

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

**NDA 21-938 (GIST)
NDA 21-968 (MRCC)**

Pharmacology Review(s)



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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-938/21-968
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: 08/10/05
PRODUCT: SU011248/Sutent
INTENDED CLINICAL POPULATION: **Gleevec-Resistant Gastrointestinal Stromal Tumors,
Metastatic Renal Cell Carcinoma**
SPONSOR: **Pfizer**
DOCUMENTS REVIEWED: **CTD Sections 1 and 4**
REVIEW DIVISION: **Division Drug Oncology Drug Products**
PHARM/TOX REVIEWER: **S. Leigh Verbois, Ph.D**
PHARM/TOX SUPERVISOR: **David E. Morse, Ph.D**
DIVISION DIRECTOR: **Robert Justice, M.D.**
PROJECT MANAGER: **Christy Cottrell**

Date of review submission to Division File System (DFS): January 20th, 2006

TABLE OF CONTENTS

EXECUTIVE SUMMARY	3
2.6 PHARMACOLOGY/TOXICOLOGY REVIEW.....	8
2.6.1 INTRODUCTION AND DRUG HISTORY	8
2.6.2 PHARMACOLOGY	13
2.6.2.1 Brief summary	13
2.6.2.2 Primary pharmacodynamics	13
2.6.2.3 Secondary pharmacodynamics:	26
2.6.2.4 Safety pharmacology	26
2.6.2.5 Pharmacodynamic drug interactions	31
2.6.3 PHARMACOLOGY TABULATED SUMMARY	31
2.6.4 PHARMACOKINETICS/TOXICOKINETICS.....	33
2.6.4.1 Brief summary	33
2.6.4.2 Methods of Analysis.....	33
2.6.4.3 Absorption	33
2.6.4.4 Distribution.....	36
2.6.4.5 Metabolism.....	41
2.6.4.6 Excretion.....	43
2.6.4.9 Discussion and Conclusions	49
2.6.4.10 Tables and figures to include comparative TK summary.....	49
2.6.5 PHARMACOKINETICS TABULATED SUMMARY	51
2.6.6 TOXICOLOGY	56
2.6.6.1 Overall toxicology summary	56
2.6.6.2 Single-dose toxicity	58
2.6.6.3 Repeat-dose toxicity	58
2.6.6.4 Genetic toxicology.....	79
2.6.6.5 Carcinogenicity.....	82
2.6.6.6 Reproductive and developmental toxicology	82
2.6.6.8 Special Toxicology Studies	95
2.6.6.9 Discussion and Conclusions	95
2.6.6.10 Tables and Figures.....	95
2.6.7 TOXICOLOGY TABULATED SUMMARY	95
OVERALL CONCLUSIONS AND RECOMMENDATIONS	101
APPENDIX/ATTACHMENTS	102

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability

The nonclinical studies submitted to this NDA provide sufficient information to support the use of sunitinib malate (Sutent™) for the treatment of gastrointestinal stromal tumor after disease progression on/or intolerance to imatinib mesylate and the treatment of advanced renal cell carcinoma.

B. Recommendation for nonclinical studies

None

C. Recommendations on labeling

See separate labeling review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

B. Pharmacologic activity

SU011248, the base of SU011398 (SU011248-L-Malate) is a receptor tyrosine kinase (RTK) inhibitor with affinity for numerous tyrosine kinases (including the TK activity of some non-growth factor transmembrane receptors). SU011248 inhibited Class V and III split kinase domain receptor tyrosine kinases VEGFR1, 2, and 3, PDGFR α and β , FLT3 and CSF-1R as well as RET in one or more biochemical, cellular or functional assays.

In vitro studies demonstrated a dose-related decrease in intrinsic or ligand stimulated cell proliferation in cell lines engineered to overexpress VEGFR2, PDGFR α and β , KIT, RET, and FLT. These findings were also observed *in vivo*, in xenograft mouse models which overexpressed or contained mutated RTKs. Anti-angiogenic properties were investigated in a subset of the xenograft mouse models which were utilized for investigation of tumor growth and metastases. Evidence of anti-angiogenic properties of SU011248 were observed, but not universally with all tumor types in which regression and reduction of metastases were observed (i.e. within 5 of 7 lines investigated). These results suggest an inhibitory activity of SU011248 on cell proliferation and tumor metastases through various as yet not fully defined pathways. Given that RTK expression dependent inhibition was not evident in several xenograft models, a direct link between RTK inhibition and efficacy cannot be made.

C. Nonclinical safety issues relevant to clinical use

Safety Pharmacology

The safety profile of orally administered and locally applied SU011248 was evaluated *in vitro*, and *in vivo* in rats, rabbits, and monkeys. Specificity was evaluated in a receptor screen. Notable off-target inhibition of receptors by SU011398 included 5HT_{2A} (IC₅₀=0.0918 μ M, 48.8 ng/mL), α_{1B} -adrenergic receptors (0.168 μ M, 89.4 ng/mL), and the serotonin transporter (0.2 μ M, 106.51 ng/mL), all at less than 2 fold the average expected steady state concentration of

SU011248. Evaluation of CNS effects did not identify SU011248 induced CNS toxicity or changes in body temperature at doses of up to 3000 mg/m2 in rats.

There does appear to be significant *in vitro* and *in vivo* cardiovascular effects. SU011248 increased the action potential duration in canine purkinje fibers [APD 70 (12 ms) and APD 90(22 ms)] at 10^{-6} M at a stimulation rate of 60 ppm. Increases were also noted at 10^{-7} [APD 90 (13 ms)] and 10^{-6} M [APD 70 (34 ms) and APD 90 (49ms)] with a low stimulation rate (20ppm). Additionally, SU011248 and SU011262 (the primary metabolite of SU011248) blocked hERG currents with IC_{50} 's of 266 nM and 4.1 μ M respectively. In clinical trials, SU011248 exposure was approximately 2 fold higher (AUC= 1262 ng.hr /mL) than SU011262 exposure (AUC=667 ng.hr/mL). Blockade by SU011248 appears to be in a use dependent manner. In monkeys, the QT interval was prolonged 40-60 ms (9-14 hours post dose) and 53-110 ms (8-18 hours post dose) compared to control, following doses of 600 mg/m2 (plasma concentration 6 hours post dose=277 \pm 47 ng/mL) and 1800 mg/m2 (plasma concentration 6 hours post dose = 288 \pm 14 ng/mL, decreased due to emesis). Rate corrected QT intervals were increased by 20-50 ms. The NOEL for cardiovascular findings in the monkey was 180 mg/m2. SU010398 effects on respiratory function were limited to a 30% increase in tidal volume 0.5-2 hours post dose following 3000 mg/m2.

In the three and nine month oral toxicity studies in monkeys, changes in cardiovascular function were observed. Reductions in heart rate were noted in both studies at a doses of 72 mg/m2 (approximately equivalent to the clinical exposure to both SU011248 and SU012662). Changes in ECHO parameters included reductions in the ratio of left atrial diameter to aortic diameter, the left atrial diameter, left ventricular ejection time and left ventricular area. One instance of premature ventricular contraction was noted at the 72 mg/m2 in the nine month study. Cardiac toxicity, as evidenced by histopathological findings in individual test animals, included minimal to slight capillary proliferation, myocardial vacuolization or inflammation of the pericardium.

In the two MRCC studies, twenty-five patients (15%) had decreases in left ventricular ejection fraction (LVEF) to below the lower limit of normal (LLN). In the placebo controlled GIST study, 22 patients (11%) on SUTENT and 3 patients (3%) on placebo had treatment-emergent LVEF values below the lower limit of normal. Nine of twenty-two GIST patients on SUTENT with LVEF changes recovered without intervention. Five patients had documented LVEF recovery following intervention (dose reduction- 1 patient; addition of antihypertensive or diuretic medications- 4 patients). Six patients went off study without documented recovery. Additionally, three patients (1%) on SUTENT had Grade 3 reductions in left ventricular systolic function to LVEF < 40%; two of these patients died without receiving further study drug. No GIST patients on placebo had Grade 3 decreased LVEF. In GIST study A, the incidence of clinical congestive heart failure was similar in patients receiving SUTENT and placebo. The changes in ECHO observed in the monkey study clearly indicated the cardiotoxic potential of SU011248.

Cardiovascular toxicity is also evidenced by an increased incidence of hemorrhage clinically and nonclinically. Clinically, bleeding events occurred in 44/169 patients (26%) receiving SUTENT for MRCC and 37/202 patients (18%) receiving SUTENT in GIST Study A,

compared to 17/102 patients (17%) receiving placebo. Epistaxis was the most common hemorrhagic adverse event reported. Less common bleeding events in MRCC or GIST patients included rectal, gingival, upper GI, genital, and wound bleeding. Most events in MRCC patients were Grade 1 or 2; there was one Grade 3 event (bleeding foot wound). In the GIST, 14/202 patients (7%) receiving SUTENT and 9/102 patients (9%) on placebo had Grade 3 or 4 bleeding events. In addition, one patient in the GIST study taking placebo had a fatal gastrointestinal bleeding event during cycle 2.

Tumor-related hemorrhage has been observed in patients treated with SUTENT. Fatal pulmonary hemorrhage occurred in 2 of 63 patients (3%) receiving SUTENT on a clinical trial of patients with metastatic non-small cell lung cancer (NSCLC). Treatment-emergent Grade 3 and 4 tumor hemorrhage occurred in 5 of 202 patients (3%) with GIST receiving SUTENT on Study A. Tumor hemorrhages were observed as early as cycle 1 and as late as cycle 6. One of these five patients received no further drug following tumor hemorrhage. None of the other four patients discontinued treatment or experienced dose delay due to tumor hemorrhage. No patients with GIST in the placebo arm were observed to undergo intratumoral hemorrhage. Tumor hemorrhage was not been observed in patients with MRCC.

Nonclinical evaluation of sunitinib indicated that hemorrhage was noted in rats in the stomach, adrenals, and eye, and in monkeys in the adrenals, gastrointestinal tract, and gall bladder. Evaluation of tissue distribution in pigmented rats indicated that high levels of sunitinib were noted at 24 hours post-dose in the adrenals and eye and were detectable at 14 days post-dose, whereas lower levels were still detected in the gastrointestinal tract. Mean concentrations of radioactivity in pigmented skin and the uveal tract were approximately 2 fold higher than concentrations observed in albino rats, which suggests a high degree melanin-associated binding. Although this suggests that divergent kinetics between racial groups may be possible, there is currently no clinical evidence to support this.

Toxicology

In rats and monkeys, the major target organs of SU010398 toxicity are the hematopoietic organs (thymus, marrow, spleen, and lymph nodes), hepatic, gastrointestinal, glands (pancreas, adrenals, salivary), skeletal, and female reproductive organs (ovaries, uterus).

Primary clinical signs were indicative of gastrointestinal toxicity. Abnormal feces were noted in both species and emesis was noted in the monkey. These findings were corroborated by histological findings of inflammation, mucosal erosion, epithelial depletion, necrosis and hemorrhage in the gastrointestinal tract. These findings were generally reversible by the end of the recovery period.

In rat and monkey repeat dose studies, hematological changes included decreases in red blood cells, with concomitant decreases in red cell mass. There was evidence of hemorrhage in numerous organs including the adrenals in rats and monkeys and the gall bladder and gastrointestinal tract in monkeys. Reductions in white blood cells were observed with histological evidence of lymphoid depletion in the spleen, thymus, and lymph nodes and atrophy in the bone marrow. Increases in serum hepatic enzymes (AST, ALT and occasionally

GGT and total bilirubin) were accompanied by histological changes of peribiliary inflammation, bile duct hyperplasia and degeneration of the portal hepatocytes.

The pancreas, adrenals and salivary glands appear to be target organs of toxicity in repeat dose studies in rats and monkeys. Histological findings in the pancreas were characterized by edema, inflammation, acinar degeneration and/or degranulation (at AUCs of ≥ 1823 ng h/mL). Slight increases in glucose levels were noted in clinical chemistry measurements. In the salivary glands, acinar hypertrophy/degeneration and apoptosis was noted in repeat dose studies in both rats and monkeys. These findings were coincident with ulceration of the oral cavity in numerous animals. In adrenals, toxicity was noted in studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Toxicity was routinely characterized by hemorrhage in both species, but necrosis, congestion, hypertrophy and inflammation were also noted. These findings were reversible within the recovery period, which varied from one to eight weeks depending on the duration of dosing.

Effects on the female reproductive system were identified in the 3-month repeat dose monkey study, where ovarian (decreased follicular development) changes were noted with exposures of 10,650 ng h/mL (144 mg/m²), while uterine changes (endometrial atrophy) were noted at greater than 1050 ng h/mL (24 mg/m²). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 72 mg/m² (2080 ng h/mL) in a nine month repeat dose monkey study.

Skeletal toxicity in the bone and teeth were noted in repeat dose studies. In rats, caries of the teeth were noted at ≥ 30 mg/m² in 3 month studies with continuous dosing, but as low as 1.8 mg/m² when administration was increased to 5 cycles (daily x 28 every 42 days). These resulted in a dose dependent increase in broken teeth. These findings were not observed in monkeys. Toxicities in the bone were observed in both rats and monkeys. These findings were characterized by brittle, malformed or fractured bones in the rat (≥ 36 mg/m², 5 cycles or 90 mg/m² daily for 3 months). Histopathologically, chondroplasia of the epiphyseal plate (≥ 30 mg/m²) and cartilage in the metaphyseal bony trabeculae (90 mg/m²) were noted in rats and thickening of the epiphyseal cartilage (120 mg/m²) and periosteal new bone formation and necrosis of the physeal cartilage were noted in monkeys (72 mg/m²). Given the continuous development of teeth in rats and the observance of toxicity in long bones of rats and monkeys, the administration of SU010398 to pediatric populations with developing teeth and bones may represent end organ toxicities that have not been evident in the adult clinical population based on clinical signs.

In rabbits, there was not evidence of dermal irritation with doses of 500 mg and slight irritation of the conjunctiva was noted at 1 and 24 hours with 100 mg.

Genetic Toxicology

SU011248 was negative for mutagenicity and clastogenicity in adequately conducted and valid ICH battery of tests (*in vitro* bacterial mutation and mammalian chromosomal aberrations and *in vivo* clastogenicity).

Reproductive and Developmental Toxicology

Assessment of the effects of SU010398 on reproductive potential was showed early embryonic development (Segment I) impairments in female rats treated with 30 mg/m² SU010398 ($AUC_{SU011248+SU012662} = 9800 \text{ ng}\cdot\text{hr/mL}$). This was manifested by a 3.5-fold increase in the number of dead embryos. The NOAEL for female reproductive toxicity in Segment I studies is 9 mg/m²/day. In males, 60 mg/m²/day ($AUC_{SU011248+SU012662} = 49,710 \text{ ng}\cdot\text{hr/mL}$) exceeded the MTD, without evidence of fertility or early embryonic development impairments.

Segment II studies with SU010398 showed teratologic changes following administration of 30 mg/m² (GD 6 through 17; $AUC_{SU011248+SU012662, \text{Day } 12} = 10600 \text{ ng}\cdot\text{hr/mL}$) and 12 mg/m² (GD 7-20; $AUC_{SU011248+SU012662, \text{Day } 14} = 557 \text{ ng}\cdot\text{hr/mL}$) in the absence of abject maternal toxicity in rats and rabbits, respectively. In rats, in life findings were limited to females treated with 30 mg/m² and consisted of a 9% decrease in body weight observed on GD21, which was promulgated by a decrease in body weight gain on days 13-21. Decreases in uterine weight were noted ($\downarrow 52\%$) but were likely due to a reduced number of fetuses and the high number of dams with complete post-implantation loss (29%). In addition, live fetal weight was decreased (7%) and the incidence of fetal skeletal malformations, was significantly increased. Skeletal malformations were characterized by misaligned, absent or fused thoracic and lumbar vertebral arches. The high dose of 30 mg/m² represents the NOAEL for maternal toxicity, whereas 18 mg/m² ($AUC_{SU011248+SU012662, \text{Day } 12} = 4430 \text{ ng}\cdot\text{hr/mL}$) represents the NOAEL for fetal toxicity. In rabbits, embryoletality was observed at 60 mg/m², while developmental effects were observed at ≥ 12 mg/m². Developmental effects consisted of cleft lip at ≥ 12 mg/m² (0.3x human $AUC_{SU011248+SU012662}$) and cleft palate at 60 mg/m² (2.7x human $AUC_{SU011248+SU012662}$). The anticipated human exposure level expressed as AUC_{24} of SU011248 and SU012662 is approximately 1888 ng·hr/mL.

Carcinogenicity Carcinogenicity studies were not conducted and are generally not required to support the safety of the product for the proposed metastatic cancer indication.

Appears This Way
On Original

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-938/21-968

Review number: 1

Sequence number/date/type of submission: 000/10 August 2005/NDA

Information to sponsor: Yes (X) No ()

Sponsor and/or agent: Pfizer, Inc

Manufacturer for drug substance: Pfizer Cork Ltd.

Reviewer name: S. Leigh Verbois, Ph.D.

Division name: Drug Oncology Products

HFD #: 150

Review completion date: January 20th, 2006

Drug:

Trade name: Sutent

Generic name: Sunitinib malate

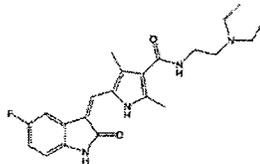
Code name: SU011248-L-Malate, SU010398, and PHA-290940AD

Chemical name: 5-(5-fluoro-2-oxo-1,2-dihydro-indol-(3Z)-ylidenemethyl)-2,4-dimethyl-1H-pyrrole-3-carboxylic acid (2-diethylamino-ethyl)-amide

CAS registry number: 341031-54-7

Molecular formula/molecular weight: C₂₂H₂₇N₄O₂•C₄H₆O₅; MW=532.57

Structure:



Relevant INDs/NDAs/DMFs: IND 62382/NDA 21938

Drug class: Receptor Tyrosine Kinase Inhibitor

Intended clinical population: Treatment of cytokine-refractory renal cell carcinoma

Clinical formulation:

Name of Ingredients	Reference to Standards	Function	Strength		
			12.5 mg	25 mg	50 mg
			Unit Formula (mg per Capsule)		
Sunitinib Malate	Pfizer	Active Ingredient			
Mannitol ⁽⁶⁾	USP/Ph. Eur.				
Croscarmellose Sodium	USNF/Ph. Eur.				
Povidone ⁽⁶⁾	USP/Ph. Eur.				
Purified Water ⁽⁶⁾	USP/Ph. Eur.		As required	As required	As required
Magnesium Stearate	USNF/Ph. Eur.				
Total Fill Weight			110,000	83,500	167,000
Hard Gelatin Capsule			Size #4	Size #3	Size #2

Route of administration: Oral

Best Possible Copy

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

Study #	Title	Module
<u>Pharmacology</u>		
SU011248- Pharm-001	Receptor tyrosine kinase (RTK) target potencies and kinase selectivity of Sunitinib in enzymatic and cellular assays <i>in vitro</i>	4.2.1.1
SU011248- Pharm-002	Inhibition of Sunitinib target RTKs and determination of target plasma levels and pharmacokinetic/pharmacodynamic relationships <i>in vivo</i>	4.2.1.1
SU011248- Pharm-003	Antitumor efficacy and antiangiogenic activity of Sunitinib in rodent models of cancer <i>in vivo</i>	4.2.1.1
<u>Pharmacokinetics/Toxicokinetics</u>		
<i>Absorption</i>		
SU011248- PDM-034	PK of SU011248 following IV and oral administration at 2 mg/kg I rats	4.2.2.2
SU011248- PDM-031	PK of SU011248 following oral administration in carboxymethylcellulose formulation at 10 mg/kg in rats	4.2.2.2
SU011248- PDM-063	Effect of food on SU011248 exposure following oral administration to male cynomolgus monkeys	4.2.2.2
<i>Distribution</i>		
SU011248- PDM-095	Determination of the Tissue Distribution of Total Radioactivity in the Rat by Quantitative Whole Body Autoradiography Following Oral Administration of [¹⁴ C]-SU010398 (The L-Malate Salt of SU011248)	4.2.2.3
SU011248- PDM-060	Plasma protein binding of SU011248	4.2.2.3
SU011248- PDM-061	Protein binding evaluation of SU012662	4.2.2.3
SU011248- PDM-038	Plasma protein binding of SU011248 using ultrafiltration and equilibrium dialysis	4.2.2.3
SU011248- PDM-057	Concentrations of SU011248 and its metabolite, SU012662, in monkey, adrenal, bone marrow, liver, kidney, pancreas, brain and white and brown fat.	4.2.2.3
<i>Metabolism</i>		
SU011248- PDM-044	SU011248 metabolite identification across species <i>in vitro</i>	4.2.2.4
SU011248- PDM-043	<i>In vitro</i> and <i>in vivo</i> profiling of SU011248 metabolites	4.2.2.4
SU011248- PDM-042	SU011248 metabolite identification across species <i>in vivo</i>	4.2.2.4
<i>Excretion</i>		
SU011248-	SU011248 metabolite identification in human plasma and urine	4.2.2.4

PDM-059		
SU011248- PDM-003	The secretion of total radioactivity in milk of lactating rats following oral administration of [¹⁴ C]SU010398 (the malate salt of SU011248)	4.2.2.5
SU011248- PDM-055	Determination of the excretion balance of radioactivity, blood and plasma pharmacokinetics and metabolite profiles in plasma, urine and feces following oral and intravenous administration of [¹⁴ C] SU010398 (L-malate salt of SU011248) to rats.	4.2.2.5
SU011248- PDM-054	Determination of excretion balance of radioactivity, blood and plasma pharmacokinetics and metabolite profiles in plasma, urine and feces following oral administration of [¹⁴ C] SU010398 (L-malate salt of SU011248) to monkeys.	4.2.2.5

Safety Pharmacology

001127.TVH	Effect of SU011248 on Cloned hERG Channels Expressed in Mammalian Cells	4.2.1.3
010122.TVH	Effect of SU012662(-Desethyl of SU011248) on cloned hERG channels expressed in mammalian cells	4.2.1.3
20000612P	Evaluation Of Effect On Cardiac Action Potential In Isolated Canine Purkinje Fibers	4.2.1.3
2001-0073	SU12662: Effect on left ventricular canine purkinje fiber cell action potential	4.2.1.3
2000-0325	SU011248: Effect on general behavior (Irwin's test) and body temperature in the rat after oral administration	4.2.1.3
2000-0339	SU011248: Effect on cardiovascular parameters and body temperature in conscious cynomolgus monkeys after oral administration	4.2.1.3
2002-0494	SU010398 (SU011248 L-malate salt): Effect on respiratory function in the unrestrained conscious rat after single oral administration	4.2.1.3
1030851	⌈ Data Report on Compound SUG-15 (AKA D-0026, SU011398, SU011248 L malate) For Sugen, Inc.	4.2.1.2

Toxicology

Repeated dose Studies

2003-0390	SU010398 (L- Malate Salt Of SU011248): 6- Month Oral Toxicity Study (5- Cycle Treatment) In The Rat Followed By An 8- Week Recovery Period	4.2.3.2
2003-0386	SU010398 (SU011248 L- Malate Salt): 9- Month Oral Toxicity Study In The Monkey (8- Cycle Treatment) Followed By An 8- Week Recovery Period	4.2.3.2
2002-0542	SU010398 (PHA-290940AD): Oral 7 day dose tolerance study in female rabbits	4.2.3.2

Reproductive Toxicology

2003-0370	SU010398 (PHA- 290940AD): Oral Fertility and Early Embryonic Development Study in the Rat	4.2.3.5
2003-0372	SU010398 (PHA- 290940AD): Oral Embryo- Fetal Development Study in the Female Rat	4.2.3.5

Genetic Toxicology

21602-0-449OECD	Chromosomal Aberrations In Cultured Human Peripheral Blood Lymphocytes with SU011248	4.2.3.3
2000-0357	SU011248: Gene Mutation Test in Bacteria (Ames test)	4.2.3.3
21602-0-422OECD	Salmonella – Escherichia Coli/Mammalian-Microsome Reverse Mutation Assay With A Confirmatory Assay With SU011248	4.2.3.3
21602-0-454OECD	In Vivo Rat Micronucleus Assay With SU011248	4.2.3.3

Studies previously reviewed within IND 62382:

Study #	Title	Module
Pharmacokinetics/Toxicokinetics		
SU011248-PDM- 030	Pharmacokinetic Study Of SU011248 Following Intravenous And Oral Administration In Mice	4.2.2.2
SU011248-PDM- 031	Pharmacokinetics Of SU011248 Following Oral Administration In A Carboxymethyl-Cellulose (CMC) Formulation At 10 Mg/Kg In Rats	4.2.2.2
SU011248-PDM- 034	Pharmacokinetics Of SU011248 Following Intravenous And Oral Administration At 2 Mg/Kg In Rats	4.2.2.2
SU011248-PDM- 035	Pharmacokinetic Study Of SU012662 Following Intravenous And Oral Administration In Rats	4.2.2.2
SU011248-PDM- 033	Pharmacokinetic Study Of SU011248 Following Intravenous And Oral Administration In Rats	4.2.2.2
SU011248-PDM- 036	Preliminary Pharmacokinetics And Oral Bioavailability Of SU011248, SU011652, SU011654 And SU011655 In Beagle Dogs Using A Solution Formulation And Cassette Dosing	4.2.2.2
SU011248-PDM- 060	Plasma Protein Binding Of SU011248	4.2.2.3
SU011248-PDM- 038	Plasma Protein Binding Of SU011248 Using Ultrafiltration And Equilibrium Dialysis	4.2.2.3
SU011248-PDM- 044	SU011248 Metabolite Identification Across Species In Vitro	4.2.2.4
SU011248-PDM- 043	In Vitro And In Vivo Profiling Of SU011248 Metabolites	4.2.2.4
SU011248-PDM- 049	The Effect Of Flavin-Containing Monooxygenases On The Formation Of SU012487 From SU011248 In Rat And Dog Liver Microsomes	4.2.2.4
SU011248-PDM- 051	In Vitro Phenotyping Of The Cytochrome P450 Enzymes Involved In The N-Deethylation Of SU011248	4.2.2.4
SU011248-	SU011248 Metabolite Identification Across Species In Vivo	4.2.2.4

PDM- 042		
SU011248-	An Interim Report On SU011248 Biotransformation In Rats	4.2.2.4
PDM- 048		

Toxicology***Single dose Studies***

2000-0184	SU011248 And SU011654: Preliminary Single Dose Oral Toxicity Study In The Beagle Dog, Followed By A 2- Week Observation Period.	4.2.3.1
E-002059	Acute Maximum Tolerated Dose Study Of SU011248 Administered Orally To Mice	4.2.3.1
7039-152	Single Dose Nasogastric Intubation Followed By Intravenous Administration Of SU011248 And SU011654 In Cynomolgus Monkeys (Report Of SU011248)	4.2.3.1
E-002066	Acute Maximum Tolerated Dose Study Of SU011248 Administered Orally To Rats	4.2.3.1
2000-0314	SU011248: Preliminary Single Dose Oral Toxicity Study (MTD) In The Cynomolgus Monkey	4.2.3.1

Repeated Dose Studies

E-002071	Fourteen Day Oral (Gavage) Study Of SU011248 Administered In Mice	4.2.3.2
2000-0211	SU011248: Exploratory Eight- Day Oral Toxicity Study In The Beagle Dog	4.2.3.2
WIL-311017	A 14- Day Oral (Gavage) Or Intravenous Toxicity Study Of SU011248 In Dogs	4.2.3.2
2000-0338	SU011248: Exploratory Seven- Day Oral Toxicity Study In The Cynomolgus Monkey	4.2.3.2
2000-0327	SU011248: Two- Week Oral Toxicity Study In The Rat	4.2.3.2
2000-0497	SU011248: Four-Week Oral Toxicity Study In The Rat Followed By A Four- Week Recovery Period	4.2.3.2
2001-0010	SU010398: Three- Month Oral Toxicity Study In The Rat Followed By A Six-Week Recovery Period	4.2.3.2
2000-0348	SU011248: Two- Week Oral Toxicity Study In The Cynomolgus Monkey	4.2.3.2
2000-0532	SU010398 (PNU-290940AD): 13-Week Oral Toxicity Study In The Monkey Followed By A 6-Week Recovery Period	4.2.3.2

Genetic Toxicology

21602-0-449OECD	Chromosomal Aberrations In Cultured Human Peripheral Blood Lymphocytes with SU011248	4.2.3.3
2000-0357	SU011248: Gene Mutation Test in Bacteria (Ames test)	4.2.3.3
21602-0-422OECD	Salmonella – Escherichia Coli/Mammalian-Microsome Reverse Mutation Assay With A Confirmatory Assay With SU011248	4.2.3.3
21602-0-454OECD	In Vivo Rat Micronucleus Assay With SU011248	4.2.3.3

Special Toxicology

2000-0508	SU011248: Acute Dermal Irritation study in the rabbit	4.2.3.7
2000-0509	SU011248: Acute Eye Irritation study in the rabbit	4.2.3.7

2.6.2 PHARMACOLOGY**2.6.2.1 Brief summary**

SU011248, the base of SU011398 (SU011248-l-malate) was evaluated in numerous *in vivo* and *in vitro* models of carcinogenesis. SU011248 is a tyrosine kinase inhibitor with affinity for numerous receptors as described.

2.6.2.2 Primary pharmacodynamicsMechanism of action:

Reports reviewed within the section include:

- **Receptor tyrosine kinase (RTK) target potencies and kinase selectivity of Sunitinib in enzymatic and cellular assays *in vitro* (SU011248-Pharm-001; Volume 4.2.1.1)**
- **Inhibition of Sunitinib target RTKs and determination of target plasma levels and pharmacokinetic/pharmacodynamic relationships *in vivo*. (SU011248-Pharm-002; Volume 4.2.1.1)**
- **Antitumor efficacy and antiangiogenic activity of Sunitinib in rodent models of cancer *in vivo* (SU011248-Pharm-003; Volume 4.2.1.1)**

In vitro assays were conducted at Pharmacia sites in the US (San Francisco and La Jolla, CA, St. Louis, MO and Bothell, WA) and internationally (Italy).

***In Vitro* Methods:**

- SU011248 and SU012662 were evaluated in a series of biochemical assays to evaluate the selectivity for RTK targets, as well as tyrosine kinases and serine-threonine kinases. Approximately 80 possible targets were assayed for SU011248. SU012662 was assayed in RTK assays.
- Biochemical K_i and IC_{50} values of SU011248 for the inhibition of kinases were determined utilizing transphosphorylation and autophosphorylation assays, [^{33}P]-ATP scintillation proximity assay with CsCl flotation, and the Upstate Cell Signaling Biochemical Kinase Assay (Kinase Profiler Report, 2003).
- Determination of K_i values of SU011248 for the inhibition of targeted kinases was conducted using an enzyme-catalyzed production of ADP from ATP that accompanies phosphoryl transfer to the random co-polymer poly (Glu₄Tyr) and is coupled to the oxidation of NADH through the activities of pyruvate kinase and lactate dehydrogenase.
- Cellular phosphorylation and proliferation assays were utilized to evaluate inhibition of RTK phosphorylation. NIH-3T3 cells engineered to express Flk-1, human PDGFR α or β , CSF-1R, or human insulin receptor, MV4;11 AML cells expressing FLT3-ITD, RS4;11 and OC1-AML5 AML cells expressing FLT3 wild-type, NCI-H526 SCLC cells expressing KIT, MO7E AML, and TT

medullary thyroid carcinoma cells expressing RET were utilized. The ability of SU011248 to inhibit phosphorylation was measured by immunoblotting.

Results:

- The inhibitory activity of SU011248 was evaluated for ~80 kinases. SU011248 showed affinity for or inhibited Class V and III split kinase domain receptor tyrosine kinases VEGFR1, 2, and 3, PDGFR α and β , FLT3 and CSF-1R as well as RET in biochemical, cellular and/or functional assays [see table (modified from the sponsor's submission) and figures (excerpted from the sponsor's submission) below]. The IC₅₀'s for these RTKs were in the range of 0.002-0.25 μ M. Biochemical screening, conducted without concomitant cellular or functional screening, indicated that additional kinases were also potential sites of SU011248 binding. These included lymphocyte specific TK, pyruvate kinase 2, focal adhesion kinase, ZC-1/HGK Kinase and human liver phosphorylase kinase. The affinity of SU011248 was somewhat less in these tyrosine kinases, but the IC₅₀'s were less than 2 fold the steady state concentration observed in clinical trials. While inhibition of insulin receptor kinase was indicated in the screen (IC₅₀=0.34 μ M), the IC₅₀ of receptor phosphorylation occurred with 1/10th the potency.

Summary of *in vitro* inhibitory activities of SU011248 and SU0112662

Receptor	Biochemical K _i ^b (μ M)	IC ₅₀ (μ M)		Cell Line (Reference)
		Receptor Phosphorylation ^b	Proliferation	
SU011248 (Parent)				
VEGFR1	0.002	ND	ND	
VEGFR2 (FLK-1/KDR)	0.009 (FLK-1)	0.004 (KDR) ^c 0.01(FLK-1)	0.004 (KDR) ^c	Mendel et al, 2003; Osusky et al, 2004 and Pfizer Notebook, CA 4408, pp158
VEGFR3	0.017	ND	ND	
PDGFR β	0.008	0.01	0.039 ^c	Mendel et al, 2003
PDGFR α	ND	ND	0.069 ^c	Mendel et al, 2003
KIT	ND	0.001-0.01	0.002 ^d	O'Farrell et al, 2003 and Abrams et al, 2003
FLT3	ND	0.25	0.01-0.1 ^d	O'Farrell et al, 2003
FLT3-ITD	ND	0.05	0.01-0.05 ^d	O'Farrell et al, 2003
CSF-1R	ND	0.05-0.1	ND	Murray et al, 2003
RET (C634W)	ND	0.05	0.05 ^d	Sugen Notebook, page 2589
Human Liver Phosphorylase Kinase	0.033 (IC ₅₀)	ND	ND	Pfizer Notebook, CA, NS
RETspa	0.083 IC ₅₀)	ND	ND	Pharmacia, Nerviano, NS
Lymphocyte –	0.41 (IC ₅₀)	ND	ND	Sugen Notebook,

Receptor	Biochemical K _i ^a (μM)	IC ₅₀ (μM)		Cell Line (Reference)
		Receptor Phosphorylation ^b	Proliferation	
specific TK				CA, NS
Pyruvate Kinase 2	0.27 (IC ₅₀)	ND	ND	Sugen Notebook, CA, NS
Focal Adhesion	0.37 (IC ₅₀)	ND	ND	Sugen Notebook, CA, NS
IR	0.34 (IC ₅₀)	>3	ND	Sugen Notebook, 2688
ZC-1/HGK Kinase	0.24 (IC ₅₀)	BD	ND	Sugen Notebook, CA, NA
SU012662				
VEGFR2 (FLK- 1/KDR)	0.02	ND	0.020 ^c	Pfizer Notebook, CA, NS
PDGFRβ	0.002	0.01 ^e	0.076 ^c	Pfizer Notebook, CA 4408, pp158
PDGFRα	ND	ND	0.100 ^c	Pfizer Notebook, CA, NS
KIT	ND	0.02 ^e		Pfizer Notebook CA 4408, pp
NS-Not specified				
^a Determined using biochemical assays using recombinant enzymes				
^b Determined using anti-phosphotyrosine immunoblots of protein immunoprecipitated with antibodies specific to the receptor from cell lysates isolated from ligand-stimulated and serum starved cells engineered to express the specific receptor.				
^c Determined by measuring proliferation using serum starved HUVECs (VEGFR2 and FGFR) or NIH-3T3 cells engineered to express PDGFRβ or PDGFRα after stimulation with the cognate ligand.				
^d Determined by measurement of cell viability in various cell lines.				
^e Determined by receptor specific phosphorylation ELISA assay using cell lysates isolated from PAE cells engineered to express the receptor.				

See the table below for the affinity of SU011248, expressed as IC₅₀, in kinase selectivity screens.

Potency (IC₅₀) Of Sunitinib In Kinase Selectivity Screens¹				
Abbreviated Name of Primary Biochemical Assay	Name of Primary Biochemical Assay	IC₅₀ (μM)	Fold Selective vs. Flk-1	Sponsor Study Site
AUR1 SPA	AURORA1 kinase	7.41	>500X	SUGEN, S. San Francisco, CA
BioEGFR	Epidermal growth factor receptor	>100	>1000X	SUGEN, S. San Francisco, CA
Biochemical Abl	Ableson kinase	0.84	95X	SUGEN, S. San Francisco, CA
FGFR1	Fibroblast growth factor receptor-1	0.83	92X	
BioDDR1-GST	Discoidin domain receptor 1	9.48	>1000X	SUGEN, S. San Francisco, CA
BioDDR2	Discoidin domain receptor 2	>20	>1000X	SUGEN, S. San Francisco, CA
Fyn TRFRET	Fyn proto-oncogene kinase	3.78	420X	SUGEN, S. San Francisco, CA
BioIGFR1 gst	Insulin-like growth factor receptor 1	2.37	260X	SUGEN, S. San Francisco, CA
Lck TR FRET	Lck--lymphocyte-specific tyrosine kinase	0.41	46X	SUGEN, S. San Francisco, CA
Bio PYK2	PYK2—pyruvate kinase 2	0.29	32X	SUGEN, S. San Francisco, CA
Src TRFRET	Src kinase—Rous sarcoma oncogene	2.17	240X	SUGEN, S. San Francisco, CA
Bio tie2 gst	TIE-2—endothelium-specific receptor tyrosine kinase 2	5.52	>500X	SUGEN, S. San Francisco, CA
Bio FAK gst	Focal adhesion kinase	0.37	41X	SUGEN, S. San Francisco, CA
Bio CDK2 gst	Cyclin dependent kinase 2	17.2	>1000X	SUGEN, S. San Francisco, CA
Bio Frk GST	Frk—fyn-related kinasekinase	1.09	120X	SUGEN, S. San Francisco, CA
Bio GST-Met transphos	Hepatocyte growth factor receptor/ c-met receptor tyrosine kinase	5.31	>500X	SUGEN, S. San Francisco, CA
Src TRFRET	Src kinase—Rous sarcoma oncogene	0.61	67X	SUGEN, S. San Francisco, CA
ZC-1 SPA transphos ELISA	ZC-1/HGK Kinase	0.242	27X	SUGEN, S. San Francisco, CA
PAK5 SPA transphos ELISA	P21 activated kinase 4	1.82	200X	SUGEN, S. San Francisco, CA
ZAP70	ZAP70—zeta chain associated protein kinase 70kD	>20	>1000X	SUGEN, S. San Francisco, CA
ZAP75	ZAP75—zeta chain associated protein kinase 70kD	9.82	>1000X	SUGEN, S. San Francisco, CA
JNK2 kinase	JNK2—jun amino-terminal kinase 2	48.5	>1000X	Pharmacia, St Louis, MO
MK2	MAPKAP kinase 2—MAP kinase activated protein kinase 2	>100	>10000X	Pharmacia, St Louis, MO
MK3	MAPKAP kinase 3-- MAP kinase activated protein kinase 3	>100	>10000X	Pharmacia, St Louis, MO

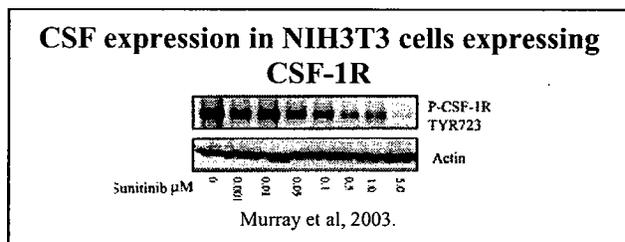
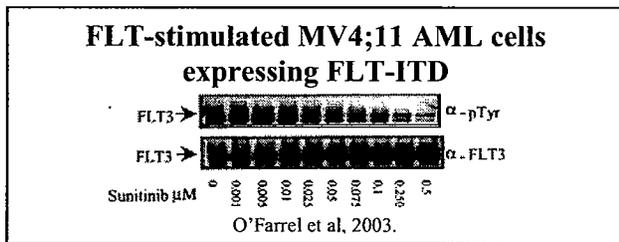
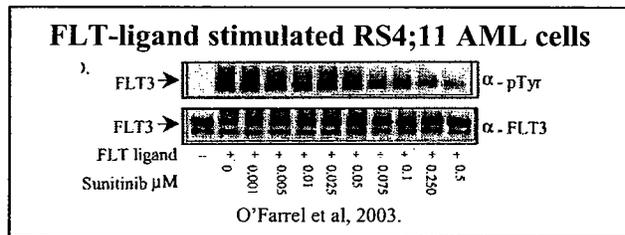
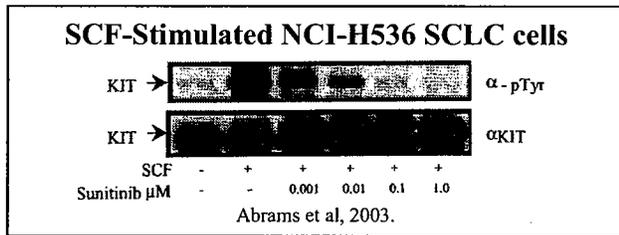
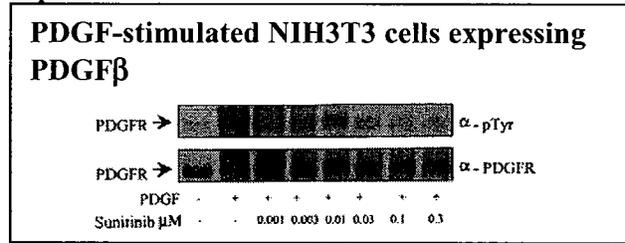
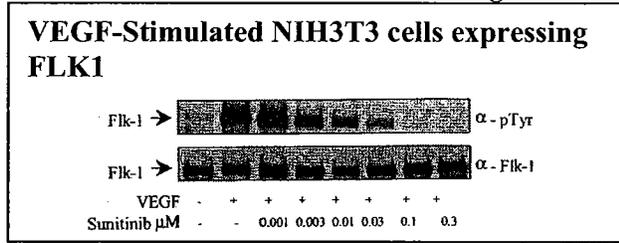
Potency (IC₅₀) Of Sunitinib In Kinase Selectivity Screens¹				
Abbreviated Name of Primary Biochemical Assay	Name of Primary Biochemical Assay	IC₅₀ (µM)	Fold Selective vs. Flk-1	Sponsor Study Site
HiTS PKC alpha	PKC alpha—protein kinase C alpha	> 56	>1000X	Pharmacia, St Louis, MO
RET alpha	RET—receptor tyrosine kinase	0.083	10X	Pharmacia, Nerviano, Italy
KSS-IGF1R	Insulin like growth factor receptor 1	1.4	160X	Pharmacia, Nerviano, Italy
KSS-IR	Insulin receptor kinase	0.34	38X	Pharmacia, Nerviano, Italy
KSS-CK2	Casein kinase 2	> 5	>500X	Pharmacia, Nerviano, Italy
KSS-Cdc7/DBF7	Cell division cycle kinase 7	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-CDK2/Cyclin A	Cyclin dependent kinase 2/cyclin A complex	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-FGFR1	Fibroblast growth factor receptor kinase 1	2.18	240X	Pharmacia, Nerviano, Italy
KSS-PKA alpha	Protein kinase A-alpha	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-PKC beta	Protein kinase C-beta	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-Lck	Lck--lymphocyte-specific tyrosine kinase	1.17	130X	Pharmacia, Nerviano, Italy
KSS-Abl	Ableson kinase	1.95	220X	Pharmacia, Nerviano, Italy
KSS-ERK2	Extracellular-regulated kinase 2	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-IKK2	Inhibitor of NFkappaB kinase 1	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-IKK2	Inhibitor of NFkappaB kinase 2	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-AUR2	AURORA 2 kinase	1.6	180X	Pharmacia, Nerviano, Italy
KSS-PAK4	P21 activated kinase 4	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-p38 alpha	P38 kinase alpha	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-chk1	Chk-1—checkpoint kinase -1	0.64	71X	Pharmacia, Nerviano, Italy
KSS-ZAP70	ZAP70 kinase—zeta chain associated protein kinase 70kD	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-PLK1	Polo-like kinase 1	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-STLK2	STLK2—STE20-like kinase 2	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-MK2	MAPKAP kinase 2—MAP kinase activated protein kinase 2	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-MK3	MAPKAP kinase 3-- MAP kinase activated protein kinase 3	>10	>1000X	Pharmacia, Nerviano, Italy
KSS-PDK1	PDK1--Phosphoinositide-Dependent protein Kinase	2.42	270X	Pharmacia, Nerviano, Italy
PKC-CDH15	Human liver phosphotyrosine kinase catalytic domain	0.025 (Ki)	10X	Pfizer, La Jolla, CA
PAK4	p21-Activated Kinase-4	1.11 (Ki)	>120X	Pfizer, La Jolla, CA

See the table below for the affinity of SU011248, expressed as % inhibition, in kinase selectivity screens.

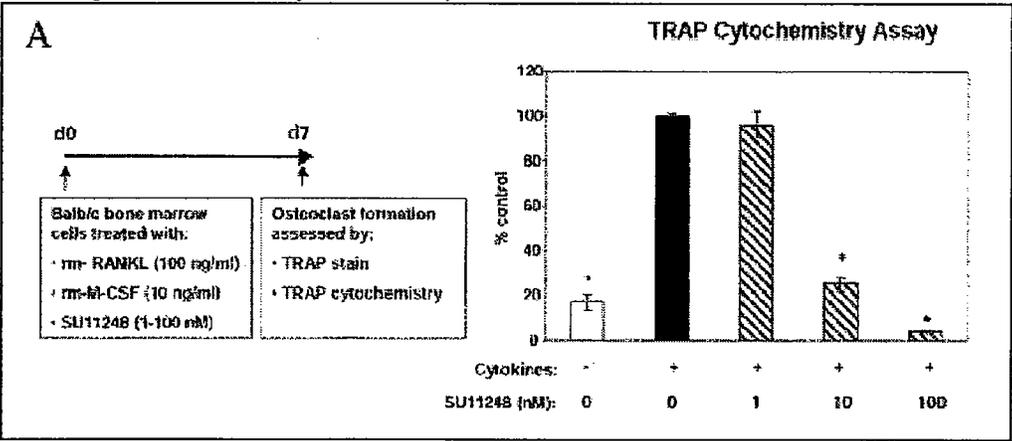
Potency (Percent Inhibition) Of Sunitinib In Kinase Selectivity Screens¹			
Abbreviated Name of Primary Biochemical Assay	Name of Primary Biochemical Assay	Percent Inhibition at 10 μM¹	Sponsor Study Site
PDGFR α	Platelet-derived Growth Factor Receptor alpha	100	Upstate
Flk1	Fms-related receptor tyrosine kinase-3	98 estimated IC ₅₀ : 0.2 μ M	Upstate
FGFR-CD-P	Fibroblast growth factor receptor-1	22	Pfizer, La Jolla, CA
FGFR3	Fibroblast growth factor receptor 3	62	Upstate
Aurora-A	Aurora-related kinase 1	39	Upstate
Arg	v-abl abelson murine leukemia viral oncogene homolog 2	65	Upstate
Axl	axl tyrosine protein kinase/urokinase receptor	95 estimated IC ₅₀ : <0.5 μ M	Upstate
Bmx	Bone marrow kinase bmx	88 estimated IC ₅₀ : <1.4 μ M	Upstate
Cdk2/Cyclin A-P	Cyclin-dependent protein kinase 2	5	Pfizer, La Jolla, CA
COT		28	Pharmacia, St Louis, MO
EGFR	Epidermal growth factor receptor	0	Upstate
EphB2	Ephrin b receptor 2	16	Upstate
Erk2_HIS	extracellular signal-regulated kinase 2	-7	Pfizer, La Jolla, CA
HGFR-P	Phosphorylated Human Growth Factor Receptor	16	Pfizer, La Jolla, CA
IGF-1R	Insulin-like Growth Factor 1 Receptor	29	Upstate
IKK2	Inhibitor of NFkappaB kinase 1	18	Pharmacia, St Louis, MO
IR	Insulin receptor	73	Upstate
MKK4	mitogen-activated protein kinase 4	8	Upstate
MKK6	mitogen-activated protein kinase 6	11	Upstate
MKK7b	mitogen-activated protein kinase 7	7	Upstate
MST2	Mammalian ste20-like kinase 2	69	Upstate
NEK2	nima-related kinase 2	59	Upstate
PAK2	p21-activated kinase 2	5	Upstate
Plk	Polo-like serine/threonine kinase	2	Pfizer, La Jolla, CA
PKCz	Protein kinase C zeta	5	Pharmacia, St Louis, MO
Tie-2	TIE-2--endothelium-specific receptor tyrosine kinase 2	14	Pfizer, La Jolla, CA
Zap70	Zeta-associated protein	15	Pfizer, La Jolla, CA

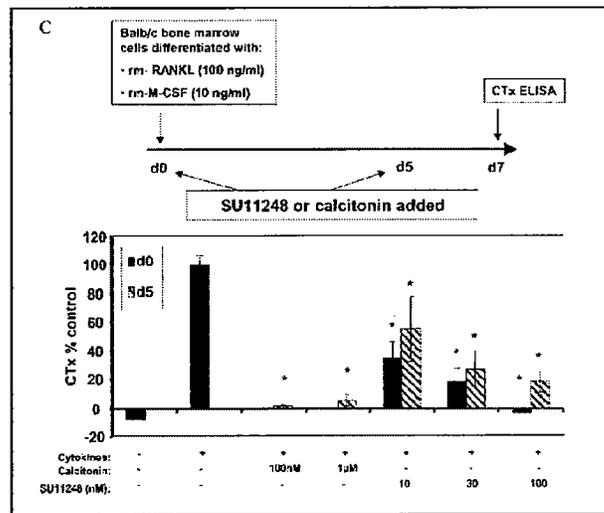
¹Raw data were generated as described in Materials and Methods. Data generated at the listed legacy Pharmacia sites, have been stored in the Pfizer Chemlink database, and are available upon request. Raw data generated at Pfizer, La Jolla labs were generated in the Department of Biochemistry and are stored in the Rgate database and are available upon request.

Immunoprecipitated total and phosphor-RTK expression in serum starved stimulated cells engineered to express RTKs



- SU011248 resulted in a time and dose-dependent reduction in CSF-dependent development of murine osteoclasts as measured by osteoclast specific differentiation markers, tartate-resistant acid phosphatase (TRAP) and type I collagen c-telopeptide (CTx) at concentrations as low as 0.01 μM (Figures excerpted from Murray et al, 2003).





***In vivo* SU011248 activity**

- Growth inhibition and regression of xenograft tumors in female athymic mice were noted in multiple models.

Appears This Way
On Original

Antitumor Efficacy of Oral Daily Sunitinib in Human Tumor Xenograft Models in Female Athymic Mice* (excerpted from the sponsor's submission)

Model (Tumor Type)	Initial Tumor Volume (mm ³)	Dose (mg/kg/day)	Overall Effect		P Value	Reference
			Growth Inh. % (Day) ¹	Regression ²	Treated Vs Control	
A431 (Epidermoid Carcinoma)	400	80	Regression	32% (d40)	0.001	Mendel, 2003
	400	40	93% (d36)	No	0.0028	Mendel, 2003
	400	20	65% (d36)	No	0.13	Mendel, 2003
Colo205 (Colon)	250	80	Regression	38% (d35)	0.001	Mendel, 2003
	250	40	Regression	13% (d35)	0.004	Mendel, 2003
	250	20	55% (d35)	No	0.06	Mendel, 2003
	250	10	No	No	NA	Mendel, 2003
C6 (Rat Glioma)	330	80	88% (d25)	No	0.002	Mendel, 2003
	330	40	82% (d25)	No	0.002	Mendel, 2003
	110	40	72% (d25)	No	<0.0001	Mendel, 2003
	110	20	41% (d25)	No	0.012	Mendel, 2003
A375 (Melanoma)	230	40	64% (d74)	No	0.02	Mendel, 2003
HT - 29 (Colon)	360	40	Regression	62% (d74)	0.003	Mendel, 2003
SF763T (Glioma)	550	80	79% (d30)	No	0.001	Mendel, 2003
NCI-H460 (lung-NSCLC)	300	80	84% (d25)	No	0.0026	Mendel, 2003
WM-266-4 (Melanoma)	410	40	NA	37% (d62)	0.04	Potapova, 2005
786-0 (Renal)	300	80	Regression	60% (d62)	<0.001	Potapova, 2005
	360	40	Regression	46% (d76)	0.05	
NCI-H226 (lung)	290	40	Regression	69% (d76)	0.001	Potapova, 2005
NCI-H526 (lung-SCLC)	280	80	86% (d36)	No	0.0002	Abrams, 2003a
	280	40	63% (d36)	No	0.001	Abrams, 2003a
	250	40	80% (d47)	No	<0.001	#1967, pp.69-75
	250	20	62% (d47)	No	0.02	#1967, pp.69-75
NCI-H82 (lung-SCLC)	250	80	98% (d43)	No	0.013	Mendel, 2003
	250	40	85% (d43)	No	0.05	Mendel, 2003

N≤8/group

N= not specified

N=10/group

N= Not specified

N≤8/group

¹Percent tumor growth inhibition was calculated as 100 X (tumor volume_{final} - tumor volume_{initial} for sunitinib-treated group/ (tumor volume_{final} - tumor volume_{initial} for vehicle group)

²Percent tumor regression was calculated as 1 - (tumor volume_{final}/ tumor volume_{initial})

- Dosing was initiated in each study when tumor reached the specified volume and was ceased when tumors reached 1000 mm³ in vehicle treated animals or when evidence of mortality was noted in vehicle treated animals.
- Timing of significant findings indicated parenthetically in the growth inhibition and regression column

Antitumor Efficacy of Daily Oral Sunitinib in Additional Models of Cancer
(excerpted from the sponsor's submission)

Model (Tumor Type)	Initial Tumor Volume (mm ³)	Dose (mg/kg/day)	Overall Effect		P Value	Reference	
			Growth Inh. % (Day) ¹	Regression ²	Treated Vs Control		
MMTV-v-Ha-ras mammary tumor model	300-500	40	Regression	82% (d20)	0.0002	Abrams, 2003b	Day 1-20 and day 54 to 74 in females; N= NS
DMBA Rat Mammary Tumor Model	700-1000	20	Regression	99% (d28)	0.0001	Abrams, 2003b	Dx28, n=12 F/gr
	700-1000	10	82% (d28)	No	0.006	Abrams, 2003b	
	700-1000	5	64% (d28)	No	0.04	Abrams, 2003b	
MV4;11 AML Xenograft	400-500	40	Regression	100% (d4)	<0.0001	O'Farrell, 2003	Dx28 initiated 21 days post-graft, n=10 F/gr
	400-500	20	Regression	100% (d4)	<0.0001	O'Farrell, 2003	
	400-500	5	No	No	NA	O'Farrell, 2003	
	400-500	1	No	No	NA	O'Farrell, 2003	
MV4;11 AML Bone marrow engraftment	NA	20	Mean survival: 46 days (vehicle = 41 days)		<0.002	O'Farrell, 2003	Daily initiated 21 days post-graft, n=10 F/gr
	NA	10	Mean survival: 56 days		<0.0001	O'Farrell, 2003	
	NA	5	Mean survival: 83 days		<0.0001	O'Farrell, 2003	
435/HAL-Luc experimental breast metastasis	NA	80	89% inhibition of photon emission in bone an d41		0.001	Murray, 2003	Dx21 initiated 20 days post-graft, n= 16 F/group
		40	64% inhibition of photon emission in bone an d41		0.006	Murray, 2003	
MO7E AML Bone marrow engraftment	NA	40	Mean survival increase from: 71 to 104 days		0.02	, #1948, pp.44	Daily beginning 9 days post-graft Gender-NS,
B16F1 Melanoma Lung Colonization	NA	80	50% inhibition of lung colonization		<0.01	, #1766, pp40-42	Dx 23 beginning 1 day post-graft, Gender- NS

¹Percent tumor growth inhibition was calculated as 100 X (tumor volume_{final} – tumor volume_{initial} for sunitinib-treated group/ (tumor volume_{final} – tumor volume_{initial} for vehicle group)

²Percent tumor regression was calculated as 1 – (tumor volume_{final}/ tumor volume_{initial})

NS=Not specified, Timing of significant findings indicated parenthetically in the growth inhibition and regression column

Dose and time dependent inhibition of Flk1/KDR and PDGFRβ phosphorylation *in vivo*

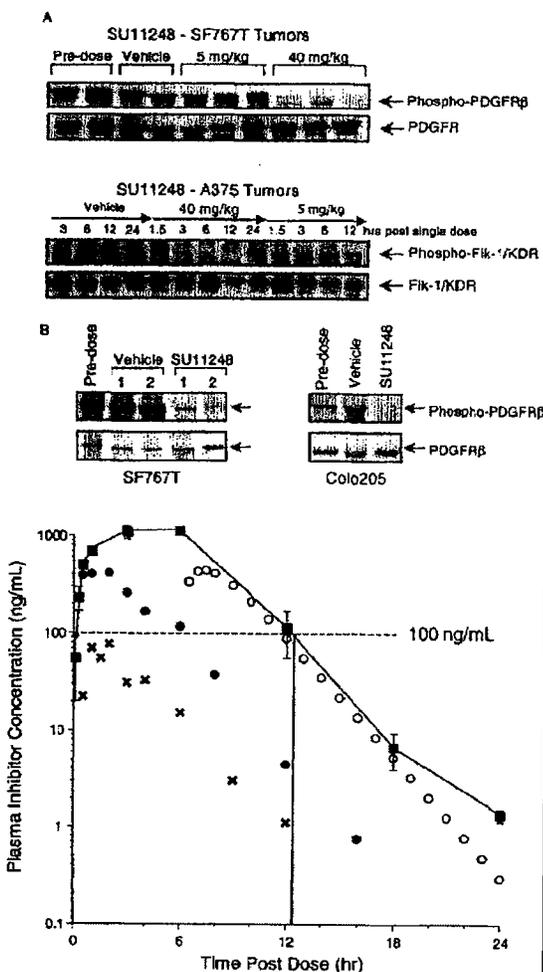
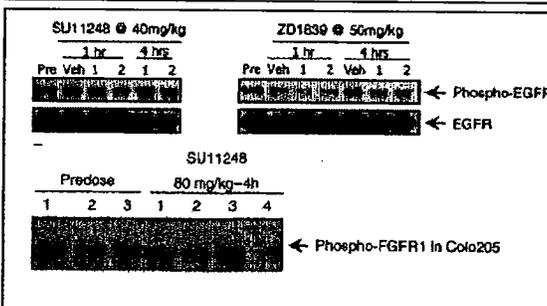


Fig. 6 Plasma inhibitor concentration versus time profile in mice given an oral dose of SU11248. Athymic mice were given a single oral dose of SU11248. At the indicated times after dosing, plasma samples were obtained from terminal bleeds of individual mice, and the concentration of inhibitor in each sample determined by LC/MS/MS. (■), data from PK study with mice dosed at 40 mg/kg; (●), data from target modulation studies at 20 mg/kg; (○), simulated projection of expected plasma inhibitor concentrations in mice given a second 20 mg/kg dose 6 h after the first dose; (×), data from target modulation studies at 5 mg/kg. For the PK study, each point represents mean for groups of three animals; bars, ±SE. For the target modulation studies, each point represents individual animals.

Dose (mg/kg)	Duration of inhibition							
	Target modulation				Vascular permeability (% Inhibition)			
	8 h	12 h	16 h	24 h	8 h	12 h	16 h	24 h
80	Yes	Yes	ND ^a	Yes	95	85	94	98
40	Yes	Yes	ND	No	97	96	0	0
20	Yes	Slight	ND	No	93	0	0	4
5	No ^b	No	ND	No	ND	ND	ND	ND

^a ND, not determined.
^b Target modulation activity only detected at 4-h timepoint.

VEGF-dependent dye leakage from the vasculature into skin was imaged using fluorescence stereomicroscopy.



- SU011248 causes dose and time dependent inhibition of VEGF-induced vascular permeability *in vivo* and PDGFRβ and VEGFR2/KDR phosphorylation. Similar findings were not observed with respect to EGFR and FGFR (see figures excerpted from Mendel et al, 2003).
- Animals were implanted with SF767T, A375 or Colo205 cells ($3-5 \times 10^6$). Once tumors were established ($300-500 \text{ mm}^3$) and single doses of SU011248 (5 or 40 mg/kg) were administered and animals were serially sacrificed. PK was conducted on athymic mice administered 5 or 40 mg/kg as a single dose to determine the plasma inhibitor concentration necessary for target modulation. Based on VEGFR2 receptor inhibition at 12 hours but not 24 hours the proposed necessary plasma inhibitor concentration is 100 ng/mL (see Plasma inhibitor concentration versus time graph excerpted from Mendel et al, 2003). Given that samples were not obtained between 12 and 24 hours it is impossible to determine if this is the exact minimum plasma concentration that would be efficacious at inhibiting VEGFR2.

- SU011248 (40 mg/kg/day) inhibited angiogenesis by more than 50% in 3 of 6 in numerous mouse models where treatment was continued for approximately 2 weeks or more.

Model	Methods	Treatment Duration (days)	% Inhibition of Angiogenesis	Citation
SF763T glioma	Mice, athymic (n≥3, 5 sections per) SC xenografts in athymic mice grown to average size of 300-400 mm ³ , 40 mg/kg/day initiated and continued until tumors in vehicle treated animals reached ~1000 mm ³ .	13	38%	SUGEN Notebook 2053, pp66
MV4;11		15	Not significant	Potapova et al, 2005
C6 Glioma		12	Not significant	
786-O renal		14	76%	
WM-266-4 Melanoma		29	68%	
NCI-H226 lung		14	89%	
Human Foreskin Chimera Model in SCID Mice	Foreskin grafted to a collagen plug implanted into SCID mice. SU01248 (40 mg/kg/ dx4) initiated	4	69%	Pfizer Notebook 7268, pp.14-16, 25-29.

*TK expression not defined

Drug activity related to proposed indication:

SU011248 and the major metabolite SU012662 were both assayed for *in vitro* inhibition of purified tyrosine-protein kinases. SU011248 affinity or inhibition was observed with VEGFR1, 2 and 3, PDGFR α and β , KIT, FLT3, RET, and human liver phosphorylase kinase at concentrations similar to *in vivo* (K_i = 0.002-0.083 μ M). SU012662 affinity for VEGFR2, PDGFR α and β and KIT was observed with similar potency to the parent (K_i = 0.002-0.020 μ M). *In vivo* inhibition of RTK phosphorylation and cellular proliferation were observed in a dose and time dependent manner. Following a single dose of SU011248 in animals with PDGFR β - (SF767T) and VEGFR2- (A3758) expressing tumors, inhibition of receptor phosphorylation was noted with 40 mg/kg. Maximal inhibition within tumor samples was noted at 12 hours post dose when evaluated at 1.5, 3, 6, 12 and 24 hours. Plasma concentrations at this time point were determined to be 50-100 ng/mL. The sponsor asserts that this is the minimal concentration necessary for inhibition of function, however, given the lack of timepoints between 12 and 24 hours, the correlation between inhibition of phosphorylation and plasma levels cannot be made at this time. The antiproliferative effects of SU011248 were evaluated in numerous animal xenograft models. Dose dependent growth inhibition and regression were noted in a number of tumor types, although inhibitory activity was not clearly linked to the degree of TK expression by the tumor tissue. Additionally, drug dependent inhibition of VEGF-induced vascular permeability and angiogenesis were observed. In summary, SU011248 appears to inhibit numerous RTKs and to inhibit the growth, metastases and angiogenesis of multiple tumor types. However, direct causality of the inhibition of tumor growth, metastases and angiogenesis via the receptors identified is not apparent. The following table illustrates the lack of tissue expression dependent response in xenograft models. Additionally, the table also illustrates a lack of enhanced expression of specific TK in renal cell carcinoma and GIST.

	VEGFR1	VEGFR2	VEGFR3	PDGFR α	PDGFR β	KIT	RET	FLT3	Effect
A431 (epidermoid)									
Colo205	1*	3	3	2	2	2	2	1	38% regression with 80 mg/kg/day
C6 Gliom									
A375 Melanoma									
HT29	4	5	1	7	3	2	2	2	62% Regression with 40 mg/kg/d
SF763T (glioma)									
NCI-H460 NSCLC	3	2	1	5	5	7	10	1	84% growth inhibition; no regression observed
WM-266-4 (melanoma)									
786-0 Renal	2	6	10	2	2	10	8	5	46-60% regression with 40-80 mg/kg/day
NCIH226 lung	7	10	7	10	10	6	9	7	69% regression with 40 mg/kg
NCIH526 (SCLC)	+	+	+		+	+			Up to 80% growth inhibition, no regression with 40 mg/kg
NCI H82 (SCLC)	+	+	+						Up to 100% growth inhibition, no regression noted with 80 mg/kg
Renal Carcinoma Cancer	1	1	1	1	1	1	1	1	
Normal Kidney	1	1	1	1	1	1	1	1	
GIST				+	+	+	+	+	

*Expression as noted at *<http://cgap.nci.nih.gov/Genes/GeneFinder>. 1 is indicative of the lowest expression observed, 10 is indicative of the highest level of expression observed. + and - are indicative of expression noted in the literature via Pubmed. + indicates that the receptor is found in this xenograft model, - indicates that the receptor expression was analyzed and not observed. Blanks in the table indicate that evidence analysis in this model with this TK was not found.

- 1 Tanno et al, Lung Cancer. 2004 Oct;46(1):11-9.
- 2 Abrams et al, Mol Cancer Ther. 2003 May;2(5):471-8.
- 3 Rakowicz-Szulczynska et al. Exp Mol Pathol. 1989 Oct;51(2):171-8.
- 4 Hirota et al, Pathol Int. 2006 Jan;56(1):1-9.
- 5 Rossi et al, Histopathology. 2005 May;46(5):522-31.
- 6 Miyaki et al, Nippon Rinsho. 2000 Jun;58(6):1225-30. Review.
- 7 Shiozawa et al, J Gastroenterol Hepatol. 2005 Jul;20(7):1132-4.

2.6.2.3 Secondary pharmacodynamics:

See section 2.6.2.4 Safety Pharmacology

2.6.2.4 Safety pharmacologyNeurological effects:**SU011248: Effect on general behavior (Irwin's test) and body temperature in the rat after oral administration (2000-0325; Volume 4.2.1.3; GLP)**

The CNS pharmacology of SU011248 was evaluated using the Irwin test and rectal temperature test in rats.

Five non-fasted rats/sex/dose were given a single oral bolus administration of SU011248 at doses of 20, 100, or 500 mg/ kg, or vehicle. General behavior was assessed 1, 3, 6, and 24 hours after treatment. Behavioral signs in individual animals were scored on an categorical scale. Rectal temperature was recorded before treatment and 1, 3, 6, and 24 hours after treatment.

Oral administration of SU011248 did not induce any modification of behavior or body temperature up to the dose of 500 mg/ kg, both in male and female animals. The dose of 500 mg/ kg was determined to be the NOEL for behavioral effects in rats.

Cardiovascular effects:**SU011248: Evaluation of effect on cardiac action potential in isolated canine purkinje fibers (20000612P; Volume 4.2.1.3; GLP).**

The effect of SU011248 on cardiac repolarization in cardiac purkinje fibers isolated from adult beagle dogs was evaluated. Isolated fibers were exposed to increasing concentrations of SU011248 [3.98, 39.8, 398, 3980 ng/mL; n=6/group]. Action potential duration was determined at 2 stimulation rates (60 and 20 pulses per minute).

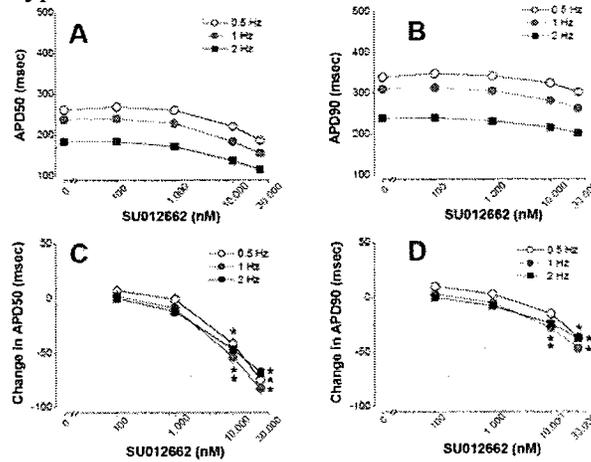
SU011248 increased the action potential duration in canine purkinje fibers [APD 70 (12 ms) and APD 90(22 ms)] at 3980 ng/mL under normal stimulation rate (60 ppm). Increases were also noted at 398 mg/mL [APD 90 (13 ms)] and 3980 [APD 70 (34 ms) and APD 90 (49ms)] with low stimulation (20ppm).

Clinically, Cmax of SU011248 on day 28 of cycle 1 was approximately 46 ng/mL.

SU12662: Effect on left ventricular canine purkinje fiber cell action potential (2001-0073; Volume 4.2.1.3, nonGLP).

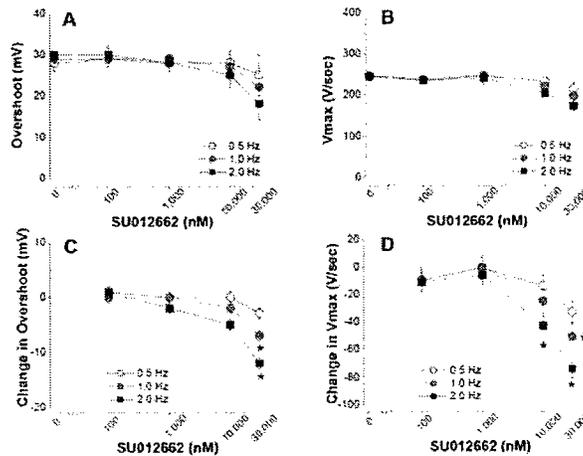
The effect of SU12662, the primary metabolite of SU011248, on repolarization of cardiac purkinje fibers isolated from adult beagle dogs was evaluated. Isolated fibers were exposed to increasing concentrations of SU12662 (37, 370, 3700, 11100 ng/mL). Action potential duration was determined at 3 stimulation rates (0.5 Hz, 1.0 Hz, 2.0 Hz).

APD50 and APD90: SU12662, at 3700 ng/mL and 11,000 ng/mL produced a concentration- dependent shortening of APD50 and APD90 at all stimulation rates relative to vehicle- time control, and reduced action potential plateau height. At a concentration of 3700 ng/mL, SU12662 shortened APD50 by up to 54 msec and APD90 by up to 28 msec. At a concentration of 11,000 ng/mL, SU12662 shortened APD50 by 83 msec and APD90 by up to 47 msec. (See graphs excerpted from the sponsor’s submission). This shortening effect was more pronounced at 50% repolarization than at 90% repolarization. The shortening of action potential duration is consistent with block of inward currents, most likely blockade of L- type calcium channels.



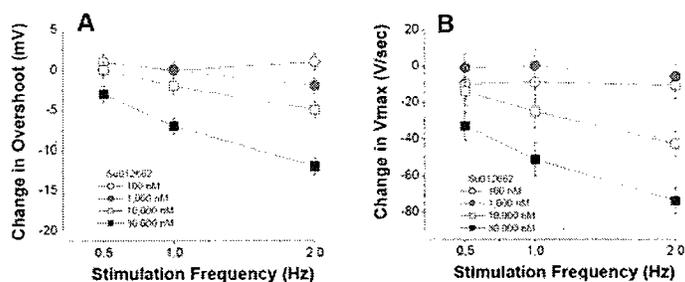
Best Possible Copy

V_{max} and Overshoot: SU- 12662 (11100 ng/mL) significantly decreased V_{max} and OS at 1 (51 V/s) and 2 Hz (74 V/s). At a concentration of 3700 ng/mL SU12662 significantly decreased V_{max} at 2 Hz (43 V/s). This inhibitory effect of SU12662 on V_{max} was rate-dependent with greater effect at faster versus slower stimulation rates. (See graphs excerpted from the sponsor’s submission.)



Best Possible Copy

These changes in APD were independent of changes in stimulation rate. No significant effect on cell repolarization was noted for 37 and 370 ng/mL SU12662.



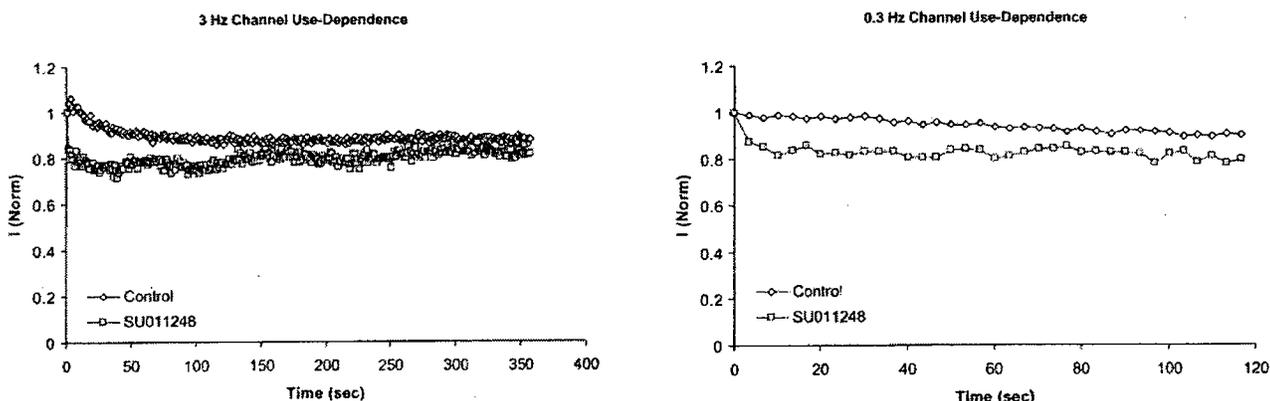
Other Action Potential Parameters: SU12662, at concentrations of 37, 370, and 3700 ng/mL had no significant biologically relevant effects on resting membrane potential. At a concentration of 11100 ng/mL, SU12662 depolarized membrane potential by 6 mV at 2 Hz. There were no notable effects on stimulation threshold and action potential morphology.

Clinically, Cmax of SU012662 on day 28 of cycle 1 was approximately 82.4 ng/mL.

Effect of SU011248 on cloned hERG channels expressed in mammalian cells. (001127.TVH; Volume 4.2.1.3, GLP)

The effect of SU011248 (3.98, 39.8, 119.4, 398 ng/mL) on *in vitro* hERG current was evaluated to assess the potential for delayed repolarization and prolongation of the QT interval. HERG (human-Ether-a-go-go Related Gene) is a gene encoding the pore forming subunit of a human delayed rectifying potassium channel, and blockade of hERG current has been associated clinically with delayed repolarization and proarrhythmic responses in humans.

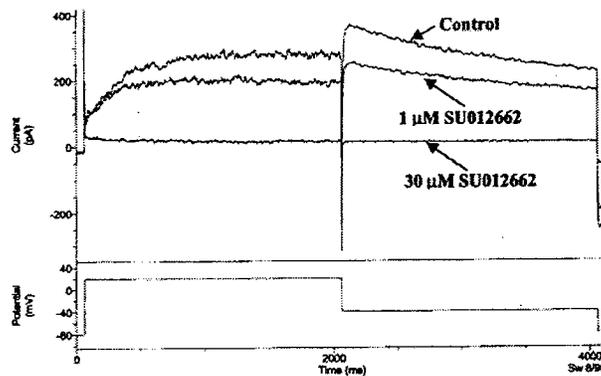
SU011248 block of hERG current was concentration dependent with an IC50 of 266 nM (105.9 ng/mL). The block of hERG current showed minimal use-dependence at 0.3 and 3 Hz. (See graph excerpted from the sponsor’s submission.)



Effect of SU012662(-Desethyl of SU011248) on cloned hERG channels expressed in mammalian cells (010122.TVH; Volume 4.2.1.3, non-GLP)

The effect of SU012662 (on *in vitro* hERG current was evaluated to assess the potential for delayed repolarization and prolongation of the QT interval

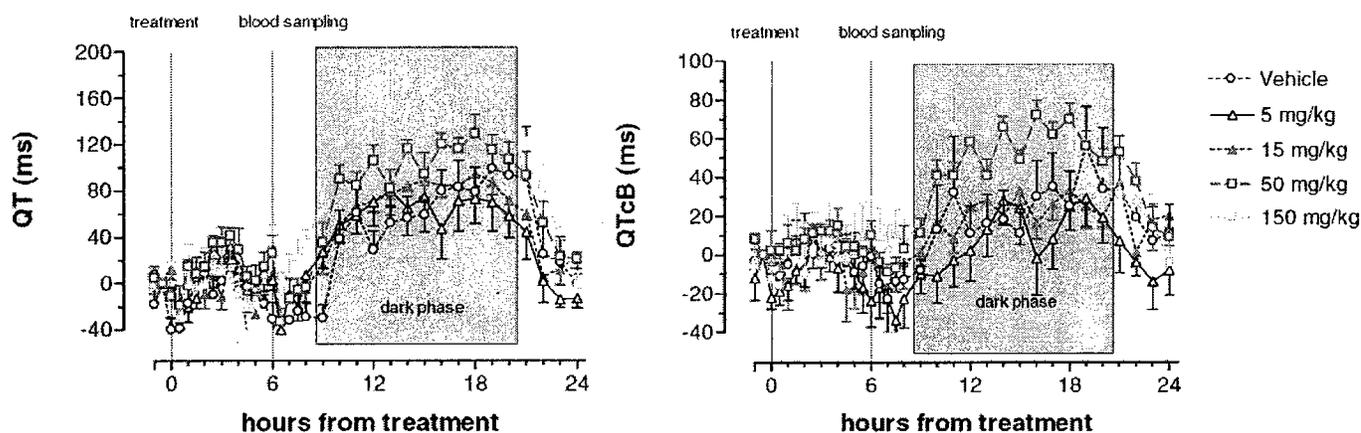
SU012662 blocked hERG currents with an IC_{50} of $4.1 \mu M$ ($1.5 \mu g/mL$; See graph excerpted from the sponsor's submission). There did not appear to be use dependence over the frequency range tested (0.3 and 3 Hz).



SU011248: Effect on cardiovascular parameters and body temperature in conscious cynomolgus monkeys after oral administration (2000-0339; Volume 4.2.1.3; GLP)

The effect of oral SU011248 on cardiovascular parameters and body temperature was assessed in telemetered cynomolgus monkeys ($n=2/\text{sex}$). SU011248 was administered at successive doses of 5, 15, 50, or 150 mg/kg producing plasma concentrations of 204 ± 33 , 277 ± 47 , 326 ± 105 , and 288 ± 14 ng/mL (due to vomiting), respectively, at 6 hours post-dose. SU012662 concentrations were not determined.

- There were no drug dependent effects on heart rate, body temperature or locomotor activity noted.
- 50 mg/kg: QT interval increased 40-60 ms from 9-14 hours
- 150 mg/kg: Emesis noted in all animals within 6 hours of dosing. Prolongation of QT interval, 53-111 ms, from 8-18 hours. QTc peak effect, identified 15 hours after treatment, was 66 msec when compared to control and higher than 400 ms from 11-18 hours post dose (see graphs excerpted from the sponsor's submission). Given PK was not conducted it is not possible to relate peak QT changes with peak plasma concentration for this study, however in other PK and toxicology studies, T_{max} occurred at < 8 hours post-dose.



Pulmonary effects:

SU010398 (SU011248 L-malate salt): Effect on respiratory function in the unrestrained conscious rat after single oral administration (2002-0494; Volume 4.2.1.3; GLP)

The effect of oral SU010398 (20, 100, and 500 mg/kg; free base equivalent) on pulmonary function was evaluated in conscious male Sprague Dawley rats (n=8/dose). Indices of pulmonary function (respiratory rate, peak inspiration flow, peak expiration flow, inspiration time, expiration time, relaxation time, tidal volume, minute volume, and enhanced pause) were measured approximately 60 minutes prior to dosing and continued 4 hour post dose every 5 minutes. Theophylline (100 mg/kg) was used as the positive control for this study.

Drug dependent findings were limited to a 30% increase in tidal volume at 30 minutes to 2 hours post-dose. The positive control resulted in clear modification of all measured parameters. Given that the increase in tidal volume occurred independent of other measures, it appears that the NOAEL for SU010398 on respiratory function is 500 mg/kg.

Other:

[] Data Report on Compound SUG-15 (AKA D-0026, SU011398, SU011248 L malate) For Sugen, Inc. (1030851; Volume 4.2.1.2)

To establish the specificity of SU011248 for receptor tyrosine kinases, SU011248 was evaluated in numerous *in vitro* ligand-binding assays of different receptor systems. The receptors included in this assay were adenosine, adrenergic (α_{1A} , α_{1B} , α_{1D} , α_{2A} , α_{2B} , β_1 , β_2), bradykinin, Ca^{2+} channel (L and N-type), cholecystokinin, dopamine receptor and transporter, endothelin, epidermal growth factor, estrogen, GABA receptors and transporters, glucocorticoid, glutamate (kainite, NMDA), histamine, imidazoline, interleukin, leukotriene, muscarinic, neuropeptide, nicotinic, opiate, phorbol ester, platelet activating factor, K^+ channel, purinergic, serotonin receptors and transporters, sigma, Na^+ channel, tachykinin, testosterone, norepinephrine transporter, and tumor necrosis factor. Significant findings ($\geq 50\%$ inhibition with $\leq 10 \mu M$) are presented in the table below (excerpted from the sponsor's submission).

Of note is the inhibition of serotonin receptors (5-HT_{2A}) and transporters, and adrenergic receptors (α_{1A}) in cellular assays at levels that are less than 2 fold the observed steady state concentrations in clinic trials (see table below, excerpted from the sponsor's submission.

RADIOLIGAND ASSAY	SPECIES	CONC.	% INH.	IC ₅₀ *	K _i	n _H
Serotonin (5-Hydroxytryptamine) 5-HT _{2A}	hum	0.1 μM	52	0.0918 μM	0.0262 μM	0.879
Adrenergic α _{1B}	rat	1 μM	83	0.168 μM	0.0928 μM	0.835
Transporter, Serotonin (5-Hydroxytryptamine) (SERT)	hum	1 μM	80	0.2 μM	0.106 μM	0.829
Sigma σ ₁	hum	1 μM	69	0.433 μM	0.182 μM	0.919
Adrenergic α _{1A}	rat	1 μM	71	0.501 μM	0.203 μM	1.28
Muscarinic M ₁	hum	10 μM	98	1.49 μM	0.359 μM	2.22
Calcium Channel L-Type, Benzothiazepine	rat	1 μM	54	0.766 μM	0.681 μM	1.13
Adrenergic α _{1D}	hum	10 μM	84	1.57 μM	0.77 μM	1.34
Histamine H ₂	rat	10 μM	74	3.26 μM	0.844 μM	1.18
Sigma σ ₂	rat	10 μM	79	1.41 μM	0.867 μM	0.741
Imidazoline I ₂ , Central	rat	10 μM	93	1.38 μM	0.92 μM	1.51
Adrenergic α _{2A}	hum	10 μM	79	2.59 μM	0.973 μM	0.929
Sodium Channel, Site 2	rat	10 μM	104	1.35 μM	1.24 μM	1.99
Muscarinic M ₃	hum	10 μM	66	5.98 μM	1.27 μM	1.3
Muscarinic M ₂	hum	10 μM	80	3.67 μM	1.3 μM	1.41
Purinergic P _{2Y}	rabbit	10 μM	50	7.64 μM	1.65 μM	1.02
Dopamine D ₂	hum	10 μM	53	5.66 μM	1.92 μM	0.865
Dopamine D _{2L}	hum	10 μM	53	6.6 μM	2.32 μM	0.396
Platelet Activating Factor (PAF)	hum	10 μM	63	5.09 μM	2.65 μM	1.29
Adrenergic α _{2B}	hum	10 μM	62	5.85 μM	2.67 μM	1.01
Transporter, Norepinephrine (NET)	hum	10 μM	72	2.75 μM	2.73 μM	0.845
Calcium Channel L-Type, Dihydropyridine	rat	10 μM	55	4.77 μM	3.07 μM	0.566
Transporter, Dopamine (DAT)	hum	10 μM	72	3.94 μM	3.13 μM	1.15

Best Possible Copy

2.6.2.5 Pharmacodynamic drug interactions

Not specifically addressed in the sponsor's application.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Summary of Safety Pharmacology Studies

Study #/ Organ System	Method of Administration	Species	Doses	Gender/N	Findings
1030851	<i>In vitro</i>	Human, Rat Rabbit Tissue/cell lines	NA	NA	Significant inhibition of 5HT _{2A} - IC ₅₀ =0.0818 μM Adrenergic (α _{1B})- IC ₅₀ =0.168 μM Serotonin Transporter- IC ₅₀ =0.2 μM
2000-0325/ CNS- Irwin's test	Oral	Rat	20, 100, 500 SU011248 mg/kg	Male Female N=5/sex/dose	No significant CNS or body temp effect up to 500 mg/kg NOEL= 500 mg/kg
20000612P/ Canine	<i>In vitro</i>	Dog Tissue	3.98, 39.8, 398, and	N=6, unspecified	60 ppm (normal stim) 3980 ng/mL:

Study #/ Organ System	Method of Administration	Species	Doses	Gender/N	Findings
Purkinje Fiber			3980 SU011248 ng/mL	gender	<p>↑ APD₇₀- 12 ms</p> <p>↑ APD₉₀- 22 ms</p> <p>20 ppm (low stim)</p> <p><u>398 ng/mL:</u></p> <p>↑ APD₉₀-13 ms</p> <p><u>3980 ng/mL:</u></p> <p>↑APD₇₀- 34 ms</p> <p>↑APD₉₀-49 ms</p>
2001-0073/ Canine Purkinje Fiber	<i>In vitro</i>	Dog Tissue	37, 370, 3700, 11100 ng/mL SU12662	N=6; unspecified gender	<p>↓APD₅₀ and APD₉₀ at all stimulation rates (28-83 ms) with ≥3700 ng/mL. More pronounced effect on APD₅₀.</p> <p>↓ Vmax and overshoot at 1 (51 V/s) and 2 Hz (74 V/s) with 11100 ng/mL and Vmax at 2Hz (43V/s) with 3700 ng/mL.</p>
001127.TVH/ hERG current	<i>In vitro</i>	NA; transgenic cell line	3.98, 39.8, 119.4, 398 ng/mL SU011248	NA; N=4-5	IC ₅₀ = 105.9 ng/mL
010122.TVH/ hERG current	<i>In vitro</i>	NA; transgenic cell line	0.37, 1.85, 3.7, 11.1 ng/mL SU12662	NA; N=3-5	IC ₅₀ = 1.5 µg/mL
2000.0339 Cardiovascular Conscious telemetered	Oral	Monkey	5, 15, 50, 150 mg/kg	Male/Female; N=2/sex	<p><u>50 mg/kg:</u> ↑QT 40-60 ms at 9-14 hours</p> <p><u>150 mg/kg:</u> ↑QT 53-111 ms at 8-18 hours in spite of emesis of drug product within 6 hours of administration.</p> <p>QTc peak effect at 15 hours and was 66 ms</p> <p>NOEL_{CV} =15 mg/kg</p>
2002-0494 Pulmonary	Oral	Rat	20, 100, 500 mg/kg free base equivalent	Male; N=8	<p><u>500 mg/kg:</u> ↑30% in tidal volume, 0.5-2 hrs post-dose</p> <p>NOAEL_{Pulmonary} =500mg/kg</p>

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

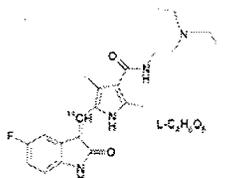
2.6.4.1 Brief summary

PK studies were conducted in mouse, rat, monkey and dog. The rat and monkey are the pivotal species reviewed herein.

2.6.4.2 Methods of Analysis

Analytical methods for the quantitation of SU011248 and SU012662 utilized high-performance liquid chromatography-tandem mass spectrometric (LC/MS/MS) methods in mice, rats, rabbits, dogs and monkeys plasma and monkey tissue. The plasma samples were prepared by solvent extraction or protein precipitation and utilized either propranolol or deuterium labeled SU011248 as the internal standard. LC/MS/MS methods were validated over a concentration range of 1-2000ng/mL in rat, dog, and monkey. In additional studies the validated concentration range of 0.1-200 ng/mL were also determined in rat and monkey plasma.

[³H]SU011248 was chemically unstable, therefore [¹⁴C]SU010398 (SU011248-L-Malate; see figure below) was used in metabolism and mass balance studies in rats, monkeys and humans. Radioactivity in plasma, urine and bile was measured by liquid scintillation counting and was determined using external standardization for quench correction.



[¹⁴C]SU010398

2.6.4.3 Absorption

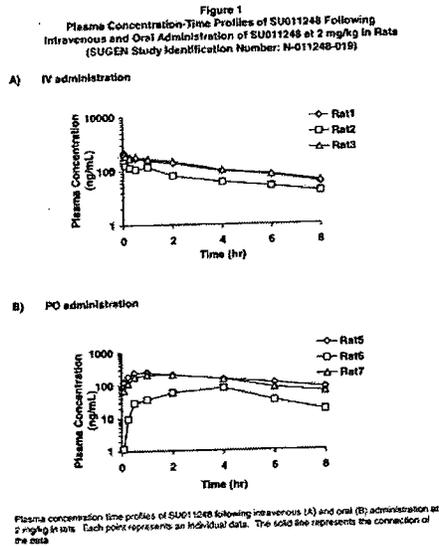
Pharmacokinetics of SU011248 following IV and oral administration at 2 mg/kg in rats (SU011248-PDM-034; Volume 4.2.2.2; nonGLP; previous review by Dr. Schmidt, Review #1, modified herein)

In rats (gender not specified) SU011248 was administered 2 mg/kg by IV bolus or PO gavage (n=3/route). The vehicle was 31.5 % Cremophor EL, 2.0% Benzyl Alcohol, 45% PEG 400, qs'd with anhydrous alcohol. PK sampling occurred at 2 (IV only), 5, 15, and 30 minutes and 1, 2, 4, 6, 9 and 12 hours post-dose. Bioavailability was estimated at approximately 100% following oral administration.

PK Parameters	IV	Oral
C _{max} (ng/mL)		177 ± 86
T _{max} (h)		2.0 ± 2.0
AUC _{0-tlast} (ng hr/mL)		896 ± 461
AUC _{0-∞} (ng hr/mL)	996 ± 439	1178 ± 691
Cl _s [ml/(min kg)]	40 ± 23	
T _{1/2} (hr)	2.52 ± 0.04	
%F*		112 ± 34

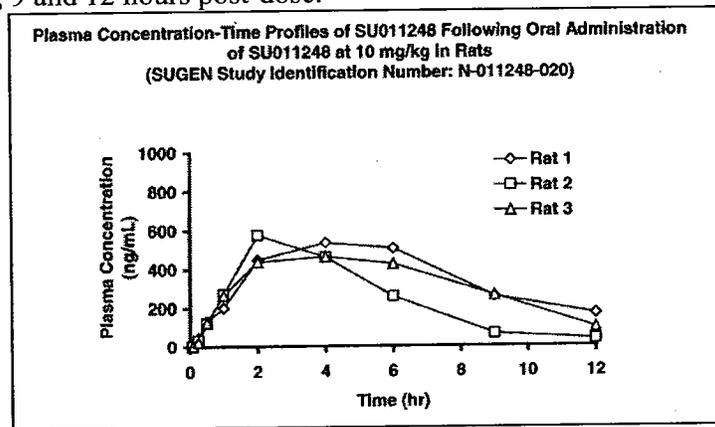
*%F was greater than 100% due to a large area determined by extrapolation.

Best Possible Copy



Pharmacokinetics of SU011248 following oral administration in a carboxymethylcellulose (CMC) formulation at 10 mg/kg in rats (SU011248-PDM-031; Volume 4.2.2.2; non-GLP; previously reviewed by Dr. Schmidt, Review #1, modified herein)

In rats, SU011248 (10 mg/kg) was administered PO (n=3). The vehicle was 0.5% CMC, 0.9% NaCl, 0.4% Polysorbate 80, 0.9% benzyl alcohol, qs'd with water. PK sampling occurred at 5, 15, and 30 minutes and 1, 2, 4, 6, 9 and 12 hours post-dose.



SU011248 was detectable in plasma with a t_{max} between 2.0 and 4.0 hours after 10 mg/kg. This is a shift in the concentration over time curve where t_{max} was observed at 2 hours post-dose with the Cremophor formulation (discussed above). C_{max} ranged from 463 to 575 ng, whereas $AUC_{0-\infty}$ ranged from 3009 to 5119 ng hr/mL. These results indicate that SU011248 pharmacokinetics are dependent on formulation (this was an impetus to change the salt form of the product.)

Effect of Food on SU011248 exposure following oral administration to male cynomolgus monkeys (SU011248-PDM-063; Volume 4.2.2.2; non-GLP)

The effects of food on the exposure to SU011248 free base after oral administration (15 mg/kg) was evaluated in male Cynomolgus monkeys as a crossover study with a 14 day washout period.

Additionally, SU011248 malate salt was evaluated in the CMC suspension and in capsule formulation following a 6 day washout under fasted conditions. Blood samples were collected predose and at 0.5, 1, 3, 6, 12, and 24 hours post-dose. Following oral administration, SU011248 was rapidly absorbed ($t_{max}=3-9$ hours). There was not a statistically significant difference in exposure when comparing the fasted and fed states as the freebase, however a clear trend toward increased AUC was observed in the second session (see graph below).

After administration of the malate salt, SU011248 was rapidly absorbed ($T_{max}3-6$ hours) regardless of formulations. In animals dosed with the CMC formulation of the L malate salt, exposure appeared higher than when dosed with the capsule. C_{max} and AUC values were approximately 63% and 69% of the SU011248 malate salt in a CMC suspension.

	Fasted (CMC)	Fed (CMC)	Fasted (Capsule)
Session I (n=3)			
C_{max} (ng/mL)	92.4 ± 30	61.9 ± 44	
T_{max} (hr)	5.0 ± 3.5	4.0 ± 1.7	
$T_{1/2}$ (hr)	4.6 ± 1.0	4.25 ± 1.0	
$AUC_{0-t_{last}}$ (ng hr/mL)	1053 ± 316	599 ± 447	
$AUC_{0-\infty}$ (ng hr/mL)	1109 ± 349	622 ± 433	
Session II (n=2)*			
C_{max} (ng/mL)	254 ± 39	139	
T_{max} (hr)	7.0 ± 1.7	3.0	
$T_{1/2}$ (hr)	5.58 ± 0.96	5.31	
$AUC_{0-t_{last}}$ (ng hr/mL)	3428 ± 218	1549	
$AUC_{0-\infty}$ (ng hr/mL)	3720 ± 221	1642	
Session III (SU011248 L malate administered)			
C_{max} (ng/mL)	246 ± 56		155 ± 68
T_{max} (hr)	4.0 ± 1.7		5.0 ± 1.7
$T_{1/2}$ (hr)	5.35 ± 0.31		6.10 ± 2.1
$AUC_{0-t_{last}}$ (ng hr/mL)	2978 ± 720		2069 ± 1126
$AUC_{0-\infty}$ (ng hr/mL)	3178 ± 797		2266 ± 1161

*due to infection

Appears This Way
On Original

Excerpted from the sponsor's submission

Mean Pharmacokinetic parameter of SU011248 Following Oral Administration of SU011248 in Monkeys at 15 mg/kg free base equivalent (SUGEN Study Identification Number: N-011248-025)

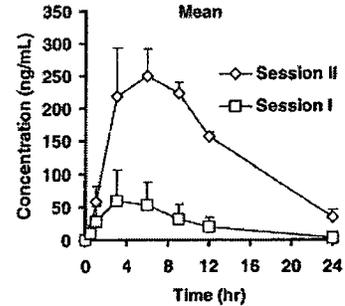
	Mean AUC _{0-t last} (ng.hr/mL)		
	Session		
	I	II	III
Group 1	1053 ±316*	1549 NA**	2978 ±720* †
Group 2	599 ±447**	3428 ±218*	2069 ±1126** †

* Fasted

** Fed

† Dosed SU011248 malate salt as API powder in capsule

‡ Dosed SU011248 malate salt as a suspension



2.6.4.4 Distribution

Determination of the Tissue Distribution of Total Radioactivity in the Rat by Quantitative Whole Body Autoradiography Following Oral Administration of [¹⁴C]- SU010398 (The L-Malate Salt of SU011248) (SU011248-PDM-056; Volume 4.2.2.3; non-GLP)

Following a single oral administration of [¹⁴C]-SU010398 to adult male and female Sprague-Dawley (SD, albino, n=5) and Lister Hooded rats (LE, pigmented, n=4) at a target dose of 15 mg/kg (free base) and 100 µCi/kg (radioactivity), the concentration of total radioactivity were determined in selected tissues up to 72 h post dose. One male and 1 female albino rat were sacrificed at 3, 6, 24, 72 and 168 hours post-dose, whereas 1 male and 1 female pigmented rat were sacrificed at 24, 72, 168 and 336 h post-dose.

Appears This Way
On Original

Table 1.1 Concentration of Total Radioactivity ($\mu\text{g.equiv./g}$) in Tissues Following a Single Oral Administration of [^{14}C]SU010398 to Male Albino Rats**Target Dose Level: 20 mg/kg SU010398 (15 mg/kg free base SU011248 equivalent)**

Tissue	Rat No.	001M	002M	003M	004M	005M
	Time	3 h	6 h	24 h	72 h	168 h
Adrenal cortex		26.98	14.16	4.53	1.89	0.43
Adrenal medulla		16.12	15.14	4.07	0.45	0.15
Adrenal (whole)		25.22	13.57	4.11	1.52	0.31
Bladder		3.22	2.56	0.35	*0.05	*0.03
Blood		1.12	0.84	0.07	*0.05	*0.03
Bone marrow		7.55	6.60	0.38	*0.05	*0.03
Brain		0.30	0.34	*0.02	0.07	*0.03
Brown fat		8.47	7.57	0.46	*0.05	*0.03
Epididymis		1.89	2.23	1.40	0.08	*0.03
Eye		1.10	1.34	0.08	*0.05	*0.03
Harderian gland		9.92	11.14	0.84	0.10	*0.03
Heart		5.58	4.61	0.36	*0.05	*0.03
Kidney cortex		12.47	8.55	0.87	0.13	*0.03
Kidney medulla		15.15	9.62	2.10	0.24	*0.03
Kidney (whole)		13.24	9.43	1.43	0.16	*0.03
Lachrymal gland		8.82	13.48	4.70	0.41	*0.03
Large intestine wall		6.05	5.38	1.50	0.08	*0.03
Liver		15.71	10.70	1.70	0.24	*0.03
Lung		20.70	17.87	0.87	*0.05	*0.03
Lymph node		8.86	11.26	0.90	*0.05	*0.03
Pancreas		11.10	9.18	1.68	*0.05	*0.03
Pineal body		NP	NP	0.60	*0.05	*0.03
Pituitary gland		24.34	22.94	7.90	2.70	0.76
Preputial gland		12.60	10.53	13.66	0.13	*0.03
Prostate		6.29	4.84	0.43	*0.05	*0.03
Rectum		2.78	2.61	1.00	0.11	*0.03
Salivary gland		17.24	12.14	1.25	0.14	*0.03
Seminal vesicles		2.69	3.15	0.40	*0.05	*0.03
Skeletal muscle		2.92	2.30	0.16	*0.05	*0.03
Skin-albino (back)		2.55	2.46	0.30	0.17	0.24
Skin-albino (abdomen)		2.81	3.45	3.39	0.27	*0.03
Small intestine wall		8.91	5.54	1.55	0.15	*0.03
Spinal cord		0.19	0.29	*0.02	*0.05	*0.03
Spleen		20.52	16.24	1.23	0.20	*0.03
Stomach wall		10.15	9.30	1.13	*0.05	*0.03
Testis		0.79	0.90	2.80	0.39	0.30
Thymus		6.89	6.43	0.58	*0.05	*0.03
Thyroid gland		18.40	18.76	1.40	0.24	*0.03
Uveal		2.63	5.08	0.13	*0.05	*0.03
White fat		0.72	0.60	*0.02	*0.05	*0.03
Limit of reliable measurement:		0.03	0.04	0.04	0.05	0.03
Right eye (LSC)		1.78	1.08	0.30	†0.01	†0.01
Whole blood (LSC)		1.37	1.25	0.13	†0.00	†0.00

* = Value below the limit of reliable measurement

NP = Tissue not present in sections

LSC = Tissue analyzed by combustion and liquid scintillation counting

† = Data calculated from results below 30 disintegrations per minute (dpm) above background

Table 1.2. Concentration of Total Radioactivity ($\mu\text{g.equiv./g}$) in Tissues Following a Single Oral Administration of [^{14}C]SU010398 to Male Pigmented Rats

Target Dose Level: 20 mg/kg SU 010398 (15 mg/kg free base SU011248 equivalent)

Tissue	Rat No.	006M	007M	008M	009M
	Time	24 h	72 h	168 h	336 h
Adrenal cortex		4.91	1.72	0.85	0.19
Adrenal medulla		2.19	0.32	0.30	0.05
Adrenal (whole)		4.30	1.40	0.74	0.16
Bladder		0.48	*0.04	0.06	*0.02
Blood		0.16	*0.04	0.06	*0.02
Bone marrow		0.55	*0.04	0.06	*0.02
Brain		0.06	*0.04	0.06	*0.02
Brown fat		0.85	*0.04	0.06	*0.02
Epididymis		0.68	*0.04	0.06	*0.02
Eye		7.80	23.98	28.52	39.40
Harderian gland		1.05	*0.04	0.06	*0.02
Heart		0.43	*0.04	0.06	*0.02
Kidney cortex		1.53	0.16	0.06	*0.02
Kidney medulla		0.98	0.28	0.06	*0.02
Kidney (whole)		1.88	0.26	0.06	*0.02
Lachrymal gland		0.94	*0.04	0.06	*0.02
Large intestine wall		0.69	0.08	0.06	*0.02
Liver		2.09	0.22	0.06	*0.02
Lung		1.55	*0.04	0.06	*0.02
Lymph node		1.03	*0.04	0.06	*0.02
Pancreas		1.23	*0.04	0.06	*0.02
Pineal body		NP	*0.04	0.06	*0.02
Pituitary gland		7.71	1.65	81.06	*0.02
Preputial gland		7.53	7.84	0.06	*0.02
Prostate		0.44	*0.04	0.06	*0.02
Rectum		1.18	*0.04	0.06	*0.02
Salivary gland		3.52	*0.04	0.06	*0.02
Seminal vesicles		0.34	*0.04	0.06	*0.02
Skeletal muscle		0.30	*0.02	0.06	*0.02
Skin-albino (back)		0.56	*0.04	0.06	*0.02
Skin-albino (abdomen)		5.57	0.64	0.58	0.30
Skin (pigmented)		4.90	1.47	4.10	*0.02
Small intestine wall		0.82	0.07	0.06	*0.02
Spinal cord		*0.05	*0.04	0.06	*0.02
Spleen		1.63	0.13	0.06	*0.02
Stomach wall		0.67	*0.04	0.06	*0.02
Testis		2.27	0.87	0.91	0.17
Thymus		0.67	*0.04	0.06	*0.02
Thyroid gland		0.72	*0.04	0.06	*0.02
Uveal		18.79	147.37	111.78	100.17
White fat		0.30	*0.04	0.06	*0.02
Limit of reliable measurement:		0.05	0.04	0.04	0.03
Right eye (LSC)		31.56	26.43	23.43	17.20
Whole blood (LSC)		0.21	†0.00	†0.00	†0.00

* = Value below the limit of reliable measurement

NP = Tissue not present in sections

LSC = Tissue analyzed by combustion and liquid scintillation counting

† = Data calculated from results below 30 dpm above background

- Highest concentrations were noted the adrenals, lung, rectum, pituitary, and spleen at 3 hours post-dose, the first timepoint analyzed, in male and female albino rats. Lowest concentrations were observed in the brain, spinal cord and white fat. Radioactivity was eliminated so that by 72 h post-dose, the majority of tissues were below the limit of measurement.
- A similar pattern of distribution was noted in pigmented rats with the exception of pigmented and some glandular tissues. The level of radioactivity in pigmented eyes of LE rats at 24 hours averaged 7.8 µg Eq/g, compared to 1.1 µg Eq/g present in albino rats. The concentration in the eye of SD rats declined gradually however concentration increased significantly in LE rats (up to 336 hours post-dose). Concentrations in the uveal tract increased in concentration up to 6 hours post dose in albino rats, but increased up to 72 hours in male LE rats and 336 hours in female LE rats. Although concentrations in the pituitary and thyroid peaked at 24 hours in albino rats, concentrations appeared to increase up to 336 hours in pigmented male rats. In female pigmented rats, concentrations (124-323 µg Eq/g) were noted throughout the sampling period, with higher concentrations noted at later timepoints.
- The mean concentrations of radioactivity in pigmented skin were approximately 2 fold higher than concentrations in albino rats at 24 hours. In albino animals, concentrations fell sharply after 24 hours in contrast to pigmented animals where concentrations remained relatively stable for up to 168 hours. These findings combined with findings in the eye and uveal tract suggest a high degree of melanin-associated binding of radioactivity.

Plasma protein binding of SU011248 (SU011248-PDM-060, Volume 4.2.2.3; GLP)

Protein binding evaluation of SU012662 (SU011248-PDM-061, Volume 4.2.2.3; non-GLP)

Plasma protein binding of SU011248 using ultrafiltration and equilibrium dialysis (SU011248-PDM-038, Volume 4.2.2.3; non-GLP)

The *in vitro* protein binding of [¹⁴C]-SU011248 and [¹⁴C]-SU012662 was determined using an ultracentrifugation technique combined with LC/MS/MS in mouse (albino and nude), rat, dog, monkey and/or human plasma at concentrations of 0.25, 1, and 10µM. To determine the extent of loss during ultrafiltration, a study was conducted. It was found that significant nonspecific binding to assay materials was observed with ultrafiltration, and accounted for a 3 - 22% loss. Based on these results, ultracentrifugation was utilized to minimize this, results are summarized below.

The fraction of bound SU011248 and SU012662 was independent of drug concentration and was similar in man, monkey and dog plasma. Higher binding was observed in the rat while lower binding was observed in the mouse.

% Bound in plasma

Conc (µM)	Albino Mouse	Nude Mouse	Rat	Dog	Monkey	Human
SU011248 ultracentrifugation						
0.25	88.28 ± 5.9	91.93 ± 2.74	97.79 ± 0.65	94.47 ± 0.57	95.21 ± 0.68	96.35 ± 0.77
1	90.72 ± 2.98	95.10 ± 2.31	97.41 ± 0.19	95.54 ± 0.31	95.32 ± 0.37	95.87 ± 0.85
10	85.4 ± 2.72	95.30 ± 0.91	98.06 ± 0.39	95.07 ± 0.28	93.50 ± 1.33	93.5 ± 1.33
SU012662 ultracentrifugation						
0.25	94		NC	81.14 ± 6.57	84.77	90.43 ± 0.58

Conc (µM)	Albino Mouse	Nude Mouse	Rat	Dog	Monkey	Human
1.0	96.29 ± 0.22		98.58 ± 0.18	87.87 ± 0.57	84.84 ± 2.02	89.90 ± 1.28
10	94.26 ± 1.16		98.67 ± 0.15	88.07 ± 0.34	88.39 ± 0.97	89.20 ± 1.21

NC- not calculated, free fraction below the limit of quantitation

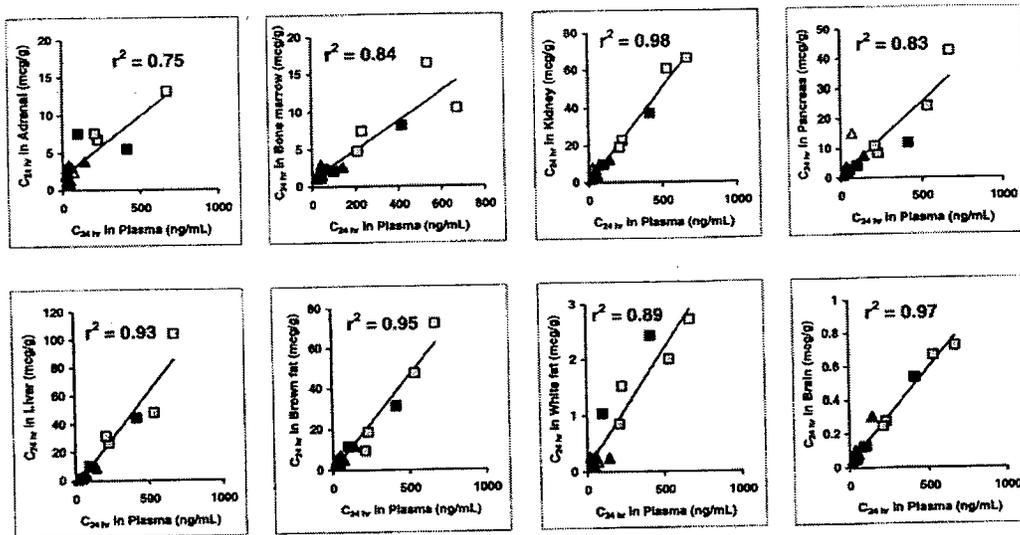
Concentrations of SU011248 and its metabolite, SU012662, in monkey adrenal, bone marrow, liver, kidney, pancreas, brain and white and brown fat (SU011248-PDM-057, Volume 4.2.2.3; non-GLP)

Tissue concentrations of SU011248 and SU012662 were determined in adrenal glands, vertebral bone marrow, liver, kidney, brown and white fat, pancreas and brain following SU011248-L-malate administration (6 and 12 mg freebase/kg; PO) to female Cynomolgus monkeys in this non-GLP study. SU011248-L-malate was administered daily x 56 followed by a 2, 4, or 6 week recovery prior to sacrifice, or 2 cycles of daily x 28 followed by a 2 week recovery period prior to sacrifice (n=4 for terminal necropsy and n=3 for recovery necropsies). (*Due to an early dosing termination, dosing in Group 4 animals was discontinued on either Day 44 or Day 45. In addition, six animals from Group 3 were mistakenly dosed for 57 rather than 56 consecutive days*)

The ratios of drug tissue levels to plasma levels (i.e. adrenal, bone marrow, pancreas, kidney, liver, and brown fat) were 13- to 308-fold at both 6 and 12 mg/kg/day dose levels. The corresponding ratio in the brain and white fat was low, i.e. 2- to 14-fold in white fat and 1- to 3- fold in the brain. At both dose levels, total drug concentrations in tissues one day after completion of the first 4-week cycle were comparable to those after the second 4-week cycle. Total drug concentrations one day after 4 weeks of dosing were comparable to those after 8 weeks of repeated dosing in most tested tissues, suggesting that drug concentrations in monkey tissues, except for adrenal and white fat, reached steady-state by 4 weeks of repeated daily dosing at 6 mg/kg/day. Total tissue drug concentrations 1 day after treatment at 6 and 12 mg/kg/day were less than 7 µg/g and 104 µg/g, respectively. After a 2-week washout, tissue levels of SU011248 and SU012662 were less than 1-5% of those observed 1 day post-dose for all dose groups. The levels of SU011248 and SU012662 were ≤0.4 µg/g after a 2- week washout at both dose levels in adrenal, bone marrow, pancreas, kidney, liver, and brown fat and ≤ 0.04 µg/g in brain and white fat tissues. After a 6-week washout, less than 0.2 µg/g was detected in all tissues. In all tissues tested, the systemic exposure (C_{max}, C_{24hr} and AUC) of the compounds correlated well (r²= 0.75-0.98) with the tissue levels (C_{24hr}) [see graphs excerpted from the sponsor's submission].

Appears This Way
On Original

Figure 3. Correlation of plasma concentration to tissue concentrations



2.6.4.5 Metabolism

SU011248 metabolite identification across species *in vivo* (SU011248-PDM-042; Volume 4.2.2.4)

In vitro and *in vivo* profiling of SU011248 metabolites (SU011248-PDM-043, Volume 4.2.2.4)

SU011248 metabolite identification across species *in vitro* (SU011248-PDM-044; Volume 4.2.2.4)

- SU011248 undergoes extensive NADPH-dependent metabolism in mouse, rat, dog, monkey and human liver microsomes. Microsomes from all species converted SU011248 to at least 8 metabolites. SU012662 is the major metabolite in mice, monkeys and human when incubated at concentrations of $\geq 2\mu\text{M}$ whereas in rat liver microsomes, SU012662 and the N-oxide (SU012487) were the major metabolites when incubated when incubated at a concentration of 2 uM SU011248, and SU012662 dominated the metabolism at 25 uM (see Table 2 on the following page, excerpted from the sponsor’s text). Additionally, hydroxylation on the phenyl ring and on one of the side chains were also detected in the mouse, rat, monkey, and human *in vitro* samples incubated at 25 uM SU011248. In dog liver microsomes, SU011248 was metabolized primarily through the formation of the N-oxide of the amine, SU012662 was detected at low abundance. Hydroxylation at various sites of the molecule was at trace levels. M7 was identified as SU012662 and M8 is SU01247 in this study. In later studies, SU012662 is designated as M1 and SU012487 as M2E.

Study System: Liver microsomes	SU011248	M1	M2	M3	M4	M5	M6	M7	M8
Species: Mouse, rat, dog, monkey and human									
Retention Time (min)	20.2	9.76	11.5	13.1	14.5	16.7	17.1	18.3	19.7
Microsomes:	SU011248 Conc. (μM) (Percent of Initial SU011248 Peak Area after 2-hour incubation)								
Mouse	2.00	45.8	1.26	2.30	6.60	1.50	NQ	0.20	1.20
	25.0	74.0	NQ	NQ	2.00	NQ	1.00	NQ	22.0
Rat	2.00	44.3	ND	ND	2.50	1.60	3.00	5.00	17.6
	25.0	72.0	ND	ND	NQ	NQ	2.00	NQ	18.0
Dog	2.00	17.3	ND	ND	ND	ND	NQ	NQ	3.40
	25.0	77.0	ND	ND	NQ	NQ	ND	ND	8.00
Monkey	2.00	53.7	ND	2.00	3.70	6.90	NQ	3.10	22.0
	25.0	84.0	1.00	NQ	NQ	2.00	5.00	1.00	36.0
Human	2.00	84.2	ND	NQ	ND	ND	3.10	ND	41.6
	25.0	47.0	NQ	NQ	ND	2.00	4.00	NQ	45.0

Additional Information: This report also contains *in vivo* data that is presented in Summary Table 2.6.5.9D
 NQ = Not quantified (conc. < 25 ng/mL [LQO]); ND = Not detectable
 Designation of metabolite M1 through M8 is used in the report only. The chemical structure of the metabolites M1 through M6 was not identified. M7 is SU012662 and M8 is SU012487. In later definitive studies, SU012662 is designated as M1 and SU012487 as M2E.

- Observations similar to the findings in *in vitro* studies were observed *in vivo* following oral (10 and 20 mg/kg) and IV (2 and 8 mg/kg) administration to mice, rats, dogs, and monkeys (see tables excerpted from the sponsor's submission).

Table 2. SU011248 *in vivo* metabolite summary.

Compound	Structure	Mouse Plasma	Rat Plasma	Dog Plasma	Monkey Plasma
SU011248		H ^a	H	H	H
SU012662 des-ethyl		H	M	M	M
N-oxide		L	M	L	L
5'-CH ₂ OH		N/D	L	L-T	L
OH on the phenyl ring		L	T	L	L
Phenyl Hydroxyl Sulfate		L	T	N/A	T
Phenyl Hydroxyl Glucuronide		L	L	N/A	T

^aAbundance of metabolites was assessed based on peak areas and labeled as H, M, L, T, N/D, N/A
H: high abundance >20%; M: medium abundance 10-20%; L: low abundance 1-10%;
T: trace level <1%; N/D: not detected; N/A: not applicable.

Species	Sample	Sample Time Points (h)	Metabolite Summary ^a								Report Number	Location		
			SU011248	M1	M2	M3	M4	M5	M6	M7		M8	Module	Volume
Rat ^b	Plasma	0.5, 1, 3, 6 and 9	18.7 36.0	9.4 NQ	11.2 ND	12.8 ND	13.4 ND	15.3 NQ	15.6 NQ	17.0 63.0	18.5 ND	SU011248- PDM-043		
Dog ^c	Plasma	2, 4, 6, 9, and 24	64.4	ND	NQ	ND	NQ	NQ	1.10	26.5	8.00			
Monkey ^d	Plasma	2, 3, 6, 9, and 24	54.3	NQ	NQ	1.40	2.20	4.00	2.10	36.0	ND			

Additional Information: This study also contains *in vitro* data that is presented in Summary Table 2.6.5.10B

^aPercent of total peak area for SU011248 and metabolites. Designation of metabolites M1 through M8 is used only in this study. The chemical structure of the metabolites M1 through M6 was not identified. M7 is SU012662 and M8 is SU012487. In later definitive studies, SU012662 is designated as M1 and SU012487 is M2E.

^bRat samples from E-002125.

^cDog samples from 2000-0184, Appendix 3.

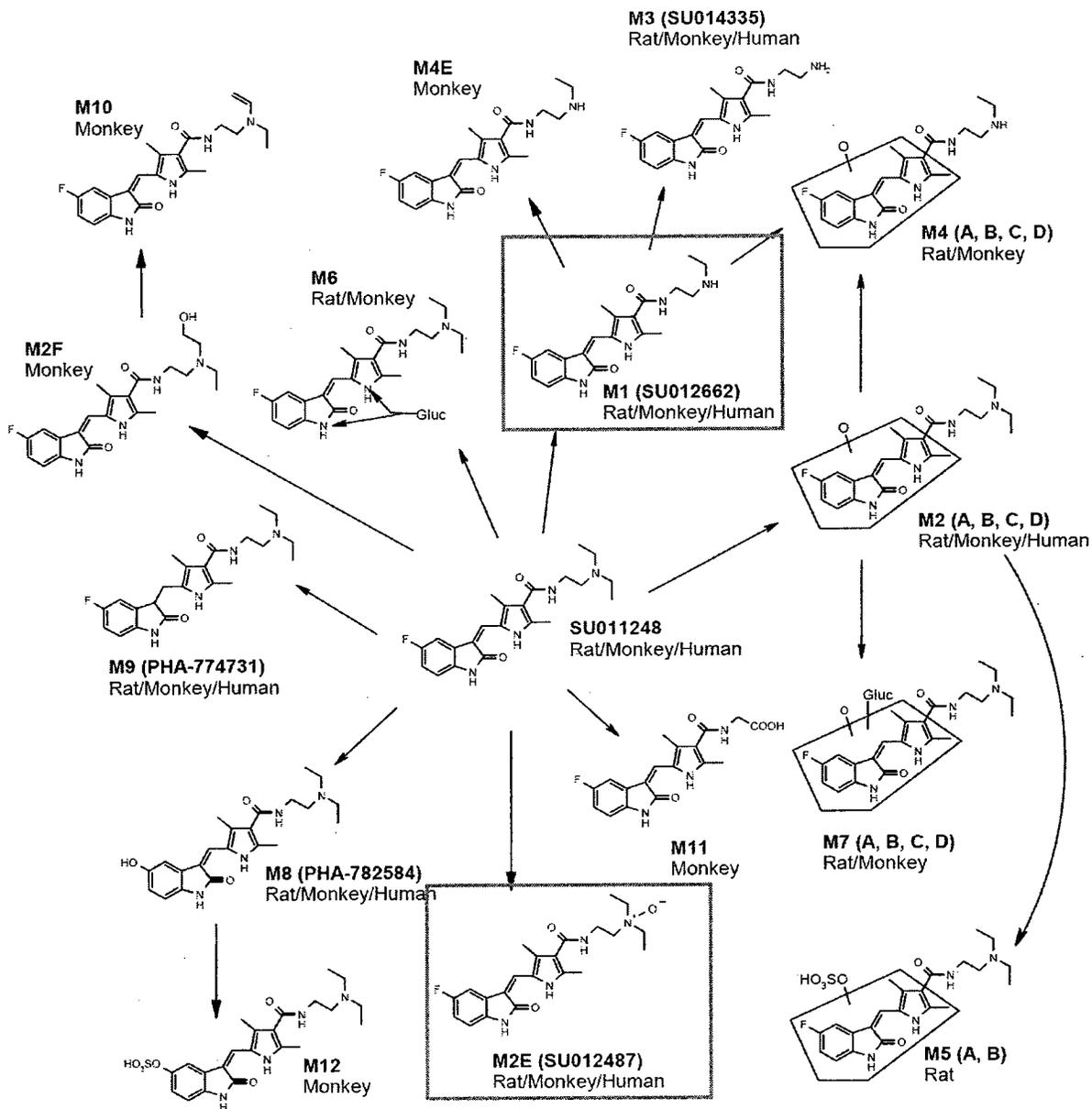
^dMonkey samples from 7039-152, Appendix 2.

N/A = Not applicable

ND = Not detectable

NQ = Not quantitated, concentration < 25 ng/ml (LLOQ)

Figure 1. Proposed Pathways of Metabolism of SU011248 in Rats, Monkeys, and Humans



2.6.4.6 Excretion

SU011248 metabolite identification in human plasma and urine (SU011248-PDM-059; Volume 4.2.2.4)

The metabolite profile of SU011248 in human urine using MS and MS/MS was determined following administration of 50 mg to healthy volunteers. SU011248 was excreted mainly as unchanged drug up to 72 hours post-dose, accounting for more than 59% of the total SU011248 (RT=18.4) equivalents in

urine. SU012662 [M1, RT=16.8 min, also referred to as M7] and SU012487 [M2E, RT=18.6, also referred to as M7] were detected at lower levels, in the range of 10-20%. All the other metabolites were at low to trace levels. (Although the study is entitled urine and plasma, only the urine was analyzed.

Compound	0-24 hr	24-48 hr	48-72 hr
SU11248	67.7	61.6	59.0
SU12662	15.0	9.9	20.2
SU12487	8.8	14.0	9.9
5' -OH	3.8	3.9	4.8
Ion m/z 471	1.6	9.0	3.3
Ring -OH	1.6	1.7	2.9
PHA774731 (401)	1.2	Trace	Trace
PHA782584 (397)	0.3	Trace	Trace
SU14335	Trace	Trace	Trace
Total	100.0	100.0	100.0

The secretion of total radioactivity in milk of lactating rats following oral administration of [¹⁴C]SU010398 (the malate salt of SU011248) (SU011248-PDM-003; Volume 4.2.2.5; GLP)

To investigate the secretion of total radioactivity in the milk of lactating rats, [¹⁴C]-SU010398 was administered (20 mg/kg; 15 mg freebase/kg) on Day 10/11 after parturition.

The mean concentration of total radioactivity in milk was relatively constant between 3 h and 6 h post dose with levels of 11.25 and 11.84 µg SU011248 equiv/mL, respectively. These levels declined at 24 h post dose to 0.86 µg SU011248 equiv/mL and were below the limit of reliable measurement at 72 h.

The mean concentration of total radioactivity in plasma was constant between 3 h (2.13 µg SU011248 equiv/mL) and 6 h (2.02 µg SU011248 equiv/mL). At 24 h post dose, the radioactivity concentration in plasma was 0.06µg SU011248 equiv/mL and at 72 h post dose was below the limit of reliable measurement.

Mean Concentration of Total Radioactivity in Milk and Plasma Following Single Oral Administration of [¹⁴C]-SU010398 (15 mg freebase/kg) to Lactating Rats (Results expressed as µg SU011248 equiv/mL; excerpted from the sponsor's submission)

Sample/Time	3 h	6 h	24 h	72 h
Milk	11.25	11.84	0.86	°0.018
Plasma	2.13	2.02	0.06	°0.003
Ratio	5.3	5.8	11.9	N.C.

Ratio = ratio of total radioactivity in milk to plasma
 ° = Results calculated from data less than 30 d.p.m. above background
 LOM = 0.02 µg SU011428 equiv.mL⁻¹
 N.C. = Not calculable

This demonstrates that the total radioactivity associated with SU011248 and/or its metabolites are easily transferred into milk. However, the total radioactivity present in the milk may be cleared at a similar rate to the total radioactivity in plasma between 3 h and 6 h.

Determination of excretion balance of radioactivity, blood and plasma pharmacokinetics and metabolite profiles in plasma, urine and feces following oral administration of [¹⁴C] SU010398 (L-malate salt of SU011248) to monkeys. (SU011248-PDM-054, Volume 4.2.2.5; GLP)

The excretion balance of radioactivity, blood and plasma pharmacokinetics and metabolite profiles in plasma, urine and feces were investigated in cynomolgus monkeys (n=3/sex) following oral administration of a single dose of 6 mg freebase/kg of [¹⁴C]-SU010398.

Plasma and Whole Blood

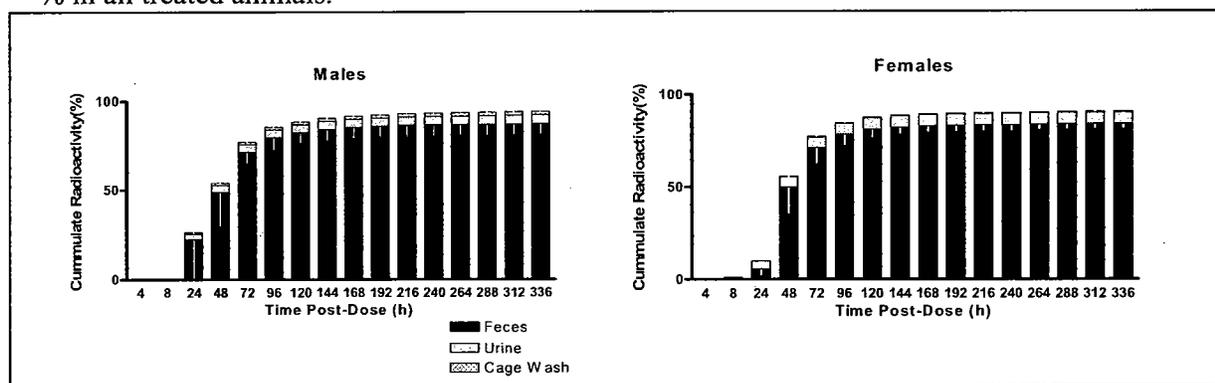
- Plasma concentrations of radioactivity were lower (50%) than those observed in whole blood. This indicates that there is radioactivity penetration into the cellular fraction. Similar findings were observed in both genders.

	Cmax * (ng Eq/mL)		Tmax (H)		T _{1/2} (h)		AUC _{0-∞} (ng Eq•hr/mL)	
	Male	Female	Male	Female	Male	Female	Male	Female
Total Radioactivity in Plasma	243 ± 13	241 ± 26	8 ± 0	4 ± 0	222 ± 40	121 ± NA	9095 ± 432	5692 ± 1151
Total Radioactivity in Blood	507 ± 19	554 ± 58	7 ± 2	4 ± 0	18 ± 7	11 ± 1	10207 ± 560	9246 ± 1417
SU011248	92 ± 10	83 ± 12	5 ± 2	4 ± 0	18 ± 4	16 ± NA ¹	1453 ± 205	1099 ± 87
SU012662	67 ± 12	54 ± 7	8 ± NA	7 ± 2	19 ± 8	19 ± 6	1383 ± 246	1272 ± 137

¹ NA- the mean of 2 animals, SD not calculated.

Blood and plasma levels of radioactivity are expressed as ng Eq/mL of free base.

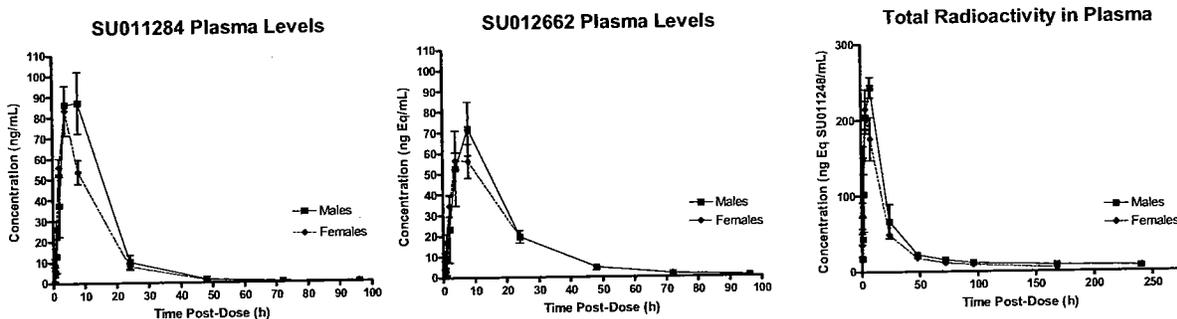
- Blood, urine and feces were collected up to 336h post- dosing. In both genders, the total radioactivity recovered in the feces was in the range 84- 87 % and an additional 4-6 % in the urine. Mean total recovery of radioactivity including cage washings within 336h was in the range 91- 94 % in all treated animals.



- After oral administration of [¹⁴C] SU010398 to monkeys, plasma levels reached, on average, maximal concentrations at 5h and 4h post- dosing in males and females respectively. The terminal half- life of the parent compound was 18h in males and ranged between 15 and 57h in females. In both genders, the metabolite SU012662 reached maximum concentrations later than the parent

compound and then declined with an apparent terminal half- life similar to that calculated for the parent compound, suggesting that SU012662 disposition is formation-rate limited.

- The levels of radioactivity in the blood declined with an average apparent half- life of 18h and 11h in males and females, respectively whilst levels of radioactivity in plasma were detectable for longer periods of time and had a correspondingly longer half- life. In both genders, the plasma levels of radioactivity were about 2 times higher than the sum of the plasma levels of the parent compound and SU012662 at early time points thus suggesting the presence of metabolites.



Metabolite Patterns

Plasma

- The SU011248 and SU012662 (the des- ethyl metabolite, M1) were the main component in the 2, 4 and 8h samples; small amounts of other metabolites were also detected, most notably the carboxylic acid (M11) and the metabolite hydroxylated on the ethyl function (M2F).

Urine

- 2-3% of the total dose was eliminated via urinary excretion.
- SU011248 was detected in all the urine samples analyzed, in the range of 3- 8% in both male and female animals.
- M1 (SU012662) ranged from 36-54% of urinary radioactivity.
- The parent was excreted also as an N- glucuronide (M6, mass to charge ratio (m/z) = 575; 1-2%).
- Metabolite M2F (mono- hydroxylated in the ethyl group, m/z = 415, trace), M11 (Carboxylic acid, m/ z = 358, 5-7%), M2E (N- oxide, SU012487, 1%), M7 (monohydroxylated metabolite with glucuronic acid, m/z=591, 2-3%) metabolites were also detected.
- A chromatographic peak accounting for about 9- 16% appeared to have an m/ z = 520. The accurate mass for this component seemed to correspond to it being a cystein adduct of the parent.

Feces

Metabolite		m/z	% Total Radioactivity
SU011248	Parent	399	4-18%
M1-SU012662	Des-ethyl	371	20-40%
M6	n-glucorinode SU011248	575	2-5%
M11	Carboxylic acid	358	9%
M8	F replaced by OH	397	8%
M9	Saturated exocyclic double bond	401	1%
M2A, B, C, D*	Mono-hydroxylated	415	16%

Metabolite		m/z	% Total Radioactivity
M2E	Monohydroxylated	324/326	Trace
M4A	Mono-oxidized M1	387	1-4%
M4E	Mono-oxidized M1	387	1-2%

*Primarily (10%) M2A

- The metabolite profiles were similar from a qualitative and quantitative point of view both in male and female monkeys and also at the different time intervals investigated.
- Although all the sample handling was done protected from direct light, isomerization of the exocyclic double bond was observed for both parent and M1 (about 2 and 10%, respectively).
- M10 (double bond in an ethyl group, m/ z = 397), M12 (sulphate conjugate of M8, m/ z = 477), additional metabolites accounting $\leq 2\%$ of radioactivity.

Determination of the excretion balance of radioactivity, blood and plasma pharmacokinetics and metabolite profiles in plasma, urine and feces following oral and intravenous administration of [¹⁴C] SU010398 (L-malate salt of SU011248) to rats. (SU011248-PDM-055, Volume 4.2.2.5; GLP)

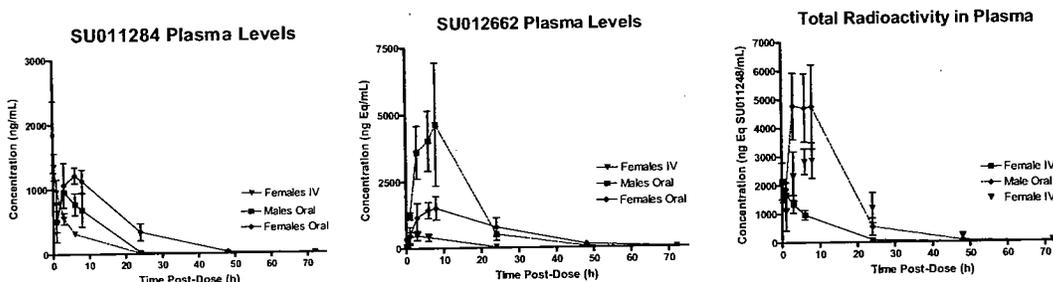
The excretion balance of radioactivity, blood and plasma pharmacokinetics and metabolite profiles in plasma, urine and feces were investigated in Sprague Dawley rats (n=2-3/sex) following oral (15 mg freebase/kg; males and females) and IV (of 5 mg freebase/kg; females) administration of a single dose of [¹⁴C]-SU010398.

- Blood, urine and feces were collected up to 72h post- dosing. In both genders, the total radioactivity recovered in the feces following oral administration was in the range 71-75% and an additional 8-9 % was recovered from the urine. Mean total recovery of radioactivity including cage washings within 72h was in the range 83-85 % in all treated animals. In females following IV administration, 9%, 77%, 1% and 0.1% were recovered in the urine, feces, cage washing and expired air, respectively.

Excreta	Time zero to hours post-dose	Males (Oral)	Females (Oral)	Females (IV)
Urine	4	0.93 ± 0.25	0.35 ± 0.26	1.14 ± 0.35
	8	3.53 ± 0.13	2.09 ± 0.20	2.67 ± 0.25
	24	7.49 ± 1.0	6.87 ± 0.73	7.80 ± 1.66
	48	8.32 ± 1.58	8.87 ± 1.18	8.80 ± 2.15
	72	8.47 ± 1.65	9.28 ± 1.40	9.06 ± 2.29
Feces	8	NA	1.69 ± NA	NA
	24	49.75 ± 17.71	35.61 ± NA	32.1 ± 25.99
	48	69.89 ± 9.80	71.30 ± NA	57.09 ± 23.08
	72	75.20 ± 4.00	71.09 ± 10.40	77.18 ± 3.58
Cage Washing	24	1.21 ± 0.82	1.25 ± 0.50	0.80 ± 0.42
	48	1.37 ± 0.91	1.67 ± 0.59	1.03 ± 0.40
	72	1.47 ± 0.94	2.18 ± 1.14	1.14 ± 0.35

Expired Air	24	Not conducted	Not conducted	0.04 ± NA
	48			0.07 ± NA
	72			0.09 ± NA
Total		85.14 ± 1.49	82.55 ± 7.92	87.41 ± 1.59

- Although sunitinib was extensively metabolized in rats, only parent drug and SU012662 were found in circulating plasma. The sum of AUC of sunitinib and SU012662 accounted for 87- 98% of plasma radioactivity AUC, indicating the absence of other significant metabolites in circulating plasma.



Metabolite Profile

- Doses excreted in the urine represented 4.2%, 5.9% and 4.8% in males and females administered orally and females IV, respectively.
- Metabolites found in the 8-24 hour urine samples following oral or IV administration

Metabolite	m/z	Urine Relative % (8-24 hr)	Feces Relative % (8-24 hr)	Feces Relative % (24-48 hr)
SU011248	399	6-12%	14-31%	6-36%
SU012662	371	11-40%	23-40 %	31-51%
SU012487 (M2E)	415	7-26%	Not observed	Not observed
M2A/B/C/D	415	2%	10-19%	12-17%
M8/M9	397	3-22%	4-9%	6-9%

- In the urine, minor metabolites included N-glucuronide of the parent drug (M6), N- deethyl SU012662 (M3, SU014335), and products from hydroxylation on the aromatic ring system and the aliphatic moieties, both free and as glucuronide and sulfate conjugates.
- Qualitatively, major differences in metabolite profiles were not observed between the route of administration and between genders in rats

A Phase 1 mass-balance study to evaluate the metabolism and excretion of [¹⁴C]-SU011248 in healthy male subjects (Study #A6181031; Volume 5.3.3.1.2; GCP)

This study was an open-label, single-dose, single-center study to evaluate the mass-balance and pharmacokinetics of SU011248 in healthy male subjects. On Day 1, each subject received a single oral 50 mg SU011248 capsule containing approximately 100 µCi of [¹⁴C]-SU011248. Serial blood samples and urine and feces were collected at specified times over 21 days.

Plasma PK parameters for SU011248, SU012662, and radioactivity following a single dose of 50 mg SU011248 (excerpted from the sponsor's submission).

Table S2. Plasma Pharmacokinetic Parameters for SU011248 and SU012662, and C_{max} and T_{max} of Plasma Radioactivity Following a Single Dose of 50 mg [¹⁴C]-SU011248 (~100 µCi)

Pharmacokinetic Parameters	Arithmetic Mean (CV %)		
	Plasma SU011248 (n=6)	Plasma SU012662 (n=6)	Plasma Radioactivity (n=6)
C _{max} (ng·mL) ^a	24.4 (16)	6.15 (29)	67.4 (29)
AUC _{0-∞} (ng·hr/mL)	1052 (25)	575 (16)	-
AUC _{0-t} (ng·hr/mL)	1063 (25)	593 (15)	-
CL _F (L/hr)	49.9 (28)	NA	-
t _{1/2} (hr)	50.9 (13)	93.2 (17)	-
T _{max} (hr) ^b	8.0 (8.0, 8.1)	6.0 (4.0, 12.0)	8.0 (8.0, 8.1)

^a For radioactivity pharmacokinetic parameters, ng is replaced by the equivalent radioactivity unit of ng-equivalent.
^b Median (min, max)

Best Possible Copy

Over the 21 day collection period, total recovery of radioactivity was approximately 77% with 61% in the feces and 16% in the urine. The majority was excreted within the first 7 days. Metabolic profiling indicated that SU011248 and SU012662 were the primary components in the plasma, urine and feces. Additionally, an N-oxide (SU012487) was identified in the urine, and a mono-oxygenated and unidentified metabolite were found in the feces. Radioactivity was greater in whole blood as demonstrated by the ratio of whole blood to plasma (>1).

2.6.4.9 Discussion and Conclusions: see comparative TK

2.6.4.10 Tables and figures to include comparative TK summary

Comparative Toxicokinetic Data for SU011248 (after approximately 3 months administration)						
AUC (ng·hr/mL)						
Daily Dose (mg/kg)	Rat		Monkey		Rabbit	Human*
	Male	Female	Male	Female	Male	
0.71						1262
1.0					332	
1.5	433	605				
2.0			561	801		
5.0	3608	3581			1720	
6.0			1976	1935		
10.0					8010	

*Day 28 2 (Study RTKC- 0511- 013).

Comparative Toxicokinetic Data for SU012662(after approximately 3 months administration)						
AUC (ng•hr/mL)						
Daily Dose (mg/kg)	Rat		Monkey		Rabbit	Human*
	Male	Female	Male	Female	Male	
0.71						667
1.0					1420	
1.5	1670	938				
2.0			325	411		
5.0	15645	5169			11000	
6.0			1217	1304		
10.0					41700	

*Day 28 2 (Study RTKC- 0511- 013)

Appears This Way
On Original

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

SU010398: 3 Month oral toxicity study in the rat followed by a 3-week recovery period (2001-0010; Volume 4.2.3.2) (Previously reviewed by Dr. Schmidt, review 2; Modified herein; GLP).

SU010398: 3 month oral toxicity study in the monkey followed by a 4-week recovery period (2000-0532; Volume 4.2.3.2) (Previously reviewed by Dr. Schmidt, review 2; Modified herein; GLP).

Toxicokinetics of SU011248

Monkeys															
Dose (mg/kg/d)	Dose mg/m 2/d	Dose ratio	Sex	Day	Cmax (ng/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation ratio	AUC (ng h/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation Ratio	
2	24	1	M	0	13	12	1			226		1			
			M	57	36	5	1		3	373	80	1		2	
			M	91	57	7	1		4	561	73	1		2	
		1	F	0	21	8	1	1.6		188	97	1	0.8		
			F	57	54	11	1	1.5	3	594	111	1	1.6	3	
			F	91	69	12	1	1.2	3	801	214	1	1.4	4	
6	72	3	M	0	93	38	7			979	510	4			
			M	57	115	35	3		1	1377	403	4		1	
			M	91	157	38	3		1	1976	450	4		1	
		3	F	0	82	29	4	0.9		794	453	4	0.8		
			F	57	132	37	2	1.1	2	1566	620	3	1.1	2	
			F	91	161	16	2	1.0	2	1935	332	2	1.0	2	
12/20	144/240	9	M	0	294	61	23			4381	1033	19			
			M	57	359	70	10		1	5857	1327	16		4	
			M	66	354	86	6		1	6620	1290	12		5	
		9	F	0	353	44	17	1.2		4697	910	25	1.0		
			F	57	345	93	6	1.0	1	5585	2316	9	1.0	1	
			F	66	354	140	5	1.0	1	6131	2864	8	0.9	1	
Rats															
Dose (mg/kg/d)	Dose mg/m 2/d	Dose ratio	Sex	Day	Cmax (ng/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation ratio	AUC (ng h/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation Ratio	
1.5	9	1	M	0	18	9	1			136	117	1			
			M	28	34	14	1		2	297	198	1		2	
			M	91	46	25	1		3	433	391	1		3	
		1	F	0	91	13	1	5.1		230	167	1	1.7		
			F	28	45	19	1	1.3	0	408	221	1	1.4	2	
			F	91	64	48	1	1.4	1	605	416	1	1.4	3	
5	30	3.3	M	0	92	25	5			1088	311	8			
			M	28	199	48	6		2	2276	624	8		2	
			M	91	302	98	7		2	3608	654	8		2	
		3.3	F	0	109	66	1	1.2		1272	1015	6	1.2		
			F	28	239	95	5	1.2	2	2687	1402	7	1.2	2	
			F	91	326	190	5	1.1	3	3581	1915	6	1.0	3	
15	90	10	M	0	403	170	22			5014	2553	37			
			M	28	676	220	20		2	9829	3423	33		2	
			M	66	440		10		1	6177		14		1	
		10	F	0	669	200	7	1.7		9121	3740	40	1.8		
			F	28	877	270	19	1.3	1	13897	4392	34	1.4	2	
			F	66	388	190	6	0.9	1	6003	1660	10	1.0	1	

Toxicokinetics of SU012662

Monkey															
Dose (mg/kg/d)	Dose mg/m 2/d	Dose ratio	Sex	Day	Cmax (ng/mL)	±SD	Dose Ratio	F:M Ratio	Accumulati on ratio	AUC (ng h/mL)	±SD	Dose Ratio	F:M Ratio	Accumula tion Ratio	
2	24	1	M	0	5	3	1			70	51	1			
			M	57	13	3	1		3	200	53	1		3	
			M	91	21	2	1		4	325	64	1		5	
			F	0	6	2	1	1.2			86	23	1	1.2	
			F	57	17	3	1	0.6		3	263	29	1	0.6	3
			F	91	24	3	1	0.6		4	411	64	1	0.6	5
6	72	3	M	0	32	1	6			422	72	6			
			M	57	46	3	4		1	720	102	4		2	
			M	91	72	13	3		2	1217	230	4		2	
			F	0	36	8	6	0.8			453	219	5	0.9	
			F	57	55	15	3	0.5		2	807	152	3	0.5	2
			F	91	83	22	3	0.4		2	1304	246	3	0.3	3
12/20	144/2 40	9	M	0	117	34	23			1971	570	28			
			M	57	167	29	13		1	3266	991	16		2	
			M	66	214	70	10		2	4769	1686	15		2	
			F	0	140	22	23	1.0			2200	369	26	1.1	
			F	57	182	67	11	0.4		1	3510	1806	13	0.5	2
			F	66	83	22	3	0.5		1	3783	631	9	0.5	2
Rats															
Dose (mg/kg/d)	Dose mg/m 2/d	Dose ratio	Sex	Day	Cmax (ng/mL)	±SD	Dose Ratio	F:M Ratio	Accumulati on ratio	AUC (ng h/mL)	±SD	Dose Ratio	F:M Ratio	Accumula tion Ratio	
1.5	9	1	M	0	28	16	1			371	234	1			
			M	28	87	33	1		3	1077	531	1		3	
			M	91	125	51	1		4	1670	1015	1		5	
			F	0	33	11	1	1.2			437	143	1	1.2	
			F	28	55	22	1	0.6		2	672	297	1	0.6	2
			F	91	81	47	1	0.6		2	938	505	1	0.6	2
5	30	3.3	M	0	186	59	7			2392	767	6			
			M	28	564	150	6		3	7998	2084	7		3	
			M	91	1060	350	8		2	15645	3845	9		2	
			F	0	155	100	5	0.8			2190	1658	5	0.9	
			F	28	267	110	5	0.5		2	3720	1962	6	0.5	2
			F	91	446	280	6	0.4		3	5169	2763	6	0.3	2
15	90	10	M	0	953	500	34			13221	7220	36			
			M	28	2550	960	29		3	38978	13661	36		3	
			M	66	1060		8		1	17588		11		1	
			F	0	982	340	30	1.0			14403	5340	33	1.1	
			F	28	1140	380	21	0.4		1	17719	5787	26	0.5	1
			F	66	573	300	7	0.5		1	8311	2288	9	0.5	1

Preterminal sacrifice was conducted in the high dose groups.

SU010398 (L-Malate salt of SU011248): 6 month oral toxicity study (5 cycle) in the rat followed by an 8 week recovery period (2003-0390; Volume 4.2.3.2)

TK of SU011248:

Rats														
Dose (mg/kg/d)	Dose mg/m 2/d	Dose ratio	Sex	Day	Cmax (ng/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation ratio	AUC (ng h/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation Ratio
0.3	1.8	1	M	1	2	2	1			16	10	1		
			M	168	3	3	1		2	26	15	1		2
			F	1	2	0	1	1		12	3	1	1	
			F	168	6	4	1	2	3	36	16	1	1	3
1.5	9.0	5	M	1	13	13	7			115	42	7		
			M	168	33	24	11		3	328	117	13		2
			F	1	48	3	24	4		341	37	28	3	
			F	168	93	22	16	3	2	791	108	22	3	2
6.0	36	20	M	1	150	141	75			966	389	60		
			M	168	401	115	133		3	4000	427	153		4
			F	1	231	32	116	2		1880	344	156	2	
			F	168	374	149	62	1	2	5100	993	141	1	3

TK of SU012662:

Rats														
Dose (mg/kg/d)	Dose mg/m 2/d	Dose ratio	Sex	Day	Cmax (ng/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation ratio	AUC (ng h/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation Ratio
0.3	1.8	1	M	1	8	6	1			78	37	1		
			M	168	12	2	1		2	133	61	1		2
			F	1	4	12	1	.5		35	4	1	.5	
			F	168	18	24	1	2	5	103	32	1	.5	3
1.5	9.0	5	M	1	33	27	4			322	94	4		
			M	168	153	81	13		5	1800	722	14		6
			F	1	65	22	16	2		583	81	17	2	
			F	168	106	14	6	.7	2	1240	116	12	.7	2
6.0	36	20	M	1	423	405	53			3840	1710	49		
			M	168	1540	233	128		4	17300	1520	129		5
			F	1	377	73	94	.9		3870	520	110	1	
			F	168	628	523	35	.4	2	8710	1740	84	.5	2

SU010398 (SU011248 L-malate salt): 9 month oral toxicity study in the monkey (8 Cycle treatment) followed by an 8 week recovery period (2003-0386; Volume 4.2.3.2)

Toxicokinetics of SU011248

Monkeys															
Dose (mg/kg/d)	Dose mg/m ² /d	Dose ratio	Sex	Day	Cmax (ng/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation ratio	AUC (ng h/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation Ratio	
0.3	3.6	1	M	1	3	1	1			17	7	1			
			M	98	5	5	1		2	23	26	1		4	
			M	274	3	1	1		1	34	14	1		2	
			F	1	3	0	1	1		23	3	1	1		
			F	98	2	1	1	.4	.7	6	1	1	.3	.4	
			F	274	2	1	1	.7	.7	26	17	1	.8	.8	
1.5	18	5	M	1	29	6	9			287	15	17			
			M	98	12	2	2		.3	114	17	5		.4	
			M	274	21	3	7		.5	248	66	7		.9	
			F	1	30	12	10	1		297	144	13	1		
			F	98	7	3	3	1	.25	74	21	12	.7	.2	
			F	274	24	7	12	1	.6	312	59	12	1	1	
6.0	72	20	M	1	130	22	43			1680	319	98			
			M	98	53	19	11		.4	1330	243	58		.8	
			F	1	123	29	41	1		871	267	26	.5		
			F	98	49	8	16	1	.4	718	148	31	.4	.8	

TK of SU012662

Monkeys														
Dose (mg/kg/d)	Dose mg/m ² /d	Dose ratio	Sex	Day	Cmax (ng/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation ratio	AUC (ng h/mL)	±SD	Dose Ratio	F:M Ratio	Accumulation Ratio
0.3	3.6	*	M	1	0	0				0	0			
			M	98	7.6	10				39	56			
			M	274	0	0				0	0			
			F	1	.4	.6				1	2			
			F	98	0	0				0	0			
			F	274	0	0				0	0			
1.5	18	1	M	1	8	0	1			105	18	1		
			M	98	4	1	1		.5	51	22	1		.5
			M	274	7	2	1		1	113	38	1		1
			F	1	11	4	1	1		119	43	1	1	
			F	98	3	1	1	1	.4	37	23	1	1	.3
			F	274	9	3	1	1	1	165	47	1	1	1
6.0	72	4	M	1	63	12	8			807	64	8		
			M	98	30	17	8		.5	530	312	10		.6
			F	1	43	17	4	.7		576	239	5	.7	
			F	98	22	8	2	.7	.5	393	140	2	.7	.7

* Since Cmax and AUC were undeterminable in many groups in the low dose group, the mid-dose group was utilized to make the determination of dose proportionality

Summary:

	Rat	Monkey
	3 month TK	3 month TK
Dose (mg/kg/day)	1.5, 5, 15	2, 6, 12/20
Dose (mg/m2/day)	9, 30, 90	24, 72, 144/240
SU011248		
Dose Proportionality	Higher than dose proportional increases in AUC and Cmax were noted at all dose levels at all timepoints.	SU011248 (Cmax and AUC) increased in a greater than dose proportional manner in females at doses of up to 12/20 mg/kg/day and up to 6 mg/kg day in males .
Gender Differences	Clear gender differences were not observed.	Clear gender differences were not observed
Accumulation	Slight accumulation was observed	Slight accumulation was observed
SU012662		
Dose Proportionality	Higher than dose proportional increases in AUC and Cmax were noted at all dose levels at all timepoints.	Greater than dose proportional increases in AUC and Cmax were noted following 12/20 mg/kg/day (up to 23 fold). This was also observed following 6 mg/kg/day but the magnitude was lower.
Gender Differences	Cmax and AUC were 2-3 fold higher in males than in females	Not apparent at on day one, however Cmax and AUC were 2-3 fold higher in males than females at later timepoints.
Accumulation	Accumulation was not apparent	Accumulation (3-4 fold) was noted at 2 mg/kg/day but not at higher doses
5 Cycle TK		
	5 Cycle TK	8 Cycle TK
Dose (mg/kg/day)	0.3, 1.5, 6.0	0.3, 1.5, 6.0
Dose (mg/m2/day)	1.8, 9, 36	3.6, 18, 72
SU011248		
Dose Proportionality	A greater than dose proportional increase was noted in both males and females at all doses assessed	Exposure was greater then dose proportional on day 1, but approximately dose proportional in all dose groups tested day 98 and 274
Gender Differences	Clear gender differences were not apparent	Clear gender differences were not apparent
Accumulation	Slight accumulation (2-4 fold) was noted at all dose levels	Accumulation was not observed. There was a reduction in exposure (up to 80%) by day 98 of dosing. In some cases this was partially reversed by day 274.
SU012662		
Dose Proportionality	A greater than dose proportional increase was noted in both males and females at all doses assessed	Approximate dose proportional increase in Cmax and AUC
Gender Differences	Clear gender differences were not apparent	Clear gender differences were not apparent
Accumulation	Slight accumulation (2-5fold) was noted at all dose levels	Accumulation was not observed. There was a reduction in exposure (up to 70%) by day 98 of dosing. In the mid dose group these findings were reversible, however in the high dose group exposure was similar on days 1 and 274.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:

In rats and monkeys, the major target organs of SU010398 toxicity are the hematopoietic organs (thymus, marrow, spleen, and lymph nodes), hepatic, gastrointestinal, glands (pancreas, adrenals, salivary), skeletal, and female reproductive organs (ovaries, uterus).

Primary clinical signs were indicative of gastrointestinal toxicity. Abnormal feces were noted in both species and emesis was noted in the monkey. These findings were corroborated by histological findings of inflammation, mucosal erosion, epithelial depletion, necrosis and hemorrhage in the gastrointestinal tract. These findings were generally reversible by the end of the recovery period.

In rat and monkey repeat dose studies, hematological changes included decreases in red blood cells, with concomitant decreases in red cell mass. There was evidence of hemorrhage in numerous organs including the adrenals in rats and monkeys and the gall bladder and gastrointestinal tract in monkeys. Reductions in white blood cells were observed with histological evidence of lymphoid depletion in the spleen, thymus, and lymph nodes and atrophy in the bone marrow. Increases in serum hepatic enzymes (AST, ALT and occasionally GGT and total bilirubin) were accompanied by histological changes of peribiliary inflammation, bile duct hyperplasia and degeneration of the portal hepatocytes.

The pancreas, adrenals and salivary glands appear to be target organs of toxicity in repeat dose studies in rats and monkeys. Histological findings in the pancreas were characterized by edema, inflammation, acinar degeneration and/or degranulation (at AUCs of ≥ 1823 ng h/mL). Slight increases in glucose levels were noted in clinical chemistry measurements. In the salivary glands, acinar hypertrophy/degeneration and apoptosis was noted in repeat dose studies in both rats and monkeys. These findings were coincident with ulceration of the oral cavity in numerous animals. In adrenals, toxicity was noted in studies of 14 days to 9 months in rats and monkeys at plasma exposures as low as 0.7 times the AUC observed in clinical studies. Toxicity was routinely characterized by hemorrhage in both species, but necrosis, congestion, hypertrophy and inflammation were also noted. These findings were reversible within the recovery period, which varied from one to eight weeks depending on the duration of dosing.

Effects on the female reproductive system were identified in the 3-month repeat dose monkey study, where ovarian (decreased follicular development) changes were noted with exposures of 10,650 ng h/mL (144 mg/m²), while uterine changes (endometrial atrophy) were noted at greater than 1050 ng h/mL (24 mg/m²). With the addition of vaginal atrophy, the uterine and ovarian effects were reproduced at 72 mg/m² (2080 ng h/mL) in a nine month repeat dose monkey study.

Skeletal toxicity in the bone and teeth were noted in repeat dose studies. In rats, caries of the teeth were noted at ≥ 30 mg/m² in 3 month studies with continuous dosing, but as low as 1.8 mg/m² when administration was increased to 5 cycles (daily x 28 every 42 days). These resulted in a dose dependent increase in broken teeth. These findings were not observed in monkeys. Toxicities in the bone were observed in both rats and monkeys. These findings were characterized by brittle, malformed or fractured bones in the rat (≥ 36 mg/m², 5 cycles or 90 mg/m² daily for 3 months). Histopathologically,

chondroplasia of the epiphyseal plate (≥ 30 mg/m²) and cartilage in the metaphyseal bony trabeculae (90 mg/m²) were noted in rats and thickening of the epiphyseal cartilage (120 mg/m²) and periosteal new bone formation and necrosis of the physeal cartilage were noted in monkeys (72 mg/m²). Given the continuous development of teeth in rats and the observance of toxicity in long bones of rats and monkeys, the administration of SU010398 to pediatric populations with developing teeth and bones may represent end organ toxicities that have not been evident in the adult clinical population based on clinical signs.

In the three and nine month oral toxicity studies in monkeys, changes in cardiovascular function were observed. Reductions in heart rate were noted in both studies at a doses of 72 mg/m² (approximately equivalent to the clinical exposure to both SU011248 and SU012662). Changes in ECHO parameters included reductions in the ratio of left atrial diameter to aortic diameter, the left atrial diameter, left ventricular ejection time and left ventricular area. One instance of premature ventricular contraction was noted at the 72 mg/m² in the nine month study. Cardiac toxicity, as evidenced by histopathological findings in individual test animals, included minimal to slight capillary proliferation, myocardial vacuolization or inflammation of the pericardium.

In rabbits, there was not evidence of dermal irritation with doses of 500 mg and slight irritation of the conjunctiva was noted at 1 and 24 hours with 100 mg.

Genetic toxicology:

SU011248 was negative for mutagenicity and clastogenicity in adequately conducted and valid ICH battery of tests (*in vitro* bacterial mutation and mammalian chromosomal aberrations and *in vivo* clastogenicity).

Carcinogenicity:

Carcinogenicity studies were not conducted and are generally not required to support the safety of SU011398 for the proposed metastatic cancer indication.

Reproductive toxicology:

Assessment of the effects of SU010398 on reproductive potential was showed early embryonic development (Segment I) impairments in female rats treated with 30 mg/m² SU010398 ($AUC_{SU011248+SU012662} = 9800$ ng•hr/mL). This was manifested by a 3.5-fold increase in the number of dead embryos. The NOAEL for female reproductive toxicity in Segment I studies is 9 mg/m²/day. In males, 60 mg/m²/day ($AUC_{SU011248+SU012662} = 49,710$ ng•hr/mL) exceeded the MTD, without evidence of fertility or early embryonic development impairments.

Segment II studies with SU010398 showed teratologic changes following administration of 30 mg/m² (GD 6 through 17; $AUC_{SU011248+SU012662, Day 12} = 10600$ ng•hr/mL) and 12 mg/m² (GD 7-20; $AUC_{SU011248+SU012662, Day 14} = 557$ ng•hr/mL) in the absence of abject maternal toxicity in rats and rabbits, respectively. In rats, in life findings were limited to females treated with 30 mg/m² and consisted of a 9% decrease in body weight observed on GD21, which was promulgated by a decrease in body weight gain on days 13-21. Decreases in uterine weight were noted ($\downarrow 52\%$) but were likely due to a reduced number of fetuses and the high number of dams with complete post-implantation loss (29%). In addition, live fetal weight was decreased (7%) and the incidence of fetal skeletal malformations, was significantly increased. Skeletal malformations were characterized by misaligned,

absent or fused thoracic and lumbar vertebral arches. The high dose of 30 mg/m² represents the NOAEL for maternal toxicity, whereas 18 mg/m² (AUC_{SU011248+SU012662 Day 12}=4430 ng•hr/mL) represents the NOAEL for fetal toxicity. In rabbits, embryoletality was observed at 60 mg/m², while developmental effects were observed at ≥12 mg/m². Developmental effects consisted of cleft lip at ≥12 mg/m² (0.3x human AUC_{SU011248+SU012662}) and cleft palate at 60 mg/m² (2.7x human AUC_{SU011248+SU012662}). The anticipated human exposure level expressed as AUC₂₄ of SU011248 and SU012662 is approximately 1888 ng•hr/mL.

Special toxicology:

In rabbits, there was not evidence of dermal irritation with doses of 500 mg and slight irritation of the conjunctiva was noted at 1 and 24 hours with 100 mg.

2.6.6.2 Single-dose toxicity

(Studies previously reviewed by Dr. Schmidt, see Appendix)

2.6.6.3 Repeat-dose toxicity

Study title: SU01398 (L Malate salt of SU011248): 6- month oral toxicity study (5 cycle treatment) in the rat followed by an 8-week recovery period

Key study findings:

The STD₁₀ from this study was 6.0 mg/kg/day for 6 month oral administration dx28 q35d. This dose yielded anemia, lymphoid depletion of the thymus, and bone marrow. Thickening of the epiphyseal cartilage (sternum), misshapen tibias which appeared like healed fractures, acinar atrophy and degranulation of the pancreas and chronic progressive nephrosis. Early changes of chronic progressive nephrosis was also noted in the mid-dose group, therefore the NOAEL in this study was 0.3 mg/kg/day.

Study no.: 2003-0390

Volume #, and page #: M4.2.3.2.2003-0390

Conducting laboratory and location: Pfizer Global Research and Dev; Kalamazoo, MI

Date of study initiation: September 23, 2003

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, and % purity: SU010398; (B2)6421-VGK-0301; purity= [] impurities []
[], Unspecified []

Methods

Doses: 0, 0.3, 1.5, 6 mg/kg/day, dx28 q35d

Species/strain: Rat/ CD(SD)IGS BR

Number/sex/group or time point (main study): 15/sex/dose

Route, formulation, volume, and infusion rate: Oral by gavage, in sterile water, 5 ml/kg

Results for formulation analysis were within acceptable limits except for the 0.06 mg/mL dose formulation from the third 28d-day cycle, which was 126% of the mean of the target. Animals were treated for one day with this formulation at the incorrect dose. Day 2 of the cycle, there was compensation for the concentration and the formulation was remanufactured for the 3rd day of dosing.

Satellite groups used for toxicokinetics or recovery: TK: 6/sex/dose; Recovery: 10/sex
 Age: 46-50 days at dose initiation for males and 48-52 days at dose initiation for females
 Weight: Male: 146.2 g- 220g; Females: 136.5-191.4
 Sampling times: TK evaluated on day 1, 28 and 168 at 1, 3, 6, 9, 12 and 24 hours post dose

(n=3)

Observations and times:

<u>Mortality:</u>	Twice daily (am and pm) during pretest, treatment, and recovery; once daily during each 7- day recovery period following cycles 1- 4
<u>Clinical signs:</u>	7 days pretest; at least twice daily during treatment, once after each dose in the morning and once in the afternoon; once daily during each 7- day recovery period following cycles 1- 4; and daily during recovery
<u>Body weights:</u>	At least once pretest; once on the first day of treatment, and weekly thereafter
<u>Food consumption:</u>	At least once pretest and weekly during treatment and recovery
<u>Ophthalmoscopy:</u>	Once pretest, once during Week 24 of treatment on main study and recovery animals only, and during Week 8 of recovery (final week of recovery) due to treatment- related findings observed during treatment. Eyes were dilated with mydriatic solution and examined by a board- certified veterinary ophthalmologist using an indirect
<u>Hematology:</u>	The last day of dosing for cycle 3 (Day 98); the last day of dosing for cycle 5 (Day 168); at the dosing phase necropsies (Days 169 and 170); Day 7 of the recovery phase; and at the recovery phase necropsies (Recovery Days 57 and 58)
<u>Clinical chemistry:</u>	The last day of dosing for cycle 3 (Day 98); the last day of dosing for cycle 5 (Day 168); at the dosing phase necropsies (Days 169 and 170); Day 7 of the recovery phase; and at the recovery phase necropsies (Recovery Days 57 and 58)
<u>Urinalysis:</u>	Day 165 and recovery day 53
<u>Gross pathology:</u>	Conducted on all animals
<u>Organ weights:</u>	See Histopath Table
<u>Histopathology:</u>	Adequate Battery: yes (X), no ()—explain Peer review: yes (X), no () See Histopath Table, tissues examined in the control and high dose. Tissues in low and mid dose were evaluated to determine the no effect level. These included the pancreas, spleen, sternum and femur

Results**Mortality:** 9 rats were found dead or sacrificed in a moribund condition

Dose (mg/kg)	Group/ Incidence	Timeframe	Signs
6	M (n=1)	Day 123	Sacrificed Moribund
	F (n=2)	Day 123 and day 3 of recovery	Found dead
1.5	M (n=1)	Day 64	Severe pyelonephritis and necrosis of the urinary bladder
0.3	F (n=3)	Day 85 and 122; Day 23 of recovery	Complications of broken teeth due to trimming, found dead with no obvious cause of death and accidental death during teeth trimming, respectively
0	M (n=1)	Day 36 of recovery	No obvious cause of death
	F (n=1)	Day 154	Complications of broken teeth due to trimming

Clinical signs:

Clinical Sign	Incidence of Clinical Observations							
	0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
	M	F	M	F	M	F	M	F
Cool to touch							1	
Activity decreased					1		1	
Urine Discolored	1		13	16	13	24	25	25
Body surface stained	4	21	10	18	17	12	25	25
Skin, abrasion/open sore							1	
Anogenital staining		1						2

*Also noted, beginning in the third dosing cycle, the normal integrity and appearance of the incisor teeth in high- dose rats, particularly in females, began to deteriorate. The poor condition of the teeth continued for the remaining dosing phase. The teeth became brittle, thin, and pink discolored. Occasionally teeth would fall out or break. During routine teeth trimming (for over-growth prevention), the teeth would sometimes disintegrate down to the gum line. Urine discoloration and body surface staining were the result of the test product coloration and were noted at all cycles.

Body weights: no effect**Food consumption:** no effect**Ophthalmoscopy:** no effect

Hematology: All changes were reversible at the end of the recovery period

Parameter	Week	Magnitude of Changes (%) in Hematology Parameters							
		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
RBC (10 ⁶ cells/ μ L)	14	9.16	8.395					↓26	↓35
	24	8.54	8.059					↓33	↓45
Hematocrit (%)	14	48.4	45.96					↓9	↓18
	24	44.91	44.19					↓15	↓30
Hemoglobin (gm/dL)	14	16.30	15.57					↓6	↓16
	24	15.03	14.88					↓13	↓26
MCH (pg)	14	17.80	18.56				↑5	↑29	↑31
	24	17.61	18.47				↑6	↑32	↑36
MCHC (gm/dL)	14	33.70	33.88					↑3	↑2.5
	24	33.45	33.64					↑2.5	↑6.1
MCV (fL)	14	52.89	54.77				↑5	↑24	↑28
	24	52.65	54.89				↑6	↑29	↑28
RDW%	14	15.72	14.86				↑5	↑54	↑60
	24	15.92	15.18					↑63	↑45

Clinical chemistry: All changes were reversible at the end of the recovery period

Parameter	Week	Magnitude of Changes (%) in Hematology Parameters							
		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
ALT (U/L)	14	27.39	36.69					↑78	↑66
	24	31.27	37.57					↑59	↑119
AST (U/L)	24		99.29		↑31		↑74		↑56
GGT (U/L)	24		5.0						↑37
ALB (gm/dL)	24	2.887	3.32					↓5.8	↓13.1
A/G ratio (%)	24		1.021						↓17
Creatine Kinase (U/L)	14		415.7						↑85
	24		380.6						↑122
Lipase (U/L)	14	15.17							↓32
	24		11.57						↑887
Triglycerides (mg/dL)	24	42.4							↑89
Urea Nitrogen (mg/dL)	24	11.6	12.43					↑49	↑45

Urinalysis: no effect

Gross pathology:

Organ	Observation	Macroscopic Observations							
		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
Adrenals	Discolored, drk red					<i>1</i>			
	Focus, dark red				1		1/1	1	4/1
Bone/stifle	Brittle								1
	Malformation								1
Bone/tibia	Fractures								2
Cecum	Contents discolored, drk red							<i>1</i>	
	Abnormal contents, mucoid							1	
Colon	Contents discolored, drk red							<i>1</i>	
Harderian, GL	Discolored, drk red, mild							<i>1</i>	
Ileum	Distended								1
Kidney	Hydronephrosis,	2				<i>1</i>		<i>1</i>	<i>1</i>
	Foci, mild					<i>1</i>			
	Pale								<i>1</i>
	Enlarged, moderate					<i>1</i>			
Liver	Lobular pattern enhanced			2		2		2	
	Bile duct enlarged							1	1
LN, mesent	Discolored, drk red							<i>1</i>	
Ovaries	Focus, black								1
Pancreas	Small							1	
Prostate	Small							<i>1</i>	
Stomach	Discolored, drk red, depress 1-2 mm							<i>1</i>	
	Nodules, moderate, white							1	
	Focus, mild red								1
Testis	Discolored, yellow			1				12/6	
Thymus	Small								
Tongue	Nodules, yellow, bulging							1	
Urinary Bladder	Distended, severe red					<i>1</i>			
	Abnormal contents, white							<i>1</i>	
	Calculus					<i>1</i>			
Ureters	Distended mod-sever					<i>1</i>		<i>1</i>	
Uterus	Dilated, mild								1

Italics indicates incidence in preterminal sacrifice, normal face is indicative of incidences in the terminal sacrifice boldface is indicative of incidence following the recovery period

Organ weights: All changes were noted in the high dose only and reversible

Organ	Dose	Sex	Absolute organ weight	% body weight	% brain weight
Thymus	6 mg/kg	Males	↓35%	↓32%	↓36%
		Females	↓42%	↓40%	↓43%
Spleen		Males	↓16%	↓13%	↓17%

Histopathology: Adequate Battery: yes (X), no ()

Peer review: yes (X), no ()

Organ	Observation	Microscopic Observations							
		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
Adrenals	Degeneration, lipid cortex, mild	4/2	1					2/6	2/1
	Cyst; cortex, present						1		3
Bone Marrow, stifle	Hypocellularity (min-marked)							1/15	2/14
Bone marrow, stern	Hypocellularity							1/14	2/14/ 1
	Old fracture with chondrodysplasia, mod								2
Bone/stifle	Thickening, epiphyseal cartilage, min-mod							1/12	2/14
Bone/sternebrae	Thickening, epiphyseal cartilage, min-mod								2/14
Bone/tibia	Old fracture with chondroplasia, mod								2
Duodenum	Inflammation, subacute, submucosa, mild							1	1
Eyes	Dysplasia, retina, min							1	
Heart	Fibrosis, myocardium, interstitium, min							2	
Kidney	Chronic progressive nephrosis (min-mod)	1/1	1	2		1/3	1	1/9/3	3/6
	Glomerulosclerosis/hyalinosis, min-mild	1	1/1	2		5/3	1		2/5/2
	Inflammatory cell infiltrate	1/5 /4	6/4	6/3	1/3	8/6	7/4	1/12/ 6	1/9/2
Lungs	Histiocytosis-alveolar, min	1/1	1			1		3	3
Liver	Deposition, pigment, hepatocytes, mild								1/4
	Deposition, hemosiderin pig; kupffer cell, min							1	2/2
	Inflammation, subacute: bile duct, mild								1

Organ	Observation	Microscopic Observations							
		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
	Hyperplasia, bile duct								1
Mammary GL	Hyperplasia, mild		2				1		1
Pancreas	Atrophy, acinus, min-mild					1		1/1	1/2
	Degranulation							1	1/2
	Inflammatory cell infiltrate, min-mod	1/1				2		2/2	2/2
	Hypertrophy, acinus, min							1	
	Necrosis, single cell	1	1/1						3
Spleen,	Hematopoiesis Increased, min-mild					1		11	1/12
Stomach	↑ mucus production, mild							1	
Thymus	Lymphoid depletion, min-severe					1		1/14	2/11
Tongue	Abcess, mod								1
	Degeneration, ballooning, epithelium, min	1							1
Trachea	Inflammatory cell infiltrate min		1						1
Teeth	Caries, dentin, min-severe							1/15/ 1	14/5
	Inflammation acute: periodontal, min-mod	2/1	1/1	1		1	3	4	4
	Inflammation/necrosis: pulp, mild-mod	1	1/1/ 2		1		3	5	3/1
	Inflammation, acute: turbinates, min-mod	1/7	1/4/ 2		2	2	8	2/3	1/3/2
	Fracture/dislocation, mechanical, present	1/1	1/2		1	1	3	2	2
Ureters	Inflammation, chronic, moderate					1			
	Dilatation, mild-mod						1		1

Italics indicates incidence in preterminal sacrifice, normal face is indicative of incidences in the terminal sacrifice boldface is indicative of incidence following the recovery period

Toxicokinetics:

Dose normalized TK parameters in rats

Daily Dose (mg/kg/day)	Day	0.3		1.5		6	
		M	F	M	F	M	F
SU011248 TK							
AUC*	1	53.3	39	76.6	227.3	161	313.3
	168	87	120.3	218.6	527.3	666.7	850
Cmax	1	5.8	7.9	8.5	31.8	25	38.5
	168	10.3	19.5	22.1	61.7	66.8	62.3

Daily Dose (mg/kg/day)	Day	0.3		1.5		6	
		M	F	M	F	M	F
SU012662 TK							
AUC	1	260	117	214.6	388.7	640	645
	168	443.3	343.3	1200	826.7	2883.3	1451.7
Cmax	1	26	11.6	21.8	43.1	70.5	62.8
	168	38.3	61.3	102	70.7	256.7	104.7

* AUC (ng h/mL)/(mg/kg/day); Cmax (ng/mL)/(mg/kg/day)

Study title: SU010398 (SU011248 L-Malate salt): 9 month oral toxicity study in the monkey (8-cycle treatment) followed by an 8-week recovery period

Key study findings:

The NOAEL of SU010398 administered to monkeys daily x28 q35d was 0.3 mg/kg/day. The high dose of 6 mg/kg/day resulted in the sacrifice of all HD animals (main study) in extremis beginning as early as day 92. By day 169 all animals in the high dose group were euthanized and dosing was ceased in recovery animals.

Study no.: 2003-0386

Volume #, and page #: M4.2.3.2.2003-0386

Conducting laboratory and location: []

Date of study initiation: 1 October 2003

GLP compliance: yes

QA report: yes (X) no ()

Drug, lot #, and % purity: SU010398, (B2)6421-VGK-0301, purity=[] impurities-

[] Any unspecified impurity except []

Methods

Doses: 0, 0.3, 1.5, 6 mg/kg

Species/strain: Monkey/cynomolgus

Number/sex/group or time point (main study): 4/sex/group

Route, formulation, volume, and infusion rate: PO, sterile water, 5 mL

Satellite groups used for toxicokinetics or recovery: 3/sex/group

Age: Juvenile to adult

Weight: males-2.5 to 3.5 kg; females-2.3-3.0 kg

Sampling times: 0, 1, 3, 6, 9, 12, and 24 hours after dosing on days 1, 28, 98, and 274. Single samples were collected from designated systemic exposure animals from all groups on day 36, 71, 106, 141, 176, 211, and 246 and 24 hours after the final day of dosing for cycles 2, 4, 5, 6, and 7.

Observations and times:

Mortality:	Once daily during pretest, twice during dosing and recovery
Clinical signs:	Twice pretest, twice daily during the dosing phase and at least once daily during the recovery phase.
Body weights:	Three times pretest and at least once weekly during the dosing and recovery phases.
Food consumption:	Not measured; however, inappetence was noted when present.

<p>Ophthalmoscopy:</p>	<p>Once pretest and twice during the dosing phase for animals in Groups 1- 3; eyes of animals from Group 4 were examined once during the dosing phase but were not examined at the end of their dosing phase due to the early cessation of dosing</p>
<p>EKG:</p>	<p>Twice pretest, 2 to 3 times during the dosing phase (Study Days 94, 164, 269) and once during recovery. Electrocardiograms (ECGs) were obtained from conscious monkeys restrained in a stock using subdermal needle electrodes. During the dosing period, ECGs were collected 3 to 4 hours after dosing Echocardiogramsc: Twice pretest (baseline), 4 to 5 times during the dosing phase (Study Days 11, 25, 95, 165, 270, and once during recovery on numerically the last 4 surviving animals/ sex/ group. Animals were immobilized with ketamine hydrochloride anesthesia (10 mg/ kg, intramuscularly, to effect) and the echocardiograms collected within 4 hours postdose. Drug- related effects by comparing the postdose change from average baseline of the vehicle and drug- treated groups using statistical and outlier analysis. A board- certified veterinary cardiologist evaluated the electrocardiograms (ECGs) for abnormalities in rate, rhythm and waveform morphology. Blood samples for systemic exposure evaluation were collected immediately after the post dose ECG measurements during the dosing phase.</p>
<p>Echocardiograms:</p>	<p>Twice pretest (baseline), 4 to 5 times during the dosing phase (Study Days 11, 25, 95, 165, 270, and once during recovery on numerically the last 4 surviving animals/ sex/ group. Animals were immobilized with ketamine hydrochloride anesthesia (10 mg/ kg, intramuscularly, to effect) and the echocardiograms collected within 4 hours postdose. Echocardiograms (ECHOs) were not performed on animals exhibiting severe clinical toxicity at the discretion of the Study Director. Detailed ECHO collection and examination procedures and the ECHO consulting cardiology report are retained in the raw data. Portions of the echocardiographic evaluations were not compliant with GLPs because the equipment used to collect the data was not validated in accordance with GLPs; however, a board- certified veterinary cardiologist made all measurements to ensure accuracy of the data. All measurements were recorded both manually and directly onto DVD. c Parameters evaluated were: Left atrial diameter; Left ventricle (LV) area in diastole; LV area in systole; LV internal diameter in diastole; LV internal diameter in systole; LV epicardial area in diastole; aortic diameter; LV ejection time; mean circumferential fiber shortening velocity; ratio of left atrial diameter to aortic diameter; myocardial area; and LV area change. A board- certified veterinary cardiologist obtained and evaluated the echocardiographic data using ¶ assessment of global LV systolic function. Data were evaluated for potential drug- related effects by comparing the average baseline values to postdose values.</p>

Hematology:	34 and 6 days before dosing, days 91, 126, 161 and 266 during dosing, and days 8, 29 and 57 of the recovery period.
Clinical chemistry:	34 and 6 days before dosing, days 91, 126, 161 and 266 during dosing, and days 8, 29 and 57 of the recovery period.
Urinalysis:	34 and 6 days before dosing, days 91, 126, 161 and 266 during dosing, and days 8, 29 and 57 of the recovery period from animals fasted overnight
Gross pathology:	All animals were necropsied.
Organ weights:	See histopath table
Histopathology:	Adequate Battery: yes (X), no () Peer Review: yes (X), no ()

Results

Mortality: 1 MD

1 MD female	Found dead with chain around neck. Gross necropsy indicated strangulation
3HD male	<ul style="list-style-type: none"> • #27-↓ appetite, hunched posture day 90, followed by diarrhea, dehydration and prostration by day 92. Euthanized in extremis. • #22/#27- euthanized day 126 and 168 in moribund condition
Remaining HD animals (1M/4F)	Euthanized preterminally day 169. Remaining animals placed into early 8 week recovery.

Clinical signs:

Clinical Sign	Incidence of Clinical Observations							
	0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
	M	F	M	F	M	F	M	F
↓ Activity							3(2)*	
Lame/limping							1(12)	
Appears dehydrated							7(13)	7(21)
Cool to touch							3 (8)	5(11)
Posture hunched							1 (2)	
Prostrate							1 (1)	
Appetite decreased							7(22)	7(26)
Struggling							1 (2)	
Scabbed area					2 (9)		2(12)	
Skin, discolored							7(75)	7(80)
Skin, pale							6(55)	6(65)
Emesis after dosing	1 (1)				1(1)	1(1)	1(1)	4(1)
Emesis, drug-like contents			3 (3)	2(3)	3 (2)		4 (5)	3(3)
Emesis, food-like material					1(1)		4(2)	2(1)
Breathing shallow							1 (1)	
Emesis, frothy							1(1)	
Feces (watery)			2(3)	1(4)			7 (8)	2(11)
Feces, discolored							3 (6)	
Feces, soft			1(5)	2(4)	3 (3)	2(4)	6(2)	4(2)

Clinical Sign	Incidence of Clinical Observations							
	0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
	M	F	M	F	M	F	M	F
Urine, discolored							2(2)	
Gums, pale							3(12)	2(13)
Gums, reddened					2(12)		7(36)	6(25)
Cheek, swollen							1(2)	
Mouth lesions							3(27)	
Teeth, darkened							1(12)	1(1)
Lips, chapped							3(5)	3(3)

*parenthesis indicates the mean number of animal days that the group displayed the signs

Body weights:

- Statistically significant reductions in body weight were noted on days 85 and 98 in males and females (6 mg/kg), respectively. By day 169 the magnitude of the difference in body weight was 23% (M) and 16% (F). These changes were reversible during the 56 day recovery period. Concomitant increases in body weight gain were also evident in these groups during the dosing period. Changes in animals treated with 0.3 and 1.5 mg/kg were not observed.

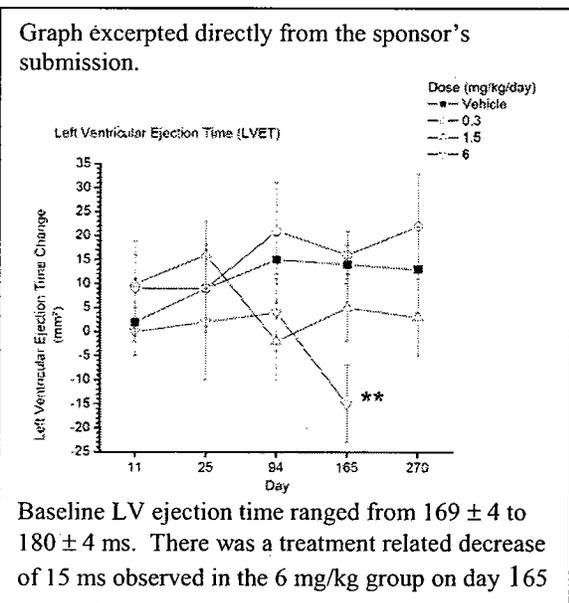
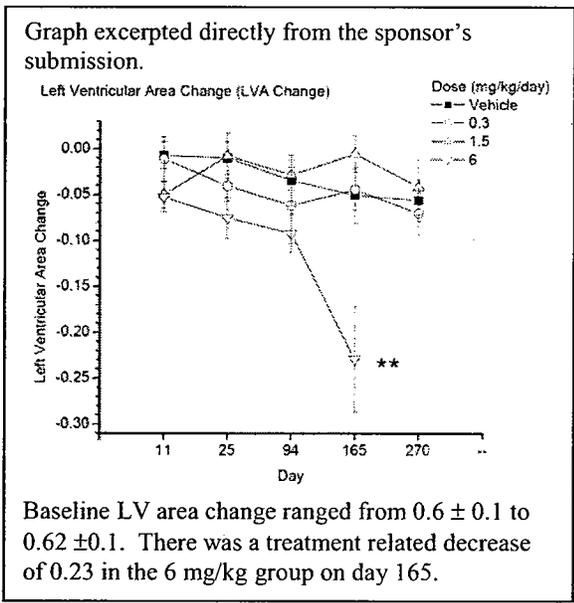
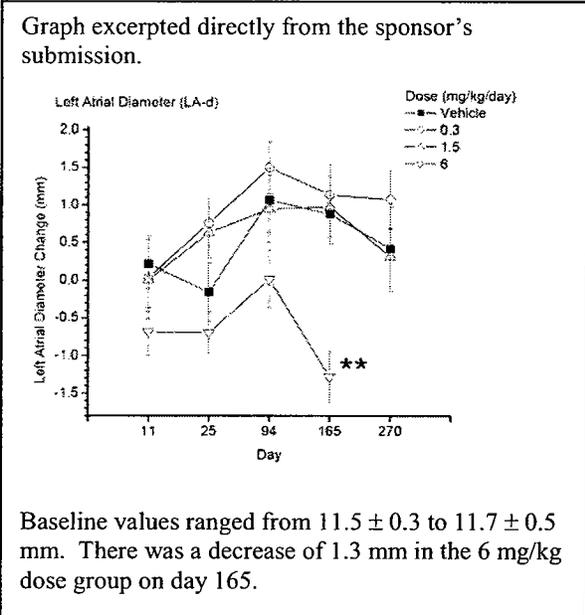
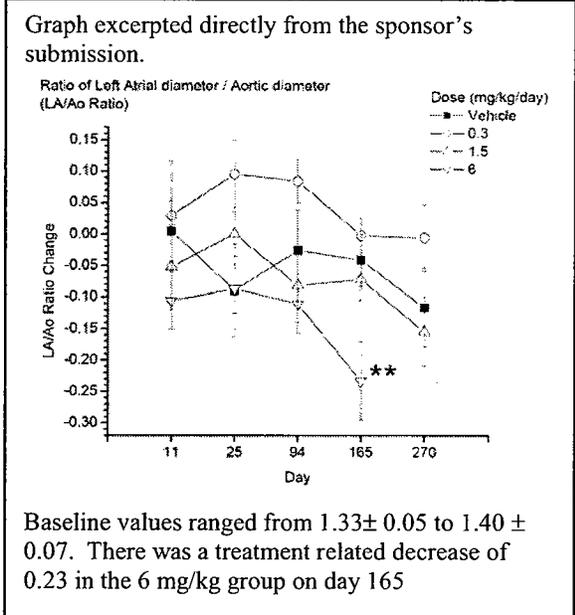
Ophthalmoscopy: none

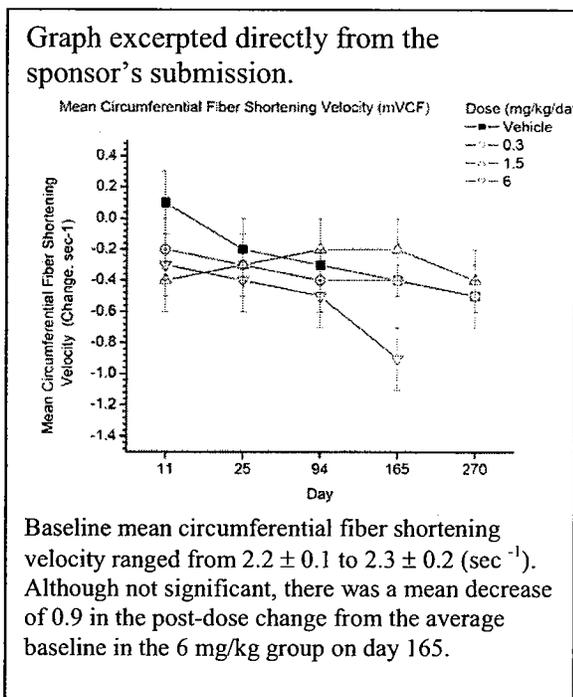
EKG:

High Dose	↓ HR day 94: 31 bpm ↓ HR day 164: 45 bpm • One instance of QR increase at 6 mg/kg (42 msec) • One instance of monomorphic premature ventricular contractions occurring in bigeminy patterns	Range: 27-87 bpm in 11 of 13 HD animals versus a 27-57 bpm change in 5 of 13 controls.
Mid dose	• One instance of irregular sinus pause lasting 1.5 sec	

Appears This Way
On Original

ECHO:





Hematology:

Changes were reversible at the end of the recovery period

% change in hematology parameters		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
Reticulocyte Count (10 ⁶ /μL)	Day 91	0.03	0.05	↓2	↓11	↓3	↓12	↓55	↓51
	Day 161	0.03	0.05	↓30	↓22	↓9	↓13	↓64	↓54
Reticulocyte Count (%)	Day 91	0.48	0.67	↓0.01	↓0.06		↓0.03	↓0.23	↓0.30
	Day 161	0.50	0.49	↓0.13	↓0.09	↓0.03	↓0.06	↓0.31	↓0.22
RBC/HG/HCT/Platelets/Prot hrombin time	Day 91	Minimal reductions of ≤20%							
	Day 161	Minimal reductions of ≤20% except for a 30-36% decrease in platelets in HD animals							
WBC (10 ³ /μL)	Day 91	11.1		↓12		↓2		↓20	
	Day 161							↓36	
Fibrinogen (10 ³ /μL)	Day 161	226	198					↑35	↑34

Clinical chemistry: All changes were reversible during the recovery period

% change in hematology parameters		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
AST (U/L)	Day 91	49	56					↑79	↑10
	Day 161	51	56					↑66	↑62
ALT (U/L)	Day 91	52	45					↑38	↑24
	Day 161	45	43					↑69	↑73
Creatine Kinase (U/L)	Day 91	100	131	↑200	↑500	↑47	↑7	↑3300	↑200

% change in hematology parameters		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
	Day 161	94	102					↑500	↑550
Inorganic Phosphorus (mg/dL)	Day 91	6.14	6.14					↓18	↓14
	Day 161	6.24	5.76					↓20	↓17
GGT (U/L)	Day 91	218	142					↓32	↓24
	Day 161	223	137					↓31	↓28

Urinalysis: None

Gross pathology:

Organ	Observation	Macroscopic Observations							
		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
		n=4/ 3	n=4/ 3	n=4/3	n=4/3	n=4/ 3	n=4/ 3	n=4/ 3	n=4/3
Adrenals	Enlarged							3	1
	Discolored							4	4
Bones	Fibula thickened							1	
Cecum	Focus							1	
	Contents discolored							1	
Colon	Focus							1	
	Contents discolored							1	
Heart	Adhesions					1	1		
Lungs	Adhesions					1	1	1	
	Mottled							1	
	Firm							1	
	Discolored							1	
Oral Cavity	Ulceration							3	1
Rectum	Focus							1	
	Abnormal Contents							1	
Stomach	Focus							1	
	Discolored							1	
Testis	Hemorrhage							1	
	Decreased size		1					1	
Thymus	Small							1	

Boldface is indicative of recovery sacrifice

Organ weights: All findings were reversible during the recovery period.

Organ	Percent change in absolute Organ Weight							
	0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
	M	F	M	F	M	F	M	F
	n=4/ 3	n=4/ 3	n=4/3	n=4/3	n=4/ 3	n=4/ 3	n=4/ 3	n=4/3
Adrenals	0.60 9		↓9		↓1		↑54	
Ovaries		0.37		↑51		↓6		↓59
Spleen	7.36	6.09	↑4	↓14	↑1	↑8	↓65	↓52
Thymus	3.18	3.51	↑33	↓16	↑7	↑39	↓82	↓87
Uterus		3.81		↑16		↓22		↓62

Histopathology:

Organ	Observation	Macroscopic Observations							
		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
		n=4/ 3	n=4/ 3	n=4/3	n=4/3	n=4/ 3	n=4/ 3	n=4/ 3	n=4/3
Adrenals	Hemorrhage, cortex, mild-mod							4	4
	Deposition, pigment, min							4	4
Aorta	Periarteritis, acute, septic mod							1	
Bone marrow	Atrophy, erythrocytes, mild							2	
	Atrophy, leukocytes, mild							1	
Bone marrow-stern	Atrophy, ethrocytes, min							3	
	Hyperplasia, leukocyte, mild							1	
	Atrophy leukocyte, min-mild							2	
	Hypocellularity, min							1	4
Brain	Inflammation, lymphocytic, choroids plexus, min-mild					1		3	3
Bones	Periosteal new bone formation							1	
Bones, Tibia	Dysplasia, physeal, mild-mod							4	4
	Necrosis, physeal cartilage, marked							1	
	Periosteal proliferation, bone and cartilage, mild-mod							3	
Cecum	Inflammation, acute, mucosa, min					1		1	1
	↓ vacuolation, min-mild							2	4
Colon	Hemorrhage, min							1	

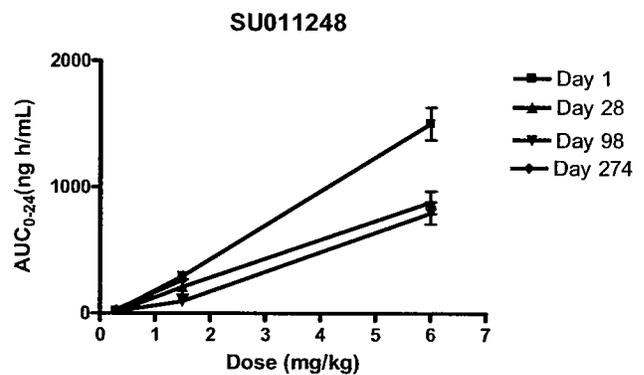
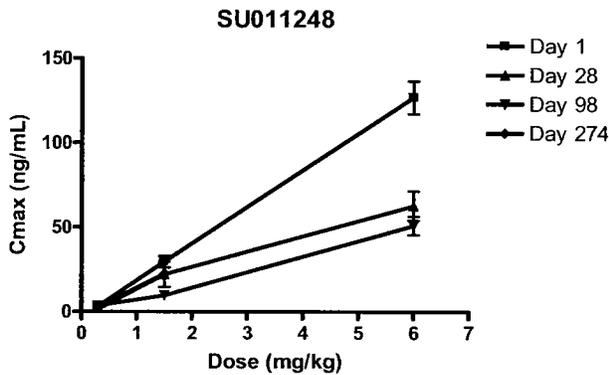
Organ	Observation	Macroscopic Observations							
		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
	Inflammation, acute: mucosa, min							2	2
	↓ vacuolation, min-mild							3	4
Cervix	Metaplasia, squamous: endometrium min-mild		2/1		2/1		4/2		3/3
Duodenum	Inflammation, acute, min							1	
Esophagus	Atrophy, epithelium, min							4	4
Heart	Inflammation, acute, pericardium							1	
Ileum,	Deposition, pigment		1					2	
	Inflammation, acute, min								1
Jejunum	Deposition, pigment/macrophages, min-mild		1		1			2	1/1
	Inflammation, acute, min							2	3
Kidneys	Deposition, pigment/tubule-cortex-min		2			1	1	4/2	2/1
	↑ mesangial matrix, min-mild							4	4
	Inflammation, acute, min							2	
LN/axilla	Depletion, min-mild	2	1	1			2	3/2	2/2
LN/bronch	Depletion, min-mild						1	2	4/2
	Plasmacytosis, mod							1	
Lungs	Deposition, pigment/alveolar macrophages, min							1	
	Inflammation, pleuritis, mod							1	
	Inflammation, bronchiole, mod							1	
	Inflammation, bronchus, mild							1	
	Deposition, foreign material						1	1	
Liver	Deposition, pigment, kupffer cell, min							2	
	Degeneration, lipid, portal hepatocytes, min							2	
	Inflammation, acute, min							1	
LN, Mesen	Depletion, lymphoid, min			1	1		2	3	1/2
	Deposition, pigment-macrophages, min-mild	2/2	2/1	3/2	2/2	2/2	3/3	3/2	4/3
	Ectasia/lymphatic							1/1	

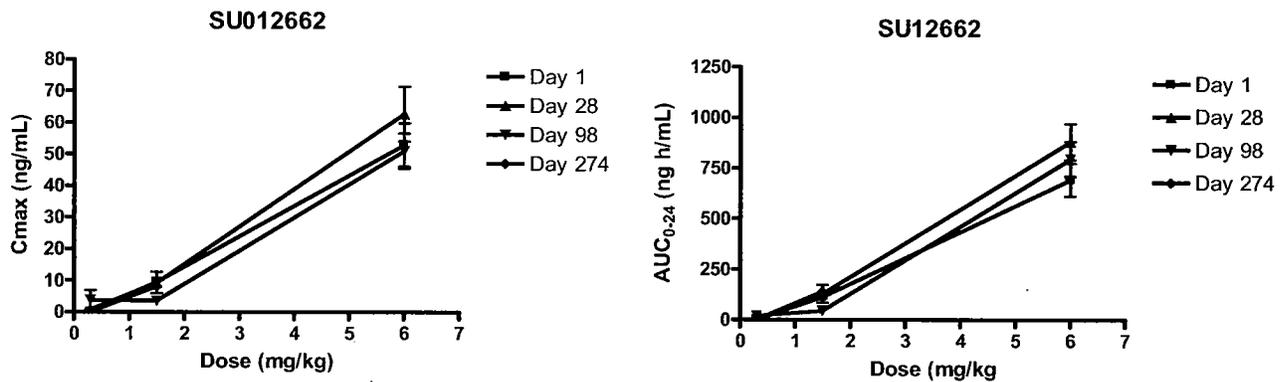
Organ	Observation	Macroscopic Observations							
		0 mg/kg		0.3 mg/kg		1.5 mg/kg		6 mg/kg	
		M	F	M	F	M	F	M	F
Oral Cavity	Ulceration, mild-mod							2	1
	Vasculitis, necrotizing							1	
Ovaries	Atresia: follicle min-mod								4
Oviducts	Atrophy, Epithelial								3
Pancreas	↓ zymogen granules, mod-marked							4	4
	Mineralization, min-mild					1		2/2	2
Pituitary	Vacuolation, mild					1			1
Peyers Patch	Lymphoid Depletion, min			1				1	
	Deposition, pigment, min							1/1	1
	Inflammation, acute, min							1	
Rectum	↓ vacuolation, crypt cells, min-mild							4	3
	Inflammation, acute							2	
	Hemorrhage							1	
Salivary Glands	Degranulation/acini, min-mod							4	4
Spleen	Deposition, pigment, min-mild					1		4	3
	Inflammation, granulomatous, min								1
Stomach	Hemorrhage, glandular, min								1
	Inflammation, acute, glandular, min-mild							1	4
Testis	Hemorrhage, mild							1	
	Giant cells, tubules							1	
Thymus	Depletion, mild-mod		1					3	4
Thyroid	Inflammation, acute, min-mild							2	4
Uterus	Atrophy, endometrium, mild								4
Vagina	Atrophy, epithelium min-mild								3

Boldface is indicative of incidence following the recovery period.

Toxicokinetics: There were no gender differences in TK.

TK Parameters in males and females following SU011398 Administration			
Day	Dose		
	0.3 mg/kg	1.5 mg/kg	6 mg/kg
Dose normalized AUC ₍₀₋₂₄₎ (ng h/mL)/(mg/kg/day)			
SU011248			
1	67	194	250
28	29.2	139	146.7
98	48.6	62.6	132.5
274	98.6	186.6	NA
SU12662			
1	1.8	74.7	115.3
28	12.7	85.3	100.8
98	65.6	29.3	77
274	0	92.7	NA
Dose normalized C _{max} (ng/mL)/(mg/kg/day)			
SU011248			
1	10.2	19.6	21.2
28	5.3	14.7	10.5
98	11.8	6.5	8.5
274	8.86	14.9	NA
SU12662			
1	0.60	6.3	8.8
28	2.5	6.2	6.4
98	12.7	2.4	4.3
274	0	5.4	NA





Histopathology inventory

Study	2003-0390	2003-0386
Species	Rat	Monkey
Adrenals	X*	X*
Aorta	X	X
Bone Marrow smear	X	
Bone (femur)	X	
Bone (tibia)		X
Brain	X	X*
Cecum	X	X
Cervix		X
Colon	X	X
Duodenum	X	X
Epididymis	X*	X
Esophagus	X	X
Eye	X	X
Fallopian tube		
Gall bladder		X
Gross lesions	X	X
Harderian gland	X	
Heart	X*	X*
Ileum	X	X
Injection site		
Jejunum	X	X
Kidneys	X*	X*
Lachrymal gland		
Larynx		X
Liver	X*	X*
Lungs	X*	X

Study	2003-0390	2003-0386
Species	Rat	Monkey
Lymph nodes, axillary		X
Lymph nodes, bronchi		X
Lymph nodes, cervical		
Lymph nodes mandibular		
Lymph nodes, mesenteric	X	X
Mammary Gland	X	X
Nasal cavity		
Optic nerves	X	
Ovaries	X*	X*
Pancreas	X	X
Parathyroid	X	X
Peripheral nerve		X
Pharynx		
Pituitary	X*	X*
Prostate	X*	X
Rectum		
Salivary gland	X	X
Sciatic nerve	X	
Seminal vesicles	X	
Skeletal muscle		X
Skin	X	X
Spinal cord	X	X
Spleen	X*	X*
Sternum	X	
Stomach	X	X
Testes	X*	X*
Thymus	X*	X*
Thyroid	X	X
Tongue	X	X
Trachea	X	X
Ureter		X
Urinary bladder	X	X
Uterus	X*	X*
Vagina	X	X
Zymbal gland		
Ureters	X	
Nasal turbinates	X	

Study	2003-0390	2003-0386
Species	Rat	Monkey
LN, inguinofemoral	X	

X, histopathology performed

*, organ weight obtained

Study title: SU010398 (PHA-290940AD): Oral 7 day dose tolerance study in female rabbits (#2002-0542; Volume 4.2.3.2)

Study Summary:

SU010398 (SU011248 L-malate; 1, 10, 20 mg/kg/day) was administered daily x7 to female New Zealand White rabbits (n=3/group) to determine dose tolerance in this non-GLP study. Body weights, food consumption, clinical observations, and gross observations were assessed. Exposure was assessed on days 1 and 7 at 0, 1, 3, 6, 9, and 24 hours. Mortality was not observed in any groups. Treatment related decreases in body weight (5-7 %), body weight change compared to control, and food consumption (36-65%) were observed in the 20 mg/kg group on days 5- 8. Dose dependent gross pathology findings were limited to yellow staining in the 20 mg/kg dose group. TK parameters for SU011248 and SU012662 are presented in the table below.

The increase in SU011248 (PHA- 290940) exposure after oral administration of the compound in the rabbits appears to be linear with dose with a slight increase in the exposure (1.7- fold increase of AUC_{24hr} on Day 7) observed only at the low dose (1 mg/ kg/ day). The increase in SU012662 (active metabolite) exposure after oral administration of SU010398 (PHA- 290940AD) in the rabbits appears to be nonlinear with dose with greater than proportional increase in the exposure with each dose observed.

Study Day	Analyte	Dose (mg/kg/day)	C _{max} (ng/mL)	Dose Normalized C _{max}	AUC (ng hr/mL)	Dose Normalized AUC
1	SU011248	1	14.6 ± 3.6	14.6	192 ± 25	192
		10	195 ± 42	19.5	2560 ± 920	256
		20	316 ± 7.1	15.8	5430 ± 350	543
	SU012662	1	3.64 ± 3.64	3.64	55.6 ± 15	3.64
		10	103 ± 24	10.3	1540 ± 540	154
		20	246 ± 13	12.3	4340 ± 330	217
7	SU011248	1	21.9 ± 2.9	21.9	313 ± 67	313
		10	173 ± 9.3	17.3	2890 ± 620	289
		20	337 ± 140	16.68	5900 ± 2100	295
	SU012662	1	8.17 ± 2.9	8.17	138 ± 74	138
		10	172 ± 61	17.2	2780 ± 1200	278
		20	620 ± 71	31	12400 ± 2300	6200

2.6.6.4 Genetic toxicology

SU011248: gene mutation test in bacteria (Ames) [2000-0357; Volume 4.2.3.3]
(Previously reviewed by Dr Schmidt; IND 62382, review #1, modified herein)

Conducting laboratory and location: Pharmacia/Upjohn, Nerviano (MI), Italy

Date of study initiation: 9/12/00

GLP compliance: Yes **QA status:** Yes

Methodology

Strains: *S. typhimurium* TA98, TA100, TA1535, TA 1537; *E. coli* WP2uvrA

Concentration/dose selection criteria: bacterial lawn inhibition

Range finding results: 0-5000 ug/plate, precipitates at 312.5 ug/plate, background lawn strongly inhibited at doses > 625 ug/plate

Test agent: SU011248, Batch # A5903-TJF-0001, ♂ pure

Metabolic Activation System: phenobarbital-methylcholantrene induced rat S9 mixture

Vehicle: DMSO

Positive Controls: 2-nitrofluorene (2-NF), 9-aminoacridine (9-AA), 2-aminoanthracene (2-AAN), 2-acetylaminofluorene (2-AAF), benzo(a)pyrene (BP), sodium azide (SA), and methylmethanesulfonate (MMS)

Exposure Conditions

Incubation and sampling times: standard

Concentrations/doses used in definitive studies

Analysis:

plates/replicates: 3 plates, 2 replicates

Counting method: image analyzer

Criteria for Positive results: positive and negative controls within historical range, both replicates show both statistically significant and 2 fold increase above controls

Results

Study validity: The study was valid.

Study Outcome: Positive controls were elevated more than 10 fold. There were no statistically significant elevations in revertants with treatment.

Comments and conclusions: The study was valid but negative for mutagenicity.

Salmonella-Escherichia coli/Mammalian-microsome reverse mutation assay with a confirmatory assay with SU012248. [21602-0-422OECD; Volume 4.2.3.3]

(Previously reviewed by Dr Schmidt; IND 62382, review #1, modified herein)

Conducting laboratory and location: ⌈

Date of study initiation: 10/31/00

GLP compliance: Yes **QA status:** Yes

Methodology

Strains: *S. typhimurium* TA98, TA100, TA1535, TA1537; *E. coli* WP2uvrA

Concentration/dose selection criteria: solubility, bacterial lawn inhibition

Range finding results: doses of 625 ug/plate caused precipitation.

Test agent: SU011248, lot # (A2)5953-TJF0003, PNU-290940

Metabolic Activation System: S9 fraction Molecular Toxicology, Inc (from Arochlor induced male Sprague Dawley rats)

Vehicle: DMSO

Positive Controls: BP, 2-NF, 2-AA, SA, ICR-191, 4-nitroquinoline-N-oxide (4-NQO)

Exposure Conditions: standard

Concentrations used in definitive studies: 0, 19.54, 39.07, 78.13; 156.25, 3212.5, 625 ug/plate

Analysis:

plates, replicates analyzed: 3 plates, 2 replicates

Counting method: manual

Criteria for Positive results: 3 fold increase above controls.

Results

Study validity: Positive controls increased the number of revertants by at least 10 fold.

Study Outcome: There were no statistically significant increases in revertants vs controls.

Comments and conclusions: The study was valid and negative for mutagenicity.

Chromosomal aberrations in cultured human peripheral blood lymphocytes with SU001248. [21602-0-449OECD; Volume 4.2.3.3]

(Previously reviewed by Dr Schmidt; IND 62382, review #1, modified herein)

Conducting laboratory and location: []

]]

Date of study initiation: 7/19/00

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, radiolabel, and % purity: SU011248, GLP Lot # 002101

Vehicle: DMSO

Methods:

Cell line: human peripheral lymphocytes (healthy adult donor)

Metabolic activation system: S9 fraction from Molecular Toxicology, Inc. from male Sprague Dawley rats induced by arochlor

Controls:

Vehicle: DMSO

Positive controls: mitomycin C (MMC), cyclophosphamide (CP)

Exposure conditions:

Incubation and sampling times: 3 hours with drug, 22 hours without, 47 hours without metabolic activation, doses up to 346 ug/mL; 57.8 ug/mL resulted in a 84% reduction in mitotic index

Doses used in definitive study: 1, 2, 3, 6, 9, 12, 15, 20, 25, 30, 40, 50 and 60 ug/mL

Analysis:

No. of replicates: duplicates with 1 replication

Counting method: 100 cells from each culture

Criteria for positive results: significant increase in # of cells with aberrations was seen at 1 or more concentrations.

Summary of individual study findings:

Study validity: In the absence of S9, MMC increased the % of cells with aberrations, as did CP in the presence of S9.

Study outcome: The % of polyploid cells SU011248 was increased beginning at 10 ug/mL in the presence and absence of S9. There were no significant increases in cells with aberrations.

Comments and conclusions: The study was valid. Although structural aberrations were not increased, polyploidy was increased at doses > 10 ug/mL.

In vivo rat micronucleus assay with SU011248. [21602-0-454OECD; Volume 4.2.3.3]

(Previously reviewed by Dr Schmidt; IND 62382, review #1, modified herein)

Conducting laboratory and location: []

Date of study initiation: 7/19/00

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, radiolabel, and % purity: SU011248, Lot # 002101, 002103.

Formulation/vehicle: 0.5% carboxymethylcellulose, 0.4% polysorbate 80, 0.9% benzyl alcohol

Species: CD (SD) BR rats, 9 weeks old, M: 270-330 g, F: 201-232 g

Dose selection criteria: toxicity/mortality; 3 rats/sex/dose were administered oral gavage

SU011248 @ 1000, 1500 or 2000 mg/kg and observed for 3 days. No rats died, but at the MD and HD, hypoactivity, soft feces and yellow skin/urogenital staining was observed.

Vehicle: see above

Positive controls: cyclophosphamide

Exposure conditions:

Incubation and sampling times: 24 (all dose groups) and 48 hours (control and HD only)

Doses used in definitive study: 0, 500, 1000, 2000 mg/kg

Analysis:

No. of replicates: 6 rats/sex/dose, 2000 PCEs counted

Counting method: manual

Criteria for positive results: statistically significant and dose dependent response

Summary of individual study findings:

Study validity: 4 HD males and all of the HD females were found dead. The study was redone at 0, 250, 750 and 1500 mg/kg.

Study outcome: The mPCEs were increased by >10 fold in the positive controls. The number of mPCEs did not increase in the drug treated animals.

Comments and conclusions: The study was valid and negative for clastogenicity.

2.6.6.5 Carcinogenicity

Carcinogenicity studies were not conducted and are generally not required to support the safety of a product for a metastatic cancer indication.

2.6.6.6 Reproductive and developmental toxicology**Fertility and early embryonic development**

Study title: SU010398 (PHA-290940AD): Oral 7 day dose tolerance study in female rabbits (#2002-0542; Volume 4.2.3.2)

Study Summary:

SU010398 (SU011248 L-malate; 1, 10, 20 mg/kg/day) was administered daily x7 to female New Zealand White rabbits (n=3/group) to determine dose tolerance in this non-GLP study. Body weights, food consumption, clinical observations, and gross observations were assessed. Exposure was assessed on days 1 and 7 at 0, 1, 3, 6, 9, and 24 hours. Mortality was not observed in any groups. Treatment related decreases in body weight (5-7 %), body weight change compared to control, and food consumption (36-65%) were observed in the 20 mg/kg group on days 5- 8. Dose dependent gross pathology findings were limited to yellow staining in the 20 mg/kg dose group. TK parameters for SU011248 and SU012662 are presented in the table below.

The increase in SU011248 (PHA- 290940) exposure after oral administration of the compound in the rabbits appears to be linear with dose with a slight increase in the exposure (1.7- fold increase of AUC_{24hr} on Day 7) observed only at the low dose (1 mg/ kg/ day). The increase in SU012662 (active metabolite) exposure after oral administration of SU010398 (PHA- 290940AD) in the rabbits appears to be nonlinear with dose with greater than proportional increase in the exposure with each dose observed.

Study Day	Analyte	Dose (mg/kg/day)	C _{max} (ng/mL)	Dose Normalized C _{max}	AUC (ng hr/mL)	Dose Normalized AUC
1	SU011248	1	14.6 ± 3.6	14.6	192 ± 25	192
		10	195 ± 42	19.5	2560 ± 920	256
		20	316 ± 7.1	15.8	5430 ± 350	543
	SU012662	1	3.64 ± 3.64	3.64	55.6 ± 15	3.64
		10	103 ± 24	10.3	1540 ± 540	154
		20	246 ± 13	12.3	4340 ± 330	217
7	SU011248	1	21.9 ± 2.9	21.9	313 ± 67	313
		10	173 ± 9.3	17.3	2890 ± 620	289
		20	337 ± 140	16.68	5900 ± 2100	295
	SU012662	1	8.17 ± 2.9	8.17	138 ± 74	138
		10	172 ± 61	17.2	2780 ± 1200	278
		20	620 ± 71	31	12400 ± 2300	6200

Study title: SU010398 (PHA-290940AD): Oral Fertility and Early Embryonic Development Study in the rat

Key study findings:

- Based on an increased number of dead embryos (↑ 3.5 fold) observed when females were treated with 5 mg/kg, the NOAEL for female reproductive toxicity is 1.5 mg/kg/day.
- 10 mg/kg exceeded the MTD in males treated prior to cohabitation. There was a 9% decrease in the number of live fetuses, however, there was not a concomitant increase in dead fetuses or decrease in the number of implantations. A slight decrease in the number of preimplantation loss was observed.

Study no.: 2003-0370

Volume #, and page #: 4.2.3.5.1

Conducting laboratory and location: Pfizer Global Research and Development, Kalamazoo, MI

Date of study initiation: 04 September 203

GLP compliance: Yes

QA reports: yes (X) no ()

Drug, lot #, and % purity: SU010398; (B2)6421-VGK-0301; 1 Impurities consist of

Methods

Doses: Female Fertility Phase: 0, 0.5, 1.5, 5 mg/kg (free base SU011248 equivalents)

Male Fertility Phase: 0, 1, 3, 10 mg/kg

Species/strain: Rat CD (SD) IGS BR

Number/sex/group: 22/group/sex in both the male and female fertility phase.

Route, formulation, volume, and infusion rate: Oral gavage, sterile water, 10 mL/kg/day.

Satellite groups used for toxicokinetics: 4 females/dose in the female fertility phase; 4 males/does in the male fertility phase

Study design: Female fertility phase: SU010398 (L-malate salt of SU011248) was administered for 14 days prior to cohabitation with untreated males, during cohabitation, and continuing through gestation day 7 and to male Sprague- Dawley rats for at least 58 days prior to cohabitation with untreated females, during cohabitation, and continuing until euthanasia. The study design consisted of 2 phases. In Phase I (female fertility phase), untreated males were paired with treated females. In Phase II (male fertility phase), the same males were then treated for 58 days prior to cohabitation with untreated females. Systemic exposure of SU011248 and its active major metabolite, SU012662 was evaluated. Systemic exposure information for the females was obtained from satellite females that were similarly dosed, but not evaluated for reproductive effects. Systemic exposure information for the males was obtained from the study animals (last 4 surviving sequentially numbered rats per treated group which had mated with their assigned untreated female).

Parameters and endpoints evaluated:

Clinical Signs	At least once daily for males and females that were not being dosed. At least twice daily during the dosing interval including a postdose observation approximately 1 hour after dosing (additional
----------------	--

	observations conducted at the discretion of the Study Director upon evidence of a change in general appearance, overt signs of toxicity, or evidence of moribundity).
Estrous Cycle Monitoring	Phase I females: 14 days prior to dose initiation, during dosing, and continuing until positive evidence of mating Phase II females: Not monitored
Body Weights	Phase I and II females: Twice weekly until positive evidence of mating (or necropsy) and on gestation days 0, 3, 7, 10, and 14 Phase II males: Twice weekly
Food Consumption(not measured during cohabitation)	Phase I females: Twice weekly during dosing until cohabitation and on gestation days 0, 3, 7, 10, and 14 Phase I toxicokinetic females: Not measured Phase II males: Twice weekly during dosing and during the week prior to dosing Phase II females: Not measured
Necropsy	All rats were given gross necropsy. Epididymides, ovaries, prostate, testes, seminal vesicles, uterus, vagina and lesions were collected. Microscopic examination was not deemed necessary.

Results

Mortality:

Phase I (female): No mortality observed

Phase II (male): 3 males (10 mg/kg) found dead on days 13, 44, 62 and 1 male (10 mg/kg) was euthanized in extremis on day 39.

Clinical signs:

Phase I (female): No treatment related clinical signs.

Phase II (males):

Observations in treated males	0 mg/kg	1 mg/kg	3 mg/kg	10 mg/kg
Appears thin				2
Cool to touch				1
Hunched Posture				1
Unkempt				1
Pale				8
Activity decreased				1
Anogenital staining				3
Urogenital staining				10
Material around eyes	1	2	1	7
Staining around eyes				1
Staining around mouth				3
Nasal matting				1

Body weight:

Phase I (female): No treatment related changes in body weight

Phase II (male): 7% and 10% reduction in body weight in the 10 mg/kg group on days 62 and 69, respectively.

Food consumption:

Phase I (female): No treatment related changes in food consumption

Phase II (male): Statistically significant reduction (10% ↓ on day 28 and a 26% ↓ on day 58) in food consumption observed in males treated with 10 mg/kg. Measurements ceased on day 58 when cohabitation began.

Toxicokinetics: Mean TK parameters for SU011248 and SU012662 after oral administration of SU010398 for dose days 14 and 70

Collection on Dose day 14 for Phase I females postdose and on dose day 70 for Phase II males at 0, 1, 3, 6, 9, 12 and 24 hours.

Dose (mg/kg/day)	SU011248			SU12662		
	C _{max} (ng/mL)	T _{max} (h)	AUC (ng* h/mL)	C _{max}	T _{max}	AUC
Day 14-Females						
0.5	19.9 ± 13.2	2.5 ± 1.0	88.6 ± 54.6	48.0 ± 31.7	2.5 ± 1.0	252 ± 144
1.50	57.2 ± 41.7	12.0 ± 0	637 ± 418	93 ± 49.0	7.5 ± 5.74	1030 ± 536
5.0	291 ± 132	6.0 ± 0	3150 ± 1640	495 171	6.0 ± 0.0	6650 ± 2360
Day "70" Males						
1.00	34.6 ± 26.5	6.0 ± 0.0	332 ± 293	107 ± 88.2	5.25 ± 1.0	1420 ± 1250
5.0	174 ± 73.0	5.25 ± 1.5	1720 ± 921	894 ± 452	5.25 ± 2.87	11000 ± 8300
10.0	609 ± 220	9.75 ± 2.87	8010 ± 1750	2820 ± 2670	9.75 ± 2.87	41700 ± 39700

Necropsy:

Phase I (female): No treatment related observations or ovarian weight

Phase II (male):

Macroscopic Observations		0 mg/kg	1 mg/kg	3.0 mg/kg	10.0 mg/kg
Adrenals	Enlarged,				1
	Discolored				1
General Comment	Organs discolored yellow				20*
Kidneys	Calculus				1*
Seminal vesicles	Small				2*
Testis	Flaccid			1	1
Urinary bladder	Distended				1*
	Thickened				1*
	Calculus				1*

*observed in animals that did not survive to their scheduled sacrifice

Fertility parameters (mating/fertility index, corpora lutea, preimplantation loss, etc.):

Phase I (female): No changes were observed in the mean number and length of estrous cycles or copulation and fertility, prior to and during dosing. At necropsy there was no difference in the # of implantations, # of live embryos, or the # of females with post-implantation loss.

Observations	0 mg/kg	0.5 mg/kg	1.5 mg/kg	5.0 mg/kg
# of pregnant females	20	21	20	20
Mean # of corpora lutea	16.50 ± 1.9	17.14 ± 2.1	16.6 ± 1.5	19.45 ± 3.7
# of dead embryos	0.7 ± 0.66	0.95 ± 0.86	1.15 ± 1.46	2.55 ± 3.03
Mean % Pre-implantation loss	5.05 ± 7.54	6.56 ± 13.33	7.19 ± 11.33	17.29 ± 15.54
Mean % Post-implantation loss	4.68 ± 4.49	6.84 ± 8.39	7.75 ± 9.60	16.73 ± 20.84
# of females with preimplantation loss	8	10	9	12

Phase II (male): No changes were observed in the copulation or fertility with 22, 21, 20 and 17 females of 22, 22, 22, and 19 females which cohabitated with males in the 0, 1, 3, and 10 mg/kg groups, respectively. There was no significant difference between the # of corpora lutea, # of implantations, # of dead embryos, or the # of post-implantation loss.

Observations	0 mg/kg	1.0 mg/kg	3.0 mg/kg	10.0 mg/kg
# of pregnant females	22	21	20	17
# of live embryos	14.50 ± 1.74	13.81 ± 1.72	13.70 ± 2.39	13.24 ± 1.35
Mean Preimplantation loss	8.76 ± 7.72	7.18 9.33	8.56 ± 11.91	10.68 ± 13.20

Sperm Analysis: There were no effects on sperm motility, morphology, or concentration observed in any dose group.

Embryofetal development

Study title: SU010398 (PHA-290940AD): Oral Embryo-Fetal Development Study in the Female Rat

Key study findings:

- Reductions in body weight gain and reduced gravid uterine weight were seen in females treated with 5 mg/kg/day and is attributed to a decreased number of live fetuses (↓52%)
- Treatment related embryofetal mortality was also evidenced by an increased number of resorptions [early and total (↑12 fold)] and a corresponding increase in the percentage of postimplantation loss (49% vs 3% in the control group. Total litter loss occurred in 29% of pregnant females at 5 mg/kg and decreased fetal body weight (~10%) was also treatment related.

- At 5 mg/kg/day, skeletal malformation (26.5% of fetuses, 55% of litters) were significantly increased and included hemicentric, misaligned and absent vertebral centra and/or arches of the thoracic and lumbar vertebrae. Additionally, increases in skeletal variations were observed following doses ≥ 3 mg/kg and were categorized as decreased ossification.

Study no.: 2003-0372

Volume #, and page #: 4.2.3.5.2

Conducting laboratory and location: Pharmacia & Upjohn Company; Kalamazoo, MI

Date of study initiation: Sept 4, 2003

GLP compliance: Yes

QA reports: yes (x) no ()

Drug, lot #, and % purity: SU010398; (B2)6421-VGK-0301; 99.4% Impurities Unspecified

Methods

Doses: 0, 0.3, 1.5, 3, 5 mg/kg/day

Species/strain: Rat CD (SD) IGS BR

Number/sex/group: 22 females/group except 5 mg/kg where 28 females were utilized

Route, formulation, volume, and infusion rate: Oral gavage, sterile water, 6 mg/mL for animals treated with 0.3, 10 mg/mL for animals treated with >0.3 mg/mL.

Satellite groups used for toxicokinetics: n=4 females/group

Study design: SU010398 was administered orally, once daily, to time-mated female Sprague-Dawley rats for gestation days 6 through 17. SU010398 (0, 0.3, 1.5, and 3.0 mg/kg/day-free base [SU-011248] equivalents) was administered as a solution to groups of 22 rats. Preliminary results did not demonstrate maternal or developmental toxicity and 2 additional dose groups (using an identical dosing regimen) were added to the study; groups of 28 rats were administered 5 mg SU010398/kg/day (freebase equivalents), and a concurrent control group of 22 rats was administered vehicle only.

Parameters and endpoints evaluated:

Clinical Signs	Once daily prior to and after the dosing interval. At least twice daily during the dosing interval including a postdose observation approximately 1 hour after dosing. Clinical and physical examinations were performed on all study animals (toxicology and toxicokinetic) until scheduled necropsy
Body Weights	On the day of receipt (gestation day 0), on gestation day 3, daily on gestation days 6 through 18, and on gestation day 21
Food Consumption(not measured during cohabitation)	On the day of receipt (gestation day 0), on gestation day 3, daily on gestation days 6 through 18, and on gestation day 21. Food weight was also recorded on gestation days 19 and 20 for animals in Groups 8 and 9.
Necropsy	On GD 21 rats were euthanized. The entire uterus and its contents were removed and weighed intact. Uteri that appeared nonpregnant were placed in 10% ammonium sulfide solution to visualize implantation sites. Live and dead fetuses and early and late resorptions were counted and their locations recorded. Any abnormalities were identified and recorded. The number of corpora

	lutea on each ovary was counted and recorded. The fetuses were numbered sequentially, beginning at the ovarian end of the left uterine horn and ending at the cervix; numbering was continued from the ovarian end of the right uterine horn to the cervix. Each placenta was examined grossly. Each fetus was removed, examined grossly, weighed and sexed. 50% of the fetuses were examined for visceral alterations. The remaining fetuses were processed for skeletal examinations
--	--

Results

Mortality (dams): there were no unscheduled deaths during the study.

Clinical signs (dams): There were no treatment related clinical signs

Body weight (dams): Changes were limited to the 5 mg/kg group, in which a 9% decrease in gross body weight was observed on GD 21, body weight gain was decreased beginning on GD 13 and continued until GD 21 with the magnitude of the difference being up to a 57% decrease. A decrease in gravid uterine weight was also observed (\downarrow 52%). Gross and weight gain changes are negated when gravid uterine weight is subtracted from the weight. Changes were due to the reduced number of fetuses at 5 mg/kg and the high number of dams with complete post-implantation loss (29%).

Food consumption (dams): there were no treatment related changes in food consumption

Toxicokinetics: Collection was conducted on dose days 1 and 12 (gestational days 6 and 17) at 0, 1, 3, 6, 9, 12, and 24 from 4 animals/group.

- SU011248 and SU012662, the primary metabolite, were absorbed with a mean tmax of approximately 4-8 hours. Mean plasma concentrations increased in a dose proportional manner. Accumulation of SU011248 and SU012662 were not observed.

Systemic Exposure (mean \pm SD) to SU011248 After Oral Administration of SU010398 to Female Rats				
Study Day	Dose (mg/kg/day)	Cmax (ng hr/mL)	Tmax (h)	AUC (ng h/mL)
1	0.3	26.5 \pm 40.9	5.25 \pm 3.77	158 \pm 214
12	0.3	20.3 \pm 18.1	3.75 \pm 4.5	108 \pm 82.8
1	1.5	65.2 \pm 34.9	6.0 \pm 0	659 \pm 362
12	1.5	86.4 \pm 41.4	5.25 \pm 1.50	809 \pm 421
1	3.0	290 \pm 189	5.25 \pm 2.87	1490 \pm 890
12	3.0	262 \pm 254	6.75 \pm 1.50	1880 \pm 1270
1	5.0	367 \pm 152	6.75 \pm 1.50	4040 \pm 1830
12	5.0	380 \pm 130	7.50 \pm 1.73	4740 \pm 2090

Systemic Exposure (mean ± SD) to SU012662 After Oral Administration of SU010398 to Female Rats				
Study Day	Dose (mg/kg/day)	Cmax (ng hr/mL)	Tmax (h)	AUC (ng h/mL)
1	0.3	75.7 ± 123	5.5 ± 3.32	464 ± 638
12	0.3	67.3 ± 90.5	6.0 ± 4.24	185 ± 47.0
1	1.5	98.1 ± 43.3	6.75 ± 1.5	1280 ± 612
12	1.5	84.9 ± 40.3	5.25 ± 1.50	955 ± 397
1	3.0	443 ± 322	5.25 ± 2.87	2670 ± 1260
12	3.0	303 ± 262	6.00 ± 2.45	2550 ± 1340
1	5.0	541 ± 221	6.75 ± 1.50	6930 ± 2980
12	5.0	431 ± 230	7.50 ± 1.73	5860 ± 3570

Terminal and necroscopic evaluations: Differences in mean #'s of females not pregnant, females pregnant, corpora lutea, implantations, preimplantation loss, and the body weight of the live fetuses were comparable across all treatment groups.

Caesarian and Fetal Parameters for Gravid Rats Dosed with SU010398 from GD 6-17						
Parameter	Dose					
	0 mg/kg	0 mg/kg *	0.3 mg/kg	1.5 mg/kg	3 mg/kg	5 mg/kg
Mean # of live fetuses	13.76 ± 1.81	13.10 ± 1.95	12.5 ± 3.08	13.62 ± 1.91	12.82 ± 3.06	6.71 ± 5.53
# of early resorptions	0.52 ± 1.21	0.52 ± 68	0.36 ± 0.90	0.52 ± 0.81	0.59 ± 1.10	6.61 ± 5.70
# of total resorptions	0.52 ± 1.21	0.57 0.75	0.36 ± 0.90	0.57 ± 0.81	0.59 ± 1.10	6.64 ± 5.67
% Post-implantation loss	3.37 ± 7.49	5.52 ± 21	2.67 ± 6.77	4.10 ± 5.88	5.52 ± 12.74	49.54 ± 41.00
# of females with post-implantation loss	5	9	4	9	7	25
Females w/ complete implantation loss	0	0	0	0	0	8 (29%)
Fetal Weight (g)	5.6 ± 0.24	5.74 ± 0.31	5.66 ± 0.34	5.57 ± 0.34	5.46 ± 0.44	5.24 ± 0.32

Control group for the 5.0 mg/kg dosing group.

Offspring (malformations, variations, etc.):

Caesarian and Fetal Parameters for Gravid Rats Dosed with SU010398 from GD 6-17						
Parameter	Dose					
	0 mg/kg	0 mg/kg *	0.3 mg/kg	1.5 mg/kg	3 mg/kg	5 mg/kg
Total # of fetuses	289	275	275	286	282	188
# of litters	21	21	22	21	22	20
Gross Malformations	0	0	0	0	2/2*	3/3
Visceral Malformations	3/3	3/3	0	0	7/3	2/2
Skeletal Malformations	1/1	3/2	1/1	2/2	3/3	26/11

Caesarian and Fetal Parameters for Gravid Rats Dosed with SU010398 from GD 6-17						
Parameter	Dose					
	0 mg/kg	0 mg/kg *	0.3 mg/kg	1.5 mg/kg	3 mg/kg	5 mg/kg
Gross variations	0	0		6	0	0
Visceral variations	1/1	4/4	1/1	3/2	4/3	11/9
Skeletal variations	16/9	30/14	9/9	34/15	42/17	90/14
Gross Malformations						
Tail bent					1	1
Gastroschisis						1
Meningocele						1
Tail Short					1	1
Visceral Malformations						
Ventricular septum absent						1
Right sided aortic arch						1
Transposition of the great vessels						1
Great vessels from pulmonary						1
Skeletal Malformations						
Ribs misaligned						3/3
Ribs fused					1	3/2
Ribs knobby		1	1	1	1	5/3
Ribs branched						1
Lumbar vert centra misaligned						1
Thoracic vert centra hemicentric						18/7
Thoracic vert centra misaligned						7/5
Thoracic vert centra absent						2/2
Thoracic vert centra absent						1/1
Lumbar vert arches misaligned						7/6
Lumbar vert arches fused						2/1
Thoracic vert arches misaligned						4/4
Thoracic vert arches absent						2/2
Lumbar vert centra fused						1
Lumbar vert centra absent						1
Lumbar vert centra hemicentric						4/3
Thoracic vert arches fused						3/3
Lumbar vert arches small						2/2
Lumbar vert arches absent						6/5
Thoracic vert arches small						2/2
Visceral Variations						
No Innominate					2/2	8/6
Retroesophageal right subclavian						2/2
Skeletal Variations						
Thoracic vert centra inc oss	5/4	18/8	3/3	11/7	24/13	69/19
Lumbar vert centra inc oss	1				3/3	6/5
Short supernumerary ribs	8/4	4/3	2/2	6/4	3/3	28/13
7 th cervical centrum unossified		3/2		3/3	9/4	17/8
Sternebra 5 and 6 unossified	1	1		4/2	1	4/2
Metacarpal unossified						1
Full supernumerary ribs		1				5/5

Caesarian and Fetal Parameters for Gravid Rats Dosed with SU010398 from GD 6-17						
Parameter	Dose					
	0 mg/kg	0 mg/kg *	0.3 mg/kg	1.5 mg/kg	3 mg/kg	5 mg/kg
Skull zygomatic inc oss						2/2
Sternebrae inc oss						2/2
Sternebrae misaligned						1

*In fetuses/per litter

Study title: SU-10398 (PHA-290940AD): Oral Dose Range- Finding Embryo- Fetal Development Study in the Female Rabbit

Key study findings:

- SU010398 administration to rabbits showed teratologic changes following 1 mg/kg when administered GD 6-17, while embryoletality was observed at 5 mg/kg/day. Developmental effects consisted of cleft lip (≥1 mg/kg) and cleft palate (5 mg/kg).
- This was a dose range-finding study. Given the definitive positive in the rat study, current division practice for indications of terminal cancer the requirement of a second definitive study can be waived.

Study no.: 2002-0613

Volume #, and page #: 4.2.3.5.2

Conducting laboratory and location: Pharmacia & Upjohn Company; Kalamazoo, MI

Date of study initiation: January 28, 2003

GLP compliance: NO

QA reports: yes () no (X), the report is signed off on, however the Quality Assurance states that this is a Non-GLP study and therefore does not require QA.

Drug, lot #, and % purity: SU010398; C

Methods

Doses: 0, 0.5, 1, 5, 20 mg freebase/kg/day
 Species/strain: Rabbit, New Zealand White
 Number/sex/group: 6 females/group
 Route, formulation, volume, and infusion rate: Oral gavage, sterile water, 5 mg/mL with exception of 0.5 mg/kg dose group where concentration was 5.6 mg/mL.
 Satellite groups used for toxicokinetics: none
 Study design: SU010398 was administered orally, once daily, to timed female rabbits on gestation days 7 through 20. SU010398 (0, 0.5, 1, 5, and 20 mg/ kg/ day-free base [SU- 011248] equivalents) was administered as a solution in vehicle to groups of rabbits.

Parameters and endpoints evaluated:

Clinical Signs	At least once daily prior to and after the dosing period (gestation days 0 through 6; gestation days 21 through 29). At least twice daily during the dosing period (gestation days 7 through 20), approximately 1 hour following dosing and in the afternoon (PM) each day.
Body Weights	On the day of receipt (gestation day 0), daily on gestation days 7

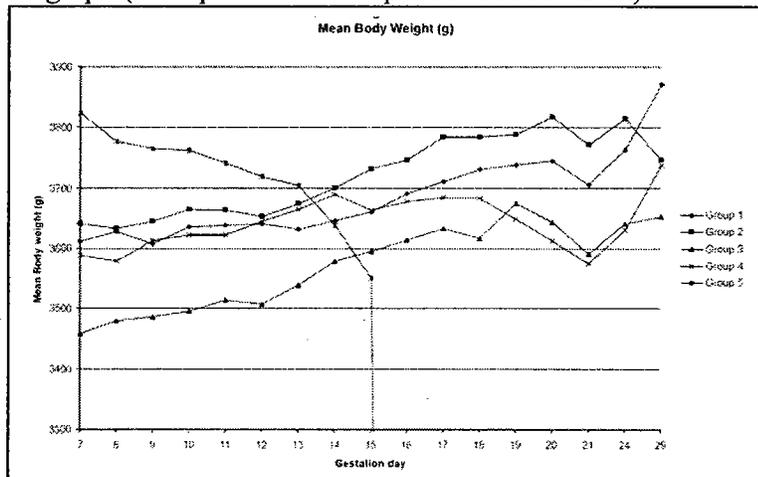
	through 21, and on gestation days 24 and 29
Food Consumption (not measured during cohabitation)	Daily from gestation day 3 through 29 (food weighed in on gestation day 2)
Necropsy	On GD 2 rabbits were euthanized. The entire uterus and its contents were removed and weighed intact. Uteri that appeared nonpregnant were placed in 10% ammonium sulfide solution to visualize implantation sites. Live and dead fetuses and early and late resorptions were counted and their locations recorded. Any abnormalities were identified and recorded. The number of corpora lutea on each ovary was counted and recorded. The fetuses were numbered sequentially, beginning at the ovarian end of the left uterine horn and ending at the cervix; numbering was continued from the ovarian end of the right uterine horn to the cervix. Each placenta was examined grossly. Each fetus was removed, examined grossly, weighed. Fetal external findings were categorized as malformations or variations. Live fetuses were euthanized by a lethal barbiturate overdose. Any unusual gross findings in the mother were recorded. For surviving does in the control and high dose groups, target tissues (adrenals, bone marrow, pancreas, and tibial growth plate) were collected.

Results

Mortality: 3 animals in the high dose group (20 mg/kg) were found dead on GD14 (n=2) and GD15 (n=1). The remaining animals were sacrificed due to overt toxicity.

Clinical signs: Dose dependent signs limited to soft decreased feces and urine discoloration (yellow) in animals that received ≥ 5 mg/kg.

Body weight: Statistical significance was not observed, however a trend toward decreases appears in the graph (excerpted from the sponsor’s submission).



Food consumption: there were no treatment related changes in food consumption

Toxicokinetics: Collection (n=3) was conducted on GD20 (dose days 14) at 0, 1, 3, 6, 9, 12, and 24. Mean plasma concentrations of SU011248 increased in a dose proportional manner, whereas SU012662 increased in a greater than dose proportional manner between 1 and 5 mg/kg.

Systemic Exposure (mean ± SD) After Oral Administration of SU010398 to Female Rabbits			
Analyte	Dose (mg/kg/day)	Cmax (ng hr/mL)	AUC (ng h/mL)
SU010398	0.5	12.9	178
	1.0	23.6	318
	5.0	143	2220
SU012662	0.5	6.74	110
	1.0	15.2	239
	5.0	176	2920

Terminal and necroscopic evaluations: (See table excerpted from the sponsor's submission) Treatment-related reductions in gravid uterine weights and number of live fetuses were due to an increase in the number of resorptions (early and total) and an increase in postimplantation loss (%) in the 5 mg/kg dose group. Complete litter loss was noted in 4 of 6 does in the 5 mg/kg dose group. No other adverse treatment-related effects were in the other dose groups surviving to scheduled necropsy. Histopathologic findings were limited to discoloration (yellow) of the renal pelvis in animals treated with 5 mg/kg.

Appears This Way
On Original

Table 4
Summary of Cesarean Section Data
Females Surviving to Scheduled Necropsy

Study Number: 2002-061

	Dose (mg/kg/day)				
	0.0	0.5	1.0	5.0	20.0
No. of Females Not Pregnant	1	0	1	0	0
No. of Females Pregnant	5	6	5	6	6
No. of Corpora Lutea	51	48	43	54	6
Mean	10.20	8.00	8.70	9.00	0.00
SD	2.59	0.89	1.14	1.00	0.00
N	5	6	5	6	6
No. of Implantations	51	46	42	54	6
Mean	10.20	7.67	8.40	9.00	0.00
SD	2.59	0.89	1.14	1.20	0.00
N	5	6	5	6	6
No. of Live Fetuses	49	45	39	7	0
Mean	9.80	7.50	7.80	1.17	0.00
SD	3.44	0.50	1.10	1.00	0.00
N	5	6	5	6	6
No. of Dead Fetuses	0	0	0	0	0
Mean	0.00	0.00	0.00	0.00	0.00
SD	0.00	0.00	0.00	0.00	0.00
N	5	6	5	6	6
No. of Early Resorptions	2	2	2	45	0
Mean	0.40	0.33	0.40	7.50	0.00
SD	0.00	0.00	0.00	3.92	0.00
N	5	6	5	6	6
No. of Late Resorptions	0	1	1	2	0
Mean	0.00	0.17	0.20	0.33	0.00
SD	0.00	0.41	0.41	0.52	0.00
N	5	6	5	6	6
No. of Total Resorptions	2	3	3	47	0
Mean	0.40	0.50	0.60	7.83	0.00
SD	0.00	0.50	0.50	3.86	0.00
N	5	6	5	6	6
Mean Preimplantation Loss (%)	0.00	0.00	2.50	0.00	0.00
SD	0.00	0.00	5.59	0.00	0.00
N	5	6	5	6	6
Mean Postimplantation Loss (%)	6.07	5.79	7.02	84.92	0.00
SD	14.91	6.16	6.65	24.54	0.00
N	5	6	5	6	6
No. of Females with Preimplantation Loss	0	0	1	0	0
No. of Females with Postimplantation Loss	1	3	3	6	0
No. of Females with Complete Postimplantation Loss	0	0	0	4	0
Body Weight of Live Fetuses (grams)					
Male					
Mean	0.00	0.00	0.00	0.00	0.00
SD	0.00	0.00	0.00	0.00	0.00
N	0	0	0	0	0
Female					
Mean	0.00	0.00	0.00	0.00	0.00
SD	0.00	0.00	0.00	0.00	0.00
N	0	0	0	0	0
Combined					
Mean	41.77	40.37	41.19	49.23	0.00
SD	7.57	9.39	4.15	2.59	0.00
N	5	6	5	2	6
Mean No. of Live Fetuses (M:F)	0.0:0.0	0.0:0.0	0.0:0.0	0.0:0.0	0.0:0.0

Mean Preimplantation loss (%) = mean of individual animal preimplantation loss (%)
Mean Postimplantation loss (%) = mean of individual animal postimplantation loss (%)

Best Possible Copy

Offspring (malformations, variations, etc.):

- Gross malformations were limited to cleft lip (≥ 1.0 mg/kg) and cleft palate (5.0 mg/kg; See table excerpted from the sponsor's submission).
- Gross variations were not observed.

	SU-10398 mg/kg				
	0.0	0.5	1.0	5.0	20.0
No. Litters Examined	5	6	5	2	0
No. Examined Grossly	49	45	39	7	0
No. Examined Viscerally	0	0	0	0	0
No. Examined Skeletally	0	0	0	0	0
	No. Fetuses/No. Litters				
<u>Gross Malformations Observed</u>					
Cleft lip	0/0	0/0	1/1	2/1	0/0
Cleft palate	0/0	0/0	0/0	1/1	0/0

2.6.6.8 Special Toxicology Studies

(Studies previously reviewed by Dr. Schmidt, IND 62382, Review 1)

2.6.6.9 Discussion and Conclusions

2.6.6.10 Tables and Figures

See tabulated summary below

2.6.7 TOXICOLOGY TABULATED SUMMARY

Appears This Way
On Original

Toxicology

Type of Study		GLP	Testing Facility	Species and Strain	Duration (formulation)	Doses (mg/kg)	Gender (n-main study/recovery)	NOAEL (mg/kg)	Max Non-Lethal dose (mg/kg)	Lethal dose (mg/kg)	Findings
E-002066	No	Sugen	Rat, SD	1 dose (CMC)	0, 50, 150, 300, 1200	4/sex/dose	50 males/150 females	500	>500	500: hypoactivity and head sway in first hour post-dose. ALT - ↑10x in females. Body weight (day 5-15): Males ≥150; ↓20-47%; females ≥300- ↓10-21%	
	No	Pharmacia	Monkey Cyno	1 dose (CMC)	0, 50, 150, 300, 600, 1200	2/sex escalating doses within monkeys with 8 day respite	Not identified	1200	>1200	Escalations made interpretation difficult. Emesis noted at all doses. Reversible ↑ in liver enzymes (2-3x). Histo: chronic inflamm of liver (1M/1F) and kidney (2M/1F). Loss of zymogen granules in acinar cells of pancreas (1F).	
Repeat Dose	Yes	Pharmacia, Upjohn, Italy	Rat, SD	Dx3month (water)	0, 1.5, 5, 15	15/sex/dose	Not identified	5	15	See expanded table for repeat dose rat studies	
			Monkey, Cyno	Dx13weeks (water)	0, 2, 6, 20/12	4/sex/dose	Not identified	6	20/12	See expanded table for repeat dose monkey studies	
			Rat, SD	Dailyx 28, q42 for 5 cycles	0, 0.3, 1.5, 6	15/sex/dose	0.3	0.3	1.5	See expanded table for repeat dose rat studies	
2003-0386	Yes	Pfizer Global Res and Dev	Monkey, Cyno	Dailyx 28, q 42 for 9 cycles	0, 0.3, 1.5, 6	4/sex/dose	0.3	1.5	6.0	See expanded table for repeat dose monkey studies	
			Monkey, Cyno	Dailyx 28, q 42 for 9 cycles	0, 0.3, 1.5, 6	4/sex/dose	0.3	1.5	6.0	See expanded table for repeat dose monkey studies	

	3 month oral toxicity study (daily x 3month)	Six month oral toxicity study (daily x 28 q42 days)
Species	Rat, SD	Rat, SD
Study #	2001-0010	2003-0390
Doses (mg base/kg)	0, 1.5, 5, 15	0, 0.3, 1.5, 6
Doses (mg base/m2)	0, 9, 30, 90	0, 1.8, 9, 36
Died or Sacrificed Moribund (drug dep)	9 males/4 females before day 65	1.5 mg/kg- 1M (day 64) 6 mg/kg- 1M (day 123)/2F (day 123 and day 3 of rec)
Body weight (%)	15 mg/kg: ↓10 % beginning day 24-29, by day 57 ↓38% in males and ↓29% in females.	No effect
Food Consumption (%)	No effect	No effect
Clinical Observations	15 mg/kg: ↓ activity, impaired limb function, soft stools, red material around nose, yellow colored fur ≥5 mg/kg: broken incisors	6 mg/kg: Cool to touch, ↓activity, discolored body/urine
Ophthalmoscopy	No effect	No effect
Hematology	↓WBC (16-50%) 15 mg/kg, including ↓lymphocytes, neutrophils, monocytes, and eosinophils; ↓RBC(13-48%) ≥5 mg/kg with concomitant increases in mean cell volume/Hg.	↓RBC/HCT/Hg (up to 45%; week 14/24) ↑MCH/MCHC/MCV/RDW (up to 65%; week 14/24)
Clinical Chemistry	↑ Urea 35%-5 mg/kg; 70%-15mg/kg ↑AST/ALT/Total Bili/ up to 3 fold with 15 mg/kg ↑ Glucose-15-30% ≥1.5 mg/kg ↑TG- 15-90% ≥5 mg/kg ↑ Cholesterol-20-75% 15 mg/kg ↑LDH/CK- 2 fold 15 mg/kg females	HD Females: unless noted ↑ALT (M&F)/AST(M&F)/GGT (<2 fold, week 14/24) ↑CK (<2.5 fold; week 14/24) ↑Lipase (9 fold; week 24) ↑TG/UN(M&F) (<2 fold; week 24)
Urinalysis	pH increased on ≥5 mg/kg	No effect
Organ weights	Irreversible ↓spleen, thymus, and uterus at 5 mg/kg.	Reversible ↓spleen and thymus
Gross pathology	≥5 mg/kg: lung discoloration; dilated renal pelvis; flaccid/discolored testes ; small thymus; broken incisors 15 mg/kg: Adrenal enlargement, discoloration; liver enlargement; and lung congestion; thickening of the duodenum; discolored kidney, intestine, stomach; enlarged mesenteric lymph node; hemorrhage stomach; fractured limb	>0.3 mg/kg: liver- lobular pattern enhanced ≥1.5 mg/kg: adrenal focus(red), hydronephrosis of the kidney 6 mg/kg: brittle/malformed/fractured bones; red discolored harderian gland/lymph nodes/stomach/; focus on the ovaries (black), stomach (yellow); bile duct enlargement; abnormal contents of the GI.
Histopathology	*Adrenal: inflammation, cortical congestion/hemorrhage/vacuolation/ mineralization/necrosis, and medullary necrosis Bone marrow atrophy (≥1.5 mg/kg) Duodenum- peritonitis with mucosal erosion; dilatation, hyperplasia, inflammation, and necrosis of the common bile duct wall Epididymis-reduced spermatazo, epithelial hyperplasia	**Bone marrow: Hypocellularity Bone: thickening of the epiphyseal cartilage fracture Kidney: progressive nephrosis, glomerulosclerosis (≥1.5mg/kg), inflammatory cell infiltrate Lungs: Histiocytosis Liver: deposition of pigment in the kupfer cell and hepatocytes, bile duct hyperplasia

	3 month oral toxicity study (daily x 3month)	Six month oral toxicity study (daily x 28 q42 days)
	Eye- periocular hemorrhage Femur-chondroplasia of the epiphyseal plate (≥5 mg/kg), cartilage in the metaphyseal bony trabeculae. Ileum-inflammation/glandular hyperplasia Kidney-cortical tubular basophilia, yellow pigment (5 mg/kg), glomerular hyalinosis, dilated pelvis Liver(>5 mg/kg)-peribiliary inflammation, yellow hepatocytes, bile duct hyperplasia, focal necros, venous thrombosis LN-lymphoid depletion Salivary glands-acinar hypertrophy (>1.5 mg/kg), apoptosis Ovaries- degen of the corpora leutea Pancreas- edema, chronic inflamm (≥1.5 mg/kg), apoptosis of acinar, peritonitis (≥5 mg/kg) Parotids- acinar degen (≥5 mg/kg); hypertrophy, apoptosis Pituitary- necrosis of ant lobe, Prostate/Sem Ves-colloid depletion Spleen/Thymus-lymphoid depletion (≥5mg/kg) Teeth – caries of the incisors (5mg/kg) Uterus-atrophy Vagina- purulent exudates in lumen	Pancreas: atrophy, degranulation inflammatory cell infiltrate (1.5 mg/kg) Spleen: ↑hematopoiesis Thymus: Lymphoid depletion Teeth (≥0.3 mg/kg): caries, periodontal/pulp/turbinate inflammation; fracture and dislocation.

*Findings noted at 15 mg/kg alone unless noted otherwise.

**Findings noted at 6 mg/kg alone unless noted otherwise.

	3 month oral toxicity study (daily x 3month)	Nine month oral toxicity study (daily x 28 q42 days)
Species	Monkey, Cynomolgus	Monkey, Cynomolgus
Study #	2000-0532	2003-0386
Doses (mg base/kg)	0, 2, 6, 20/12	0, 0.3, 1.5, 6
Doses (mg base/m2)	0, 24, 72, 240/144	0, 3.6, 18, 72
Died or Sacrificed Moribund	20/12 mg/kg- 4M/3F day 29-70	6 mg/kg- 4M/4F; remaining animals placed in recovery group
Body weight (%)	20/12mg/kg- day 29 ↓16-18% 6 mg/kg- ↓6-9%	6 mg/kg: reversible ↓ noted as early as day 85, nadir was 23 and 16% decreases compared to control on day 169.
Food Consumption (%)	20 mg/kg-50-75%↓ day 14- 6 mg/kg-↓25% week 8, ↓50% week 12	
Clinical Observations	6 mg/kg: Alopecia discoloration of the skin 20 mg/kg: ↓activity, hypothermia, hunched posture, pale skin, emesis, discolored/ bloody gums/oral lesion, soft watery feces, red/swollen eyes	≥0.3 mg/kg: emesis, abnormal feces, reddened gums 6 mg/kg: ↓activity, dehydration, cool to touch, hunched posture, skin/urine discoloration, pale gums
Ophthalmoscopy	20 mg/kg- day 36 ulcerative blepharitic/hyperemia (n=3-4/sex). Canthal ulceration of both eyes(1F)	None

	3 month oral toxicity study (daily x 3month)	Nine month oral toxicity study (daily x 28 q42 days)
EKG	↓HR (10%) 20 mg/kg (day 3) and 6 mg/kg (day 39)	6 mg/kg: ↓HR day 94 (31 bpm) and 164 (45 bpm) One instance of 42 msec ↑ in QR One instance of premature ventricular contractions 1.5 mg/kg: One instance of irregular sinus pause
ECHO	Not conducted	6 mg/kg: • 18% in the ratio of Left Atrial Diameter to Aortic Diameter • 10% ↓ in Left Atrial Diameter and LV ejection time • 30% ↓ in LV area change
Hematology	↓WBC (≥6 mg/kg; Day 14/29/63) ↓RBC (≥6 mg/kg; Day 29/63/88) ↓Platelets (≥2 mg/kg; Day 14/29/63/rec)	6 mg/kg: ↓Reticulocyte (Day 91/161), ↓WBC (Day 91/161) ↑Fibrinogen (Day 161)
Clinical Chemistry	↑ Chol (20 mg/kg; Day 14/31) ↑BUN (20 mg/kg; Day29/63/rec) ↑AST/ALT/TG (≥6 mg/kg; Day14, 29, 37, 63) ↓Phosphate/CK (≥2mg/kg; Day 14, 29, 37, 63) ↑Lipase (20 mg/kg; day 29) ↓Na (20 mg/kg; Day 14)	↑AST/ALT/GGT/CK/In Phos I(Day 91/161)
Urinalysis	No effect	No effect
Organ weights	20 mg/kg: ↑ Adrenal, ↓Heart, prostate, thyroid. ≥6 mg/kg: ↓ Epididymis, spleen, testes, thymus ≥2 mg/kg: ↓ovaries, uterus At end of recovery, ↑ thyroid and ↓ovaries and uterus ≥2 mg/kg	6 mg/kg: ↑ Adrenal, ↓Spleen, thymus ≥1.5 mg/kg: ↓Ovary, uterus No dose dependent changes at the end of the recovery period.
Gross pathology	≥6 mg/kg: Foci in the colon and oral cavity 20 mg/kg: Foci of the adrenals heart, lungs, liver, stomach, small intestine. Discoloration of the gall bladder, heart, kidneys, adrenals, lung, testes	6 mg/kg: Enlarged/discolored adrenals; Ulceration of the oral cavity; Discoloration of the contents and Focus on the cecum/colon/rectum/stomach; Hemorrhage of testis 1.5 mg/kg (end of rec): Adhesions on the heart/lung
Histopathology	20 mg/kg (primarily observed in moribund animals)- thymus- lymphoid atrophy (≥6 mg/kg) spleen- lymphoid atrophy/neut infiltration marrow- decreased erthypoiesis lymph nodes-atrophy and congestion adrenals- hemorrhage (≥6 mg/kg) and edema) salivary glands- acinar degeneration pancreas- acinar degeneration (≥6 mg/kg) ovaries-↓ follicular development uterus- endometrial atrophy (≥6 mg/kg) gastrointestinal tract- inflammation, epithelial depletion, mucosal erosion, necrosis and hemorrhage gall bladder- hemorrhage/inflammation bone (≥6 mg/kg)- epiphyseal/chondrocyte nec Recovery: inflammation/fibrosis in the kidney, lung and lymph nodes.	Findings primarily limited to 6 mg/kg unless noted otherwise. Adrenals-hemorrhage and pigment deposition Bone marrow- atrophy, Hypocellularity Brain- inflammation Bones- periosteal new bone formation and proliferation, necrosis of the physéal cartilage Cervix: Squamous Metaplasia (≥1.5 mg/kg) GI tract-inflammation of the mucosa and pigment deposition Esophagus-epithelial atrophy Kidney- pigment deposition, inflammation and ↑ mesangial matrix (≥1.5 mg/kg) Liver-pigment deposition, degeneration of the portal hepatocytes Oral cavity-ulceration/necrotizing vasculitis. Ovaries/oviducts/uterus/vagina: follicular atresia/atrophy Pancreas: decreased zymogen granules/

	3 month oral toxicity study (daily x 3month)	Nine month oral toxicity study (daily x 28 q42 days)
		mineralization Spleen/Thymus/Peyers Patch/LN- depletion Salivary Glands: Acinar degranulation Recovery: Mineralization of the pancreas, depletion of lymph nodes, deposition of pigment in the kidneys and an increased incidence of squamous metaplasia in cervix was noted.

Genotoxicity

Title	Study #	Without Metabolic Activation	With Metabolic Activation
SU011248: gene mutation test in bacteria (Ames)	2000-0357	Negative	Negative
Salmonella-E coli/Mammalian microsome reverse mutation assay with a confirmatory assay with SU011248	21602-0-422OECD	Negative	Negative
Chromosomal aberrations in cultured human peripheral blood lymphocytes with SU011248	21602-0-449OECD	Negative	Negative
In vivo rat micronucleus assay with SU011248	21602-0-454OECD	Negative	Not applicable

Reproductive and Developmental Toxicity

Study #	2003-0370	2003-0372	
Title	Oral Fertility and Early Embryonic Development in the Rat	Oral Embryofetal Development in the Female Rat	Oral Embryofetal Development in the Female Rabbit
Methods	In females, drug administered 14 days prior to mating through GD 7. (n=22/group) In males, drug administered 58 days prior to cohabitation, and during and after cohabitation. (n=22/group)	Administered GD 6-17 to presumed pregnant females (n=22-28)	Administered GD 7-20 to presumed pregnant females (n=6/group)
Key Findings	Female: NOAEL 1.5 mg/kg/d Male: No evidence of fertility or embryonic development impairment (10 mg/kg/d- exceeded MTD)	NOAEL: 1.5 mg/kg/day Skeletal variations observed at 3 mg/kg, increased resorptions/post implantation loss/total litter loss/↓ fetal body weight and skeletal malformations noted at 5 mg/kg.	NOAEL _{embryoethality} : 1 mg/kg NOAEL _{development abnormality} : 0.5 mg/kg.
Species	Sprague Dawley Rat	Sprague Dawley Rat	New Zealand White Rabbit
Doses (expressed as free-base Eq)	Female: 0, 0.5, 1.5, 5 mg/kg (0, 3, 9, 30 mg/m2) Male: 0, 1, 3, 10 mg/kg (0, 6, 18, 30 mg/m2)	0, 0.3, 1.5, 3, 5 mg/kg/day (0, 1.8, 9, 18, 30 mg/m2)	0, 0.5, 1, 5, 20 mg/kg/day (0, 6, 12, 60, 240 mg/m2)
Mortality and Clinical Signs	Obtained twice daily during dosing Females: no mortality observed; no clinical signs	Twice daily during dosing including 1 hour post-dose/Once daily otherwise	Twice daily during dosing including 1 hour post-dose/Once daily otherwise 20 mg/kg: 3 animals found dead on

	Males: 10 mg/kg- 4 males found dead or euthanized on day 13,39, 44, and 62; signs included thin/pale/cool, hunched posture, decreased activity and staining around eye and ano/urogenitals.	No unscheduled deaths during study	days 14 and 15, remaining sacrificed due to overt toxicity (BW). Signs: ≥5 mg/kg soft decreased feces and urine discoloration (yellow)
Body Weight/ Food Consumption	Obtained twice weekly Females: no effect Males (10 mg/kg): 7-10% ↓ in BW	GD 0, 3, 6-18, and 21. <u>5 mg/kg:</u> BW: 9% ↓ in observed on GD 21 BW gain: decreases noted day 13 to day 57 (magnitude up to 57%) No change in food consumption	BW: GD 0, 7-21, 24 and 29. At 20 mg/kg- Body weight gain significantly reduced GD7-15. 12 and 60 mg/kg- ↓ body weight gain day 18-21. FC: Daily GD3-29; no changes seen
Necropsy	Females: 5 mg/kg: 3.5 ↑ in the # dead embryos, no changes in # implantations, #live embryos, or # with post-implantation loss Males: 9% ↓ in # of live fetuses w/out changes in # dead or # implantations Both: No differences in # corpora lutea, implantation sites, dead fetuses, early or late resorptions.	Rats euthanized on GD 21. ↓Gravid uterine weight (5 mg/kg) attributed to ↓# live fetuses (52%). ↑# early/total resorptions (12x). ↑%post-implantation loss (49% vs. 3% in control). Total litter loss (29%). ↓10% in fetal body weight. Skeletal malformations (27% of fetuses; 55% of litters). ↑Skeletal variation following 3 mg/kg.	5 mg/kg: ↓gravid uterine weights # of live fetuses; ↑# resorptions (early and total) and ↑ in postimplantation loss (%). Complete litter loss (4 of 6 does). Histopath: discoloration (yellow) of the renal pelvis in animals treated with 5 mg/kg. Gross malformations: cleft lip (≥1mg/kg), cleft palate (5 mg/kg) Gross variations: none

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: The nonclinical studies submitted to this NDA provide sufficient information to support the use of sunitinib malate (Sutent™) for the treatment of gastrointestinal stromal tumor after disease progression on or intolerance to imatinib mesylate and the treatment of advanced renal cell carcinoma.

Suggested labeling: See separate labeling review

Signatures:

Reviewer Signature S. Leigh Verbois, Ph.D.

Supervisor Signature David Morse, Ph.D. Concurrency Yes No

APPENDIX/ATTACHMENTS**Single Dose Toxicology**

Acute maximum tolerated dose study of SU011248 administered orally to rats. (E-002066; Volume 4.2.3.1) (Previously reviewed by Dr. Schmidt, IND 62383, review 1)

Conducting laboratory and location: Sugen, Inc., South San Francisco, CA

Date of study initiation: 2/25/00

GLP compliance and QA status: non-GLP with no QA

Species and strain: Sprague Dawley rats

#/sex/group or timepoint: 4/sex/dose

age: 8 weeks

weight: 208-336 g

drug, lot #: SU011248, lot 001014M

formulation/vehicle: 0.5% carboxymethylcellulose (see formulation)

dosage groups: 0, 50, 150, 300, 500 mg/kg

route, form, volume, infusion rate: oral gavage, 10 mL/kg

Frequency of administration, duration of observation: single dose, observed through day 15

Observations:

Clinical signs (Daily except on weekends): One 50 mg/kg male and one 500 mg/kg female died on-study prior to day 5. Deaths were attributed to gavage error. At 500 mg/kg, hypoactivity, and head sway were noted within the first hour after administration. No other noteworthy changes were seen.

Body weights (daily except on weekends, was actually days 1, 5, 6, 7, 8, 11, 12, 13, 14, 15): At day 5, the 500 mg/kg males and females had lost approximately 5% of their initial body weight. By day 15, body weights were decreased dose dependently to maximums of 47% and 21% in 500 mg/kg males and females (see table below).

% change from day 1 to day 15 in body weight as compared to controls		
Dose (mg/kg)	Males	Females
50	↑7%	↑28%
150	↓20%	↑18%
300	↓28%	↓10%
500	↓47%	↓21%

Serum chemistry (day 15): ALT was increased by almost 10 fold over controls in 3/4 500 mg/kg females, but there was no effect in males. Similar increases were seen in 2/8 control rats and in AST values in the HD females.

Gross pathology (day 15): There were no noteworthy changes.

Histopathology (day 15, limited tissue panel, see histopathology table): There were no remarkable differences with treatment.

Comments/conclusions: The NOAEL based on body weights was 50 mg/kg in the males, 150 mg/kg

in the females. The LD10 was >500 mg/kg (3000 mg/m²) assuming that the HD female died of gavage error, which is questionable based on lack of histopathologic data. Effects on liver enzyme values were questionable given the high degree of background noise.

Single dose nasogastric intubation followed by intravenous administration of SU011248 and SU011654 in cynomolgus monkeys. (7039-152; Volume 4.3.2.1) (Previously reviewed by Dr. Schmidt, IND 62383, review 1).

Conducting laboratory and location: []

Date of study initiation: 6/6/00

GLP compliance and QA status: non-GLP, QA status not specified.

Methods (if unusual): drug administered by nasogastric tube on day 1, by iv on day 8

Species and strain: cynomolgus monkeys

#/sex/group or timepoint: 2 females

age: 2-4 years

weight: 2-4 kg

drug, lot #, % purity: SU011248, lot # 002026, [] pure (note—in appendix protocol, the lot # was 002027 with a purity of []).

formulation/vehicle: 0.5% carboxymethylcellulose, 0.9% NaCl, 0.4% Tween 80, 0.9% benzyl alcohol for nasogastric administration, 10 mM citrate buffer, polysorbate 80, polyethylene glycol 300, 0.1 N HCl for intravenous

dosage groups: for ng tube: 50 mg/kg at 2 mL/kg, for iv 2 mg/kg @ 1 mL/kg

route, form, volume, infusion rate: see above

Observations:

Clinical signs (twice daily): After the iv dose, 1 monkey had “unformed” feces.

Body weights (pretest, days 1, 4, 8): There were no remarkable changes.

Toxicokinetics (day 1, day 8 at pretest, 0.5, 1, 1.5, 2, 3, 6, 9, 24 hours post-dose):

Appears This Way
On Original

Individual Pharmacokinetic Parameters for SU011248 in Female Monkey Plasma

Single Dose Nasogastric Intubation Followed by Intravenous Administration of SU011248 and SU011654 in Cynomolgus Monkeys

Oral

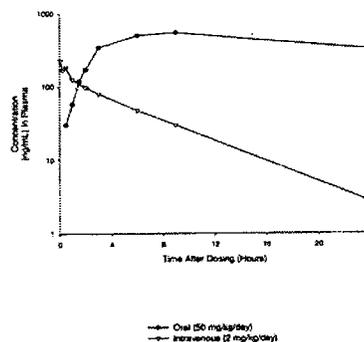
Animal Number	Dose Level Group	C _{max} (ng/mL)	T _{max} (Hour)	AUC _{0-1 last} (ng·hr/mL)	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (Hour)	%F _{0-24hr}
IS1184	1	[]
IS1185	1						
Mean		549	7.50	9817	NA	NA	41

Intravenous

Animal Number	Dose Level Group	C _{max} (ng/mL)	T _{max} (Hour)	AUC _{0-1 last} (ng·hr/mL)	AUC _{0-∞} (ng·hr/mL)	t _{1/2} (Hour)	CL (mL/hr/kg)	Vd (L/kg)
IS1184	1	[]
IS1185	1							
Mean		223	0.0833	929	945	4.31	2142	13.3

Note: %F_{0-24hr} refers to %F determined using oral AUC_{0-1 last} data.

Figure 2-1. Mean plasma concentrations of SU011248 in female monkeys. Single Dose Nasogastric Intubation Followed by Intravenous Administration of SU011248 and SU011654 in Cynomolgus Monkeys.



Best Possible Copy

Analysis was by LC/MS/MS technique, with a limit of quantitation of 1.0 ng/mL.

Comments/conclusions: The NOAEL based on very limited observations was >50 mg/kg by the oral route. The bioavailability of SU011248 is approximately 40% in the monkey.

SU011248: preliminary single dose oral toxicity study (MTD) in the cynomolgus monkey. (2000-0314; Vol 4.3.2.1) (Previously reviewed by Dr. Schmidt, IND 62383, review 1).

Conducting laboratory and location: Pharmacia/Upjohn, Nerviano, Milan, Italy.

Date of study initiation: 6/26/00

GLP compliance (OECD): Yes **QA status:** Yes

Methods (if unusual): escalating doses were used in individual monkeys with at least 8 days between doses

Species and strain: cynomolgus monkeys (*Macaca fascicularis*)

#/sex/group or timepoint: 2/sex

age: "adults"

weight: 3-4 kg

drug, lot #, % purity: SU011248, batch # 002101, [] pure

formulation/vehicle: 0.5% carboxymethylcellulose (see formulation)

dosage group: 50, 150, 300, 600, 1200 mg/kg/dose (given on days 1, 9, 19, 29, 40)

route, form, volume, infusion rate: rhinogastric gavage (ng tube), 10 mL/kg

Observations:

Clinical signs (daily): Emesis on the day of dosing was seen with increasing frequency with increasing dose.

Body weights (pretest, days 1, 3, 6, 9, 11, 14, 19, 21, 29, 31,34,40, 42, 45, 47): Body weights did not differ by more than 0.2 kg in males; however, by the end of the study, body weights in HD

females had decreased by 10-20% as compared to initial weight.

EKG (predose on days -1, 8; 8 hours post-treatment on days 1, 9, 19, 29, 40): There were no consistent effects with dose.

Hematology (pretest, days 2, 4, 8, 12, 15, 22, 25, 32, 36, 43, 47): Lack of concurrent controls, as well as potential cumulative damage made data interpretation difficult. All comparisons are made to the day 2 values. Changes in males and females were similar. WBC # decreases ranged from 35% to 50% of the day 2 values. WBC # nadirs were seen at day 22 (1) day 36 (2) and day 43 (1); there were no patterns of increasing toxicity with repeated cycles of increased dosing. The RBC # also decreased by approximately 25% with 3/4 monkeys having a nadir on day 12 (the other monkey hit nadir on day 47). Changes in platelet number showed no pattern with dose or time.

Serum chemistry (pretest, days 4, 8, 12, 15, 22, 25, 32, 36, 43, 47): Several enzymes (AST, ALT, LDH and CK) appeared to be elevated between 2 and 3 fold above pretest levels 3 days after SU011248 administration. The magnitude of elevation did not correlate well with the dose or the number of doses.

Urinalysis (pretest, days 4, 8, 12, 15, 22, 25, 32, 36, 43, 47): In the females, there was an increase in ketone bodies with each cycle of administration.

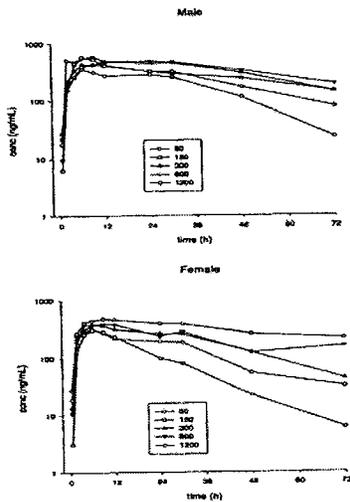
Gross pathology (1 week after last dose i.e. day 47): There were no remarkable changes.

Histopathology (1 week after last dose i.e. day 47, limited panel—see histopathology table): All of the findings were “minimal”. Chronic inflammation was found in the liver (1/2 M, F) and kidneys (2/2 M, 1/2 F). In the pancreas, loss of zymogen granules in the acinar cells were seen in 1/2 F.

Toxicokinetics (after each dose on days 1, 9, 19, 29, 40: 0, 0.5, 2, 4, 6, 9, 12, 24, 30, 48, 72 hrs): A LC/MS/MS method was used to assay plasma for SU011248. The “V”s in the following table indicate which monkeys vomited after dosing. It is not clear if the lack of linearity at higher doses is due to emesis of drug or absorption/metabolism effects.

Appears This Way
On Original

Fig. 1 Mean plasma levels of SU011248 after single 50, 150, 300, 600 and 1200 mg/kg oral doses of the compound to male (upper panel) and female (lower panel) cynomolgus monkeys



SUGEN Identification No.: G-011248-004

9(32)

000266

Best Possible Copy

Table 6. Individual non-compartmental plasma pharmacokinetic parameters of SU011248 after single 50, 150, 300, 600 and 1200 mg/kg oral doses of the compound to male and female cynomolgus monkeys

Dose mg/kg	Monkey no.	Gender	t _{max} h	C _{max} ng/mL	AUC ₀₋₇₂ ng·h/mL	C _{max, norm} ng/mL	AUC _{0-72, norm} ng·h/mL
50	1123	— M	6	402	8723	8.04	174
	1125	— M	24	376	17268	7.51	345
	1037	— F	9	320	11551	6.40	231
	1045	✓ F	2	400	7859	8.00	157
150	1123	— M	12	597	31367	3.98	209
	1125	✓ M	6	367	7419	2.44	49
	1037	✓ F	4	241	6065	1.61	40
	1045	✓ F	6	372	6862	2.48	46
300	1123	✓ M	30	554	28536	1.85	95
	1125	— M	6	493	20318	1.64	68
	1037	✓ F	9	421	16632	1.40	55
	1045	— F	6	337	10956	1.12	37
600	1123	✓ M	9	693	26913	1.16	45
	1125	✓ M	9	491	27666	0.82	46
	1037	✓ F	4	342	9936	0.57	17
	1045	✓ F	12	458	21859	0.76	36
1200	1123	✓ M	9	616	21870	0.51	18
	1125	✓ M	6	567	16413	0.47	14
	1037	✓ F	6	373	16387	0.31	14
	1045	✓ F	9	597	29874	0.50	25

SUGEN Identification No.: G-011248-004

20(32)

000277

Comments/Conclusions: The study was difficult to interpret as each animal received increasing doses of drug separated by 8-10 day intervals and no concurrent controls were included. Emesis was the

major toxicity. Possible liver and kidney effects were seen. However, only a limited tissue panel was examined. Both males and females were used. Emesis may have affected the absorption of drug (although minimal effects were apparent at doses up to 600 mg/kg).

REPEAT DOSE STUDIES

Repeated dose oral toxicity study of SU011248 in Sprague-Dawley rats. (E-002054; Vol 4.3.2.2) (Previously reviewed by Dr. Schmidt, IND 62383, review 1).

Conducting laboratory and location: Sugen, Inc., South San Francisco

Date of study initiation: 2/28/00

GLP compliance and QA status: non-GLP

Methods (if unusual): a second study was conducted with lower doses (5, 25, 50 mg/kg/day)

Species and strain: Sprague Dawley rats

#/sex/group or timepoint: 4/sex/dose, second study: 2/sex/dose

age: not reported

weight: 180-214 g, F: 160-194 g

drug, lot #, % purity: SU011248, lot # 001039M; second study: lot # 1045

formulation/vehicle: carboxymethylcellulose, see table

dosage groups: 0, 50, 150, 300, 500 mg/kg; second study: 0, 5, 25, 50 mg/kg/day

route, form, volume, infusion rate: oral gavage at 10 mL/kg

frequency/duration: Daily for 14 consecutive days, observed through day 15

Observations: Note: the second study at lower doses is discussed separately. Observation intervals were the same as in the first study.

FIRST STUDY:

Clinical signs (daily—pretest, 30 minutes and 4 hours post-dose except for weekends): With the exception of the control rats and 5/8 50 mg/kg rats, all rats died during the study. The rats in the 500 mg/kg group were dying by day 5. One 50 mg/kg male died by gavage error (sponsor's assessment) on day 10, while one male and 1 female died on day 13.

The clinical signs included enlarged abdomen, head shakes, emaciation, hypoactivity, irregular respiration, impaired muscle coordination, ocular discharge, piloerection, anal stain/diarrhea, and soft or discolored stool. Yellow fur/skin/urine was probably due to drug staining.

Body weights (daily except for weekends): At 50 mg/kg, the lowest dose tested, males showed a 20% decrement in body weight at the end of 12 days as compared to controls, while females showed no significant difference in body weight. Weight losses were dose dependent.

Clinical Chemistry (day 15 or death, where possible): In all treated rats, BUN values were increased by >3 fold, creatinine was minimally affected (0.3 mg/dl in controls, 0.5 in treated), total protein was decreased by >10%, AST/ALT/ALP increased by > 2 fold and phosphates doubled in the 500 mg/kg males. Other electrolytes did not appear to be affected.

Gross pathology (day 15 or at death): At the end of 14 days, surviving 50 mg/kg rats had large adrenal glands or pale kidneys/liver. Other observations included bloating or fluid filling of the gi tract,

enlargement/dicoloration of the adrenals, and yellow discoloration of skin/organs.

Histopathology (day 15 or at death, limited panel—see histopathology table): The histopathology findings are summarized in the following table. While the stomach had yellow staining, the rest of the gastrointestinal tract was not affected by SU011248.

	Males (n=4/dose)					Females (n=4/dose)				
	Vehicle	50	150	300	500	Vehicle	50	150	300	500
Liver—individ. Cell necrosis			1	3	2					1
Liver microvacuolization			2	4	4			2	4	4
Liver—multi-focal necrosis				1	3					
Kidney—tub. Degen	1	1	2	4	4		2	2	4	4
Kidney—glomerulopathy		1								
Kidney—lymph. infiltration		1	1							
Kidney—chronic infarct							1			
Adrenals—congestion/telangectasia		2	1	1			1	2		
Adrenals—necrosis			3	1			3	3	2	
Pancreas—individ. Cell necrosis			1	1	2			3	3	2
Pancreas—↓decr zymogen				1				2		
Mes LN—necrosis		4	3	1	1		3	3	2	2
Mes LN—follicular atrophy		1	3	1	2			3	2	3

Second study at 0, 5, 25, 50 mg/kg/day

Clinical signs: One HD male died at day 14. There were no changes at 5 mg/kg in males, although 1 female showed irregular respiration and collapse. The remainder of observations were made after day 9. At 25 mg/kg ocular discharge in males and yellow fur/skin in both genders were observed. With 50 mg/kg, hypoactivity, hyporesponsiveness, piloerection, impaired muscle coordination, anal staining, and sedation were noted.

Body weight: All dosed rats lost a few grams during the first week of dosing. There were no concurrent controls for comparison. There was a dose-dependent decrease in body weight gain with the 50 mg/kg rats gaining less than 10% of their initial body weight.

Serum Chemistry: (limited panel: ALT,AST, Trig, ALP, Urea): AST and ALT were elevated in all

rats (with the exception of one 5 mg/kg male) by several fold. Urea was increased by >5 fold in the surviving 50 mg/kg male. Increases in triglycerides and ALP were not dose-dependent.

Gross Pathology: Yellow discolorations of the fur (all doses) and organs (>5 mg/kg) were observed. At the 50 mg/kg dose, pale or reddened kidneys, and enlarged, reddened adrenals (also seen in 5 mg/kg females) were the major observations.

Histopathology: There were no noteworthy findings in the gastrointestinal tract, or spleen. The remaining observations are shown in the following table.

	Males (n=2/dose)			Females (n=2/dose)		
	5	25	50	5	25	50
Liver—degeneration	2	2	2	1	1	
Liver—periportal chronic inflamm			2	1		1
Kidney—nephropathy		1	2	1	2	
Kidney—chronic inflam		1	1		2	
Adrenals—angiectasis			2		1	2
Adrenals—cortical hypertrophy		1		2	1	
Adrenals—necrosis			2		1	2
Pancreas—apoptotic necrosis		1				1
Pancreas--↓decr zymogen		1			1	
Thymus—lymphoid necrosis/hemorrhage	2	2	2	---	2	2
Thymus—lymphoid depletion	---	---	2	---	---	2

Comments/Conclusions: The LD10 for SU011248 on a DX14 schedule in the rat was <50 mg/kg (300 mg/m²). Further investigation of lower doses suggests that the LD10 is between 25 and 50 mg/kg. The NOAEL is < 5 mg/kg based on adrenal observations. Target organs of toxicity were liver, kidney, adrenals and pancreas. Hematologic parameters were not included. No concurrent controls were included on the second section of the study.

SU011248: two-week oral toxicity study in the rat. (2000-0327; Vol 4.3.2.2) (Previously reviewed by Dr. Schmidt, IND 62383, review 1).

Conducting laboratory and location: Pharmacia/Upjohn, Nerviano, Milan, Italy

Date of study initiation: 7/12/00

GLP compliance: Yes

QA status: Yes

Methods (if unusual):

Species and strain: Sprague Dawley :CD (SD) BR rats

#/sex/group: 10/sex/dose

age: 40 days

weight: M: 172-210 g, F: 142-176 g

satellite groups used for TK or recovery: 3/sex/dose for PK

drug, lot #, % purity: SU011248, batch # 002101, by HPLC, area % = 100, pure, by weight % 100, pure

formulation/vehicle: 0.5% carboxymethyl cellulose

dosage groups: 0, 5, 15, 45 mg/kg/day

route, form, volume, infusion rate: oral gavage, 5 mL/kg/day

Frequency/duration: daily for 14 consecutive days, observed for 15 days

Observations:

Clinical signs (daily): Two males and 7 females in the 45 mg/kg group died prior to scheduled sacrifice. Death in 1 female was attributed to an excess of anesthesia during blood collection on day 14. Changes in clinical signs were seen only in the 45 mg/kg group. These included yellow colored skin and fur, decreased activity, ruffled fur, and cold to touch.

	Males		Females	
	# dead	Day of death	# dead	Day of death
45 mg/kg	2/10	10, 17	7	10, 11, 14 (3), 15 (2)

Body weights (pretest, weekly): All rats gained weight during the study. Body weight was decreased dose dependently in males, while females only showed a decrement in body weight at the highest dose (see table below).

% decrease in body weight at day 12 as compared to controls			
	5 mg/kg	15 mg/kg	45 mg/kg
Males	---	8.8%	32%
Females	---	---	20%

Food consumption (weekly): Food consumption was decreased by 10-20% in the 45 mg/kg at day 6 and was decreased to 1/3 of the controls at day 12.

Ophthalmoscopy (pretest, day 10): There were no remarkable changes with treatment.

Hematology (day 13): The major changes at day 13 are summarized in the following table. The decrease in WBC# reflected decreases in lymphocytes, neutrophils, monocytes and eosinophils.

% change at day 13 as compared to controls		
	Males	Females
WBC #	↓35% MD, ↓50% HD	↓35% HD
RBC #	↓10% MD, ↓8% HD	↓13% MD, ↓23% HD
Platelet #	↓65% HD	↓70% HD

Serum chemistry (days 7, 13, corticosterone/aldosterone @ d15): The major changes in serum chemistry are summarized in the following table. Aldosterone and corticosterone decreased dose dependently to approximately 1/4 and 1/3 (1/12 in females) of the levels in control rats.

% change as compared to controls				
	Males		Females	
	Day 7	Day 13	Day 7	Day 13
Urea	↑62% M, ↑71% H	↑21% L, ↑61% M, ↑128% H	↑43% H	↑48% M, ↑167% H

% change as compared to controls				
	Males		Females	
	Day 7	Day 13	Day 7	Day 13
AST	↑>2X H	↑2X M, ↑>2X H	↑> 2X H	↑>3X
ALT	↑2X M, ↑> 4X H	↑2X M, ↑> 4X H	↑2X M, ↑5X H	↑> 2X M, >9X H
Total bilirubin	---	---	---	↑3X H
Total protein	↑10% H	↓20% H	---	↓32% H
Ca	---	↓11% H	---	↓13% H
Pi	↓23% H	↓43% H	↓12% H	↓23% H

Urinalysis (day 13): Urinary volume decreased to less than half of the controls in the HD animals. Protein and hemoglobin/RBC # in the urine increased.

Organ weights (day 17): Changes in organ weights are shown in the following table. The major changes were increases in adrenal weight and decreases in gonad, thymus/spleen weights.

% change in organ weights as compared to controls				
	Males		Females	
	Absolute	Rel. to body wt	Absolute	Rel. to body wt
Spleen	↓10% L, 37% M, 63 H	↓25% M, 40% H	↓38% H	---
Kidneys	↓32% H	---	↓19% H	---
Liver	↓10% L, 25% M, 46% H	---	↓27% H	---
Thymus	↓40% M, 77% H	↓30% M, 63% H	↓12% L, 36% M, 71% H	↓14% L, 34% M, 61% H
Heart	↓20% M, 38% H	---	↓20% H	---
Pituitary	↓18% M, 35% H	---	↓25% H	---
Adrenals	↑110% H	↑>2X H	↑133% H	↑>3X H
Epididymis	↓31% H	---		
Prostate	↓60% H	↓35% H		
Ovaries			↓18% L, 24% M, 50% H	↓20% L, 20% M, 30% H
Uterus			↓50% H	↓32% H
Lung	↓15% M, 30% H	----	---	---

Gross pathology (day 17): The following table summarizes the relevant macroscopic findings. Yellow discolorations were seen in internal organs, skin and fur.

Incidence of macroscopic findings				
	Males		Females	
	Day 17	Early death	Day 17	Early death
Adrenals—enlarged	8/8 H	2/2	3/3 H	7/7
Adrenals-dark	1/10 M, 8/8 H	---	---	---
Lungs—red area	---	---	----	1/7 H
Prostate—small	8/8 H	2/2 H		
Spleen—small	7/8 H	1/2 H	1/3 H	---
Thymus—small	8/8 H	1/2 H	3/3 H	1/7 H
Femur—soft bone marrow	8/8 H	---	3/3 H	---
Sem. Ves—small	8/8 H	2/2 H		
Intestine—red walls	---	---	---	1/7

Histopathology (day 17, all control, MD, HD organs; all doses in treatment related changes):

Incidence of microscopic observations in 2 wk rats				
	Males		Females	
	Term.	Early death	Term.	Early death
Adrenals—congestion	6/8 H	2/2 H	2/10 M, 3/3 H	5/7 H
Adrenals—hemorrhage	1/10 M, 8/8 H	2/2 H	3/3 H	7/7 H
Adrenals—necrosis	1/10 M, 8/8 H	2/2 H	1/10 M, 3/3 H	7/7 H
Adrenals—acute inflammation	8/8 H	2/2 H	3/3 H	7/7 H
Bone marrow—atrophy	6/10 M, 8/8 H	---	6/10 M, 3/3 H	---
Colon—peritonitis	3/8 H	---	1/3 H	2/7
Sm intestine—congestion of villus tip	1/8 H	---	---	---
Sm. Intestine—acute inflammation in mucosa	4/8 H	---	2/3 H	2/7 H
Epididymis—immature germ cells in lumen	5/8 H	---		
Femur/sternum—atrophy of bone marrow	10/10 M, 8/8 H	2/2 H	8/10 L, 10/10 M, 3/3 H	7/7 H
Femur/sternum—increased thickness of cartilage plates	10/10 M, 8/8 H	2/2 H	10/10 M, 3/3 H	7/7 H
Femur—reduced metaphyseal bony trabeculae	8/10 M, 8/8 H	2/2 H	7/10 M, 3/3 H	7/7 H
Kidney—glomerular hyalinosis	6/8 H	1/2 H	3/3 H	3/7 H
Kidney—cortical tub. Necrosis	---	---	---	1/7 H
LN—lymphoid depletion	8/8 H	2/2 H	3/3 H	7/7 H
Sal.gland—acinar hypertrophy	6/8 H	2/2 H	1/3 H	4/7 H
Sal.gland—acinar cell degeneration	8/8 H	2/2 H	3/3 H	5/7 H
Ovaries—degeneration of corpora lutea			2/10 C, 1/10 L, 10/10 M, 3/3 H	6/7 H
Ovaries—cystic corpora lutea			1/10 C, 2/10 L, 6/10 M, 1/3 H	1/7 H

Incidence of microscopic observations in 2 wk rats				
	Males		Females	
	Term.	Early death	Term.	Early death
Pancreas—edema	7/8 H	1/2 H	3/3 H	1/7 H
Pancreas—acinar apoptosis	9/10 M, 2/8 H	---	8/10 M	---
Pancreas—acinar degranulation	8/10 M, 8/8 H	2/2 H	7/10 M, 1/3 H	6/7 H
Pancreas—vasculitis	6/8 H	---	1/3 H	1/7 H
Pancreas—acute inflamm in adipose	5/8 H	1/2 H	1/3 H	---
Parotids—acinar cell degeneration	7/8 H	---	1/3 H	3/7 H
Pituitary—castration cells	7/8 H	2/2 H	3/3 H	5/7 H
Pituitary—reduction of acidophilic cells	6/8 H	1/2 H	2/3 H	5/7 H
Pituitary—necrosis of anterior lobe	2/8 H	---	1/3 H	3/7 H
Prostate—colloid depletion	8/8 H	2/2 H		
Seminal vesicle—colloid depletion	8/8 H	2/2 H		
Spleen—lymphoid depletion	6/10 M, 7/8 H	2/2 H	3/3 H	6/7 H
Stomach—dilated mucosal glands	4/8 H	---	3/3 H	1/7 H
Stomach—apoptosis of glandular cells	4/8 H	---	3/3 H	---
Testes—tubular cell degeneration	2/8 H	---		
Thymus—lymphoid depletion	2/10 M, 8/8 H	1/2 H	4/10 M, 3/3 H	7/7 H
Uterus—atrophy			3/3 H	5/7 H

Toxicokinetics (day 1, 15 predose, 1, 3, 6, 9, 24 hours; electron microscopy on liver and kidneys):

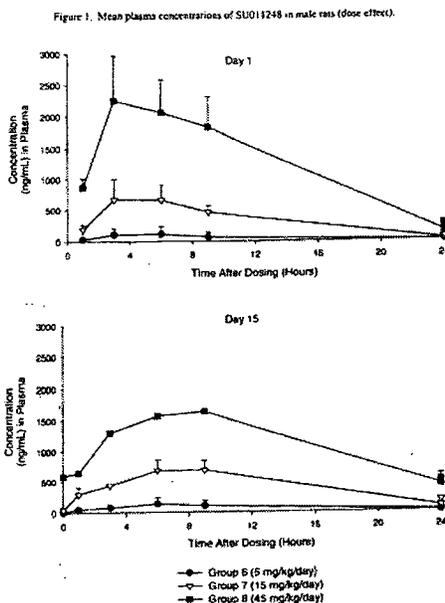
Summary of Mean Toxicokinetic Parameters of SU011248 in Rats: Day 1

Group	Dose Level (mg/kg/day)	Sex	Mean	C _{max} (ng/mL)	T _{max} (Hours)	AUC _{0-1hr} (ng-hr/mL)	AUC ₀₋₂₄ (ng-hr/mL)	t _{1/2} (Hours)
6	5	M	Mean	116	4.00	1132	1269	5.07
			SD	110	1.7	1403	1313	2.0
			N	3	3	3	3	3
		F	Mean	255	3.00	1979	2014	2.46
			SD	140	0.0	1289	1239	0.08
			N	3	3	3	3	3
7	15	M	Mean	693	4.00	8200	8313	3.63
			SD	290	1.7	2405	2386	0.52
			N	3	3	3	3	3
		F	Mean	1150	5.00	13312	12421	2.98
			SD	360	3.5	3077	NA	NA
			N	3	3	3	2	2
8	45	M	Mean	2270	4.00	30671	31781	4.14
			SD	709	1.7	8639	9979	1.6
			N	3	3	3	3	3
		F	Mean	2880	7.00	42152	NA	NA
			SD	720	3.5	10158	NA	NA
			N	3	3	3	NA	NA

NA Not applicable.

Summary of Mean Toxicokinetic Parameters of SU011248 in Rats: Day 15

Group	Dose Level (mg/kg/day)	Sex	Mean	C _{max} (ng/mL)	T _{max} (Hours)	AUC _{0-1hr} (ng-hr/mL)	AUC ₀₋₂₄ (ng-hr/mL)	t _{1/2} (Hours)
6	5	M	Mean	134	5.00	1317	1752	3.62
			SD	96	1.7	1424	NA	NA
			N	3	3	3	2	1
		F	Mean	175	3.00	1773	1773	3.00
			SD	68	0.0	749	749	0.44
			N	3	3	3	3	3
7	15	M	Mean	712	8.00	10190	10190	4.93
			SD	180	1.7	1881	1881	NA
			N	3	3	3	3	1
		F	Mean	830	7.00	12380	12380	5.61
			SD	150	1.7	2243	2243	NA
			N	3	3	3	3	2
8	45	M	Mean	1680	7.50	27113	27113	4.24
			SD	NA	NA	NA	NA	NA
			N	2	2	2	2	1
		F	Mean	1130	9.00	17687	17687	NA
			SD	NA	NA	NA	NA	NA
			N	1	1	1	1	NA



Best Possible Copy

Comments and conclusions:

The LD10 on the DX14 day dosing schedule was between 15 and 45 mg/kg/day. Target organs of toxicity included hematopoietic, adrenal, hepatic, reproductive and renal organs. No NOAEL (<5 mg/kg) could be established based on changes in BUN and incomplete histopathology (LD was not examined consistently). The HNSTD was 15 mg/kg.

SU011248: two week oral toxicity study in the cynomolgus monkey. (2000-0348; Volume 4.3.2.2) (Previously reviewed by Dr. Schmidt, IND 62383, review 1).

Date of study initiation: 7/13/2000

GLP compliance: Yes

QA status: Yes

Methods (if unusual)

Species and strain: Cynomolgus monkeys

#/sex/group or timepoint: 3/sex/dose

age: "adult"

weight: M: 2.4-4.7 kg, F: 2.3-3.1 kg

drug, lot #, radiolabel, % purity: SU011248, batch # 002101, [] pure

formulation/vehicle: 0.5% carboxymethylcellulose (see formulation)

dosage groups: 0, 5, 15, 45 mg/kg/day

route, form, volume, infusion rate: oral gavage at 10 mL/kg

frequency: daily for 14 consecutive days; animals sacrificed after dosing (day 15)

Observations:

Clinical signs (daily): All monkeys survived to scheduled sacrifice. Behavioral changes were confined to the HD and included decreased activity, depression, emesis, reduced food intake, and in females only, diarrhea.

Body weights (pretest, twice weekly): The HD females lost approximately 20% of their initial weight by day 14.

Food consumption (daily): Data was not found.

Ophthalmoscopy (pretest, day 11): There were no remarkable changes.

EKG (pretest, day 1, 11 at 8 hours post-dose): In the HD females only, a decrease in heart rate (approximately 10%) and an increase in QT (and R-R) interval (<20%) were seen at day 14.

Hematology (pretest, day 4, 7, 14): WBC # was decreased by approximately 20% and 50% in the MD and HD males and females. RBC # was decreased by 15-20% in all treated males and HD females. PT and APPT times did not change with treatment.

Serum chemistry (pretest, day 4, 7, 14): AST and ALT were increased by >2 fold beginning at day 4 primarily in the HD, although there were changes at the MD. Creatinine kinase also increased by approximately 8 fold at the HD. In the HD females only, BUN and amylase were approximately doubled at day 14. Cortisol levels approximately doubled at the MD (week 1 only) and HD (weeks 1 and 2). Although aldosterone values showed great variability, a 5 fold increase was seen in the HD females at week 2.

Urinalysis (pretest, days 7, 14): There were no remarkable changes with treatment.

Organ weights (day 15): The major changes included decreases in absolute and relative weights of spleen and thymus in both sexes. Ovarian and uterine weights were decreased in the females while adrenal weights were increased. The values are shown in the table below.

% change as compared to controls in organ weights				
	Males		Females	
	Absolute	Rel to bw	Absolute	Rel to bw
Spleen	↓34% M, 33% H	↓24% M, 14% H	↓48% H	↓40% H
Thymus	↓55% M, 80% H	↓52% M, 73% H	↓65% H	↓57% H
Heart	↓10% L, 22% M, 29% H	---	↓11% L, 8% M, 27% H	---
Adrenals	---	↑20%	↑10% M, 27% H	↑62% H
Ovaries			↓76% M, 83% H	↓76% M, 79% H
Uterus			↓27% L, 34% M, 32% H	----

Gross pathology (day 15): Yellow discoloration of organs was seen at the MD and HD. Other observations included darkening of the adrenals (1/3 L, M, H females), dark mucosa of the gi tract (1-2 H females, 1 H male), small spleen (1 HD female), and small thymus (2 MD males, 3 H males and females).

Histopathology (day 15, liver and kidney analyzed by EM): The findings are summarized in the following table. The major target appeared to be hemato-reticular organs (lymph nodes, spleen,

thymus, marrow). Damage was slightly more severe in females than in males.

Incidence of histopathologic findings		
Observation	Males n=3/dose	Females n=3/dose
Adrenal cortex—congestion (min)	1 M, 3 H	(Sl-mod), 1 M, 2 H
Bone marrow—myeloid cell depletion (mod-marked)	2 H	1 M, 3 H
Diaphragm—macrophage aggregation	---	1 H
Duodenum—hemorrhage (mod)	---	1 H
Heart—capillary proliferation (sl)	1 H	---
Heart—myocardial vacuolization (min)	1 M	1 M
Jejunum—hemorrhage	1 H	---
Lacrimal gland—duct dilatation (min)	1 L, 1 M	1 M, 2 H
Mammary gland—duct dilatation (min-sl)	1L, 2 M	1 C, 1L, 1 M, 2 H
Mammary gland—secretory activity (min)	---	1 L, 1 M, 1 H
Mandibular lymph node—lymphoid depletion (min-sl)	2 H	2 H
Salivary gland—degranulation of acinar cells	---	2 H
Mesenteric lymph node—lymphoid depletion (min-mod)	3 H	3 H
Pancreas—loss of zymogen granules (min-sl)	2 M, 3 H	3 H
Parotids—degranulation of acinar cells (min-sl)	1C, 1L, 1 M, 3 H	1C, 2 M, 3 H
Spleen—lymphoid depletion (min-sl)	1 M, 3 H	2 M, 3 H
Sternum—atrophy of bone marrow (sl-marked)	2 M, 3 H	2 M, 3 H
Stifle joint—atrophy of bone marrow (sl-marked)	2L, 3M, 3H	1 M, 3 H
Stomach—dilated mucosal glands (min)	1 L	1 H
Thymus—lymphoid depletion (sl-marked)	2 M, 3 H	1C, 1 L, 1 M, 3 H
Thymus—degeneration in Hasall's corpuscles (min-marked)	3 M, 3 H	1 M, 3 H
Thyroids—ultimobranchial cysts	1 M, 2 H	2 M, 1 H
Tongue—epithelial necrosis on dorsum		1 H

Toxicokinetics (days 1, 14; pre-dose, 0.5, 1, 3, 6, 9, 12, 24 hours post-dose, HPLC/MS/MS detection):

Appears This Way
On Original

Table 1-4

Individual Toxicokinetic Parameters of SU011248 in Cynomolgus Monkeys: Day 14

Group	Dose Level (mg/kg/day)	Animal Number	Sex	C _{max} (ng/mL)	T _{max} (Hours)	AUC _{0-12h} (ng-hr/mL)	AUC _{0-24h} (ng-hr/mL)	t _{1/2} (Hours)
2	5	1140	M	120	6.00	1275	1276	5.67
		1145	M					
		1160	M					
Mean								
SD			26	0.0	250	250	1.6	
2	5	1186	F	94.7	4.00	942	942	9.06
		1189	F					
		1199	F					
Mean								
SD			16	1.7	219	219	2.8	
3	15	1137	M	389	6.00	6039	6039	16.3
		1148	M					
		1159	M					
Mean								
SD			64	0.0	732	732	6.3	
3	15	1181	F	250	4.00	3085	3085	7.54
		1185	F					
		1200	F					
Mean								
SD			6.7	1.7	331	331	1.5	
4	45	1142	M	638	6.00	13174	13174	NA
		1154	M					
		1155	M					
Mean								
SD			76	5.2	1791	1791	NA	
4	45	1183	F	779	7.00	13322	13322	NA
		1190	F					
		1195	F					
Mean								
SD			210	1.7	1884	1884	NA	

NA Not applicable.
Note: AUC_{0-12h} is equivalent to AUC_{0-24h} in all animals.

Best Possible Copy

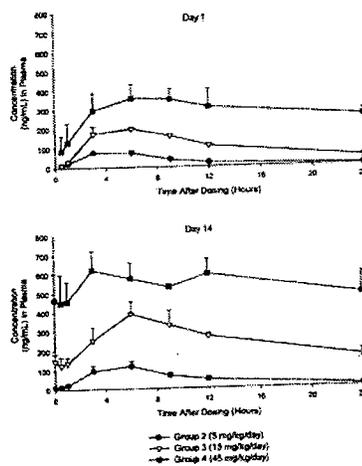
Table 1-3

Individual Toxicokinetic Parameters of SU011248 in Cynomolgus Monkeys: Day 1

Group	Dose Level (mg/kg/day)	Animal Number	Sex	C _{max} (ng/mL)	T _{max} (Hours)	AUC _{0-12h} (ng-hr/mL)	AUC _{0-24h} (ng-hr/mL)	t _{1/2} (Hours)
2	5	1140	M	80.5	4.00	746	773	4.60
		1145	M					
		1160	M					
Mean								
SD			4.8	1.7	70	78	0.79	
2	5	1186	F	97.4	3.00	692	714	3.69
		1189	F					
		1199	F					
Mean								
SD			26	0.0	266	271	1.3	
3	15	1137	M	201	5.00	2634	3171	8.40
		1148	M					
		1159	M					
Mean								
SD			5.3	1.7	190	226	0.16	
3	15	1181	F	231	5.00	2482	2632	5.13
		1185	F					
		1200	F					
Mean								
SD			39	1.7	452	527	1.3	
4	45	1142	M	370	8.00	6970	NA	NA
		1154	M					
		1155	M					
Mean								
SD			74	1.7	1413	NA	NA	
4	45	1183	F	465	5.00	7889	NA	NA
		1190	F					
		1195	F					
Mean								
SD			24	1.7	1093	NA	NA	

NA Not applicable.

Figure 1. Mean plasma concentrations of SU011248 in male monkeys (dose effect)



Comments: there were a few minimal histopathologic changes at the LD, the significance is questionable. Thus, the NOAEL is 5 mg/kg, and the LLD > 45 mg/kg. Changes in serum chemistry were evident by day 4, with the number of enzymes/parameters increasing through day 14. Marrow, liver, kidney, and adrenals were affected by this drug.

SU011248; four week oral toxicity study in the rat followed by a four-week recovery period. (2000-0497; Vol 4.3.2.2) (Previously reviewed by Dr. Schmidt, IND 62383, review 1).

Conducting laboratory and location: Pharmacia/Upjohn, Milan, Italy

Date of study initiation: 10/31/2000

GLP compliance: Yes

QA status: Yes

Methods (if unusual)

Species and strain: Sprague Dawley CD (SD)Br rat

#/sex/group or timepoint: 15/sex/dose; 10/sex/dose killed at the end of treatment, 5/sex/dose killed at end of recovery

age: M: 47 days, F: 51 days

weight: M: 136-155 g, F: 126-155 g

satellite groups used for TK or recovery: 6 rats/sex/dose for PK

drug, lot#, radiolabel, % purity: SU011248, batch # (A2)5953-TJF00003

formulation/vehicle: 0.5% carboxymethylcellulose

dosage groups in actually administered units: 0, 2.5, 5, 15 mg/kg/day (0, 15, 30, 90 mg/m²/day) daily for 28 consecutive days

route, volume: oral gavage at 5 mL/kg/day

Observations:

Clinical signs (daily): All rats survived to scheduled sacrifice. All of the HD males had abnormally colored fur, 4/15 had ruffled fur, 5/15 had broken incisors and 1/15 showed decreased activity. In the females, all HD rats had discolored fur, 2/15 showed decreased activity. 2/15 MD and 5/15 HD females had broken incisors, while 1/15 MD and 4/15 HD females had ruffled fur.

Body weights (weekly): Body weight was affected in the HD males and females. In the HD males, body weight was decreased by 9% as compared to controls at day 27, from day 36-55, body weight was decreased by up to 40% as compared to controls. In the females, a 15% decrease was seen at day 36, with decrements of approximately 25% between days 36 and 50.

Food consumption (weekly): The decrement in body weight is reflected in the decrease in food consumption in the HD animals after day 27. In the females, decreased food consumption was also seen at the MD.

Ophthalmoscopy (pretest, days 23, 53): There were no remarkable changes.

Hematology (days 7, 14, 28, 43, 58): The significant changes are summarized in the following table. With the exception of RBC # in the females, all parameters reverted to normal by the end of the recovery period.

% change in hematology as compared to controls		
	Male	Females
RBC #	↓10% H, D28	↓12% H D14 ↓13% M, 26% H D28
WBC #	---	↓25% H D14 --- D21
Neutrophil #	Decrease dose dependently to max of 50% D14, 21	Decrease dose dependently to max of 50% D14, 21

Serum chemistry (days 28, 43 and 58): The changes in serum biochemistry are summarized in the following table. The majority of differences are indicative of liver damage, although the increase in BUN suggests renal alterations.

% change as compared to concurrent controls						
	Males			Females		
	D28	D43	D58	D28	D43	D58
BUN	↑18%M, 39%H	3/5 H ↑2X or >	---	↑19% H	3/5 H ↑2X or >	---
AST	↑ H up to 2X	1/5 H ↑6X	---	1/10 H ↑2X	1/5H ↑2X	---
ALT	6/10 H ↑2-3X	1/5 ↑ 10X	---	6/10 ↑2-3X	1/5↑ 2X	---
Total protein	---	↓10% H	---	---	↓10%M, H	---
Albumin	---	↓11% H	---	---	↓13% M, 18% H	---
Triglyceride	---	↓47% H	↓30% H	↑23% M, 83% H	↓29% H	---

Urinalysis (days 28, 43, and 58): The pH increased from approximately 7.0 to 8.0 in males on days 28 and 58 and in females on days 43 and 58.

Organ weights (days 29, 59): The changes with treatment are shown in the following table. Only the thymus relative weights were changed significantly (approximately 40% decrease at the HD). At the end of the recovery period, changes had resolved, although in females thymus weight was still slightly decreased (approximately 20% at HD).

% change in absolute organ weights as compared to controls at day 28		
	Males	Females
Spleen	↓29% H	↓12% H
Liver	↓11% M, 19% H	---
Thymus	↓18% L, 20% M, 48% H	↓11% M, 42% H
Ovaries		↓33% H

Gross pathology (day 29, 59 for main study, day 91 and 115 for satellite): Changes were seen only in the HD groups. Yellow discoloration of the fur was seen in almost all HD males and females. Yellow discoloration of the gi tract was seen in 1-4 males and females at HD; yellow discoloration of the testes was seen in 6/10 males. Other observations included dark areas of the adrenals and enlarged adrenals (females only), and small spleen/thymus. At the end of the recovery phase, the yellow discoloration of the fur and testes persisted. Broken incisors were found in 4/5 HD males and 1/5 MD, 5/5 HD females.

Histopathology (All tissues examined in control, HD; at LD, and MD examined organs with "treatment-related changes" from adrenals, marrow, femur, kidneys, ileum, lymph nodes, pancreas, pituitary, spleen sternum and thymus; duodenum from females only; in 2 month satellite animals, examined thymus, spleen, adrenals, sternum, femur and marrow). No changes were seen at 2 and 3 months post-recovery.

Incidence of microscopic observations				
	Males		Females	
	Treatment (n=10)	Recovery (n=5)	Treatment (n=10)	Recovery (n=5)
Adrenal—cortical cell vacuolization (min-sl)	---	1 C, 2 H	4 H	---
Adrenal—cortical hemorrhage (min-mod)	2 H	---	8 H	---
Adrenal cortical necrosis (mod)	---	----	1 H	---
Adrenal--Cortical single cell necrosis (min-sl)	2 H	---	1 M, 8 H	---
Adrenals—inflammation (min)	---	---	2 H	2 H
Bone marrow—atrophy (sl-mod)	6 H	---	7 H	---
Sm intestine— inflammation/crypt dilatation (sl)	2 H	---	1-4 H	----
Femur—bone marrow atrophy (min-mod)	5 L, 7 M, 10 H	3 L, 3 M, 5 H (min-sl)	7 L, 10 M, H	1 L, 1 M, 2 H
Femur—incr. Thickening of cartilage plates (mod-marked)	10 H	---	10 H	---
Femur—reduced metaphyseal bony trabecular (sl-mod)	10 H	4 H	10 H	3 H
Femur—reduced osteoblasts	10 H	---	10 H	---
Kidneys—glomerular hyalinosis	4 H	---	6 H	---
Ovaries—corpora lutea			2 C, 4 L, 8 M,	3C, 2 L, 2 M,

Incidence of microscopic observations				
	Males		Females	
	Treatment (n=10)	Recovery (n=5)	Treatment (n=10)	Recovery (n=5)
degeneration (min-mod)			10 H	3 H (min-sl)
Ovaries—cystic corpora lutea min-mod)			1 C, 7 H	1 L, M, H (sl)
Pancreas—acinar apoptosis, degranulation (min-mod)	10 H	---	7-9 H	---
Pancreas—acinar atrophy (min)	---	1 L	1 H	----
Parotids—acinar degranulation/inflam (mod)	1 H	Not listed	---	Not listed
Pituitary—hypertrophy of basophilic cells (min-mod)	2 C, 2 L, 3 M, 9 H	5 C, 4 L, 4 M, 3 H	1 C, 1 M, 7 H	---
Spleen—lymphoid depletion (min)	1 M, 1 H	1 H	---	---
Teeth—caries (sl-mod)	---	5 H	---	1 M, 5 H
Thymus—lymphoid depletion (sl)	1 M, 1 H	1 H	3 H	1H

Toxicokinetics (day 1, 28 @ pre-dose, 1, 3, 6, 9, 24 hours post-dose; HPLC w/ MS/MS detection):

Appears This Way
On Original

Table 1.3

Individual Toxicokinetic Parameters for SU011248 in Rats: Day 1
 SU011248: Four-Week Oral Toxicity Study in the Rat Followed by a Four-Week Recovery Period

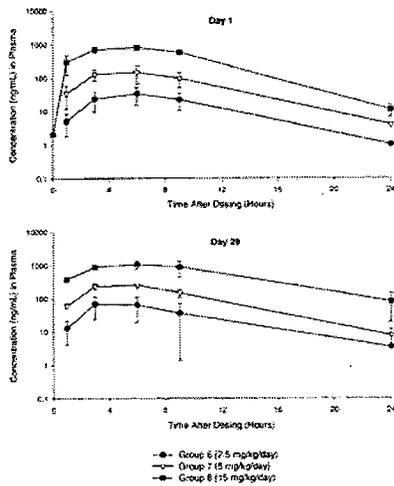
Group	Dose Level (mg/kg/day)	Sex	Animal Number	C _{max} (ng/mL)	T _{max} (Hours)	AUC _{0-24h} (ng-hr/mL)
6	2.5	M	3861	33.9	6.00	297
			3862			
			3863			
Mean						
SD			19	0.0	279	
6	2.5	F	3881	69.9	3.00	543
			3882			
			3883			
Mean						
SD			26	0.0	380	
7	5	M	3867	155	5.00	1622
			3868			
			3869			
Mean						
SD			75	1.7	1034	
7	5	F	3887	181	4.00	1895
			3888			
			3889			
Mean						
SD			120	1.7	1339	
8	15	M	3873	801	6.00	9873
			3874			
			3875			
Mean						
SD			130	0.0	1910	
8	15	F	3893	968	8.00	13183
			3894			
			3895			
Mean						
SD			390	1.7	5763	

Table 1.4

Individual Toxicokinetic Parameters for SU011248 in Rats: Day 28
 SU011248: Four-Week Oral Toxicity Study in the Rat Followed by a Four-Week Recovery Period

Group	Dose Level (mg/kg/day)	Sex	Animal Number	C _{max} (ng/mL)	T _{max} (Hours)	AUC _{0-24h} (ng-hr/mL)	AUC _{0-24h} (ng-hr/mL)
6	2.5	M	3861	69.5	4.00	639	938
			3862				
			3863				
Mean							
SD			43	1.7	659	NA	
6	2.5	F	3881	168	4.00	1513	1513
			3882				
			3883				
Mean							
SD			77	1.7	980	980	
7	5	M	3867	264	5.00	2784	2784
			3868				
			3869				
Mean							
SD			18	1.7	402	402	
7	5	F	3887	393	4.00	4447	4447
			3888				
			3889				
Mean							
SD			250	1.7	2777	2777	
8	15	M	3873	1100	6.00	14525	14525
			3874				
			3875				
Mean							
SD			250	3.0	5271	5271	
8	15	F	3893	775	6.00	11946	11946
			3894				
			3895				
Mean							
SD			210	3.0	4274	4274	

Figure 1: Mean plasma concentration of SU011248 in male rats. (Dose Proportionality). Error bars represent standard deviation.



Other (aldosterone and corticosterone: pretest, days 28, 43, and 58): There were no significant changes at day 28.

Best Possible Copy

Comments/conclusions:

The changes in liver and kidney serum biochemistry values were not reflected in microscopic findings. The major changes in histopathology were changes in bone/teeth, pancreas, adrenals and ovaries (females), and hematopoietic organs. Yellow discoloration of organs persisted after drug withdrawal. Serum biochemistry data suggested that liver toxicity may progress after removal of drug. No lethality was observed. The NOAEL was < 2.5 mg/kg based on marrow atrophy.

SU010398: 3 Month oral toxicity study in the rat followed by a 3-week recovery period (2001-0010; Volume 4.2.3.2) (Previously reviewed by Dr. Schmidt, IND 62383, review 2).

Conducting laboratory and location: ☐

☑ Pharmacia &

UpJohn, Nerviano, Milan, Italy

Date of study initiation: 1/16/01

GLP compliance: conducted according to OECD GLP

QA report: yes (X) no ()

Drug, lot #, radiolabel, and % purity: SU010398 (malate salt of SU011248) batch no (A2)5975-MTM-0002

Formulation/vehicle: Sterile water for injection

Methods: Due to poor condition, HD rats were sacrificed on day 65, HD satellite TK animals were kept for a 6 week recovery point.

Dosing:

Species/strain: Sprague Dawley :CD (SD)BR rats

#/sex/group or time point (main study): 20/sex/dose, 15/sex killed at end of treatment, remaining 5 held for 7 week recovery.

Satellite groups used for toxicokinetics: 6/sex/dose for TK

Age: 43 days

Weight: M: 164-197 g, F: 134-171 g

Doses in administered units: 0, 1.5, 5, 15 mg/kg/day (doses expressed as free base)

Route, form, volume, and infusion rate: oral gavage, 5 mL/kg/day

Observations and times/results:

Clinical signs (daily): All rats in the control, LD and MD groups survived to scheduled sacrifice. At the HD, 9/20 males and 3/20 females were found dead or sacrificed moribund prior to day 65. The females died on days 23, 56, and 63, while the males died on days 43-65. At the HD, clinical signs included decreased activity, impaired limb function, soft stools, reddish material around nose, and abnormal colored/ruffled fur (yellow, same color as drug). Broken incisors were still seen in the recovery period. At the MD and HD, broken incisors were seen (23/4 MD, 38/40 HD). There were no noteworthy observations in controls or LD.

Body weights (pretest, twice weekly in first month, weekly thereafter): Body weights in the HD animals were decreased by at least 10% beginning on days 24-29. At day 57 (the last day before the HD was sacrificed) body weight was decreased by 38% in males and 29% in females. During the recovery period, the animals gained approximately 5 fold the weight as the other groups in the study during the same period. There were no remarkable changes at LD or MD. Food consumption was not measured as the sponsor claimed there was significant wasting of the powdered food.

Ophthalmoscopy (days -4, 87, 129, not conducted on HD): There were no remarkable observations.

Hematology (day 25 for all, D 91-93, 113, 134 for C, LD, MD and days 53, 102 for HD): The changes in blood elements are shown in the table below. Decrements in WBC # represent decreases in lymphocytes, neutrophils, monocytes, and eosinophils. Decrements in RBC # were accompanied by increases in mean cell volume/hemoglobin.

% change in hematology parameters in rats						
Day	Males			Females		
	WBC #	RBC #	PLT #	WBC #	RBC #	PLT #
25 (C, L, M, H)	↓26% H	↓17% H	---	↓14% M, 32% H	↓21% H	---
53 (C, H)	↓48% H	↓41% H	↓24% H	↑16% H	↓48% H	↑40%
92 (C, L, M)	---	↓29% M	---	↑34% M	↓26% M	↑21% M
113 (C,L,M)	---	↓13% M	---	---	↓12%	---
134 (C,L,M)	---	---	---	---	---	---

Clinical chemistry (see hematology for times): Samples were taken from the HD animals with no concurrent controls on days 63 and 102. As a rough approximation, values in the HD group did not change significantly between day 53 and 63 or between control values and day 102 values. Differences between genders were minimal. Renal and liver parameters were deranged in the MD and HD groups (changes seen first at HD, then with additional doses, at MD), but resolved within 2 weeks of cessation of dosing.

Appears This Way
On Original

% change in serum chemistry values as compared to controls						
Gender	Parameter	Day 25	D53*	D92	D113	D134
Males	Urea	↑35% M, 70% H	↑21% H	↑46% M	---	---
	Creatinine	---	↓19% H	---	---	---
	AST	↑2X H	---	---	---	---
	ALT	↑3X H	↑3X H	---	---	---
	Total bilirubin	↑2X H	↑25% H	---	---	---
	Glucose	↑23% H	---	---	---	---
	Triglycerides	↑15% M, H	↑34% H	---	---	---
	Cholesterol	↑27% H	↑75% H	---	---	---
	Total protein	---	↓17% H	---	---	---
	Albumin	---	↓22% H	---	---	---
	Pi	---	↓20% H	---	---	---
	Females	Urea	↑37% H	↑50% H	↑30% M	---
Creatinine		---	↓16% H	---	---	---
AST		↑2X H	↑2X H	---	---	---
ALT		↑3X H	↑4X H	---	---	---
Total bilirubin		↑1.5 X H	↑33% H	---	---	---
Glucose		↑15% L, M; ↑28% H	---	---	---	---
Triglycerides		↑28% M, 90% H	↑22% H	---	---	---
Cholesterol		↑19% H	↑19% H	---	---	---
Total protein		---	↓14% H	---	---	---
Albumin		---	↓27% H	---	---	---
LDH		---	↑2X	---	---	---
CK		---	↑2X	---	---	---
Phosphate	↑12% M	↑15% H	↑22% M	---	---	

- indicates HD only compared to controls. --- indicates no remarkable changes.

Urinalysis (see hematology for times): Urinary pH increased by day 25 in the HD animal of both sexes. At the end of dosing, urinary pH was also increased in the MD animals. There were no other remarkable changes.

Gross pathology (days 63, 105 for HD, days 94, 135 for C, LD, MD): The gross findings are summarized in the following table. There were no remarkable gross observations at day 135.

Observation	Unscheduled deaths (H only)	Sac D 63 H only	Sac D 94 15/sex C, L, M	Sac D105 HD only n=4
Adrenals—enlarged	♂: 6/9 H ♀: 3/3 H	♂: 5/7 H ♀: 10/13 H	---	---
Adrenals—discolored	♂: 2/9 H	♂: 7/7 H ♀: 8/13 H	---	---

Observation	Unscheduled deaths (H only)	Sac D 63 H only	Sac D 94 15/sex C, L, M	Sac D105 HD only n=4
Duodenum—thickened	♂: 1/9 H	♂: 4/7 H ♀: 12/13 H	---	---
Epididymis—small	---	---	---	♂: 1 H
Jejunum—enlarged	---	---	♂: 1/15 M	---
Kidney—discolored area	---	♂: 1/7 H	---	---
Kidney—dilated pelvis	---	---	♂: 1/15 M ♀: 1/15 M	---
Liver—enlarged common bile duct	♂: 2/9 H ♀: 1/3 H	♂: 2/7 H ♀: 1/13 H	---	---
Lung—discolored area	♂: 1/9 H	---	♂: 1/15 L, 3/15 M	---
Lung—congestion	♂: 1/9 H	---	---	---
Mes. LN—enlarged	---	---	♂: 1/15 M	♂: 1/4 H ♀: 1/4 H
Skin (fur)—yellow discoloration	♂: 7/9 H ♀: 2/3 H	♂: 7/7 H ♀: 13/13 H	---	♂: 4/4 H ♀: 4/4 H
Spleen—cyst	---	---	♂: 1/15 M	---
Spleen—enlarged	---	---	---	♀: 1/4 H
Spleen—small	♂: 1/9 H ♀: 1/3 H	---	---	---
Stomach—yellow discoloration	---	---	♂: 2/15 M	---
Stomach—dilated	♂: 2/9 H	---	---	---
Stomach—discolored area	♂: 2/9 H ♀: 1/3 H	---	---	---
Stomach—hemorrhagic area	♂: 1/9 H	---	---	---
Testes—flaccid	♂: 4/9 H	♂: 4/7 H	---	♂: 2/4 H
Testes—yellow discoloration	♂: 4/9 H	♂: 6/7 H	♂: 3/15 M	♂: 2/4 H
Thymus—small	♂: 8/9 H ♀: 2/3 H	♂: 6/7 H ♀: 6/13 H	♂: 1/15 C, 1/15 M	---
Femur—soft bone marrow	---	♂: 7/7 H	---	---
Seminal ves.—small	♂: 5/9 H	♂: 1/7 H	---	---
Teeth—broken incisors	♂: 9/9 H ♀: 2/3 H	♂: 7/7 H ♀: 13/13 H	♂: 8/15 M ♀: 9/15 M	♂: 4/4 H ♀: 4/4 H
Limbs—fracture	---	♂: 1/7 H	---	---
Intestine—yellow discoloration	---	♀: 1/13 H	---	---

Organs weights: The changes in the low and mid doses at days 94 and 135 only are summarized in the following table. The HD animals were not sacrificed with concurrent controls so valid comparisons could not be made.

% change as compared to controls in LD and MD animals		
Organ	Males	Females

	Day 94		Day 135		Day 94		Day 135	
	Absolute	Relative	Absolute	Relative	Absolute	Relative	Absolute	Relative
Kidney	↓10% M	---	---	---	↓11% M	---	---	---
Liver	↓10% M	---	↓16% M	↓12% M	↓13% M	---	---	---
Pituitary	---	---	---	---	↓11% M	---	↑19% M	↑21% M
Prostate	↓15% M	---	---	---				
Spleen	↓21% M	↓22% M	---	---	↓10% L, ↓25% M	↓21% M	---	---
Thymus	↓30% M	↓27% M	↓17% M	---	↓30% M	↓21% M	↓30% M	↓30% M
Uterus					↓16% M	---	↓14% M	---

Histopathology (see table, at end of treatment, all C, MD, HD; at end of recovery all HD, select C, LD, MD):

Incidence of microscopic observations					
Observation	Death < D63 H only	D 63 H only	D94 C, L, M	D105 H only	D135 C, L, M
Adrenals—acute inflam	♂: 7/9 H ♀: 3/3 H	♂: 1/7 H ♀: 3/13 H	---	---	---
Adrenals—cortical congestion	♀: 1/3 H	♂: 1/7 H ♀: 5/13 H	---	---	---
Adrenal—cortical hemorrhage	♂: 8/9 H ♀: 3/3 H	♂: 7/7 H ♀: 4/13 H	---	---	---
Adrenals—cortical blood filled cysts	♂: 3/9 H ♀: 1/3 H	♂: 2/7 H ♀: 12/13 H	♂:1/15 C	---	---
Adrenals—cortical cell vacuolation	♂:1/9 H ♀: 1/3 H	♂: 5/7 H ♀: 6/13 H	---	♂: 3/4 H	♂: 1/5 C, 1/5 L, 1/5 M
Adrenals—cortical necrosis	♂: 8/9 H ♀:2/3 H	♂: 2/7 H ♀: 6/ 13 H	---	---	---
Adrenals—cortical mineralization	♂: 1/3 H	♂: 1/7 H ♀: 2/13 H	---	---	---
Adrenals—cortical fibrosis	---	---	---	♂: 1/4 H ♀: 2/4 H	---
Adrenals—medullary necrosis	♂: 5/9 H ♀: 2/9 H	♂: 1/7 H	---	---	---
Bone marrow—atrophy	♂: 9/9 H ♀: 3/3 H	♂: 7/7 H ♀: 13/13 H	♂: 5/15 M ♀: 1/15 L, 5/15 M	---	---
Duodenum—acute inflam in mucosa	♂: 5/9 H ♀: 1/3 H	♂: 4/7 H ♀: 6/13 H	---	---	---
Duodenum—lumen dilatation	♀: 1/3 H	♂: 1/7 H ♀: 9/13 H	---	---	---
Duodenum—purulent exude in lumen	♀: 1/3 H	♀: 6/13 H	---	---	---
Duodenum—mucosal erosion	♂: 2/9 H ♀: 1/3 H	♂: 1/7 H ♀: 3/13 H	---	---	---

Incidence of microscopic observations					
Observation	Death < D63 H only	D 63 H only	D94 C, L, M	D105 H only	D135 C, L, M
Duodenum—peritonitis	♂: 3/9 H ♀: 1/3 H	♂: 4/7 H ♀: 1/13 H	---	---	---
Duodenum—glandular hyperplasia	♂: 6/9 H ♀: 3/3 H	♂: 7/7 H ♀: 13/13 H	---	♂: 2/4 H ♀: 2/4 H	---
Duodenum—dilatation of common bile duct	♂: 5/9 H ♀: 1/3 H	♂: 4/7 H ♀: 2/13 H	---	♂: 1/4 H	---
Duodenum—inflam of common bile duct wall	♂: 6/9 H ♀: 1/3 H	♂: 5/7 H ♀: 7/13 H	---	♂: 2/4 H ♀: 1/4 H	---
Duodenum—necrosis of common bile duct wall	♂: 5/9 H ♀: 1/3 H	♂: 3/7 H ♀: 2/13 H	---	---	---
Duodenum—hyperplasia of common bile duct wall	♂: 4/9 H ♀: 1/3 H	♂: 3/7 H ♀: 3/13 H	---	♂: 1/4 H ♀: 1/4 H	---
Epididymis—reduced spermatozoa	♂: 5/9 H	♂: 2/7 H	---	♂: 2/4 H	---
Epididymis—epith. Hyperplasia	♂: 2/9 H	---	---	♂: 1/4 H	---
Eye—nerve fiber degen	---	---	♀: 1/15 M	---	---
Eye—periocular hemorrhage/inflam	---	---	---	♂: 1/4 H ♀: 2/4 H	---
Femur—incr. thickness of cartilage plate/red. Metaphyseal bony trabeculae/dec.osteoblasts	♂: 9/9 H ♀: 3/3 H	♂: 7/13 H ♀: 13/13 H	♂: 1/15 M	♂: 1/4 H ♀: 1/4 H	---
Femur—myelofibrosis	---	---	♀: 1/15 M	---	---
Femur—cartilage in metaphyseal bony trabeculae	---	---	---	♂: 3/4 H ♀: 4/4 H	---
Femur—condrodysplasia of epiphyseal plate	---	---	---	♂: 3/4 H ♀: 3/4 H	♂: 1/5 M
Harderian gland—adenitis	♂: 1/9 H	---	---	♀: 2/4 H	---
Ileum—acute inflam	♂: 1/9 H	♂: 1/7 H ♀: 6/13 H	---	---	---
Ileum—glandular hyperplasia	♂: 1/9 H	♂: 3/7 H ♀: 7/13 H	---	---	---
Kidney—cortical tubular basophilia	♂: 4/9 H	♂: 7/7 H ♀: 1/13 H	♂: 4/15 C, 3/15 L, 5/15 M	♂: 3/4 H	♂: 3/5 C, 1/5 L, 1/5 M ♀: 1/5 L
Kidney—yellowish	♀: 2/3 H	♂: 1/7 H	♀: 3/15 M	♀: 4/4 H	---

Incidence of microscopic observations					
Observation	Death < D63 H only	D 63 H only	D94 C, L, M	D105 H only	D135 C, L, M
pigment in tub. epith		♀: 13/13 H			
Kidney—glomerular hyalinosis	♂: 8/9 H ♀: 1/3 H	♂: 7/7 H ♀: 8/13 H	---	---	---
Kidney—dilated pelvis	---	---	♂: 1/15 M ♀: 1/15 M	---	---
Liver—peribiliary inflam	♂: 4/9 H ♀: 2/3 H	♂: 1/7 H ♀: 1/13 H	♂: 1/15 M	♂: 1/4 H ♀: 3/4 H	---
Liver—yellow pigment in hepatocytes	♀: 3/3 H	♂: 2/7 H ♀: 13/13 H	♀: 10/15 M	♀: 4/4 H	---
Liver—bile duct hyperplasia	♂: 3/9 H ♀: 2/3 H	♀: 1/13 H	♂: 1/15 M	♂: 1/4 H ♀: 3/4 H	---
Liver—focal necrosis	♂: 2/9 H ♀: 1/3 H	---	♂: 1/15 M ♀: 1/15 L, M	---	♂: 1/5 L
Liver—arteritis/venous thrombosis	♂: 1/9 H	---	♂: 1/15 M ♀: 1/15 L	---	---
Lung—acute inflam	♂: 1/9 H	---	♂: 1/5 L, 4/15 M	---	---
LN—lymphoid depletion	♂: 9/9 H ♀: 3/3 H	♂: 6/7 H ♀: 7/13 H	---	---	---
Salivary glands— apoptosis	---	♂: 3/7 H ♀: 6/13 H	---	---	---
Salivary glands—acinar hypertrophy	♂: 9/9 H ♀: 3/3 H	♂: 7/7 H ♀: 11/13 H	♂: 9/15 L, 11/15 M ♀: 4/15 L, 11/15 M	♂: 3/4 H	---
Ovaries—mineralization degen of corpora lutea	♀: 3/3 H	♀: 12/13 H	♀: 5/15 C, 11/15 L, 12/15 M	♀: 4/4 H	---
Pancreas—edema	♂: 7/9 H ♀: 3/3 H	♂: 7/7 H ♀: 10/13 H	---	---	---
Pancreas—chr. inflam	♂: 2/9 H	♂: 3/7 H	♂: 2/15 C, 3/15 L, 3/15 M	♀: 1/4 H	♂: 1/5 C, 1/5 L, 2/5 M ♀: 1/5 M
Pancreas—acinar vacuolation	---	♂: 2/7 H ♀: 2/13 H	♂: 1/15 M	---	---
Pancreas—acinar degranulation	♂: 7/9 H ♀: 3/3 H	♂: 7/7 H ♀: 13/13 H	♂: 1/15 M	---	---
Pancreas—acinar atrophy	♂: 4/9 H	♂: 3/7 H ♀: 2/13 H	♂: 2/15 C, 1/15 L, 2/15 M	♀: 1/4 H	---
Pancreas—apoptosis of acinar cells	---	♂: 2/7 H ♀: 5/13 H	♂: 1/15 M	---	---
Pancreas—peritonitis	♂: 6/9 H	♂: 3/7 H	♂: 1/15 M	---	---

Incidence of microscopic observations					
Observation	Death < D63 H only	D 63 H only	D94 C, L, M	D105 H only	D135 C, L, M
	♀: 2/3 H	♀: 3/13 H			
Parotids—acinar degranulation	♂: 5/9 H ♀: 2/3 H	♂: 1/7 H	♂: 1/15 M	---	---
Parotids—acinar hypertrophy	♀: 1/3 H	♂: 2/7 H ♀: 8/13 H	---	---	---
Parotids—acinar cell apoptosis	---	♀: 1/13 H	---	---	---
Pituitary—hypertrophy of basophilic cells	♂: 8/9 H ♀: 1/3 H	♂: 7/7 H ♀: 11/13 H	♂: 8/15 C, 10/15 L, 8/15 M	♂: 2/4 H	♂: 3/5 C, 1/5 L, 2/5 M
Pituitary—necrosis of anterior lobe	♂: 1/9 H	♂: 1/7 H	---	---	---
Prostate—colloid depletion	♂: 5/9 H	♂: 4/7 H	---	---	---
Seminal ves—colloid depletion	♂: 8/9 H	♂: 1/7 H	---	---	---
Spleen—lymphoid depletion	♂: 9/9 H ♀: 2/3 H	♂: 7/7 H ♀: 7/13 H	♂: 1/5 M ♀: 2/15 M	---	♂: 1/5 M
Teeth—caries of incisors	♂: 9/9 H ♀: 3/3 H	♂: 7/7 H ♀: 13/13 H	♂: 14/15 M ♀: 14/15 M	♂: 4/4 H ♀: 4/4 H	♂: 5/5 M ♀: 3/5 M
Testes—tubular atrophy	♂: 3/9 H	♂: 3/7 H	---	♂: 2/4 H	---
Testes—interstitial edema/giant cells	♂: 3/9 H	♂: 2/7 H	---	♂: 1/4 H	---
Thymus—lymphoid depletion	♂: 9/9 H ♀: 2/3 H	♂: 5/7 H ♀: 6/13 H	♂: 4/15 M ♀: 2/15 M	♀: 1/4 H	♂: 1/5 L, M
Uterus—atrophy	♀: 2/3 H	♀: 6/13 H	---	---	---
Vagina—purulent exudate in lumen	♀: 1/3 H	♀: 5/13 H	---	---	---

Toxicokinetics (day 1, 28, 65 [HD only], 91; predose, 1, 3, 6, 9, 24 hours post-dose): Plasma sample were analyzed by a HPLC with MS/MS detection. The values are summarized in the following table. Both C_{max} and AUC continues to increase as the duration of dosing increased. AUCs did not plateau with dose, nor were there statistically significant differences in AUC/C_{max} with gender. The ratio of parent compound to metabolite SU012662 crept up slightly during the course of the experiment; AUC of metabolite was much higher than that of the parent compound. The half life of the parent compound was between 3.2-5.7 hours on day 1 and between 4.6 and 6.8 hours on day 91, a minimal difference. The half-life of SU012662 ranged from 4.0 to 6.8 hours at day 1 to 8.0 to 9.9 hours on day 91.

SU011248 and SU012662 in Rats: Mean Values (\pm SD)

Group	Dose Level*** (mg/kg/day)	Sex	C _{max} (ng/mL)	AUC _{0-t last} (ng-hr/mL)	C _{max} (ng/mL)	AUC _{0-t last} (ng-hr/mL)
			<u>SU011248</u>		<u>SU012662</u>	
<u>Day 1</u>						
6	1.5	M	18.1 (\pm 8.7)	136 (\pm 117)	27.8 (\pm 16)	371 (\pm 234)
		F	30.5 (\pm 13)	230 (\pm 167)	33.4 (\pm 11)	437 (\pm 143)
7	5	M	92.3 (\pm 25)	1088 (\pm 311)	186 (\pm 59)	2392 (\pm 767)
		F	109 (\pm 66)	1272 (\pm 1015)	155 (\pm 100)	2190 (\pm 1658)
8	15	M	403 (\pm 170)	5014 (\pm 2553)	953 (\pm 500)	13221 (\pm 7220)
		F	669 (\pm 200)	9121 (\pm 3740)	982 (\pm 340)	14403 (\pm 5340)
<u>Day 28</u>						
6	1.5	M	34.2 (\pm 14)	297 (\pm 198)	86.8 (\pm 33)	1077 (\pm 531)
		F	44.6 (\pm 19)	408 (\pm 221)	54.9 (\pm 22)	672 (\pm 297)
7	5	M	199 (\pm 48)	2276 (\pm 624)	564 (\pm 150)	7998 (\pm 2084)
		F	239 (\pm 95)	2687 (\pm 1402)	267 (\pm 110)	3720 (\pm 1962)
8	15	M	676 (\pm 220)	9829 (\pm 3423)	2550 (\pm 960)	38978 (\pm 13661)
		F	877 (\pm 270)	13894 (\pm 4392)	1140 (\pm 380)	17719 (\pm 5787)
<u>Day 65</u>						
8	15	M	440*	6177*	1060*	17588*
		F	388 (\pm 190)**	6003 (\pm 1660)**	573 (\pm 300)**	8311 (\pm 2288)**
<u>Day 91</u>						
6	1.5	M	45.9 (\pm 25)	433 (\pm 391)	125 (\pm 51)	1670 (\pm 1015)
		F	64.0 (\pm 48)	605 (\pm 416)	80.9 (\pm 47)	938 (\pm 505)
7	5	M	302 (\pm 98)	3608 (\pm 654)	1060 (\pm 350)	15645 (\pm 3845)
		F	326 (\pm 190)	3581 (\pm 1915)	446 (\pm 280)	5169 (\pm 2763)

Note: 6 animals/sex/group.

* N=2.

** N=3.

*** SU011248 free base equivalents.

Comments and conclusions: The lowest lethal dose was 15 mg/kg/day. It is questionable whether the LD (1.5 mg/kg/day) is a NOAEL.

SU010398: 3 month oral toxicity study in the monkey followed by a 4-week recovery period (2000-0532; Volume 4.2.3.2) (Previously reviewed by Dr. Schmidt, IND 62383, review 2).

Conducting laboratory and location: Toxicology Pharmacia/UpJohn, Kalamazoo, MI

Date of study initiation: 1/16/01

GLP compliance: Yes

QA report: yes (X) no ()

Drug, lot #, radiolabel, and % purity: malate salt SU010398, Lot # (a) 5975-MTM-002, 73.3% free base, 25.6% malate salt in bulk drug. \square \downarrow impurities \square \uparrow)

Formulation/vehicle: sterile water

Methods (unique aspects): The high dose was decreased from 20 mg/kg/day to 12 mg/kg/day beginning on day 29 (see full description of dosing below).

Dosing:

Species/strain: cynomolgus monkey (*Macaca fascicularis*)

#/sex/group or time point (main study): 6/sex/dose (4/sex/dose sac'd at end of dosing)

Satellite groups used for toxicokinetics or recovery: 2/sex/dose used for recovery

Age: "juvenile to young adult"

Weight: M: 2.8-3.6 kg, F: 2.5-3.2 kg

Doses in administered units: 0, 2, 6, 20/12 mg/kg/day (dose decreased beginning on day 29, dosing ceased from days 34-42, stopped at day 67)

Route, form, volume, and infusion rate: PO by gastric intubation, maximum volume 5 mL/kg (reduced to 3 mL/kg when HD was reduced).

Observations and times:

Clinical signs (daily): The following table describes the mortality and clinical signs in the monkeys.

Dose	Unsched deaths	Day of death	Clinical signs
0	0	---	---
2	0	---	---
6	0	---	Alopecia, yellow discoloration of mouth/skin
20/12	4/6 M 3/6 F	D29 (1M, 2F--MS) D31 (1M--MS) D63 (1M--FD, 1F--MS) D67 (1M, 1F--SS) D70 (1M-MS)	Decreased activity, hypothermia, hunched posture, pale skin, emesis ("a few hours after dosing"), eyes red/swollen/discharging (males only), discolored/bloody gums/oral lesions, soft/watery feces

MS= moribund sacrifice; FD= found dead, SS= scheduled sacrifice

Body weights (weekly): In the HD males, body weight was decreased by > 10% beginning on day 22. At day 29, when monkeys were moribund sacrificed, body weight in HD males and females were decreased by 18% and 16% respectively. At the MD, body weights were decreased by up to 9% and 6% in males and females at the end of dosing. Monkeys regained the majority of the weight difference during the recovery period.

Food consumption (twice daily): Food consumption was decreased to approximately half in the HD monkeys beginning in around day 14 (consumption was decreased by more than 75% in the HD females). In MD male monkeys, consumption decreased by about 25% beginning around the 8th week and reached a nadir of 50% of control in the last few days of dosing. Food consumption rebounded to control levels at the start of the recovery period.

Ophthalmoscopy (pretest, end of dosing, end of recovery): In the HD males at day 36, ulcerative blepharitis/hyperemia were seen in 3-4/4 male and female monkeys. Additionally one HD female had canthal ulceration in both eyes. All observations resolved by day 63.

EKG (twice pretest, day 3, 39, 84 @ predose and +6 hrs; end of recovery): The HD animals were only monitored on day 3. Heart rate was decreased by more than 20 BPM (approximately 10% of

pretest rate) at 6 hrs post-dose. At the MD at day 39, similar decrements were observed. There were no remarkable and dose response dependent changes in QT intervals etc. There were no major differences between genders.

Hematology (twice pretest, day 14, 29, 31, 37, 63, 88 and recovery D43): Decrements in WBC, RBC and platelet # were seen in the MD and HD animals (decrements at MD merely appeared later than those at the HD). The majority of damage resolved by the end of the recovery period. Shifts in WBC # were primarily attributable to eosinophils, monocytes and neutrophils.

% change in hematology vs controls								
Sex	Parameter	D 14 C,L,M, H	D29* H	D31* H	D 37 C, L, M, H	D 63 C, L, M, H	D88 C, L, M	Rec D 43 C, L, M, H
Male	WBC	---	↓>50% H	↓>75% H	---	↓27% H	---	---
	RBC	---	---	---	↓28% H	↓21% H	↓8% M	---
	PLT	↓30% H	---	↓>50% H	↓27% H	↓26% H	---	---
Female	WBC	↓11% H	↓>75% H		↓25% H	↓10% M ↓41% H	---	---
	RBC	---	↓>25% H		↓13% M ↓26% H	↓12% M ↓18% H	↓11% M	---
	PLT	↓14% L, 7% M 29% H	---		---	↓25% H	---	↓30 % M ↓36% H

*no concurrent controls were available so values are a rough approximation

Clinical chemistry (see hematology for sampling): The data is summarized in the following table. Again, there were no concurrent controls on days 29 and 31, so comparisons are a rough approximation with either pretest or recent values. The majority of the changes resolved during the recovery period.

% change in serum chemistry vs controls								
Sex	Parameter	D 14 C,L,M, H	D29* H	D31* H	D 37 C, L, M, H	D 63 C, L, M, H	D88 C, L, M	Rec D 43 C, L, M, H
Male	Cholesterol	↑42% H	---	↑70%	↓13% H	---	---	
	BUN	---	↑2X	↑3X	↓36% M	---	---	↑43% H
	Glucose			↓60%	↑17% M, 33% H	---	---	
	AST	↑4X H	↑3X	↑7X	1/6 M ↑2X	↑2-3X H	---	

% change in serum chemistry vs controls								
Sex	Parameter	D 14 C, L, M, H	D29* H	D31* H	D 37 C, L, M, H	D 63 C, L, M, H	D88 C, L, M	Rec D 43 C, L, M, H
	ALT	↑3X H	---	↑3X	1/6 M ↑2X	↑2X H	---	
	Phosphate	↓10% M ↓27% H	↓75%		↓12% M, 60% H	↓18% H	↓10% M	↑15% M, H
	CK	↑10X H	↑6X	↑35X	↑3X M, H	↑4-9X H	2/6 ↑3, 7X M	
	Trigly	↑97% H	↑3X	↑20X	↑34% H	2/6 ↑3X M; 2/3 ↑2- 3X H	2/6 ↑2- 3X M	
	Lipase		↑2.5X		---		---	
	Na		↓to 134		--		---	
	Total protein	---	---	---	↓16% H	---	---	
	Total bilirubin					↓50% H	---	↑2-3X M, H
Female	Cholesterol	---	---		↓28% H	---	---	
	BUN	---	↑3X		↓25% M	1/3 H ↑6X	---	↑38% H
	Glucose	---	↓50%		↑15% M, 22% H	---	---	
	AST	↑3X H	↑5X		3/6 M ↑2X	↑2-3 X H	---	
	ALT	↑2X H	---		4/6 M ↑ 2-3X	↑2X H	---	
	Total protein				↓12% H	---	---	
	Phosphate	↓11% L, 19% M, 38% H	↓40%		↓11% L, 15% M, 49% H	↓9% H	↓10% M	↑21% H
	CK	↑6X H	↑130X		↑2X L, 8X M, 3X H	↑4-30X	4/6 ↑2- 3X	
	K+	↑13% H			↑14% H	↑19% H	---	
	Trigly	---	↑2X		↑64% H	1/4 ↑2X H	---	

% change in serum chemistry vs controls								
Sex	Parameter	D 14 C,L,M, H	D29* H	D31* H	D 37 C, L, M, H	D 63 C, L, M, H	D88 C, L, M	Rec D 43 C, L, M, H
	Lipase		↑3X		---	---	---	
	Na	---	↓to 133		---	---	---	

*no concurrent controls were available so values are a rough approximation

Urinalysis (end of dosing, end of recovery): There were no remarkable differences versus controls or pretest values.

Gross pathology (n=4/sex on day 92 at C,L, M; 2 H on day 67): The gross changes are shown in the table below. There were no remarkable findings in the females at the end of the treatment phase, or in the males at the end of the recovery phase.

Observation	Males			Females		
	Early death	Treatment	Recovery	Early death	Treatment	Recovery
Adrenal—discolored	2/5 H	---	---	2/4 H	---	---
Adrenals—foci	---	---	---	1/4 H	---	---
Sm intest—foci	---	---	---	1/4 H	---	---
Colon—foci	---	1/4 C, 1/4 M	---	1/4 H	---	---
Gall bladder—contents discolored	1/5 H	---	---	---	---	---
Heart—foci	1/5 H	---	---	---	---	---
Heart—discolored	--	---	---	2/4 H	---	---
Kidney—discolored	---	---	---	1/4 H	---	---
Lungs—foci/dicolor	1/5 H	---	---	1/4 H	---	---
Lungs—nodule		---	---		---	2/2 H
Liver—foci	4/5 H	---	---	1/4 H	---	---
Oral cavity—foci	1/5 H	1/4 M	---		---	---
Parathyroids—enlarged		1/4 M	---		---	---
Stomach—foci	3/5 H	---	---	1/4 H	---	---
Testes—discolored	1/4 H	---	---		---	---
Thyroid—cyst		---	---	1/4 H	---	---

Organs weights: Changes in organ weights are shown in the following table.

Sex	Organ	End of Treatment		End of Recovery	
		Absolute	Relative to BW	Absolute	Relative to BW
M	Adrenals	↑40% H	↑87% H	↑12% H	---
	Epididymis	↓29% M	↓23% M	---	---
		↓54% H	↓38% H		
	Heart	↓28% H	---	---	---
	Kidneys	---	↑26% H		↑21% H
Prostate	↓60% H	↓50% H	---	---	

Sex	Organ	End of Treatment		End of Recovery	
		Absolute	Relative to BW	Absolute	Relative to BW
	Spleen	↓32% M ↓24% H	---	---	---
	Testes	↓40% M ↓60% H	↓31% M ↓45% H	---	---
	Thymus	↓50% M ↓85% H	↓46% M ↓82% H	↓27% L ↑45% M	↓20% L ↑50% M
	Thyroids	↓19% H	---	↑16% L ↑22% M ↑29% H	---
F	Heart	↓13% M ↓25% H	---	---	---
	Kidneys	---	↑36% H	---	---
	Liver	↓16% L ↓10% M, H	---	---	---
	Ovaries	↓37% L ↓44% M	Questionable	↓10% L ↓19% M ↓53% H	↓50% H
	Spleen	↓36% H	---	---	---
	Thymus	↓32% M ↓84% H	↓23% M ↓80% H	---	---
	Thyroid	---	---	↑23% L ↑28% M ↑52% H	↑75% H
	Uterus	↓40% L ↓62% M ↓71% H	↓36% L ↓60% M ↓65% H	↓39% M ↓72% H	↓35% M ↓70% H

Histopathology (see table for tissues sampled): The table below captures the noteworthy changes in microscopic observations. Again, the HD group was not treated for the full 3 months and during the period which animals were treated, the dose was reduced. The majority of observations were made in the early death/moribund sacrifice HD monkeys. Major targets were hematopoietic organs (thymus, marrow lymph nodes), glands (adrenals, salivary, pancreas), and female reproductive organs (ovaries, uterus). Damage in the LD and MD monkeys was confined to adrenals, bone, lymph nodes, pancreas, thymus and uterus. With the exception of minimal inflammation/fibrosis in the kidney, lung and lymph nodes (which may not be remarkable), there were no remaining changes at the end of the recovery period.

Incidence of microscopic observations

Observation	Males			Females		
	Unsched	Treatment	Recovery	Unsched	Treatment	Recovery
Adrenal cortex hemorrhage	5/5 H (G1-3)	4/4 M (G1-2)	---	4/4 H (G3-4)	3/4 M (G1-3)	---
Adrenal cortex—edema	3/5 H (G1-3)	1/4 H (G3)	---	3/4 H (G1-3)	---	---
Bone marrow—decreased erythropoiesis	4/5 H (G3-4)	---	---	2/4 H (G3-4)	1/4 M (G1)	---
Bone—ephyseal dysplasia	5/5 (G2-3)	4/4 M (G3-4)	---	3/4 (G2-3)	2/4 L (G1) 4/4 M (G1-3)	---
Bone—chondrocyte necrosis	1/5 H (G3)	1/4 M (G4)	---	---	---	---
Cecum—epith. Necrosis	---	---	---	2/4 H (G1)	---	---
Cecum—mucosal inflam	1/5 H (G1)	---	---	2/4 H (G1)	---	---
Colon—lymphoid atrophy	---	---	---	1/4 H (G1)	---	---
Colon—acute inflam	---	---	---	2/4 H (G1)	---	---
Colon—mucosal epith depletion	1/5 H (G1)	---	---	---	---	---
Sm intest—mucosal erosion/necrosis	---	---	---	1/4 H (G1-3)	---	---
Gall bladder—hemorrhage	2/5 H (G1, 4)	---	---	---	---	---
Gall bladder—mucosal hemorrhage	---	---	---	1/4 H (G1)	---	---
Gall bladder—acute inflam	1/4 H (G3)	---	---	---	---	---
Heart—myocardial acute inflam	1/4 H (G2)	---	---	---	---	---
Ileum—lymphoid atrophy	2/5 H (G2, 3)	---	---	2/4 H (G2)	---	---
Jejunum—acute inflam	---	---	---	2/4 H (G2, 3)	---	---
Kidney—interstitial inflam	---	---	---	1/4 H (G1)	---	1/2 H (G1)
Kidney—interstit fibrosis	---	---	1/1 H (G2)	---	---	---
LN—lymphoid atrophy	3-5/5 H (G2-4)	---	---	23/4 H (G2-4)	---	---
LN (bronchial, mand)—acute inflam	2/5 H (G2-4)	1/4 M (G1)	---	1-2/4 H (G1-4)	---	1/2 H (G4)

Incidence of microscopic observations						
Observation	Males			Females		
	Unsched	Treatment	Recovery	Unsched	Treatment	Recovery
Lungs—congestion	---	---	---	1/4 H (G2)	---	---
Lung—acute inflam/hemorrhage/pleuritis	1/5 H (G4)	---	---	---	---	1/2 H (G2)
Liver—acute inflam/ectasia/fatty changes	---	---	---	1/4 H (G1)	---	---
Liver—hemorrhage	1/5 (G4)	---	---	---	---	---
Liver—peritonitis	1/5 (G3)	---	---	---	---	---
Mammary gland—acute inflam of duct	1/5 H (G2)	---	---	---	---	---
Oral cavity—chronic inflam of gingiva	1/5 H (G2)	1/4 M (G2)	---	---	---	---
Ovaries—decr. Follicular devel			---	3/4 (G3)	---	---
Pancreas—acinar degranulation	5/5 (G2-4)	4/4 M (G1-3)	---	4/4 (G3-4)	1/4 L (G1) 3/4 M (G1-2)	---
Salivary gland—acinar degranulation	3/5 (G1-2)	2/4 M (G1)	---	3/4 (G1-2)	1/4 M (G1)	---
Skin—necrosis/ulceration	---	---	---	1/4 (G3)	---	---
Skeletal muscle (diaphragm)—neutrophil infiltr	1/5 H (G1)	---	---	1/4 H (G2)	---	---
Skeletal muscle—degen in muscle fiber	---	---	---	1/4 H (G1)	---	---
Spleen—lymphoid atrophy	1/5 H (G2)	---	---	3/4 H (G1-2)	---	---
Spleen—neutrophil infiltr	---	---	---	1/4 H(G3)	---	---
Stomach—atrophy/inflam glandular mucosa	1/5 H (G1)	---	---	1/4 H (G2)	---	---
Stomach—gland. Mucosa, hemorrhage	3/5 (G1-2)	---	---	1/4 H (G2)	---	---
Stomach (gland. Mucosa)—necrosis	1/5 H (G1)	---	---	---	---	---
Thymus—lymphoid atrophy	5/5 (G2-4)	2/4 M (G1)	---	3/4 (G4-5)	2/4 M (G1)	---
Tongue—acute inflam/hemorrhage	1/5 H (G1-3)	---	---	2/4 H (G3)	---	---
Urinary bladder—	---	---	---	1/4 H	---	---

Incidence of microscopic observations						
Observation	Males			Females		
	Unsched	Treatment	Recovery	Unsched	Treatment	Recovery
microcysts				(G2)		
Uterus—endometrial atrophy			---	3/4 H (G3)	1/4 L (G2) 3/4 M (G2)	---

G1= min, G2= mild, G3= moderate, G4= marked, G5= severe

Toxicokinetics (days 1, 57, 91 at 0, 1, 3, 6, 9, 12, 24 hours; day 15, 29, 66, 71 @ 0, 6 hours; day 57 at 0, 6, 24, 48, 72 hours; recovery days 8, 15, and 22 single samples): The plasma samples were analyzed by HPLC with MS/MS detection. The internal standard was DL-propranolol hydrochloride. The lower limit of quantitation (LOQ) was 1.0 ng/mL for both SU011248 and SU012662.

The Cmax and AUC parameters are shown in the table below. Cmax and AUC continue to increase with increased dosing duration. No apparent saturation of absorption was seen at any timepoint and the ratio of parent drug to metabolite SU012662 remained relatively constant with time. The half-life of parent compound was approximately 5-9 hours at day 1 while at day 91 half life ranged from 9 to 30 hours. The half life for metabolite SU012662 was 8-13 hours at day 1 and increased to 13-20 hours at day 91. At 2 and 6 mg/kg/day, parent and metabolites were still detectable in plasma at day 8, but not day 15 of the recovery period, while at the highest dose, 20/12 mg/kg/day, samples were still detectable at day 22 post-dose (albeit at very low levels).

Appears This Way
On Original

SU011248 and SU012662 in Monkeys: Mean Values (\pm SD)

Group	Dose Level*** (mg/kg/day)	Sex	SU011248		SU012662	
			C _{max} (ng/mL)	AUC _{0-24 hr} (ng·hr/mL)	C _{max} (ng/mL)	AUC _{0-24 hr} (ng·hr/mL)
<u>Day 1</u>						
2	2	M	13.2 (\pm 12)	226*	4.84 (\pm 2.9)	70.3 (\pm 51)**
		F	20.6 (\pm 8.3)	188 (\pm 97)	6.45 (\pm 1.8)	85.5 (\pm 23)
3	6	M	92.7 (\pm 38)	979 (\pm 510)	31.9 (\pm 1.3)	422 (\pm 72)
		F	81.5 (\pm 29)	794 (\pm 453)	35.6 (\pm 7.7)	453 (\pm 219)
4	20	M	294 (\pm 61)	4381 (\pm 1033)	117 (\pm 34)	1971 (\pm 570)
		F	353 (\pm 44)	4697 (\pm 910)	140 (\pm 22)	2200 (\pm 369)
<u>Day 57</u>						
2	2	M	35.9 (\pm 4.7)	373 (\pm 80)	13.1 (\pm 2.4)	200 (\pm 53)
		F	53.7 (\pm 11)	594 (\pm 111)	17.4 (\pm 2.6)	263 (\pm 29)
3	6	M	115 (\pm 35)	1377 (\pm 403)	46.1 (\pm 3.4)	720 (\pm 102)
		F	132 (\pm 37)	1566 (\pm 620)	55.3 (\pm 15)	807 (\pm 152)
4	12	M	359 (\pm 70)	5857 (\pm 1327)	167 (\pm 29)	3266 (\pm 991)
		F	345 (\pm 93)	5585 (\pm 2316)	182 (\pm 67)	3510 (\pm 1806)
<u>Day 66</u>						
4	12	M	354 (\pm 86)**	6620 (\pm 1290)**	214 (\pm 70)**	4769 (\pm 1686)**
		F	354 (\pm 140)**	6131 (\pm 2864)**	180 (\pm 10)**	3783 (\pm 631)**
<u>Day 91</u>						
2	2	M	57.0 (\pm 7.3)	561 (\pm 73)	21.0 (\pm 1.8)	325 (\pm 64)
		F	68.9 (\pm 12)	801 (\pm 214)	24.0 (\pm 3.2)	411 (\pm 64)
3	6	M	157 (\pm 38)	1976 (\pm 450)	71.9 (\pm 13)	1217 (\pm 230)
		F	161 (\pm 16)	1935 (\pm 332)	82.8 (\pm 22)	1304 (\pm 246)

Note Four animals/sex/group

The AUC_{0-24 hr} is equivalent to AUC_{0-24 hr} on Days 57, 66, and 91.

* N=2

** N=3

*** SU011248 (the free base equivalent of SU010398).

Comments and conclusions: The lethal dose was 20/12 mg/kg/day. Based on histopathology and changes in platelet #, decreased organic phosphate, it is questionable if the LD (2 mg/kg/day) is a NOAEL.

Appears This Way
On Original

Data Possible Copy

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

/s/

Leigh Verbois
1/20/2006 05:29:02 PM
PHARMACOLOGIST

David Morse
1/23/2006 12:01:07 PM
PHARMACOLOGIST