%	↑12.3%
	F	250.3	↓19.2%	--	↓14.1%
Pituitary	M	0.037	↑18.2%	↑27.3%	↑27.3%
	F	0.043	↑30.8%	↑7.7%	--
Thymus	M	4.75	↓25.6%	↑21.6%	↑27.7%
	F	4.39	↓22.6%	↓14.4%	↑6.6%
Ovary	F	0.83	--	↑79.9%	↑59.0%
Uterus		5.0	↓31.9%	↑114.1%	↑32.4%

Histopathology

Adequate Battery: Yes
Peer Review: Yes

-

Histological Findings

Table 50: Histological findings

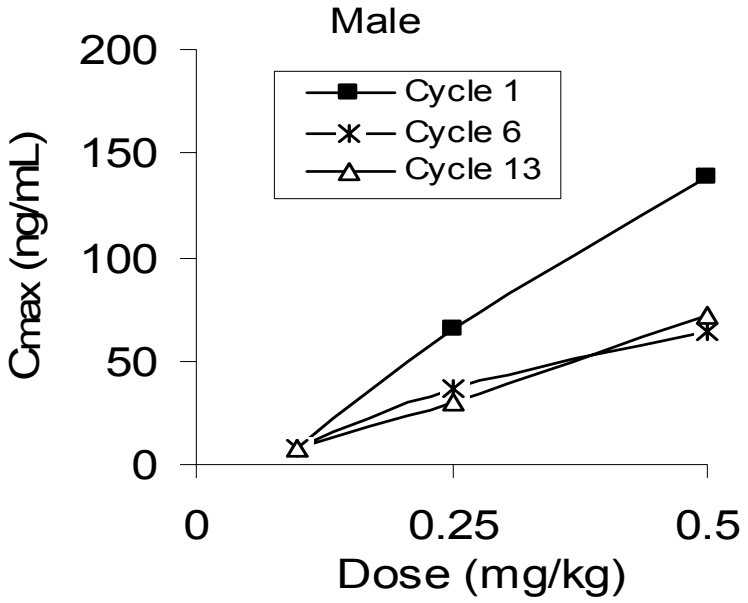
Microscopic Findings		Control		0.1 mg/kg		0.25 mg/kg		0.5 mg/kg	
		M	F	M	F	M	F	M	F
	Group Size:	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*
	Grade	**Pre-terminal**/Terminal/*Recovery*							
Bone Marrow Sternum ↓Cellularity	Min.	--	--	--	--	--	--	1	--
	Mild	--	--	--	--	--	--	1	2
	Mod.	--	--	--	--	--	--	1	1
	All	--	--	--	--	--	--	3	3
GI Tract									
Regenerative hyperplasia: epithelium	Min.	--	--	--	--	--	2	--	--
	Mild	--	--	--	--	--	--	3	3
	All	--	--	--	--	--	2	3	3
Dilation: crypt with cell debris	Min.	--	--	1	1	2	--	3	3/*1*
Congestion: lamina propria	Min.	--	--	--	--	--	--	1	--
	Mild	--	--	--	--	--	--	--	1
Atrophy: villi	Mild	--	--	--	--	--	--		1
↓lymphocytes	Min	--	--	--	--	--	--	2	1
Epididymides									
↑vacuolation: epithelium tail	Mild	--	--	--	--	*1*	--	2	
Single cell necrosis	Min	--	--	--	--	--	--	1	
Esophagus, Single cell necrosis: epithelium	Min	--	--	--	--	--	--	--	2
Heart									
Hemorrhage: endocardium	Min	--	--	--	--	1	--	--	--
Injection site									
Thrombus vein	Min	--	--	--	--	1	--	--	1
Necrosis/Inflamma-tion: subcutis perivascular	Min	1	--	--	2	--	--	1	--
	Mild	--	--	1	--	--	--	--	--
Hemorrhage:subcutis	Min	2	2	2	2	--	1	1	1
	Mild	1	--	1	1	1	2		2
	Mod	--	--	--	--	1	--	--	--
	All	3	2	3	3	2	3	1	3
Granuloma: dermis	Min	--	--	--	--	1/*1*	1/*1*	--	--
Kidneys									
Infiltrate: mononuclear inflammatory cerlls	Min	2	2	3	--	1	--	1	--
	Mild	--	--	--	--	1	--	--	--
	All	2	2	3	--	2	--	1	--

Microscopic Findings		Control		0.1 mg/kg		0.25 mg/kg		0.5 mg/kg	
		M	F	M	F	M	F	M	F
	Group Size:	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*	**0**/3/*2*
	Grade	**Pre-terminal/**Terminal/*Recovery*							
Basophilic tubule	Min	1	--	--	--	2	1	1	--
Liver Fibrosis	Min	--	--	--	--	--	1	1	--
LN: Iliac Sinus erythrocytes/ erythrophagocytosis	Min	--	--	--	1	1	--	1	--
	Mild	--	--	1	--	--	--	--	--
	Mod	--	--	--	--	1	--	1	--
	All	--	--	1	1	2	--	2	--
LN: Retropharyngeal Sinus erythrocytes/ erythrophagocytosis	Mild	--	1	1	--	1	--	--	--
Lungs Infiltrate: mixed inflammatory cells	Min	--	--	1	1	1	1	1	--
	Mild	--	--	2	--	--	--	--	*1*
	Mod	--	--	--	--	--	--	1	--
	All	--	--	3	1	1	1	2	--
Mammary glands									
↑secretion products	Mild	--	--	--	--	--	--	--	1
Pituitary Gland Cyst: pars distalis	Min	1	1	1	1	1	2	--	--
	Mild	--	--	--	--	--	--	--	1
Salivary Gland: Parotid Infiltrate: lymphocytes	Min	1	--	1	2	1	2	--	--
Stomach									
↑single cell necrosis: mucosa pylorus	Min	--	--	--	--	--	--	3	3
Congestion/hemorrhage: lamina propria	Min	--	1	--	1	--	--	2	2
Testes, Atrophy tubule	Min	--	--	3	--	1	--	--	--
Uterus									
Hypoplasia: unilateral	Severe	--	--	--	1	--	--	--	--
Cyst: epithelium	Mild	--	--	--	--	--	--	--	1

Special Evaluation: None

Toxicokinetics

Figure 14: Cmax



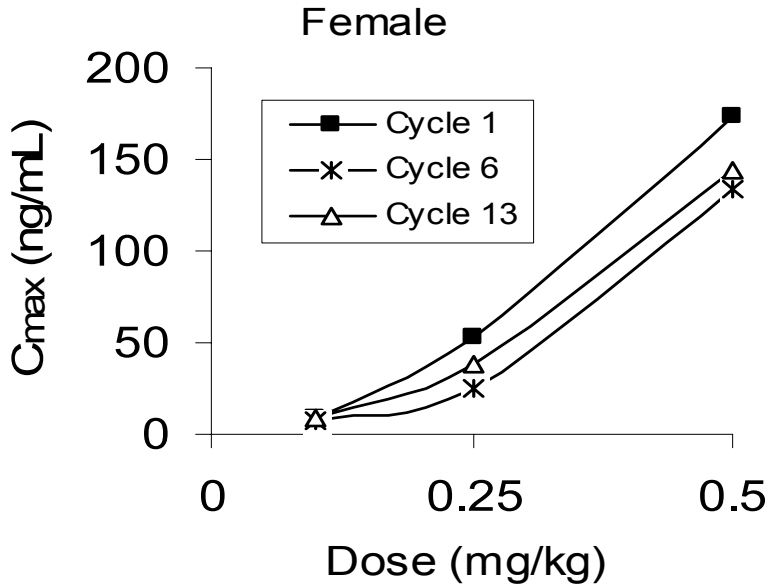
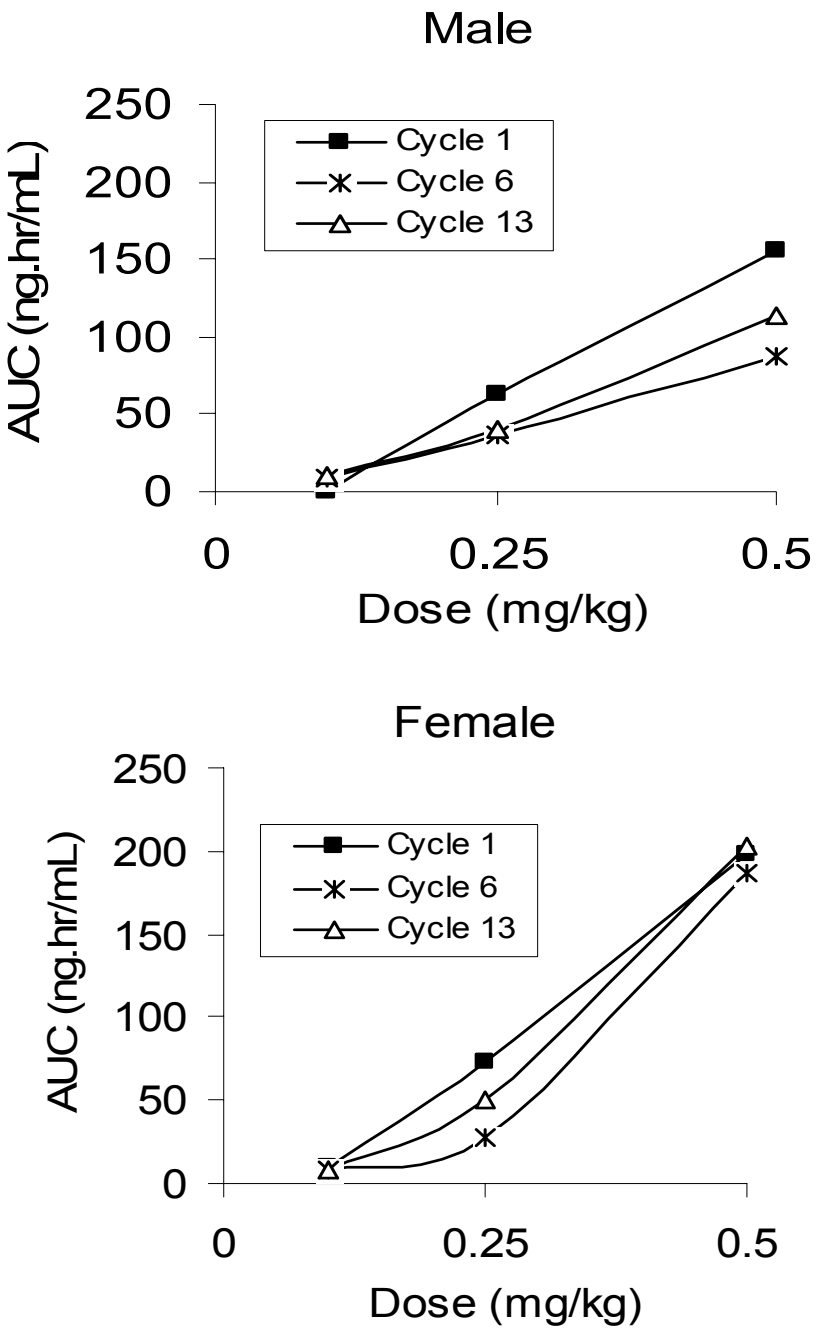


Figure 15: AUC



7 Genetic Toxicology

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

Study title: RPR 116258: Bacterial Reverse Mutation Test (Ames)

Study no.:	DS/CRVA/98-020
Study report location:	4.2.3.3.1
Conducting lab and location:	Rhone-Poulenc Rorer, France
Date of study initiation:	02/03/1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Batch #BFC 611/ % purity 96.5

Key Study Findings

- Cabazitaxel was negative in the bacterial reverse mutation (Ames) test
- In the two mutagenicity assays, plate incorporation and preincubation, with cabazitaxel, no increase in the number of revertant colonies was observed.
- In the positive controls with and without S9 mix, cabazitaxel induced a measurable increase in the number of revertant colonies.

Methods

Strains:	*S. typhimurium* TA1535, TA1537, TA98, TA100 and TA102
Concentrations in definitive study:	10, 50, 100, 500, 1000 µg/plate without S9-mix and 50, 100, 500, 1000, 2500 µg/plate with S9-mix
Basis of concentration selection:	Based on preliminary range finding study
Negative control:	Ethanol (0.05% ml/plate)
Positive control:	**Without S9-mix**: sodium azide at 0.2 µg/plate for TA1535 and at 2 µg/plate for TA100, 9-aminoacridine at 20 µg/plate for TA1537, 2-nitrofluorene at 0.5 µg/plate for TA98, and mitomycin C at 1 µg/plate for TA102. **With S9-mix:** Cyclophosphamide at 100 µg/plate for TA1535 using the plate incorporation and 25 µg/plate using the preincubation methods, benzo(a)pyrene at 1 µg/plate for TA1537 and TA98 and 2 µg/plate for TA100, 2-aminofluorene at 200 µg/plate for TA102 using incorporation and 100

	µg/plate using preincubation methods.
Formulation/Vehicle:	RPR 116258 was dissolved and diluted in ethanol
Incubation & sampling time:	48 hours after treatment

Study Validity

The validity of the study is based on the following criteria:

- genetic characterization of the strains to ensure that they possess *uvrB* mutation (sensitivity to ultra–violet radiation for TA1535, TA1537, TA98 and TA100), the *rfa* mutation (cell wall deficiency), and ampicillin resistance (strains TA98, TA100 and TA102) or ampicillin sensitivity (strains TA1535 and TA1537), and tetracyclin resistance (strain TA102)
- the mean number of spontaneous revertant colonies for the three negative control plates remained within the range of historical data for the conducting facility.
- the number of revertant colonies for the three positive control plates represents at least a twofold increase compared to the number of spontaneous revertant colonies in the negative control plates,
- the increase in number of revertant colonies is dose–related or observed at the highest dose level, and is reproducible.

Results

Cabazitaxel was tested in two mutagenicity studies, the plate incorporation and preincubation methods. In the first assay, cabazitaxel was tested at 10, 50, 100, 500 and 1000 µg/plate with and without S9-mix. Precipitates were observed at 1000 µg/plate with and without S9 mix on all strains. In the second assay, cabazitaxel was tested at 10, 50, 100, 500 and 1000 g/plate without S9-mix and at 50, 100, 500, 1000 and 2500 µg/plate with S9-mix using the preincubation method. Precipitates were observed at 1000 µg/plate without S9 mix on all strains, and at 1000 and 2500 µg/plate with S9-mix on all strains. In the two mutagenicity assays with cabazitaxel, no increase in the number of revertant colonies
was observed. The positive controls with and without S9 mix induced a clear increase in the number of revertant colonies.

Under the experimental conditions of this study, cabazitaxel was found negative in the bacterial reverse mutation test conducted on the five *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102 in the presence or absence of metabolic activation.

Study title: RPR 116258 (Batch P98041ME): Bacterial Reverse Mutation Test (Ames)

Study no.:	DS/CRVA/98-156
Study report location:	4.2.3.3.1
Conducting laboratory and location:	Rhone-Poulenc Rorer
Date of study initiation:	04/20/1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Batch # P90841ME/ % purity 98.2

Key Study Findings

- Cabazitaxel was negative in the bacterial reverse mutation (Ames) test
- In the two mutagenicity assays, plate incorporation and preincubation, with cabazitaxel, no increase in the number of revertant colonies was observed.
- In the positive controls with and without S9 mix, cabazitaxel induced a measurable increase in the number of revertant colonies.

Methods

Strains:	*S. typhimurium* TA1535, TA1537, TA98, TA100 and TA102
Concentrations in definitive study:	10, 50, 100, 500, 1000 µg/plate without S9 mix and 50, 100, 500, 1000, 2500 µg/plate with S9-mix
Basis of concentration selection:	Based on results of Study DS/CRVA 98-020
Negative control:	Ethanol (0.05% ml/plate)
Positive control:	**Without S9:** sodium azide at 0.2 µg/plate for TA1535 and at 2 µg/plate for TA100, 9-aminoacridine at 20 µg/plate for TA1537, 2-nitrofluorene at 0.5 µg/plate for TA98, and mitomycin C at 1 µg/platefor TA102. **With S9 mix:** Cyclophosphamide at 100 µg/plate for TA1535 using the plate incorporation and 25 µg/plate using the preincubation methods, benzo(a)pyrene at 1 µg/plate for TA1537 and TA98 and 2 µg/plate for TA100, 2-aminofluorene at 200 µg/plate for TA102 using incorporation and 100 µg/plate using preincubation methods.
Formulation/Vehicle:	Cabazitaxel was dissolved and diluted in ethanol
Incubation & sampling time:	48 hours after treatment

Study Validity

The validity of the study is based on the following criteria:

- genetic characterization of the bacterial strains to ensure that they possess *uvrB* mutation (sensitivity to ultra–violet radiation for TA1535, TA1537, TA98 and TA100), the *rfa* mutation (cell wall deficiency), and ampicillin resistance (strains

TA98, TA100 and TA102) or ampicillin sensitivity (strains TA1535 and TA1537), and tetracyclin resistance (strain TA102)

- the mean number of spontaneous revertant colonies for the three negative control plates remains within the range of historical data for the conducting facility.
- The mean number of revertant colonies for the three positive control plates represents at least a twofold increase compared to the number of spontaneous revertant colonies in the negative control plates,
- the increase in number of revertant colonies is dose–related or observed at the highest dose level, and is reproducible.

Results

Cabazitaxel (P98041ME, the clinical batch) was tested in the two mutagenicity assays, the plate incorporation and preincubation methods, at 10, 50, 100, 500 and 1000 µg/plate with and without S9-mix. In the first assay, precipitates were observed at 500 and 1000 µg/plate with and without S9-mix on all strains. In the second assay, precipitates were observed at 500 and 1000 µg/plate without S9-mix on all strains and only at 1000 µg/plate with S9-mix on all strains. In the two mutagenicity assays, no increase in the number of revertant colonies was observed. The positive controls with and without S9 mix induced a clear increase in the number of revertant colonies.

Under the experimental conditions of this study, cabazitaxel was found negative in the bacterial reverse mutation test conducted on the five *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102 in the presence or absence of metabolic activation.

7.2 In Vitro Chromosomal Aberration Assays in Mammalian Cells

Study title: RPR 116258: *In vitro* chromosome aberration test in cultured human peripheral blood lymphocytes

Study no.:	DS/CRVA 98-022
Study report location:	4.2.3.3.1
Conducting laboratory and location:	Rhone-Poulenc Rorer, France
Date of study initiation:	03/10/1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258, batch #BFC611/% purity 96.5

Key Study Findings

- Cabazitaxel was positive in the *in vitro* chromosome aberration test.

In the assay in human lymphocytes from a female donor (Table 19),

without or with S9-mix:

- No significant increase in the number of cells with chromosome aberrations was observed at any concentration considered.
- Increased number of polyploid cells were observed.

In the assay in human lymphocytes from a male donor (Table 20 & 21),

without S9-mix:

- No statistically significant increase in the number of cells with chromosome aberrations was observed at any of the concentrations or harvest times considered.
- Increased number of polyploid cells were observed only at the 20-hour harvest time.

with S9-mix:

- Statistically significant increase in the number of cells with chromosome aberrations were observed at 0.001 and 0.05 µg/mL at 20-hour harvest time.
- Increased number of polyploid cells were observed at 20- and 44-hour harvest times.

Methods

Cell line:	Human peripheral blood lymphocytes
Concentrations in definitive study:	**Female:** 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05 and 0.1 µg/ml without and with S-9 mix **Male:** 0.0001, 0.0005, 0.001, 0.005, 0.01, 0.05 and 0.1 µg/ml without and 0.001, 0.005, 0.01, 0.05 µg/ml with S9-mix
Basis of concentration selection:	Based on preliminary cytotoxic assay
Negative control:	Ethanol diluted in treatment medium, final concentration 1% with and without S9-mix.
Positive control:	Mitomycin C (0.4 µg/ml female and 0.2 µg/ml male) without S9-mix and Cyclophosphamide (7.5 µg/ml) with S9-mix
Formulation/Vehicle:	Ethanol diluted in treatment medium, final concentration 1%
Incubation & sampling time:	**Female:** Cells treated for 3 hours with and without S9-mix and harvested 20 h after the beginning of treatment. **Male:** Cells were treated for 3 h with S9-mix and 20 h without S9-mix and harvested 20 h or 44 h after the beginning of treatment.

Study Validity

Cabazitaxel is considered positive if all of the following criteria are fulfilled:

- it induces a statistically significant increase in the number of cells with chromosome aberrations for at least one harvest time,
- the increase in number of cells with chromosome aberrations is concentration–related or observed at the highest concentration,
- the increase is reproducible in two independent assays,
- the incidence of cells with chromosome aberrations is out of the range of historical negative control data.

These criteria establish the validity of the test.

Results

Table 51: Results of assay of lymphocytes from a female donor (20 h)

(b) (4)

In the assay in human lymphocytes from a female donor (Table 19),

without S9-mix:

- No cytotoxicity was observed as defined by a reduced mitotic index.
- However, a dose–dependent increase in mitotic index ranging from 143 to 338% was observed from 0.005 to 0.1 µg/ml.
- No statistically significant increase in the number of cells with chromosome aberrations was observed at any concentration considered.
- Increased numbers of polyploid cells were observed.

with S9-mix:

- No cytotoxicity was observed as defined by a reduced mitotic index.
- However, increases in mitotic index were observed at 0.05 and 0.1 µg/ml corresponding to 146 to 179% , respectively
- No statistically significant increase in the number of cells with chromosome aberrations was observed at any concentration considered.
- Increased numbers of polyploid cells were observed.

Table 52: Results of assay of lymphocytes from a male donor (20 h)

(b) (4)

Table 53: Results of assay of lymphocytes from a male donor (44 h)

(b) (4)

(Excerpted from the sponsor's submission)

In the assay in human lymphocytes from a male donor (Table 19 & 20),

Without S9-mix:

- There was severe cytotoxicity at concentrations >0.005 µg/ml
- At 0.0001, 0.0005, 0.001 and 0.005 µg/ml, the mitotic indexes were 99, 103, 108 and 165% at 20 hours, respectively,
- the mitotic indexes were 77, 89, and 80% at 44 hours for 0.0001, 0.0005 and 0.001 µg/ml, respectively
- No statistically significant increase in the number of cells with chromosome aberrations was observed at any of the concentration or harvest time considered.
- Increased numbers of polyploid cells were observed only at the 20-hour harvest time.

with S9-mix:

- There was severe cytotoxicity at concentrations of 0.1 µg/ml
- At 0.001, 0.005, 0.01 and 0.05 µg/ml, the mitotic indexes were 114, 92, 113 and 162% at 20 hours, respectively and
- The mitotic indexes were 83, 104, 100 and 89% at 44 hours, respectively.
- Statistically significant increase in the number of cells with chromosome aberrations were observed at 20-hour harvest time at 001 and 05 µg/mL.
- Increased numbers of polyploid cells were observed at 20- and 44-hour harvest times.

Table 54: *In vitro* chromosome abberation test

HISTORICAL DATA

			Cells with aberrations excluding gaps
S9 (–) 20–hour treatment	Negative control	Number of observations	4
		Minimum	0
		Maximum	4
		Mean	1.25
		Standard deviation	1.89
	Mitomycin C 0.2 µg/ml	Number of observations	2
		Minimum	19
		Maximum	21
		Mean	20.00
		Standard deviation	1.41
S9 (–) 3–hour treatment	Negative control	Number of observations	7
		Minimum	0
		Maximum	1
		Mean	0.57
		Standard deviation	0.53
S9 (+) 3–hour treatment	Negative control	Number of observations	9
		Minimum	0
		Maximum	4
		Mean	1.11
		Standard deviation	1.54
	Cyclophosphamide 7.5 µg/ml	Number of observations	6
		Minimum	13
		Maximum	31
		Mean	20.17
		Standard deviation	6.74

Calculated on data obtained from April 4, 1995 to July 15, 1997 (historical data not audited).

(Excerpted from the sponsor's submission)

On the whole, cabazitaxel was negative in the *in vitro* chromosome aberration test in cultured human peripheral blood lymphocytes based on lack of concentration-dependent structural aberrations, even though increase in numerical aberrations were evident at ≥0.005 µg/mL in lymphocytes from male and female donors irrespective of the experimental conditions or harvest times (Tables 23-26) .

7.3 In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title: RPR 116258: Intravenous bone marrow micronucleus test in rats

Study no.:	DS/CRVA 98-023
Study report location:	4.2.3.3.2.1
Conducting laboratory and location:	Rhone-Poulenc Rorer
Date of study initiation:	03/31/1998
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258, batch #BFC611/purity 96.5%

Key Study Findings

- Cabazitaxel was positive in the rat bone marrow micronucleus test.
- Cabazitaxel (1.5 mg/kg (9 mg/m^2)) induced a more severe bone marrow cytotoxicity at the 48–hour than at the 24–hour sampling times.
- Cabazitaxel induced a statistically significant and dose–related increase in the incidence of micronucleated polychromatic erythrocytes in all treated groups and sampling times.
- Vehicle control did not induce an increase in the incidence of micronucleated polychromatic erythrocytes compared to the absolute control (5% glucose).
- The positive control cyclophosphamide induced a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes.

Methods

Table 55: Experimental design

Groups	Number of animals	Compound	Dose (mg/kg)	Volume (ml/kg)	Concentration (mg/ml)	Sampling time (a)
1	5 M, 5 F	Vehicle	0	5	0	24 h
2	5 M, 5 F	cyclophosphamide (positive control article)	20	10	2	24 h
3	5 M, 5 F	5% glucose (absolute control)	0	5	0	24 h
4	5 M, 5 F	RPR 116258	0.5	5	0.1	24 h
5	5 M, 5 F	RPR 116258	1	5	0.2	24 h
6	5 M, 5 F	RPR 116258	1.5	5	0.3	24h
7	5 M, 5 F	Vehicle	0	5	0	48 h
8	5 M, 5 F	5% glucose (absolute control)	0	5	0	48 h
9	5 M, 5 F	RPR 116258	1.5	5	0.3	48 h

M = Males F = Females
(a) = After treatment

(Excerpted from the sponsor's submission)

Doses in definitive study:	0.5, 1, 1.5 mg/kg (3, 6, 9 mg/m^2)
Frequency of dosing:	Once
Route of administration:	RPR 116258, IV; cyclophosphamide, ip
Dose volume:	5 ml/kg
Formulation/Vehicle:	40 mg/ml stock solution prepared in pure polysorbate 80 and diluted in 13% ethanol to acghieve a premix solution containing 10 mg/ml. For intravenous administration, the premix solution was diluted in 5% glucose. The vehicle was 0.8% polysorbate+0.3% ethanol+5% glucose
Species/Strain:	Crl CD (SD)BR rats
Number/Sex/Group:	5
Satellite groups:	None
Basis of dose selection:	Based on the results of preliminary range finding study in SD rats
Negative control:	5% glucose (absolute control); Vehicle control, aqueous solution of approximately 0.8% polysorbate 80 and 0.3% ethanol diluted in 5% glucose
Positive control:	Cyclophosphamide 2 mg/ml in water for injection
Sampling time:	24 and 48 h after treatment

Study Validity

Cabazitaxel is considered positive in the bone marrow micronucleus test if all of the following criteria are fulfilled:

- it induces a statistically significant increase in the incidence of micronucleated polychromatic erythrocytes (PE),
- the increase incidence of micronucleated PE is dose–related or observed at the highest dose level,
- the incidence of micronucleated PE observed is out of the range of historical control data.

If the above criteria are not fulfilled cabazitaxel is, the considered negative.
Results

Table 56: Cytotoxicity and incidence of micronucleated PE

RPR 116258 – CYTOTOXICITY – % PE

MEAN VALUES

Time	Sex	5% glucose	Vehicle (a)	RPR 116258			Cyclophosphamide
				0.5 mg /kg	1 mg /kg	1.5 mg /kg	20 mg /kg
24 h	Males	67.10	60.16	59.86	57.82	44.86	46.04
	Females	60.18	57.74	52.48	51.86	40.02	38.50
	Males + Females	63.64	58.95	56.17	54.84	42.44	42.27
48 h	Males	69.70	67.06	NT	NT	32.86	NT
	Females	62.68	57.58	NT	NT	20.70	NT
	Males + Females	66.19	62.32	NT	NT	26.78	NT

(a) aqueous solution of approximately 0.8% polysorbate 80 and 0.3% ethanol USP diluted in 5% glucose
NT Not tested

RPR 116258 – INCIDENCE OF MICRONUCLEATED POLYCHROMATIC ERYTHROCYTES

MEAN VALUES

(per 1000 polychromatic erythrocytes)

Time	Sex	5% glucose	Vehicle (a)	RPR 116258			Cyclophosphamide
				0.5 mg /kg	1 mg /kg	1.5 mg /kg	20 mg /kg
24 h	Males	2.50	2.30	4.30*	7.50***	7.50***	19.00***
	Females	2.50	1.50	3.60**	4.20***	4.20***	11.90***
	Males + Females	2.50	1.90	3.95***	5.85***	5.85***	15.45***
48 h	Males	1.00	2.00	NT	NT	8.70***	NT
	Females	1.90	1.60	NT	NT	17.00***	NT
	Males + Females	1.45	1.80	NT	NT	12.85***	NT

(a) aqueous solution of approximately 0.8% polysorbate 80 and 0.3% ethanol USP diluted in 5% glucose
* Significant increase $p \leq 0.05$
** Significant increase $p \leq 0.01$
*** Significant increase $p \leq 0.001$
NT Not tested

(Excerpted from the sponsor's submission)

Table 57: Historical controls

RPR 116258 – HISTORICAL DATA – NEGATIVE CONTROL

	Micronucleated polychromatic erythrocytes/1000 PE	% PE
mean	1.23	59.0 %
standard deviation	0.67	38.3%
minimium	0.00	35.1%
maximum	3.50	77.5%

PE: Polychromatic erythrocytes

Values obtained since September 27, 1994 on 152 male and female rats.
Values of 24 and 48–hour sampling times are pooled.
Historical data base non audited

RPR 116258 – HISTORICAL DATA – POSITIVE CONTROL

	Micronucleated polychromatic erythrocytes/1000 PE	%PE
mean	16.42	40.1%
standard deviation	6.51	18.7%
minimium	7.50	20.0%
maximum	33.50	61.2%

PE: Polychromatic erythrocytes

Values obtained since September 27, 1994 on 86 male and female rats.
Historical data base non audited

(Excerpted from the sponsor's submission)

Cabazitaxel (1.5 mg/kg) induced more severe bone marrow cytotoxicity at 48- than 24-hour sampling time. Also cabazitaxel induced a significant dose-dependent increase in the incidence of micronucleated polychromatic erythrocytes in all groups and at all sampling times (Table 28). Therefore under the experimental conditions, cabazitaxel was found positive in the rat bone marrow micronucleus test.

7.4 Other Genetic Toxicity Studies

Study title: RPR 116258 (Batch spiked with impurities): Bacterial Reverse Mutation Test (Ames)

Study no.:	HIS1883
Study report location:	4.2.3.7.6.1
Conducting laboratory and location:	Rhone-Poulenc Rorer
Date of study initiation:	03/10/2009
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	P-33125-270-1 (batch 0800032719 of XRP6258 [spiked with impurities: (b) (4) purity 91.2%.

Key Study Findings

- Cabazitaxel (batch spiked with impurities) was negative in the bacterial reverse mutation test
- Neither cytotoxicity nor increase in the number of revertant colonies was observed whatever the strain or the experimental conditions.

Methods

Strains:	*Salmonella typhimurium* TA1535, TA1537, TA98, TA100 and TA102
Concentrations in definitive study:	Plate incorporation: 25, 50, 100, 250, 500, 1000 µg/plate with and without S9-mix Preincubation: 10, 25, 50, 100, 250, and 500 g/plate without S9 mix and 50, 100, 250, 500, and 2500 µg/plate with S9-mix
Basis of concentration selection:	Based on a range finding experiment
Negative control:	Ethanol (0.05% ml/plate)

Positive control:

		Positive control	Dose levels (µg/plate)	Positive control	Dose levels (µg/plate)
Strains	Method	Without S9-mix		With S9-mix	
TA1535	Plate incorporation	Sodium azide	0.2	Cyclophosphamide	100
TA1537	Plate incorporation	9-amino acridine	25	2-aminoanthracene	2.0
TA 98	Plate incorporation	2-nitrofluorene	0.5	2-aminoanthracene	2.0
TA100	Plate incorporation	Sodium azide	2.0	2-aminoanthracene	2.0
TA102	Plate incorporation	Mitomycin C	1.0	2-aminoanthracene	20
TA1535	Preincubation	Sodium azide	0.2	Cyclophosphamide	25
TA1537	Preincubation	9-amino acridine	25	2-aminoanthracene	2.0
TA 98	Preincubation	2-nitrofluorene	0.5	2-aminoanthracene	2.0
TA100	Preincubation	Sodium azide	2.0	2-aminoanthracene	2.0
TA102	Preincubation	Mitomycin C	0.1	2-aminoanthracene	20

Mitomycin C, sodium azide and cyclophosphamide were dissolved in sterile injectable water. All the other positive reference substances were dissolved in DMSO.

Formulation/Vehicle: XRP6258 (batch spiked with impurities) solutions were dissolved and diluted in ethanol immediately prior to usage.

Incubation & sampling time: 48 hours after treatment

Study Validity

The assay is considered valid if the following criteria are met:

- the bacterial cultures used for the mutagenicity experiments have grown properly during the overnight culture (between 50 and 500 colonies after 10-6 dilution);
- the mean number of spontaneous revertant colonies for the three negative control plates remains consistent with the range of the testing facility's historical data.
- the mean number of revertant colonies for the three positive control plates represents at least a two fold increase (TA98, TA100 and TA102) or a three-fold increase (TA1535 and TA1537) when compared to the mean number of spontaneous revertant colonies in the negative control plates;
- at least five dose levels for cabazitaxel can be determined for each strain in each experimental condition;
- at least three non-cytotoxic dose levels and at least three dose levels without precipitates are observed.

Results

Cabazitaxel is considered to induce a positive response in the bacterial reverse mutation test if all of the following criteria are fulfilled:

- it induces at least a two-fold increase in the number of revertant colonies for one or more dose levels for *S. typhimurium* strains TA98, TA100 or TA102 or at least a three-fold increase in the number of revertant colonies for one or more dose levels for *S. typhimurium* strains TA1535 and TA1537;
- the increase in the number of revertant colonies is dose-related or observed at the highest dose level;

- the increase number of revertant colonies is reproducible;
- the number of revertant colonies exceeds the upper value of the range of historical negative control data.

If the above criteria are not fulfilled, cabazitaxel is considered negative.

Using the plate incorporation method (Tables 30-33, left panel), cabazitaxel (batch spiked with impurities) was tested at 25, 50, 100, 250, 500 and 1000 µg/plate with and without S9-mix. A precipitate was seen at 1000 µg/plate, both with and without S9-mix.

Using the preincubation (Tables 30-33, right panel) method, cabazitaxel (batch spiked with impurities) was tested at 10, 25, 50, 100, 250 and 500 µg/plate without S9-mix, and at 50, 100, 250, 500, 1000 and 2500 µg/plate with S9-mix. A precipitate was seen at 500 µg/plate without S9-mix, and at 2500 µg/plate with S9- mix.

Table 58: TA1535 and TA1537

Table 3 - Results of the first mutagenicity assay on Salmonella typhimurium strains TA1535 and TA1537 Plate incorporation method with and without metabolic activation

Strain	Compound	Dose level per plate	S-9 mix	Mean revertant colony counts	SD	Ratio treated / solvent	Individual revertant colony counts
TA1535	ETHANOL		-	8	3		8, 11, 5
	XRP6258	25 µg	-	7	1	0.9	6, 8, 7
		50 µg	-	10	3	1.3	9, 14, 8
		100 µg	-	6	2	0.7	4, 7, 6
		250 µg	-	5	2	0.7	5, 4, 7
		500 µg	-	6	1	0.7	6, 5, 6
		1000 µg	-	10	2	1.3	8(P), 10(P), 12(P)
	SA	0.2 µg	-	103	3	12.9	100, 106, 103
	ETHANOL		+	10	1		11, 9, 11
	XRP6258	25 µg	+	7	3	0.7	6, 10, 5
		50 µg	+	7	3	0.7	5, 6, 11
		100 µg	+	11	4	1.0	6, 14, 12
		250 µg	+	9	4	0.9	4, 11, 12
		500 µg	+	8	3	0.8	5, 10, 9
		1000 µg	+	10	3	1.0	12(P), 6(P), 12(P)
	CP	100 µg	+	53	6	5.2	55, 47, 58
TA1537	ETHANOL		-	4	2		5, 2, 4
	XRP6258	25 µg	-	5	1	1.3	4, 5, 5
		50 µg	-	5	1	1.4	4, 5, 6
		100 µg	-	5	3	1.3	5, 7, 2
		250 µg	-	5	2	1.3	5, 3, 6
		500 µg	-	7	4	1.8	7, 10, 3
		1000 µg	-	4	2	1.0	4(P), 2(P), 5(P)
	9AA	25 µg	-	22	7	5.9	16, 29, 20
	ETHANOL		+	5	2		8, 4, 4
	XRP6258	25 µg	+	5	2	1.0	7, 6, 3
		50 µg	+	3	2	0.6	2, 2, 6
		100 µg	+	4	3	0.8	7, 4, 2
		250 µg	+	4	2	0.7	2, 4, 6
		500 µg	+	5	2	0.9	3, 4, 7
		1000 µg	+	9	4	1.6	9(P), 12(P), 5(P)
	2AA	2 µg	+	29	5	5.4	23, 32, 31

SD Standard deviation
\- Without metabolic activation
\+ With metabolic activation
SA Sodium azide
CP Cyclophosphamide
9AA 9-Aminoacridine
2AA 2-aminoanthracene
P Precipitate

Table 6 - Results of the second mutagenicity assay on Salmonella typhimurium strains TA1535 and TA1537 Preincubation method with and without metabolic activation

Strain	Compound	Dose level per plate	S-9 mix	Mean revertant colony counts	SD	Ratio treated / solvent	Individual revertant colony counts
TA1535	ETHANOL		-	10	4		5, 12, 12
	XRP6258	10 µg	-	10	4	1.1	12, 13, 6
		25 µg	-	7	1	0.7	6, 8, 7
		50 µg	-	7	2	0.7	5, 7, 8
		100 µg	-	8	1	0.8	7, 9, 7
		250 µg	-	7	2	0.7	5, 7, 8
		500 µg	-	4	1	0.4	4(P), 4(P), 5(P)
	SA	0.2 µg	-	146	7	15.1	153, 145, 140
	ETHANOL		+	12	2		11, 14, 11
		50 µg	+	12	4	1.0	15, 13, 8
		100 µg	+	15	1	1.3	15, 16, 15
		250 µg	+	15	2	1.3	14, 17, 15
		500 µg	+	10	3	0.9	7, 13, 11
		1000 µg	+	14	3	1.2	17, 11, 14
		2500 µg	+	15	2	1.3	17(P), 13(P), 16(P)
	CP	25 µg	+	76	7	6.3	71, 84, 73
TA1537	ETHANOL		-	5	2		7, 6, 3
	XRP6258	10 µg	-	6	2	1.1	7, 7, 4
		25 µg	-	5	2	0.9	3, 5, 7
		50 µg	-	4	2	0.7	3, 3, 6
		100 µg	-	6	2	1.1	4, 6, 7
		250 µg	-	6	3	1.1	8, 2, 7
		500 µg	-	4	2	0.7	3(P), 3(P), 6(P)
	9AA	25 µg	-	51	11	9.5	63, 46, 43
	ETHANOL		+	8	3		6, 6, 11
		50 µg	+	9	2	1.2	11, 7, 9
		100 µg	+	6	1	0.8	5, 7, 7
		250 µg	+	6	1	0.8	6, 7, 6
		500 µg	+	9	1	1.1	9, 9, 8
		1000 µg	+	8	4	1.0	8, 4, 11
		2500 µg	+	9	2	1.1	8(P), 11(P), 7(P)
	2AA	2 µg	+	89	2	11.7	88, 91, 89

SD Standard deviation
\- Without metabolic activation
\+ With metabolic activation
SA Sodium azide
CP Cyclophosphamide
9AA 9-Aminoacridine
2AA 2-aminoanthracene
P Precipitate

Table 59: TA98 and TA100

Table 4 - Results of the first mutagenicity assay on Salmonella typhimurium strains TA98 and TA100 Plate incorporation method with and without metabolic activation

Strain	Compound	Dose level per plate	S-9 mix	Mean revertant colony counts	SD	Ratio treated / solvent	Individual revertant colony counts
TA98	ETHANOL		-	17	7		20, 9, 21
	XRP6258	25 µg	-	19	3	1.1	21, 20, 16
		50 µg	-	19	1	1.2	19, 20, 19
		100 µg	-	23	2	1.4	24, 24, 21
		250 µg	-	24	4	1.4	27, 20, 24
		500 µg	-	16	3	1.0	17, 18, 13
		1000 µg	-	18	4	1.1	13(P), 19(P), 21(P)
	2NF	0.5 µg	-	235	18	14.1	243, 214, 248
	ETHANOL		+	30	3		33, 30, 27
	XRP6258	25 µg	+	33	2	1.1	32, 32, 35
		50 µg	+	31	8	1.0	34, 22, 37
		100 µg	+	27	3	0.9	24, 28, 29
		250 µg	+	34	8	1.1	28, 43, 31
		500 µg	+	28	9	0.9	17, 34, 32
		1000 µg	+	34	5	1.1	39(P), 33(P), 29(P)
	2AA	2 µg	+	1384	234	46.1	1395, 1613, 1145
TA100	ETHANOL		-	134	4		139, 132, 132
	XRP6258	25 µg	-	112	6	0.8	119, 107, 111
		50 µg	-	112	10	0.8	101, 120, 115
		100 µg	-	117	14	0.9	124, 101, 125
		250 µg	-	126	6	0.9	122, 124, 133
		500 µg	-	119	7	0.9	122, 111, 124
		1000 µg	-	123	17	0.9	111(P), 142(P), 115(P)
	SA	2 µg	-	1395	30	10.4	1364, 1423, 1398
	ETHANOL		+	162	10		171, 152, 163
	XRP6258	25 µg	+	146	10	0.9	155, 148, 135
		50 µg	+	148	10	0.9	138, 148, 157
		100 µg	+	152	11	0.9	141, 163, 153
		250 µg	+	136	20	0.8	142, 152, 114
		500 µg	+	143	9	0.9	153, 141, 136
		1000 µg	+	144	4	0.9	147(P), 139(P), 145(P)
	2AA	2 µg	+	1693	198	10.4	1471, 1853, 1754

SD Standard deviation
\- Without metabolic activation
\+ With metabolic activation
2NF 2-Nitrofluorene
2AA 2-aminoanthracene
SA Sodium azide
P Precipitate

Table 7 - Results of the second mutagenicity assay on Salmonella typhimurium strains TA98 and TA100 Preincubation method with and without metabolic activation

Strain	Compound	Dose level per plate	S-9 mix	Mean revertant colony counts	SD	Ratio treated / solvent	Individual revertant colony counts
TA98	ETHANOL		-	30	2		28, 32, 29
	XRP6258	10 µg	-	27	8	0.9	20, 35, 25
		25 µg	-	22	5	0.7	18, 20, 28
		50 µg	-	27	7	0.9	34, 27, 21
		100 µg	-	24	8	0.8	29, 15, 28
		250 µg	-	20	1	0.7	20, 19, 21
		500 µg	-	24	4	0.8	20(P), 23(P), 28(P)
	2NF	0.5 µg	-	153	4	5.1	153, 156, 149
	ETHANOL		+	35	7		38, 41, 27
		50 µg	+	42	4	1.2	38, 43, 45
		100 µg	+	35	3	1.0	38, 34, 32
		250 µg	+	34	11	1.0	23, 45, 34
		500 µg	+	36	4	1.0	33, 34, 40
		1000 µg	+	27	1	0.8	26, 28, 28
		2500 µg	+	37	4	1.0	41(P), 33(P), 37(P)
	2AA	2 µg	+	1677	109	47.5	1568, 1678, 1786
TA100	ETHANOL		-	100	2		101, 98, 102
	XRP6258	10 µg	-	92	16	0.9	103, 99, 74
		25 µg	-	91	10	0.9	103, 84, 87
		50 µg	-	88	7	0.9	93, 90, 80
		100 µg	-	88	6	0.9	81, 90, 93
		250 µg	-	102	6	1.0	101, 97, 108
		500 µg	-	100	12	1.0	89(P), 100(P), 112(P)
	SA	2 µg	-	1414	99	14.1	1374, 1341, 1526
	ETHANOL		+	112	13		103, 107, 127
		50 µg	+	131	6	1.2	131, 126, 137
		100 µg	+	136	10	1.2	145, 126, 136
		250 µg	+	122	23	1.1	143, 98, 126
		500 µg	+	116	6	1.0	117, 121, 110
		1000 µg	+	118	21	1.1	129, 131, 94
		2500 µg	+	129	5	1.2	135(P), 126(P), 127(P)
	2AA	2 µg	+	1743	20	15.5	1764, 1725, 1739

SD Standard deviation
\- Without metabolic activation
\+ With metabolic activation
2NF 2-Nitrofluorene
2AA 2-aminoanthracene
SA Sodium azide
P Precipitate

(Excerpted from the sponsor's submission)

In the experiment with the strain TA100 (Table 31, left panel), using the plate incorporation method (with and without S9-mix), the number of spontaneous (ethanol vehicle control) revertant colonies was slightly above the upper limit of the historical negative control data (Table 33). Similarly, in the experiments with the strain TA98 using the preincubation method ((with S9-mix) Table 31, right panel), the number of spontaneous (ethanol vehicle control) revertant colonies was slightly above the upper limit of the historical negative control data (Table 33). However, these differences were not statistically significant.

Table 60: TA102

Table 5 - Results of the first mutagenicity assay on Salmonella typhimurium strain TA102 Plate incorporation method with and without metabolic activation

Strain	Compound	Dose level per plate	S-9 mix	Mean revertant colony counts	SD	Ratio treated / solvent	Individual revertant colony counts
TA102	ETHANOL		-	251	25		226, 253, 275
	XRP6258	25 µg	-	259	12	1.0	260, 247, 270
		50 µg	-	242	14	1.0	228, 255, 244
		100 µg	-	256	7	1.0	263, 249, 255
		250 µg	-	237	21	0.9	217, 258, 237
		500 µg	-	254	10	1.0	245, 253, 264
		1000 µg	-	263	5	1.0	267(P), 264(P), 258(P)
	MMC	1 µg	-	2096	26	8.3	2079, 2126, 2083
	ETHANOL		+	321	19		335, 329, 300
	XRP6258	25 µg	+	327	28	1.0	298, 354, 330
		50 µg	+	328	26	1.0	317, 357, 309
		100 µg	+	310	18	1.0	297, 302, 331
		250 µg	+	292	60	0.9	224, 315, 336
		500 µg	+	317	11	1.0	329, 309, 312
		1000 µg	+	308	19	1.0	286(P), 317(P), 320(P)
	2AA	20 µg	+	1435	71	4.5	1425, 1369, 1510

SD Standard deviation
- Without metabolic activation
+ With metabolic activation
MMC Mitomycin C
2AA 2-aminoanthracene
P Precipitate

Table 8 - Results of the second mutagenicity assay on Salmonella typhimurium strain TA102 Preincubation method with and without metabolic activation

Strain	Compound	Dose level per plate	S-9 mix	Mean revertant colony counts	SD	Ratio treated / solvent	Individual revertant colony counts
TA102	ETHANOL		-	245	33		248, 276, 210
	XRP6258	10 µg	-	232	8	0.9	233, 240, 224
		25 µg	-	255	17	1.0	260, 236, 269
		50 µg	-	242	49	1.0	238, 195, 292
		100 µg	-	221	16	0.9	235, 223, 204
		250 µg	-	199	25	0.8	181, 228, 188
		500 µg	-	206	10	0.8	204(P), 197(P), 217(P)
	MMC	0.1 µg	-	2933	188	12.0	2717, 3022, 3060
	ETHANOL		+	339	8		339, 332, 347
		50 µg	+	360	8	1.1	369, 354, 356
		100 µg	+	357	9	1.1	349, 355, 366
		250 µg	+	407	45	1.2	400, 366, 456
		500 µg	+	333	19	1.0	351, 313, 335
		1000 µg	+	346	16	1.0	351, 328, 359
		2500 µg	+	334	19	1.0	344(P), 312(P), 347(P)
	2AA	20 µg	+	2686	385	7.9	3005, 2794, 2259

SD Standard deviation
- Without metabolic activation
+ With metabolic activation
MMC Mitomycin C
2AA 2-aminoanthracene
P Precipitate

Table 61: Historical controls

Table 9 - Historical data

NEGATIVE CONTROL

WITHOUT METABOLIC ACTIVATION - PLATE INCORPORATION METHOD

	Salmonella typhimurium				
	TA1535	TA1537	TA98	TA100	TA102
Minimum	6	4	9	52	143
Maximum	13	11	20	129	251
Mean	9	6	14	81	185
Standard deviation	1.9	2.0	3.1	18.4	26.0
Number	26	25	25	25	25

WITH METABOLIC ACTIVATION - PLATE INCORPORATION METHOD

	Salmonella typhimurium				
	TA1535	TA1537	TA98	TA100	TA102
Minimum	7	4	19	78	231
Maximum	14	13	35	143	320
Mean	10	8	25	101	261
Standard deviation	2.2	2.1	3.8	16.2	23.6
Number	25	25	26	26	26

WITHOUT METABOLIC ACTIVATION - PREINCUBATION METHOD

	Salmonella typhimurium				
	TA1535	TA1537	TA98	TA100	TA102
Minimum	7	4	12	62	139
Maximum	13	17	25	146	304
Mean	10	8	17	86	202
Standard deviation	1.9	4.0	3.3	20.4	39.3
Number	26	26	26	26	27

WITH METABOLIC ACTIVATION - PREINCUBATION METHOD

	Salmonella typhimurium				
	TA1535	TA1537	TA98	TA100	TA102
Minimum	7	5	20	79	176
Maximum	15	18	36	163	364
Mean	12	10	28	104	281
Standard deviation	2.0	3.9	4.5	20.8	43.2
Number	26	26	27	27	26

Calculated on the mean number of revertant colonies from data obtained between September 8, 2005 and January 30, 2009 (historical data are not audited).

Table 9 - Historical data (page 2)

POSITIVE CONTROL

WITHOUT METABOLIC ACTIVATION - PLATE INCORPORATION METHOD

	Salmonella typhimurium				
	TA1535	TA1537	TA98	TA100	TA102
Minimum	71	16	113	966	1755
Maximum	199	104	255	1792	2538
Mean	137	42	175	1472	2150
Standard deviation	44.1	21.4	40.6	240.1	221.4
Number	26	25	25	25	25

WITH METABOLIC ACTIVATION - PLATE INCORPORATION METHOD

	Salmonella typhimurium				
	TA1535	TA1537	TA98	TA100	TA102
Minimum	61	21	599	655	796
Maximum	106	86	1848	1936	1996
Mean	81	61	1370	1493	1329
Standard deviation	12.4	15.1	279.9	325.2	333.1
Number	25	25	26	26	26

WITHOUT METABOLIC ACTIVATION - PREINCUBATION METHOD

	Salmonella typhimurium				
	TA1535	TA1537	TA98	TA100	TA102
Minimum	83	22	119	1097	2458
Maximum	252	153	281	1800	3710
Mean	170	55	168	1520	3079
Standard deviation	54.3	34.3	33.6	204.1	359.1
Number	26	26	26	26	27

WITH METABOLIC ACTIVATION - PREINCUBATION METHOD

	Salmonella typhimurium				
	TA1535	TA1537	TA98	TA100	TA102
Minimum	72	52	698	815	1091
Maximum	130	109	2071	2034	2990
Mean	92	80	1316	1314	2229
Standard deviation	14.5	14.9	289.9	263.3	452.4
Number	26	26	27	27	26

Calculated on the mean number of revertant colonies from data obtained between September 8, 2005 and January 30, 2009 (historical data are not audited).

(Excerpted from the sponsor's submission)

Therefore, under the experimental conditions of the study, Cabazitaxel (batch spiked with impurities) was found negative in the bacterial reverse mutation test conducted on the five *S. typhimurium* strains TA1535, TA1537, TA98, TA100 and TA102 up to 1000 µg/plate with and without S9-mix using the plate incorporation method, and up to 500 µg/plate without S9-mix and 2500 µg/plate with S9-mix using the preincubation method.

8 Carcinogenicity

Not done and not required in this patient population

9 Reproductive and Developmental Toxicology

9.1 Fertility and Early Embryonic Development

Study title: RPR116258A: Intravenous Male Fertility Study in Rats

Study no.:	RPR/RD/SA/CRVA 99-246
Study report location:	EDR 4.2.3.5.1
Conducting laboratory and location:	Rhone-Poulenc Rorer Vitry sur Seine, France
Date of study initiation:	September 24, 1999
GLP compliance:	Yes (France)
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258A/ P99043S/ 99.6%

Key Study Findings

- F0 NOAEL=0.10 mg/kg
- F1 NOAEL= 0.20 mg/kg
- There was no obvious effect on male fertility at doses up to 0.20 mg/kg
- No dedicated examination of sperm was included
- Prostate weight was not included

Methods

Doses: 0, 0.05, 0.1, 0.3/0.2 mg/kg/day
Frequency of dosing: Daily
Dose volume: 5 mL/kg/day 1mL/min
Route of administration: IV
Formulation/Vehicle: Polysorbate 80 (PS80) in95% Ethanol/water (13% w/w) ratio: diluted in 5% (w/w) aqueous solution of glucose to reach ~0.15%/0.1% PS80, 0.06%/0.04% EtOH,
Species/Strain: Sprague Dawley Crl: CD (SD)IGS BR rats
Number/Sex/Group: 26 males/group
Study design: Males were dosed for 70 days prior to cohabitation, during cohabitation, and then until Day 81; females were not dosed and were euthanized on GD21.
F0 males: macroscopic examination, organ weights (testes, epididymes), limited histopathology
Uterine examinations
Fetal examinations

Deviation from study protocol:
Animals in the high dose group were dose reduced after Day 13 due to decreases in weight.

Observations and Results

Mortality: Checked Daily

Table 62: Male Fertility Mortality

Animal #	Dose (mg/kg)	Day of Death	Observations		
			Reason for Removal	Cause of Mortality	General
70	0.05	79	Euthanized	Morbidity	Accidental Fracture (tooth)
163	0.3/0.2	67	Euthanized	Morbidity	Accidental Fracture (tibia, fibula) Injection site wound
170	0.3/0.2	47	Euthanized	Morbidity	Skin lesion at injection site
176	0.3/0.2	18	Found Dead	Bacterial infection	Red/brown staining around muzzle/anogenital area;no feces; ↓food consumption/body weight; pale areas liver/heart;fibrinous adhesion between liver and stomach, red fluid in thoracic cavity; large coalescing bacterial colonies in heart, liver, stomach

Clinical Signs: Examined Daily
In treated males, there was a dose-dependent increase in decreased defecation along with a significantly longer duration of the sign compared to control.

Table 63: Clinical Signs

Observation Dose (mg/kg) N	0 26	0.05 26	0.1 26	0.3/0.2 26
Convulsions			2	
Decreased Defecation	1	1	3	25
Emaciated		1		6
Limited/Lost Use of Limbs				2
No Feces		1		3
Skin Lesion	1			2
Stained Fur				2

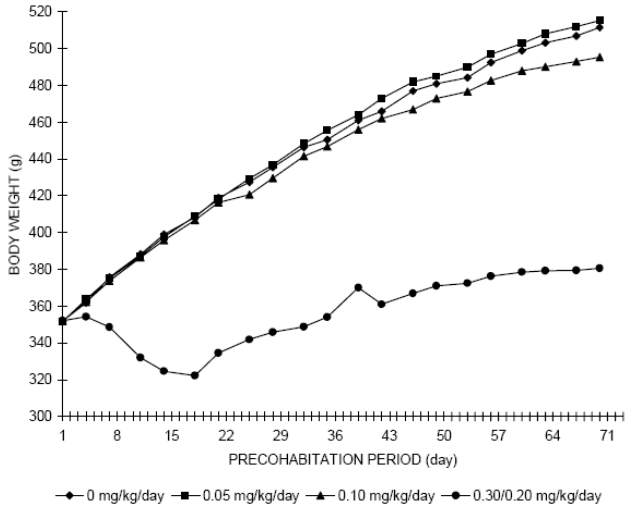
Body Weight: Males-twice weekly; Females-weekly during cohabitation, GD 0, 6, 12, 18, and 21

Males in the high dose group lost weight following initiation of treatment and continued to lose weight until after Day 18 (5 days after the dose decrease from 0.3 to 0.2 mg/kg/day). The high dose group males then began gaining weight though less rapidly than controls. High dose males consistently weighed between 20 and 30% less than controls. Treated males in the 0.1 mg/kg dose group gained ~ 15% less than controls over the course of the study. Males in the 0.3/0.2 mg/kg group gained ~85% less. There were no significant treatment related differences in female weight during gestation.

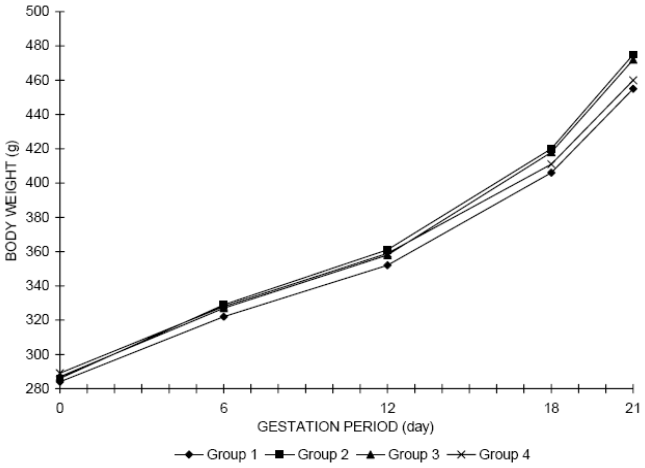
(Excerpted from Sponsor)

Figure 16: Male and Female Body Weights

Male Body Weight-Precohabitation



Female Body Weight-Gestation

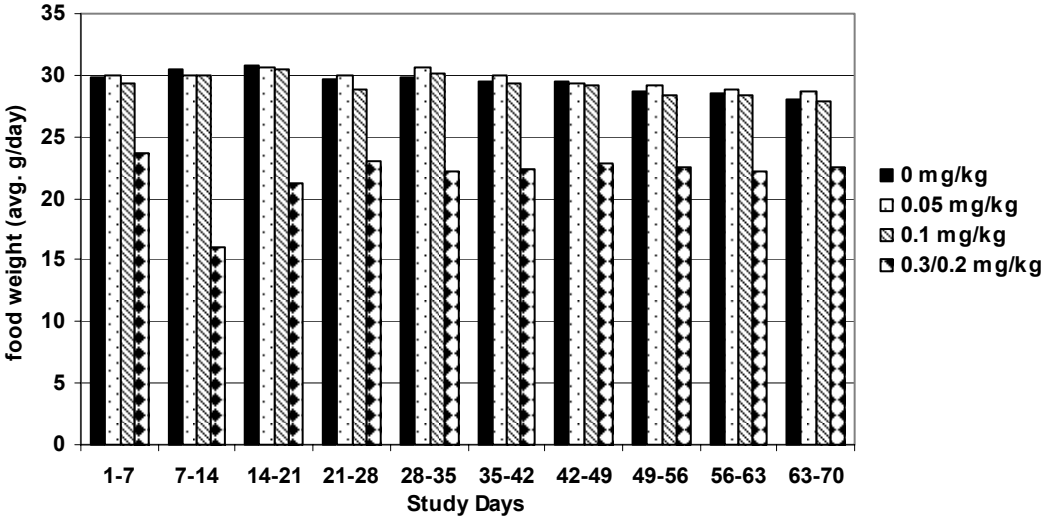


Groups 1 to 4= Untreated females mated with males treated at 0, 0.05, 0.10 and 0.30/0.20 mg/kg/day

Feed Consumption: Males-weekly pre-cohabitation

Males in the high dose group had a decrease in food consumption compared to control. This decrease persisted (though not as significantly) even after the dose reduction on Day 13 to 0.2 mg/kg/day

Figure 17: Male Food Consumption-Precohabitation



Toxicokinetics: Not performed

Stability and Homogeneity:

No data included. QA analysis was performed, results were reported as acceptable.

Necropsy

F0 Male Necropsy Results:

Organ Weights: There were no significant changes in the weights of testis or epipdidymes between controls and males in any of the dosing groups.

Macroscopic Observations: Single males in the 0.1 and 0.3/0.2 mg/kg/day dose groups had findings of an abnormally shaped epididymis and an oval mass on the epididymis respectively. With the exception of the early death animals, there were no other gross pathological findings noted. Animal # 176, which died on Day 18, had findings of pale areas in the heart, liver, and spleen, red fluid in the thoracic cavity, liver adhesions, and an enlarged adrenal glands. Findings in other early death animals were limited to fractures and injection site wounds.

F0 Female Necropsy Results:

There were no significant findings in F0 females.

F1 Necropsy Results:

Table 64: F1 Necropsy Results

Dose (mg/kg)	0	0.05	0.10	0.3/0.2
Mean Male Fetal Weight	5.4	5.5	5.41	5.46
Mean Female Fetal Weight	5.11	5.21	5.12	5.21

There were no drug related malformations/variations noted in gross observations of fetuses.

Fertility Parameters

Table 65: Fertility Parameters

Dose (mg/kg) Cohabited Pairs N	0 26	0.05 26	0.10 26	0.3/0.2 23
Mating Index (#mated/#treated)	100%	100%	100%	100%
Number Pregnant	24	24	25	22
Fertility Index (#preg/#mated)	92.3%	92.3%	96.2%	95.7%
Days to Mating	2.2	2.3	2.4	2.2

Pregnancy Parameters

Table 66: Pregnancy Parameters

Means/Female Dose (mg/kg) Females N	0 24	0.05 24	0.10 25	0.3/0.2 22
Number of Corpora Lutea	17.2	17	17.4	16.1
Number of Implantations	16.1	16.1	16.2	15.1
Percent Pre-Implantation Loss	6.4%	5.3%	6.9%	6.2%
Number of Resorptions Early Late	1 1 0	0.75 0.71 0.04	0.72 0.64 0.08	1.27 1.27 0
Percent Implants Resorbed	6.2%	4.7%	4.4%	8.4%
Number Liver Fetuses Percent Male	15.1 49.5%	15.3 51.7%	15.4 51.9%	13.8 51.4%

Study title: RPR 116258A- Intravenous Female Fertility and Early Embryonic Developmental Toxicity Study in Rats

Study no.: RPR/RD/SA/CRVA 00-069
Study report location: EDR 4.2.3.5.1
Conducting laboratory and location: Aventis Pharma
Vitry sur Seine, France
Date of study initiation: February 23, 2000
GLP compliance: Yes (France)
QA statement: Yes
Drug, lot #, and % purity: RPR116258A/ P99043S/ 99.6%

Key Study Findings

- F0 NOAEL=0.05 mg/kg due to decreased weight gain and dose-dependent increase in resorption at doses ≥ 0.1 mg/kg
- F1 NOAEL=0.1 mg/kg due to findings of malformation/variation at 0.2 mg/kg
- There was no effect on fetal birth weight

Methods

Doses:	0, 0.05, 0.10, 0.20 mg/kg/day
Frequency of dosing:	Daily
Dose volume:	5 mL/kg
Route of administration:	IV infusion (1mL/min)
Formulation/Vehicle:	Polysorbate 80 (PS80) in 95% Ethanol/water (13% w/w) ratio: diluted in 5% (w/w) aqueous solution of glucose to reach ~0.1% PS80, 0.04% EtOH (the levels achieved in the highest dose group)
Species/Strain:	Sprague Dawley Crl: CD (SD)IGS BR rat
Number/Sex/Group:	26/females/group
Study design:	Females were dosed daily for 15 days prior to cohabitation, during cohabitation, and through GD6. Males were not dosed. Mated females were euthanized on GD 21. Necropsies for all animals, female reproductive organ weights, macroscopic examinations. Uterine contents F1 macroscopic examinations
Deviation from study protocol:	None

Observations and Results

Mortality: Checked Daily

No early deaths occurred during the study.

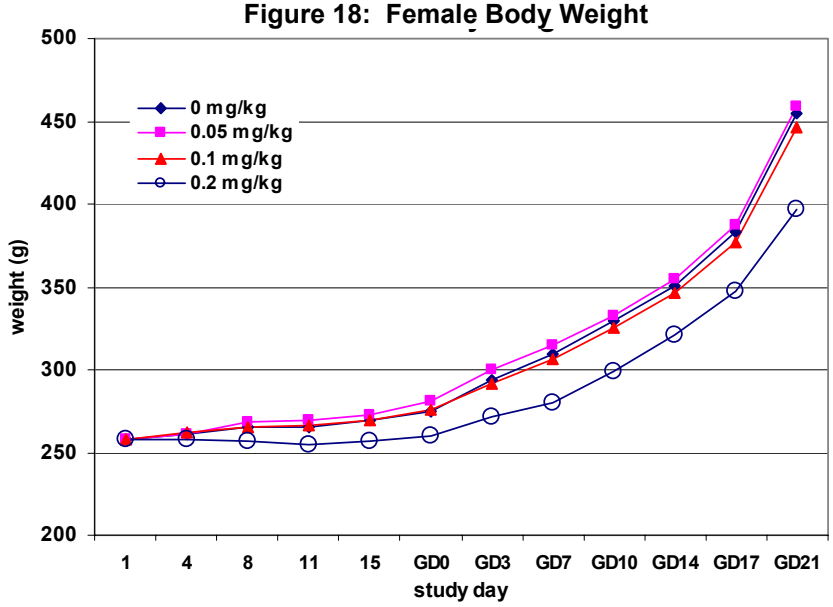
Clinical Signs: Females examined Daily

No drug related clinical signs were noted.

Body Weight: Females weighed twice weekly

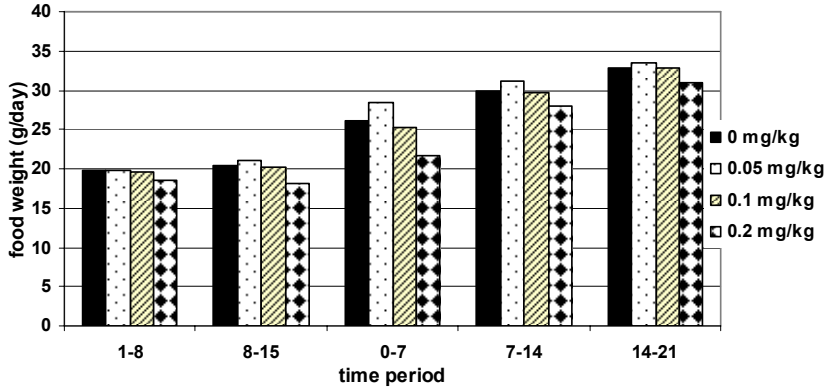
During the pre-cohabitation dosing period, females in the 0.2 mg/kg high dose group failed to gain weight. By the end of this period high dose females weighed ~5% less than controls. Over the entire gestation period high, there was a dose-dependent decrease in the amount of weight gained, with mid dose (0.1 mg/kg) and high dose (0.2 mg/kg) females gaining ~5% and 30% less weight than controls. The largest difference in weight gain during the gestational period was during the first week when dams were still receiving daily doses of RPR 116258.

Figure 18: Female Body Weight



Feed Consumption: Determined weekly

Figure 19: Female Food Consumption



Toxicokinetics: Not performed

Stability and Homogeneity

The data was not submitted. Samples of dosing solutions were submitted for determination of RPR 116258 (the drug not in solvated form) during Weeks 1 and 3. The concentration and stability were reported to be in the acceptable range.

Necropsy

F0 Necropsy Results:

There were no significant drug-related findings from the gross observations performed.

F1 Necropsy Results:

There was a single tail malformation detected in the high dose group upon external observation. Additionally, there were 2 cases (in 2 different litters) of anasarca (accumulation of fluid in tissues and body cavity) in fetuses from the high dose group. A single case of anasarca was seen in a fetus from the male fertility study at the mid dose level, making a determination of a drug related effect questionable. No other malformations/variations were noted.

Table 67: F1 Necropsy Results

Dose (mg/kg)	0	0.05	0.10	0.2
Mean Male Fetal Weight	5.45	5.52	5.48	5.55
Mean Female Fetal Weight	5.18	5.25	5.19	5.10

Fertility Parameters

Table 68: Fertility Parameters

Dose (mg/kg) Cohabited Pairs N	0 26	0.05 26	0.10 26	0.2 26
Mating Index (#mated/#treated)	100%	100%	100%	100%
Number Pregnant	25	26	24	25
Fertility Index (#preg/#mated)	96.2%	100%	92.3%	96.2%
Days to Mating	2.6	2.9	2.6	3.0

Pregnancy Parameters

Table 69: Pregnancy Parameters

Mean/Female Dose (mg/kg) Females N	0 25	0.05 26	0.10 24	0.2 25
Number of Corpora Lutea	16.5	15.9	16.3	14.6
Number of Implantations	15.1	15.6	15.7	13
Percent Pre-Implantation Loss	9.6%	3.1%	6.1%	12.3%
Number of Resorptions	0.64	0.85	1.54	3.6

Mean/Female Dose (mg/kg) Females N	0 25	0.05 26	0.10 24	0.2 25
Early	0.6	0.77	1.46	3.52
Late	0.04	0.08	0.08	0.08
Percent Implants Resorbed	4.23%	5.44%	9.8%	27.6%
Number Liver Fetuses	14.4	14.8	14.1	9.4
Percent Male	49.5%	44.2%	48.8%	45.4%

Embryonic Fetal Development

Study title: RPR 116258A: Intravenous Embryofetal Developmental Toxicity Study in Rats

Study no:	DS/CRVA 99-018
Study report location:	EDR 4.2.3.5.2
Conducting laboratory and location:	Rhone-Poulenc Rorer Research & Development, Nonclinical Safety Assessment-Alfortville Alfortville, France
Date of study initiation:	January 4, 1999
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258A/ P98058ME/ 98%

Key Study Findings

- Maternal NOAEL= 0.08 mg/kg due to drug related mortality at 0.16 mg/kg
- Decreased birth weight at all dose levels ≥ 0.08 mg/kg
- At the high dose level of 0.16 mg/kg there was obvious maternal toxicity including death
- Increased post implantation loss was evident at the 0.16 mg/kg dose level
- There were skeletal variations and incomplete ossifications seen at doses ≥ 0.08 mg/kg

Methods

Doses: 0, 0.04, 0.08, and 0.16 mg/kg
Frequency of dosing: Daily
Dose volume: 5 mL/kg
Route of administration: IV injection (1 mL/min)
Formulation/Vehicle: 0.08% polysorbate 80 and 0.03% ethanol USP diluted in 5% glucose
Species/Strain: Sprague Dawley Crl: CD(SD) IGS BR rats
Number/Sex/Group: 29 females/group
Satellite groups:
Study design: Mated female rats were dosed daily from GD6-17; Scheduled euthanasia was on GD21.
F0: External examinations were conducted on all animals along with uterine examinations.
F1: External examinations were conducted and weight was recorded. Half were examined for visceral alterations, half for skeletal alterations.
Deviation from study protocol: None

Observations and Results

Mortality: Checked daily

Table 70: Maternal Rat Mortality

Animal #	Dose (mg/kg)	Day of Death	Observations		
			Reason for Removal	Cause of Mortality	General
161	0.16	20	Euthanized	Morbidity	↓Motor activity and body weight; pale mucous membranes and skeletal muscle; cold to touch, red anogenital staining; pale carcass, pale liver; red liquid content in uterus

Clinical Signs: **Examined daily**

Table 71: Maternal Rat Clincal Signs

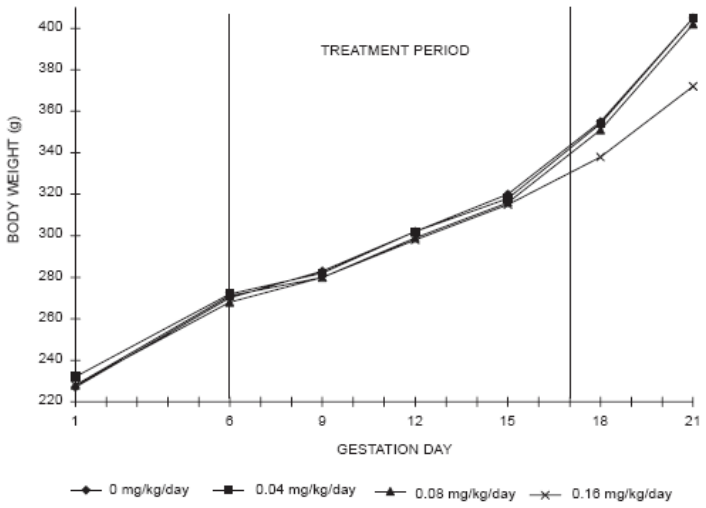
Observation Dose (mg/kg) Pregnant N	0 23	0.04 23	0.08 24	0.16 23
Anogenital Staining (red/brown)				7
Cold to Touch				1
↓Motor Activity				1
Discolored Skin (white)				2
Emaciated				2
Genital Discharge (red/brown)	1	5	1	10
Material in Cage Pan (red)				3

Body Weight: Measured on GD 1, 6, 9, 12, 15, 18, and 21

Animals in the high dose group (0.16 mg/kg/day) gained approximately 19% less weight over the entire course of the study compared to controls. The largest differences were seen after GD15. No significant differences were seen between controls and low or mid dose group females.

(Excerpted from Sponsor)

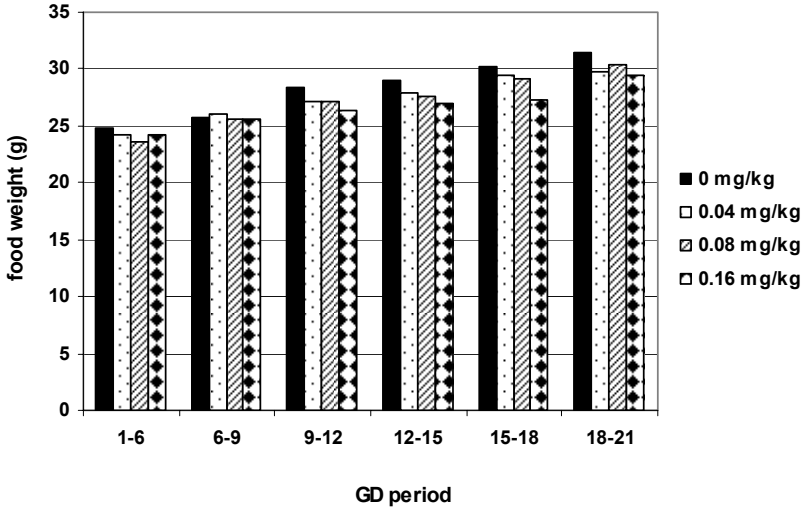
Figure 20: Female Body Weight



Feed Consumption: Calculated every 3 days after the beginning of dosing

There was a 10% decrease in food consumption in the high dose females compared to controls between GD15 and GD18. While animals in all dosing groups showed decreased food consumption compared to controls after the beginning of dosing on GD6, these differences were all < 8%.

Figure 21: Female Food Consumption



Toxicokinetics
Not performed.

Stability and Homogeneity:
Within acceptable limits.

Necropsy
The single early death female was in the high dose group. Gross findings in this female included a pale liver with accentuated lobulation, pale skeletal muscle, and red liquid uterine contents. There were no remarkable findings in the nonpregnant females. Among surviving pregnant females there was an increase in liquid uterine content in the high dose group. No other drug-related findings were noted.

Cesarean Section Data

There was a treatment related increase in post-implantation loss at the high dose group level of 0.16 mg/kg. Only in the high dose group were there females with late post-implantation loss or dead fetuses. One female in this group suffered a 93% post implantation loss and 1 other had a dead fetus.

Table 72: Rat Cesarean Section Data

Mean/Female Dose (mg/kg)	0	0.04	0.08	0.16
Females N	23	23	24	22*
Number of Corpora Lutea	16.2	16.3	17	15.7
Number of Implantations	15.1	15.1	14.8	14.8
Percent Pre-Implantation Loss	9.3%	7.4%	13.5%	8.9%
Post Implantation Loss	2	1.74	1	5.86

Mean/Female Dose (mg/kg)	0	0.04	0.08	0.16
Females N	23	23	24	22*
Early	2	1.74	1	5.64
Late	0	0	0	0.18
Dead	0	0	0	.05
Percent Post-Implantation Loss	13.2%	11.5%	6.8%	40%
Number Liver Fetuses	13.1	13.4	13.8	9.0
Percent Live Males	42.5%	52.6%	49%	57.5%
Live Birth Index (%) (live/implants)	87%	89%	93%	61%

*the single early death female was pregnant, but was not included in the calculations

Offspring

Necropsy: There was a dose-dependent decrease in fetal birth weight for males and females at doses ≥ 0.08 mg/kg. No drug-related external observations were noted. At doses ≥ 0.08 mg/kg there were slight increases in skeletal variations and incomplete ossifications. Other changes in visceral or skeletal formation were incidental and unlikely to be treatment related.

Table 73: F1 Birth Weight

Dose (mg/kg)	0	0.04	0.08	0.16
Mean Male Fetal Weight	5.46	5.31	5.21	4.68
Mean Female Fetal Weight	5.15	5.07	4.89	4.65

Table 74: F1 Malformations/Variations

Malformation/ Variation Dose (mg/kg)	0	0.04	0.08	0.16
Fetuses N	153	152	167	98
Litters N	23	23	24	22
Sternabra variation				
Fetal Incidence	1	2	4	5
Litter Incidence	1	2	2	4
Mean % Affected Fetuses/Litter	0.5%	1.4%	2.1%	5.4%
Supernumerary Rib-Variation				
Fetal Incidence	3	1	14	5
Litter Incidence	3	1	5	5
Mean % Affected Fetuses/Litter	1.8%	0.6%	7.7%	5.5%
Incompletely Ossified Metatarsal				
Fetal Incidence	26	41	52	58
Litter Incidence	17	15	21	20
Mean % Affected Fetuses/Litter	18.1%	24.6%	30.3%	61.1%
Incompletely Ossified Hindpaw Phalanx				
Fetal Incidence	104	92	134	83
Litter Incidence	23	22	24	22
Mean % Affected Fetuses/Litter	69.6%	57.7%	80%	85.3%

Malformation/ Variation Dose (mg/kg) Fetuses N Litters N	0 153 23	0.04 152 23	0.08 167 24	0.16 98 22
Incompletely Ossified Sternebra				
Fetal Incidence	4	5	4	9
Litter Incidence	4	4	4	7
Mean % Affected Fetuses/Litter	2.5%	3.3%	4.1%	11.1%

Study title: RPR 116258: Intravenous Range-Finding Toxicity Study in Pregnant Rats

Study no: RPR-RD-DS/CRVA 98-036
Study report location: EDR 4.2.3.5.2
Conducting laboratory and location: Rhone-Poulenc Rorer Research & Development Drug Safety Division-Alfortville
Alfortville, France
Date of study initiation: March 9, 1998
GLP compliance: Yes (France)
QA statement: Yes
Drug, lot #, and % purity: RPR 116258/BFC 611/ 96.5%

Key Study Findings

- F1 NOAEL=0.08 mg/kg based on decreased fetal birth weight and increased post implantation loss (mainly early) at doses ≥0.16 mg/kg
- Maternal NOAEL was not established as decreased platelets were seen at the lowest administered dose
- Exposure, as determined by Cmax alone, plateaued at the 0.16 dose level
- The highest drug exposure was .06X the Cmax predicted for the human clinical dose

Methods

Doses:	0, 0.08, 0.16, and 0.25 mg/kg
Frequency of dosing:	Daily
Dose volume:	5 mL/kg
Route of administration:	IV injection (1mL/min)
Formulation/Vehicle:	0.13% polysorbate 80, 0.05% ethanol USP diluted in 5% glucose
Species/Strain:	Sprague Dawley Crl: CD(SD)BR rats
Number/Sex/Group:	9 females/group
Satellite groups:	6 females/group (toxicokinetics)
Study design:	Mated females were dosed daily from GD6-17 and euthanized on GD21 F0 females underwent external, gross, and uterine examination at necropsy. Samples for clinical chemistry and hematology were taken on GD14. F1 fetuses were weighed and underwent external examination
Deviation from study protocol:	None

Observations and Results

Mortality: Examined daily
No early deaths occurred during the study.

Clinical Signs: Examined daily
There was a dose-dependent increase in red genital discharge seen between GD14-17.

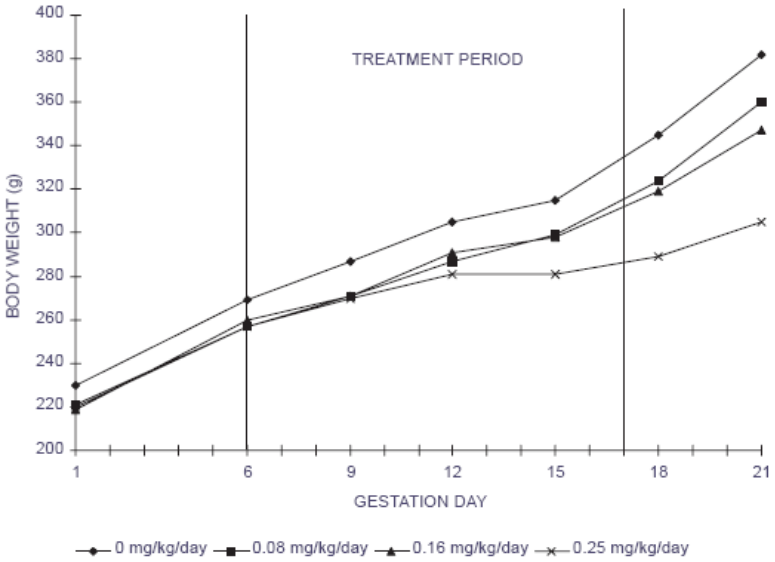
Table 75: Rat Maternal Clinical Signs

Observation Dose (mg/kg) N	0 9	0.08 9	0.16 9	0.25 9
Red Genital Discharge	1	1	2	6

Body Weight: Weights taken on GD1, 6, 9, 12, 15, 18, and 21
Over the course of the study there was a dose-dependent decrease in weight gain. The largest differences in weight gain came between GD12 and GD15.

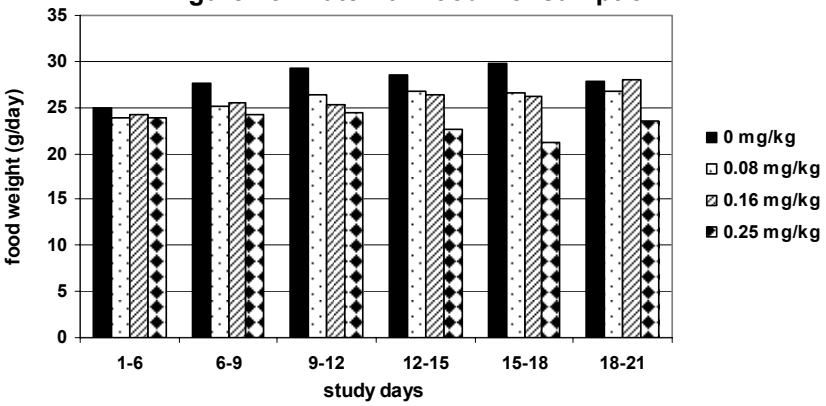
(Excerpted from Sponsor)

Figure 22: Maternal Body Weight



Feed Consumption: Determined in 3 day intervals beginning after dosing
There were dose-dependent decreases in food consumption between control and all dose groups between days 6 and 18. These differences were resolved after the end of dosing except in the high dose group. Between days 18 and 21 the high dose females consumed ~15% less food than controls.

Figure 23: Maternal Food Consumption



Toxicokinetics:
Samples were taken on GD12 at the 2 and 30 min, and 2and 6 hr. time-points following infusion. Plasma concentrations of RPR 116258 and the active metabolite RP 56976 were determined. Neither drug nor metabolite could be detected after the 2 minute time-point. There was an increase in exposure as determined by Cmax in the mid and high dose groups compared to that seen in the low dose group. The Cmax increase plateaued at doses ≥ 0.16 mg/kg.

(Excerpted from Sponsor)

Figure 24: Maternal Rat Toxicokinetics

Dose (mg/kg/day)	RPR 116258 Gestational Day 12		RP 56976 Gestational Day 12
	Cmax (ng/ml)	Tmax (min)	Cmax (ng/ml)
0.08	5.53	2	BLQ
0.16 (x2.0)	15.5 (x2.8)	2	BLQ
0.25 (x3.1)	11.9 (x2.2)	2	BLQ

Stability and Homogeneity
Within acceptable limits.

Necropsy
Gross Examination: There were no drug related findings in the gross examinations.

Hematology: There were small decreases in RBC parameters at the high dose of 0.25 mg/kg along with a dose dependent decrease in platelet numbers compared to control. While some changes in WBC parameters were present, these changes did not appear to be drug related.

Table 76: Hematology

Parameter Dose(mg/kg) N	0.08 6	0.16 5	0.25 7
RBC			↓8%
HB			↓7%
HCT			↓6%
Platelets	↓15%	↓24%	↓36%
Reticulocytes	↓8%	↑3%	↓23%

Clinical Chemistry: There were small, but dose-dependent increases in AST which corresponded with small, but dose-dependent decreases in triglycerides and cholesterol. Decreases in triglycerides and cholesterol also correlated with decreased food consumption. No other significant changes were observed.

Table 77: Clinical Chemistry

Parameter Dose(mg/kg) N	0.08 6	0.16 5	0.25 7
AST	↑10%	↑18%	↑27%
TG	↓8%	↓22%	↓30%
CHOL	↓9%	↓13%	↓14%

Cesarean Section Data

Table 78: Cesarean Section Data

Mean/Female Dose (mg/kg)	0	0.08	0.16	0.25
Pregnant Females N	6	6	5	7
Number of Corpora Lutea	13.7	16.7	13.8	13.7
Number of Implantations	12.3	12.4	11.4	13.4
Percent Pre-Implantation Loss	9.5%	16.1%	17.4%	6.6%
Post Implantation Loss	1.3	1.7	3.8	9.7
Early	1.3	1.7	3.6	8.1
Late	0	0	0.2	1.4
Dead	0	0	0	0.1
Percent Post-Implantation Loss	10.6%	13.7%	33.3%	72.4%
Number Liver Fetuses	11	10.7	7.6	3.7
Percent Live Males	47.3%	66.7%	53.9%	81.1%
Live Birth Index (%) (live/implants)	89.4%	86.3%	66.7%	27.6%

Offspring

Fetal birth weight decreases of 4.5 and 7.1% at the 0.16 mg/kg dose level and of 15.4 and 18.8% at the 0.25 mg/kg in males and females respectively were observed. In the gross examinations of fetuses, no drug-related findings were reported.

Table 79: Fetal Birth Weight

Dose (mg/kg)	0	0.08	0.16	0.25
Mean Male Fetal Weight	5.12	5.33	4.89	4.33
Mean Female Fetal Weight	4.9	5.05	4.55	3.98

Study title: RPR 116258A: Intravenous Embryofetal Developmental Toxicity Study in Rabbits

Study no:	RPR/RD/SA/SCRVA 99-019
Study report location:	EDR 4.2.3.5.2
Conducting laboratory and location:	Rhone-Poulenc Rorer Research & Development, Nonclinical Safety Assessment—Alfortville Vitry sur Seine, France
Date of study initiation:	February 11, 1999
GLP compliance:	Yes (France)
QA statement:	Yes
Drug, lot #, and % purity:	RPR 116258A/ P98058ME/ 98%

Key Study Findings

- No maternal toxicity was noted
- Fetal birth weights were unaffected
- F0, F1 NOAEL > 0.03 mg/kg

Methods

Doses:	0, 0.01, 0.02, and 0.03 mg/kg
Frequency of dosing:	Daily
Dose volume:	1 mL/kg
Route of administration:	IV Injection (1 mL/min)
Formulation/Vehicle:	0.08% polysorbate 80 and 0.03% ethanol USP diluted in 5% glucose
Species/Strain:	New Zealand white rabbits
Number/Sex/Group:	22 females/group
Study design:	Mated females were dosed daily from GD6-18. Animals underwent scheduled necropsy on GD28; gross and uterine examinations were performed. F1: External examinations were conducted and weight was recorded. Half were examined for visceral alterations, half for skeletal alterations.
Deviation from study protocol:	None

Observations and Results

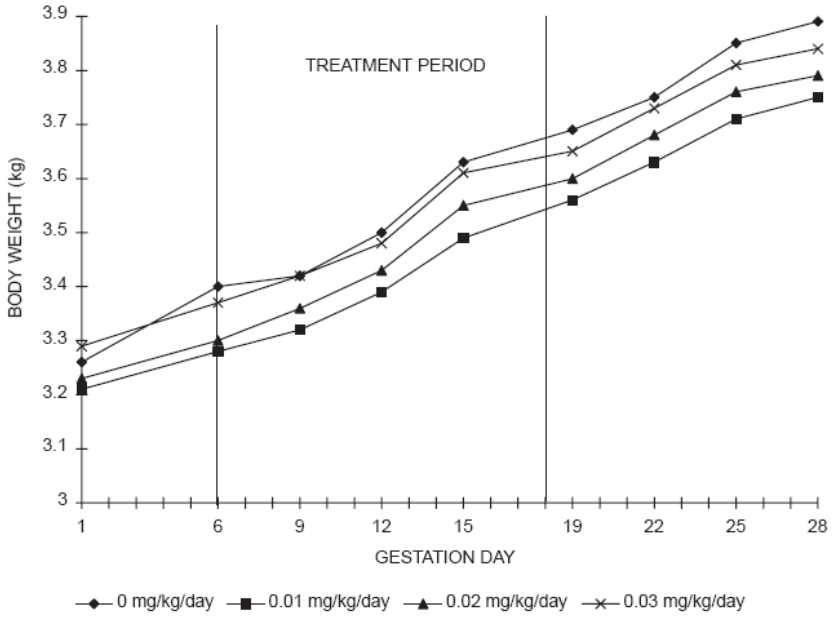
Mortality: Checked daily
No early deaths occurred during the study.

Clinical Signs: Examined daily
There was a single observation of red liquid in the cage pan from a high dose female. No other significant findings were noted.

Body Weight: Taken on GD1, 6, 9, 12, 15, 19, 22, and 28.
There was no significant effect of treatment on female body weight during gestation.

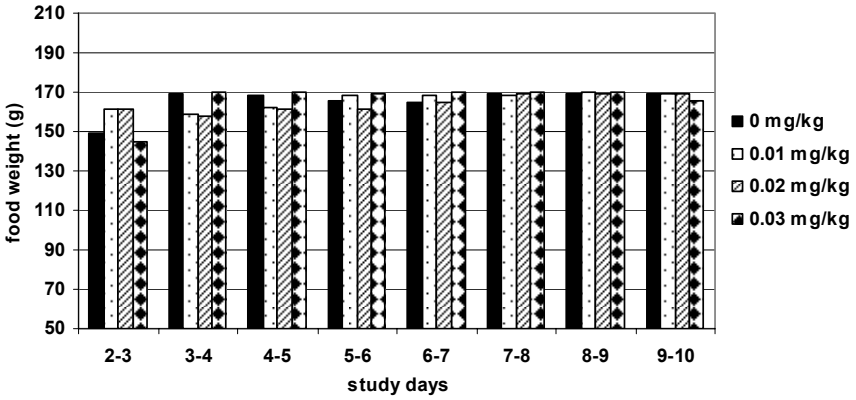
(Excerpted from Sponsor)

Figure 25: Female Body Weight



Feed Consumption: Determined daily from GD2-28
There were no significant effects on maternal food consumption.

Figure 26: Female Food Consumption



Toxicokinetics: Not determined
Stability and Homogeneity: Within acceptable limits

Necropsy
There were no drug-related findings reported.

Cesarean Section Data

Table 80: Rabbit Cesarean Section Data

Mean/Female Dose (mg/kg)	0	0.01	0.02	0.03
Pregnant Females N	19	21	19	20
Number of Corpora Lutea	10.5	9.9	9.6	10.1
Number of Implantations	9.4	8.7	8.1	9.0
Percent Pre-Implantation Loss	13.3%	11.1%	17.7%	12%
Post Implantation Loss	0.58	0.71	0.42	0.5
Early	0.53	0.48	0.26	0.45
Late	0.05	0.24	0.16	0.05
Dead	0	0	0	0
Percent Post-Implantation Loss	6.1%	8.2%	5.2%	5.6%
Number Liver Fetuses	8.8	8	7.6	8.5
Percent Live Males	58.9%	51.1%	49.8%	54.4%
Live Birth Index (%) (live/implants)	93.6%	92%	93.8%	94.4%

Offspring

Fetal birth weight was unaffected by *in utero* exposure to RPR 116258. There was a single case of a malrotated paw in the high dose group. Other findings in the external examination were limited to single findings in the control or low dose group. While there were some findings in the results of the visceral and skeletal fetal examinations, none were obviously dose-dependent and were within the range of historical controls.

Table 81: Rabbit Fetal Body Weight

Dose (mg/kg)	0	0.01	0.02	0.03
Mean Male Fetal Weight	32.7	33.8	34.6	32.9
Mean Female Fetal Weight	32.9	33.2	32.8	31.8

Table 82: Rabbit F1 Malformations/Variations

Malformation/ Variation Dose (mg/kg)	0	0.01	0.02	0.03
Fetuses N	168	167	145	170
Litters N	19	21	19	20
Brain-Dilated Cerebral Lateral Ventricle				
Fetal Incidence				1
Litter Incidence				1
Mean % Affected Fetuses/Litter				0.7%
Subclavian Artery-Malpositioned Subclavian Branch				
Fetal Incidence	26	31	31	39
Litter Incidence	13	15	11	13
Mean % Affected Fetuses/Litter	16.3%	19.7%	18.4%	23.1%

Malformation/ Variation Dose (mg/kg)	0	0.01	0.02	0.03
Fetuses N	168	167	145	170
Litters N	19	21	19	20
Kidney-Dilated Renal Pelvis				
Fetal Incidence			3	1
Litter Incidence			2	1
Mean % Affected Fetuses/Litter			1.8%	0.6%
Skull-Misshapen Hyoid				
Fetal Incidence				1
Litter Incidence				1
Mean % Affected Fetuses/Litter				0.6%
Membranous Skull Bone Variation				
Fetal Incidence	7	10	10	24
Litter Incidence	5	8	7	12
Mean % Affected Fetuses/Litter	3.5%	6.6%	5.9%	13.4%

Study title: RPR 116258: 13-Day Intravenous Exploratory Toxicity Study in Female Rabbits

Study no: RPR-RD-DS/CRVA 98-034
Study report location: EDR 4.2.3.5.2
Conducting laboratory and location: Rhone-Poulenc Rorer Research & Development, Drug Safety Division-Alfortville
Alfortville, France
Date of study initiation: January 30, 1998
GLP compliance: No
QA statement: No
Drug, lot #, and % purity: RPR 116258/ BFC 611/96.5%

Key Study Findings

- There was significant toxicity resulting in death in all dose groups
- A NOAEL was not established
- Toxicity was primarily along the GI tract with anorexia and weight loss

Methods

Doses:	0, 0.1, 0.3, and 0.6 mg/kg
Frequency of dosing:	Daily
Dose volume:	1 mL/kg
Route of administration:	IV injection (1 mL/min)
Formulation/Vehicle:	1.5% PS80 and 0.58% EtOH diluted in 5% glucose
Species/Strain:	New Zealand white rabbits
Number/Sex/Group:	4 females/group
Study design:	Daily dosing for 13 days in female rabbits to establish toxicity levels for this species
Deviation from study protocol:	Dosing was stopped in the 0.3 and 0.6 mg/kg dose groups on Days 7 and 8 respectively and animals were euthanized due to morbidity

Observations and Results

Mortality: Checked daily

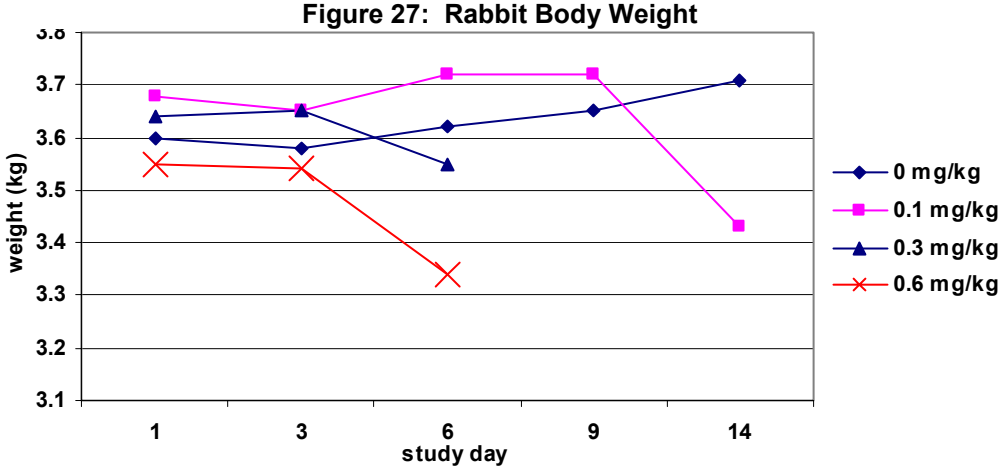
Table 83: Rabbit Mortality

Animal #	Dose (mg/kg)	Day of Death	Observations		
			Reason for Removal	Cause of Mortality	General
053	0.1	10	Euthanized	Morbidity	Weight loss and decreased food consumption were observed in all early death animals
101	0.3	8	Found Dead	Morbidity	
102	0.3	8	Euthanized	Morbidity	
103	0.3	8	Euthanized	Morbidity	
104	0.3	8	Euthanized	Morbidity	
151	0.6	7	Euthanized	Morbidity	
152	0.6	7	Euthanized	Morbidity	
153	0.6	7	Euthanized	Morbidity	
154	0.6	7	Euthanized	Morbidity	

Clinical Signs: Examined daily
Decreased defecation was the most common clinical sign. All treated animals showed this decrease. In the high dose group decreased defecation was seen as early as Day 3. Over time, animals progressed to no feces. The only other clinical sign was in a single animal in the 0.6 mg/kg dose group. This animal had a constricted pupil with a red iris on Day 7.

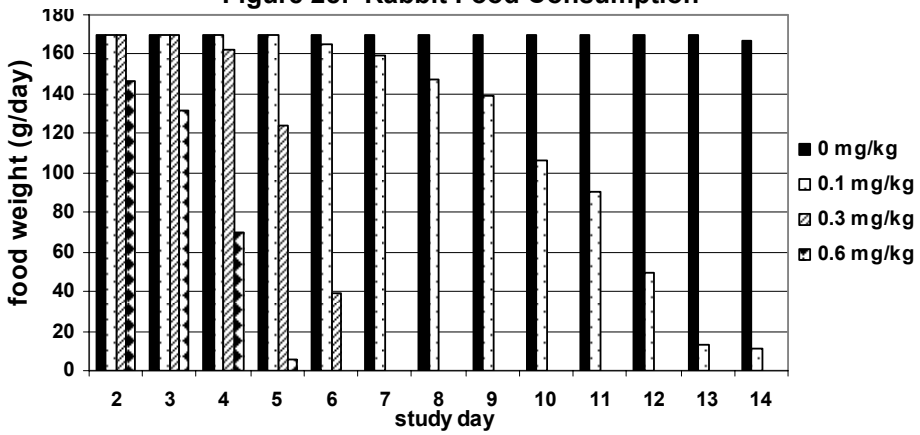
Body Weight: Pretest (Day -2), dosing Days 3, 6, 9, and 14
Significant weight loss occurred in every dose group. While weight loss was delayed in the 0.1 mg/kg (low) dose group compared to the higher doses, total weight loss by the end of the study in the low dose animals was similar to that seen at the final time-point for high dose animals.

Figure 27: Rabbit Body Weight



Feed Consumption: Determined daily
Significant decreases in food consumption were seen at every dose level. At the 0.6 mg/kg dose level this decrease was apparent following the first day of drug administration.

Figure 28: Rabbit Food Consumption



Toxicokinetics
Not performed.

Stability and Homogeneity
Within acceptable limits.

Necropsy
Macroscopic findings were limited to changes along the GI tract and liver.

Table 84: Rabbit Macroscopic Findings

Macroscopic Findings	Dose(mg/kg)	0	0.1	0.3	0.6
	N	4	4	4	4
Colon	Liquid Content				1
	Dilation/Distention				1
	Mucosal Redness			1	3
	Serosal Redness				1
Jejunum	Liquid Content		1	3	4
	Dilation/Distention		1		
	Gas Excess			1	
Liver	White Spots				1
	White Area				1
Lungs	Discoloration		1		
Stomach	Liquid Content		2	3	2
	Dilation/Distention		1		4
	Mucosal Depression		2	1	1
	Mucosal Disruption		1		3
	Mucosal Red/Dark Spots		3	4	2
	Mucosal Redness				2
	Thickened Wall		1	3	3

Study title: RPR116258: Intravenous Range-Finding Toxicity Study in Pregnant Rabbits

Study no: RPR-RD-DS/CRVA 98-035
Study report location: EDR 4.2.3.5.2.1
Conducting laboratory and location: Rhone-Poulenc Rorer Research & Development Drug Safety Division-Alfortville
Alfortville, France
Date of study initiation: February 18, 1998
GLP compliance: Yes (France)
QA statement: Yes
Drug, lot #, and % purity: RPR 116258/BFC 611/ 96.5%

Key Study Findings

- A NOAEL was not established for females due to decreased weight gain, food consumption, and WBC levels at all dose levels
- A NOAEL was not established for F1 progeny due to small decreases in the fetal birth weight at all dose levels
- Mortality at doses ≥ 0.04 mg/kg
- The highest exposure (determined by Cmax alone) was 0.03X that predicted from the human clinical dose

Methods

Doses:	0, 0.02, 0.04, and 0.08 mg/kg
Frequency of dosing:	Daily
Dose volume:	1 mL/kg
Route of administration:	IV injection (1 mL/min)
Formulation/Vehicle:	0.20% polysorbate 80 and 0.08% ethanol USP diluted in 5% glucose
Species/Strain:	New Zealand white rabbits
Number/Sex/Group:	8 females/group
Satellite groups:	6 females/group (toxicokinetics)
Study design:	Daily dosing from GD6 through GD18; scheduled euthanasia on GD28
Deviation from study protocol:	None

Observations and Results

Mortality

Table 85: Rabbit Maternal Mortality

Animal #	Dose (mg/kg)	Day of Death	Observations		
			Reason for Removal	Cause of Mortality	General
102	0.04	22	Euthanasia	Morbidity	Dilation/distension of stomach; ↓body weight, ↓food consumption
152	0.08	22	Euthanasia	Morbidity	Red spots in cecum
158	0.08	21	Euthanasia	Morbidity	

Clinical Signs

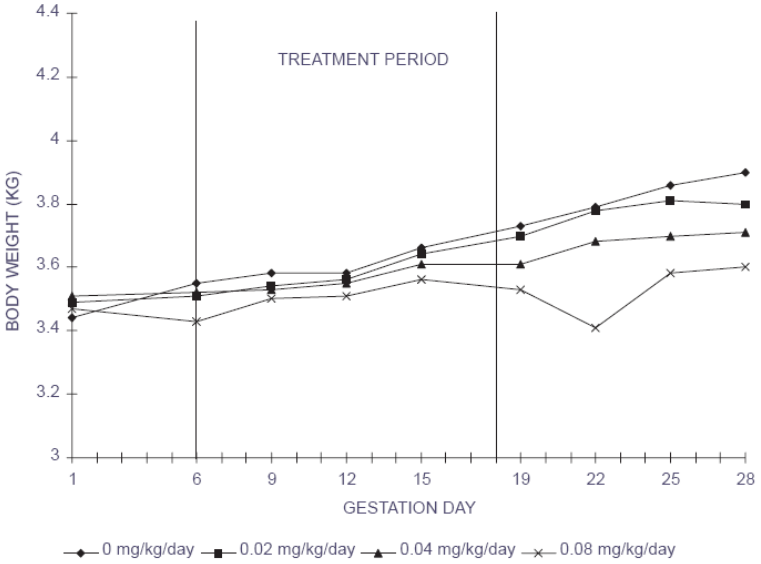
Decreased defecation was the major clinical sign noted. This was seen even in control animals. There was a dose-dependent increase in the amount of time animals presented with this finding. In addition there was a single pregnant female in the 0.04 mg/kg mid dose group that had red discolored urine on Study Day 9.

Body Weight:

Over the dosing period females in the high and mid dose groups gained 44-50% less weight than control animals. Over the course of the entire study there was a dose-dependent decrease in the amount of weight gained (33%, 57%, and 72% less than controls for the low, mid, and high dose groups).

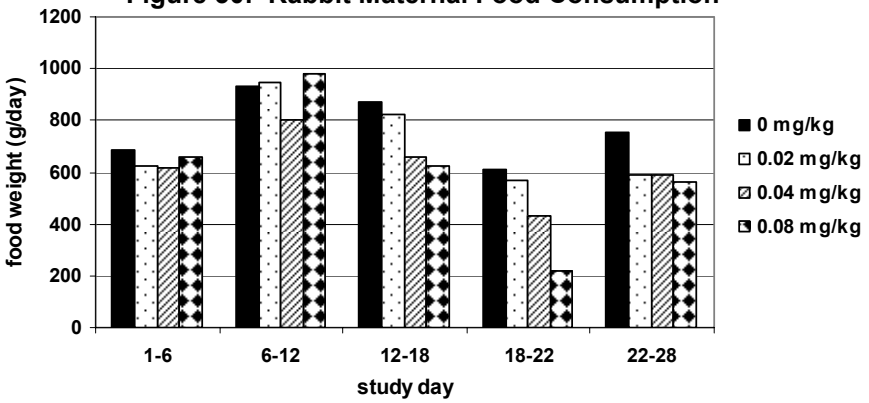
(Excerpted from Sponsor)

Figure 29: Rabbit Maternal Body Weight



Feed Consumption:
Over the course of the study females in the high and mid dose groups consumed ~20% less than control animals. The largest differences were apparent from GD13-GD24, approximately a week after the beginning and ending of the dosing period. During this period there was a dose-dependent decrease in food consumption.

Figure 30: Rabbit Maternal Food Consumption



Toxicokinetics: Taken Day 12 at 2, 15, and 30 mins., and 2 and 4 hrs. post-dosing Blood samples were taken from 2 or 3 toxicokinetic animals/time-point for determination of RPR 116258 and the active metabolite RP 56976. No drug was detected in control samples. No drug or metabolite was detected in samples after the 2 minute time-point. There was a dose-dependent and dose-proportional increase in exposure of RPR

116258 as determined by Cmax alone. Levels of the RP 56979 metabolite were below the level of quantitation at every time-point.

Table 86: Rabbit Maternal Toxicokinetics

Dose (mg/kg)	RPR 116258		RP 56976	
	Cmax (ng/mL)	Tmax (min)	Cmax (ng/mL)	Tmax (min)
0.02	BLQ	NA	BLQ	NA
0.04	3.63	2	BLQ	NA
0.08	7.26	2	BLQ	NA

Stability and Homogeneity
Within acceptable limits

Necropsy
Gross Examinations: No significant maternal findings.

Hematology: Blood samples were taken after then end of dosing on GD19.

Table 87: Rabbit Maternal Hematology

Parameter Dose(mg/kg) N	0.02	0.04	0.08
RBC			↓12%
HCT			↓12%
HB			↓14%
PLATELETS		↓23%	↓44%
RETIC		↓15%	↓60%
WBC	↓11%	↓15%	↓56%
NEUT		↓14%	↓97%
EOS			↓83%
LYMPH			↓42%
MONO			↓31%

Clinical Chemistry:

Table 88: Rabbit Maternal Clinical Chemistry

Parameter Dose(mg/kg) N	0.02	0.04	0.08
ALP	↓13%	↓29%	↓35%
GLU			↑12%
PHOSPHOROUS	↓6%	↓11%	↓14%

Cesarean Section Data

Table 89: Rabbit Fertility Data

Dose (mg/kg)	Main Study Animals			Toxicokinetic Animals	
	Mated	Pregnant	Surviving Pregnant	Mated	Pregnant
0	8	7	7	6	5
0.02	8	6	6	6	6
0.04	8	7	6	6	6
0.08	8	6	4	6	5

Table 90: Rabbit Cesarean Section Data

Mean/Female Dose (mg/kg)	0	0.02	0.04	0.08
Pregnant Females N	7	6	6	4
Number of Corpora Lutea	9.9	10.8	10	9.5
Number of Implantations	8	9.3	9.2	8
Percent Pre-Implantation Loss	19%	14%	10%	16%
Post Implantation Loss	0.6	1.5	0.8	0.5
Early	0.6	0.7	0.7	0.5
Late	0	0.8	0.2	0
Dead	0	0	0	0
Percent Post-Implantation Loss	7.5%	16%	8.7%	6.3%
Number Liver Fetuses	7.4	7.8	8.3	7.5
Live Birth Index (%) (live/implants)	92.5%	83.9%	90.2%	93.8%
Mean Fetal Weight (males and females)	31.7	30.5	30.3	26.7

Offspring

There was a dose-dependent decrease in the mean fetal birth weight with a 16% decrease in fetuses from high dose group dams. No drug-related abnormalities were noted in the external examinations.

11 Integrated Summary and Safety Evaluation

Pharmacology

Both *in vitro* and *in vivo* studies were conducted to investigate the pharmacologic and anti-tumor activity of cabazitaxel. Cabazitaxel is an analogue of docetaxel and, like other taxanes, affects microtubule function by binding to tubulin and promoting microtubule polymerization and stabilizing their structure. The inhibition of microtubule disassembly caused by binding of taxanes eventually leads to apoptotic cell death. Because of the well-established mechanism of action of taxanes on microtubules, limited investigation of the activity of cabazitaxel was included. Cabazitaxel was able to promote tubulin polymerization as measured by decreased lag time to achieve turbidity

in vitro. The drug was also able to prevent tubulin depolymerization. The effects of cabazitaxel on tubulin were comparable to those of docetaxel at similar concentrations and more pronounced than those of paclitaxel. Receptor binding was also examined *in vitro*. An IC25 was not established for any of the measured receptors indicating that cabazitaxel is not an effective inhibitor of receptor binding for a panel of physiologically important proteins including hormone, neuroendocrine, and ion channel receptors.

Anti-tumor activity was assessed *in vitro* and *in vivo*. IC_{50}s were determined for cabazitaxel against panels of cell lines including some derived from docetaxel and paclitaxel resistant tumors. In these assay cabazitaxel inhibited proliferation of these cells at physiologically relevant levels that were similar to or exceeding those of docetaxel. The IC_{50} ratio of docetaxel/cabazitaxel in taxane resistant cell lines reached up to 10.5 fold. Interestingly, cell lines with the highest docetaxel/ cabazitaxel IC_{50} ratios had detectable levels of mdr1 mRNA suggesting that cabazitaxel may not be as easily recognized by P-gp as some other taxanes. While this hypothesis was not fully investigated, improvements in life span of SCID mice intracranially implanted with glioblastomas after treatment with cabazitaxel compared to docetaxel suggest that further examination of this hypothesis could be warranted. While cabazitaxel had improved activity against intracranially implanted gliobastomas compared to docetaxel or two other clinical candidates, when the same tumor cell lines were implanted subcutaneously, the activity of cabazitaxel was similar or reduced compared to docetaxel. Additional *in vivo* tumor implant experiments were also performed in either nude or SCID mouse models. Treatment with cabazitaxel led to delayed tumor progression compared to untreated controls in nude mice implanted with several different human gastric, prostate, colon, lung, pancreatic, kidney, and head and neck tumors. With 4/9 lines tested in this model (including a colon, a head and neck, a pancreatic, and a prostate line) tumor free survival was recorded. When treatment with cabazitaxel was compared directly to treatment with docetaxel in these lines, cabazitaxel had similar or improved activity. In a human docetaxel resistant breast tumor model, cabazitaxel treatment of implanted SCID mice resulted in a significant delay in tumor growth compared to either docetaxel or ixabepilone. The submitted pharmacology studies support the conclusion that cabazitaxel is microtubule inhibitor that has the potential to be an important therapeutic choice in a number of potential cancer indications, including situations in which resistance to docetaxel or other taxanes has already occurred.

Pharmacokinetics

Cabazitaxel exposure is dose-dependent; the drug appears to distribute rapidly into tissues and crosses both the blood-brain and placental barriers. Metabolism of cabazitaxel is NADPH-dependent with 3 major metabolites detected in rat, dog, and human liver microsomes (RPR123142, RPR112698 and RP56976 (docetaxel)) Human metabolism of the drug appeared to be faster than that of dogs or rats as the rate of disappearance of the parent drug in liver microsomes from each species was highest in human and lowest in rats. Total plasma clearance was rapid in all species tested but

tended to decrease with increasing dose in dogs. The *in vitro* plasma protein binding was similar between species with ≤ 10% of the drug being free; percent of free drug was highest in humans and lowest in dogs. Cabazitaxel (10 μM) induced CYP3A in primary cultures of rat hepatocytes, however, this induction it is not believed to be clinically relevant as the *in vitro* concentration at which induction was observed was significantly higher (~16 fold) than the physiologically relevant concentrations. Excretion of the drug is primarily in the feces though small amounts were detectable in urine and in breast milk.

Safety pharmacology

Both *in vivo* and *in vitro* safety pharmacology studies were performed to assess the effects of RPR 116258 on the CNS, cardiovascular system, and renal and GI function. While there was some variation in dosing among the studies due to dose concentration errors, Sprague-Dawley rats were generally administered single doses of a 5% glucose solution or 0, 0.5, 1.5 , or 5 mg/kg (0, 3, 9, or 30 mg/m^2) RPR 116258 in a series of GLP compliant studies to observe the effects on the CNS. There were no drug-related effects noted in the Irwin test, on locomotion, or on nociception in male rats treated with RPR 116258 at doses up to 30 mg/m^2. Similarly, RPR 116258 did not act as either a pro or anti-convulsant when administered 30 minutes prior to treatment of rats with drugs to either prevent (in the pro-convulsant test) or cause (in the anti-convulsant test) seizures. In a final CNS study, the sponsor examined the effects of RPR 116258 on hexobarbital induced sleep time in male rats. Hexobarbital was administered to animals 30 minutes after a single dose of RPR 116258 or the positive control article, chlorpromazine HCl. While there was no difference between drug and control treated animals in time to loss of righting reflex, there was a small increase (~5%) in sleeping time at the 30 mg/m^2 dose level compared to either vehicle or glucose treated animals. Thus, RPR 116258 may have a mild sedative effect, but of uncertain physiologic importance.

In vitro studies conducted to examine the effects of RPR 116258 on cardiovascular parameters included the hERG assay and the cardiac purkinje fiber assay. While there was increased inhibition seen in potassium channel conductivity with increased concentration of RPR 116258, an IC25 was not established even at the highest concentration of 30 μM, a concentration 50 fold higher than the reported Cmax at the clinically recommended dose. Similarly, in the purkinje fiber assay at concentrations up to 10 μM (~16 fold higher than the Cmax in humans) there were no significant drug-dependent increases in action potential duration (APD30, APD60, or APD90). Neither *in vitro* assay, therefore, predicted strong QT prolongation. In an *in vivo* assay assessing cardiovascular safety, male beagle dogs were anesthetized, surgically implanted with devices to measure heart rate, blood pressure, ventricular pressure, ECG parameters, peripheral resistance, femoral arterial blood flow and conductance, cardiac output, stroke volume, and respiration rate. Arterial blood gases were also recorded. After implantation and stabilization the anesthetized animals were administered either a 5% glucose solution, vehicle alone, or RPR 116258 at 0.45 mg/kg

(9 mg/m^2) over a 1 hour time period. Data was collected at baseline, 2, 5, 15, 30, 45, and 60 minutes during dosing as well as at 15 and 30 minutes and 1 and 2 hours following dosing. There were significant vehicle related effects on all parameters with the exception of blood gases and pH. These changes included decreased heart rate and blood pressure in vehicle treated animals compared to glucose treated animals apparent by the 15 minute time-point. After the end of dosing these changes were reversed or were reversing so that by the 2 hour post-dose time-point they were returned to baseline. Generally, treatment with RPR 116258 resulted in the same changes in cardiac parameters as those seen in vehicle alone, however, there was a mild prolongation of QTc seen in RPR 116258 treated animals that was not seen in vehicle treated animals. This increase was > 10% compared to baseline in these animals from the 45 until the 75 minute interval, a difference of ≥ 40 ms. Respiration rate was increased in vehicle and RPR 116258 treated animals compared to baseline or glucose control treated animals. The increased respiration rate was apparent after the 5 minute time-point and remained high until 30 minutes after the end of dosing. Though reversing following the 30 minute post-dose time-point, respiration did not fully return to the baseline level by the end of the study. This finding was in contrast to the effect of RPR 116258 or vehicle on respiration rate in the male rat. Male rats were given a single dose IV infusion of either 5% glucose, vehicle, or 3, 9, or 30 mg/m^2 RPR 116258 and placed in a plethsmography chamber 15 minutes later. There was no effect on either respiration rate or body temperature noted in vehicle or drug treated animals. The cardiovascular safety pharmacology studies suggest that the major effects on cardiovascular parameters are vehicle related, but that there may be a mild QTc prolongation that is drug substance related.

In an *in vivo* study of renal function, male Sprague-Dawley rats were treated with 5% glucose, vehicle, furosemide (positive control), or 0, 0.415, 1.5, or 5 mg/kg (0, 2.49, 9, or 30 mg/m^2) RPR 116258. Rats were placed in metabolic cages and samples were collected at 3, 6, and 24 hours after dosing. There were no drug induced changes in urine volume or pH. At the 3 hour time-point there were mild increases in urinary electrolytes in animals treated with ≥ 9 mg/m^2. By the 24 hour time-point there was a dose-dependent decrease in urinary potassium levels seen in RPR 116258 treated animals compared to vehicle or glucose only controls (~53% and 61% decreases respectively in the 30 mg/m^2 dose group). There were also very decreases in amounts of urinary chloride detected at the 24 hour time-point in the high dose group animals. While there was no clear indication of renal injury, there was some indication that RPR 116258 was affecting electrolyte levels in treated animals.

Single *in vitro* and *in vivo* studies were conducted to asses the effects of RPR 116258 on gastrointestinal function. In the *in vitro* assay, guinea pig ileums were isolated and treated with the spasmogens acetylcholine, histamine, 5-hydroxytryptamine creatinine sulphate, or barium chloride in order to establish concentrations at which the compounds reproducibly induced maximum contractions. Concentrations at which the same compounds caused 50-70% of maximum contraction in the ileum fragments were determined. RPR 116258 at 1, 3, and 10 μM concentration or vehicle at corresponding

concentrations were then applied to the segments for 30 minutes before the addition of the submaximal concentrations of the spasmogens and effects of the drug on contractility were assessed. At high concentrations, the addition of vehicle alone resulted in significant foaming and the need for reducing the rate of gassing in the system. At concentrations of RPR 116258 <10 µM, effects of the drug on response to any of the spasmogens was small. The application of vehicle alone inhibited the response of the tissue to acetylcholine or 5-hydroxytrptamine. When RPR 116258 was present, this inhibition was reversed. Conversely, the vehicle enhanced barium chloride responsiveness and RPR 116258 diminished this enhancement. Neither vehicle alone or RPR 116258 had an effect on histamine responsiveness. In the *in vivo* study, male Sprague-Dawley rats were administered by IV injection with 5% glucose, vehicle, morphine, or 0.5, 1.5, or 5 mg/kg (3, 9, or 30 mg/m^2) RPR 116258 and then, 30 minutes later, were fed a charcoal meal. Gastric emptying and distance the charcoal had traveled in the intestine were measured after 30 minutes. No differences were seen between RPR 116258 or vehicle treated animals and controls in gastric transit. These studies do not predict a strong effect of single dose treatment of RPR 116258 directly on gastric movement.

Toxicology

Single dose studies in mice, rats and dogs as well as 5-day repeat dose studies in rats and dogs were previously reviewed under IND 56,999 (*Margaret Brower, PhD; 1998*). In the current submission, the pivotal cabazitaxel toxicity studies reviewed are a 10-cycle study in rats and a 13-cycle study in dogs. Rats were administered 0, 1, 5 and 20/10 mg/kg (0, 6, 30 and 120/60 mg/m^2) of cabazitaxel every 3 weeks over a 6-month period. Dogs were administered 0, 0.1, 0.25, and 0.5 mg/kg (0, 2, 5 and 10 mg/m^2) every 3 weeks over a 9-month period. In both species, cabazitaxel was administered by IV infusion for 1 hour.

In the rat study, 11M/10F dosed at 120/60 mg/m^2 died or were sacrificed during treatment period due to severe toxicities and 2M/1F died before scheduled sacrifice during the recovery period. Clinical signs included thin body, decreased activity, paleness, unsteady gait, hunched gait, noisy breathing, wheezing, swelling, extensive hair loss, loss of whiskers and piloerection. The dose level was reduced to 60 mg/m^2 following the second cycle. Despite the decrease, treatment at 120/60 mg/m^2 was stopped after the 4th cycle for males and the 6th cycle for females based on high mortality and the poor clinical condition of the animals.. The main histopathological changes leading to mortality and early termination of treatment consisted of pronounced depletion of the lymphoid and hematopoietic systems (thymus, lymph nodes, spleen, bone marrow) and kidney necrosis/pyelonephritis. In accordance with the histopathological findings, hematological parameters including, reticulocyte, platelet, neutrophil, lymphocyte, monocyte, eosinophil, basophil and LUC counts were decreased, Histopathological changes were not noted in the kidney outside of pyelonephritis in the high dose group. There were, however, findings of decreased urinary volumes at doses ≥ 30 mg/m^2 . These observations along with the decreased

levels of potassium noted in the single dose safety pharmacology study suggest the kidney as an important target organ for cabazitaxel related toxicity. At the 30 mg/m^2 dose level 1M/1F died during the treatment period and 1F during the recovery period. Clinical signs and pathological findings of rats dosed at 30 mg/m^2 were similar to those seen at 120/60 mg/m^2.

In the dog study, there were no unscheduled deaths. Clinical signs included decreased motor activity, tremors, vocalization, liquid feces, and reddened skin. Food consumption curves for vehicle- (polysorbate 80 (PS80)) and HD cabazitaxel-treated groups have a similar trend and are lower than LD and MD groups up to week 13 in males and week 19 in females. PS80 may have effect on food consumption in dogs. Three days after each dosing cycle there were decreases in platelets, lymphocytes and neutrophils,total WBCs and basophils. Histopathological findings included epithelial regenerative hyperplasia in the small and large intestines, single cell necrosis in the stomach mucosa, decreased cellularity of bone marrow in the sternum, inflammatory cells in the lungs, and increased epididymal vacuolation.

Reproductive toxicty

Both fertility and early embryonic development studies and embryonic fetal development studies were submitted to support NDA 201023. The sponsor assessed effects of RPR 116258 on both male and female fertility. In the male fertility study performed in Sprague Dawley rats, animals were dosed daily with 0, 0.05, 0.1, or 0.3/0.2 mg/kg (0, 0.3, 0.6, or 1.8/1.2 mg/m^2) by IV injection for 70 days before cohabitation with untreated females. There were no changes in mating behavior, fertility, or fetal body weight in response to treatment of males with RPR116258 at any tested dose level. At the high dose level of 1.8 mg/m^2, F0 male animals suffered significant weight loss and after 13 days, were dose reduced to 1.2 mg/m^2. Four early deaths occurred over the course of the study, three of which occurred in the high dose group. Two of the three deaths in the high dose group had injection site wounds that were related to the decision to euthanize the animals. All three deaths in this group occurred before animals were mated. The earliest death occurred at Day 18; this animal appeared to have a systemic infection with bacterial colonies in the heart, liver, and stomach. This animal also had areas of necrosis in the heart and liver along with red fluid in the thoracic cavity. The most common clinical sign was decreased defecation at doses ≥ 0.6 mg/m^2. This correlated with significant weight loss and decreased food consumption in the high dose group. Despite decreased body weight, the absolute weights of the testis and epididymes were not decreased in any of the treatment groups. The sponsor failed to include an evaluation of sperm or prostate weight in this study; both of these factors would be highly relevant to a full understanding of the effects of the drug on male fertility. In the chronic toxicity study performed in rats there were findings of oligospermia in the epididymis, degeneration/regeneration in the seminal vesicle, and seminiferous tubule atrophy in the testis at doses ≥ 6 mg/m^2 (~0.2-0.35X the AUC in humans at the clinically

recommended dose). These findings occurred in only 1/10 males at the 6 mg/m2 dose level, but increased in both frequency and severity at higher dose levels.

Female fertility was also examined. While there was no effect of the drug on mating or the ability to become pregnant, there was an increase in resorptions seen at the high dose level. Females were dosed for 15 days prior to cohabitation and continued to receive daily doses of 0, 0.05, 0.1, or 0.2 mg/kg (0, 0.3, 0.6, or 1.2 mg/m^2) RPR 116258 until GD6 in order to study the fertility/early *in utero* exposure effects of the drug. There were no mortalities in this study. Females in the 0.6 and 1.2 mg/m^2 dose groups had a dose related decrease in body weight gain which was most pronounced during the first week of gestation when dosing was still ongoing and which correlated with decreased food consumption. Despite the recorded increase in resorptions, there was no effect of RPR 116258 on fetal birth weight nor was there a clear teratogenic effect based on external examinations of the progeny in any dose group. Though toxicokinetic findings were not included in this report, the exposure levels at doses up to 1.5 mg/m^2 in pregnant rats obtained in the embryofetal development studies suggest that the increase in resorptions occurred at exposures significantly below the expected human exposure.

Embryofetal development studies were conducted in both Sprague Dawley rats and New Zealand White rabbits. Two studies were performed in pregnant rats; the first was a dose-range finding study which included abbreviated toxicokinetic information. Mated females were treated from GD6 to GD17 at doses of 0, 0.08, 0.16, or 0.25 mg/kg (0, 0.48, 0.96, or 1.5 mg/m^2) and euthanized at GD21. Blood samples were taken from the toxicokinetic animals on GD12 and were analyzed for both RPR 116258 and the active metabolite RP 56976. The metabolite was not detectable at any time-point. RPR 116258 was not detectable after the 2 minute time-point. AUC was not determined for the drug, but the Cmax for RPR 116258 plateaued at the 0.96 mg/m^2 dose level. The Cmax value at this dose was only 0.06 times the low end of the expected human exposure at the clinically recommended dose. There was a dose-dependent increase in post implantation loss at doses ≥ 0.96 mg/m^2. In addition, mean fetal birth weight declined at doses ≥0.96 mg/m^2, though fetuses did not display any external abnormalities. Maternal toxicity included decreased weight gain at the low and mid dose levels with weight loss at high dose level along with decreased food consumption at every dose level during the dosing period. In addition there were dose-dependent decreases in platelets compared to control animals at doses ≥ 0.48 mg/m^2. At the 1.5 mg/m^2 dose levels, animals showed mild decreases in RBC parameters, particularly in reticulocyte numbers. In the second rat embryofetal development study, 29 mated females/group were dosed daily with 0, 0.04, 0.08, or 0.16 mg/kg (0, 0.24, 0.48, or 0.96 mg/m^2) RPR 116258 from GD6-17. A single mortality occurred at the 0.96 mg/m^2 dose level after the end of the dosing period. This female was euthanized due to morbidity and had decreased motor activity and body weight. Necropsy showed that there was red liquid content in the uterus along with pale mucous membranes, liver, and skeletal muscle. Clinical signs were primarily limited to high dose group females and included red anogenital staining, red genital discharge, and red material in the cage pan

indicative of abortion. High dose females also showed reduced weight gain and a small decrease in food consumption compared to control animals. Measurements of gravid uterine weight were not included in this assessment; however, the 0.96 mg/m^2 females did have an increase in post implantation loss that could account for the reduced maternal body weights. Decreased fetal birth weight was apparent in both males and females in a dose-dependent manner at doses ≥ 0.24 mg/m^2. Finally, at doses ≥ 0.48 mg/m^2 there were mild increases in incidences of skeletal variations (sternabra and supernumerary ribs) and delayed or incomplete skeletal ossification (sternabra, metatarsal, and hindpaw phalanx).

In rabbits, three studies were included to assess the effects of *in utero* exposure of RPR 116258 on embryo-fetal development. Two were dose-range studies in non-pregnant and pregnant female rabbits to determine the appropriate test doses in this species. Rabbits (4 females/group) were dosed daily for 13 days with 0, 0.1, 0.3, or 0.6 mg/kg (0, 1.2, 3.6, or 7.2 mg/m^2) RPR 116258. Early deaths occurred at every dose level including the low dose of 1.2 mg/m^2. All animals in the 3.6 mg/m^2 and 7.2 mg/m^2 dose groups were euthanized on Days 8 and 7, respectively, due to morbidity including significant weight loss and severely decreased food consumption. Findings at necropsy were limited to changes in the GI tract and liver at every dose level. In pregnant rabbits, 8 females (and an additional 6 in toxicokinetic groups) were dosed daily from GD6-18 with 0.02, 0.04, or 0.08 mg/kg (0, 0.24, 0.48, or 0.96 mg/m^2) RPR 116258. Similar to the results in the pregnant rats, in the toxicokinetic analysis performed on blood samples taken from rabbits on GD12, RPR 116258, but not the RP 56976 metabolite, was detected. The drug could only be detected at the 2 minute time-point. There was a dose-dependent increase in exposure, as determined by Cmax, at doses ≥ 0.48 mg/m^2. At the high dose of 0.96 mg/m^2, the Cmax was 0.01 times the Cmax at the low end of the range of human clinical exposure at the recommended dose. There was maternal mortality at doses ≥ 0.48 mg/m^2. Females in all dose groups had dose-dependent decreases in body weight gain, food consumption, and defecation. In addition, decreases in both red and white blood cells were detected. There was a dose-dependent decrease in white blood cells at doses ≥0.24 mg/m^2. Neutrophils, specifically were decreased at doses ≥ 0.48 mg/m^2. At the highest dose, there were decreases in all WBC parameter along with mild decreases in RBCs, hemoglobin, and hematocrit. Finally, there were dose-dependent decreases in platelets and reticulocytes at doses ≥ 0.48 mg/m^2. Despite the observed maternal toxicity, RPR 116258 did not appear to affect pregnancy parameters. Post implantation loss and live birth index were similar between controls and all dose groups. In the F1 animals no drug-related abnormalities were noted, although there was a mild dose-dependent decrease in fetal birth weight. At the high dose this difference was ~16% less than controls. In the final rabbit embryo-fetal development study, 22 mated females were dosed daily by IV injection from GD6-18 with 0, 0.01, 0.02, or 0.03 mg/kg (0, 0.12, 0.24, or 0.36 mg/m^2) RPR 116258. No early deaths occurred during the study and there was no significant effect on body weight or food consumption at any dose level. There was no effect on pregnancy parameters at any dose level. Fetal birth weights were also unaffected at

any dose level. Finally, while there were some findings in the visceral and skeletal fetal examinations, none were obviously drug-related. One finding of membranous skull bone variation was increased at the highest dose level and, therefore, could be treatment related; however, this finding was still within the range of historical control data for the species. Overall, at doses < 0.36 mg/m^2, RPR 116258 did not appear to affect rabbit embryo-fetal development.

In both rats and rabbits RPR 116258A was embryotoxic, fetotoxic, and abortifacient at doses significantly below the dose recommended for humans.

Genetic toxicity

Cabazitaxel was negative in bacterial reverse mutation (Ames) test, negative in the chromosome aberration test in cultured human peripheral lymphocytes from male and female donors, but increased the number of polyploid cells. Finally, cabazitaxel was positive in the rat bone marrow micronucleus test.

(b) (4)

Table 91: Safety Pharmacology Summary

Study #/Organ System	Method of Administration/ GLP?	Species	Doses	Gender/N	Findings
RPR/RD/DS/CRVA 98-092 RKT00101 CNS	IV injection Single dose GLP	SD Rat	0, 0.5, 1.5, 5 mg/kg 0, 3, 9, 30 mg/m2	6 ♂/group	FOB test; no drug related findings
RPR/RD/DS/CRVA 98-095 RKT00104	IV injection Single dose GLP	SD Rat	0, 0.5, 1.5, 4.4 or 5 mg/kg 0, 3, 9, 26.4	8♂/group 4♂/group in 4.4 and 5 mg/kg groups	Locomotion test: no significant effects on locomotion/rearing

Study #/Organ System	Method of Administration/ GLP?	Species	Doses	Gender/N	Findings
CNS			or 30 mg/m2		
RPR/RD/DS/CRVA 98-093 RKT00102 CNS	IV injection Single dose GLP	SD Rat	0, 0.5, 1.5, 5 mg/kg 0, 3, 9, 30 mg/m2	8♂/group anti-convulsant 8♂/group pro-convulsant	No anticonvulsant or proconvulsant effects were observed
RPR/RD/DS/CRVA 98-103 RKT00107 CNS	IV injection Single dose GLP	SD Rat	0, 0.5, 1.7, 5 mg/kg 0, 3, 10.2, 30 mg/m2	8♂/group	Minor ↑(~5% ↑) in hexobarbital induced sleeping time was observed at 5 mg/kg. Small magnitude of increase and lack of strong dose-dependent signal make it of questionable concern.
RPR/RD/DS/CRVA 98-094 RTK00103 CNS	IV injection Single dose GLP	SD Rat	0, 0.5, 1.5, 5 mg/kg 0, 3, 9, 30 mg/m2	8♂/group	No drug-related changes in nociception at ≤ 5 mg/kg RPR 116258
PAT0192 Cardiovascular	*In vitro* hERG Assay	NA	1.1, 3, 10, 30 μM		No IC_{50} or IC_{25} established A concentration dependent increase in inhibition was observed with ~10% inhibition at 10 μM 10 μM is significantly greater than human Cmax at the clinically recommended dose
RPR/RD/DS/CRVA 98-104 RKT00111 Cardiovascular	*In vitro* Cardiac Purkinje Fibers (Sheep)	NA	0, 1, 3, and 10 μM		No remarkable findings

Study #/Organ System	Method of Administration/ GLP?	Species	Doses	Gender/N	Findings
RPR/RD/DS/CRVA 98-102 RKT00110 Cardiovascular	IV infusion Single dose GLP Anesthetized animals	Beagle Dogs	0, 0.45 mg/kg 0, 9 mg/m2	4♂/group	↓ heart rate, blood pressure, cardiac output , left ventricular pressure and stroke volume in vehicle or RPR 116258 compared to glucose only group beginning 15 minutes after the beginning of 1 hr. infusion. Reversing following the end of dosing ↑ respiration rate beginning 5 minutes after dosing started and starting to reverse after the end of dosing Changes appeared primarily vehicle related Mild ↑QTc in RPR 116258 compared to vehicle
RPR/RD/DS/CRVA 98-101 RKT00108 Cardiovascular	IV injection Single dose GLP	SD Rat	0, 0.5, 1.5, 5 mg/kg 0, 3, 9, 30 mg/m2	8♂/group	No remarkable changes in body temp. or respiration rate
RPR/RD/DS/CRVA 98-098 RKT00105 Renal	IV injection Single dose GLP	SD Rat	0, 0.415, 1.5, 5 mg/kg 0, 2.49, 9, 30 mg/m2	8♂/group	≥0.415 mg/kg: ↓potassium excretion at 24 hrs. post dose compared to vehicle or glucose only; mild ↑ electrolytes at 3 hr post dose No remarkable changes in urine volume Potential RPR 116258 effect on systemic potassium levels
RPR/RD/DS/CRVA 98-100 RKT00109	*In Vitro* Guinea Pig Isolated Ileum	NA	0, 1, 3, and 10 μM		Vehicle: ↓ contractility in acetylcholine or 5-hydroxytryptamine; RPR 116258 abrogates effect

Study #/Organ System	Method of Administration/ GLP?	Species	Doses	Gender/N	Findings
GI	Spasmogens: Acetycholine, 5-hydroxytryptamine, histamine, barium chloride				Vehicle ↑ contractility in response to barium chloride; RPR 116258 reduces effects No remarkable findings with histamine No significant changes in response to spasmogens at ≤ 3 μM
RPR/RD/DS/CRVA 98-099 RKT00106 GI	IV injection Single dose GLP	SD Rat	0, 0.5, 1.5, 5 mg/kg 0, 3, 9, 30 mg/m2	8♂/group	No remarkable findings on gastric motility

Table 92: Reproductive Toxicology Summary

Reproductive Toxicology								
	Study #, Title, Conducting Lab	Methods	Key Findings	Species	Doses	Mortality and Clinical Signs	Body Weight/ Food Consumption	Necropsy
Fertility and Early Embryonic Deveopment	RPR/RD/SA/ CRVA-99-246 RPR116258A: Intravenous Male Fertility Study in Rats Rhone-Poulenc Rorer	F0 males dosed daily until Day 81. Cohabited at Day 70. F0 females not treated, euthanized on GD21.	*F0 NOAEL=0.10 mg/kg *F1 NOAEL= 0.20 mg/kg *There was no obvious effect on male fertility at doses up to 0.20 mg/kg *No dedicated examination of sperm was included *Prostate weight was not included	Sprague Dawley Rat	0, 0.05, 0.1, 0.3/0.2 mg/kg/day 0, 0.3, 0.6, 1.8/1.2 mg/m^2/day	0.05 mg/kg: 1 death, accidental fracture 0.3/0.2 mg/kg: 3 deaths; 1 accidental fracture, 2 injection site lesions; 1 death at Day 18 had large coalescing bacterial colonies in the heart, liver, and kidney	0.3/0.2 mg/kg: Weight loss until dose reduction, ↓weight gain, ↓food consumption	No significant changes in weights of testis or epididymes Day 18 early death animals had pale areas in the heart, liver, and kidney; red fluid in the abdominal cavity
	RPR/RD/SA/ CRVA-00-069 RPR 116258A-Intravenous Female Fertility and Early Embryonic Developmental Toxicity Study in Rats Aventis Pharma	F0 females dosed daily for 15 days prior to cohabitation and through GD6. Euthanized on GD21.	*F0 NOAEL=0.05 mg/kg *F1 NOAEL=0.1 mg/kg *There was a dose-dependent increase in resorption at doses ≥ 0.1 mg/kg *There was no effect on fetal birth weight	Sprague Dawley Rat	0, 0.05, 0.1, 0.2 mg/kg/day 0, 0.3, 0.6, 1.2 mg/m^2/day	No mortalities	0.2 mg/kg: ↓weight gain ~30% during the dosing period, mild ↓food consumption 0.1 mg/kg: mild ↓weight gain	No significant findings

Reproductive Toxicology								
	Study #, Title, Conducting Lab	Methods	Key Findings	Species	Doses	Mortality and Clinical Signs	Body Weight/ Food Consumption	Necropsy
Embryonic Fetal Development	DS/CRVA 99-018 RPR 116258A: Intravenous Embryofetal Developmental Toxicity Study in Rats Rhone-Poulenc Rorer	Daily dosing of mated females from GD6-17; scheduled euthanasia and C-section at GD21 29♀/group	*Maternal NOAEL= 0.08 mg/kg *At the high dose level of 0.16 mg/kg there was obvious maternal toxicity including death *Increased post implantation loss was evident at the 0.16 mg/kg dose level *Fetal birth weight was decreased at dose levels ≥0.08 mg/kg for both male and female offspring *Delayed ossification and skeletal variations were observed at doses ≥ 0.08 mg/kg Abortifacient ≥0.16 mg/kg	Sprague Dawley rat	0, 0.04, 0.08, 0.16 mg/kg 0, 0.24, 0.48, 0.96 mg/m^2	0.16 mg/kg: 1 death-↓ motor activity, body weight, body temp. Anogenital staining, genital discharge, and red material in cage pan were common	0.16 mg/kg: ↓ body weight gain, mild ↓food consumption	↑ post implantation loss at early and late timepoints (including stillborn) resulting in ↓ birth rates at 0.16mg/kg *Females* 0.16 mg/kg: ↑ liquid uterine content Early death animal had a pale liver, pale skeletal muscle No other remarkable findings *F1* Dose dependent ↓ in fetal birth weight at doses ≥ 0.04 mg/kg; mild ↑ skeletal variations, incomplete ossifications

Reproductive Toxicology								
	Study #, Title, Conducting Lab	Methods	Key Findings	Species	Doses	Mortality and Clinical Signs	Body Weight/ Food Consumption	Necropsy
	RPR/RD/SA/S CRVA 99-019 RPR 116258A: Intravenous Embryofetal Developmental Toxicity Study in Rabbits Rhone-Poulenc Rorer	Daily dosing of mated females from GD6-18; scheduled euthanasia on GD28	*No maternal toxicity was noted *Fetal birth weights were unaffected *F0, F1 NOAEL > 0.03 mg/kg	Rabbit, NZW	0, 0.01, 0.02, and 0.03 mg/kg 0, 0.12, 0.24, and 0.36 mg/m2	No mortalities 0.03 mg/kg: 1 observation of red liquid in cage pan	No significant findings	No changes in pregnancy parameters *Females* No significant findings *F1* 0.03 mg/kg: ↑ incidence of membranous skull bone variation (within range of historical control data)

Reproductive Toxicology								
	Study #, Title, Conducting Lab	Methods	Key Findings	Species	Doses	Mortality and Clinical Signs	Body Weight/ Food Consumption	Necropsy
	RPR-RD-DS/CRVA 98-036 RPR 116258: Intravenous Range-Finding Toxicity Study in Pregnant Rats Rhone-Poulenc Rorer	Daily dosing of mated females from GD6-17; scheduled euthanasia on GD21	*F1 NOAEL=0.08 mg/kg *Maternal NOAEL was not established as decreased platelets were seen at the lowest administered dose *Decreased fetal birth weight was seen at doses ≥0.16 mg/kg *There was an increase in post implantation loss (mainly early) at ≥ 0.16 mg/kg *Exposure as determined by Cmax alone plateaued at the 0.16 mg/kg dose level *The highest drug exposure was .06 x the Cmax predicted for the human clinical dose	Sprague Dawley rat	0, 0.08, 0.16, and 0.25 mg/kg 0, 0.48, 0.96, 1.5 mg/m2	No mortalities Dose dependent increase in red genital discharge	Dose-dependent ↓ in weight gain, food consumption	↑ post implantation loss (early, late, dead) at doses ≥ 0.16 mg/kg Females Dose-dependent ↓ in platelets; ↓reticulocytes at 0.25 mg/kg; no other significant drug-related findings F1 Dose-dependent ↓ fetal birth weight (males and females) at ≥ 0.16 mg/kg

Reproductive Toxicology								
	Study #, Title, Conducting Lab	Methods	Key Findings	Species	Doses	Mortality and Clinical Signs	Body Weight/ Food Consumption	Necropsy
	RPR-RD-DS/CRVA 98-034 RPR 116258: 13-Day Intravenous Exploratory Toxicity Study in Female Rabbits Rhone-Poulenc Rorer	Daily dosing for 13 days in female rabbits 4♀/group	*There was significant toxicity resulting in death in all dose groups *A NOAEL was not established *Toxicity was primarily along the GI tract with anorexia and weight loss	Rabbit, NZW	0, 0.1, 0.3, and 0.6 mg/kg 0, 1.2, 3.6, and 7.2 mg/m^2	0.6 mg/kg: 100% mortality, euthanized on Day 7 0.3 mg/kg: 100% mortality, euthanized Day 8 0.1 mg/kg: 1/4 animals euthanized early (Day 10) ↓/absence of defecation was seen in all dose groups; severity and timing were dose-dependent	Weight loss and ↓ food consumption observed at all dose levels in a dose-dependent manner	GI tract findings in the stomach, jejunum, and colon included liquid content, mucosal redness, and dilation/distention White areas were seen in the high dose liver

Reproductive Toxicology								
	Study #, Title, Conducting Lab	Methods	Key Findings	Species	Doses	Mortality and Clinical Signs	Body Weight/ Food Consumption	Necropsy
	RPR-RD-DS/CRVA 98-035 RPR116258: Inravenous Range-Finding Toxicity Study in Pregnant Rabbits Rhone-Poulenc Rorer	Daily dosing in mated females from GD6-18; scheduled euthanasia on GD28 Main: 8 ♀/group Toxico: 6 ♀/group	*A NOAEL was not established for females due to decreased weight gain, food consumption, and WBC levels *A NOAEL was not established for F1 progeny due to small decreases in the fetal birth weight at all dose levels *Mortality at doses ≥ 0.04 mg/kg *The highest exposure (determined by Cmax alone) was 0.03X that predicted from the human clinical dose	Rabbit, NZW	0, 0.02, 0.04, and 0.08 mg/kg 0, 0.24, 0.48, and 0.96 mg/m^2	0.08 mg/kg: 2/8 early deaths; red spots in cecum 0.04 mg/kg 1/8 early deaths; dilation/distention of the stomach, ↓body weight/food consumption All deaths due to morbidity	↓ weight gain at all dose levels Weight loss at doses ≥ 0.04 mg/kg Dose-dependent ↓ in food consumption at all dose levels	No effect on pregnancy parameters Females No drug-related gross findings ↓ Platelets, reticulocytes, WBCs (general) and neutrophils at doses ≥ 0.04 F1 No drug-related abnormalities noted; dose-dependent decrease in fetal birth weight

12 Appendix/Attachments

ATTACHMENT #1

(Excerpted from IND 56,999 reviewed by Margaret Brower, PhD.)

DIVISION OF ONCOLOGY DRUG PRODUCTS, HFD-150
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original, Review No. 1

IND No. 56,999

Serial No: 000 **Type:** IND **Date(s) of Submission:** IND dated: Sept.30, 1998
Received by CDER: Oct. 1, 1998

Information to be Conveyed to Sponsor: Yes

Reviewer: Margaret E. Brower, Ph.D.

Date Review Completed: October 29, 1998

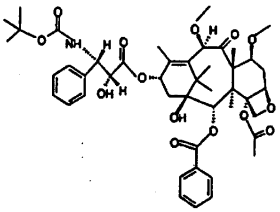
Sponsor: Rhone-Poulenc Rorer
Collegeville, PA

Drug Name: Primary: RPR 116258A Other Names: none

Chemical Name: 4-acetoxy-2α–benzoyloxy-5β,20-epoxy-1,13α–dihydroxy-7β,10β–dimethoxy-9-oxo-tax-11-ene, 13 ester with (2R, 3S)-N-tert-butyloxycarbonyl-3-phenylisoserine, acetone

CAS Number: N/A

Structure:



$.CH_3COCH_3$

Molecular Weight: 835.95

Related INDs/NDAs/DMFs: IND 35555 (Taxotere)

Class: Taxane

Indication: Brain metastases, colon cancer

Clinical Formulation: 2ml vial + (b) (4) (b) (4) consisting of:

Ingredient	Amount
RPR 116258A	40.00mg
Polysorbate 80 q.s.	(b) (4)
Solvent vial:	
(b) (4) alcohol	(b) (4)
water for injection	(b) (4) (b) (4)

Route of Administration: iv

Proposed Clinical Protocol:

Objective: To establish the MTD and recommended dose and schedule of administration of RPR 116258A, to determine qualitative and quantitative toxicity, clinical pharmacology, and antitumor activity of the drug

Dose: 10mg/m2 as 1hr infusion (escalations to 15, 20, 30, 40, 60, 80, 110mg/m2); proposed using double step increment of escalation to non-dose limiting toxicity

Frequency: q3w

Duration of clinical study: 16months

Age of patient population: between ages 18 and 70yrs

Previous Review(s), Date(s), and Reviewer(s): none

Studies reviewed in this submission:

I. Pharmacology Deferred

II. Safety Pharmacology

DS 98-026	Local intravenous, paravenous or intra-arterial tolerance study in male rabbits (Vol.10, p.227)
DS 98-025	*In vitro* compatibility and hemolytic potential with human plasma, serum and blood (Vol. 10, p.262)

III. Pharmacokinetics

DMPK/FR. 2244	Pharmacokinetics and tissue distribution study in mammary 16/C tumor bearing mice (C3H/HeN) after a single, intravenous administration of 4 0mg/kg (Vol 4, p. 65)
DMPK/FR.2242	Pharmacokinetics in dogs after a single, intravenous infusion of 0.25, 0.5, and 1mg/kg (Vol 4, p. 101)
DMPK/FR. 2238	Plasma protein binding and plasma blood cells partitioning study (Vol. 4, p.156)
DMPK/CRVA/032/98	In vitro metabolism of RPR 116258 in mouse, rat, guinea pig, rabbit, dog, monkey, and human liver microsomes (Vol 4, p. 196)

IV. Toxicology

Single dose Studies

DS 97-114	Single-dose intravenous range-finding lethality study in mice with a 2-week observation period (Vol 5, p.1)

DS 98-027	Single-dose intravenous lethality study in mice with a 4-week observation period (Vol 5, p. 42)
DS 98-030	Single-dose intravenous neurotoxicity study in mice with 2-week and 10-week observation periods (Vol 5, p. 102)
DS 98-157	Single-dose intravenous lethality study in mice with a 4- week observation period (Vol 5, p.189)
DS 98-028	Single-dose intravenous toxicity study in rats with a 4-week observation period (Vol 6, p.1)
DS 98-029	Single-dose intravenous toxicity study in dogs with an 8-wek observation period (Vol 7, p.1)
DS 97-115	Single-dose intravenous range-finding study in dogs with a 4-week observation period (Vol 7, p.177)

Multiple dose Studies

DS 97-116	5-day intravenous range-finding lethality study in mice with a 2-week observation period (Vol 7, p.236)
DS 98-031	5-day intravenous lethality study in mice with a 4-week observation period (Vol 7, p.276)
DS 98-032	5-day intravenous toxicity study in rats with a 4-week observation period (Vol 8, p.1)
DS 97-117	5-day intravenous range-finding toxicity study in dogs (Vol 9, p.378)
DS 98-033	5-day intravenous toxicity study in dogs with an 8-week observation period (Vol 10, p.1)

V. Reproductive Toxicity Deferred

VI. Genetic Toxicity

DS 98-020	Bacterial reverse mutation test (Vol 11, p.125)
DS 98-022	In vitro chromosome aberration test in cultured human peripheral blood lymphocytes (Vol 11, p. 158)
DS 98-023	Intravenous bone marrow micronucleus test in rats (Vol 11, p.199)
DS 98-156	Bacterial reverse mutation test (Vol 11, p.232)

VII. Special Toxicology none

VIII. Previous human experience RPR 116258A has not been administered clinically

Studies not reviewed:

DMPK/US-98-044	Method and validation of an automated LC/MS/MS assay for analysis of RPR 116258 and RP 56976 in rat or rabbit plasma (Vol 4, p. 228)
DS 98-034	13-day intravenous exploratory toxicity study in female rabbits (Vol 9, p.330)
DS 98-036	Intravenous range-finding toxicity study in pregnant rats (Vol. 10, p.285)
DS 98-035	Intravenous range-finding toxicity study in pregnant females (Vol 11, p.1)

Note that portions of this review were excerpted directly from the sponsor's submission.

Review

Introduction:

Taxanes are cytotoxic agents that promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization. RPR 116258 is a new taxane which differs from other taxanes in its ability to cross the blood-brain barrier and its minimal recognition with the multidrug resistance P-glycoprotein. These characteristics enable the taxane to reach lesions within the brain and to effect mdr expressing tumors.

Pharmacology

Safety Pharmacology
DS 98-026 Local intravenous, paravenous or intra-arterial tolerance study in male rabbits. Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France
in May, 1998 according to French GLP.

The study has been checked and does not influence the conclusions of the review.

DS 98-025 *In vitro* compatibility and hemolytic potential with human plasma, serum and blood. Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in April, 1998 according to French GLP.

The study has been checked and does not influence the conclusions of the review.

Pharmacokinetics

DMPK/FR. 2244 **Pharmacokinetics and tissue distribution study in mammary 16/C tumor bearing mice (C3H/HeN) after a single, intravenous administration of 40mg/kg –interim report**. Conducted by Centre de Recherche de Vitry-Alfortville, France in September, 1998. The study was not conducted according to GLP; it is currently ongoing. RPR116258 exhibits a rapid and sustained distribution into the brain. The ratio of the AUC(0-48h) of RPR116258 in tumor to plasma was 1.6, while the ratio of AUC (0-48) in brain to plasma was 10.6 (study author indicates ratio =3.7). When Tmax=0.25hr for all parameters, the ratio of tumor:plasma=44.5 and the ratio of brain:plasma=292.

Species: female C3H/HeN mice with subcutaneous mammary adenocarcinoma 16/C
Drug/dose: single iv 40mg/kg dose of RPR116258
Sample collection: blood, tumor, brain samples collected at 2, 5, 15min and 2, 4, 8, 12, 24, 48, 96, 168hr following 45second infusion
Assay: LC/MS/MS for RPR116258 and RP56976, metabolite
LOQ: 2.5ng/ml in plasma, 25ng/g in tumor and 50ng/g in brain

Tissue	Drug	Tmax (h)	Cmax(ng/ml)	AUC (0-t) (ng/ml/h)	AUC (0-inf) (ng/ml/h)	T1/2 (h)
Plasma	RPR116258	0.03	23784	23824	24113	26 (12-96hr)
	RP56976	0.25	360	865	867	1.1 (2-12hr)
Tumor	RPR116258	0.25	6232	38485	69123	47 (8-48hr)
	RP56976	2	178	2794	4593	33 (4-48)
Brain	RPR116258	0.25	3545	252743	510350	183 (12-168)

DS 98-028 Single-dose intravenous toxicity study in rats with a 4-week observation period . Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in August, 1998 according to GLP guidelines issued by the French Secretariat for Health of the Ministry of Social Affairs and National Solidarity.

Refer to toxicokinetics reviewed under above study #, section IV. Toxicology. The Cmax and AUC of RPR116258 increased more than proportionally with dose. AUC (0-6hr) tended to be higher in female rats from 2.5 to 10mg/kg.

DS 98-032 5-day intravenous toxicity study in rats with a 4-week observation period Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in August, 1998 according to OECD GLP guidelines.

Refer to toxicokinetics reviewed under above study #, section IV.Toxicology. Cmax and AUC(0-6hr) values of RPR116258 increased proportionally with dose from 0.25 to 0.5mg/kg and > proportionally from 0.5 to 1.0mg/kg/day. Cmax values were similar for males and females on days 1 and 5; AUC values generally were slightly higher for males than females. The study author indicated that plasma concentrations of RPR116258 following administration of 0.25 and 0.5mg/kg/day to rats were detectable up to 0.5hr; following administration of 1.0mg/kg/day, plasma concentrations were detectable up to 6hrs.

DMPK/FR.2242 Pharmacokinetics in dogs after a single, intravenous infusion of 0.25, 0.5, and 1mg/kg . Conducted by Centre de Recherche de Vitry-Alfortville, France in September, 1998. The study was not conducted according to GLP.

Species: male and female beagle dogs
Drug/dose: RPR116258 (batch # 611) single iv dose of 0.25, 0.5, 1mg/kg
Sample collection: 30min following initiation of infusion, 2min prior to end of infusion, and 5, 15, 30min, and 1, 2, 4 and 6hr following end of infusion
Assay: LC/MS/MS
LOQ: 2.5ng/ml

Dose (mg/kg)	Cmax (ng/ml)	AUC(0-6) (ng/ml/h)	AUC(0-inf) (ng/ml/h)	Cl (L/h/kg)	Vss (L/kg)	t1/2(h)
0.25	22.0 (17.5Γ;26.5E)	24.6 (24.2Γ; 25E)	Not determined	Not determined	Not determined	Not determined
0.5	80.9 (64.8Γ; 97E)	83.5 (79.1Γ; 87.9E)	98.2	5.2	13.7	3.7
1	261.8 (164Γ; 360E)	298 (205Γ; 391E)	323.3	3.4	6.4	3.4

The volume of distribution at steady state was > body water (0.6L/kg) suggesting rapid tissue distribution of the drug; the Vss tended to decrease with increasing dose. Cmax and AUC values increased more than proportionally with dose. As a result, total plasma clearance of RPR116258 tended to decrease with increasing dose. T1/2 were similar at MD and HD.

DS 97-117 5-day intravenous range-finding toxicity study in dogs. Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in Sept., 1997; it was not conducted according to GLP

Refer to toxicokinetics reviewed under above study #, section IV. Toxicology. The number of detectable plasma levels were insufficient to provide meaningful conclusions.

DS 98-033 5-day intravenous toxicity study in dogs with an 8-week observation period. Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in August, 1998 according to OECD GLP.

Refer to toxicokinetics reviewed under above study #, section IV. Toxicology. Maximum plasma concentrations were obtained 2 min prior to the end of infusion. There did not appear to be an effect of gender on HD animals or differences between days 1 and 5.

DMPK/FR. 2238 *In Vitro* interspecies protein binding and partitioning study between human plasma and blood cells. Conducted by Centre de Recherche de Vitry-Alfortville, France in September, 1998. The study was not conducted according to GLP.

Species: mouse, rat, rabbit, dog, monkey plasma; human blood and plasma
Drug/dose: 3H-RPR116258 (batch # 611) 0.005-10ug/ml (specific activity 2.75uCi/ug)
Assay: liquid scintillation

species	RPR116258 (ug/ml)				
	0.005	0.05	0.5	5	10
human	84.2	79.5	84.8	83.5	84.8
monkey	85.9	84.0	80.2	79.3	83.0
dog	86.3	85.1	89.2	90.0	90.8
rabbit	68.9	66.4	69.2	72.9	75.9
rat	85.1	82.6	85.5	80.9	84.6
mouse	Not determined	97.6	93.5	90.6	92.1

The extent of binding of RPR116258 to plasma proteins for various species: mouse>dog>rat>human>monkey>rabbit.

In vitro partitioning between human blood and plasma

	Concentrations of RPR116258 in ug/ml				
	0.005	0.05	0.5	5	10
Blood/plasma ratio	1.03	0.92	0.87	0.88	0.81
Blood cells/plasma ratio	0.37	0.33	0.32	0.30	0.29

The *in vitro* partitioning between blood cells and human plasma is constant between 0.005-10ug/ml RPR116258 with a low blood cell/plasma ratio, indicating a low affinity for red cells.

DMPK/CRVA/032/98 In vitro metabolism of RPR 116258 in mouse, rat, guinea pig, rabbit, dog, monkey, and human liver microsomes . *No data on study investigator, date or GLP status.*

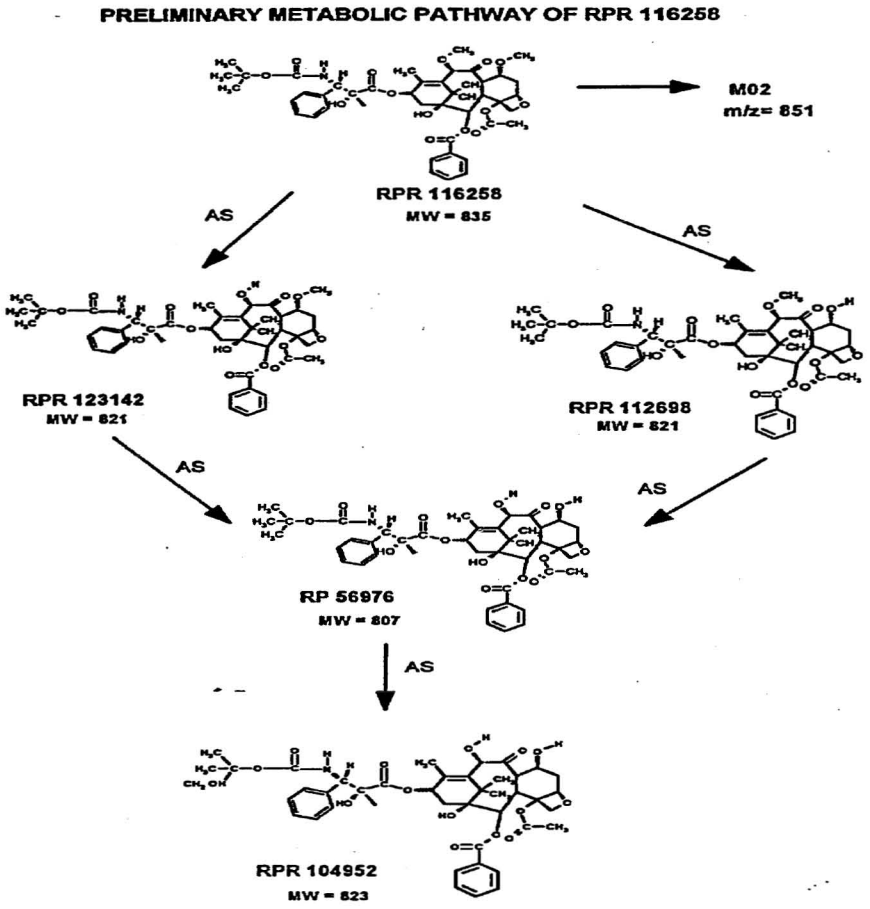
Species: mouse, rat, guinea pig, rabbit, dog, monkey and human liver microsomes
Drug /drug metabolites: RPR116258 (batch PHI13665), RPR123142 (batch LIE 843), RPR112698 (batch HEB577), RP56976(batch 14PROC92320), RPR104952 (batch BEZ5952)
Assay: HPLC

There were no significant qualitative interspecies differences in the metabolic profiles of RPR116258 in liver microsomes. Metabolism was NADPH-dependent with 3 major metabolites detected in rat, dog, monkey and

human liver microsomes (RPR123142, RPR112698 and RP56976). Two additional minor metabolites were detected (RPR104952 and MO2). Following 60m of incubation, the rate of disappearance of RPR116258 in liver microsomes was highest in dog >human>monkey>guinea pig>rabbit>mouse>rat.

Summary of Pharmacokinetics

RPR 116258 exposure increases with dose; the drug appears to distribute rapidly into tissues and crosses the blood-brain barrier. Metabolism of RPR116258 is NADPH-dependent with 3 major metabolites detected in rat, dog, monkey and human liver microsomes (RPR123142, RPR112698 and RP56976) (see metabolic pathway of RPR116258 below). The rate of disappearance of the parent drug in liver microsomes was highest in the dog followed by the human. Total plasma clearance was rapid in all species tested and tended to decrease with increasing dose in dogs. The *in vitro* plasma protein binding is approximately 83% and is higher in mouse>dog>rat> human> monkey>rabbit. The *in vitro* partitioning between blood cells and human plasma is constant between 0.005-10ug/ml RPR116258 with a low blood cell/plasma ratio of approximately 0.32, indicating a low affinity for red cells.



IV. Toxicology

Single dose studies

DS 97-114 **Single-dose intravenous range-finding lethality study in mice with a 2-week observation period.** Conducted by Rhone-Poulenc Rorer Research and Development Drug Safety, Alfortville, France in July, 1997. The study was not conducted according to GLP.

DS 98-027 **Single-dose intravenous lethality study in mice with a 4-week observation period.** Conducted by Rhone-Poulenc Rorer Research and Development Drug Safety, Alfortville, France in April, 1998 according to OECD guidelines.

DS 98-157 **Single-dose intravenous lethality study in mice with a 4- week observation period .** Conducted by Rhone-Poulenc Rorer Research and Development Drug Safety, Alfortville, France in July, 1998 according to OECD guidelines

Single Dose Toxicology Studies in Mice*					
Study# (batch # of RPR116258	#/sex/doses (mg/kg)	Lethality (sex)/Day of death	Obs. period	HNLD/ STD_{10} (mg/kg) /LD_{10}	Significant findings
97-114 (PHI3665)	5/sex/ 25, 50, 75, 100	50:3m,1f/d7,11 75:5m,5f/d6 100:5m,5f/d1,5	2wk	25/50/ between 25-50	PS control*, 100mg/kg:↓motor activity following dosing 100mg/kg: 2/10 convulsions ≥50mg/kg: absence of hindlimb extension, incoordination, loss of use of limbs,prostration, labored breathing, ↓respiration, piloerection, emaciation, anogenital staining, ↓skin elasticity, BW↓ 24% at 50mg/kg, no BW evaluation >50mg/kg due to mortality
98-027 (BFC611)	10/sex/20, 30, 40, 60	40:1m/d28 60:10m,9f/d6-8	4wk	30/30/ between 40-60	30mg/kg:absence of hindlimb extension from d13-24(4/10m), incoordination (m only), ↓size ovaries 40mg/kg:absence of hindlimb extension from d11-23(8/10m,5/10f),incoordination, ↓motor activity, ↓size ovaries 60mg/kg: incoordination, prostration, hunched back, emaciation, labored breathing, ↓skin elasticity,BW↓22% (m) ↓14%(f), ↓size thymus(f) all doses: ↓size of testes, secondary sex organs/males to study termination
98-157 (P98041ME	10/sex/20, 30,40,60	60:10m,9f/d6-8	4wk	40/60/ between 40-60	60mg/kg: impaired righting reflex d6-8 (6m, 2f), ↓motor activity, incoordination, prostration, hyporeactivity, loss of use of limbs, labored breathing, ↓skin elasticity, anogenital staining, BW↓23%(m), ↓18%(f), white discoloration of epicardium(3m,2f) 40mg/kg:anogenital staining all doses: ↓size of testes

*species: CD2F1 mice; route: iv, PS= polysorbate vehicle control

The reviewer questions the results of the repeat lethality study in mice (study #98-157). Absence of hindlimb extension was not observed at doses up to 60mg/kg even though the identical study conducted 3months earlier reported the occurrence of absence of hindlimb extension at doses of ≥30mg/kg; impaired righting reflex was observed at 60mg/kg in study #98-157 but not in study # 98-027 or at higher doses in study # 97-114.

The LD10 in mice was between 40-50mg/kg (120-150mg/m2). Absence of hindlimb extension was observed at doses ≥30mg/kg. Impaired righting reflex was observed at 60mg/kg. Incoordination and ↓motor activity were exhibited at 30 and 40mg/kg with additional signs of prostration, labored breathing and emaciation observed at 50 and 60mg/kg. Male mice were consistently more sensitive to the effects of RPR116258. ↓ in testicular size was observed at all doses.

DS 98-030 Single-dose intravenous neurotoxicity study in mice with 2-week and 10-week observation periods. Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in July, 1998 according to OECD guidelines. Administration of a single dose of RPR116258 at 45mg/kg resulted in deaths, body weight loss, peripheral neurotoxicity (exhibited as absence of hindlimb extension, incoordination, prostration and axon fragmentation and ↓motor activity) and degeneration of the sciatic nerve and lumbosacral nerve roots at 2 weeks and after 10 weeks recovery. Incidence of effects was less pronounced at 30mg/kg. As with previous studies, males appeared to be more sensitive to the effects of RPR1162578. The NOEL/HNLD was 15mg/kg.

species: CD2F1/ CrlBR mice (12/sex/dose)
drug: RPR 116258 (batch #BFC611) in polysorbate and ethanol diluted in glucose
vehicle: ~4.5%polysorbate 80 and 1.75% ethanol in 5% glucose
dosage: 15, 30, 45mg/kg followed by 2week observation for 6mice/sex/dose and 10weeks for 6mice/sex/dose; dosing volume: 25ml/kg
age; weight: 6-7wks, 20-26g (males), 17-20g (females)
route: iv

Mortality, clinical observations and body weight changes:

Dose (mg/kg/day)	Mortality	Day of Death (# dead)	Clinical observations and body weights
Polysorbate veh	0/24		Alopecia (m)
15	0/24		none
30	1/24	d34(1m)	↓motor activity, hunched back, anogenital staining, ↓skin elasticity(d33,m)
45	3/24	d9-13(3m)	Absence of hindlimb extension (d7-16, 4m), incoordination, ↓motor activity, prostration, hunched back, anogenital staining, ↓skin elasticity (d7-16, m); incoordination only (d49-50,m); incoordination, hunched back(d8-62,f); BW↓4-8%, 20-50%BW loss (d3-7, m), 12%BW loss throughout study(f)

Histopathology:

Organ/finding*	Males (mg/kg)			Females (mg/kg)		
	15	30	45	15	30	45
Sciatic nerve/degeneration and axon fragmentation		4	9		4	6
/vacuolation		3	4		3	8
Dorsal root ganglia (lumbosacral nerve root)/axon dilatation, swelling	2	6	7		3	6
/vacuolation		7	9		5	8

/degeneration, chromatolysis		1	4		5	
Brain/soft		1				
Spinal cord/soft		1				
/vacuolation						3
Kidneys/small, unilateral		1				
Adrenals/unilateral		1				

*Sciatic nerve, spinal cord and brain sections missing or distorted for multiple animals

DS 98-028 Single-dose intravenous toxicity study in rats with a 4-week observation period . Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in August, 1998 according to GLP guidelines issued by the French Secretariat for Health of the Ministry of Social Affairs and National Solidarity. Neurotoxicity was observed in polysorbate controls with enhanced neurotoxicity observed in 5.0mg/kg RPR116258-dosed rats. Lethality was observed at —5mg/kg; there were no clinical signs of neurotoxicity at this dose.

species: Crl:CD(SD)BR rats 10/sex/dose, main study; 8/sex/dose, toxicokinetic study
drug: RPR 116258 (batch #BFC611) in polysorbate and ethanol diluted in glucose
vehicle: 5%polysorbate 80 and 1.9% ethanol in 5% glucose
dosage: 2.5, 5, 10mg/kg; dosing volume 5ml/kg
age; weight:6-7weeks; 185-216g (males), 148-179g (females)
route: iv
recovery period: 5/sex/dose: 3-4days; 5/sex/dose: 4weeks

Observations

Mortality and clinical observations	daily (day of dosing: predosing, following dosing, 1 and 4hr following dosing)
Body weight	pretest, d2, 7, 13, 19, 26
Food consumption	weekly
Hematology, clinical chemistry	d3, 8, 14, 20, 27
Urinalysis	d14, 27
Toxicokinetics	blood samples for plasma concentrations collected from 4rats/sex/dose/time point at 2, 30min, 2 and 6hr following infusion
Organ weights	at necropsy
Gross pathology	d3-4 or 28-29
Histopathology	d3-4 or 28-29

Mortality, clinical observations and body weight:

Dose* (mg/kg)	Sex	Mortality and Day of Death	Observations
2.5	M		11% BW loss wk1; 7-9% loss by wk4 28% FC reduction wk1; recovery by wk4
	F		12% FC reduction wk1; recovery by wk4
5	M		alopecia 18% BW loss wk1; 11% loss by wk4 40% FC reduction wk1; recovery by wk4
	F	1/10 (d8)	alopecia; unkempt coat, staining around muzzle 9% BW loss wk1; 7% loss by wk4 40% FC reduction wk1; recovery by wk4
10	M		alopecia 20% BW loss by wk1; 23% loss by wk4 50% FC reduction wk 1; 31% loss by wk4

	F	2/10 (d8)	alopecia; chromodacryorrhea 15% BW loss by wk1; 8% loss by wk4 44% FC l reduction wk1; 13% loss by wk4

*n=10/sex/dose

Body weight loss was dose related in all dosed males and MD and HD females; BW loss remained depressed >10% throughout the recovery period in MD and HD males. Reduction in food consumption was also dose related and remained depressed throughout the recovery period in HD animals.

Hematology:

Hematological indices in males: % difference from controls

Dose	RBC		Hemoglobin		Hematocrit		Reticulocytes		Platelets		WBC	
	D3	D8	D3	D8	D3	D8	D3	D8	D3	D8	D3	D8
2.5	-	↓17	-	↓17	-	↓16	↓70	↓28	↓32	↓13	↓40	↓9
5	-	↓25	-	↓27	-	↓30	↓76	↓99	↓30	↓51	↓47	↓27
10	-	↓30	-	↓29	-	↓31	↓88	↓99	↓47	↓63	↓53	↓32

- = insignificant change

Hematological indices in females: % difference from controls

Dose	RBC		hgb		hct		Reticulocytes		Platelets		WBC	
	D3	D8	D3	D8	D3	D8	D3	D8	D3	D8	D3	D8
2.5	-	↓12	-	↓13	-	↓8	↓62	↓39	↓30	-	↓20	-
5	-	↓25	-	↓31	-	↓30	↓82	↓99	↓48	↓46	↓36	↓45
10	-	↓25	-	↓34	-	↓35	↓83	↓99	↓49	↓63	↓47	↓56

Dose related reduction in reticulocytes, thrombocytes, and WBC were observed in all dosed animals on days 3 and 8 following dosing with RPR116258. RBC parameters were depressed on day 8 in a dose related manner. Recovery of red cell parameters (including reticulocytes) was observed to day 27. Reticulocytes remained ↓35% in HD animals. WBC remained ↓24 –35% at the MD and HD dose following recovery. Platelets remained ↓21-24% in males at all doses following recovery.

Clinical chemistry:

Glucose was ↑ from 37-59% in MD and HD animals on days 3 and 8 when compared to concurrent controls. Other changes [↑ASAT (23-38%, d3) ↓ALP (21-49%, d3,8), ↓triglycerides (25-48%, d3,8) and ↑ urea (35-51%] were considered by the study authors to be a result of depressed food consumption.

Urinalysis: Not remarkable

Toxicokinetics:

Dose (mg/kg)	Sex	Cmax* (ng/ml)	AUC (0-6hr)* (h.ng/ml)
2.5	M	579	218
	F	717	279
5	M	2275	860
	F	2073	1107
10	M	5238	3096
	F	6483	4233

*Tmax=2min; N=8/sex/dose

The Cmax and AUC of RPR116258 increased more than proportionally with dose. AUC (0-6hr) tended to be higher in female rats from 2.5 to 10mg/kg.

Organ weights:

Thymic weights were ↓ in all dosed animals (males:LD –20%, MD-52%, HD-52%; females: LD-17%, MD-55%, HD-56%) compared to concurrent controls following dosing at day 3 and in males following recovery at day 28 (LD-6%, MD-15%, HD-31%). This finding correlates with the histopathological observation of thymic atrophy in these animals. Depressed thymic weights following recovery may be a reflection of depressed body weights. Splenic weights of MD and HD males were ↓16% at day 3 and ↑11 and 26%, respectively, following recovery. In addition, kidney and liver weights of MD and HD males were ↓up to 17% and adrenal weights of HD males were ↓23% following recovery.

Gross pathology:

Small thymus: MD male (1/5) and female (1/5), HD female (1/5)
Small seminal vesicles: LD (1/5) and HD (2/5)

Histopathology:

Ellipsoids (characterized by disorganized fibers containing broken myelin and/or nucleus of Schwann cell) and spheroids (characterized by focal axonal dilatation) were observed in the sciatic nerves as follows:

Day	Males at mg/kg*				Females at mg/kg*			
	0	2.5	5	10	0	2.5	5	10
3	0	0	0	1	0	1	1	0
28	1	1	1	2	0	0	2/4	2/3

*N=5 with exception of MD and HD E as indicated above

Even though ellipsoids and spheroids were observed in 1/5 control males (or 1/10 combined incidence) following recovery, the incidence in surviving mid- and high-dose animals was significant (combined incidence of 3/9MD and 4/8HD animals), indicating neurotoxicity with polysorbate and enhanced neurotoxicity with doses between 2.5-5.0mg/kg RPR116258 *(This is not the opinion of the sponsor as indicated in the study discussion).*

Organ/finding*	Males at mg/kg				Females at mg/kg			
	0	2.5	5	10	0	2.5	5	10
Thymus/↑lymphocytolysis	0	5	5	5	0	5	5	4
/cortical atrophy	0	0	5	5	0	1	5	5
Spleen/↑lymphocytolysis	0	0	1	3	0	0	0	3
Bone marrow/↓myelopoiesis	0	5	5	5	0	4	5	5
Testis/spermatid necrosis	0	-**	0	5				
Epididymides/epithelial necrosis/ regeneration	0	-	0	5				
Seminal vesicles/epithelial necrosis/ regeneration	0	1/4	5	5				
Ileum/villus fusion and atrophy	0	0/4	1/4	3	0	0	3	3
/crypt regeneration	0	0/4	2/4	2	0	0	3	2
Cecum/single cell necrosis	0	0	0	1	0	0	0	3
/crypt degeneration /regeneration	0	0	1	2	0	0	2	2
Liver/↑# mitotic figures	0	-	0	1	0	-	0	2
Lungs/metaplasia	0	0	0	1	0	0	0	0
Adrenals/↑# mitotic figures	0	0	4	3	0	0	2	3

*Findings on day 3; N=5/sex/dose except where indicated
**No data available

DS 98-029 Single-dose intravenous toxicity study in dogs with an 8-week observation period (Vol 7, p.1) Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville France in August, 1998 according to French GLP. RPR116258 was lethal following a single dose of 20mg/m^2; hyporeactivity and ↓motor activity, hepatocellular atrophy and necrosis, depletion of the germinal centers of the lymph nodes, and degeneration of organs of the GI tract and epididymides were observed at this dose. Edema of the face, ears and legs, and erythema of the ears and face were observed at all doses.

species: Beagle dogs (2 dogs/sex/group)
drug: RPR116258 in polysorbate and ethanol (batch # BFC611); 40mg/ml stock solution batch # GRV1236P
vehicle: 0.21% polysorbate 80 in 5% glucose
dosage: 0.25, 0.5, 1.0 mg/kg/day (5, 10, 20mg/m2), dosing volume 12ml/kg/day
age; weight: 9-10months; 9-11kg(males) and 8-11(kg) females
route: iv
duration of observation: 8 weeks

Observations

Mortality and clinical observations	daily
Body weights	pretest, day 1, 3, 7, 14, 20, 28, 35, 42, 49, 56
Food consumption	daily
Hematology and clinical chemistry	pretest, day 3, 8, 15, 21, 29, 59
Urinalysis	pretest, day 15, 29, 59
Organ weights	at necropsy
Gross pathology	day 5, day 56
Histopathology	day 5, day 56

Toxicokinetics 30min following initiation of infusion, 2min prior to end of infusion, and 5, 15, 30 min and 1, 2, 4, 6hr following infusion

Mortality, clinical observations and body weight:

Dose (mg/kg/day)	Mortality	Day of Death (# dead)	Clinical observations and body weights
Polysorbate veh	0/4		Soft feces, edema of face, legs, erythema of ears
0.25	0/4		Emesis, edema of face, ears, legs, erythema of ears, face, ↓defecation
0.50	0/4		Edema of face, ears, erythema of ears, face, emesis, ↓defecation, soft feces, red colored feces, BW↓up to 7% d7
1.0	4/4	5 (2Γ, 2E)	Hyporeactivity (E), emesis, edema of face, ears, legs, erythema of ears, face, emesis, soft feces, red colored feces, salivation, ↓motor activity (E), anogenital staining, BW↓6% d3 compared to pretest

Toxicokinetics: These data were included in the submission as a separate Pharmacokinetics study; therefore, these data are reviewed in III. Pharmacokinetics.

Urinalysis: not remarkable

Organ weights: not remarkable

Gross pathology:
GI tract: mucosal redness, black and /or red spots, serosal redness : HD
Heart: red spots: HD
Lymph nodes: red spots: HD

Histopathology:

Organ/finding	Males at mg/kg*				Females at mg/kg*			
	0	0.25	0.5	1.0	0	0.25	0.5	1.0
Adrenals/vacuolation	0	0	1	0	0	2	2	0
Colon/hyperplasia	0	0	0	0	0	0	0	1
/congestion, degeneration	0	0	0	1	0	0	0	2
Cecum/degeneration	0	0	0	0	0	0	0	2
Epididymides/necrosis	0	0	0	2				
Ileum/atrophy, degeneration	0	0	0	0	0	0	0	2
/hyperplasia	0	0	0	0	0	0	0	1
Kidneys/atrophy	0	0	1	0	0	0	0	0
/chronic inflammation	0	1	0	0	0	0	0	0
Liver/atrophy	0	1	0	2	0	0	0	2
/necrosis, individual hepatocellular	0	0	0	2	0	0	0	1
/hyperplasia, bile duct	0	0	1	0	0	0	0	2
Mesenteric and retropharyngeal lymph node/depletion of germinal centers, congestion	0	0	0	2	0	0	0	2
Stomach/necrosis, hemorrhage	0	0	0	0		0	0	2
Testes/degeneration	0	0	0					

*N=2dogs/sex/dose

DS 97-115 Single-dose intravenous range-finding study in dogs with a 4-week observation period. Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in September, 1997. The study was not conducted according to GLP. Lethality and signs of neurotoxicity were observed at doses —30mg/m^2 ; hepatocellular atrophy and necrosis were observed histologically. ↓motor activity and signs of erythema and edema were exhibited at 10mg/m^2.

species: Beagle dogs (1 dog/sex/group)
drug: RPR116258 in polysorbate and ethanol (batch 3665) 40mg/ml stock solution batch # TT11232
vehicle: 0.5% polysorbate 80 in 5% glucose
dosage: 0.5, 1.5, 2.5 mg/kg/day (10, 30, 50/m2), dosing volume 12ml/kg/day
age; weight: 8-10months; 10-12kg(males) and 7-9 (kg) females
route: iv
duration of observation: 4weeks

Observations

Mortality and clinical observations	daily
Body weights	pretest, day 3, 8, 14, 21, 28

Food consumption	daily
Hematology and clinical chemistry	pretest, day 3, 8, 15, 28
Organ weights	at necropsy
Gross pathology	at necropsy
Histopathology	at necropsy

Mortality and clinical observations:

Dose (mg/kg/day)	Mortality	Day of Death (# dead)	Clinical observations and body weights
Polysorbate veh	0/2		Agitation, ↓motor activity, focal swelling, erythema, salivation, ↓defecation
0.5	0/2		Agitation, ↓motor activity, focal swelling, erythema, soft feces, salivation, yellow colored feces, ↓defecation
1.5	2/2	4(1Γ, 1E)	Agitation, ↓motor activity, focal swelling, erythema, salivation, yellow colored feces, BW loss up to 11% compared to pretest
2.5	2/2	3(1E), 4(1Γ)	Agitation, absence of motor activity, prostration, hyporeactivity, hypothermic, labored breathing, focal swelling, erythema, salivation, red /yellow colored feces, BW loss up to 11% compared to pretest*

*Dose-related BW loss with depression in food consumption
Organ weights: Animals/tissues too few in number to be relevant
Gross pathology:
Stomach: red, distended: MD, HD
Thymus: red: MD, HD
GI tract: mucosal redness: MD, HD
Heart: mass: HD Γ

Histopathology:

The liver was the only organ with noted histopathological findings.

Liver findings	Males at mg/kg*				Females at mg/kg			
	0	0.5	1.5	2.5	0	0.5	1.5	2.5
Necrosis	0	0	0	0	0	0	0	1
Atrophy	0	0	1	1	0	0	1	1
Sinusoidal congestion	0	0	1	1	0	0	1	1

*N=1

Multiple dose Studies

DS 97-116 5-day intravenous range-finding lethality study in mice with a 2-week observation period. Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in August, 1997. The study was not conducted according to GLP. Mortality was observed at all dose levels (—15mg/m^2). Signs of neurotoxicity (including absence of hindlimb extension) was observed at doses —30mg/m^2 .

species: CD2F1 mice (5/sex/dose)
drug: RPR 116258 (batch # PHI 3665)
vehicle: polysorbate 80 in 5% glucose
dosage: 5, 7.5, 10, 12.5mg/kg/day for 5days followed by 2week observation dosing
volume: 25ml/kg/day
age; weight: 6-7wks, 23-26g (males), 18-22 (females)

route: iv

Mortality, clinical observations and body weight:

Dose (mg/kg/day)	Mortality	Day of Death (# dead)	Clinical observations and body weights
Polysorbate veh	0/10		none
5	2/10 (1male, 1female)	9 (2)	Piloerection, hunched back, emaciation, BW loss 9-25% from day 5-14(maximal loss day 8) compared to control weights
7.5	10/10*	2 (1), 7(4), 8 (3), 9(1), 11(1)	Hunched back, anogenital staining, piloerection , emaciation, closed eyelids, no feces or soft feces, prostration, BW loss 10% day 5*
10	10/10*	7(8), 8(1), 9(1)	Absence of hindlimb extension, incoordination, hunched back, emaciation, piloerection, decreased motor activity, no feces, BW loss 11% day 5*
12.5	10/10*	6(1), 7(4), 8(4), 9(1)	Absence of hindlimb extension, incoordination, hunched back, emaciation, piloerection, decreased motor activity, closed eyelids, no feces, BW loss 13% day 5*

*BW measured day 5 only due to mortality
Mortality: 5 males, 5females

Body weight loss in males suggested slightly increased sensitivity to the effects of RPR 116258. There was no listing for gross pathology; the discussion indicated that no compound-related macroscopic findings were observed.

DS 98-031 5-day intravenous lethality study in mice with a 4-week observation period. Conducted by Rhone-Poulenc Rorer Research and Development Alfortville, France in 1998 according to OECD guidelines. The HNLD, STD10 and NOAEL for neurotoxicity was 3mg/kg/day (9mg/m2/day) for both sexes. Fragmentation and vacuolation of the sciatic nerve was observed at 5 (15mg/m2) and 7 (21mg/m2) mg/kg/day.

species: CD2F1/CrlBR mice
drug: RPR 116258 (batch # BFC611) in polysorbate 80 and ethanol
vehicle: 0.7% polysorbate and 0.27% ethanol diluted in 5% glucose
dosage: 1, 3, 5, 7 mg/kg/day for 5 days; 4-wk observation period
age; weight: 6-7wks; 21-25g (males), 17-21g (females)
route: iv

Observations

Mortality and clinical observations daily
Body weights pretest, study days 5, 8, 14, 21, 28, 33
Gross and histopathology following observation period

Mortality and clinical observations:

Dose (mg/kg/day)	Mortality	Day of Death (# dead)	Clinical observations and body weights
Polysorbate veh	0/20		none
1	0/20		none
3	0/20		Decreased defecation, anogenital staining, unkempt coat, scabs at injection site
5	7/20 (5males,	8(2), 9(2), 10(1), 12(1), 15(1)	Decreased defecation, unkempt coat, reduced skin elasticity, hunched back, anogenital staining, reduced

	2females		motor activity, incoordination
7	12/20 (9males, 3females	7(3), 8(4), 9(4), 10(1)	Convulsions, incoordination, hunched back, reduced skin elasticity, labored breathing, reduced motor activity, closed eyelids, decreased defecation, unkempt coat, anogenital staining, hunched back, hypothermic, alopecia

Percent changes in body weights compared to controls:

Dose	Males						Females					
mg/kg/day	D5	D8	D14	D21	D28	D33	D5	D8	D14	D21	D28	D33
1	-1.3	-2.5	-2.0	-2.4	-1.6	-2.2	0	0.5	1.0	3.1	-1.0	0
3	-6.3	-13.1	-5.2	-2.4	-0.8	0	-6.4	-16	-1.0	2.1	1.0	1.0
5	-11.8	-25.8	-16.9	-6.8	-0.8	-0.4	-9.1	-22.5	-11.3	-2.1	0	1.9
7	-11.8	-24.6	-11.6	-1.6	-0.8	-0.4	-11.2	-26.7	-14.3	-1.6	1.9	3.8

Males were, in general, more sensitive to the effects of RPR116258. The only exception appeared to be lower body weights observed on days 8 and 14 in females administered 7mg/kg/day RPR116258. Body weight loss was most significant on study day 8 for males and females. Surviving animals began recovery of body weights on day 14.

Gross and microscopic pathology

Macroscopic observations:

Thymus—reduced size [males at 5mg/kg (3/5) and 7mg/kg (4/9)] and females [7mg/kg (2/3)

Heart—epicardial mineralization [polysorbate-treated and RPR116258-treated animals]

Kidneys—cystic enlargement [polysorbate-treated and RPR116258-treated females]

Microscopic observations *(Microscopic examination of sciatic nerve only in animals administered 1 and 3mg/kg RPR11625)*:

Sciatic nerve—focal or multifocal periaxonal vacuolation [males (3/5) and females (2/7) at 5mg/kg and males (1/1) and females (5/7) at 7mg/kg

Sciatic nerve—axonal fragmentation [females at 5mg/kg(2/7) and males (1/1) and females (4/7) at 7mg/kg

DS 98-032 5-day intravenous toxicity study in rats with a 4-week observation period

Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in August, 1998 according to OECD GLP guidelines. The HNLD=0.50mg/kg(3mg/m^2). An NOEL could not be established due to depressed reticulocytes, platelets and lymphocytes, lymphoid depletion and liver and seminal vesicle necrosis at 0.25mg/kg (1.5mg/m^2), the lowest dose tested. Transient body weight loss associated with ↓food consumption, ↓RBC, WBC, reticulocytes and platelets following dosing, ↓thymic weights and bone marrow depletion, thymic hemorrhage, and lymphoid and seminal vesicle atrophy were observed at 3mg/m^2 . In addition, degeneration of the GI tract and necrosis of the pancreas was observed at 1mg/kg (6mg/m^2).

species: Sprague Dawley Crl:CD (SD)BR rats (15rats/sex/dose main study; 4 rats/group/time point for pharmacokinetics)
drug: RPR116258 in polysorbate and ethanol (batch # BFC611; stock soln batch # GRV1233)
vehicle: 0.5% polysorbate 80 and 0.19% ethanol
dosage: 0.25, 0.5, 1mg/kg/day, dosing volume 5ml/kg
age; weight: 6-7wks; 218-271g (males) 174-236g (females)
route: iv
duration: 5 days of dosing; 5 rats/sex/dose sacrificed 3days following final dosing; 10 rats/sex/dose sacrificed 4weeks following final dosing

Observations

Mortality and clinical observations	daily
Body weights	pretest, days 7, 14, 20, 27, 32
Food consumption	weekly
Hematology and clinical chemistry	days 8, 15, 21, 28
Urinalysis	days 15, 28
Organ weights	at necropsy
Gross pathology	day 8, day 33/35
Histopathology	day 8, day 33/35
Toxicokinetics	Days 1 and 5 at 2min and 0.5, 2 and 6hrs following infusion

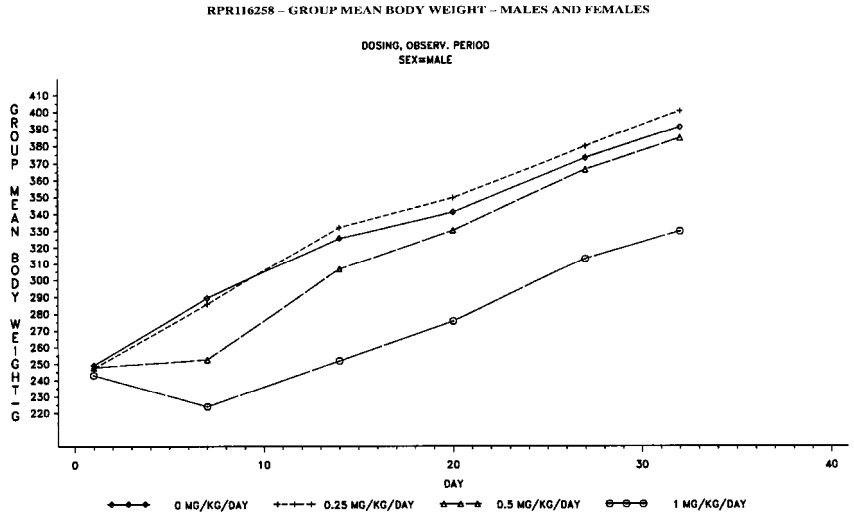
Mortality

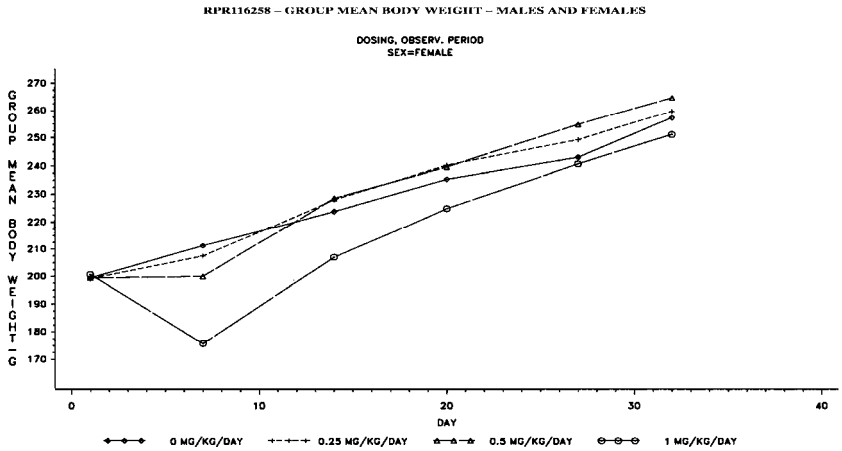
Mortality and clinical observations:

Dose (mg/kg/day)	Mortality	Day of Death (# dead)	Clinical observations and body weights
Polysorbate veh	0/15		Alopecia, soft feces, anogenital staining, chromodacryorrhea
0.25	0/15		Chromodacryorrhea, staining @ muzzle, alopecia
0.50	0/15		Decreased defecation, eye opacity, protruding eye, scabbing, skin lesion, staining @ muzzle, alopecia, small eye
1.0	1/15 (1male)	12	Decreased defecation, alopecia, reduced skin elasticity, unkempt coat, staining @ muzzle, chromodacryorrhea, emaciation, scabbing, focal swelling, mass/neck (diagnosed as abscess in 1female)

Body weight and food consumption:

Body weights of males and females administered HD RPR116258 were 22.5 and 16.6%, respectively, below control weights on study day 7. Female weights recovered to within 8% of contol weights by day 14, whereas, male weights remained 15-16% below control weights throughout the study. Weights of MD males were similarly lower than those of females. Food consumption changes were consistent with changes in body weights with up to 50% loss in HD males and females on study day 7.





Food consumption

Dose (mg/kg/d)	Males at day				Females at day			
	7	14	20	32	7	14	20	32
0.25	- 7.4	0.3	-1.2	1.9	- 5.1	7.1	6.2	3.9
0.5	-30.5	-10.3	2.0	3.5	-19.2	10.7	6.7	5.9
1.0	-50.2	-40.8	-8.2	-5.4	-49.0	- 8.7	9.2	1.5

↓in food consumption was dose related to day 14. Males were more sensitive to the effects of RPR116258 and food consumption remained depressed in HD males throughout the recovery period.

Toxicokinetics:

Dose (mg/kg/day)	Sex*	Day 1			Day 5		
		Cmax (ng/ml)	AUC (h ng/ml)	Tmax (min)	Cmax (ng/ml)	AUC (h.ng/ml)	Tmax (min)
0.25	M	25.1	11.8	2	30.4	15.4	2
	F	25.1	9.10	2	22.4	8.3	2
0.5	M	38.7	28.2	2	44.2	24.2	2

	F	42.6	15.6	2	35.0	14.4	2
1.0	M	140	78.2	2	149	79.4	2
	F	164	63.4	2	185	86.5	2

*N=4

Cmax and AUC(0-6hr) values of RPR116258 increased proportionally with dose from 0.25 to 0.5mg/kg and > proportionally from 0.5 to 1.0mg/kg/day. Cmax values were similar for males and females on days 1 and 5; AUC values generally were slightly higher for males than females. The study author indicated that plasma concentrations of RPR116258 following administration of 0.25 and 0.5mg/kg/day to rats were detectable up to 0.5hr; following administration of 1.0mg/kg/day, plasma concentrations were detectable up to 6hrs.

Gross pathology:
Thymus: small: HD
Seminal vesicles: small: MD, HD

Histopathology:

Organ/finding	Male at mg/kg*				Female at mg/kg*			
	0	.25	.5	1.0	0	.25	.5	1.0
Thymus/lymphoid atrophy	0	0	0	5	0	0	0	4
/hemorrhage	0	1	2	0	1	0	0	0
Sternum/marrow/ marrow depletion	0	0	2	5	0	0	1	5
Femur/marrow/marrow depletion	0	0	5	5	0	0	5	5
Seminal vesicles/atrophy	0	0	1	4				
/necrosis	0	2	5	4				
Liver/necrosis	0	1	0	0	0	0	0	0
/bile duct hyperplasia	0	0	1	0	0	0	0	0
/hematopoiesis	1	0	3	1	1	3	0	0
Pancreas/necrosis	0	0	0	1				
Stomach/duodenum/jejunum/cecum/ degeneration, regeneration	0	0	0	5	0	0	0	5
Ileum/degeneration, regeneration	0	0	0	4	0	0	0	3
Rectum/degeneration, regeneration	0	0	0	3	0	0	0	3
Colon/degeneration, regeneration	0	0	0	1	0	0	0	1
Spleen/hematopoiesis	5	5	5	0	5	0	5	0
Mesenteric lymph node/absence of germinal centers	5	0	5	0	5	0	5	0
Submandibular lymph node/absence of germinal centers	3	4	2	0	4	0	5	0

*N=5/sex/dose/interim sacrifice

Many histopathological findings were reversible by the end of the recovery period. Lymphoid atrophy was observed following recovery at the HD.

DS 97-117 5-day intravenous range-finding toxicity study in dogs. Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in Sept., 1997; it was not conducted according to GLP. Mortality, neurotoxicity and hepatocellular necrosis and atrophy were observed at doses —4mg/m^2 RPR116258.

species: Beagle dogs (1dog/sex/group)

drug: RPR116258 in polysorbate and ethanol (batch # PHI 3665); 40mg/ml stock solution batch # TT11232
vehicle: 0.06% polysorbate 80 in 5% glucose
dosage: 0.1, 0.2, 0.3 mg/kg/day (2, 4, 6mg/m^2), dosing volume 12ml/kg/day
age; weight: 8-10 months; 10-13kg (males) and 8-10(kg) females
route: iv
duration: 5 days of dosing; 4 weeks observation

Observations

Mortality and clinical observations	daily
Body weights	pretest, 6, 9, 14, 21, 28
Food consumption	daily
Hematology and clinical chemistry	pretest, days 8, 15, 28
Organ weights	at necropsy
Gross pathology	day 8, day 33/35
Histopathology	day 8, day 33/35
Toxicokinetics	Days 1 and 5 at 2min and 0.5, 2 and 6hrs following infusion

Mortality and clinical observations, body weight, food consumption:

Dose (mg/kg/day)	Mortality	Day of Death (# dead)	Observations
Polysorbate veh			Agitation, focal edema/erythema, emesis, tremors, yellow colored feces, salivation, soft feces
0.1			Agitation, focal edema/erythema, emesis, soft feces, ↓defecation, salivation
0.2	2/2	7 (1Γ, 1E)	Soft feces, focal edema/erythema, soft feces, no feces, prostration, ↓motor activity, red colored feces, salivation, BW loss 10-16% compared to pretest throughout study with associated ↓FC
0.3	2/2	5(1Γ), 6 (1F)	Agitation, ↓motor activity, prostration, focal edema/erythema, salivation, yellow colored feces, soft feces, emesis, labored breathing, red colored feces, BW loss 10-16% compared to pretest throughout study with associated ↓FC

Toxicokinetics:

The number of detectable plasma levels were insufficient to provide meaningful conclusions. However, the study author provided the following conclusions:
Plasma levels were not detectable within 30 min of infusion in all dosed animals. After 5 days of repeat dosing, plasma levels were lower following infusion as compared to day 1.

Organ weights: Not relevant as a result of insufficient number of organ weights

Gross pathology:
GI tract: mucosal redness: MD, HD
Thymus: red: MD, HD
Uterus: discoloration: MD
Spleen: mineralized: HD
Lungs: depressed area, red: LD

Histopathology:
Histopathological data were submitted for liver only:
Necrosis (arteriolar/periarteriolar):MD, HD
Necrosis (individual cell): MD, HD
Hyperplasia/bile duct: MD, HD
Atrophy: MD, HD
Congestion: MD, HD

DS 98-033 5-day intravenous toxicity study in dogs with an 8-week observation period. Conducted by Rhone-Poulenc Rorer Research and Development, Alfortville, France in August, 1998 according to OECD GLP. *Summary data were not tabulated.* Platelet counts were depressed in all dosed animals following dosing. Hyperplasia of the gastrointestinal tract was observed in LD and HD animals following dosing and HD females following recovery. Inflammation and necrosis of the stomach was exhibited in HD animals following dosing and recovery. Degeneration of the testes in HD males corresponded to depressed testicular weights.

species: Beagle dogs (4 dogs/sex/group)
drug: RPR116258 in polysorbate and ethanol (batch #BFC 611); 40mg/ml stock solution batch # GRV1233 diluted in 13% ethanol
vehicle: polysorbate 80 in 5% glucose
dosage: .025, 0.05, 0.1mg/kg/day (.5, 1, 2mg/m2), dosing volume 12ml/kg/day
age; weight: 9-10months; 7-10kg (males) and 6-9(kg) females
route: iv
duration: 5 days of dosing; 8 weeks observation

Observations

Mortality and clinical observations	daily
Body weights	weekly
Food consumption	daily
Hematology and clinical chemistry	pretest, days 8, 15, 21, 28, 58
Urinalysis	pretest, days 15, 28, 58
Organ weights	at necropsy
Gross pathology	day 8/9, 8weeks
Histopathology	day 8/9, 8weeks

Toxicokinetics days 1 and 5 at 30m following initiation of infusion, 2m prior to end of infusion and 15m, 1h and 2h following infusion

Mortality and clinical observations:
There were no deaths during the study. Salivation and edema and erythema of face, ears and legs of polysorbate vehicle and RPR116258-dosed animals were observed to day 6; these observations were not unexpected since the drug is known to release histamines in dogs. Soft red-colored feces were observed in ¼ HD males.

Body weight and food consumption: unremarkable

Toxicokinetics:

Dose (mg/kg/day)	Sex*	Day 1		Day 5	
		Cmax (ng/ml)	AUC 0-2h (h.ng/ml)	Cmax (ng/ml)	AUC 0-2h (h ng/ml)

0.025	M	BLQ	NA	BLQ	NA
	F	BLQ	NA	BLQ	NA
0.05	M	BLQ	NA	BLQ	NA
	F	BLQ	NA	BLQ	NA
0.1	M	4.6	5.46	5.45	7.36
	F	5.95	6.15	5.92	7.83

*N=4

BLQ= below the limit of quantitation; NA= not available; LOQ 2.5ng/ml

Maximum plasma concentrations were obtained 2min prior to the end of infusion. There did not appear to be an effect of gender on HD animals or differences between days 1 and 5.

Hematology:

Platelet counts of all dosed animals were depressed (up to 51% of concurrent control values) on day 8 with partial recovery by day 15.

Clinical chemistry and urinalysis: unremarkable

Organ weights:

Testicular weights of HD males were depressed 20-30% at interim sacrifice only. Kidney weights were increased by 25% in HD males and females at interim sacrifice; liver weights were increased by 28% in HD females only at this time. Weights were similar to controls following the observation period. Individual variation in splenic and thymic weights was attributed to efficiency of technique (i.e. trimming of organs, exsanguination).

Gross pathology: unremarkable

Histopathology:

Tissue/finding	Males				Females			
	Cont	.025	.050	0.1	Veh	.025	.050	0.1
Brain/extramedullary hematopoiesis			F/1	I/1* F/1	I/1		I/1	
Stomach/acute inflammation, single-cell necrosis				I/1 F/1				I/1
Ileum/crypt hyperplasia		I/1						F/1
/congestion		I/1	I/1					F/1
Cecum/regenerative hyperplasia				I/1				I/1
/necrosis				I/1				
/congestion			I/1					
Colon/congestion			I/1 F/1	I/1	F/2			I/1 F/1
Rectum/regenerative hyperplasia				I/1				I/1
/mucosal atrophy and congestion	F/1			I/1				
Liver/acute inflammation				F/1	I/1	F/1		I/1
/necrosis						F/1		
Lungs/granuloma			F/1	F/1				
Duodenum/congestion			I/1					
Jejunum/congestion		I/1	I/1				I/1	
/crypt hyperplasia								F/1
Urinary bladder/degeneration						F/1		F/1
Testes/degeneration				F/1				

*Time of sacrifice (I=interim, F=final)/incidence
N=2/dose/sex

Hyperplasia of the ileum, cecum and rectum and necrosis of the cecum were observed in LD and HD males and HD females following dosing; hyperplasia of the jejunum was exhibited in HD females at final sacrifice following recovery. *Study authors indicate that gastrointestinal changes were not observed in recovery animals.* Congestion of the ileum, cecum, colon, and rectum was observed sporadically at all dose levels in males and in HD females. Inflammation and necrosis of the stomach of HD males and females following dosing and recovery was indicated by the study author to have been a result of spontaneous inflammatory disease. Degeneration of the testes in HD males corresponded to depressed testicular weights. Acute inflammation of the liver was exhibited in HD males and control, LD and HD females; this finding was observed following dosing and recovery.

Summary of Toxicology:

Single dose studies were conducted in mice, rats and dogs. The LD10 in mice was between 120-150mg/m^2. Signs of peripheral neurotoxicity, including absence of hindlimb extension, incoordination, ↓motor activity and prostration were observed at iv doses —90mg/m^2 RPR116258. Microscopically, degeneration and vacuolation of the sciatic nerve and degeneration, vacuolation, dilatation and swelling of the lumbosacral nerve root, and axon fragmentation were observed at this same dose, with lumbosacral nerve root dilitation and swelling also observed at 45mg/m^2 in mice. Males appeared to be more sensitive to the effects of RPR116258 in mice. Lethality was observed following a single iv dose of 30mg/m^2 (LD10) in rats; enhanced peripheral neurotoxicity (presence of ellipsoids and spheroids) was observed microscopically at this dose. Lymphoid atrophy, ↓myelopoiesis of the bone marrow and depressed hematological parameters were observed at doses —15mg/m^2. RPR116258 was lethal (4/4) in dogs following a single dose of 20mg/m^2; major findings included signs of peripheral neurotoxicity, hepatic and lymphoid atrophy and degeneration of the GI tract. Female dogs appeared to be more sensitive to RPR116258. Polysorbate-treated dogs exhibited edema and erythema of the head and legs, agitation and ↓motor acitivity; these findings were enhanced by the effects of RPR116258.

Five-day studies were conducted in mice, rats and dogs. Lymphoid and bone marrow depletion were observed in rats and dogs. Infusion of 5 daily 15mg/m^2 doses was lethal to mice and resulted in vacuolation and axonal fragmentation of the sciatic nerve; the HNLD was 9mg/m^2. The HNLD in rats following 5 daily doses of RPR116258 was 3mg/m^2; ↓ WBC, reticulocytes and platelets, and lymphoid atrophy and hepatocellular necrosis was observed at doses —1.5mg/m^2. In addition, ↓RBC, bone marrow depletion, thymic hemorhage and necrosis of seminal vesicles were exhibited at 3mg/m^2. Daily doses of 4mg/m^2 administered over 5 days to dogs was lethal, neurotoxic and resulted in hepatocellular necrosis and atrophy. In a separate study, hyperplasia and congestion of the organs of the GI tract and ↓platelet counts were exhibited at doses of 0.5 and 2 mg/m^2 administered daily over 5 days to dogs; testicular degeneration was observed at 2mg/m^2.

A 13-day study was conducted in rabbits. Lethality, body weight loss and dilatation and irritation of the GI tract were observed at 1.2mg/m^2 .

Histopathology Inventory for IND # 56,999

Study	98-031	98-032	97-117	98-033	98-027	98-030	98-157	98-028	98-029	97-115
Species	mouse	rat	dog	dog	mouse	mouse	mouse	rat	dog	dog
Adrenals	X	X	X	X	X		X	X	X	X
Aorta		X		X				X	X	
Bone Marrow smear		X		X				X	X	
Bone (femur)		X		X				X	X	
Brain	X	X		X		X		X	X	
Cecum		X		X				X	X	
Cervix										
Colon		X		X				X	X	
Duodenum		X		X				X	X	

Epididymis	X		X	X	X		X	X	X	X
Esophagus		X		X				X	X	
Eye		X		X				X	X	
Fallopian tube										
Gall bladder				X					X	
Gross lesions		X		X						
Harderian gland		X						X		
Heart	X	X	X	X	X		X	X	X	X
Hyphophysis										
Ileum		X		X				X	X	
Injection site	X	X	X	X	X	X	X	X	X	X
Jejunum		X		X				X	X	
Kidneys	X	X	X	X	X		X	X	X	X
Lachrymal gland		X		X				X	X	
Larynx										
Liver	X	X	X	X	X		X	X	X	X
Lungs	X	X	X	X	X		X	X	X	X
Lymph nodes, submandibular		X						X		
Lymph nodes, medial retropharyngeal				X					X	
Lymph nodes, mesenteric		X		X				X	X	
Mammary Gland		X		X				X	X	
Nasal cavity									X	
Optic nerves								X		
Ovaries	X	X	X	X	X		X	X	X	X
Pancreas		X		X				X	X	
Parathyroid		X		X				X	X	
Peripheral nerve										
Pharynx										
Pituitary		X		X				X	X	
Prostate	X	X	X	X	X		X	X	X	X
Rectum		X		X				X	X	
Salivary gland		X		X				X	X	
Sciatic nerve	X	X		X		X		X	X	
Seminal vesicles	X	X			X		X	X		
Skeletal muscle		X		X				X	X	
Skin		X		X				X	X	
Spinal cord	X	X		X		X		X	X	
Spleen	X	X	X	X	X		X	X	X	X
Sternum		X		X				X	X	
Stomach		X		X				X	X	
Testes	X	X	X	X	X		X	X	X	X
Thymus	X	X	X	X	X			X	X	X
Thyroid		X		X				X	X	
Tongue		X		X				X	X	
Trachea		X		X				X	X	

Urinary bladder		X		X				X	X	
Uterus	X	X	X	X	X		X	X	X	X
Vagina		X		X				X	X	
Nerve root						X				

V. Reproductive Toxicity Deferred

VI.Genetic Toxicity:

DS 98-020 **Bacterial reverse mutation test.** Conducted by Rhone Poulenc Rorer Research and Development, Alfortville, France in April, 1998 according to OECD guidelines.

DS 98-022 **In vitro chromosome aberration test in cultured human peripheral blood lymphocytes.** Conducted by Rhone Poulenc Rorer Research and Development, Alfortville, France in July, 1998 according to OECD guidelines.

DS 98-023 **Intravenous bone marrow micronucleus test in rats.** Conducted by Rhone Poulenc Rorer Research and Development, Alfortville, France in June, 1998 according to OECD guidelines.

DS 98-156 **Bacterial reverse mutation test.** Conducted by Rhone Poulenc Rorer Research and Development, Alfortville, France in June, 1998 according to OECD guidelines.

Summary of Genetic Toxicity

RPR116258 was negative for bacterial mutations in batch BFC611 and P98041ME. Polyploidy was induced at doses —0.005ug/ml and weak but significant chromosomal aberrations were induced at 0.001 and 0.05ug/ml in human lymphocytes. RPR116258 induced bone marrow toxicity in rodent marrow and ⎫incidence of micronucleated polychromatic erythrocytes at —3mg/m^2.

OVERALL SUMMARY AND EVALUATION

RPR 116258 is a taxane which acts to promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization. It differs from other taxanes in its ability to cross the blood-brain barrier and its activity with mdr- resistant tumors.

RPR 116258 exposure increases with dose; the drug appears to distribute rapidly into tissues and crosses the blood-brain barrier. Metabolism of RPR116258 is NADPH-dependent with 3 major metabolites detected in rat, dog, monkey and human liver microsomes (RPR123142, RPR112698 and RP56976) (see metabolic pathway of RPR116258 below). The rate of disappearance of the parent drug in liver microsomes was highest in the dog followed by the human. Total plasma clearance was rapid in all species tested and tended to decrease with increasing dose in dogs. The *in vitro* plasma protein binding is approximately 83% and is higher in mouse>dog>rat> human> monkey>rabbit. The *in vitro* partitioning between blood cells and human plasma is constant between 0.005-10ug/ml RPR116258 with a low blood cell/plasma ratio of approximately 0.32, indicating a low affinity for red cells.

Single dose studies were conducted in mice, rats and dogs. The LD10 in mice was between 120-150mg/m^2. Signs of peripheral neurotoxicity, including absence of hindlimb extension, incoordination, ↓motor activity and prostration were observed at iv doses —90mg/m^2 RPR116258. Microscopically, degeneration and vacuolation of the sciatic nerve and degeneration, vacuolation, dilatation and swelling of the lumbosacral nerve root, and axon fragmentation were observed at this same dose, with lumbosacral nerve root dilitation and swelling also observed at 45mg/m^2 in mice. Males appeared to be more sensitive to the effects of RPR116258 in mice. Lethality was observed following a single iv dose of 30mg/m^2 (LD10) in rats; enhanced peripheral neurotoxicity (presence of ellipsoids and spheroids) was observed microscopically at this dose. Lymphoid atrophy, ↓myelopoiesis of the bone marrow and depressed hematological parameters were observed at doses —15mg/m^2. RPR116258 was lethal (4/4) in dogs following a single dose of 20mg/m^2; major findings included signs of peripheral neurotoxicity, hepatic and lymphoid atrophy and degeneration of the GI tract . Female dogs appeared to be more sensitive to RPR116258.

Polysorbate-treated dogs exhibited edema and erythema of the head and legs, agitation and ⌋motor activity; these findings were enhanced by the effects of RPR116258.

Five-day studies were conducted in mice, rats and dogs. Lymphoid and bone marrow depletion were observed in rats and dogs. Infusion of 5 daily 15mg/m^2 doses was lethal to mice and resulted in vacuolation and axonal fragmentation of the sciatic nerve; the HNLD was 9mg/m^2. The HNLD in rats following 5 daily doses of RPR116258 was 3mg/m^2; ↓ WBC, reticulocytes and platelets, and lymphoid atrophy and hepatocellular necrosis was observed at doses —1.5mg/m^2. In addition, ↓RBC, bone marrow depletion, thymic hemorhage and necrosis of seminal vesicles were exhibited at 3mg/m^2. Daily doses of 4mg/m^2 administered over 5 days to dogs was lethal, neurotoxic and resulted in hepatocellular necrosis and atrophy. In a separate study, hyperplasia and congestion of the organs of the GI tract and ↓platelet counts were exhibited at doses of 0.5 and 2 mg/m^2 administered daily over 5 days to dogs; testicular degeneration was observed at 2mg/m^2.

A 13-day study was conducted in rabbits. Lethality, body weight loss and dilatation and irritation of the GI tract were observed at 1.2mg/m^2.

RPR116258 was negative for bacterial mutations in batch BFC611 and P98041ME. Polyploidy was induced at doses —0.005ug/ml and weak but significant chromosomal aberrations were induced at 0.001 and 0.05ug/ml in human lymphocytes. RPR116258 induced bone marrow toxicity in rodent marrow and ↑incidence of micronucleated polychromatic erythrocytes at —3mg/m^2.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-201023	ORIG-1	SANOFI AVENTIS SPA	CABAZITAXEL (XRP6258)

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