CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-923

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:	**21,923**
SERIAL NUMBER:	**000**
DATE RECEIVED BY CENTER:	**4/29/05**
PRODUCT:	**NEXAVAR (Sorafenib Tosylate)**
INTENDED CLINICAL POPULATION:	**Renal Cell Carcinoma**
SPONSOR:	**Bayer Pharmaceuticals Corporation**
DOCUMENTS REVIEWED:	**Pharmacology/Toxicology Information**
REVIEW DIVISION:	**Division of Drug Oncology Products (HFD-150)**
PHARM/TOX REVIEWER:	**Haleh Saber-Mahloogi; Ph.D.**
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Date of review submission to Division File System (DFS): 10/28/05

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: There are no Pharmacology/Toxicology issues which preclude approval of the requested product indication.

B. Recommendation for nonclinical studies: None.

C. Recommendations on labeling: will be provided as a separate addendum review.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Based on the safety pharmacology studies, sorafenib has the potential to cause cardiac toxicity by blocking the K-channel and the Ca- inward channel, sensory neuropathy, and hypoglycemia.

Acute toxicity studies determined the GI tract and the liver to be primary target organs /tissues of toxicity. The following list outlines the primary product related toxicities considered biologically significant as observed in the repeat-dose toxicology studies:

- Skin: alopecia, pustules, red/blue spots on skin, atrophy/degeneration of hair follicles, acanthosis, dermatitis
- GI: vomiting, liquid feces, red/bloody feces, inflammation, hemorrhage/ necrosis
- Hematopoietic system: depletion/atrophy/cellular necrosis of lymphatic tissues; bone marrow hypocellularity; thymus and spleen atrophy, ↑iron deposition in spleen (possibly due to hemolytic anemia)
- Liver (hepato/hepatobiliary): ↑ALT, AST, GLDH, ALP, GGT; ↑cholesterol, ↓albumin, cirrhotic changes, liver hypertrophy, bile duct proliferation
- Kidneys: hypertrophy; glomerulopathy, tubular dialation, ↑urinary protein, ↑NAG, proteinaceous casts
- ♂ reproductive system: ↑weights of testes/prostate/epididymis; degeneration and tubular dilation of testes; oligospermia
- ♀ reproductive system: retardation of ovaries/ arrested follicular development, necrosis of corpora lutea
- Bone: incomplete epiphyseal closing; thickening of the growth plate (chondrodystrophy), ↑marrow fat (appears to be secondary to hypocellularity)
- Teeth: dentin alteration (in juvenile animals), osteodystrophy of jaw (rats only)
- Adrenal glands: necrosis and hemorrhage
- Thyroid and parathyroid: hypothyroidism (↓T3, ↓T4, ↑TSH), fibrosis of parathyroid, hypophosphatemia
- Pancreas: hypertrophy/ atrophy, degeneration/ regeneration, changes in serum alpha-amylase
- Heart: inflammation/ congestion, ↑CK (no findings in ECG, heart rate, blood pressure)
- Coagulation parameters: ↑or↓ platelets, ↑or↓ PT/aPTT

Although clear adverse cardiovascular effects were not seen in the dog telemetry studies (no relevant changes in the QTc intervals, blood pressure, and heart rate at toxic doses in the 52 week dog toxicology study), there is a high potential for cardiovascular toxicity, based on the limited histopathological findings in few toxicology studies, the positive finding in the in vitro hERG and action potential assays, the ↑CK in the chronic dog toxicity study, and the general knowledge on the family of compounds directly or indirectly targeting tyrosine kinase receptors, e.g. VEGF/R and EGF/R inhibitors.

The clinical data with sorafenib also demonstrated the potential for cardiovascular toxicity, e.g. hypertension (all grades 8% in sorafenib arm vs. <1% in the placebo arm). Although rare, cases of valvular disease and heart failure were reported as cause of death in the sorafenib arm.

Growth plate suppression, as was seen with sorafenib, is a characteristic of many receptor kinase inhibitors, including VEGFR, PDGFR, and FGFR inhibitors.

Sorafenib was genotoxic in the CHO chromosome aberration test, in the presence of S9. Sorafenib is teratogenic and can cause embryo-fetal toxicities at sub-therapeutic doses.

M-2 appears to be the major metabolite in human. Since the metabolic profile of rats and dogs differed from that in human, the sponsor conducted a 4-week toxicology study with M-2 metabolite in rats. The Ames test was also conducted with the M-2 metabolite. The M-2 metabolite appears to be an active metabolite, since the pattern of toxicity obtained with M-2 is similar to that observed with the parent compound. Treatment with M-2 resulted in ↓platelet counts, dentin alteration, ↑liver enzymes, and ↑adipocytes in bone marrow in the general toxicology study. The M-2 metabolite was not genotoxic in the Ames assay.

The main impurity [ ] was shown to be genotoxic in the Ames (+S9) assay.

Sorafenib can cross the blood-brain barrier. In addition, the single dose safety pharmacology revealed the potential for sorafenib to cause sensory neuropathy. Sensory neuropathy (mostly low grade) was observed in the Phase 2 clinical trial conducted with sorafenib.

In vitro data indicate that sorafenib is metabolized by CYP3A4 and UGT1A9 pathways. Sorafenib inhibits glucuronidation by the UGT1A1 (K_i = 1 μM) and UGT1A9 pathways (K_i = 2 μM). In clinical studies, when administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. Protein binding of sorafenib appears to be high: 0.5% in mouse, rat, and human, 0.9% in dogs, and 2% in rabbits. Sorafenib showed the potency to inhibit CYPs 2B6 and 2C8 (ki= 1-2 μM), and 2C9 (ki= 7-8 μM). The excretion in rats and dogs was mainly through the biliary/fecal route. The urinary route of excretion was minimal (1-3%) in rats and dogs. The urinary excretion appears to be more pronounced in human (about 20%).

B. Pharmacologic activity

Mechanism of action:

Sorafenib is a multi-kinase inhibitor. Sorafenib inhibited the following kinases (at nM concentrations): CRAF, BRAF, V600E BRAF, FLT-3, c-KIT, VEGFR2, VEGFR3, and PDGFR-β. Sorafenib did not inhibit the following kinases at concentrations as high as 10 μM: MEK-1, ERK-1, EGFR, HER2/neu, c-MET, PKA, PKB, IGFR-1Cdk-1/cyclinB, PIM-1, GSK3-b, CK-2, PKC-α, PKC-β, or PKC-γ.

Drug activity related to proposed indication:

RAS functions downstream of several receptor tyrosine kinases (RTKs), such as vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), and platelet-derived growth factor receptor (PDGFR) (1-3). Once in the active GTP-bound state, Ras interacts with several effector proteins such as Raf and phosphoinositide-3-kinase (PI-3 kinase). Activation of Raf will in turn result in the activation of MAP-kinase-kinase (MAPKK, MEK) and MAPK (ERK). These conserved signaling cascades are involved in cell survival and proliferation.

In several human cancers, the processes of tumor progression and metastasis are initiated by activation of RTKs and the signaling cascades. Therefore, receptor tyrosine kinases and proteins involved in their downstream events have been the target of several anticancer drugs (4).

The therapeutic target(s) of sorafenib in RCC remains unclear. BRAF mutations are found not to play an important role in renal cell tumors (5;6); however, overall activation of the signaling cascade (RAS/RAF/MEK pathway) has been observed (7;8).

Sorafenib was shown to have antitumor activity in several human tumor models, including antitumor activity in RENCA murine renal cell cancer model. Oral doses of 7.5 to 90 mg/kg/day in mice resulted in 30% to 84% tumor growth inhibition.

C. Nonclinical safety issues relevant to clinical use

All toxicities described above may be occurring in humans; hence the corresponding parameters need to be monitored. Special attention should be given to monitoring of cardiovascular toxicities. Several tyrosine kinase inhibitors have shown to cause DVT and cardiovascular toxicities. It should be noted that sorafenib can affect thyroid /parathyroid functions; indirectly increasing the potential to cause cardiovascular toxicities. In addition, cancer patients are prone to electrolyte imbalances, secondary to GI toxicity, which may in turn augment this toxicity.

Sorafenib can cross the placental barrier, is teratogenic at sub-therapeutic doses, and can be excreted in milk. Therefore women of childbearing potential should be advised to avoid becoming pregnant while taking sorafenib. Women should be advised to avoid breast-feeding while taking the drug.

There is a potential for sorafenib to inhibit CYPs 2B6, 2C8, and 2C9 as well as to inhibit glucuronidation by UGT1A1 and UGT1A9. Therefore systemic exposure to substrates of CYP2B6, CYP2C8, 2B9, UGT1A1 and UGT1A9 may increase when co-administered with sorafenib.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21,923
Review number: 1
Sequence number/date/type of submission: 000/April 29, 2005/original NDA CMA, Pilot 1

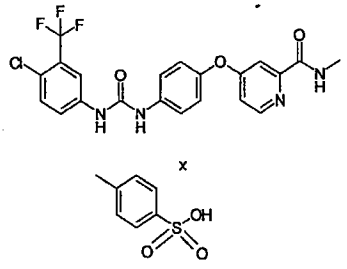
Information to sponsor:	Yes (X) No ( )
Sponsor and/or agent:	Bayer Pharmaceuticals Corporation 400 Morgan Lane West Haven, CT 06516
Manufacturer for drug substance:	Bayer HealthCare AG Friedrich-Ebert-Str.217-333 42117 Wuppertal Germany
Reviewer name:	Haleh Saber-Mahloogi, Ph.D.
Division name:	Division of Drug Oncology Products
HFD #:	150
Review completion date:	9/15/05

Drug:

Trade name:	Nexavar
Generic name:	Sorafenib tosylate
Code name:	BAY 54-9085 (Tosylate salt of BAY 43-9006)
Chemical name:	4-[4-[3-(4-Chloro-3-trifluoromethyl-phenyl)-ureido]-phenoxy]-pyridine-2-carboxylic acid methylamide-4-methylbenzenesulfonate
CAS registry number:	BAY 54-9085 (tosylate salt): 475207-59-1 BAY 43-9006 (free base): 28844-1-73-01

Molecular formula/molecular weight: $C_{21}H_{16}ClF_3N_4O_3 \cdot C_7H_8O_3S$/ 637

Structure:



Relevant INDs/NDAs/DMFs: IND 60,453

Drug class: Multi-kinase inhibitor; originally designed as a RAF kinase inhibitor

Intended clinical population: advanced renal cell carcinoma

Clinical formulation: 200 mg tablet
Inactive Ingredients, Tablet Core: croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulfate and magnesium stearate
Tablet Coating: hypromellose, polyethylene glycol, titanium dioxide and ferric oxide red

Route of administration: Oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise. Parts of this review are excerpted directly from the NDA package and parts are excerpted from Dr. Lilliam A. Rosario's review of the studies submitted with IND 60,453 (reviews 1-5).

Studies reviewed within this submission: see Table below
In addition to the study reports listed below the following article, published by Bayer, was also reviewed.

Pharmacology
Wilhelm SM et al.
Bay 43-9006 exhibits broad spectrum oral antitumor activity and targets the RF/MEK/ERK pathway and receptor tyrosine kinases involved in tumor progression and angiogenesis.
Cancer Research 2004; 64: 7099-7109

Studies not reviewed within this submission: see Table below

Title	Report #	Review	
		Yes	No
PHARMACOLOGY			
In Vivo Activity of the Raf Kinase Inhibitor BAY 43- 9006 in Human Tumor Xenograft Models.	MRC-01019	X	
Efficacy of Repeated Cycles of Therapy with BAY 54- 9085 Against DLD- 1 Human Colon Tumor Xenograft	MRC-01203		X
Anticancer Efficacy of BAY 43- 9006 Against a Murine Renal Adenocarcinoma (Renca)	MRC-01271	X	
Response of SC A498 Renal to Treatment with BAY 54-9085	RMI-00118		X
Response of SC CAKI- 1 Renal Tumor to Treatment BAY 54- 9085	RMI-00119		X
Response of SC LOX IMVI melanoma to treatment with BAY 54- 9085 (SRI Study BAY-30)	RMI-00120		X
Response of SC LOX IMVI melanoma to treatment with BAY 54- 9085 (SRI Study BAY-34)	RMI-00121		X
Evaluation of the Anti- tumor Efficacy of BAY 54- 9085 or Cisplatin Against Subcutaneously Implanted NCI- H23 Human NSCLC Tumor Xenografts	RMI-00091		X
BAY 43- 9006 Exhibits Broad Spectrum Oral Anti- tumor Activity and	MRC- 01264	X	

Title	Report #	Review	
		Yes	No
Targets the RAF/ MEK/ ERK Pathway and Receptor Tyrosine Kinases Involved in Tumor Progression and Angiogenesis			
BAY 43- 9006 is a potent inhibitor of FLT3 tyrosine kinase	MRC- 01276-		X
Analysis of changes in protein phosphorylation levels in human melanoma cell line LOX treated with BAY 43- 9006 in vitro	MRC- 01275		X
Phosphoproteomic analysis of MDA- MB- 231 human breast tumor xenografts after treatment with BAY 43- 9006	MRC- 01274		X
Activity of BAY 43- 9006 and Its Major Metabolites: In Vitro Kinase and Cellular Signaling Assays	MRC- 01279		X
Proquinase and DCAR In Vitro Kinase Data for BAY 43- 9006 and Its Major Metabolites	MRC-01273		X
Anti- tumor efficacy of BAY 67- 3472, a major metabolite of BAY 43- 9006 against MDA- MB- 231 human mammary tumor xenografts in NCr mice	MRC-01272		X
SAFETY PHARMACOLOGY			
Influence of Haemodynamics, ECG and Respiration in Anaesthetized Dogs after Single Intraduodenal Administration Study no. T 1065145	PH-30073	X	
BAY 54- 9085: Plasma Concentrations of BAY 43- 9006 From a Cardiovascular Safety Study in Dogs Dosed with BAY 54- 9085 [T1065145: RS013]	MRC-1054	X	
Effects of a single oral administration of BAY 54- 9085 on the central nervous system of rats (Study T 4065148)	PH-29497	X	
Effect of a single oral administration of BAY 54- 9085 on the behavioral and physiological state of rats (Study T 8065151)	PH-29507	X	
Effect of a single oral administration of BAY 54- 9085 on diuresis and blood pharmacological parameters of rats (Study T 2065146)	PH-29405	X	
Effect of a single oral administration of BAY 54- 9085 on blood glucose of fasted and fed rats (Study T 3065147)	PH-29451	X	
Effects of a single oral administration of BAY 54- 9085 on the intestinal charcoal transit in rats (Study T 5065149)	PH-29498	X	
Effects of BAY 54- 9085 on the contractility of the isolated guinea pig ileum (Study T 7065150)	PH-29499		X
Electrophysiological examination of the effect of BAY 54- 9085 on the HERG- mediated potassium current (Study No. T 2064589)	R-8318	X	
Effects of BAY 54-9085 (BAY 43- 9006 tosylate) on the action potential of isolated rabbit cardiac Purkinje fibers (Study No. T 0063119)	PH-32907	X	
PHARMACODYNAMIC DRUG INTERACTIONS			
Combination Chemotherapy of the Mia- PaCa- 2 Human Pancreatic Tumor Xenograft with BAY 54- 9085 and Gemzar	MRC-01138		X
Combination Chemotherapy of the DLD- 1 Human Colon Tumor Xenograft with BAY 54- 9085 and Camptosar and Efudex	MRC-01139		X
Combination Chemotherapy of Human Tumor Xenographs with BAY 54- 9085 and ZD1839 (Iressa)	MRC-01195		X
Evaluation of the Sequence Dependency of the Anti- tumor Efficacy of Combinations of BAY 43- 9006 and Paclitaxel Against Subcutaneously Implanted NCI- H460 NSCLC Tumor Xenografts	RMI-00083		X
Evaluation of the Anti- tumor Efficacy of a Combination of Reduced Dosage BAY 43- 9006 and Paclitaxel Against Subcutaneously Implanted NCI- H460 NSCLC Tumor Xenografts	RMI-00084		X
Evaluation of the Sequence Dependency of the Anti- tumor Efficacy of Combinations of BAY 43- 9006 and Paclitaxel Against Subcutaneously Implanted MX- 1 Mammary Tumor Xenografts	RMI-00085		X

Title	Report #	Review	
		Yes	No
Anti- tumor Efficay of BAY 54- 9085 Plus Cisplatin as Combination Chemotherapy Against Subcutaneously Implanted NCI- H23 Human NSCLC Tumor Xenographs	RMI-00092		X
Combination Chemotherapy of the MX- 1 Human Mammary Tumor and NCI- H460 Non- small Cell Lung Tumor Xenografts with BAY 54- 9085 and Doxorubicin	MRC-01169		X
Effect of Combination Therapy of the Raf Kinase Inhibitor, BAY 54- 9085, Plus Doxorubicin on Tolerance and PK in Non- tumor- bearing Mice	MRC-01230		X
Response of SC MX- 1 Mammary Tumor to Combination Treatment with BAY 54- 9085 and Doxorubicin (— Study BAY- 23)	RMI-00122		X
PHARMACOKINETICS			
Analytical methods and validation			
BAY 43- 9006: Bioanalytical methods and validation for preclinical and toxicokinetic studies	PH-33484		X
BAY 43-9006: Cross Validation of the Bioanalytical Method with Plasma Samples obtained from the 1-Year Chronic Toxicity Study in Beagle Dogs Study No.: T 9071362	PH-33311		X
Radiosyntheses of [14C]BAY 43- 9006 and [14C]BAY 54-9085	PH-29431		X
Synthesis of [2H39 15N]BAY 43- 9006 and [2H39 15N]BAY 54-9085	PH-29433		X
Analytical Method and Validation Report for the Determination of BAY 43-9006 Concentrations in Rat and Dog Plasma using [ ] (MD0026)	MRC-01079		X
BAY 43- 9006: Labeling syntheses of the metabolites M- 2 (BAY 67-3472) and M-3 (BAY 72- 1973) of BAY 43- 9006 with stable isotopes	PH-33302		X
Labeling synthesis of BAY 67- 3472, the N- oxide of BAY 43- 9006, with carbon-14	PH-33090		X
Absorption			
[14C]BAY 54- 9085: Pharmacokinetics in Female CD 1 Mice Following Intravenous and Oral Administration (PDM E310)	MRC-01034	X	
[14C] BAY 54-9085: Pharmacokinetics and Mass Balance in Male Wistar Rats Following Intravenous and Oral Administration (PDM E245)	MRC-01014	X	
[14C] BAY 54-9085: Pharmacokinetics and Mass Balance in Female Beagle Dogs Following Intravenous and Oral Administration (PDM E261)	MRC-01051	X	
BAY 43- 9006 (Sorafenib) Absorption and Excretion of the Radioactivity in Male Bile Duct- Cannulated Wistar Rats after Single Administration of [14C]BAY 54- 9085. Study No.: I 6001636, I 6001762	PH-33474	X	
Distribution			
Plasma and Tumor Exposure of the Raf Kinase Inhibitor, BAY 43-9006, in Tumor- bearing NCr Mice	MRC-01267		X
BAY 43- 9006: Quantitative Whole- body Autoradiography. Distribution of Radioactivity and Elimination from Blood, Organs and Tissues and Fetuses after Single Oral Administration to Pregnant Wistar Rats of [14C]BAY 54-9085. Study No.: I 8001700	PH-33343	X	
[14C]BAY 54- 9085 (Tosylate of [14C] BAY 43- 9006): Whole- body Autoradiography in Rats After Single Intravenous and Oral Administration. Study- No. I 8001287	PH-30643	X	
BAY 43- 9006: Investigation of the Stability in Plasma, Binding to Plasma Proteins, Reversibility of Binding, and Erythrocyte/ Plasma Partitioning of BAY 43- 9006 using [14C]BAY 54- 9085 in Vitro	PH-33358		X
BAY 43- 9006 (Sorafenib): Extended Investigation of the Binding to Plasma Proteins and Interaction Studies of BAY 43-9006 using [14C]BAY 54-9085 in Human Plasma in Vitro	PH-33412		X

Title	Report #	Review	
		Yes	No
Quantitative Whole- body Autoradiography. Distrib of Radioactivity & Elimination from Blood, Organs & Tissues after Single Oral Admin to Male Wistar Rats & pigmented Long Evans rats of [14C]BAY 54- 9085 (tosylate salt of [14C]BAY 43- 9006). Study No.: I 8001548	PH-32654		X
***Metabolism**			
BAY 43- 9006: Lack of Interaction of BAY 43- 9006 with Human Dihydropyrimidine Dehydrogenase In Vitro	PH-33287		X
BAY 43- 9006: Evaluation of the CYP Induction Potential of BAY 43-9006 in Cultured Human Hepatocytes	PH-33323		X
[14C]BAY 43- 9006: Biotransformation in Man	PH-33427		X
BAY 43- 9006: Determination of the Inhibitory Potency of BAY 43- 9006 Towards Human UDPglucuronosyltransferases (UGTs)	PH-33798		X
[14C]BAY 43- 9006: Biotransformation in Rats	PH-33292		X
BAY 43- 9006: Determination of the Inhibitory Potency Towards Human CYP1A2, 2C8, 2C9, 2D6 and 3A4	PH-33400		X
[14C]BAY 43- 9006: Glucuronidation of BAY 43- 9006 In Vitro	PH-33504		X
BAY 43- 9006: Determination of the inhibitory potency of BAY 54- 9085 (Tosylate of BAY 43- 9006) towards human CYP isoforms	PH-30285		X
BAY 43-9006 - Incubation of [14C]BAY 54- 9085 with Liver Microsomes of Different Species Including Man - Elucidation of the Most Human like Animal	PH-32439		X
[14C] BAY 43- 9006: Biotransformation in Hepatocytes from Rat and Man	PH-33059		X
[14C] BAY 43- 9006: Biotransformation in Dogs	PH-33063		X
BAY 43- 9006: Inhibition of cytochromes P4501A2, P4502C8, P4502C9, P4502D6, and P4503A4 catalytic activity by the test substance 54-9085 (Tosylate of BAY 43- 9006): Determination of Ki values	R-7864		X
Examination of the Time- and NADPH- Dependent Inactivation of CYP2C9, CYP2D6, CYP3A4 by BAY 54- 9085	RMI-00096		X
Identification of Human CYP Isoforms involved in the In Vitro Metabolism of BAY 43- 9006	PH-31789		X
BAY 43- 9006: In Vitro Metabolic Stability in Mouse, Rat, Dog and Human Hepatic Mircrosomes [D177]	MRC-01031	X	
Excretion			
BAY 43- 9006 Secretion of Radioactivity into Milk of Lactating Rats after Single Oral Administration of [14C]BAY 54- 9085 Study No.: I 4001689	PH-33190	X	
Other Pharmacokinetic Studies			
[14C] BAY 43- 9006: Metabolic Pattern in Plasma following Oral Administration of [14C] BAY 67- 3472 (M-2) to Male Wistar Rats	PH-33215		X
BAY 43- 9006: Determination of the Inhibitory Potency of Metabolite M- 2 (BAY 67- 3472) Towards Human CYP Isoforms	PH-3331		X
BAY 43- 9006 (Sorafenib): Investigation of the Stability in Plasma, Binding to Plasma Proteins, Reversibility of Binding, and Erythrocyte/ Plasma Partitioning of BAY 67- 3472 (M- 2 of BAY 43- 9006) using [14C]BAY 67- 3472 in Vitro	PH-33442		X
TOXICOLOGY			
Single-dose			
Bay 54- 9085. Acute Toxicity in the mouse and rat after oral administration (Study T 9069220 and T5069226)	PH-29961	X	
A single oral dose Pharmacokinetic/ tolerance study of BAY 54-9085 in the Beagle dog	RMI-00069	X	
A Single Oral Dose Pharmacokinetic/ Tolerance Study of BAY 54-9085	RMI-00070	X	

Title	Report #	Review	
		Yes	No
(Powder and Solution) in the Beagle dog			
Repeat-dose			
BAY 54- 9085: Subacute toxicity study in rats after oral administration (gavage) for 4 weeks (including 4 weeks recovery)	PH-30261	X	
BAY 54- 9085: Plasma Concentrations of BAY 43- 9006 from a 4- Week Toxicity Study in Rats Dosed with BAY 54- 9085 [T3068937; RS010]	MRC-01052	X	
BAY 43- 9006 Tosylate Salt (BAY 54- 9085): A Subchronic Toxicity Testing Study in the Rat	MRC-01249	X	
BAY 54- 9085: Plasma Concentrations of BAY 43- 9006 from a 13- Week Toxicity Study in Rats Dosed with BAY 54- 9085 [00S12- SV; RS025]	MRC-01124		X
BAY 54- 9085 Project: BAY 43- 9006. Study on Chronic Toxicity in Wistar rats. Administration by Gavage over 6 Months For up to 191 Days. Study No. T 5071052	PH-32607	X	
BAY 54- 9085 Project: BAY 43- 9006 Study on Chronic Toxicity in Wistar Rats Administration by Gavage over 6 Months For up to 191 Days	PH-32607A		X
§BAY 54- 9085: Plasma Concentrations of BAY 43- 9006 from a 6- Month Toxicity Study in Rats Dosed with BAY 54- 9085 [T5071052; RS033]	MRC-01165	X	
BAY 54- 9085 Subacute toxicity study in Beagle dogs (4 week gavage study + 4 week recovery period) [Study No.: T 3069071]	PH-30221	X	
BAY 54- 9085: Plasma Concentrations of BAY 43- 9006 from a 4- Week Toxicity Study in Dogs Dosed with BAY 54- 9085 [T3069071; RS011]	MRC-01053	X	
BAY 54- 9085 (Tosylate salt of BAY 43- 9006) Subchronic toxicity study in beagle dogs (13 week gavage study)	PH-31490	X	
BAY 54- 9085: Plasma Concentrations of BAY 43- 9006 from a 13-Week Toxicity Study in Dogs Dosed with BAY 54- 9085 [T7069994; RS024]	MRC-01121		X
BAY 54- 9085: Chronic toxicity study in Beagle dogs. (52 Weeks Administration by Gavage) Study No. T 9071362	PH-33532	X	
§BAY 54- 9085: Plasma Concentrations of BAY 43- 9006 from Weeks 1 and 18 of a 12- Month Toxicity Study in Dogs Dosed with BAY 54- 9085 [T9071362; RS043]	MRC-01181	X	
§BAY 43- 9006 Plasma Concentrations of BAY 43- 9006 and of the Metabolites M- 1, M- 2, M- 3, M- 4 and M- 5 in a 52 Weeks Oral Toxicity Study on Beagle Dogs Dosed with BAY 54- 9085 [T9071362]	PH-33306	X	
BAY 54- 9085: Plasma Concentrations of BAY 43- 9006 from a 6- Month Toxicity Study in Rats Dosed with BAY 54- 9085 [T 5071052; RS033]	MRC-01165A		X
GENOTOXICITY			
BAY 54- 9085 Salmonella/ Microsome test plate incorporation and preincubation method (Study No.: T 7068427)	PH-29467	X	
BAY 54- 9085 In Vitro Chromosome Aberration Test with Chinese Hamster V79 Cells Study No.: T 8068851	PH-29598	X	
BAY 54- 9085 Micronucleus- test on the male mouse (Study No.: T 9068429)	PH-29474	X	
REPRODUCTIVE AND DEVELOPMENTAL TOXICITY (Embryo-Fetal Development)			
BAY 54- 9085(Tosylate Salt of BAY 43- 9006): Developmental Toxicity Study in Rats after Oral Administration. Study Number: T 0063010)	PH-33514	X	
BAY 54- 9085 (Tosylate Salt of BAY 43- 9006): Developmental Toxicity Study in Rabbits after Oral Administration. Study Number: T4063177	PH-33531	X	
LOCAL TOLERANCE			
BAY 43- 9006 Acute Skin Irritation/ Corrosion on Rabbits (Study No.: T 6074393)	PH-33574		X
BAY 43- 9006 Acute Eye Irritation on Rabbits (Study No.: T7074394)	PH-33613		X

Title	Report #	Review	
		Yes	No
BAY 43- 9006 Local Lymph Node Assay in Mice (LLNA/ IMDS) Study No.: T 6074159	PH-33608		X
OTHER TXICITY STUDIES			
Mechanistic Studies			
BAY 54- 9085. Subacute toxicity study in Beagle dogs (4 week gavage study). Study No. T0069663	PH-31108		X
BAY 54- 9085: Plasma Concentrations of BAY 43- 9006 from a 4- Week Toxicity Study in Female Dogs Dosed with BAY 54- 9085 [T0069663; RS015]	MRC-01101		X
BAY 54- 9085 (BAY 43- 9006 tosylate). Subacute Oral Toxicity Study in Female Wistar Rats (2- weeks Admin. by Gavage). Special Study to Investigate Potential Effects on the Pancreas, Amylase and Lipase Activity. Study No.: T 807373738	PH-33039		X
Metabolites			
BAY 67- 3472 project BAY 43- 9006 Salmonella/ Microsome Test Plate Incorporation and Preincubation Method Study No.: T 0073226	PH-33299	X	
BAY 67- 3472 (Project BAY 43- 9006) Subacute Oral Toxicity Study in Rats (4- Weeks Administration by Gavage) Study No.: T 2073903	PH-33534		X
Impurities			
[ ] Salmonella/ Microsome Test Plate Incorporation Method Study No.: T 6070883	PH-31850	X	
[ ] (Project BAY 43- 0006) Subacute oral toxicity study in rats (4 weeks administration by gavage) (Study No.: T 5071124)	PH-33379		X
[ ] Salmonella/ Microsome Test Plate Incorporation Method Study No.: T 7074286	PH-33614	X	
Other			
BAY 54- 9085 (Tosylate Salt of BAY 43- 9006) Study on Subchronic Toxicity in CD- 1 Mice. Administration by Gavage for 3 Months (Project BAY 43- 9006) Study No. T5071881	PH-32953		X
Pharmacokinetics/ Tolerance of BAY 54- 9085 Following Mulitple Administrations to Female Sprague- Dawley Rats	RMI-00067	X	
BAY 54- 9085: 7- Day Toxicokinetics of BAY 43- 9006 in Female Rats after Oral Administration of BAY 54- 9085 [E144]	MRC-01032	X	
A 7- Day Oral Dose Pharmacokinetic/ Tolerance Study of BAY 54- 9085 in the Beagle Dog	RMI-00068	X	
BAY 54- 9085 7- Day Toxicokinetics of BAY 43- 9006 in Dogs after Oral Administration of BAY 54- 9085 [E270, E290]	MRC-01033	X	

* Summary of the studies is reported in this review.
§ Reviews of the studies are under the corresponding toxicology studies.

2.6.2 PHARMACOLOGY

2.6.2.1 Recommendations on labeling

Recommendations on labeling will be provided as a separate addendum review.

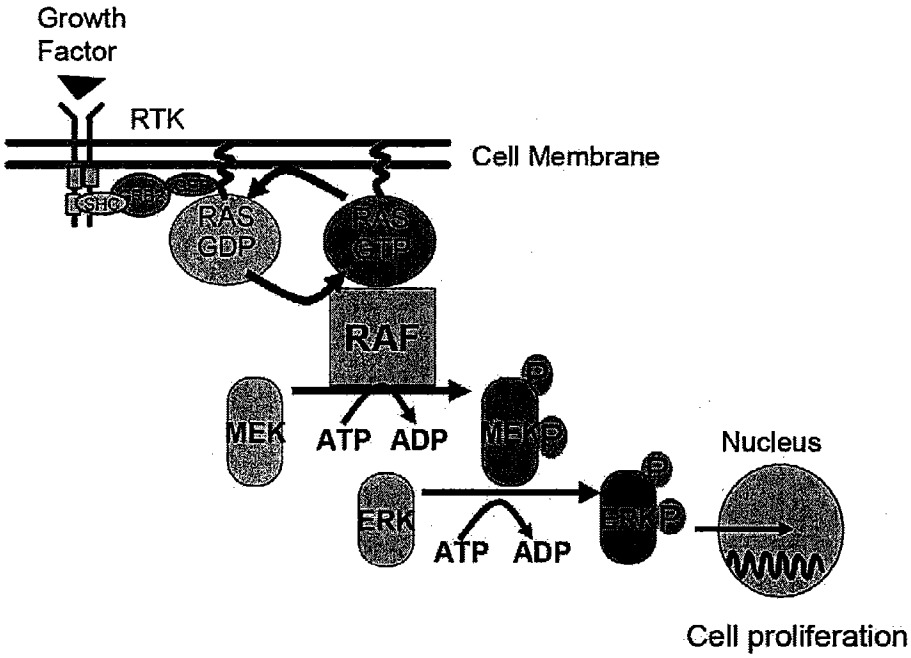
2.6.2.2. Pharmacology of sorafenib

RAS functions downstream of several receptor tyrosine kinases (RTKs), such as vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), and platelet-derived growth factor receptor (PDGFR) (9-11). Once in the active GTP-bound state, Ras interacts with several effector proteins such as Raf and phosphoinositide-3-kinase (PI-3

kinase). Activation of Raf will in turn result in the activation of MAP-kinase-kinase (MAPKK, MEK) and MAPK (ERK). These conserved signaling cascades are involved in cell survival and proliferation.

Raf kinases are serine/threonine protein kinases that exist as 3 isoforms, ARaf, BRaf, and CRaf (or Raf-1) in mammalian cells with different tissue distribution (12;13).

In several human cancers, the processes of tumor progression and metastasis are initiated by activation of RTKs and the signaling cascades. Therefore, receptor tyrosine kinases and proteins involved in their downstream events have been the target of anticancer drugs (14).



Schema provided by the sponsor

Sorafenib was initially developed as CRAF kinase inhibitor. However, it was later shown that sorafenib could inhibit other kinases as well (15). Table below demonstrates that sorafenib potently inhibits wild- type CRAF, BRAF and mutant V600E BRAF (MRC-01264, previously identified as V599E BRAF (16)). Sorafenib is also a potent inhibitor of several RTKs linked to tumor progression, including FLT- 3, c- KIT, VEGFR2, VEGFR3, and PDGFR- ß (17). IC50s for these kinases are in the nM ranges.

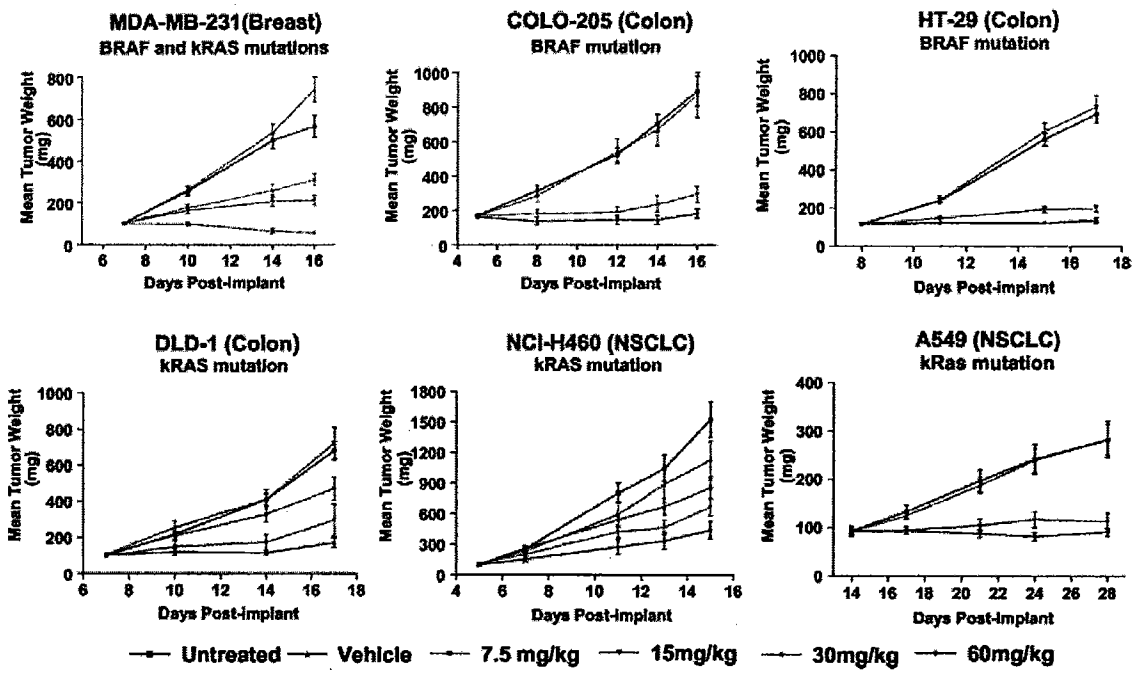
Summary of the in vitro profile of sorafenib

Biochemical Assay [a]	IC50 (nM)
CRAF [b]	6
BRAF wild-type	22
BRAF V600E mutant	38
VEGFR2	90
mVEGFR2	15
mVEGFR3	20
mPDGFR-β	57
FLT3	58
c-KIT	68
FGFR1	580
Cellular Mechanism [c]	**IC50 (nM)**
MDA MB 231 MEK phosphorylation (Human Breast)	40
MDA MB 231 ERK phosphorylation (Human Breast)	90
BxPC-3 ERK phosphorylation (Human Pancreatic)	1200
LOX ERK phosphorylation (Human Melanoma)	880
VEGFR-2 receptor phosphorylation (Human, 3T3 cells)[d]	30
VEGF-stimulated ERK phosphorylation (HUVECs)[e]	60
BFGF-stimulated ERK phosphorylation (HUVECs)	620
MVEGFR-3 receptor phosphorylation (Mouse, 293 cells)	100
PDGFR-β phosphorylation (HAoSMC)[f]	80
FLT-3 receptor phosphorylation (Human ITD, 293 cells)	20
Cellular Proliferation	**IC50 (nM)**
MDA MB 231 (10% FCS) [g]	2600
PDGFR-β-stimulated HAoSMC [f] (0.1% BSA) [h]	220

a Recombinant enzyme assay
b Raf kinase activated with Lck (full length CRAF)
c Mechanistic cellular assays all performed in 0.1% BSA
d Western blot assay format with Phospho-VEGFR-2 antibody
e Human umbilical vein endothelial cells
f Human aortic smooth muscle cells
g Fetal calf serum
h Bovine serum albumin

Table provided by the sponsor.

Sorafenib showed antitumor activity in several xenograft models. Mice bearing 75 to 150 mg tumors were treated orally with BAY 43-9006 at dose levels of 7.5 to 60 mg/kg (22.5 to 180 mg/m^2), daily for 9 days. Tumor growth inhibition was observed in several human tumor models tested, including: breast, colon, and non-small cell lung carcinoma (see graphs below) (18).



Graphs provided by the sponsor.

Study Title: In Vivo Activity of the Raf Kinase Inhibitor BAY 43- 9006 in Human Tumor Xenograft Models

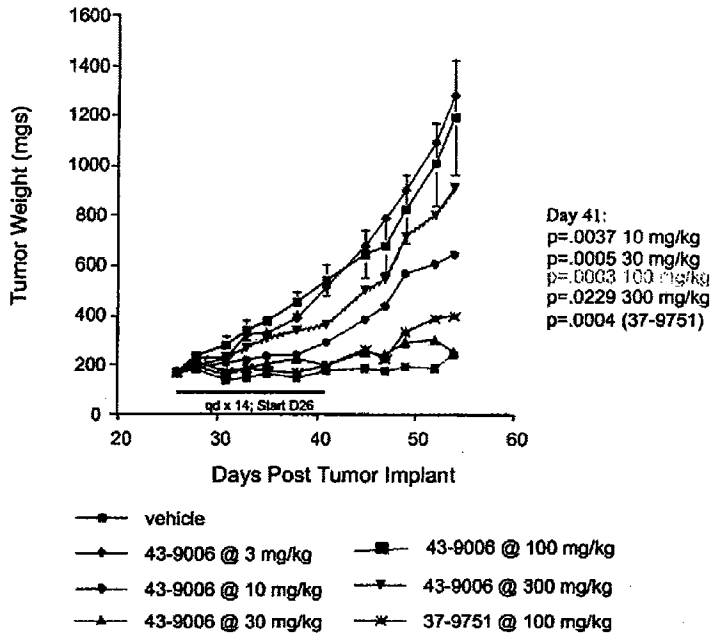
Report# MRC-01019

Study design

The Antitumor activity of sorafenib was tested in the following human tumor s.c. xenograft models: HCT116 colon, MiaPaCa pancreatic, H460 lung, and SKOV-3 ovarian. Fragments from donor SC tumors were implanted SC into recipient female CD-1 nude mice. Tumors were allowed to grow to an approximate size of 150 mgs as determined by caliper measurements and the formula L X [W X W)/ 2 = tumor weight in mgs. At this point the animals were randomized into groups with mean tumor sizes differing by no more than 10%, and dosing was initiated. Dosing in early studies was performed IV, but in the majority of the studies was performed PO. Dosing continued daily for 14 days.

Results

In HCT 116 human colon cell line, BAY 43-9006 significantly inhibited tumor growth in a dose-dependent manner when dosed at 10-100 mg/kg for 14 days (Study Days 26-40). At the highest dose tested, 300 mg/kg, animals had reduced exposure to the test article. This finding was said to be due to poor solubility of the test article in the ethanol/cremophor vehicle; however, saturation of absorption cannot be excluded.



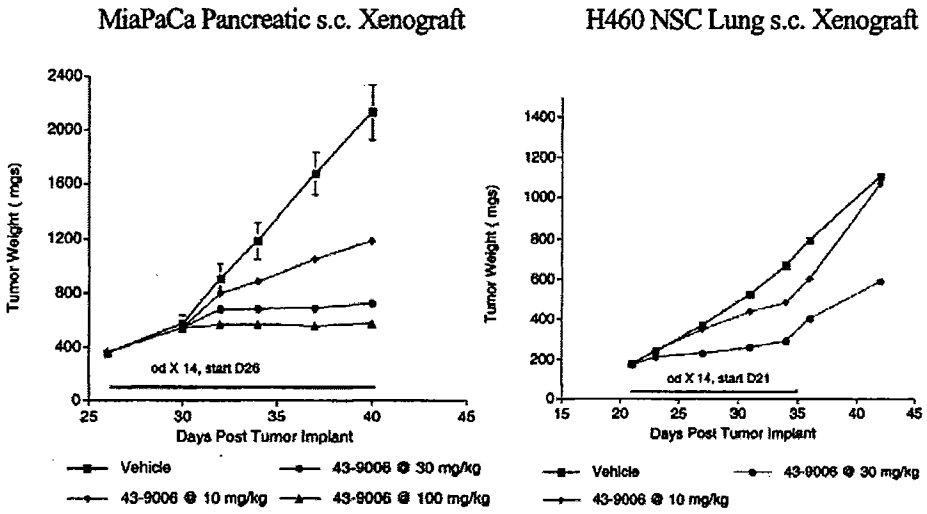
: Inhibition of HCT 116 Tumor Growth by BAY 43-9006

Graph provided by the sponsor

BAY 43-9006 (mg/kg)	% inhibition
10	45
30	64
100	68
300	33*

*The reduced effect at the highest dose appeared to be due to poor absorption from the suspension. BAY 43-9006 was not soluble in ethanol/cremaphor EL 50:50 vehicle above 100 mg/kg

In MIA PaCa-2 and H460 Tumor Models with K-ras mutations, BAY 43-9006 inhibited the growth of subcutaneously implanted MIA PaCa-2 (pancreatic carcinoma) or H460 (non-small cell lung carcinoma) xenografts.



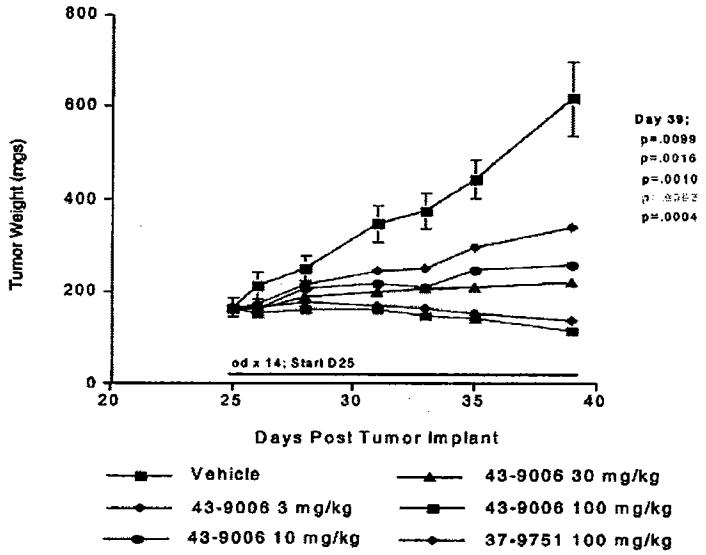
Activity of BAY 43-9006 Against K ras Mutant Human Xenografts

Graphs provided by the sponsor

BAY 43-9006 (mg/kg)	% Inhibition	
	*PaCa-2**	*H460*
10	45	27
30	66	56*
100	73	NA

* Statistically significant
NA: not available; the highest dose of test article tested in the H460 model was 30 mg/kg

BAY 43-9006 exhibited anti tumor activity against human SKOV-3 xenografts with 14 days of treatment. SKOV-3 is an ovarian tumor cell line with wild-type Ras and overexpressing EGF and Her2 receptors, which are known to signal through Ras/Raf/MEK pathway.



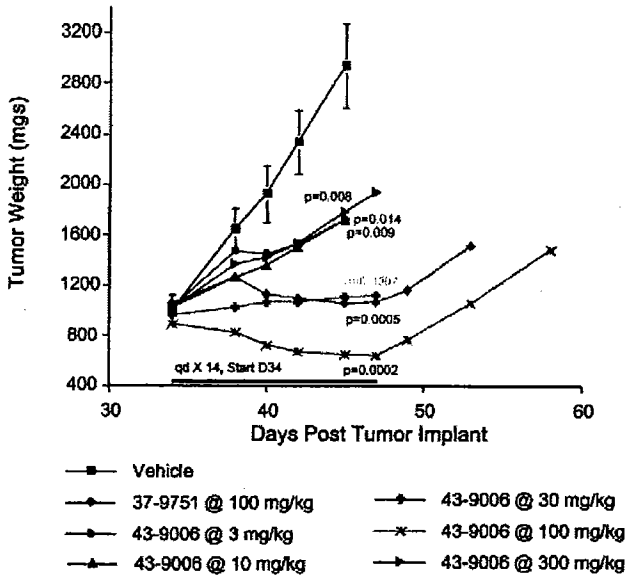
: **Activity of BAY 43-9006 Against Human Ovarian SKOV-3 SC Xenograft**

Graph provided by the sponsor

BAY 43-9006 (mg/kg)	% inhibition*
3	45
10	58
30	64
100	81

* Statistically significant

BAY 43-9006 was tested for activity in the HCT 116 human colon model where the initial pre-treatment size of the tumors was approximately 1 gram. Mice were dosed daily, p.o., for 14 days.



Activity Against HCT 116 SC Tumors with a Larger Starting Size

Graph provided by the sponsor

BAY 43-9006 (mg/kg)	% inhibition
3	41
30	63
100	78

Summary

BAY 43-9006 demonstrated activity in colon, pancreatic, lung, and ovarian tumor types. This activity appeared to be cytostatic in nature when dosing occurred for 14 days.

The anti-tumor activity of BAY 43-9006 appeared to be dose-dependent at doses up to 100 mg/kg.

Study Title: Anticancer Efficacy of BAY 43- 9006 Against a Murine Renal Adenocarcinoma (Renca)

Report # MRC-01271

Study design

Female athymic mice (NCr- *nu/ nu*) were implanted s. c. with Renca cells. Treatment was initiated on Day 4 when all animals had tumors averaging 50 mg. BAY 43-9006 (or vehicle) was administered orally once a day for 8- 9 days at dose levels of 7.5, 15, 30, 60, or 90 or mg/kg. Toxicity was assessed as net body weight loss and/ or lethality. Efficacy was assessed as the ratio of the mean final tumor mass of the test article-treated animals to that of the control groups. Two separate experiments were conducted.

Vehicle: Cremophor EL/ Ethanol/ water (12.5: 12.5: 75)

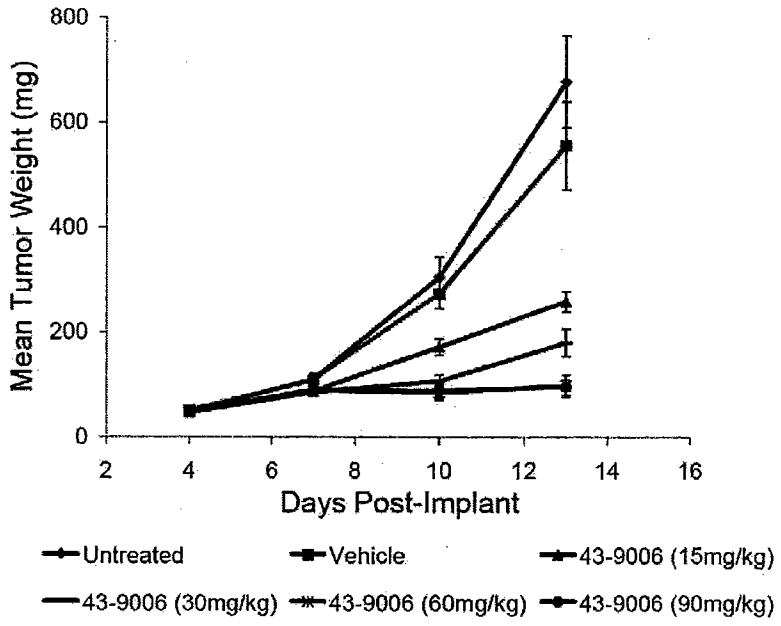
Results

Body weight loss was 7% -11%.

Tumor growth inhibition (TGI) ranged from 30% at 7.5 mg/kg to 84% at 60 or 90 mg/kg of BAY 43-9006. It should be noted that TGI was less than dose proportional as the dose was increased from 15 mg/kg to 90 mg/kg, suggesting saturation of anti-tumor activity. Since pharmacokinetic data were not submitted, it is not clear whether the non-proportional increase in the anti-tumor activity was due to a non-proportional increase in the BAY 43-9006 exposure.

BAY 43-9006 (mg/kg/dose)[a]	Percent TGI ((1-T/C)*100) Expt. 1 (qd x 9)	Percent Gross Body Weight Loss Expt. 1 (qd x 9)	Percent TGI ((1-T/C)*100) Expt. 2 (qd x 8)	Percent Gross Body Weight Loss Expt. 2 (qd x 8)
Control		11		7
Vehicle	18	11	-1	10
7.5	ND	ND	30	8
15	53	12	61	8
30	68	10	70	7
60	82	14	84	6
90	83	11	84	5

TGI: tumor growth inhibition



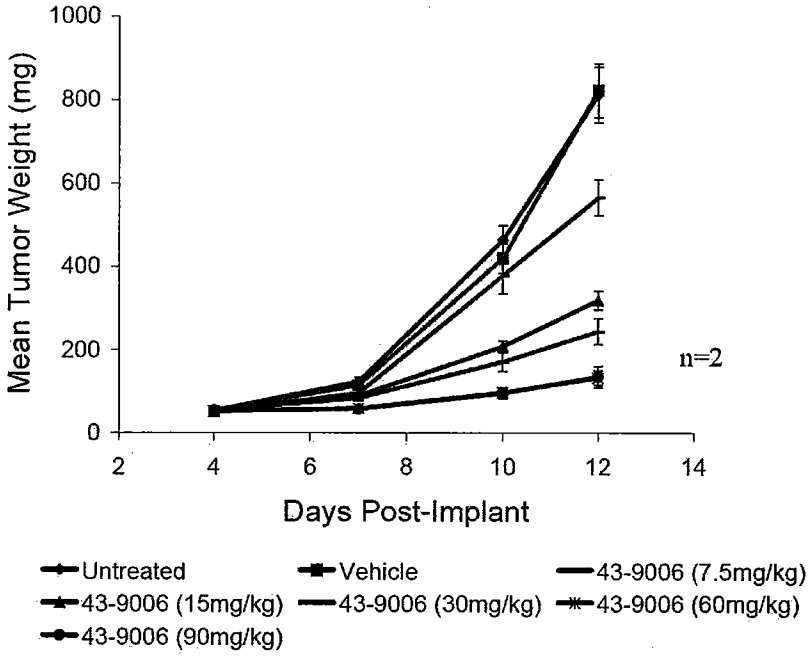


Table and graphs provided by the sponsor

Response of the murine renal cell carcinoma, Renca, to treatment with BAY 43-9006

Summary
BAY 43-9006 exhibited anti-tumor activity against the murine renal cell cancer model (Renca), when dosed orally for 8 or 9 days. Tumor growth inhibitions ranged from 30% to 84%, were non-dose-proportional from 15 to 90 mg/kg BAY 43-9006 and reached saturation at 60 mg/kg.

2.6.2.3 Primary pharmacodynamics

Mechanism of action:
Sorafenib is a multi-kinase inhibitor. Sorafenib can potently inhibit the following kinases (at nM concentrations):
CRAF, BRAF, V600E BRAF, FLT-3, c-KIT, VEGFR2, VEGFR3, and PDGFR-β

Sorafenib did not inhibit the following kinases at concentrations as high as 10 μM:
MEK-1, ERK-1, EGFR, HER2/neu, c-MET, PKA, PKB, IGFR-1Cdk-1/cyclinB, PIM-1, GSK3-b, CK-2, PKC-α, PKC-β, or PKC-γ.

Drug activity related to proposed indication:
RAS functions downstream of several receptor tyrosine kinases (RTKs), such as vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor (EGFR), and platelet-derived growth factor receptor (PDGFR) (19-21). Once in the active GTP-bound state, Ras interacts with several effector proteins such as Raf and phosphoinositide-3-kinase (PI-3

kinase). Activation of Raf will in turn result in the activation of MAP-kinase-kinase (MAPKK, MEK) and MAPK (ERK). These conserved signaling cascades are involved in cell survival and proliferation.

In several human cancers, the processes of tumor progression and metastasis are initiated by activation of RTKs and the signaling cascades. Therefore, receptor tyrosine kinases and proteins involved in their downstream events have been the target of several anticancer drugs (22).

The therapeutic target(s) of sorafenib in RCC remains unclear. BRAF mutations are found not to play an important role in renal cell tumors (23;24); however, overall activation of the signaling cascade (RAS/RAF/MEK pathway) has been observed (25;26).

Sorafenib was shown to have antitumor activity in several human tumor models. Additionally, sorafenib had antitumor activity in RENCA murine renal cell cancer model (M.4.2.1.1.3, MRC-01271). Oral doses of 7.5 to 90 mg/kg/day resulted in 30% to 84% tumor growth inhibition.

2.6.2.3 Secondary pharmacodynamics
Not evaluated

2.6.2.4 Safety pharmacology

Effect of a single oral administration of BAY 54-9085 on diuresis and blood pharmacological parameters of rats. A GLP/QA study conducted by BAYER AG, Wuppertal-Elberfeld

Report # PH-29405
Study # T 2065146

BAY 54-9085 was administered orally to rats at doses of 30, 100, and 300 mg/kg. Control animals received the vehicle (Pluronic F68/PEG400/propylene glycol-15.4:42.3:42.3% w/w/w). Urine was sampled for two hours, starting immediately after dosing. Thereafter, blood was collected from the abdominal aorta for the hematological analysis.

- BAY 54-9085 mediated a dose-dependent anti-diuretic effect that was statistically significant at the high dose (300 mg/kg).
- At 300 mg/kg, urinary excretion of sodium and chloride was significantly decreased, which appears to be due to the anti-diuretic effect of the test article.
- Water retention was increased as reflected by an increase in blood volume parallel to decrease in blood erythrocyte counts (100 and 300 mg/kg), hematocrit (300 mg/kg), and hemoglobin concentration (100 and 300 mg/kg).
- There was no evidence of hemolysis; the counts of leukocytes and thrombocytes in blood, and blood coagulation parameters were unaffected by BAY 43-9006. Slight increase (7.7%) in thromboplastin time was observed at 30 mg/kg.

Group	Dose BAY 54-9085 (mg/kg) p.o.	Number of animals	Volume ml/(kg, 2 hrs); Mean ± S.D.	Electrolyte excretion in mmol/(kg, 2 hrs); Mean ± S.D.		
				Sodium	Potassium	Chloride
1 (Control)	0 (Vehicle)	10	11.5 ± 5.11	0.46 ± 0.282	0.37 ± 0.246	0.36 ± 0.268
2	30	10	8.7 ± 3.18	0.45 ± 0.289	0.21 ± 0.122	0.33 ± 0.344
3	100	10	7.8 ± 2.43	0.31 ± 0.145	0.22 ± 0.075	0.19 ± 0.119
4	300	10	5.0 ± 2.67*	0.10 ± 0.060**	0.17 ± 0.085	0.07 ± 0.063**

* $p < 0.05$ compared to vehicle-treated controls, Kruskal Wallis test followed by adjusted U test
** $p < 0.05$ compared to vehicle-treated controls, adjusted Welsh test

Table provided by the sponsor.

Effect of a single oral administration of BAY 54-9085 on blood glucose of fasted and fed rats. A GLP/QA study conducted by BAYER AG, Wuppertal-Elberfeld

Report # PH-29451
Study # T 3065147

BAY 43-9006 tosylate was administered orally to rats at doses of 30, 100, and 300 mg/kg body weight. Control animals received the vehicle (Pluronic F68/PEG400/propylene glycol-15.4:42.3:42.3% w/w/w). Blood glucose levels were monitored 30, 60, 120, and 180 minutes after treatment.

Effect on blood glucose concentration in fasted rats

Group	Dose BAY 54-9085 (mg/kg, p.o.)	Number of animals	Blood glucose concentration (mmol/l; Mean ± S.D.) Time after treatment (minutes)			
			30	60	120	180
1 (Control)	0 (Vehicle)	6	4.63 ± 0.299	5.42 ± 0.647	5.44 ± 0.293	5.78 ± 0.218
2	30	6	4.49 ± 0.568	5.24 ± 0.469	5.53 ± 0.342	5.93 ± 0.297
3	100	6	4.16 ± 0.212	4.67 ± 0.373*	5.13 ± 0.216	5.37 ± 0.406
4	300	6	3.87 ± 0.326*	5.14 ± 0.503	5.30 ± 0.395	5.73 ± 0.326

* $p<0.05$ compared to vehicle-treated controls, Dunnett's test

Effect on blood glucose concentration in fed rats

Group	Dose BAY 54-9085 (mg/kg, p.o.)	Number of animals	Blood glucose concentration (mmol/l; Mean ± S.D.) Time after treatment (minutes)			
			30	60	120	180
1 (Control)	0 (Vehicle)	5	5.79 ± 0.370	6.54 ± 0.865	6.72 ± 0.936	6.42 ± 0.437
2	30	6	5.60 ± 0.199	5.46 ± 0.405*	5.74 ± 0.616	5.89 ± 0.603
3	100	6	5.34 ± 0.228	5.41 ± 0.290*	5.69 ± 0.631*	5.60 ± 0.502*
4	300	6	5.23 ± 0.450*	5.48 ± 0.336*	5.34 ± 0.352*	5.56 ± 0.330*

* $p<0.05$ compared to vehicle-treated controls, Dunnett's test

Tables provided by the sponsor.

- BAY 54-9085 had hypoglycemic effect as shown by post-treatment reductions in blood glucose levels of fed and fasted rats.
- Fasted rat: 30 mg/kg no effect, 100 mg/kg decrease 60 min post-dose., 300 mg/kg decrease 30 min post-dose.; Maximal reduction 16%
- Fed rat: 30 mg/kg decrease 60 min post-dose, 100 mg/kg decrease 60-180 min post-dose, 300 mg/kg decrease 30-180 min post-dose; Maximal reduction by 21%
- Fed rats were more sensitive than fasted rats. One hour after administration, the 30 mg/kg dose significantly decreased blood glucose levels only in fed rats.
- The effect on blood glucose was short lasting in fasted rats while in fed rats the effect was still evident up to 3 hours after administration of 100 and 300 mg/kg.
- The maximal reduction relative to control values was by 21% in fed rats and by 16% in fasted rats, respectively (300 mg/kg dose group).

Effect of a single oral administration of BAY 54-9085 on the central nervous system of rats.
A GLP/QA study conducted by BAYER AG, Wuppertal-Elberfeld

Study Report PH-29497
Study # T 4065148

BAY 54-9085 administered orally to rats at doses of 30, 100, and 300 mg/kg body weight. Control animals received the vehicle (Pluronic F68/PEG400/propylene glycol-15.4:42.3:42.3% w/w/w). Treatment related effects were assessed on 5 different parameters: open field behavior, body temperature, nociception on a hot plate, duration of hexobarbital-induced anesthesia, and the convulsive threshold dose of pentylenetetrazole.

- Potential for test article-induced sensory neuropathy: The hot plate test indicated that animals treated with sorafenib appeared to respond later than vehicle-treated controls. Other parameters tested were not affected by the single dose of the test article.

Effects on nociceptive responses

Group	Dose BAY 54-9085 (mg/kg; p.o.)	Number of animals	Time to nociceptive reaction (in seconds; Mean ± S.D.)
1 (Control)	0 (Vehicle)	8	19.9 ± 8.03
2	30	8	33.3 ± 19.25
3	100	8	35.9 ± 12.74*
4	300	8	32.8 ± 14.79

* $p<0.05$ compared to vehicle-treated controls, Duncan's multiple range test

Table provided by the sponsor.

Effect of a single oral administration of BAY 54-9085 on the behavioral and physiological state of rats. A GLP/QA study conducted by BAYER AG, Wuppertal-Elberfeld

Report # PH-29507
Study # T 8065151

BAY 43-9006 tosylate was administered orally to rats at doses of 30, 100, and 300 mg/kg body weight. Control animals received the vehicle (Pluronic F68/PEG400/propylene glycol-15.4:42.3:42.3% w/w/w). Animals were observed in intervals of 15 min for 3 hours after treatment and subsequently at 24 hours. Group size for test article was 6 animals/group whereas there were 5 animals/group on the control group.

- Test article-induced tremor: 100 mg/kg (2 out 6 rats) and 300 mg/kg (3 out 6 rats) dose exhibited tremors. Tremor started 30 min after administration, reached maximal incidence at 45 min and completely resolved within 75 min post-administration. No effect at 30 mg/kg.
- Chewing was noted between 45 and 60 min post administration in 2 or 3 animals in each group, including the control group.
- No evidence of ptosis, exophthalmus, lacrimation, salivation, piloerection, diarrhea, excitation, sedation, limb abduction, prone position, kyphosis, Straub tail, clonic or tonic seizures, vocalization, or paw beating.

Effect of a single oral administration of BAY 54-9085 on the intestinal charcoal transit in rats. A GLP/QA study conducted by BAYER AG, Wuppertal-Elberfeld-

Report # PH-29498
Study # T 5065149

BAY 54-9085 was administered orally to rats at doses of 30, 100, and 300 mg/kg body weight. Control animals received the vehicle (Pluronic F68/PEG400/propylene glycol-15.4:42.3:42.3%

w/w/w). A charcoal suspension was given orally by gavage 30 min after drug or vehicle administration. Animals were sacrifice 30 min after charcoal administration to assess the length of the intestinal segment covered with charcoal.

- Although results were not statistically significant and not dose-dependent, there appears to be a tendency for increased intestinal motility induced by the test article, as indicated by the increased length of the intestine covered by charcoal in Groups 2-4.

Group	Dose BAY 54-9085 (mg/kg p.o.)	Number of animals	Length of the intestine covered by charcoal (in cm; Mean ± S.D.)
1 (Control)	0 (Vehicle)	5	68.0 ± 11.31
2	30	5	82.2 ± 19.98[a]
3	100	5	86.4 ± 15.22
4	300	5	84.2 ± 9.47

[a] One animal had transported the charcoal up the caecum. The result was entered as full length of intestine covered with charcoal (110 cm).

Table provided by the sponsor.

BAY 54-9085: Influence on Haemodynamics, ECG, and Respiration in Anesthetized Dogs after Single Intraduodenal Administration. A GLP/ QA study conducted by BAYER AG, Wuppertal-Elberfeld

Report # PH-30073 (referred to as Study Report MRC-01036 in the IND)
Study # T 1065146

Note: The review of the pharmacokinetic assessments for this study is presented under "Pharmacokinetics/ Toxicokinetics"; Report # MRC-01054/ Study # T1065145:RS013

In anesthetized Beagle dogs, the BAY 54-9085 was administered intraduodenally at 10, 30, and 60 mg/kg (approx. 7, 22, and 44 mg/kg of the free base) and hemodynamics, the electrocardiogram, blood gasses, serum electrolytes, and pulmonary function were measured.

- Plasma levels reached a mean maximum of 2.84 mg/L (mean Cmax) after application of 60 mg/kg of BAY 54-9085.
- Bradycardia (↓hear rate by 15%) was observed in the first hour after administration of all doses.
- No other effects were noted.

Electrophysiological examination of the effect of BAY 54-9085 on the HERG-mediated potassium current

Report # R-8318
Study # T 2064589

BAY 54-9085 was tested in stably transfected CHO cells (n= 3-12) using the whole cell patch-clamp technique at concentrations of 1, 3, and 10 μM.

- At 1 and 3 μM the current was reduced by 11% and 19%, (not statistically significant).
- At 10 μM a reduction by 37 % was measured, but at this concentration unspecific membrane effects were observed interfering with the evaluation of hERG-specific blockade.
- Higher concentrations were not tested due to poor solubility.

Study item	Concentration	Vehicle (% DMSO)	Relative block (%) (mean ± SD)
BAY 54-9085	1 μM	0.1	11 ± 6 (n=3)
	3 μM	0.1	19 ± 16 (n=4)
	10 μM	1	37 ± 25 (n=12)
Vehicle control		0.1	0 ± 14 (n=4)
Vehicle control		1	0 ± 13 (n=3)

Vehicle: DMSO.
Table provided by the sponsor.

Effects of BAY 54-9085 (BAY 43-9006 tosylate) on the action potential of isolated rabbit cardiac Purkinje fibers

Report # PH-32907
Study # T 0063119

BAY 54-9085 was tested in vitro at of 0, 0.1, 1, 10, and 20 μmol/1 (approx. 30 minutes per concentration). Higher concentrations could not be tested due to poor solubility. Action potentials were elicited by electrical stimulation at various frequencies (rates: 0.2, 1, 2.5 Hz) and were recorded with conventional glass microelectrodes [ ]. The effects of BAY 54-9085 were compared (i) to pre-drug control values, (ii) to those observed in time-matched control experiments, and (iii) to those induced by the reference compound E-4031.

- Potential for inhibition of hERG K+ current: APD90 was prolonged in 5 out of 6 Purkinje fibers. The prolongation was dose-dependent and was statistically significant at ≥ 10 μM. APD90 prolongation was reverse frequency dependent; see Table below [(-5 ± 3)% at 2.5 HZ, (+11 ± 3)% at 1.0 Hz, and (+21 ± 6)% at 0.2 Hz].
- Potential for inhibition of Ca2+ inward current: depression of action potential plateau was also dose-dependent and was statistically significant at ≥ 1 μM.

- Both effects (AP prolongation and depression of AP plateau) exceeded the observations in the time matched controls.
- Prolongation of action potential and depression of action potential plateau were not reversible after washout of the test article.

BAY 54-9085 (μM)	plateau pot. (mV)			APD_{20} (ms)			APD_{50} (ms)			APD_{90} (ms)		
	mean	SEM	N	mean	SEM	N	mean	SEM	N	mean	SEM	N
control	-5.0	1.8	5	8.7	0.7	5	162.0	10.3	5	259.6	14.2	5
0.1	-8.6	1.7	5	8.1	0.7	5	167.1	10.1	5	273.6	16.9	5
1	-13.6*	1.3	5	7.8	0.6	5	162.1	9.8	5	277.2	16.5	5
10	-16.8*	1.9	4	7.8	0.6	4	174.7	5.7	4	296.5	22.5	4
20	-20.2*	1.5	4	7.5	0.8	4	166.1	6.4	4	304.0	23.6	4
washout	-20.5	2.1	3	7.0	0.6	3	168.7	11.4	3	329.5	42.8	3
control				16.1	6.9	20	187.9	19.3	20	362.4	11.3	20
E-4031 (10 nM)				14.4	4.9	20	243.7	33.3	20	493.0	24.6	20

APD20, APD50, APD90: action potential durations at 20%, 50%, and 90% repolarization.
E-4031: reference compound.

Frequency-dependence of APD90 prolongation by BAY 54-90S5 (10 μM) and E-4031 (10 nM) in rabbit cardiac Purkinje fibers stimulated at rates of 0.2, 1.0 and 2.5 Hz.[&]

Compound	Parameter	0.2 Hz			1.0 Hz			2.5 Hz		
		mean	SEM	N	mean	SEM	N	mean	SEM	N
predrug control	APD_{90} (ms)	388.7	47.7	4	259.6	14.2	5	210.5	12.0	4
BAY 54-9085 (10 μM)	ΔAPD_{90} (ms)	89.8	35.0	4	28.8	9.3	4	-9.6	5.6	4
BAY 54-9085 (10 μM)	ΔAPD_{90} (%)	21.1*#	6.4	4	10.5	3.0	4	-4.6	2.8	4
predrug control	APD_{90} (ms)	542.0	56.6	13	362.4	11.3	20	235.9	9.2	13
E-4031 (10 nM)	ΔAPD_{90} (ms)	657.5	150.9	13	130.6	17.8	20	32.4	4.8	13
E-4031 (10 nM)	ΔAPD_{90} (%)	116.0§	22.2	13	35.4	4.6	20	14.1	2.1	13

* BAY 54-9085 (10 μM: 0.2 vs 1.0 vs 2.5 Hz): one-way ANOVA ($F = 8.57$, $p = 0.0082$) followed by Bonferroni's multiple comparisons test (0.2 Hz vs 2.5 Hz, $p < 0.01$; 0.2 Hz vs 1.0 Hz, not significant; 1.0 Hz vs 2.5 Hz, not significant).
# BAY 54-9085 vs E-4031 at individual stimulation rates: one-way ANOVA ($F = 11.64$, $p < 0.0001$) followed by Bonferroni's multiple comparisons test (0.2 Hz, $p < 0.001$; 1.0 Hz, not significant; 2.5 Hz, not significant).
§ E-4031 (10 nM: 0.2 vs 1.0 vs 2.5 Hz): one-way ANOVA ($F = 19.45$, $p < 0.0001$) followed by Bonferroni's multiple comparisons test (0.2 Hz vs 2.5 Hz, $p < 0.001$; 0.2 Hz vs 1.0 Hz, $p < 0.001$; 1.0 Hz vs 2.5 Hz, not significant).
& The tabulated values were calculated excluding the outlier experiment M30627.

Pre-drug: prior to drug exposure.
Tables provided by the sponsor.

Overall Safety Pharmacology Summary

Tabulated summary as submitted by the sponsor:

Test Article: **BAY 54-9085 (tosylate salt of BAY 43-9006)**

Table 4-1: *in-vivo* studies

Organ Systems Evaluated	Species /Strain	Method of Admin.[b]	Doses[c] [mg/kg]	Gender and No. per Group	Noteworthy Findings	GLP	Report/ CTD Module
Cardiovascular and respiratory system							
hemodynamics, ECG, respiration	dog / Beagle[d]	i.d.	0 - 10 - 30 - 60	male and female; 3 per group	transient decreased in heart rate by a mean maximum of 15 %, otherwise no effects; mean maximal plasma levels were 2.84 mg/l at a dose of 60 mg/kg	Yes	PH-30073/ 4.2.1.3.1 PH-01054/ 4.2.1.3.2
Central nervous system							
behavioral and physiological state	rat[a]	p.o.	0 - 30 - 100 - 300	male 6 per group	transient tremor at 100 mg/kg (2 of 6 animals) and at 300 mg/kg (3 of 6 animals), otherwise no treatment-related effects	Yes	PH-29507/ 4.2.1.3.4
psychomotoric activity (open field test)	rat[a]	p.o.	0 - 30 - 100 - 300	male 10 per group	--	Yes	PH-29497/ 4.2.1.3.3
body temperature	rat[a]	p.o.	0 - 30 - 100 - 300	male 6 per group	--	Yes	PH-29497/ 4.2.1.3.3
anti- / proconvulsive effect (pentylenetetrazole threshold test)	rat[a]	p.o.	0 - 30 - 100 - 300	male 8 per group	--	Yes	PH-29497/ 4.2.1.3.3

Organ Systems Evaluated	Species /Strain	Method of Admin.[b]	Doses[c] [mg/kg]	Gender and No. per Group	Noteworthy Findings	GLP	Report/ CTD Module
nociceptive responsiveness (hot plate test)	rat[a]	p.o.	0 - 30 - 100 - 300	male 8 per group	--	Yes	PH-29497/ 4.2.1.3.3
duration of hexobarbital-induced anesthesia	rat[a]	p.o.	0 - 30 - 100 - 300	male 8 per group	--	Yes	PH-29497/ 4.2.1.3.3
Renal / urinary system							
urine volume, electrolyte excretion	rat[a]	p.o.	0 - 30 - 100 - 300	male 10 per group	dose-dependent antidiuretic effect and decreased excretion of sodium and chloride (both statistically significant at 300 mg/kg)	Yes	PH-29405/ 4.2.1.3.5
Gastrointestinal system							
gastrointestinal motility	rat[a]	p.o.	0 - 30 - 100 - 300	male 5 per group	--	Yes	PH-29498/ 4.2.1.3.7
Blood							
blood cell counts, hemoglobin	rat[a]	p.o.	0 - 30 - 100 - 300	male 10 per group	dose-dependent decrease in erythrocyte number, hematocrit and hemoglobin (statistically significant at 100 and 300 mg/kg)	Yes	PH-29405/ 4.2.1.3.5
coagulation	rat[a]	p.o.	0 - 30 - 100 - 300	male 10 per group	--	Yes	PH-29405/ 4.2.1.3.5
Metabolism							

Organ Systems Evaluated	Species /Strain	Method of Admin.[b]	Doses[c] [mg/kg]	Gender and No. per Group	Noteworthy Findings	GLP	Report/ CTD Module
blood glucose	rat[a]	p.o.	0 - 30 - 100 – 300	male 6 per group	fasted rats: short-lasting, dose-dependent reduction in blood glucose concentration by a mean maximum of 16 % (statistically significant at 100 and 300 mg/kg); fed rats: long-lasting, dose-dependent reduction in blood glucose concentration by a mean maximum of approximately 20 % (statistically significant at 30, 100 and 300 mg/kg)	Yes	PH-29451/ 4.2.1.3.6

a - strain of rats: [redacted] !Cpb: WU
b - p.o. = per oral (by gavage), i.d. = intra duodenal
c - single dose unless specified otherwise; 100 mg/kg of BAY 54-9085 (tosylate salt) is equivalent to 73 mg/kg of BAY 43-9006 (free base); vehicle (rat): Pluronic F68 / PEG400 / propylene glycol (15.4:42.3:42.3); vehicle (dog): 2-pyrrolidone / Cremophor RH40 / propylene glycol (10:45:45)
d - anesthetized dogs

Table 4-2: *In-vitro* studies

Organ Systems Evaluated	Test System	Concentration	Noteworthy Findings	GLP	Report/CTD Module
Smooth muscle contractility					
ileal contractions	isolated guinea pig ileum	$10^{-8} – 10^{-7} – 10^{-6}$ g/ml	--	Yes	PH-29499/ 4.2.1.3.8
Electrophysiology					
hERG K^+ current	transfected CHO cells	1 – 3 – 10 µM	average current reduction by < 20 % at 1 and 3 µM (statistically not significant); at 10 µM, compound-specific hERG current blockade could not be evaluated because of unspecific membrane effects	No	R-8318/ 4.2.1.3.9
action potential	rabbit cardiac Purkinje fibers	0.1 – 1 – 10 – 20 µM	depression of action potential plateau at > 1 µM and prolongation of APD_{90} at > 10 µM in a shallow reverse frequency-dependent manner, suggesting inhibition of Ca^{2+} inward current and hERG K^+ current at concentrations approaching the solubility limit	No	PH-32907/ 4.2.1.3.10

- No noteworthy finding

Tables provided by the sponsor.

Neurological effects:

- A single dose of BAY 54-9085 in rats at doses equivalent to 22, 73, and 220 mg/kg of the free base resulted in non-dose-dependent increases in "time to nociceptive reaction", suggesting the potential for sorafenib to cause **sensory neuropathy**.
- 73 mg/kg (2 out 6 rats) and 220 mg/kg (3 out 6 rats) doses exhibited **tremors** starting 30 min after administration. Tremor reached maximal incidence at 45 min and completely resolved within 75 min post-administration. No effect at 22 mg/kg.
- No evidence of ptosis, exophthalmus, lacrimation, salivation, piloerection, diarrhea, excitation, sedation, limb abduction, prone position, kyphosis, Straub tail, clonic or tonic seizures, vocalization, or paw beating.

Cardiovascular effects:

- Bradycardia (mean reduction in heart rate: 15%) was observed in Beagle dogs in the first hour after administration of all doses (single doses: 7, 22, and 44 mg/kg of the free base).
- The hERG assay showed potential for K-channel blockade: at 10 μM the current was reduced by 37 %, but there was also unspecific membrane effects at this concentration (possibly due to the high concentration of DMSO utilized to solubilize the test article)
- Action potential studies in Purkinje fibers suggested potential for inhibition of hERG K-current and Ca-inward current.
- No effects were observed on the blood pressure, QT interval, or heart rate in the toxicology studies conducted, under the conditions of the studies.

Pulmonary effects: no effect

Renal effects:
Based on the single dose study in rats at 22, 73, and 220 mg/kg of the free base:

- BAY 54-9085 tosylate mediated a dose-dependent anti-diuretic effect that was statistically significant at the high dose (220 mg/kg of the free base).
- At 220 mg/kg of the free base, urinary excretion of sodium and chloride was statistically significantly decreased.
- Water retention was increased as reflected by an increase in blood volume parallel to decrease in blood erythrocyte counts, (100 and 300 mg/kg) hematocrit (300 mg/kg), and hemoglobin concentration (100 and 300 mg/kg).

Gastrointestinal effects:

- There appears to be a tendency for increased intestinal motility induced by the test article.
- Acute toxicity studies revealed the GI tract a target for drug-induced toxicities (soft feces and vomiting). In addition, GI toxicity was observed in the repeat dose toxicity studies.

Abuse liability: no studies conducted

Other: Sorafenib had hypoglycemic effect as shown by post-treatment reductions in blood glucose levels of fed and fasted rats. This effect was more evident in fed rats.

2.6.2.5 Pharmacodynamic drug interactions

The Pharmacodynamic drug-interaction studies submitted consisted of combination chemotherapy in xenografted tumor models in mice. These studies have not been reviewed.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

Table below represent the IC50 of sorafenib to inhibit various kinases in several in vitro or cell-based systems.

Biochemical Assay [a]	IC50 (nM)
CRAF [b]	6
BRAF wild-type	22
BRAF V600E mutant	38
VEGFR2	90
mVEGFR2	15
mVEGFR3	20
mPDGFR-β	57
FLT3	58
c-KIT	68
FGFR1	580
Cellular Mechanism [c]	**IC50 (nM)**
MDA MB 231 MEK phosphorylation (Human Breast)	40
MDA MB 231 ERK phosphorylation (Human Breast)	90
BxPC-3 ERK phosphorylation (Human Pancreatic)	1200
LOX ERK phosphorylation (Human Melanoma)	880
VEGFR-2 receptor phosphorylation (Human, 3T3 cells)[d]	30
VEGF-stimulated ERK phosphorylation (HUVECs)[e]	60
BFGF-stimulated ERK phosphorylation (HUVECs)	620
MVEGFR-3 receptor phosphorylation (Mouse, 293 cells)	100
PDGFR-β phosphorylation (HAoSMC)[f]	80
FLT-3 receptor phosphorylation (Human ITD, 293 cells)	20
Cellular Proliferation	**IC50 (nM)**
MDA MB 231 (10% FCS)[g]	2600
PDGFR-β-stimulated HAoSMC[f] (0.1% BSA)[h]	220

a Recombinant enzyme assay
b Raf kinase activated with Lck (full length CRAF)
c Mechanistic cellular assays all performed in 0.1% BSA
d Western blot assay format with Phospho-VEGFR-2 antibody
e Human umbilical vein endothelial cells
f Human aortic smooth muscle cells
g Fetal calf serum
h Bovine serum albumin

Table provided by the sponsor.

2.6.4. PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Pharmacokinetics of sorafenib administered as the tosylate salt BAY 54-9085 was investigated in vivo in Wistar rats, CD-1 mice, and in Beagle dogs. Additionally, in vitro studies were performed to investigate plasma protein binding, blood cell/ plasma partitioning and drug metabolism in several species including man. For studies that have not been reviewed, the summary information as submitted by the sponsor is reported in this section.

Based on the mouse, rat, and dog single dose PK studies reviewed:

- The absorption of radioactivity (unchanged compound and radioactive metabolites) was almost complete in mice (90%) and rats (80%) and limited in dogs (68%). The absolute bioavailability of the unchanged compound was moderate to high (60 % in dogs, 80 % in rats and mice).
- Plasma clearance in rats (0.04 L/h/kg) was markedly lower than in mice and dogs (0.13 - 0.15 L/h/kg).
- Vss was moderate, approximately 0.7 L/kg in rat, mouse, and dog.
- The plasma elimination $t_{1/2}$ of unchanged substance was approx. 6 hrs in mice, 9 hrs in rats, and 4 hrs in dogs and independent from the route of administration.
- The radioactivity was rapidly and homogeneously distributed to almost all organs and tissues.
- Sorafenib can cross both the blood/ brain and the placental barriers
- No evidence of irreversible binding or retention of radioactivity in organs and tissues of rats.
- [14C] sorafenib tosylate related radioactivity was secreted markedly into the milk of lactating rats.

Based on the rat and dog repeat-dose studies reviewed:

- Sorafenib plasma concentrations were slightly (not toxicologically significantly) higher in ♀ rats and dogs in several studies.
- Reduced absorption was observed at higher doses in the toxicology studies conducted in rats and dogs. This was attributed to the poor solubility of the test article at higher doses. However, saturation of the transport system cannot be excluded.
- There was a potential for drug accumulation after repeated dosing for the low and intermediate doses used in the toxicology studies.
- There appeared to be potential for metabolic auto-induction of sorafenib metabolism at high doses used in the toxicity studies. The in vitro assays did not reveal induction of CYP isozymes 1A2 and 3A4, under the conditions tested.

Based on the sponsor's summary:

- The protein binding of sorafenib was high and species dependent. The fraction unbound to plasma proteins (fu) was about 0.5 % in mouse, rat, and man, 0.9 % in dogs, and 2.0 % in rabbits, respectively. Albumin was identified as an important binding component in human plasma.
- Sorafenib exhibited no inductive potential on major CYP isoforms.
- Sorafenib showed a potency to inhibit CYP isoforms (e. g. CYP2B6, 2C8, and 2C9) and UDP-glucuronosyltransferase UGT1A1 and 1A9 in vitro
- In vitro species comparison based on liver microsomal incubations revealed N-oxidation (M-2) to be prominent in humans, monkeys, and mice, whereas rats and dogs preferentially formed M-3 by N-methylhydroxylation.
- Table below shows metabolic profile in various species.

Table 5-1: Metabolite profiles in incubations of [^{14}C]BAY 54-9085 (16 µM) with liver microsomes of different species (protein concentration 0.5 mg/mL, 90 min) (M4.2.2.4.9, PH-32439)

Compound	Man (pool)	Rhesus monkey	Wistar rat	CD-1 mouse	NMRI mouse	Beagle dog	New Zealand rabbit
			% of radioactivity				
M-1	4.9	9.0	1.3	2.4	-	-	-
M-5	-	1.2	-	-	-	-	-
M-2	36.4	29.4	9.6	23.2	10.7	3.8	6.0
M-3	14.2	17.9	16.8	11.0	5.4	19.7	3.2
M-4	1.6	4.6	1.4	1.9	-	2.4	-
Drug	41.0	35.3	70.8	61.5	83.9	74.1	90.8

Table provided by the sponsor.

- CYP3A4 is the enzyme responsible for phase I reactions (oxidative metabolism) of sorafenib in man.
- Human hepatocytes were capable of forming sorafenib glucuronide M-7. Glucuronidation was also catalyzed by human liver and kidney microsomes fortified with UGPGA. UDP-glucuronosyltransferase (UGT) 1A9 was identified to be responsible for conjugation of sorafenib with glucuronic acid.
- In man, sorafenib is subject to two parallel metabolic pathways yielding as primary metabolites the N-oxide (M-2) and the drug glucuronide (M-7).

2.6.4.2 Methods of Analysis

See under individual study reviews

2.6.4.3 Absorption

Absorption was near complete in CD-1 mice (92% when given as a single oral dose at 11 mg/m2 of the free base; MRC-01034).

Absorption was high in Wistar rats (approx. 80%, when given as a single oral dose of 21 mg/m2 or 30 mg/m2 of the free base; MRC-01014 and PH-33474).

Absorption was only 68% in Beagle dogs when compound was given as a single oral dose equivalent to 82 mg/m2 of the free base (MRC-01051).

The bioavailability of unchanged compound was 80% in CD-1 mice and Wistar rats and 60% in Beagle dogs.

2.6.4.4 Distribution

Tissue distribution studies conducted in Wistar rats with radioactive compound revealed distribution into all organs and tissues (PH-30643 and PH-33343). Radioactivity was also detected in brain, placenta, and fetus, which demonstrates the compound (and/or its metabolites) is able to cross both the blood brain and the placental barriers. Radioactivity was detected in both ♂ and ♀ reproductive organs. When assessed qualitatively, distribution appeared to be independent of the route of administration (i.v. versus p.o.). Distribution pattern were similar between ♂ and ♀ rats.

In non-pregnant rats, the highest levels of radioactivity after oral administration of the test article were detected in the following: adrenal cortex, GI tract/bile ducts, liver, pancreas, and Harderian gland. The levels of radioactivity were still high in most organs 24 hrs post oral dose, suggesting slow elimination. Seven days post oral dose radioactivity was still detectable in the following: large intestine, liver, kidneys, and intervertebral discs.

Radioactivity was detected markedly in the milk of lactating rats, suggesting secretion of sorafenib and/or its metabolites into the milk (PH-33190).

According to the sponsor, the protein binding of sorafenib was high and species-dependent. The fraction unbound to plasma proteins (fu) was about 0.5% in man, rat, and mouse, 0.9 % in dogs, and 2.0 % in rabbits, respectively. Albumin was identified as an important binding component in human plasma. (PH- 33358; PH- 33412)

2.6.4.5 Metabolism

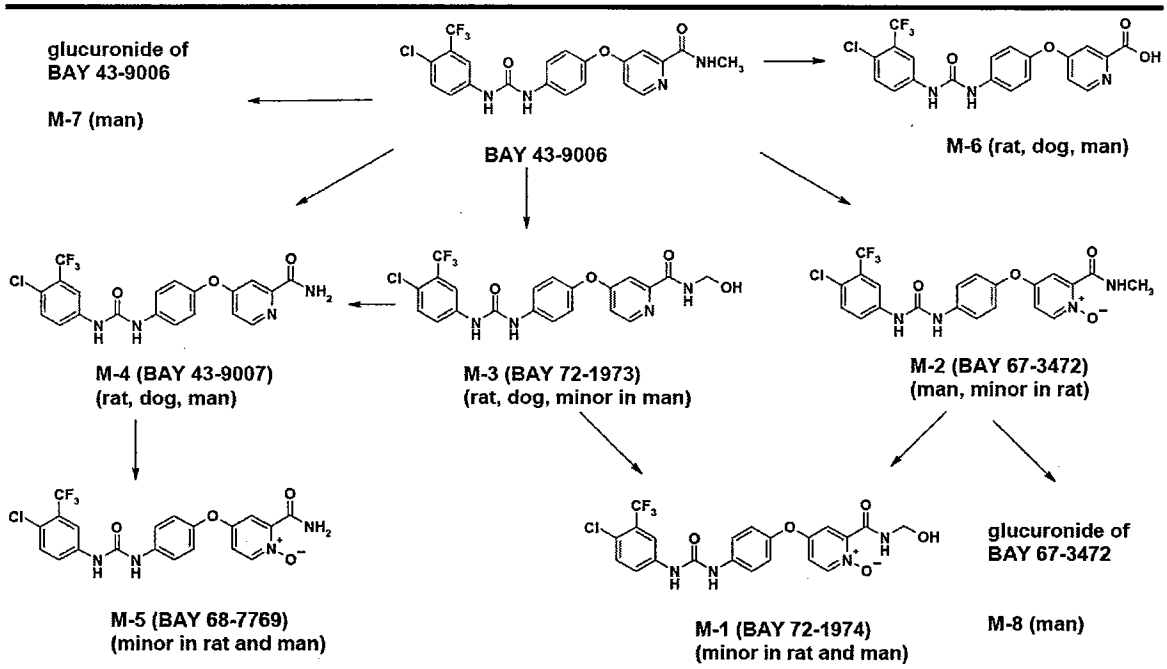
Summary as submitted by the sponsor:
Sorafenib exhibited no inductive potential on major CYP isoforms (CYP1A2 and 3A4) (M4.2.2.4.2, PH-33323). Sorafenib showed a potency to inhibit CYP isoforms; e.g. CYP2B6, 2C8, and 2C9 (PH-30285; R-7864; PH-33400; RMI-00096) and UDP- glucuronosyltransferases UGT1A1 and 1A9 (PH- 33798) in vitro.

In vitro species comparison based on liver microsomal incubations revealed N-oxidation (M-2) to be prominent in humans, monkeys, and mice, whereas rats and dogs preferentially formed M-3 by N-methylhydroxylation (PH-32439). CYP3A4 is the enzyme responsible for phase I reactions (oxidative metabolism) of sorafenib in man (PH-31789).

Human hepatocytes were capable of forming sorafenib glucuronide M-7 (PH-33059). Glucuronidation was also catalyzed by human liver and kidney microsomes fortified with UGPGA. UDP-glucuronosyltransferase (UGT) 1A9 was identified to be responsible for conjugation of sorafenib with glucuronic acid (PH-33504).

In man, sorafenib is subject to two parallel metabolic pathways yielding as primary metabolites the N- oxide (M-2) and the drug glucuronide (M-7) (PH-33504; PH-33427).

The proposed metabolic pathways derived from in vitro and in vivo studies are depicted below:



Metabolic pathway provided by the sponsor.

In vivo, following oral administration, the unchanged compound was the major component in rat, dog, and human plasma (PH-33292; PH-33063; PH- 33427). In rat and dog plasma, M-3 (BAY72-1973) was a main metabolite, whereas in human plasma M-2 was prominent. In man, total plasma radioactivity and sorafenib are subject to enterohepatic re-circulation (PH- 33427).

Sorafenib was a major component in feces extracts of man and rat. The carboxylic acid M-6 was a main metabolite in feces of rat, dog, and man (PH-33292; PH- 33063; PH- 33427).

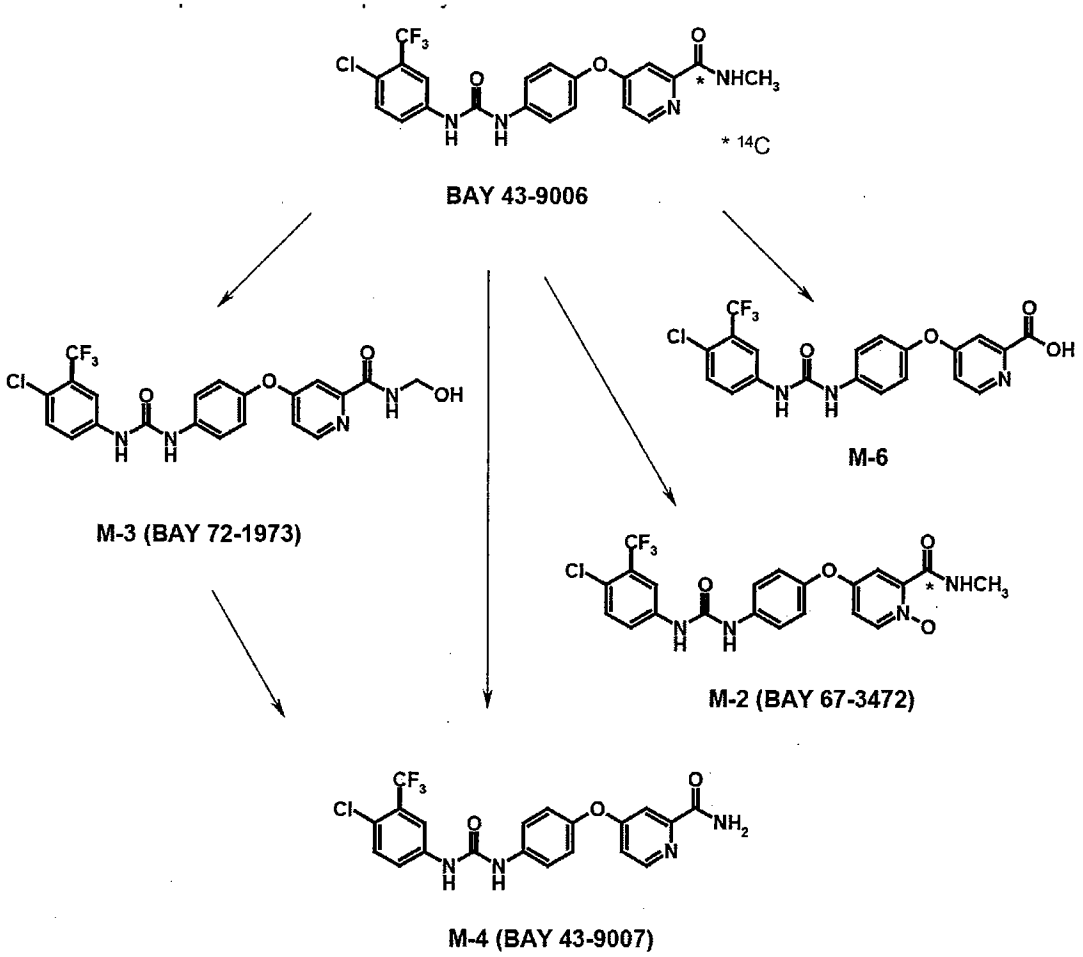
Comparison of the biotransformation of sorafenib in man and animal species revealed significant differences in phase II as well as in phase I reactions in vitro and in vivo. In man, N- oxidation of the pyridine (M-2, BAY 67-3472) was much more pronounced than methyl hydroxylation (M-3, BAY 72-1973) in vitro and in vivo. Glucuronidation only played an important role in the biotransformation of sorafenib in man (PH- 33427).

Metabolic profiles

Compound	Man (pool)	Rhesus monkey	Wistar rat	CD-1 mouse	NMRI mouse	Beagle dog	New Zealand rabbit
			% of radioactivity				
M-1	4.9	9.0	1.3	2.4	-	-	-
M-5	-	1.2	-	-	-	-	-
M-2	36.4	29.4	9.6	23.2	10.7	3.8	6.0
M-3	14.2	17.9	16.8	11.0	5.4	19.7	3.2
M-4	1.6	4.6	1.4	1.9	-	2.4	-
Drug	41.0	35.3	70.8	61.5	83.9	74.1	90.8

Table provided by the sponsor.

Proposed metabolic pathway in rats (excerpted from Report# PH-33474)



2.6.4.6 Excretion

In rats and dogs the radioactivity was excreted mainly via the biliary/fecal route; urinary excretion was low (MRC-01014; PH-33474; MRC-01051; PH-33063). In rats the radioactivity was almost completely excreted 72 hours after dosing.

According to the sponsor, renal excretion of radioactivity was more pronounced in man than in rat and dog due to species dependent formation of M-7 sorafenib glucuronide, which was excreted into human urine (PH-33427).

Sorafenib and/or its metabolites can be excreted into the milk (PH-33190).

The plasma elimination half lives of unchanged compound were approximately 6 hrs in mice, 9 hrs in rats, and 4 hrs in dogs, independent of the route of administration.

Study Title: [14C]BAY 54-90S5: Pharmacokinetics in Female CD 1 Mice Following Intravenous and Oral Administration (PDM E310)

Report # MRC-01034
Study # PDM E310
Study initiation date: 11/15/1999

Assessments: The pharmacokinetics of total radioactivity and unchanged compound as well as the plasma concentration profiles were determined.

Study Design: The radiolabeled compound [14C] BAY 54-9085 was administered in solution as a single oral and intravenous dose to fasted ♀ CD 1 mice (n=3/time point) at 5 mg/kg (equivalent to 3.65 mg/kg or 11 mg/m^2 free base BAY 43-9006). Blood/plasma samples were obtained at 0.08 (intravenous), 0.25, 0.5, 1, 2, 4, 7, 24, 30, 48, 54 and 72 h post-administration by means of terminal cardiac puncture under CO2 anesthesia. The plasma samples were analyzed for total substance-associated radioactivity via liquid scintillation counting (LSC) as well as for parent and metabolite levels by [redacted]

Results:

Substance-associated radioactivity

Pharmacokinetic Parameter	Intravenous	Oral
AUC (mg-eq*h/l)	26.79	24.75
AUC_{norm} (kg-eq*h/l)	7.34	6.78
$AUC_{0\text{-}tn}$ (mg-eq*h/l)	26.24	24.41
$AUC_{n0\text{-}tn}$ (kg-eq*h/l)	7.19	6.69
C_{max} (mg-eq/l)	13.46	1.33
$C_{max,norm}$ (kg-eq/l)	3.69	0.36
T_{max} (h)	--	2.0
MRT (h)	4.97	15.65
t ½ (h)	6.75	6.06
% Absorption		92.4

Table provided by the sponsor.

Unchanged compound

Pharmacokinetic Parameter	Intravenous	Oral
AUC (mg*h/l)	24.33	19.13
AUC_{norm} (kg*h/l)	6.67	5.24
AUC_{0-tn} (mg*h/l)	23.91	18.92
AUC_{n0-tn} (mg*h/l)	6.55	5.18
C_{max} (mg/l)	13.17	1.15
$C_{max,norm}$ (kg/l)	3.61	0.32
T_{max} (h)	--	1.0
MRT (h)	4.55	14.72
t ½ (h)	6.53	5.77
Vss (l/kg)	0.68	--
Vz/f (l/kg)	--	1.59
Cl (l/h/kg)	0.15	0.19*
% Bioavailability		78.6

* CL/f

Table provided by the sponsor.
AUC: area under the curve; AUC norm: AUC divided by dose per kg body weight; CL: clearance; Cmax: maximum concentration; Cmax norm: Cmax divided by dose per kg body weight; t1/2: half-life associated with terminal phase of plasma concentration vs time curve; tmax: time to reach maximal drug concentration; Vss: apparent volume of distribution at steady state; Vz/f: apparent volume of distribution during the terminal phase

Summary of Mean (geometric) concentrations (mg/L) for total radioactivity, BAY 43-9006 and metabolites following 5 mg/kg [14C] BAY 54-9085 (3.65 mg/kg BAY 43-9006), following oral administration.

Time (h)	1.6 min Peak	4.7min* Peak	5.1 min Peak	5.9 min Peak	43-9006 Peak	Sum of Peaks	Total Radioact.
0.25					0.48	0.48	0.49
0.50					0.67	0.67	0.68
1	.02		.04		1.15	1.21	1.22
2	.05		.04	.01	1.10	1.20	1.33
4	.05		.03	.03	0.65	0.76	0.83
7	.02		.02	.04	0.73	0.81	0.88
24	.20			.06	0.47	0.73	0.65
30					0.19	0.19	0.28
48							
72							
Total % circ.	9.52		0.92	4.53	78.68	93.65	

Total % circulating metabolites is based on comparison of AUC 0-tn of metabolites to total radioactivity following oral administration

Table provided by the sponsor.
* trace amounts

- The bioavailability of the parent compound was 80%, whereas the amount of test article absorbed was 92%. This suggests a rapid metabolic effect, likely due to the first pass liver/GI effect.

- When administered i.v., the parent compound is 91% of the total radioactivity and when administered orally, the parent compound accounts for 77% of the total radioactivity absorbed.
- Tmax of 1 hr for the parent compound and 2 hrs for the total radioactivity (oral)
- Relatively low clearance and long elimination half-life
- 4 metabolites were detected one of which was in trace amounts.

Study Title: [14C]BAY 54-90S5: Pharmacokinetics and Mass Balance in Male Wistar Rats Following. Intravenous and Oral Administration (PDM E245)

Report#: MRC-01014
Study # PDM E245
Study initiation: 9/28/1999

Assessments: The pharmacokinetics, mass balance and the elimination of radioactivity were determined.

Study Design: The radiolabeled compound [14C] BAY 54- 9085 was administered to ♂ Wistar rats in solution as a single intravenous dose (n=5/group) at 5.63 mg/kg (equivalent to 4.11 mg/kg or 25 mg/m^2 BAY 43-9006) and as a single oral dose at 4.85 mg/kg (equivalent to 3.54 mg/kg or 21 mg/m^2 BAY 43- 9006).

Serial plasma samples were obtained from each individual animal at 0.03 (intravenous), 0.08, 0.17, 0.33, 0.67, 1, 2, 4, 7, 24, 30, 48, 54 and 72 h post-administration by means of an indwelling carotid catheter. The plasma samples were analyzed for total substance-associated radioactivity via liquid scintillation counting as well as for parent and metabolite levels by [illegible] Mean plasma concentrations and pharmacokinetic parameters were determined for each group. Urine and fecal samples were taken throughout the study at specified time-points, for the determination of mass balance and excretion of the radioactivity. Analysis of the excreta samples were conducted via direct liquid scintillation counting (LSC) and [illegible] followed by LSC.

Substance-associated radioactivity

Pharmacokinetic Parameter	Intravenous Mean	SD	Oral Mean	SD
AUC (mg-eq*h/l)	117.33	1.21	78.33	1.22
AUC_{norm} (kg-eq*h/l)	28.58	1.24	22.14	1.23
$AUC_{0\text{-}tn}$ (mg-eq*h/l)	116.39	1.22	77.51	1.22
$AUC_{n0\text{-}tn}$ (kg-eq*h/l)	28.32	1.24	21.91	1.23
C_{max} (mg-eq/l)	8.13	1.17	3.84	1.14
$C_{max,norm}$ (kg-eq/l)	1.98	1.21	1.09	1.13
Tmax (h)	--		1.74	1.79
MRT (h)	16.16	1.16	17.54	1.10
t ½ (h)	8.81	1.13	11.21	1.20
% Absorption			77.4	

Unchanged compound

Pharmacokinetic Parameter	Intravenous Mean	SD	Oral Mean	SD
AUC (mg*h/l)	94.16	1.18	64.26	1.24
AUC_{norm} (kg*h/l)	22.91	1.18	18.15	1.25
AUC_{0-tn} (mg*h/l)	92.90	1.19	62.67	1.23
AUC_{n0-tn} (mg*h/l)	22.60	1.18	17.70	1.24
C_{max} (mg/l)	8.35	1.22	3.65	1.14
$C_{max,norm}$ (kg/l)	2.03	1.16	1.03	1.14
Tmax (h)	--	--	1.74	1.79
MRT (h)	14.87	1.11	16.08	1.13
t ½ (h)	9.33	1.10	8.86	1.14
Vss (l/kg)	0.65	1.07	--	--
Vz/f (l/kg)	--		0.71	1.17
Cl (l/h/kg)	0.04	1.17	0.06	1.25
% Bioavailability			79.1	

* CL/f

Tables provided by the sponsor.
Note: Slightly different i.v. and oral doses were given.
i.v.: 25 mg/m2 of BAY 43-9006
p.o.: 21 mg/m2 of BAY 43-9006

AUC: area under the curve; AUC norm: AUC divided by dose per kg body weight; CL: clearance; Cmax: maximum concentration; Cmax norm: Cmax divided by dose per kg body weight; t1/2: half-life associated with terminal phase of plasma concentration vs time curve; tmax: time to reach maximal drug concentration; Vss: apparent volume of distribution at steady state; Vz/f: apparent volume of distribution during the terminal phase

Summary of mean (geometric) Concentrations for BAY 43-9006 and metabolites, following oral administration of [14C] BAY 54-9085

Time (h)	4.7min Peak	5.1 min Peak	5.9 min Peak	43-9006 Peak	Sum of Peaks	Total Radioact.
0.08	blq	blq	blq	blq	blq	0.04
0.17	blq	blq	blq	0.15	0.15	0.16
0.33	blq	blq	blq	1.08	1.08	1.1
0.67	blq	0.02	blq	2.20	2.22	2.24
1	blq	0.06	blq	3.33	3.39	3.43
2	blq	0.14	blq	3.33	3.47	3.51
4	0.02	0.18	0.02	2.78	3.00	3.04
7	0.05	0.25	0.06	2.59	2.94	2.96
24	0.02	0.27	0.10	1.19	1.58	1.61
30	blq	0.12	0.07	0.63	0.83	0.85
48	blq	0.04	0.01	0.17	0.22	0.24
54	blq	blq	blq	0.06	0.06	0.13
72	blq	blq	blq	blq	blq	0.05

blq = below limit of quantitation

Table provided by the sponsor.

Mass balance

Sample	Intravenous	Oral
Urine	3.93 ± 1.02	2.87 ± 0.45
Feces	89.48 ± 4.20	90.12 ± 1.64
GIT	1.48 ± 1.04	1.61 ± 1.61
Animal body	1.98 ± 0.67	1.59 ± 0.46
Blood (*)	1.15 ± 0.18	0.56 ± 0.04
Cage wash	0.31 ± 0.08	0.69 ± 0.13
Total	98.34 ± 5.75	97.30 ± 2.23

Table provided by the sponsor.
* Includes radioactivity present in serial blood samples taken for determination of pharmacokinetic parameters.
GIT: GI tract

- Comparable data for the i.v. and oral administration
- The amount of parent drug bioavailable was comparable to the total amount of radioactivity absorbed (79% vs 77%); suggesting no first pass liver/GI metabolism.
- T_{max}: approx. 1.7 hrs
- Relatively long $t_{1/2}$ and low clearance
- Approx. 90% biliary/fecal excretion
- Low (3% for oral) urinary excretion
- 3 metabolites were detected

Study Title: Absorption and Excretion of the Radioactivity in Male Bile Duct- Cannulated Wistar Rats after Single Administration of [14C] BAY 54- 9085.

Report# PH-33474
Study initiation: 11/26/02

Assessments: absorption and excretion

Design: The administered dose was [14C] BAY 54- 9085 6.85 mg/kg equivalent to 5 mg/ kg or 30 mg/m2 BAY 43- 9006 in all experiments.

Results:
After oral administration of [14C] BAY 54- 9085 to bile duct-cannulated rats, the amount of radioactivity recovered in bile, urine and the body (excluding the GI tract) was added to estimate absorption. This resulted in an estimation of approx. 53% absorption. However, if extrabiliary excretion of radioactivity occurs, this might underestimate the real extent of the absorption. When [14C] BAY 54-9085 was given i.v. to bile duct-cannulated rats, the extrabiliary excretion accounted for 28.6%. Taking the extrabiliary radioactivity excretion into account, the absorption was about 80 %.

Oral administration
- Absorption after oral administration: ~80%
- Excretion mainly via biliary/ fecal route

- 33.1 % biliary excretion (24 hr collection)
- 31.5 % fecal excretion (24 hr collection)
- 18% of the radioactivity was in the GI tract (incomplete absorption and/or extrabiliary excretion)
- Approx. 20% of radioactivity residing in the animals at 24 hr post-dose (27% after i.v. administration)
- less than 1 % of dose was excreted in urine

Comparison of mass balance in per cent of the administered dose after single administration of [14C] BAY 54- 9085 to ♂ bile duct- cannulated Wistar rats.

Dose[A] [mg/kg]	5		5	
Route	i.v.		p.o.	
No. of animals	5		5	
Duration [h]	24		24	
	Mean arithm.	C.V. [%]	Mean arithm.	C.V. [%]
Urine	0.961	33.4	0.871	13.2
Ur.-Rinse	0.376	18.4	n.a.	n.a.
Bile	39.3	7.15	33.1	10.5
Feces	15.2	29.8	31.5	12.6
Cage Rinse	n.a.	n.a.	0.0206	43.2
Body e GIT	27.3	19.7	18.8	6.58
GIT	13.4	34.2	17.8	17.8
Total Body	40.7	15.6	36.6	11.1
Balance	96.6	0.828	102	2.98

1636 Ratte bdc.xls \ Table 2 \ Bu/wkj \ 23.08.04

n.a. not applicable
Ur.-Rinse = urine rinsing water
GIT = gastrointestinal tract
Body e GIT = body excluding gastrointestinal tract
Total Body = sum of GIT and Body e GIT
A = Dose related to sorafenib

Table provided by the sponsor.

Study title: [14C] BAY 54-9085: Pharmacokinetics and Mass Balance in Female Beagle Dogs Following Intravenous and Oral Administration (PDM E261)

Report # MRC-01051
Study initiation: 11/15/1999

Assessments: PK parameters and mass balance

Study Design: [14C] BAY 54-9085 was administered in solution as a single intravenous dose of 5.77 mg/kg (equivalent to 4.2 mg/kg or 84 mg/m^2 free base) and as a single oral dose of 5.65

mg/kg (equivalent to 4.12 mg/kg or 82 mg/m^2 of free base) to fasted ♀ Beagle dogs (n = 3/group).

Serial plasma samples were obtained from each individual animal at 0.03 (intravenous), 0.08, 0.17, 0.33, 0.67, 1, 2, 4, 7, 24, 30, 48, 54 and 72 h post-administration by means of an indwelling cephalic catheter through the 7 h time-point and by direct venipuncture from 24 to 72 h. The plasma samples were analyzed for total substance-associated radioactivity via liquid scintillation counting as well as for parent compound levels by LC/UV detection. Mean plasma concentrations and pharmacokinetic parameters were determined for each group. Urine and fecal samples were taken throughout the study at specified time-points, for the determination of mass balance.

Results:

Substance-associated radioactivity

Pharmacokinetic Parameter	Intravenous Mean	SD	Oral Mean	SD
$AUC_{0\text{-}inf}$ (mg-eq*h/l)	55.02	1.32	36.44	1.20
AUC_{norm} (kg-eq*h/l)	13.08	1.28	8.84	1.21
$AUC_{0\text{-}tn}$ (mg-eq*h/l)	52.26	1.30	35.28	1.20
$AUC_{n0\text{-}tn}$ (kg-eq*h/l)	12.42	1.26	8.56	1.21
$C_{max\ (2\ min\ i.v.)}$ (mg-eq/l)	13.61	1.59	4.59	1.42
$C_{max,norm}$ (kg-eq/l)	3.24	1.60	1.11	1.43
Tmax (h)	--		2.0	1.00
MRT (h)	9.38	1.14	8.83	1.19
t ½ (h)	7.25	1.17	5.83	1.20
% Absorption			67.6	

Unchanged compound

Pharmacokinetic Parameter	Intravenous Mean	SD	Oral Mean	SD
$AUC_{0\text{-}inf}$ (mg*h/l)	33.30	1.44	19.54	1.07
AUC_{norm} (kg*h/l)	7.91	1.44	4.74	1.07
$AUC_{0\text{-}tn}$ (mg*h/l)	32.34	1.41	19.29	1.07
$AUC_{n0\text{-}tn}$ (kg*h/l)	7.68	1.41	4.68	1.07
$C_{max\ (2\ min\ i.v.)}$ (mg/l)	13.30	1.76	3.70	1.30
$C_{max,norm}$ (kg/l)	3.16	1.76	0.90	1.30
Tmax (h)	--		1.59	1.49
MRT (h)	5.83	1.32	5.5	1.23
t ½ (h)	4.33	1.40	3.59	1.24
Vss (l/kg)	0.74	1.09	--	--
Vz/f (l/kg)	--	--	1.09	1.16
Cl (l/h/kg)	0.13	1.44	0.21*	1.07
% Bioavailability			59.9	

* CL/f

Note: different techniques were used to detect total radioactivity (scintillation counting) and unchanged compound (LC/UV)

Sample	Intravenous	Oral
Urine	0.67 ± 0.05	0.76 ± 0.07
Feces	92.69 ± 4.00	91.35 ± 3.72
Blood	0.32 ± 0.07	0.12 ± 0.02
Cage wash	1.21 ± 1.16	2.24 ± 1.40
Total	94.89 ± 2.96	94.47 ± 3.80

Values expressed as percent of administered dose.
Arithmetic means and standard deviations given.

	Observation period (h)	Female fasted (IV)	Female fasted (PO)
Excretion via Urine	0-7	0.23*	0.17*
	7-24	0.26 (0.14)	0.39 (0.13)
	24-48	0.29 (0.21)	0.23 (0.13)
	48-72	0.06 (0.03)	0.04 (0.02)
	72-96	0.03 (0.01)	0.02 (0.02)
	96-120	0.02 (0.01)	0.01 (0.01)
	120-144	0.01 (0.00)	0.02 (0.01)
	144-168	bld	0.01
Total		**0.67 (0.05)**	**0.76 (0.07)**
Excretion via Feces	0-7	n.s.	n.s.
	7-24	30.13 (42.51)	59.24 (19.94)
	24-48	39.87 (36.33)	39.06 (33.32)
	48-72	24.19 (33.50)	10.27 (5.97)
	72-96	6.01 (8.68)	1.33 (1.51)
	96-120	1.75 (2.85)	0.58 (0.46)
	120-144	0.53 (0.66)	0.45 (0.34)
	144-168	0.25 (0.33)	0.26 (0.07)
Total		**92.69 (4.00)**	**91.35 (3.72)**
Blood	0-72	**0.32 (0.07)**	**0.12 (0.02)**
Cagewash	0-168	**1.21 (1.16)**	**2.24 (1.40)**
Recovery	0-168	**94.89 (2.96)**	**94.47 (3.80)**

(*) single sample
n.s. = no sample
bld = below limit of detection

Tables provided by the sponsor.

- Bioavailability of the parent compound was 60% and the total radioactivity absorbed was 68%, suggesting slight liver/GI first pass metabolism
- After oral administration, the unchanged compound accounts for 54% of the radioactivity absorbed (19.54/ 36.44), which is comparable to that after i.v. administration (61% unchanged)
- Major route of excretion: biliary/fecal (90% excretion; 168 hrs collection time)
- Urinary excretion accounted for less than 1% of the dose
- 95% of the radioactivity was recovered after 168 hrs for both oral or iv administration

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Study Title: [14C]BAY 54-9085 (tosylate of [14C]BAY 43-9006): Whole-body Autoradiography in Rats after Single Intravenous and Oral Administration.

Report # PH-30643
Study initiation: 10/12/1999

Assessments: distribution; whole body autoradiography

Study design:
Single oral dose of [14C]BAY-54-9085 in ♂ and ♀ Wistar rats and to 1 pigmented ♂ Long Evans rat, at the dose of 13.7 mg/kg (10 mg/kg or 60 mg/m^2 of the free base).
Single i.v. dose of [14C]BAY-54-9085 to ♂ Wistar rats, at the dose of 4.11 mg/kg (3 mg/kg or 18 mg/m^2 of the free base).

Sacrifice time: 5 min and 2 hrs post-i.v. dose
up to 7 days post-oral dose
♂ (Wistar): at 2, 4, 8, 24, 72, 168 hrs post-dose
♂ (Long Evans): at 24 hrs post-dose
♀: at 2, 24 hrs post-dose

Detection of radioactivity: radioluminography; estimation of radioactivity was qualitative (visual ranking of radiographic intensity), using spiked blood standards and pseudo-colored gradation.

Results:
- [14C]BAY 54-9085 associated radioactivity was rapidly and homogeneously distributed to almost all organs and tissues.
- The qualitative distribution patterns of radioactivity in rats were independent of the route of administration (oral and i.v.) and of the gender.
- Penetration of the blood/brain barrier was moderate.
- Radioactivity was detected in both ♂ and ♀ reproductive organs.
- During the absorption and main elimination phases, post-orally, concentrations of radioactivity were highest (higher than blood) in adrenal cortex, contents of gastrointestinal tract and bile-ducts, liver, pancreas, and Harderian gland.
- High concentrations (approx. equivalent to blood) were detected in most other organs and tissues, such as adrenal medulla, brown adipose tissue, most genital glands, salivary glands, kidneys (particularly cortex and medulla), heart, skeletal muscles, lungs, spleen,

thyroid, pineal body, hypophysis, gastrointestinal mucosa, and ♀ reproductive organs (ovaries, uterus, vagina).

- Moderate exposure (lower than in blood) occurred in testes, epididymides, skin, brain, spinal cord, and contents of the seminal vesicles.
- Twenty-four hours post-orally, radioactivity concentrations were still high in most organs, suggesting slow elimination. After 7 days residues were low, highest concentrations were still present in large intestinal contents, liver, kidneys (cortex and outer medulla), and intervertebral discs. The other organs and tissues showed low concentrations or had fallen below the limit of autoradiographic detection.
- There were no indications of irreversible binding or retention of [14C]BAY 54-9085 associated radioactivity in organs and tissues.
- No specific accumulation of radioactivity have been observed in pigmented tissues (eyewall, skin) of the pigmented Long Evans rats, 24 h post-orally.

Study Title: BAY 43- 9006: Quantitative Whole- body Autoradiography. Distribution of Radioactivity and Elimination from Blood, Organs and Tissues and Fetuses after Single Oral Administration to Pregnant Wistar Rats of [14C] BAY 54- 9085

Report# PH-33343
Study No.: I 8001700
Study initiation: 11/4/2003

Assessments: tissue distribution in pregnant rats of parent compound and metabolites

Study design:
[14C] BAY 54-9085 was administered at a single oral dose equivalent to 10 mg/kg or 60 mg/m2 of BAY 43-9006

Sacrifice time: The rats (3 per time point) were sacrificed at 1, 2, 4, 8, and 24 hrs post-dose.

Detection of radioactivity:
The distribution of total radioactivity in maternal and fetal organs and tissues was determined quantitatively. The radioactivity distribution in the dry whole- body sections was detected employing the [ ] imaging system. The quantitation of equivalent-concentrations in organ and tissues was performed using 14C-spiked blood standards for calibration.

The pharmacokinetic parameters were calculated by non-compartmental analysis using the bootstrap resampling technique.

Results:

Table below represents PK parameters calculated with the BOOTSTRAP resampling technique derived from individual concentration vs. time data of radioactivity in blood, organs and tissues of female pregnant Wistar rats and fetuses.

Organ / tissue	CEQ_{max} [mg-eq/L] Mean geom.	S.D. geom.	CEQ_{max} Ratio Organ / blood	t_{max} [h] Mean geom.	S.D. geom.
adipose tissue (brown)	13.5	1.10	1.53	4.02	1.65
adipose tissue (white)	8.60	1.11	0.973	4.49	1.39
adrenal glands	40.4	1.07	4.57	3.93	1.85
amnion	8.70	1.01	0.985	2.79	1.67
amniotic fluid[A]	0.851	n.a.	0.0962	24.0	n.a.
blood (heart)	**8.84**	**1.04**	**1.00**	**2.57**	**1.83**
brain	0.704	1.06	0.0796	5.99	1.41
cardiac muscle	17.4	1.04	1.96	2.72	1.41
Harderian gland	26.7	1.16	3.02	9.25	1.45
kidney cortex	19.4	1.05	2.19	2.96	1.41
kidneys	15.4	1.05	1.74	2.33	1.33
liver	49.9	1.05	5.65	2.31	1.33
lungs	14.2	1.03	1.61	2.34	1.34
mammary glands	13.2	1.01	1.50	4.00	1.00
ovaries	23.3	1.02	2.63	4.33	1.25
placentae	8.74	1.04	0.988	4.67	1.33
skeletal muscles, dorsal	5.96	1.06	0.675	4.64	1.33
skin	7.06	1.06	0.799	2.82	1.55
spleen	13.0	1.05	1.47	4.67	1.33
submandibulary gland	20.6	1.03	2.33	4.80	1.51
uterus	7.42	1.06	0.839	3.54	1.68
fetuses (average)	4.66	1.07	0.527	5.07	1.39
fetal blood	6.12	1.11	0.692	6.85	1.34
fetal brain	1.72	1.13	0.194	7.43	1.24
fetal kidney	4.90	1.11	0.554	5.50	1.41
fetal liver	4.84	1.07	0.547	5.36	1.41
fetal skeletal muscle	4.91	1.14	0.555	5.07	1.39
fetal skin	7.17	1.10	0.811	6.37	1.39

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Organ / tissue	AUC(0-24) [mg-eq·h/L] Mean geom.	AUC(0-24) [mg-eq·h/L] S.D. geom.	AUC [mg-eq·h/L] Mean geom.	AUC [mg-eq·h/L] S.D. geom.	$t_{1/2}$ [h] Mean geom.	$t_{1/2}$ [h] S.D. geom.	regression range [h]
adipose tissue (brown)	245	1.05	618	1.34	31.3	1.46	4-24
adipose tissue (white)	142	1.08	279	1.14	21.6	1.27	4-24
adrenal glands	766	1.07	2751	1.65	48.7	1.72	2-24
amnion	173	1.02	479	1.18	36.0	1.20	2-24
amniotic fluid[A]	15.3	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
blood (heart)	**165**	**1.04**	**411**	**1.24**	**31.4**	**1.28**	**2-24**
brain	13.3	1.05	34.3	1.19	32.1	1.24	4-24
cardiac muscle	323	1.03	858	1.19	33.8	1.21	2-24
Harderian gland	507	1.08	1861	1.50	43.4	1.75	8-24
kidney cortex	381	1.03	1414	1.43	50.6	1.47	2-24
kidneys	303	1.03	1217	1.44	55.4	1.47	2-24
liver	965	1.02	3466	1.25	49.1	1.29	2-24
lungs	277	1.02	1057	1.18	52.7	1.21	2-24
mammary glands	257	1.05	1116	2.11	57.9	2.19	4-24
ovaries	465	1.06	2745	2.40	81.4	2.50	4-24
placentae	172	1.02	431	1.08	31.4	1.10	4-24
skeletal muscles, dorsal	115	1.04	348	1.26	39.0	1.31	4-24
skin	129	1.04	308	1.24	29.5	1.28	2-24
spleen	246	1.04	631	1.22	31.8	1.27	4-24
submandibulary gland	400	1.04	1188	1.22	38.4	1.26	4-24
uterus	131	1.04	277	1.10	24.6	1.16	4-24
fetuses (average)	84.9	1.06	204	1.36	27.5	1.51	8-24
fetal blood	111	1.06	230	1.12	22.4	1.27	8-24
fetal brain	30.8	1.07	63.7	1.19	22.0	1.36	8-24
fetal kidney	86.2	1.08	174	1.22	21.7	1.41	8-24
fetal liver	94.7	1.02	304	1.23	41.7	1.29	4-24
fetal skeletal muscle	85.3	1.09	179	1.13	22.8	1.38	8-24
fetal skin	123	1.06	221	1.11	17.9	1.24	8-24

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A = no bootstrap evaluation possible, due to t_{max} = 24 h (data from non-compartmental analysis)
n.a. = not applicable

Ratios of equivalent concentrations and AUCs of radioactivity in selected organs /body fluids of female pregnant Wistar rats and fetuses

Time after administration Ratios	1 h	2 h	4 h	8 h	24 h	AUC(0-24)-ratio
placentae / maternal blood	0.862	0.892	1.03	1.07	1.08	1.04
amniotic fluid / maternal blood	0.0206	0.0328	0.0735	0.0777	0.162	0.0929
fetus / maternal blood	0.165	0.344	0.527	0.559	0.540	0.514
fetus / placentae	0.192	0.385	0.513	0.523	0.500	0.495
fetus / amniotic fluid	8.04	10.5	7.17	7.20	3.34	5.53
fetal blood / maternal blood	0.265	0.479	0.636	0.759	0.680	0.673
fetal liver / maternal liver	0.0401	0.0782	0.104	0.107	0.0977	0.0982
fetal brain / maternal brain	1.28	1.83	2.20	2.51	2.27	2.32

I8001700_Berichtstabellen.xls \ Table 10 \ wkj \ 12.05.04

Tables provided by the sponsor.

- The radioactivity was distributed to both maternal and fetal organs and tissues. Based on the distribution of the radioactivity, the test article can cross both the placenta and the blood-brain barriers.
- The maximum radioactivity concentrations were reached between 2 and 5 hours post-dose in most maternal organs, tissues and blood.
- In fetal organs, maternal brain and Harderian gland, maximum concentrations were achieved later.
- Most of the investigated maternal organs showed similar or higher maximum levels than blood. The highest maximum concentrations occurred in the maternal liver and adrenals, with 49.9 mg-eq/L and 40.4 mg-eq/L, respectively.
- Maternal blood maximum concentration was comparatively low, being 8.8 mg-eq/L; also indicating high distribution.
- Highest fetal maximum concentrations were found in skin and fetal blood.
- In contrast to the dam a significantly higher fetal blood-brain penetration occurred, resulting in 2.3-fold higher brain AUC(0-24) in the fetuses than in the dams.
- The average exposure in the fetuses as a whole reached 52 % of the exposure in maternal blood (165 mg-eq h/L).
- The AUC(0-24) for mammary glands was 1.6-fold higher than the AUC(0-24) for the maternal blood.
- Relatively high residual radioactivity concentrations were still present in dams as well as in the fetuses after 24 hours, with highest radioactivity concentrations in maternal organs (liver, adrenals, Harderian gland, and ovaries).
- Terminal half- lives derived from the elimination period between 4 and 24 hours were determined to be between 20 and 80 hours. The average elimination $t_{1/2}$ from fetuses was 28 hours.

Study Title: BAY 43- 9006: Secretion of Radioactivity into Milk of Lactating Rats after Single Oral Administration of [14C] BAY 54- 9085

Report # PH-33190
Study # I 4001689
Study initiation: 7/31/2003

Assessments: secretion into the milk

Study design:
[14C] BAY 54-9085 was administered to lactating Wistar rats as a single oral dose equivalent to 5 mg/kg or 30 mg/m2 of the free base BAY 43-9006. Milk and plasma samples were collected at up to 32 hrs post-dose.

Species: rat, female, lactating approx. 8-10 days post partum
Strain: [ ] Cpb: Wu Breeder
Age: approx. 3 months

Administration volume: 5 mL/kg
Observation time: 2, 4, 8, 24, and 32 hrs postdose

Results:
Pharmacokinetic parameters of radioactivity in milk and plasma, and corresponding milk/ plasma concentration ratios

		Milk		Plasma		Ratio milk/plasma
Number of animals		5		5		
Time [h]		Mean geom.	S.D. geom.	Mean geom.	S.D. geom.	
2		5.73	1.15	2.44	1.06	2.35
4		12.2	1.32	2.92	1.08	4.16
8		13.0	1.42	2.99	1.11	4.35
24		4.11	1.57	0.691	1.21	5.94
32		2.28	1.38	0.335	1.24	6.80
AUC	[mg-eq·h/L]	257	1.37	52.6	1.11	4.89
AUC_{norm}	[kg·h/L]	49.1	1.37	10.0	1.11	4.89
AUC(0-24)	[mg-eq·h/L]	200	1.35	44.9	1.09	4.46
$AUC(0\text{-}24)_{norm}$	[kg·h/L]	38.2	1.35	8.57	1.09	4.46
$AUC(t_n\text{-}\infty)$	[%]	12.3	1.17	6.98	1.23	n.c.
CEQ_{max}	[mg-eq/L]	14.6	1.35	3.09	1.07	4.72
$CEQ_{max.norm}$	[kg/L]	2.79	1.35	0.590	1.07	4.72
t_{max}	[h]	6.96	1.36	6.96	1.36	1.00
$t_{1/2}$	[h]	9.57	1.07	7.61	1.09	1.26
points*		3		3		
Interval*	[h]	8-32		8-32		

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* = used for regression to determine $t_{1/2}$

Table provided by the sponsor.

- Total radioactivity was remarkably high in the milk. Within 32 hrs, about 27% of the administered dose was excreted into the milk.
- AUC of radioactivity for the milk was higher than for the plasma; the milk/plasma ratio was 4.9 (257 vs. 52.6 mg-eq h/L).

MRC-01031 BAY 43-9006: In vitro metabolic stability in mouse, rat, dog, and human hepatic microsomes [D177].

Report# MRC-01031
Study # D177

Methods
Disappearance of BAY 43-9006 from mouse (♂), rat (♂ and ♀), dog (♂ and ♀) and human (mixed pool of ♂ and ♀) hepatic microsomal fractions was measured in duplicate for 0, 2, 5, 10, and 20 min at 37°C.
Initial drug concentration was 10 µg/ml and the protein concentration was 0.5 mg/ml.
Assay: [redacted] HPLC
Rates of BAY 43-9006 disappearance were estimated by comparing peak areas at each time point to the peak areas at the start of the incubation (0 min).

Results:

Species	nmol/mg/min
♂ mouse	0.37
♀ rat	0.04
♂ rat	0.06
♀ dog	0.17
♂ dog	0.11
human	0.69

- BAY 43-9006 was stable in the presence of hepatic microsomes from mouse, rat and dog (<20% loss of parent compound in 20 min) but only moderately stable in human microsomal incubations (~30% loss of parent compound in 20 min).
- Stability in liver microsomes: ♀ rat> ♂ rat> ♂ dog> ♀ dog> ♂ mouse>human.
- Metabolism of BAY 43-9006 was evident in the appearance of additional peaks in HPLC chromatograms.

Pharmacokinetics after repeated dosing
(Also see the repeat-dose toxicology studies)

Study Title: BAY 54-9085: 7-day toxicokinetics of BAY 43-9006 in female rats after oral administration of BAY 54-9085 [E144].

Report # MRC-01032 (this study is the PK report of toxicology Report # RMI-00067)

Study #: E144

A non GLP study conducted by [ ] Study dates: June 25, 1999-July 12, 1999.
Species and strain: Sprague Dawley rat (Rattus Sp.) (8 groups of 4 female animals/group)
Age/Weight: Age was not provided/ weight ~200-250 g
Lot#: 505003
Formulation/vehicle: BAY 54-9085 was suspended in 15% Pluronic® F68, 42.5% propylene glycol and 42.5% polyethylene glycol 400

Dosage: Once daily for 7 days (see table below)
Route: Oral gavage (10 ml/kg)

Group Number	Number of Females	Substance	BAY 54-9085 (mg/kg)	BAY 43-9006	
				mg/kg	mg/m²
1	4	Vehicle	0	0	0
2	4		0	0	0
3	4	BAY 54-9085	34	25	150
4	4		34	25	150
5	4		171	125	750
6	4		171	125	750
7	4		343	250	1500
8	4		343	250	1500

Observations

Toxicokinetics: Plasma samples were collected at 1, 2, 4, and 24 hours after administration on day 1 and 7. The plasma samples were analyzed by [ ] method [ ] with ethyl acetate. A total of 4 animals were used for each dose group.

Findings

Toxicokinetics: Method of detection: [ ]

BAY 43-9006		Day 1			Day 7		
mg/kg	mg/m2	C_{max} (mg/l)	T_{max} (h)	AUC $_{0-24}$ (mg*h/l)	C_{max} (mg/l)	T_{max} (h)	AUC $_{0-24}$ (mg*h/l)
25	150	25.5 ± 1.1	2.25 ± 1.3	414.7 ± 1.1	33.0 ± 1.1	3.5 ± 1.0	695.2 ± 1.1
125	750	41.2 ± 1.1	2 ± 0	746.9 ± 1.1	33.7 ± 1.2	3 ± 1.2	649.9 ± 1.1
250	1500	39.2 ± 1.3	2 ± 1.4	649.4 ± 1.2	29.8 ± 1.2	3.3 ± 1.5	594.7 ± 1.1

Values are expressed as mean ± SD

- For the LD but not for the MD or HD groups, exposure (mainly AUC 0-24) increased significantly from Day 1 to Day 7 indicating a potential drug accumulation of BAY 43-9006 in the female rat after multiple oral administration.
- For the HD group, drug exposure was similar to the MD group but decreased on Day 7.
- Cmax and AUC levels are not proportional to dose suggesting saturation of drug absorption. Sponsor previously suggested drug crystallization in the GI tract.

BAY 54-9085: 7-day toxicokinetics of BAY 43-9006 in dogs after oral administration of BAY 54-9085. A non-GLP study conducted by (
)

Report # MRC-01033 (This is the PK data of toxicology Study Report# RMI-00068)
Study # E270, E290

Study initiation:	16-Sept-1999
Species:	Beagle dogs (3 groups of 2/sex/group)
Age/Weights:	~7 months/Males: (8 to 11 kg) Females (8 to 10 kg)
Test Article:	BAY 54-9085 Lot # 505003
Vehicle:	2-Pyrrolidon (10%), Propyleneglycol (45%) and Cremophor RH 40 (45%)
Dosage:	BAY 54-9085: 41.1 mg/kg (Group 1); 82.2 mg/kg (Group 2); 82.2 (BID) mg/kg (Group 3) for 7 consecutive days (30, 60, 60 BID mg/kg BAY 43-9006)
Route:	oral gavage

Observations

Toxicokinetics: Blood samples for plasma drug determination were collected on

- Day 1 and Day 7 from Groups 1 and 2 at 0.5, 1, 2, 4, 8, and 24 hours after dosing.
- On Day 1 and 7 from Group 3, after second administration at 0.5, 1, 2, 4, 8, and approximately 18 hours.

Results:

Toxicokinetics: Method of detection: (

PK parameters	Day 1			Day 7		
	Group 1 30 QD	Group 2 60 QD	Group 3 60 BID	Group 1 30 QD	Group 2 60 QD	Group 3 60 BID
C_{max} (mg/l)	7.3 ± 1.1	7.1±2.1	17.7±1.2	6.2±1.5	7.0±1.5	9.8±1.4
AUC_{0-24} (mg.h/l)	74.7 ± 1.4	86.3±2.4	228*±1.2	79±1.2	82.8±2.0	114±1.6
T_{max} (h)	3.36 ± 1.4	2±1	4±1	3.4±1.4	2.4±1.9	2.8±1.5
$t_{1/2}$ (h)	6.29 ±1.7	7.5±1.5	13.5±2.0	7.6±1.7	4.9±1.3	3.6±1.3

(*) $AUC_{(0-18)}$
30, 60, and 60 mg/kg bid of BAY 43-9006, or
600, 1200, and 1200 mg/m2 bid of BAY 43-9006

- Drug exposure in dogs appears to plateau at 60 mg/kg after a single oral dose.
- Drug exposure was similar between 30 and 60 mg/kg QD showing no drug accumulation or autoinduction after multiple oral administration of BAY 43-9006 in dogs.
- Increased drug exposure and Cmax were observed for 60 BID after the 2nd dose as compared to 60 mg/kg QD group. These results suggest a possible autoinduction of metabolism after multiple 60 mg/kg BID for 7 days.

- No gender-dependence in the drug exposure of BAY 43-9006 for the 30 mg/kg QD group, whereas female dogs showed higher plasma concentrations than males at 60 mg/kg QD.
- Cmax and AUC levels are not proportional to dose suggesting saturation of drug absorption. Sponsor previously suggested drug crystallization in the GI tract.

Study Title: Plasma Concentrations of BAY-43-9006 from a 4-Week Toxicity Study in Rats Dosed with BAY 54-9085 (T3068937; RS010)

Report: MRC-01052
Study # T3068937; RS010 (This is the TK data of Study Report PH-30261)
A GLP study conducted by PH-PDT Toxicology, Bayer AG, Germany.

Study dates: December 14, 1999-January 4, 2000
Species and strain: Rat (strain not specified) (4 groups of 3 animals/time point/sex/group) Control group (6 rats)
Age/Weight: Age and weight not provided
Batch#: BAY 54-9085 batch # 990722
Formulation/vehicle: BAY 54-9085 was suspended in 15% Pluronic® F68, 42.5% propylene glycol and 42.5% polyethylene glycol 400
Dosage: 0, 1.5, 7, 35, and 170 mg/kg BAY 54-9085 x 3 to 4 consecutive weeks 1, 5, 25, and 125 mg/kg (free base equivalent)
Route: Oral gavage (10 ml/kg)
Methods: Blood was collected at 0.5, 1, 2, 4, 7, and 24 hours post administration. The two high dose groups were drawn early due to the poor health of the animals. Blood was obtained from the control group animals at 0.5 and 1 hour post administration on Day 1 and Day 28.
[redacted] method; LOQ= [redacted] µg/l.

Results:

*BAY 43-9006 (mg/kg)	Sex	Day 1					
		$AUC_{(0-24)}$ (µg*h/l)	Fold-difference	AUC/dose	C_{max} (µg/l)	Fold difference	C_{max}/dose
1	♂	6622	-	6622	503.9	-	504
	♀	7616	-	7616	544.1	-	544
5	♂	32531	5	6506	2284.8	5	457
	♀	45143	6	9029	3246.3	6	649
25	♂	228228	7	8778	13841.7	6	532
	♀	279274	6	10741	16089.9	5	619
125	♂	308654	1	2489	19836.6	1	160
	♀	403537	1	3254	26167.2	2	211

*Doses: 6, 30, 150, and 750 mg/m2 of BAY-43-9006

*BAY 43-9006 (mg/kg)	Sex	Day 21/28					
		$AUC_{(0-24)}$ (µg*h/l)	Fold-difference	AUC/dose	C_{max} (µg/l)	Fold difference	C_{max}/dose
1	♂	10342.6		10343	727.3		727
	♀	12961.6		12962	853.6		854
5	♂	60903.0	6	12181	3723.6	5	745
	♀	73213.9	6	14643	4716.3	6	943
25	♂	283315.0	5	10897	15158.	4	583
	♀	261002.0	4	10039	13541.1	3	521
125	♂	205429.0	1	1657	12412.8	1	100
	♀	219715.0	1	1772	10244.7	1	83

* Doses: 6, 30, 150, and 750 mg/m2 of BAY 43-9006

BAY 43-9006 (mg/kg)	Sex	Comparison between Day 1 and Day 21/28			
		AUC fold accumulation	AUC % change from day 1	C_{max} fold accumulation	C_{max} % change from day 1
1	♂	2	↑56	1	↑44
	♀	2	↑70	2	↑57
5	♂	2	↑87	2	↑63
	♀	2	↑62	1	↑45
25	♂	1	↑24	1	↑10
	♀	1	↓7	1	↓16
125	♂	1	↓33	1	↓37
	♀	1	↓46	0	↓61

Conclusions:

- Females appeared to have slightly higher exposures than ♂s in most cases.
- In the 1 – 5 mg/kg and the 5 – 25 mg/kg dose ranges, approximately dose proportional increases in exposure were observed (5-7 fold increase in exposure to ~5-fold dose increments). However, in the 25 – 125 mg/kg dose range the increase in exposure was less than dose proportional (1-fold increase in exposure to ~5-fold increment in dose). On Day 1, the $AUC_{(0-24)}$ for 124 mg/kg dose was only marginally higher than that for the 25 mg/kg dose, and on the last day of sampling the $AUC_{(0-24)}$ for the 124 mg/kg dose was actually lower compared to the 25 mg/kg dose (possibly due to poor solubility of the drug).
- There is a moderate accumulation for the 1 and 5 mg/kg doses, as evidenced by an increase of approximately 56-87% in $AUC_{(0-24)}$ from Day 1 to Day 28. However, there was no increase in exposure for the 25 mg/kg dose, and a decrease in exposure (33-46%) for the 125 mg/kg dose.

Study Title: Plasma Concentrations of BAY-43-9006 from a 4-Week Toxicity Study in Dogs Dosed with BAY 54-9085 (T3069071; RS011)

Study Report: MRC-01053
Study #: T3069071; RS011 (This is the TK data of Study Report PH-30221)

A GLP study conducted by PH-PDT Toxicology, Bayer AG, Germany.
Study dates: February 16, 2000

Species and strain: Dog (strain not specified) (3 groups of 4 dogs /sex/group)
2 control groups (0 mg/kg) with 4 animals/sex/ group
2 recovery groups (0 & 60 mg/kg) with 2 animals/sex/group

Age/Weight: Age and weight not provided

Lot#: BAY 54-9085 lot # 505003

Formulation/vehicle: BAY 54-9085 (tosylate salt of BAY 43-9006), formulated in 2-Pyrrolidon /Propylene glycol Cremophor RH 40 10/45/45 %,

Dosage: 10, 30, and 60 mg/kg (free base equivalent). This study began with twice daily dosing (total daily doses of 20, 60, and 120 mg/kg), with a 5 hour interval between the first and second daily dose. From Day 14 onward, due to ill health of the animals, dosing was reduced to once daily.

Route: Oral gavage (10 ml/kg)

Methods: On Day 1 and Week 4, blood was collected at 1, 3, 7, and 24 hours post administration from the dosed groups. From the control group and 0 mg/kg recovery group, blood was obtained only at the 1 hour time point, on Day 1 and on Week 4. Blood samples were also drawn from the recovery animals on week 8.

[redacted] method; LOQ=~ – µg/l.

Results:

Dose (mg/kg)*	Sex	Day 28 (week 4)						
		$AUC_{(0-24)}$ (µg*h/l)	Fold-difference	AUC/dose	% change from ♂	C_{max} (µg/l)	Fold difference	C_{max}/dose
10	♂	15326		1533		2292		229
	♀	19007		1901	24	2043		204
30	♂	34374	2	1146		3167	1	106
	♀	45163	2	1505	31	4998	2	167
60	♂	40707	1	678		4939	2	82
	♀	66200	1	1103	63	5671	1	95

*BID dosing days 1-14, QD day 14 onward.

Conclusions:

- The sampling design for Day 1 was inadequate for obtaining pharmacokinetic parameters, so conclusions are based on Week 4 data.
  - Females exhibited higher exposure levels (24-63%) compared to males and it appears to increase with dose.
  - The increase in $AUC_{(0-24)}$ and C_{max} was less than dose proportional for both the 10 – 30 (2-fold increase in parameters for 3-fold increment in dose), and the 30 – 60 mg/kg dose ranges (1-2 fold increase in parameters to 2-fold dose increment).

Study Title: Plasma Concentrations of BAY-43-9006 from a Cardiovascular Safety Study in Dogs Dosed with BAY 54-9085 (T1065145; RS013)

Report MRC-01054
Study # T1065145; RS013

A GLP study conducted by PH-PDT Toxicology, Bayer AG, Germany.
Study dates: March 1, 2000
Species and strain: Beagle dog (3 groups)

Dose (mg/kg)	♂(n=)	♀(n=)
7	1	2
22	1	2
44	1	2

1 control groups (0 mg/kg) with 3 animals/sex/ group. Data was not analyzed.

Age/Weight: Age and weight not provided
Batch#: 990722
Formulation/vehicle: BAY 54-9085 (tosylate salt of BAY 43-9006), formulated in 2-pyrrolidone / cremophor RH40/ propyleneglycol 10/45/45 % w/w/w

Dosage: 10, 30, and 60 mg/kg BAY 54-9085
7.3, 22, and 44 mg/kg BAY 43-9006 (free base)
146, 438, and 876 mg/m2 BAY 43-9006
Route: Intraduodenal

Methods: Blood was collected at pre-dose and at 0.5, 1, 2, and 4 h post administration.
( ) method; LOQ=( ) µg/l.

Results:

Dose	Day 1					
(free base eq.) (mg/kg)	$AUC_{(0-4)}$ (µg*h/l)	Fold-difference	AUC/dose	C_{max} (µg/l)	Fold difference	C_{max}/dose
7	1939		277	588		84
22	4666	2	212	1497	3	68
44	8246	2	187	2841	2	65

Conclusions:

- AUC_{0-4} appears approximately proportional between the 3 doses.
- Dose normalized C_{max} values from this study (84.05, 68.07 and 64.56 g/l for 7, 22, and 44 mg/kg, respectively) are approximately half the values obtained after oral administration in the 4-week toxicity study in dogs. The dose normalized C_{max} in the 4-week toxicity study were 215 and 133 µg/l at doses of 10 and 30 mg/kg, respectively.
- The route of administration differs between study #MRC 01053 (oral gavage) and #MRC 01054 (intraduodenal).

PK/TK of sorafenib (parent compound) from the repeat dose toxicology and the safety pharmacology studies:

Rat 7 day toxicology at 150, 750, and 1500 mg/m2 of free base- po

- Saturation of absorption when sorafenib was dosed for 7 days to ♀ SD rats at 750 and 1500 mg/m2 of the free base. Slightly lower exposure at 1500 mg/m2 of sorafenib on Day 7 compared to the 750 mg/m2 dose on Day 7.

Rat 4-week toxicology at 6, 30, 150, and 750 mg/m2 of the free base (LD, LMD, HMD, and HD, respectively)- po

- No significant differences in exposure between ♂a and ♀s
- Dose proportional increases in exposure were observed going from LD to LMD to HMD (5-7 fold increase in exposure to ~5-fold dose increments).
- When going from HMD to HD the increase in exposure was less than dose proportional. According to the sponsor, this was due to the poor solubility of the test article at HD.
- There is a moderate accumulation for the LD and LMD, as evidenced by an increase of approximately 56-87% in $AUC_{(0-24)}$ from Day 1 to Day 28. However, there was no increase in exposure for the HMD, and a decrease in exposure (33-46%) for the HD.

Rat 6-month toxicology at 0.6, 6, and 15 mg/m2 of the free base- po
TK assessments were done on Days 5, 111, and 187 (Weeks 1, 15, and 26 respectively)

- Female plasma concentrations were slightly higher than males (♀/♂: approximately 150%)
- The drug was absorbed relatively slowly, with a t_{max} of approx. 4 hours
- There was a large increase in exposure from Week 1 to Week 15 at all dose levels (Week 15/Week 1 was approximately 190%), indicating accumulation. There was no significant difference in exposure levels from Week 15 to Week 26.
- Slightly greater than dose proportional increase in exposure from LD to MD (a 13-fold increase for a 10-fold increase in dose) and from MD to HD (a 3-fold increase for a 2.5-fold increase in dose)

Dog single dose at 146, 438, and 876 mg/m2 of the free base (cardiovascular safety pharmacology)- intraduodenal

- Dose proportional increase in the AUC(0-24)s
- The normalized Cmax values (Cmax: dose) were approx. half the values obtained after 4 weeks of oral administration in dogs. The normalized AUC(0-24) values (AUC: dose) were approx. 1/6 the values obtained after 4 week of dosing. This suggests potential for drug accumulation by repeated dosing.

Dog 7 day toxicology at 600, 1200, and 1200 bid (mg/m2 of free base)- po

- Administration of sorafenib to ♂ and ♀ beagle dogs showed possible auto-induction of sorafenib metabolism at the dose of 1200 mg/m2 bid (free base) after 7 day of dosing.
- Doubling the dose (600 to 1200 mg/m2) resulted in only 15% increase in the AUC, suggesting possible saturation of absorption. However doubling the dose from 1200 mg/m2 to 1200 mg/m2 bid resulted in 165% increase in the AUC (Day 1 data); this might be due to the drug-induced GI lesions observed microscopically with ↑incidence at 1200 mg/m2 bid dose.

Dog 4-week toxicology at 200, 600, and 1200 mg/m2 of the free base (bid for Days 1-14; thereafter once daily)- po

- The sampling design for Day 1 was inadequate for obtaining pharmacokinetic parameters, so conclusions are based on Week 4 data.

- Females exhibited higher exposure levels compared to males which appeared to increase with dose (↑20% at LD and ↑60% at HD).

Dog 1-year toxicology at 60, 200, 600, and 1200 mg/m2 of the free base- po
TK assessments on Weeks 1 and 18

- There were no significant gender related differences in plasma concentrations.
- There were dose proportional increases in exposure from LD to LMD for both sampling times. Increases in exposure were nearly dose proportional from LMD to HMD and from HMD to HD on Week 1, but less dose proportional on Week 18.
- There were significant increases in exposure from week 1 to week 18 for the LD, LMD, and HMD, but not for the HD. Increases in the AUCs were approximately 145%, 190% and 135%, for LD, LMD, and HMD, respectively, indicating accumulation upon multiple dosing at these levels.

2.6.4.7 Pharmacokinetic drug interactions

Only one study submitted appears to have information on PK drug interactions. The study is entitled: Effect of Combination Therapy of the Raf Kinase Inhibitor, BAY 54- 9085, Plus Doxorubicin on Tolerance and PK in Non- tumor- bearing Mice (MRC-01230). This study has not been reviewed.

The following information provides insights into potentials for drug-drug interactions:

- Sorafenib exhibited no inductive potential on major CYP isoforms, CYP1A2 and 3A4.
- Sorafenib showed a potency to inhibit CYP isoforms (e. g. CYP2B6, 2C8, and 2C9) and UDP-glucuronosyltransferase UGT1A1 and 1A9 in vitro
- CYP3A4 is the responsible enzyme for phase I reactions (oxidative metabolism) of sorafenib in man.
- In man, sorafenib is subject to two parallel metabolic pathways yielding as primary metabolites the N- oxide (M-2) and the drug glucuronide (M-7). UDP-glucuronosyltransferase (UGT) 1A9 was identified to be responsible for conjugation of sorafenib with glucuronic acid.

The following is information on the CYP inhibition by M-2, the major metabolite of sorafenib. It should be noted that the contribution of M-2 to the overall sorafenib drug-drug interaction is minimal, considering the plasma levels of the metabolite compared to the parent compound.

- M-2 did not inhibit CYP2A6 and 2E1 (IC50> 50μM).
- M-2 is an inhibitor of CYP2C8 (Ki= 3 μM). M-2 moderately inhibits CYP2C9 (Ki= 22 μM), 2C19 (Ki= 15 μM), 2D6 (Ki= 10 μM), and 3A4 (Ki= 13 μM).

2.6.4.8 Tables and figures to include comparative TK summary

See the PK tabulated summary.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

Doses and plasma exposure (at steady state) in the toxicity studies with sorafenib

Study Type	Dose Sorafenib [mg/kg/day]	Dose Sorafenib [mg/m^2/day]	C_{max} [a] [mg/L]	AUC_{0-24h} [a] [mg·h/L]	Module in CTD
		Single-dose			
Rat, Mouse	Up to 1460	Up to 8760 Up to 4380	no data	no data	4.2.3.1.1 4.2.3.1.2
Dog	Up to 1000	Up to 20000	no data	no data	4.2.3.1.3
		Repeat-dose Rodent			
Rat 7-day	25 125 250	150 750 1500	33 34 30	695 650 595	4.2.3.7.7.2 4.2.3.7.7.3
Rat 2-week (to study effects on pancreas)	1 5 25	6 30 150	no data	no data	4.2.3.7.3.3
Rat 4-week & 4-week recovery	1 5 25 125	6 30 150 750	0.8 4.2 14 11	12 67 272 213	4.2.3.2.1 4.2.3.2.2
Rat 13-week & 4-week recovery	1 5 25	6 30 150	0.7 5.6 no data	10 92 no data	4.2.3.2.3 4.2.3.2.4
Rat 6-month	0.1 1.0 2.5	0.6 6 15	0.06 0.7 1.9	0.9 11 34	4.2.3.2.5 4.2.3.2.6 4.2.3.2.7
Mouse 13-week	30 100 300	90 300 900	12 25 31	59 147 254	4.2.3.7.7.1

a: plasma exposure of sorafenib, average of males and females at steady state (end of study)
no data: plasma exposure not measured or available, can be extrapolated from other studies

Study Type	Dose Sorafenib [mg/kg/day]	Dose Sorafenib [mg/m^2/day]	C_{max} [a] [mg/L]	AUC [a,b] [mg·h/L]	Module in CTD
		Repeat-dose Non-rodent			
Dog 7-day	30	600	6.2	79	4.2.3.7.7.4
	60	1200	7.0	83	4.2.3.7.7.5
	2x60	2x1200	9.8	114	
Dog 4-week & 4-week recovery	2x10 / 10	2x200 / 200	2.2	17	4.2.3.2.8
	2x30 / 30	2x600 / 600	4.0	39	4.2.3.2.9
	2x60 / 60	2x1200 / 1200	5.3	52	
Dog 4-week (evaluation of effects on bone and teeth)	60	1200	7	67	4.2.3.7.3.1 4.2.3.7.3.2
Dog 13-week	10	200	1.7	14	4.2.3.2.10
	30	600	3.9	35	4.2.3.2.11
	60	1200	5.8	45	
Dog 12-month	3	60	0.39	3.9	4.2.3.2.12
	10	200	1.5	17	4.2.3.2.13
	30	600	2.1	22	4.2.3.2.14
	60	1200	4.9	45	
		Reproductive Toxicity			
Rat Developmental Toxicity	0.2	1.2	0.20	0.90 [b]	4.2.3.5.2.1
	1.0	6	0.64	3.6	
	2.5	15	1.1	6.0	
Rabbit Developmental Toxicity	0.3	3.6	0.06	0.98 [b]	4.2.3.5.2.2
	1.0	12	0.21	3.4	
	3.0	36	0.72	12	

a: plasma exposure of sorafenib, average of males and females at steady state (end of study)
b: $AUC_{0\text{-}24h}$, except for $AUC_{0\text{-}7h}$ in reproductive toxicity studies with females

Exposure at steady state (end of study) of sorafenib and metabolites following continuous daily oral administration in toxicity studies

Study Type (Module in CTD)	Dose [mg/kg]	Plasma Exposure		sorafenib	M-2	M-3	M-4	M-5
Rat	0.1	$AUC_{0-24\,h}$	[mg · h/L]	0.70	n.c.	0.19	0.051	0.010
6-month		C_{max}	[mg/L]	0.049	0.001	0.011	0.003	0.001
male	1.0	$AUC_{0-24\,h}$	[mg · h/L]	10	0.12	2.1	0.603	0.086
(4.2.3.2.5,		C_{max}	[mg/L]	0.72	0.007	0.12	0.030	0.005
4.2.3.2.6,	2.5	$AUC_{0-24\,h}$	[mg · h/L]	28	n.d.	n.d.	n.d.	n.d.
4.2.3.2.7		C_{max}	[mg/L]	1.9	n.d.	n.d.	n.d.	n.d.
4.2.3.2.15)								
Rat	0.1	$AUC_{0-24\,h}$	[mg · h/L]	1.1	n.c.	0.15	0.037	n.c.
6-month,		C_{max}	[mg/L]	0.074	n.c.	0.001	0.002	n.c.
female	1.0	$AUC_{0-24\,h}$	[mg · h/L]	13	0.028	1.6	0.42	0.035
(4.2.3.2.5,		C_{max}	[mg/L]	0.74	0.001	0.089	0.021	0.002
4.2.3.2.6,	2.5	$AUC_{0-24\,h}$	[mg · h/L].	42	0.11	4.5	1.3	0.081
4.2.3.4.7		C_{max}	[mg/L]	2.2	0.006	0.25	0.058	0.005
4.2.3.2.15)								
Dog	3	$AUC_{0-24\,h}$	[mg · h/L]	3.9	n.c.	0.93	0.029	n.c.
12-month		C_{max}	[mg/L]	0.39	n.c.	0.063	0.002	n.c.
male&female	10	$AUC_{0-24\,h}$	[mg · h/L]	17	0.034	5.3	0.13	n.c.
		C_{max}	[mg/L]	1.5	0.002	0.3	0.008	n.c.
(4.2.3.2.12,	30	$AUC_{0-24\,h}$	[mg · h/L]	22	0.036	6.0	0.17	n.c.
4.2.3.2.13,		C_{max}	[mg/L]	2.2	0.003	0.33	0.010	n.c.
4.2.3.2.14,	60	$AUC_{0-24\,h}$	[mg · h/L]	45	0.14	17	0.57	0.080
		C_{max}	[mg/L]	4.9	0.014	1.1	0.041	0.006
Mouse	30	$AUC_{0-7\,h}$	[mg · h/L]	n.c.	3.1	1.4	2.3	0.54
3-month		$AUC_{0-24\,h}$	[mg · h/L]	59	n.c.	n.c.	n.c.	n.c.
male&female		C_{max}	[mg/L]	12	0.63	0.35	0.47	0.12
(4.2.3.7.7.1)								
	100	$AUC_{0-7\,h}$	[mg · h/L]	n.c.	11	5.4	7.9	2.4
		$AUC_{0-24\,h}$	[mg · h/L]	147	n.c.	n.c.	15	n.c.
		C_{max}	[mg/L]	25	1.8	1.3	1.7	0.63
	300	$AUC_{0-7\,h}$	[mg · h/L]	n.c.	15	11	18	5
		$AUC_{0-24\,h}$	[mg · h/L]	254	23	15	37	10
		C_{max}	[mg/L]	31	2.6	2.3	5.0	1.5

n.c. = not calculated, n.d. = not determined

Plasma exposure (geometric mean) at steady state of sorafenib and metabolites following continuous daily oral administration in cancer patients

Dose [mg/day]	Dose [a] [mg/m²/day]	Plasma Exposure [b]		Sorafenib (n=27)	M-2 (n=8)	M-4 (n=8)	M-5 (n=3)
2 x 400	500	$AUC_{0-12\,h}$	[mg · h/L]	64.3	7.7	3.2	3.3
		$AUC_{0-24\,h}$	[mg · h/L]	128.6	15.4	6.4	6.6
		C_{max}	[mg/L]	7.7	0.9	0.4	0.5

a: based on 60 kg person, b: AUC_{0-24h} extrapolated
Reference: Studies 10164, 100277, 100283 and 100342 (Modules 5.3.5.2.3, 5.3.5.2.5, 5.3.5.2.1, 5.3.5.2.7)

Tables provided by the sponsor.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

General toxicology:
Acute Toxicities were observed in the GI tract (soft feces and vomiting) and in the liver (↑liver enzymes). In the pivotal repeat-dose toxicology studies, conducted in rats and dogs, clear signs of toxicities were observed in the following organs/tissues: liver, kidney, hematopoietic system, skin, bone, teeth, reproductive system, GI tract, adrenals, and pancreas. In addition, hypothyroidism was noted in the chronic dog toxicity study. No adverse cardiovascular effects were seen in the dog telemetry studies under the conditions tested (no relevant changes in the QTc interval, blood pressure, or heart rate at toxic doses).

Genetic toxicology:
Sorafenib was not mutagenic in the Ames assay, in the presence or absence of S9 metabolic activation mix.

Sorafenib was clastogenic for mammalian cells in vitro, in the presence of S9 mix.

Sorafenib was negative in the in vivo micronucleus assay conducted in male mice. IP administration of BAY 54-9085 did not increase the incidence of micronucleated polychromatic erythrocytes in the bone marrow.

Additionally, Ames Test was performed to evaluate the genotoxic potential of the major metabolite (N-oxide or M-2 metabolite) as well as specific impurities of sorafenib. The M-2 metabolite was non-genotoxic in the presence or absence of S9 mix. Based on the Ames Assay, [ ] was genotoxic in TA100 and TA98 in the presence of S9.

Carcinogenicity: no studies conducted

Reproductive toxicology:
Segment 2 reproductive studies were conducted in rats and rabbits. Sorafenib was teratogenic in both species and resulted in embryo-fetal toxicities at doses that did not cause maternal toxicity.

Specific fertility and early embryonic development or pre/post-natal development studies including maternal function have not been conducted with sorafenib. Repeat-dose toxicity studies and pharmcokinetic investigations on the secretion of sorafenib into breast milk indicate a potential to adversely affect fertility and post-natal development, respectively.

Special toxicology:
Local tolerance study did not reveal signs of irritation.

2.6.6.2 Single-dose toxicity

Study Title: A single oral dose pharmacokinetic/tolerance study of BAY 54-9085 in the beagle dog.
A non-GLP study conducted by C J

Key study findings: No toxicologically significant effects following single oral administration of BAY 54-9085 (30, 60, and 120 mg/kg of BAY 43-9006) to Beagle dogs.

Report # RMI-00069

Date of study initiation: 16 July 1999

Species: Beagle dogs (3 groups of 2/sex/group)
Age/weight: At start of treatment, animals were approximately 7 months of age and ranged in weight as follows: males 7.4 to 11.1 kg; females 7.7 to 9.5 kg
Test Article: BAY 54-9085 Lot # 505003
Vehicle: 15% Poloxamer 188 NF/42.5% Propylene Glycol/42.5% Polyethylene glycol 400
Dosage: 30, 60, and 120 mg/kg of BAY 43-9006 free base are equivalent to 41.1 mg/kg; 82.2 mg/kg; 164.4 mg/kg of BAY 54-9085 tosylate, respectively.

BAY 54-9085 (mg/kg)	BAY 43-9006		Number of Animals	
	mg/kg	mg/m2	♂	♀
41.1	30	600	2	2
82.2	60	1200	2	2
164.4	120	2400	2	2

Route: oral gavage; dose volume was 3 ml/kg.

Observations
Clinical signs: Twice daily for mortality and reactions to treatment.
Body weights: Measured at randomization, on Days -3 and -1 for dose calculations
Hematology: Once prior to treatment and approximately 24 hours after the vehicle and test articles doses.
Clinical chemistry: Once prior to treatment and approximately 24 hours after the vehicle and test articles doses.
Toxicokinetics: Blood samples for plasma drug determination were collected from each animal after test article administration at the following time-points: prior to start of dosing and 0.5, 1, 2, 4, 8, 24, 30 and 48 hours after dosing with the test article.

Results
Clinical signs: One low and mid dose male and one mid and high dose female exhibited vomitus within 30 min of dosing with the test article. No mortality was associated with this study.

Hematology: within historical laboratory ranges after administration of the vehicle or test article.
Clinical chemistry: within historical laboratory ranges
Toxicokinetics: TK data were not submitted in this Study Report

Comments: Detailed examination omitted on day 3 due to technical error.

Study Title: A single oral dose pharmacokinetic/tolerance study of BAY 54-9085 (Powder and Solution) in the beagle dog.
A non-GLP study conducted by [redacted]

Key study findings: No toxicologically significant effects following single oral administration of powder or solution of BAY 54-9085 at 1370 (powder), 41.1 (solution) and 82.2 (solution) mg/kg to Beagle dogs. These doses are equivalent to 500, 30, and 60 mg/kg of BAY 43-9006 free base, respectively.

Report # RMI-00070

Date of study initiation: 27 August 1999

Species: Beagle dogs (3 groups of 2/sex/group)
Age/weight: At start of treatment, animals were approximately 7 months of age and ranged in weight as follows: males 8.3 to 10.9 kg; females 7.9 to 9.7 kg.
Test Article: BAY 54-9085 Lot # 505003
Vehicle: 15% Poloxamer 188 NF/42.5% Propylene Glycol/42.5% Polyethylene glycol 400
Dosage: Group 1 (powder) 1370 mg/kg BAY 54-9085/ 500 mg/kg 43-9006
Group 2 (liquid) 41.1 mg/kg BAY 54-9085/ 30 mg/kg 43-9006
Group 3 (liquid) 82.2 mg/kg BAY 54-9085/ 60 mg/kg 43-9006
On Day 1, Group 1 animals were treated with powder (test article) in a gelatin capsule
Groups 2 and 3 were dosed with vehicle by gavage.
On Day 4 Groups 2 and 3 were gavaged with test article (solution)

Group No. Identification	Dose Level (mg/kg)	Number of Animals Males	Females
1 BAY 54-9085 (Powder)	1370	2	2
2 BAY 54-9085 (Liquid)	41.1	2	2
3 BAY 54-9085 (Liquid)	82.2	2	2

Table provided by the sponsor.

Route: oral (either capsule or gavage).

Observations
Clinical signs: Animals were observed twice daily for mortality and reactions to treatment.
Body weights: Measured at randomization, on Days –1 and Day 3 for dose calculations

Hematology: Once prior to treatment and approximately 24 hours after the vehicle and test articles doses.

Clinical chemistry: Once prior to treatment and approximately 24 hours after the vehicle and test articles doses.

Toxicokinetics: Blood samples for plasma drug determination were collected from each animal after test article administration at the following time-points: prior to start of dosing and 0.5, 1, 2, 4, 8, 24, 30 and 48 hours after dosing with the test article.

Results

Clinical signs:

Group 1 (500 mg/kg 43-9006) Test article (powder), males had moderate to large amount of vomitus on day 1 post dose. No mortality observed in this study.
One female exhibited soft feces (Days 1, 2, and 4) and red skin (Day 6)

Groups 2/3 vehicle administration on Day 1 resulted in red skin persisting until 2 days post administration of test article on Day 4.
Group 2 (30 mg/kg 43-9006) females and both Group 3 (60 mg/kg 43-9006) females showed increased corneal vascularization after vehicle administration.

Groups 2/3 test article (solution) administration on Day 4, one Group 2 (mid dose) and both Group 3 males and all Group 2/3 females exhibited liquid feces which generally did not persist more than one day.
Group 3 (high dose) males were warm in the cranial region on Days 4-6.
Two mid dose females experienced suspected vaginal prolapse but this was considered unlikely to be related to treatment.

Hematology: within historical laboratory ranges after administration of the vehicle or test article.

Clinical chemistry: Serum biochemistry parameters, except for AST and ALT, were within historical laboratory ranges.
Group 1 male (powder- day 2) showed increases in AST (1.6-fold) and ALT (2.7-fold).

Toxicokinetics: TK data were not submitted in this Study Report.

Study Title: BAY 54-9085: Acute Toxicitiy in the Mouse and Rat after Oral Administration.

A GLP/QA study conducted by BAYER AG, Wuppertal-Elberfeld

Key study findings: No toxicologically significant effects following single oral administration of BAY 54-9085 at 500 and 2000 mg/kg (365 and 1460 mg/kg BAY 43-9006) to the mouse or rat. No effect on acute dosing lethality was observed at these doses.

Study Report PH-29961 (referred to as MRC-01037 in the IND)

Study #s T 9069220 (mouse) and T 5069226 (rat)

Date of study initiation: 11 Nov. 1999

Species/strain:	Mouse/[C J]:NMRI (5/group/sex)
	Wistar Rat/[C J]Cpb:WU (5/group/sex)
Age/Weight:	Mice: age-not provided/Males 20-24 g; females 17-23 g
	Rats: age-not provided/Males 193-211 g; females 180-195 g
Batch number	990722,
Formulation/vehicle:	BAY 54-9085 [C J] was suspended in 15% Pluronic® F68, 42.5% propylene glycol and 42.5% polyethylene glycol 400
Dosage:	500 and 2000 mg/kg body weight BAY 54-9085 (365 and 1460 mg/kg BAY 43-9006)
Route:	Oral gavage, administration volume was 10 ml/kg body weight.

Observations

Clinical signs:	daily/14 days
Body weights:	weekly
Gross pathology	end of the study

Results:

Clinical signs:	Mouse: No clinical signs. No mortality observed in study.
	Rat: Soft feces lasting 2 d for low (500 mg/kg) dose and 2-3 d for the high (2000 mg/kg) dose. No mortality observed in study
Body weights:	No drug-induced changes in body weights.
Gross pathology	Necropsies revealed no particular findings

2.6.6.3 Repeat-dose toxicity

Study Title: Pharmacokinetics/Tolerance of BAY 54-9085 Following Multiple Administrations (7-day) to Female Sprague-Dawley Rats. A non GLP study conducted by [redacted]

Key study findings: Doses up to 342.5 mg/kg BAY 54-9085 (1500 mg/m^2 BAY 43-9006) for 7 days were generally tolerated in female rats.

Study Report RMI-00067

Species and strain: Sprague Dawley rat (4 ♀s/group)
Age/Weight: Age was not provided/ weight 211-236 g
Lot#: 505003
Formulation/vehicle: BAY 54-9085 was suspended in 15% Pluronic® F68, 42.5% propylene glycol and 42.5% polyethylene glycol 400
Dosage: Once daily for 7 days (see table below)
Route: Oral gavage (10 ml/kg)

Group Number	Number of Females	Substance	BAY 54-9085 (mg/kg)	BAY 43-9006	
				mg/kg	mg/m^2
1	4	Vehicle	0	0	0
2	4		0	0	0
3	4	BAY 54-9085	34.3	25	150
4	4		34.3	25	150
5	4		171.3	125	750
6	4		171.3	125	750
7	4		342.5	250	1500
8	4		342.5	250	1500

Table generated by the reviewer

Observations

Clinical signs: Throughout dosing and sample collection
Body weights: Prior to dosing on Days 1 and 7, and prior to necropsy
Hematology: Plasma collected on Days 1 and 7 at the following time-points: 1 and 4 hours post dose for Groups 1, 3, 5, and 7 and at 2 and 24 hours post dose for Groups 2, 4, 6, 8.
Additional blood samples were collected from all animals prior to necropsy for routine hematology (CBC)
Clinical chemistry: Prior to necropsy for routine serum chemistry analysis.
Gross pathology: Macroscopic findings and selected organs were dissected.
Histopathology: End of study
Toxicokinetics: Plasma samples were collected over 24 h after administration on day 1 and 7. The plasma samples were analyzed by [redacted] method after [redacted] with ethyl acetate.

Groups	Timepoint	Clinical Pathology		MAP
		Hematology	Serum Chemistry	Plasma for Sponsor
1, 3, 5, 7	Days 1 and 7 (1 and 4 hr post-dose)			X
2, 4, 6, 8	Days 1 and 7 (2 and 24 hr post-dose)			X
all	Day 8 (prior to necropsy)	X	X	
Volume of Whole Blood/Timepoint		~0.5 mL	~1.8 mL	~0.75 mL
Anticoagulant		EDTA	None	Heparin

Table provided by the sponsor.

Findings

Clinical signs: 3 animals (one from each Groups 2, 3, and 6) were observed on Day 1 and/or Day 7 to have eye-related abnormalities (e.g. opacity, protruding eyes). Sponsor attributes these observations to the method of interim blood collection (retro-orbital sampling).

No mortality observed in this study.

Body weights: No treatment-related change in body weight.

Hematology: Decrease in red blood cell counts (~15%), hemoglobin (~17%), and hematocrit (~16%) in treated animals from all treatment groups. There was no dose-dependency effect.

Clinical chemistry: Elevated liver enzymes [ALT (↑6-fold), AST (↑3-fold), and ALK (↑2-fold)] in animals from all treatment groups. There was no dose-dependency effect.

Gross pathology: No gross pathological changes at any dose. Liver and thymus discoloration was observed in 1 animal at 25 mg/kg, lung discoloration in 2 animals at 250 mg/kg, and mandibular lymph node discoloration in 3 animals at 25 mg/kg and 3 animals at 125 mg/kg.

Histopathology: Liver: Increased incidence of hepatocellular karyomegaly (7/16 at 25; 8/16 at 125; 8/16 at 250 mg/kg) and apoptosis (8/16 at 25; 8/16 at 125; 8/16 at 250 mg/kg) in all test article treated animals. Severity of liver changes was greater in 125 and 250 mg/kg (karyomegaly Grade 2 or higher: 4/16 at 250 mg/kg; apoptosis Grade 3 or higher: 1/16 at 250 mg/kg)

Kidney: Increased incidence of renal and tubular dilatation and protein/hyaline casts in animals from all treatment groups. Severity was mild and similar among all treatment groups (4/16 at 25; 4/16 at 125; 7/16 at 250 mg/kg).
Spleen: Increased incidence of splenic coagulative/congestive degeneration in animals from all treatment groups (8/16 at 25; 8/16 at 125; 8/16 at 250 mg/kg). Severity was slightly greater at 250 mg/kg.
Bone Marrow: Dose-dependent degeneration of hematopoietic cells within the femoral marrow cavity of all test-article treated animals (8/16 at 25;

8/16 at 125; 8/16 at 250 mg/kg). Severity of this finding increased with dose from 25 mg/kg to 250 mg/kg.

Toxicokinetics: Method of detection: [ ]

Dose of BAY 43-9006		Day 1			Day 7		
mg/kg	mg/m^2	C_{max} (mg/l)	T_{max} (h)	AUC $_{0-24}$ (mg*h/l)	C_{max} (mg/l)	T_{max} (h)	AUC $_{0-24}$ (mg*h/l)
25	150	25.53	2.25	414.7	33.03	3.5	695.2
125	750	41.15	2	746.9	33.66	3	649.9
250	1500	39.22	2	649.4	29.76	3.25	594.7

- Drug-exposure appears to be dose-dependent up to 125 mg/kg.
- Highest drug exposure occurred at 125 mg/kg. No further increase in drug concentration was seen at 250 mg/kg.
- Oral absorption occurred with T_{max} of 2-4 hr for all doses.
- There was potential accumulation in the female rats after multiple oral administration of 25 mg/kg. Drug accumulation or auto-induction was not observed at higher doses of 125 and 250 mg/kg.

Summary of the study

Oral doses of 25, 125, and 250 mg/kg BAY 43-9006 for 7 days were generally tolerated in female rats. There was no mortality or treatment-related changes in body weight observed in this study. Treatment resulted in dose-dependent bone marrow degeneration, as well as elevated liver enzymes (ALT, AST, and ALP) in animals from all treatment groups. Histopathological changes were observed in the liver, kidney, spleen, and bone marrow. Pharmacokinetic experiments show that drug exposure is dose-dependent up to 125 mg/kg BAY 43-9006. Also, there is a potential accumulation in the female rats after multiple oral administration of 25 mg/kg but drug accumulation was not observed at 125 and 250 mg/kg.

Study Title: BAY 54-9085: Subacute Toxicity Study in Rats Oral Administration (Gavage) for 4 weeks (including 4 Weeks Recovery). A GLP study conducted by BAYER AG, Wuppertal-Elberfeld.

Key study findings: Treatment of rats with BAY 54-9085 over a period of 4 weeks induced dose-dependent toxic signs in most of the assayed parameters. These signs did not completely return to normal after a treatment-free recovery period of additional 4 weeks in the highest dose group. The no-adverse effect dose in this study is below 1.5 mg/kg body weight.

Study Report PH-30261 (referred to as MRC-01027 in the IND)

Study initiation: 13-Oct-1999
GLP and QA: Yes
Species and strain: Rats [ ] Cpb:Wu) (10 rats/group/sex)
Age/Weights: 6-7 weeks/Males: (136-192 g) Females (113-156 g)

Groups (recovery): 10 rats/group/sex treated analogously with 0 and 170 mg/kg body weight and observed for a subsequent 29 day treatment-free period for reversibility, continuation or delayed occurrence of possible toxic effects.

Groups (toxicokinetics): 4 rats/sex for each dose and time series (3 rats/sex for controls)
Drug lot #: BAY 54-9085, Batch # 990722
Formulation/vehicle: BAY 54-9085 was dissolved in 15% Pluronic® F68, 42.5% propylene glycol and 42.5% polyethylene glycol 400
Dosage: Daily 0, 1.5, 7, 35, 170 mg/kg bw BAY 54-9085 for 4 weeks (0, 1, 5, 25, 125 mg/kg BAY 43-9006)
Route: Oral gavage (5 ml/kg body weight)

Observations
Clinical signs: Twice a day
Body weights: Daily before drug administration or necropsy. During period of recovery, rats were weighed once a week.

Food/water consumption: Weekly
Hematology: Week 4 of the study, as well as week 8 in recovery group.
Clinical chemistry Week 4 of the study, as well as week 8 in recovery group.
Urinalysis: Over periods of about 16 h, on days 3/4 and 23/24 of the study from all animals of the groups 1-10 and in week 4 and 8 from all animals of the recovery group.
Gross pathology End of study
Organs weighed: Brain, heart, liver, spleen, kidneys, adrenals, testes, epididymis, and thymus
Histopathology: End of study
Toxicokinetics: Blood was collected at 0.5, 1, 2, 4, 7, and 24 h post administration from the main study groups. The two high dose groups were drawn early due to the poor health of the animals. Blood was obtained from the control group animals at 0.5 and 1 hour/post administration on Day 1 and day 28.
Other: Determination of fluoride in rat femurs and teeth.

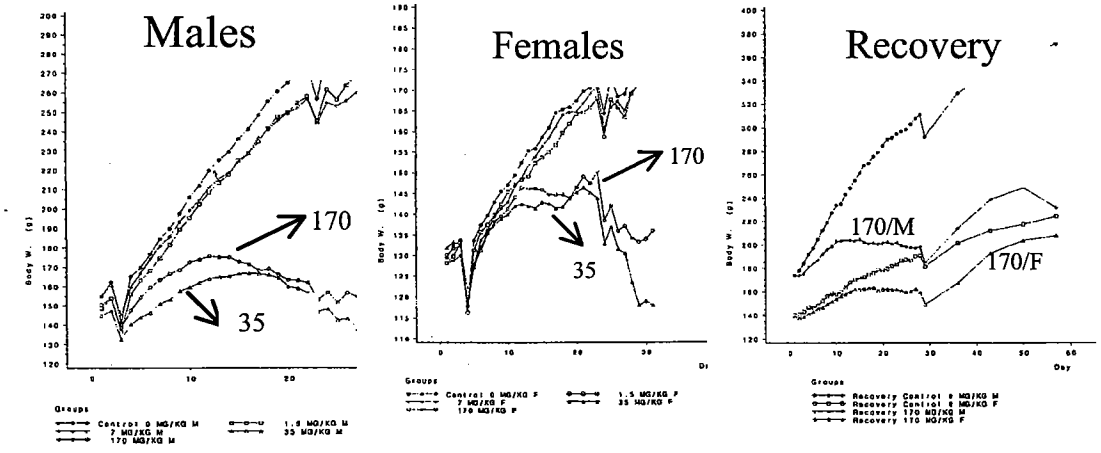
Results:
Clinical signs: Mortality included the following:

Study Groups	BAY 43-9006		BAY 54- 9085	Mortality			
	mg/kg	mg/m2	mg/kg	♂	Test days	♀	Test days
Test Groups	0	0	0	0		0	
	1	6	1.5	0		0	
	5	30	7	0		0	
	25	150	35	3	24,25,25	9	19,20,21,22,26 27(3♀), 29
	125	750	170	3	23,25,26	1	20
Recovery Groups	0	0	0	0		0	
	125	750	170	2	52,53	1	34
TK Groups	1	6	1.5	1*	16	0	
	25	150	35	2	17,19	1	21

*Sponsor believes this death is not related to the test article as there are no distinguishing toxicities in this animal to explain its death.

BAY 43-9006 (mg/kg)	Clinical symptoms
1	soft feces
5	piloerection, pallor
25	piloerection, pallor, reduced motility, flaccidity, squatting position, labored breathing, soft feces, red tears
125	piloerection, pallor, reduced motility, abdominal position, extension spasm (tonic), flaccidity, labored breathing , soft feces
Recovery groups	
0	loss of hair on abdomen on flank, eye injured (blood sampling)
125	teeth cut, piloerection, pallor, emaciation, swelling on abdomen, swelling on head-both sides, reduced motility, flaccidity, high stepping gait, labored breathing, increased urine excretion, soft feces, increased feces excretion, white teeth.

Body weights: Strong decreasing effect on the weight gain of the male and female rats in the 25 and 125 mg/kg dose groups. Especially in males the body weight did not reach the weight of controls after the recovery period. The 25 mg/kg dose appears to cause more toxic effect than the highest dose tested.



Food and water consumption: Decreased in the 25 and 125 mg/kg groups but returned to control levels during recovery period.

Hematology:

Parameters	Dose of BAY 43-9006; mg/kg			
	1 (M/F)	5 (M/F)	25 (M/F)	125 (M/F)
Hb	—	—	↓(27/64%)	↓(16/25%)
Erythrocytes	—	—	↓(34/70%)	↓(21/33%)
Reticulocytes	—	↓(30/14%)	↑(88/979%)	↑(27/600%)
Thrombocytes*	—	↓(19/15%)	↓(60/57%)	↓(55/27%)

* Only parameter to recover after treatment-free period.

Statistical evaluation of hematological investigation

Hematology	Controls		1.5 mg/kg		7 mg/kg		35 mg/kg		170 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
LEUCO 10E9/l	10.94	8.59	11.99 -	8.13 -	12.22 -	8.20 -	7.22 **	7.27 -	7.54 **	7.22 -
ERY 10E12/l	7.73	7.99	7.93 -	8.07 -	8.04 -	8.19 -	5.12 **	2.37 **	6.14 **	5.33 **
HB g/l	147	146	151 -	151 -	158 -	153 -	107 **	52 **	124 **	110 **
HCT l/l	0.457	0.441	0.463 -	0.453 -	0.484 -	0.451 -	0.311 **	0.158 **	0.363 **	0.330 **
MCV fl	59.1	55.2	58.5 -	56.1 -	60.2 -	55.2 -	61.2 -	67.1 **	59.3 -	62.5 **
MCH pg	19.1	18.2	19.0 -	18.7 -	19.6 -	18.7 -	21.0 **	21.9 **	20.3 **	20.8 **
MCHC g/l ERY	323	330	325 -	334 -	326 -	339 *	343 **	327 -	342 **	333 -
RETI ‰	26	14	26 -	18 -	18 **	12 -	49 -	151 **	33 -	98 **
THRO 10E9/l	1247	1105	1135 -	1114 -	1007 *	936 -	494 **	479 **	563 **	804 **
HQICK sec	29.6	29.3	29.4 -	29.1 -	28.8 -	28.1 -	27.3 *	27.1 -	27.6 -	27.0 *

- : no significant difference
* : difference at the 5% significance level
** : difference at the 1% significance level
Underlining : outside the 2s-range of historical controls
double underl. : outside the 3s-range of historical controls

HQICK: thromboplastin time

Table provided by the sponsor.

Doses of 1.5, 7, 35, and 170 mg/kg BAY 54-9085 correspond to approx 1, 5, 25, and 125 mg/kg of BAY 43-9006, respectively.

Statistical evaluation of hematological investigation of recovery groups

Hematology	Control				170 mg/kg			
	♂		♀		♂		♀	
week	5	8	5	8	5	8	5	8
LEUCOX 10E9/l	11.95	9.68	8.13	5.89	10.25 -	9.58 -	8.67 -	4.90 *
ERY 10E12/l	8.20	8.24	8.23	7.74	6.36 **	7.28 *	4.86 **	6.94 **
HB g/l	152	149	148	147	129 **	146 -	104 **	147 -
HCT l/l	0.468 -	0.445	0.442	0.431	0.387 **	0.439 -	0.320 **	0.440 -
MCV fl	57.2	54.1	53.7	55.7	61.3 *	60.5 **	67.3 **	63.5 **
MCH pg	18.5	18.1	18.0	18.9	20.4 **	20.1 **	21.8 **	21.1 **
MCHC g/l ERY	324	334	335	340	333 **	332 -	325 *	333 **
RETI ‰	21	24	15	19	55 **	26 -	117 **	26 -
THRO 10E9/l	1183	1092	1189	1147	915 **	1188 -	1007 *	1118 -
HQICK sec	31.5	31.1	28.3	28.4	26.3 **	28.5 -	25.3 **	26.9 -

- : no significant difference
* : difference at the 5% significance level
** : difference at the 1% significance level
Underlining : outside the 2s-range of historical controls
double underl. : outside the 3s-range of historical controls

HQICK: thromboplastin time

Table provided by the sponsor.

Clinical chemistry: Fold change compared to pre-treatment.

Serum Chemistry Parameters	1 mg/kg (Males/Females)	5 mg/kg (Males/Females)	25 mg/kg (Males/Females)	125 mg/kg (Males/Females)
AST	—	↑(1.6/1.6)	↑(3.9/4.7)	↑(2.6/2.8)
ALT	↑(1.2/1.2)	↑(1.9/2.3)	↑(3.3/4.8)	↑(2.4/2.7)
ALP	—	↑(1.3/1.4)	↓(0.3/0.6)	↓(0.4/0.5)
GLDH*	—	—	↑(17/5)	↑(5/2.7)
LDH	—	—	↑(9.9/9.4)	↑(6.2/5.4)
Cholesterol*	—	↑(1.1/1.5)	↑(2.3/2)	↑(2.3/2.2)
Bilirubin	—	↑(1.3/1.5)	↑(4.3/3.4)	↑(3.9/3.9)
Urea	—	—	↑(1.3/2)	—
Protein	—	—	↓(0.7/0.7)	↓(0.8/0.8)
Calcium	—	—	↓(0.9/0.9)	↓(0.9/0.9)

* Parameter did not or only partially changed after recovery period.

Clinicochemical investigation		Controls ♂	Controls ♀	1.5 mg/kg ♂	1.5 mg/kg ♀	7 mg/kg ♂	7 mg/kg ♀	35 mg/kg ♂	35 mg/kg ♀	170 mg/kg ♂	170 mg/kg ♀
K	mmol/l	4.9	4.3	4.9 -	4.1 -	4.8 -	4.5 -	4.5 *	4.1 -	4.5 *	4.6 -
Ca	mmol/l	2.69	2.60	2.64 -	2.62 -	2.68 -	2.62 -	2.37 **	2.40 *	2.43 **	2.38 **
P	mmol/l	2.35	1.84	2.23 -	1.87 -	1.61 **	1.47 **	1.74 **	1.59 -	1.81 **	1.75 -

- : no significant difference
* : difference at the 5% significance level
** : difference at the 1% significance level
Underlining : outside the 2s-range of historical controls
double underl. : outside the 3s-range of historical controls

Table provided by the sponsor.

Urinalysis: At 25 and 125 mg/kg, dose-related changes in protein, urine creatinine, NAG, GGT, AAP, and LDH. Recovery group did not return to normal values in all parameters

Urinalysis	25 mg/kg (Males)	25 mg/kg (Females)	125 mg/kg (Males)	125 mg/kg (Females)
Protein	—	↑4.5	—	↑1.9
GGT	↓0.6	↓0.8	↓0.6	↓0.8
AAP	↓0.7	↓0.9	↓0.7	↓0.9
LDH	—	↑2.4	↑1.2	↑1.9
NAG *Vol)	—	↑1.5	—	—
GGT *Vol)	↓0.6	↓0.7	↓0.6	↓0.7
AAP*Vol	↓0.6	↓0.8	↓0.6	↓0.8
LDH/Crea	—	↑2.0	↑1.2	↑1.6
NAG/Crea	—	↑1.6	↑1.2	↑1.3
GGT/Crea	↓0.6	↓0.8	↓0.6	↓0.8

AAP: L-alanine aminopeptidase; NAG: N-acetyl-beta-D-glucosaminidase; GGT: gamma-glutamyl transpeptidase; LDH: lactate dehydrogenase; Crea: creatinine

Organ Weights: Most absolute organ weights showed differences beginning at 5 mg/kg. In recovery group, these changes were still measurable.

Organ Weights (mg)	5 mg/kg (M)	5 mg/kg (F)	25 mg/kg (M)	25 mg/kg (F)	125 mg/kg (M)	125 mg/kg (F)
Brain	—	—	—	—	—	—
Adrenals	—	—	↑1.9	↑2.6	↑1.7	↑2.4
Heart	↓0.8	—	↓0.6	—	↓0.6	—
Liver	↓0.8	—	↓0.4	↓0.7	↓0.5	↓0.8
Spleen	—	—	↓0.4	↓0.6	↓0.6	↓0.8
Thymus	—	↓0.7	↓0.2	↓0.2	↓0.2	↓0.3
Kidneys	—	—	↓0.8	—	↓0.7	—
Testes	—	—	↓0.4	—	↓0.6	—
Epididymis	—	—	↓0.3	—	↓0.5	—

Gross pathology: Table shows incidence of findings

		♂				♀			
	BAY 43-9006 (mg/kg)	1	5	25	125	1	5	25	125
Adrenal glands	discoloration/s	0		9	10			3	9
	enlarged			7	8			7	9
Liver	discoloration/s	1							
	distinct lobulation	0		1					
	Area/s							1	
Duodenum	abscess-like lesion	0			1				
	change in contents	0			2				
	dilation/s				1				
	discoloration/s	0			1				
	thickened			5	9			2	7
	Area/s							1	
Pancreas	adhesion/s				1				
	consistency-change/s	0			1				
	discoloration/s	0			1			1	
Stomach	Area/s			4	2			2	4
	Change in contents	0			5			1	6
	dilation/s							2	
	discoloration/s	0		3	2				2
Kidneys	discoloration/s	0		3					
	enlarged	0		3					1
	dilations								1
	surface-change/s	0		1	1			2	3
Testes	consistency-change/s	0	1						
	diminished in size	1							
	displacement	1	1						

At 25 and 125 mg/kg, changes were observed in the digestive tract, kidney, and adrenal glands. After recovery period, clinical signs of retardation were still present in males. Also, animals showed findings in the teeth that were not previously observed in the main group.

Histopathology:

	BAY 43-9006 (mg/kg)	♂ 0	♂ 1	♂ 5	♂ 25	♂ 125	♀ 0	♀ 1	♀ 5	♀ 25	♀ 125
Adrenal glands	peliosis				10	8				10	10
	necrosis				6	8				7	6
Liver	Glycogen Decr.				10	8	0	0	0	7	2
	Bile duct proliferation				7	9					
	Multi focal/Necropsis				6	1					
	Nuclear activation				8	7					
Stomach	Hyperkeratosis/Fore.			1	7	10			2	2	8
	Foc. Dyskeratosis				1	1				1	1
	Ulcer				1						1
	Cel. Hypert./Pylor				7	8				3	10
	Autolytic Changes				3	1				7	
Duodenum	Hypertrophy/Mucosa			5	9	7			1	5	9
	Hypertrophy/Muscul				4	7				1	7
	Necrosis/Bile Duct					4				2	1
	Inflam Infiltration				6	8				4	9
	Autolytic Changes				1	1				7	
Pancreas	Atrophy				9	10				5	7
	Edema				9	9				7	8
	Inflammation				1						1
	Autolytic Changes				4	2	2		1	7	
Kidneys	basophilic tubules	6	5	6	9	10	2	2	5	4	10
	Tubular Dil/Cortex	1		4	9	5	1		2	5	7
	Tubular Dil/medulla					1					1
	Hyaline Casts/Detr.	1		1	8	7			2	5	7
	glomerulopathy			2	5	7	0	0	0	2	10
	Granulocytic Infiltr.				3					2	
Heart	Chron. Inflam./Fibr.			1	1						
	Deg./Inflamm.				3	1					
	Autolytic Changes				3	2				8	1
Lymph Nodes	Mesenteric/atrophy	0			6	6				3	6
	Mesenteric/follicular necrosis	0		4	2	4			7	4	5
	Autolytic Changes	0			1					4	
	Mandibular/follicular necrosis	0			2	1			3	3	1
	Autolytic Changes	0			1					4	
Thymus	atrophy				6	6	1			8	8
Spleen	Necrosis/White Pulp				1	3				8	
	Necrosis/red Pulp				1	2				6	
	Granulocytic infilt.				1	1					
	Inc Blood content				4	6				5	7
	Lymphoid Depletion				1	1	1			8	1
	Dec hemopoiesis				8	4				9	
Femur	hypocell/Growth Plate				10	10			1	10	10
	Growth Plate thick			6	10	10			6	10	10
Teeth	Dentin degeneration			10	10	10					

Ovaries	Retardation									10	10
	necr/corp lutea							1	9	6	6
	Autolytic Changes									7	
Testes	Tub. Degen/Retard.		1	1	10	10					
	Autolytic Changes				1	1					

At 25 and 125 mg/kg, degeneration changes were observed in adrenal glands, liver, stomach, duodenum, pancreas, kidneys (also at 5 mg/kg), heart (also at 5 mg/kg), testes (also at 5 mg/kg), and ovaries (also at 5 mg/kg).

- Regenerative changes in liver, pancreas, duodenum (also at 5 mg/kg), and kidneys.
- Cytotoxic effects in bone marrow (also at 5 mg/kg and 1 mg/kg males), spleen, lymph nodes (also at 5 mg/kg), thymus, and tongue (also at 7 mg/kg).
- Findings were noted in the teeth (e.g. dentin/ ameloblast degeneration and hyperostosis/ osteolysis of the jawbone) and proximal growth plate of the femoral bone (5, 25, and 125 mg/kg)
- Severe testicular degeneration at 5, 25 and 125 mg/kg.
- After 4 weeks of recovery, most findings were shown to be reversible except for liver and kidneys changes were observed with almost the same severity when compared to the 125 mg/kg group of the main study.
- Recovery animals still showed a prominent decrease in number of mast cells in the tongue, as well as degenerative processes on incisors. Furthermore, osteolytic and /or osteodystrophic processes became evident in the 125 mg/kg recovery groups. Thickening of the growth plate of the femoral bone was also still present in some treated animals of the recovery group. Also increased bone formation beneath the growth plate and abnormal formation or epiphysiolysis was observed in some 125 mg/kg animals

Recovery	♂		♀	
mg/kg	**0**	**125**	**0**	**125**
HEART				
- Infiltr. Mononuclear:	3	1	1	
- Chron.inflam./Fibr.	2	2		1
TONGUE				
- Intracytopl.Vacuol. -		3	1	1
- Mast Cells/Decr. -		10		8
STOMACH				
- Hyperkeratosis/Fore.		1		1
- Glandular Dilation	2	5		2
- Forestomach Edema				
- Hemorrhage				
- Autolytic Changes				1
DUODENUM				

- Degener./Regener.		1		1
- Hemorrhage		1		
- Chron.Inflamm.		1		1
- Autolytic Changes		1		1
LIVER				
- Glycogen Decr. -		8		2
- Bile Duct Prolifer. -		7		9
- (Multi-)Focal/Necr. -		1		
- Single Cell Necroses: -		5		1
- Mononuclear Infiltr.: -		1	3	
- Nuclear Activation -		7		1
- Periportal Fibrosis -		2		
PANCREAS				
- Atrophy -		1		2
- Degener./Regener. -		8		3
- Edema -		3		1
- Infiltr. Mononuclear:	1	-	1	
- Autolytic Changes -		2		1
KIDNEYS				
- Basophilic Tubules	10	8	3	8
- Tubular Dil./Cortex	2	6		5
- Hyaline Casts/Detr. -		5		2
- Glomerulopathy -		5		4
- Tubular Pigment -		6		9
- Macroph.Intraglom. -		3		3
- Inf:Mononuclear	2	3	1	4
- Autolytic Changes -		1		1
TESTES				
- Tub.Degen./Retardat.: S	5	8		
- AUtolytic Changes -		1		
ADRENAL GLANDS				
- Intracyt.Vac./Incr. 6	6	8		8
- Pigmentl.Macrophag. -		6		2
- Fibrotic Tissue -		6		3
SPLEEN				
- Lymphoid Depletion		2		1
- Decr. Hemopoiesis		7		2
THYMUS				
- Atrophy -		5		1
- Incr.Necr./Single C.: -		3		1
MESENT. LYMPH NODE				
- Atrophy -		5		1
- Histiocytosis		3	8	6
MANDIB.LYMPH NODES				
- Granulocytic Infil. -		2		
FEMUR				
Hypocell./Grow.Plate		4		1
Fat Tissue	10	8	6	4
Increased Blood Con.		4		1
Growth Plate Thick.		4		4
Bone For./Growth. Plate: -		9		6
Bone malformation		2		

Epiphysiolysis		1		1
Incr.Granulocytes		7	3	7
TEETH				
Peridon.inflamm./	2	6		1
Dent.Degen./Necr./		10		9
Amelob.Degenerat./		10		9
Ilyperpl./Per.Lig./		10		10
Hyperostosis		8		6
Osteolysis/Osteodys.		6		3
Deg./Macr./Den.Pulp		4		1

Toxicokinetics: Method of detection: C

BAY 43-9006 (mg/kg)		Day 1		Day 21/28	
		AUC_{0-24} (mg*h/l)	C_{max}	AUC_{0-24} (mg*h/l)	C_{max}
1	♂	6.62	0.5	10.34	0.73
	♀	7.62	0.54	12.96	0.85
5	♂	32.53	2.28	60.9	3.72
	♀	45.14	3.25	73.21	4.72
25	♂	228.23	13.84	283.32	15.16
	♀	279.27	16.09	261	13.54
125	♂	308.65	19.84	205.43	12.41
	♀	403.54	26.17	219.72	10.24

- Females appeared to have slightly higher exposures than ♂s in most cases.
- In the 1 – 5 mg/kg and the 5 – 25 mg/kg dose ranges, approximately dose proportional increases in exposure were observed (5-7 fold increase in exposure to ~5-fold dose increments). However, in the 25 – 125 mg/kg dose range the increase in exposure was less than dose proportional (1-fold increase in exposure to ~5-fold increment in dose). On Day 1, the $AUC_{(0-24)}$ for 124 mg/kg dose was only marginally higher than that for the 25 mg/kg dose, and on the last day of sampling the $AUC_{(0-24)}$ for the 124 mg/kg dose was actually lower compared to the 25 mg/kg dose (either due to poor solubility of the drug or saturation of absorption at higher doses).
- There is a moderate accumulation for the 1 and 5 mg/kg doses, as evidenced by an increase of approximately 56-87% in $AUC_{(0-24)}$ from Day 1 to Day 28. However, there was no increase in exposure for the 25 mg/kg dose, and a decrease in exposure (33-46%) for the 125 mg/kg dose.

Other: Fluoride in rat femurs and teeth:
Significant increase (30-35%) in fluoride concentrations in treated males compared to controls. Mild increase in fluoride concentration in females (p=0.054).

Summary of the study:
Daily oral treatment of rats with 0, 1, 5, 25, 125 mg/kg BAY 43-9006 over a period of 4 weeks induced dose-dependent toxic signs in most of the parameters evaluated. These signs did not completely return to normal after a treatment-free recovery period of additional 4 weeks in the highest dose group. Mortality prior to end of 4 weeks in the main group was observed in the 25 mg/kg and 125 mg/kg groups. There was a strong decreasing effect on the weight gain of the

male and female rats in the 25 and 125 mg/kg dose groups. There were reductions in the levels of WBC, erythrocytes, hemoglobin, and platelets as well as increases in reticulocytes, which were mainly evident at 25 mg/kg and 125 mg/kg. A host of clinical chemistry parameters were increased mainly at the 25 and 125 mg/kg of BAY 43-9006, including AST, ALT, LDH, cholesterol and bilirubin, suggesting test article-induced hepatotoxicity. Reductions were seen in the levels of calcium and phosphate. Degeneration was observed in adrenal glands, liver, stomach, duodenum, pancreas, kidneys, heart, testes and ovaries. Severe testicular degeneration was observed at 5, 25 and 125 mg/kg. Cytotoxic effects were evident in bone marrow, spleen, lymph nodes, thymus, and tongue.

Findings were noted in the teeth (25 and 125 mg/kg) and proximal growth plate of the femoral bone (5, 25, and 125 mg/kg). Findings in the teeth included: degenerative processes on incisors, and osteolysis and/or osteodystrophy in the jawbone. Findings in the growth plate of the femurs included: thickening of the growth plate, ↑bone formation beneath the growth plate, and bone malformation.

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Histopathology Inventory for the 7-day and 28-day rat and dog toxicology studies

Study	RMI-00067	MRC-01027	RMI-00068	MRC-01028			
Species	Rat	Rat	Dog	Dog			
Study duration	7 days	28 days	7 days	28 days			
Adrenals	X	X	X	X			
Aorta							
Bone Marrow smear	X		X				
Bone (femur)	X sternum						
Brain		X		X			
Cecum	X		X				
Cervix							
Colon	X		X				
Duodenum	X		X				
Epididymis		X		X			
Esophagus	X						
Eye							
Fallopian tube							
Gall bladder				X			
Gross lesions							
Harderian gland							
Heart	X	X	X	X			
Ileum	X		X				
Injection site							
Jejunum			X				
Kidneys	X	X	X	X			
Lachrymal gland							
Larynx			X				
Liver	X	X	X	X			
Lungs	X		X	X			
Lymph nodes, cervical							
Lymph nodes mandibular	X		X				
Lymph nodes, mesenteric	X		X				
Mammary Gland							
Nasal cavity							
Optic nerves							
Ovaries				X			
Pancreas				X			
Parathyroid							
Peripheral nerve							
Pharynx			X				
Pituitary (or hypophysis)			X	X			
Prostate				X			
Rectum			X				
Salivary gland							
Sciatic nerve							
Seminal vesicles							
Skeletal muscle							
Skin							
Spinal cord							
Spleen	X	X	X	X			
Sternum							
Stomach	X		X				
Testes		X	X	X			
Thymus	X	X	X	X			
Thyroid				X			
Tongue							
Trachea	x						

Urinary bladder							
Uterus				X			
Vagina							
Zymbal gland							

Study title: BAY 43-9006 Tosylate Salt (BAY 54-9085): A Subchronic (13-week) Toxicity Testing Study in the Rat

Study Report MRC-01249
Study #: 00-S12-SV

Key study findings:

- A marked increase in mortality was noted in both sexes at 5 and 25 mg/kg/d BAY 43-9006. With the exception of two females, all 25-mg/kg/d animals (including subchronic, recovery, and toxicokinetic animals) were either found dead or sacrificed within approximately 1 month of the study initiation.
- Hematological changes in 5-mg/kg/d animals included decreased total leukocytes counts in both sexes and increased hemoglobin, hematocrit, and macrocytic erythrocyte count in males.
- Clinical chemistry changes included increases in liver enzymes, triglycerides, and cholesterol, as well as decreased total protein, albumin, and glucose in both sexes. Changes also included increased sodium, chloride, and urea nitrogen in both sexes and decreased calcium concentration in females only.
- Microscopic lesions were noted in the adrenal (hemorrhage and total necrosis), bone (thickening of the growth plate), liver (pigmentation individual cell necrosis), kidney (nephrosis), ovary (arrested follicular development), parathyroid (fibrosis), spleen (lymphoid depletion), and teeth (dysplasia of the incisor teeth- failure of formation of the dentin layer).
- No recovery phase.

Conducting laboratory and location: Bayer Corporation, Agriculture Division, Toxicology Stilwell, KS 66085-9104
Date of study initiation: 12-6-00
GLP compliance: yes
QA report: yes (x) no ( )
Drug, lot #, and % purity: BAY 54-9085 (Lot No. 0006047; Batch No. 527891); [ ] (analysis 11-3-00; expiration 5- 29-01). BAY 54-9085 is the tosylate salt of BAY 43-9006. In accordance with Bayer Pharmaceutical, the identification of the project is based on the free base/acid, namely BAY 43-9006.
Formulation/vehicle: 15% Poloxamer 188 (Pluronic F68), 42.5% Propylene Glycol, and 42.5% PEG 400

Methods:
Dosing:
Species/strain: Wistar Hanover rats [— WI[Glx/ — Han]IGS BR) from [ ]
#/sex/group or time point (main study): 10/ sex/dose

Satellite groups used for toxicokinetics:	6/ sex/dose (except for control group n=3/sex)
Satellite groups used for recovery:	5 sex/dose (0 and HD: 25 mg/kg/d dose)
Age:	6-week old male and female
Weight:	♂: ~180 g and ~♀: ~130 g
Doses:	0, 1, 5, or 25 mg BAY 43-9006/kg/day daily x 13 weeks. Note: The conversion factor between BAY 43-9006 and BAY 54-9085 is 1.37 - actual test article administered was to be 0, 1.37, 6.85, and 34.25 mg/kg /day.

The concentration of the test article in the various dosing solutions was analytically verified, from samples collected within 1 day of preparation, at approximately 1 month intervals during the exposure phase of the study. Based on these analyses, BAY 54-9085 was administered at a rate of 0, 1.0, 5.1, and 25.9 mg/kg/day.

Route, form, volume: Gastric gavage; 10 ml/kg

Observations and times:

Clinical signs:	Daily
Body weights:	Weekly
Food consumption:	Weekly
Ophthalmoscopy:	Initiation and termination of study.
EKG:	Not performed
Hematology:	Prior to termination
Clinical chemistry:	Prior to termination
Urinalysis:	Prior to termination
Gross pathology:	Complete early die-off of the 25 mg/kg/d groups. The clinical pathology, gross pathology, and microscopic data were evaluated only on animals from control, 1, and 5 mg/kg/d groups, but regardless of fate within those groups. Recovery groups were not evaluated.
Organs weighed:	Adrenal glands, brain, heart, kidneys, liver, lungs, ovaries, spleen, testicles, thymus, and thyroids.
Histopathology:	Day 91/92
Toxicokinetics:	Blood was obtained at approximately 0.5, 1, 2, 4, 7, and 24 hours post-administration on the first day of dosing (Day 0) and again at the same time points on Day 91. Following dosing, 3 treated animals per sex were bled at 0.5, 2, and 7 hours post-treatment; the remaining 3 were bled at 1, 4, and 24 hours. Control animals were bled at 0.5 and 1 hour only.

Results:

Mortality:

A marked increased in mortality was noted in both sexes at 5 and 25 mg/kg. With the exception of two females, all 25-mg/kg animals (including subchronic, recovery, and toxicokinetic animals) were either found dead or sacrificed in extremis within approximately 1 month of the initiation of the in-life phase of the study. As such, the in-life phase of this study ended with the terminal sacrifice of all non-recovery animals (i.e., the recovery phase of the study was not executed).

BAY 43-9006 (mg/kg/d)	Males				Females			
	0	1	5	25	0	1	5	25
No. animals (main group)	**10**	**10**	**10**	**10**	**10**	**10**	**10**	**10**
Total number of dead animals	0	2	3	10	0	0	6	10
Total found dead on study	0	1	3	6	0	0	5	8
Total sacrificed moribund	0	1	0	4	0	0	1	2
Mean time of death (days)	89	84	80	22	91	91	74	22
Animals surviving at study termination	10	8	7	0	10	10	4	0

Clinical signs:

mg/kg/d BAY 43-9006	Males				Females			
	0	1	5	25	0	1	5	25
↑incidence of urine staining	**3**	**2**	**8***	**3**	**0**	**0**	**6***	**2**
Broken teeth	0	0	5*	0	0	0	2	0
Soft feces	0	0	3	4*	0	0	0	0
Rough coat	0	1	8*	6*	2	0	8*	4
Fecal stains	6	5	10*	8	0	0	2	2
Pale Body	0	0	0	4*	0	0	0	3

* indicates statistical significance. Some clinical observational findings appeared to be altered (compared to control values); however. not always in a clear, dose-dependent manner. The lack of dose response may be due to the increased mortality noted in the high-dose group (i.e., the animals died before the lesion could fully develop).

Body weights:

Terminal body weight was significantly decreased in 5 mg/kg/d males (24.5%) and moderately, but not significantly, decreased in 5 mg/kg/d females (7.2%).

Sex	Dose (mg/kg/d)	BW on Day 0 (g)	% change*	BW on Day 21 (g)	% change	BW on Day 56 (g)	% change	BW on Day 84 (g)	% change
♂	0	186.6	—	305.4	—	390.3	—	427.4	—
	1	186.1	0	292.8	↓4	380.4	↓3	414	↓3
	5	180.1	↓3	269.1	↓12	333.3	↓15	330	↓23
	25	179.3	↓4	221.9	↓27	NA	NA	NA	NA
♀	0	131.4	—	176.4	—	207.3	—	239.1	—
	1	133.6	↑2	173	↓2	206	↓1	218.8	↓8
	5	130.7	↓1	170.3	↓3	202.5	↓2	218.3	↓9
	25	129.4	↓2	172.7	↓2	NA	NA	NA	NA

* % change from controls (dose 0 mg/kg/d)
NA- no data available due to mortality

- Body weight gain (BWG) remained unaffected in both sexes at doses of 1 mg/kg in males and up to 5 mg/kg in females.
- A decline of 23% BWG was noted in 5-mg/kg males.
- There was no clear effect on BWG in females.

Food consumption (g/animal/day):

Sex	Dose (mg/kg/d)	FC Day 7	% change	FC Day 21	% change	FC Day 63	% change	FC Day 84	% change
♂	0	18.97	—	21.89	—	20.42	—	19.9	—
	1	19.32	↑2	20.86	↓5	19.77	↓3	18.73	↓6
	5	17.63	↓7	18.53	↓15	15.93	↓22	14.7	↓26
	25	16.98	↓10	13.52	↓38	NA	NA	NA	NA
♀	0	101.78	—	81.41	—	52.36	—	47.27	—
	1	103.97	↑2	80	↓2	51.91	↓1	45.91	↓3
	5	97.73	↓4	77	↓5	47.63	↓9	44.78	↓5
	25	94.59	↓7	62	↓24	NA	NA	NA	NA

FC: food consumption

- Food consumption remained unaffected in both sexes at doses of 1 mg/kg in males and up to 5 mg/kg in females.
- A decline of 26% in food consumption was noted in 5-mg/kg males.
- A decline of 24-38% in food consumption was noted in both sexes by day 21 (last measurement) in 25 mg/kg/d animals.

Ophthalmoscopy:

	Males				Females			
N=	10	8	7	0	10	10	5	0
mg/kg/d BAY 43-9006	0	1	5	25*	0	1	5	25*
Retinal degeneration	0	0	2	-	1	1	2	-
Corneal opacity	4	1	0	-	0	1	0	-

* no data available due to mortality

Electrocardiography: Not measured

Hematology: Data shows percent difference from controls.

Sex	Dose mg/kg/d	WBC $10^3/mm^3$	Hgb g/dl	Hct g/dl	MCV μm^3	MCH pg	Seg (%)	Lymph (%)	Mono (%)	Eosin (%)	Macro
♂	0	4.8	15.8	45	52.6	18.5	17.8	76.6	2.9	1.4	1
	1	-	-	-	0	-	-	-	↓14	↓14	-

	5	↓19	↑11*	↑9*	↑11*	↑13*	↑73*	↓15*	↓28*	↓36	↑100*
	25	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
♀	0	3.9	15.4	43.7	53.7	19	17	77.2	3	1.7	0
	1	↓18	-	-	-	-	-	-	↓17	-	-
	5	↓28*	-	-	↑7*	↑5*	↑104*	↓22*	↓23	↓53*	-
	25	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

p≤5% two sided anova + dunnett's test
ND; no data available due to mortality
Note: Given that these parameters were examined at the end of the study, these values only include animals that survived until scheduled necropsy (i.e., decedent information is not included).

- Decreased total leukocyte count in 5-mg/kg males and females.
- Increased hemoglobin concentration, percent hematocrit, and macrocytic erythrocyte count in 5-mg/kg males.
- Leukocyte differential counts indicated changes in the 5 mg/kg/d group including an increased percentage of segmented neutrophils, as well as decreased percentages of lymphocytes, monocytes, and eosinophils in males and females.

Clinical chemistry: Data shows percent difference from controls.

Sex	dose	Trig mg/dl	Chol (mg/dl	AST U/L	ALT U/L	ALP U/L	T-Prot g/dL	Alb g/dL	Glucose mg/dL	Na mmol/L	Cl mmol/L	Calc mg/dl	Urea N mg/dL
♂	0	64	76	69	30	97	7.1	4.6	107	146	101	11.6	20
	1	-	-	-	↑27	-	-	-	↓7	-	-	-	-
	5	↑131*	↑75*	↑54*	↑317*	↑11	↓8*	↓20*	↓7	↑1*	↑2*	↓3	↑25*
	25	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
♀	0	50	51	71	24	36	7.2	4.9	87	145	101	11.3	20
	1	↑82	↑41	↑13	-	-	-	-	↓10*	-	-	-	↑10
	5	↑86	↑57	↑108*	↑263*	↑56	↓15*	↓29*	-	↑1*	↑3	↓6*	↑10
	25	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

* p≤5% two sided anova + dunnett's test
ND; no data available due to mortality
Note: Given that these parameters were examined at the end of the study, these values only include animals that survived until scheduled necropsy (i.e., decedent information is not included).

- Changes included increased aspartate aminotransferase, alanine aminotransferase, ALP, triglyceride, cholesterol concentrations in both sexes.
- Decreased total protein, albumin, and glucose in males and females.
- Changes also included increased sodium, chloride, and urea nitrogen in both sexes and decreased calcium concentration in females only.

Urinalysis: Data shows percent difference from controls.

Sex	mg/kg/ d	Protein mg/dL	U-Leu	Spec Gr
♂	0	73.5	0.1	1.0395
	1	—	0	0
	5	↑308*	↑3300*	1
	25	ND	ND	ND
♀	0	30.5	0.1	1.0331
	1	—	0	0

	5	↑884*	↑1900*	↑3*
	25	ND	ND	ND

p≤5% two sided anova + Dunnett's test
ND; no data available due to mortality

Note: Given that these parameters were examined at the end of the study, these values only include animals that survived until scheduled necropsy (i.e., decedent information is not included).

Organ weights: Absolute organ weights for control (g). % from control for treatment groups

Sex	dose	Adrenal	Heart	Kidney	Liver	Lung	Spleen	Thyroid	Thymus	Ovary	Testis
♂	0	0.068	1.205	3.219	15.222	1.667	0.647	0.027	0.436	NA	3.8
	1	-	-	↓11*	↓10	-	-	↓7	↓12	NA	-
	5	↑13	↓27*	↓24*	↓37*	↓17*	↓38*	↓26*	↓50*	NA	↓15*
	25	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
♀	0	0.08	0.77	1.763	7.609	1.17	0.4536	0.021	0.391	0.146	NA
	1	-	-	-	-	-	-	↓10	↓12	-	NA
	5	↑125*	↓16*	↓8	-	↓15*	↓23	-	↓32*	↓41*	NA
	25	ND	ND	ND	ND	ND	ND	ND	ND	ND	NA

* p≤5% two sided anova + dunnett's test
ND: no data available due to mortality
NA: not applicable

Gross pathology:

BAY 43-9006 (mg/kg/d)	Males (n=10)				Females (n=10)			
	0	1	5	25*	0	1	5	25*
Adrenal-discoloration	-	-	5	ND	-	-	9	ND
Enlarged	-	-	3	ND	-	-	9	ND
Thyroid-discolored zone	-	-	1	ND	-	-	6	ND
Kidney-calculus/mass	-	-	1	ND	-	-	1	ND
Liver-dilated	-	-	-	ND	-	-	2	ND

* no data available due to mortality
—: no incidence

Histopathology: Microscopic lesions associated with drug exposure were noted in 1- and 5-mg/kg animals. Changes occurring in many or most animals at 5 mg/kg could generally be categorized as serious/ severe, while those lesions noted in 1- mg/kg animals were few in number in terms of animals affected and low in severity when observed.

BAY 43-9006 (mg/kg/d)	Males				Females			
	0	1	5	25	0	1	5	25
Adrenal: hemorrhage	-	-	7	ND	-	-	1	ND
Pronounced cortical or total necrosis	-	-	4	ND	-	-	9	ND
Increased individual cell cortical necrosis	-	5	6	ND	1	4	1	ND
Slight or moderate congestion,	-	2	2	ND	-	1	-	ND
Spleen: Lymphoid depletion[A]	-	-	-	ND	-	-	4	ND
Bone: chondrodystrophy[B]	-	-	-	ND	-	-	-	ND
Rib/costochondral junction	-	-	-	ND	-	1	1	ND
Sternum	-	-	-	ND	-	-	6	ND
Femorotibial joint	-	1	5	ND	-	-	9	ND
Kidney: nephrosis	-	-	9	ND	-	-	6	ND
Liver: increased pigmentation	-	-	-	ND	-	-	6	ND
Individual cell necrosis	3	3	8	ND	-	1	6	ND
Markedly dilated bile ducts[C]	-	-	-	ND	-	-	3	ND
Ovary: Inactive [D]	-	-	-	ND	-	-	9	ND
Parathyroid: fibrosis	-	-	-	ND	1	-	5	ND
Teeth: dysplasia of the incisor teeth [E]	-	-	1	ND	-	1	1	ND
Lymph Node, cervical- plasma cell hyperplasia	-	-	-	ND	-	-	4*	ND

ND No data available. Complete early die-off of the 25 mg/kg/d groups. The clinical pathology, gross pathology, and microscopic data were evaluated only on animals from control, 1, and 5 mg/kg/d groups, but regardless of fate within those groups. Recovery groups were not evaluated.

- = no incidence

[A] This change in spleen was not seen in males and does not reflect the general condition of the animal, as the thymus was generally normal and some lymph nodes were slightly hyperplastic

[B] Chondrodystrophy, defined as thickening of the bone growth plate. Note: changes in the femur are included in the femorotibial joint tabulation to avoid double entry.

[C] Associated with hypertrophy of the duodenum in the area of the bile duct and with biliary hyperplasia. This condition did not occur in males, but the 2/1- incidence of this unusual lesion in females suggests a treatment-related effect. Biliary hyperplasia was noted in one other 5-mg/kg female, without the common bile duct involvement described above, for a total of 3 of 1- animals.

[D] Both corpora lutea and follicles were generally present; however, large mature follicles were not present. In addition, all corpora lutea were aged; no new corpora lutea were noted. The change might be described as "arrested follicular development". This treatment-related change was not observed at 1 mg/kg.

[E] Dysplasia of the incisor teeth, specifically of the dentin layer (the enamel is not well-visualized on decalcified sections)

Histopathology information on the unscheduled deaths at 5 mg/kg

Animals dead or sacrificed	Males (n=3)			Females (n=6)					
BAY 43-9006 (mg/kg/d)	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**	**5**
Animal ID	SV2 002	SV2 004	SV2 009	SV2 102	SV2 104	SV2 106	SV2 108	SV2 109	SV2 110
Day (dead or sacrificed)	54	53	71	64	72	47	90	67	44
Adrenal: hemorrhage and necrosis	X	X	X	X	X	X	X	X	X
Bone: chondrodystrophy	X	X	X	X	X	X	X	X	X
Kidney: nephrosis, bilateral tubular regeneration	X	X	X	X	X		X	X	
Liver: necrosis Hyperplasia, fibrosis	X	X		X	X		X	X	X
Spleen: diffuse pigementation Lumphoid depletion	X	X		X		X		X	X
Teeth: dysplasia of the incisor	X	X	X	X	X	X	X	X	X

Toxicokinetics: Submitted in a different study report

Summary of study findings:

BAY 54-9085 (the tosylate salt of BAY 43-9006) was administered via daily gastric gavage for 13-weeks to rats at 0, 1, 5, or 25 mg BAY 43-9006/kg/day. An increased mortality was noted in both sexes at 5 and 25 mg/kg. With the exception of two females, all 25-mg/kg animals (including subchronic, recovery, and toxicokinetic animals) were either found dead or sacrificed in extremis by approximately 1 month into the in-life phase of the study. The Sponsor did not determine the cause of death or examine histopathological tissues from any of the HD animals (early deaths). At 5 mg/kg/d, 3 ♂s and 6 ♀s out of 10 rat/set died before the end of the treatment.

Clinical observational evidence of toxicity was observed at 5 and 25 mg/kg and included increased incidence of broken teeth, pale body, urine staining, soft feces, rough coat, and fecal stains in males and/or females. Body weight gain (BWG) and food consumption were decreased in 5-mg/kg males; there was no clear effect on BWG in females. Hematological changes included a decreased total leukocyte count in 5-mg/kg animals, increased hemoglobin, hematocrit, and macrocytic erythrocyte count in 5-mg/kg males, as well as a general disruption of leukocyte differential profile of both sexes, indicated by counts of segmented neutrophils, lymphocytes, monocytes, and eosinophils. Clinical chemistry changes included increases in liver enzymes, triglyceride, and cholesterol concentrations, as well as decreased total protein, albumin, and glucose in both sexes. Changes also included increased sodium, chloride, and urea nitrogen in both sexes and decreased calcium concentration in females only. Urinalysis indicated treatment-related change, also limited to 5-mg/kg animals, and included increased urine protein and urinary leukocyte count in males and females, as well as increased specific gravity in females.

Gross pathological findings included adrenal discoloration in 5- mg/kg males and females, and adrenal enlargement and thyroid discoloration in 5-mg/kg females. Organ weight effects were noted at 5 mg/kg as increased adrenal weight and decreases in heart, kidney, liver, lung, spleen, thyroid, thymus, testis, and ovarian weight in both sexes. BAY 43-90006 (5 mg/kg/d) -induced microscopic lesions were noted in the adrenal

(hemorrhage and total necrosis), bone (thickening of the growth plate), liver (pigmentation individual cell necrosis), kidney (nephrosis), ovary (arrested follicular development), parathyroid (fibrosis), spleen (lymphoid depletion), and teeth (dysplasia of the incisor teeth- failure of formation of the dentin layer).

Study title: Study on Chronic Toxicity in Wistar Rats. Administration by gavage over 6 months for up to 191 days

Key study findings: Mortality in all groups, most evident at HD
↓BW at MD and HD; more evident in ♂s
Significant ↓ in platelet counts at HD
Slightly ↑ALT, AST, and ALP at HD
Nephrotoxicity at MD and HD
Effects on teeth and bones at MD and HD: dentin degeneration, osteodystrophy of the jaw, and fatty replacement of sternum

Report #PH-32607-5
Study # T 5071052

Volume #, and page #: Module 4 of the eNDA (CTD); M4.2.3.2.5
Conducting laboratory and location: Bayer AG
Friedrich-Ebert-Strabe 217-333
42096 Wuppertal, Germany
Date of study initiation: 17 August 2001
GLP compliance: Yes- In compliance with the OECD Principles of GLP
Deviations from the GLP:
The amendment to the Toxicokinetic Report was not audited.
QA report: yes (X) no ( )
Drug, lot #, and % purity: BAY 54-9085, Batch # 000217, [ ] pure
Vehicle: Pluronic®F68/Propylene Glycol/Polyethylene Glycol 400 (15:42.5:42.5 w:w:w)

Methods
Doses: BAY 54-9085: 0, 0.14, 1.4, and 3.43 mg/kg/day
Corresponding to:
BAY 43-9006 (free base) of 0, 0.1, 1.0, and 2.5 mg/kg/day
0, 0.6, 6.0, and 15 mg/m^2/day
Daily dosing for 6 months

Group No.	Dose (mg/kg/day) BAY 54-9085	Corresponds to BAY 43-9006	Sex	Number of Animals	Animal Number
1	0	0	m	20	1 - 20
2	0.14	0.1	m	20	21 - 40
3	1.4	1.0	m	20	41 - 60
4	3.43	2.5	m	20	61 - 80
5	0	0	f	20	81 - 100
6	0.14	0.1	f	20	101 - 120
7	1.4	1.0	f	20	121 - 140
8	3.43	2.5	f	20	141 - 160

m = males, f = females
Conversion factor: 1.37

Toxicokinetics

Days of blood sampling:	days 5 (first exposition day), 111 and 187
Time Points per Day:	6 (0.5, 1, 2*, ,4, 7 and 24 hours after administration) for groups 2-4 and 6-8
	1 (0,5 hour after administration) for groups 1 and 5
Number of Animals per Time Point:	3 (group 2-4 and 6-8, ascending animal numbers of the first 18 per group)

* 2.5 hours for day 5 (first exposition day)

Tables provided by the sponsor.

Species/strain: rat/ Wistar
Number/sex/group (main study): 20/sex/group
Route, formulation, volume: oral (gavage)/solution
Satellite groups used for toxicokinetics: 3 animals/time point; see Table above
Age: 5 weeks at delivery
Weight: Mean initial weights at study start and the range:
Males: 183 (165 – 203) g
Females: 143 (129 - 158) g

Observations and times:

Mortality: twice daily; once daily on weekends and public holidays

Clinical signs:

Clinical examination: daily

Detailed clinical examination: once weekly

Open field observation: once before study start, weekly during course of the study (except exposure week 24 when Functional Observation Battery, FOB, was conducted. which includes standard arena observation)

Functional Observation Battery (FOB): Once at study end (week 25, exposure days 169 and 171, for males and females, respectively)- this was an assessment of neurotoxicity and was conducted on 10 animals/group

Group No.	Dose [mg/kg Body/ weight]	Animal No.	No. of Animals	Neurotox Identification No.
1	0	2, 4, 5, 8, 10, 13, 14, 16, 18, 20	10	0001-0010
2	0.14	21, 23, 26, 28, 32, 34, 35, 37, 38, 39	10	1001-1010
3	1.4	43, 44, 45, 46, 48, 49, 50, 51, 52, 54	10	2001-2010
4	3.43	61, 64, 68, 71, 72, 73, 75, 76, 77, 80	10	3001-3010
5	0	82, 83, 84, 85, 90, 94, 95, 97, 99, 100	10	0101-0110
6	0.14	101, 103, 104, 105, 110, 113, 116, 117, 118, 120	10	1101-1110
7	1.4	121, 123, 126, 127, 128, 129, 132, 135, 136, 137	10	2101-2110
8	3.43	141, 142, 143, 145, 147, 148, 151, 154, 157, 159	10	3101-3110

Table provided by the sponsor.

Body weights: weekly
Food/ water consumption: weekly
Ophthalmoscopy: All rats before start of treatment;
control and high-dose rats at the end of treatment
EKG: not done
Hematology: twice (on 10 randomized rats animals/group)
Clinical chemistry: twice (on 10 randomized rats animals/group)
Urinalysis: twice (on 10 randomized rats animals/group); 16 hrs collection
Gross pathology: at necropsy
Heart, larynx, lungs, esophagus, liver, kidneys, testes, epididymides, uterus, adrenal glands, thymus, mandibular lymph nodes, salivary glands, eyes, body cavities,
Organ weights: at necropsy, at the end of the 6-month study
Brain, adrenals, heart, liver, spleen, thymus, kidneys, testes, epididymides, uterus, ovaries
Histopathology: at necropsy
Adequate Battery: yes (X), no ( )—explain
Peer review: yes (X), no ()
The following table represents organs that were fixed and evaluated. In addition, the organs of all unexpected deaths were examined.

Table: List of fixed and histopathologically evaluated organs:

Organ	Fixative	Groups evaluated histopathologically
Adrenal glands	F	01, 04 (males) 01 - 04 (females)
Aorta	F	01, 04
Brain (cerebrum, cerebellum, brain stem)	F	01, 04
Epididymides	F	01, 04
Esophagus	F	01, 04
Eyes	F	01, 04
Eyelids	F	not done
Exorbital lacrimal glands	F	01, 04
Femur	F	01 - 04
Harderian glands	F	01, 04
Head	F	
- Nasal Cavity/Teeth		01 - 04
Heart	F	01, 04 (males) 01 - 04 (females)
Intestine	F	not done
- Peyer's Patches	F	01, 04
- Duodenum	F	01, 04
- Jejunum	F	01, 04
- Ileum	F	01, 04
- Cecum	F	01, 04
- Colon	F	01, 04
- Rectum	F	01, 04
Remaining intestine	F	not done
Kidneys	F	01 - 04
Larynx	F	01, 04
Liver	F	01 - 04
Lungs	F	01 - 04
Lymph nodes, mandibular	F	01, 04
Lymph nodes, mesenteric	F	01 - 04
Optic nerves	F	01, 04
Ovaries	F	01, 04
Oviducts	F	01, 04

F = 10 % neutral buffered formalin

Table: List of fixed and histopathologically evaluated organs (contd.)

Organ	Fixative	Groups evaluated histopathologically
Pancreas	F	01, 04
Pituitary gland	F	01, 04
Prostate	F	01, 04
Salivary glands (parotid, submandibular, sublingual)	F	01, 04
Sciatic nerve	F	01, 04
Seminal vesicles (incl. coagulation glands)	F	01, 04
Skeletal muscle (thigh)	F	01, 04
Skin (mammary region)	F	01, 04
Spinal cord (cervical, thoracal, lumbar)	F	01, 04
Spleen	F	01 - 04
Sternum	F	01 - 04
Stomach (forestomach and glandular stomach)	F	01, 04
Testes	F	01, 04
Thymus	F	01, 04
Thyroid glands (with parathyroids)	F	01, 04
Tongue	F	01, 04
Trachea	F	01, 04
Ureters	F	01, 04
Urethra	F	not done
Urinary bladder	F	01, 04
Uterus (with cervix)	F	01, 04
Vagina	F	01, 04
Zymbal's glands	F	not done
Organs and tissues with macroscopic findings	F	01 - 04
Physical identifier	F	not done

F = 10 % neutral buffered formalin

Tables provided by the sponsor.

Results

Mortality: A total of 11 animals (5 ♂s and 6 ♀s) from different dose groups:

- 4 animals were found dead

- a control ♂ (# 13)
- a MD ♀ (# 123)
- a HD ♂ (# 65)
- a HD ♀ (# 160)

- 5 animals were sacrificed in moribund conditions
  - a control ♀ (# 81)
  - a LD ♀ (# 102)
  - a MD ♂ (# 47)
  - a HD ♂ (# 69)
  - a HD ♀ (# 152)
- An additional 2 animals (a LD ♂, #32, and a MD ♀, # 134) died during blood sampling

Clinical signs:

- Emeciation: 3 HD ♀s; (Days 120-172), one of which was sacrificed moribund. Although ↓BW was more evident in ♂s, emaciation was not reported for ♂s
- Breathing sound or labored breathing: 2 MD ♂s (Days 81-191), 1 MD ♀ (Day 60), 3 HD ♂s (Days 172-191)

Body weights: ↓BW in MD and HD animals, more evident in males

Sex		m	m	m	m	f	f	f	f
Dose BAY 43-9006 (mg/kg)		0	0.1	1.0	2.5	0	0.1	1.0	2.5
Day	1	183	182	183	183	142	143	142	143
	8	233	228	226	225	166	165	164	164
	15	269	263	260	258	179	180	177	177
	22	301	292	286	283+	190	190	187	189
	29	324	315	308	303+	201	200	195	200
	36	342	332	322+	316++	207	208	203	207
	43	362	352	342	334++	214	215	210	215
	50	379	367	354+	347++	220	221	214	220
	56	391	380	364+	357++	226	226	219	225
	64	403	392	375+	365++	229	229	222	229
	71	414	404	385+	376++	234	234	226	236
	78	420	412	388+	382++	237	237	231	238
	85	425	417	393+	386++	240	241	232	241
	92	430	421	395+	388++	239	236	232	238
	99	440	431	405+	398++	243	243	236	244
	106	448	439	411+	404++	246	246	238	247
	113	451	443	413+	408++	245	243	239	248
	123	457	451	414++	417++	251	249	245	247
	126	460	452	417++	419++	252	251	246	250
	133	466	456	420++	423++	254	251	248	253
	141	468	461	428++	427++	256	257	250	256
	148	472	466	433+	435+	256	258	252	260
	155	478	470	438+	438+	262	263	255	263
	162	477	473	438+	438+	261	264	256	262
	169	480	475	440+	437++	263	266	257	262
	176	481	476	442+	440+	261	266	258	262
	183	478	476	439+	438+	258	263	254	258
	190	480	474	443+	439+	263	266	257	260

063055/02.001 T5071052

The dosages correspond to 0, 0.14, 1.4, 3.43 mg BAY 54-9085/kg/day.

+ $p < 0.05$, ++ $p < 0.01$
Table provided by the sponsor.

Food/ water consumption:

Food: comparable to control for both sexes
Water: comparable to control for males and for LD and MD females/
↓11% in HD females

Ophthalmoscopy: no treatment-related effect

EKG: not done

Hematology:

- Hemoglobin concentration and hematocrit were increased at MD and HD in males and females

- MCV and MCH were increased at HD, in males and females. In addition, MCHC was significantly increased at HD in males at study end.
- Thrombocyte (platelet) counts were significantly decreased in both sexes at HD.

Dose BAY 43-9006	LEUCO	ERY	HB	HCT	MCV	MCH	MCHC	RETI	THRO	HQUICK
mg/kg	10E9/l	10E12/l	g/l	l/l	fl	pg	g/l ERY	o/oo	10E9/l	sec
m Day 90/91										
0	12.35	8.97	153	0.466	52.0	17.1	329	20	1386	30.4
0.1	12.28	9.08	157	0.476	52.5	17.3	330	20	1226+	30.0
1.0	11.89	9.25	159+	0.484+	52.3	17.2	329	22	1253	29.6
2.5	12.56	9.33	170++	0.510++	54.7++	18.3++	334	21	1117++	29.1
m Day 181/182										
0	11.13	9.16	150	0.477	52.1	16.4	315	19	1403	28.9
0.1	11.17	9.20	154	0.482	52.4	16.7	320	22	1260	28.6
1.0	11.00	9.50+	157++	0.492+	51.8	16.6	320	19	1303	27.8
2.5	11.81	9.46	169++	0.519++	54.9++	17.8++	325++	23	1171++	28.1
f Day 90/91										
0	8.44	8.68	156	0.467	53.8	17.9	333	19	1307	27.4
0.1	8.41	8.74	159	0.471	53.9	18.2	336	17	1182	27.5
1.0	7.98	8.79	163+	0.483	54.9	18.5	337	16	1238	26.3
2.5	7.84	8.90	166++	0.490+	55.1	18.6+	338	19	1140+	27.7
f Day 181/182										
0	6.95	8.39	151	0.458	54.7	18.0	329	14	1223	24.7
0.1	7.64	8.62	155	0.470	54.5	18.0	331	16	1192	24.8
1.0	7.27	8.46	156	0.471	55.7	18.5	331	16	1097	24.8
2.5	6.90	8.63	161++	0.486+	56.3	18.7+	332	18	998++	25.2

067755/02.001 T5071052

The dosages correspond to 0, 0.14, 1.4, 3.43 mg BAY 54-9085/kg/day.

+ $p < 0.05$, ++ $p < 0.01$
HQuick: thromboplastin time

Dose BAY 43-9006 mg/kg	NEUTRO	LYM	MONO	EOS	BASO	ATYP
			10E9/l			
m Day 90/ 91						
0	1.06	10.71	0.26	0.19	0.04	0.08
0.1	1.12	10.61	0.29	0.14	0.03	0.08
1.0	1.64	9.76	0.28	0.12+	0.03	0.07
2.5	1.32	10.71	0.27	0.13+	0.03	0.10
m Day 181/ 182						
0	1.23	9.22	0.30	0.21	0.03	0.15
0.1	1.16	9.42	0.27	0.17	0.03	0.13
1.0	1.35	9.08	0.26	0.15	0.03	0.13
2.5	1.56	9.61	0.27	0.21	0.03	0.14
f Day 90/ 91						
0	0.89	7.24	0.17	0.09	0.02	0.05
0.1	0.64	7.46	0.15	0.09	0.02	0.06
1.0	0.74	6.92	0.16	0.09	0.01	0.06
2.5	0.69	6.85	0.15	0.08	0.02	0.06
f Day 181/ 182						
0	0.93	5.63	0.18	0.11	0.01	0.08
0.1	0.70	6.60	0.14	0.08	0.02+	0.10
1.0	0.83	6.12	0.13	0.09	0.02	0.08
2.5	0.85	5.63	0.15	0.10	0.02+	0.14

062995/02.001 T5071052

The dosages correspond to 0, 0.14, 1.4, 3.43 mg BAY 54-9085/kg/day.

+ $p < 0.05$, ++ $p < 0.01$

LEUCO: Leucocytes; ERY: Erythrocytes; HB: Hemoglobin; HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; THRO: Platelets/Thrombocytes; NEUTRO: Neutrophils; LYMPH: Lympbocytes; MONO: Monocytes; EOS: Eosinophils; BASO: Basophils; ATYP: Atypical Leucocytes; RETI: Reticulocytes

Tables provided by the sponsor.

Clinical chemistry:

Dose BAY 43-9006 mg/kg	ASAT	ALAT	APh	GGT
		U/l		
m Day 90/ 91				
0	69.4	30.4	222	0
0.1	69.5	32.4	211	0
1.0	72.3	35.0	220	0
2.5	78.0	42.7++	234	0
m Day 181/ 182				
0	67.2	30.8	159	2
0.1	64.3	32.5	142	1
1.0	72.9	35.8	144	1
2.5	75.7	46.3++	144	2
f Day 90/ 91				
0	68.4	26.6	130	1
0.1	70.5	25.7	135	1
1.0	78.5	29.9	136	1
2.5	86.8++	39.8++	162	1
f Day 181/ 182				
0	93.4	45.4	79	1
0.1	83.1	35.0	82	1
1.0	92.6	41.1	80	1
2.5	93.8	47.8	101	1

063025/02.001 T5071052

The dosages correspond to 0, 0.14, 1.4, 3.43 mg BAY 54-9085/kg/day.

+ $p < 0.05$, ++ $p < 0.01$

ASAT: Aspartate aminotransferase or AST; ALAT: Alanine aminotransferase or ALT; APh: alkaline phosphatase or ALP

Table provided by the sponsor..

Urinalysis:

- The significantly lower mean pH value in males (3.43 mg/kg day 90/91) was considered incidental by the sponsor, since there was no clear dose dependence and no time dependence.
- There was a trend to higher excreted total protein amounts at 1.4 and 3.43 mg/kg (males both dates) and at 3.43 mg/kg (females study end).

Dose BAY 43-9006 mg/kg	VOL ml	Density g/l	PH	PROT g/l	PROT*VOL mg
m Day 90/ 91					
0	11.6	1024	8.0	1.97	15.5
0.1	10.2	1025	7.6	2.08	12.5
1.0	11.7	1023	7.7	1.58	18.7
2.5	11.5	1021	7.3+	2.69	28.4
m Day 181/ 182					
0	6.3	1036	7.7	2.31	11.6
0.1	6.2	1035	7.8	2.80	15.5
1.0	6.3	1039	7.2	3.16	20.4
2.5	6.1	1036	7.5	6.19	32.7
f Day 90/ 91					
0	7.9	1021	7.1	0.24	1.5
0.1	11.4	1017	7.1	0.20	2.7
1.0	7.0	1022	6.9	0.19	1.1
2.5	7.2	1024	6.9	0.24	1.8
f Day 181/ 182					
0	4.6	1032	6.3	0.92	4.9
0.1	8.0	1028	6.8	0.29	2.2
1.0	6.5	1027	6.4	0.58	3.0
2.5	4.4	1039	6.2	1.94	6.2

063105/02.001 T5071052

The dosages correspond to 0, 0.14, 1.4, 3.43 mg BAY 54-9085/kg/day.

+ $p < 0.05$, ++ $p < 0.01$
Table provided by the sponsor.

Gross pathology: No treatment related effect

Organ weights:

- Relative liver weights in females were decreased at MD and HD
- Absolute and relative thymus weights were reduced at HD

Only relative weights are presented below, since changes in the absolute organ weights appeared to be secondary to the change in the body weights.

Dose BAY 43-9006 mg/kg	Body W. G	Brain	Adrenals	Heart	Liver	Spleen	Thymus	Kidneys	Testes	Epididymides
m Terminal Sacrifice						mg/100g				
0	481	436	10	306	3415	157	68	566	779	353
0.1	477	443	11	287	3376	158	66	569	775	375
1.0	444+	469+	11	291	3321	159	61	543	764	369
2.5	445+	471+	11	303	3421	157	51+	581	793	355
f Terminal Sacrifice									Ovaries mg/100g	Uterus mg/100g
0	267	718	26	351	3386	182	101	621	54	479
0.1	268	711	27	356	3442	172	93	621	58	445
1.0	260	732	27	350	3116++	178	94	595	59	487
2.5	260	730	27	338	3197+	175	86	626	61	434

063095/02.001 T5071052

The dosages correspond to 0, 0.14, 1.4, 3.43 mg BAY 54-9085/kg/day.

+ $p < 0.05$, ++ $p < 0.01$

Table provided by the sponsor.

Histopathology:

Histopathology showed treatment related findings in the following organs:

- liver: minimal pigment storage in Kupffer cells in males and females dosed at 3.43 mg/kg (this appeared to be accumulation of the stain used for processing)
- kidneys: nephropathy in both sexes
- teeth: dentin degeneration in the incisors of males and females; osteodystrophy of the jaw in females
- mesenteric lymph nodes: increased mast cells in males and females
- sternum: fatty replacement of the bone marrow in males at 1.4 mg/kg and above

Incidence and severity of drug-related histopathology findings (out of 20 examined/group)

Findings		Control (Grade)	LD (Grade)	MD (Grade)	HD (Grade)
Teeth	Dentin degeneration	♂: 0 ♀: 0	♂: 0 ♀: 4 (1.3)	♂: 3 (1.3) ♀: 4 (1.0)	♂: 10 (1.5) ♀: 12 (1.8)
	†Osteodytrophy; jaw	♀: 0	♀: 0	♀: 1 (1.0)	♀: 4 (2.0)
Liver Pigments in kupffer cells		♂: 1 (1.0) ♀: 0	♂: 1 (1.0) ♀: 1 (1.0)	♂: 2 (1.0) ♀: 0	♂: 8 (1.0) ♀: 6 (1.2)
Kidneys	Basophilic tubules	♂: 14 (1.2) ♀: 4 (1.3)	♂: 16 (1.4) ♀: 3 (1.0)	♂: 17 (1.6) ♀: 4 (1.0)	♂: 19 (2.2) ♀: 14 (1.5)
	*Infiltration; mononuclear	♂: 7 (NP)	♂: 10 (NP)	♂: 11 (NP)	♂: 14 (NP)
	Tubular dilation	♂: 9 (1.1) ♀: 1 (2.0)	♂: 10 (1.2) ♀: 1 (1.0)	♂: 11 (1.4) ♀: 1 (1.0)	♂: 17 (1.5) ♀: 8 (1.6)
	Hyaline casts	♂: 6 (1.0) ♀: 2 (1.5)	♂: 7 (1.7) ♀: 2 (1.5)	♂: 9 (1.9) ♀: 2 (1.0)	♂: 16 (1.7) ♀: 13 (1.8)
	†Glomerulus; hyaline	♂: 0	♂: 0	♂: 4 (1.0)	♂: 9 (1.2)
	†Corticomed. mineralization	♂: 4 (1.3)	♂: 10 (1.2)	♂: 10 (1.3)	♂: 12 (1.6)
Spleen †hematopoiesis		♂: 2 (1.0) ♀: 1 (1.0)	♂: 9 (1.6) ♀: 5 (2.4)	♂: 13 (1.8) ♀: 9 (1.7)	♂: 15 (1.6) ♀: 15 (1.9)
Mesenteric lymph node Mast cells		♂: 2 (1.5) ♀: 2 (1.0)	♂: 1 (1.0) ♀: 1 (1.0)	♂: 9 (1.2) ♀: 7 (1.1)	♂: 11 (1.0) ♀: 10 (1.1)
*Sternum Fatty replacement		♂: 18 (1.6)	♂: 19 (1.6)	♂: 20 (2.0)	♂: 20 (2.4)

* Incidence was comparable among all groups for females.
† Seen in one gender only.
NP, not provided
Grades are represented as mean numbers.
Grade 1= minimal/very few/very small
Grade 2= slight/few/small
Grade 3= moderate/ moderate number/moderate size
Grade 4= marked/many/large
Table generated by the reviewer.

Toxicokinetics:

- Female plasma concentrations are slightly higher than males (♀/♂ is approximately 150%)
- The drug is absorbed relatively slowly, with a t_{max} of approx. 4 hours
- There was a large increase in exposure from Week 1 to Week 15 at all dose levels (Week 15/Week 1 was approximately 190%), indicating accumulation. There was no significant difference in exposure levels from Week 15 to Week 26.
- Slightly greater than dose proportional increase in parent compound exposure from LD to MD (a 13-fold increase for a 10-fold increase in dose) and from MD to HD (a 3-fold increase for a 2.5-fold increase in dose)

Mean pharmacokinetic parameters:

*Dose (mg/kg)	Week 1 AUC 0-24 (ug*h/l)	Week 1 Cmax (ug/l)	Week 15 AUC 0-24 (ug*h/l)	Week 15 Cmax (ug/l)	Week 26 AUC 0-24 (ug*h/l)	Week 26 Cmax (ug/l)
0.1	434.5	29.8	887.9	58.4	866.6	60.4
1.0	6030.1	476.6	10511.1	674.3	11361.3	726.3
2.5	17575.5	1205.1	31836.2	1947.7	33943.2	1943.3

*Dose in free base (BAY 43-9006) equivalent
Table provided by the sponsor.

Tmax (hour)

Dose Group	Week 1	Week 2	Week 3
LD	7	4	4
MD	4	4	4
HD	7	4	4

The following is from Study Report PH-32607A, TK of metabolites:
The exposure towards BAY 43- 9006, the major human metabolite M-2 and the major rat metabolite M-3 in Week 26 (geometric means, n=3) was as follows:

Male		BAY 43-9006 *			M-2 (BAY 67-3472)			M-3 (BAY 72-1973)		
Dose: BAY 54-9085 [mg/kg]		0.140	1.40	3.43	0.140	1.40	3.43	0.140	1.40	3.43
Dose: BAY 43-9006 [mg/kg]		0.100	1.00	2.50	0.100	1.00	2.50	0.100	1.00	2.50
AUC(0-24)	[µg·h/L]	698	10076	27575	n.c.	122	n.c.	187	2069	n.c.
$AUC(0-24)_{norm}$	[kg·h/L]	6.98	10.1	11.0	n.c.	0.119	n.c.	1.82	2.01	n.c.
C_{max}	[µg/L]	49.2	722	1852	0.590	6.77	10.8#	10.2	115	197#
$C_{max,norm}$	[kg/L]	0.492	0.722	0.741	0.00573	0.00658	0.00415#	0.105	0.111	0.0762#
$C(24)/C_{max}$	[%]	30.5	25.8	28.7	n.c.	51.6	n.c.	55.3	53.4	n.c.
t_{max}	[h]	4.00	4.00	4.00	4.00	7.00	n.c.	2.00	24.0	n.c.
MR_1	[%]				1.20	0.938	1.04	21.9	15.9	10.6
MR_2	[%]				n.c.	1.22	n.c.	26.8	20.5	n.c.

n.c. = not calculated t5071052_summary.xls \ AUC_43-9006_M-3_M-4\Müh\04.06.03\mod Bec\06.04.04
# = C(1h)
* = Parameters were calculated from the geom. mean plasma concentrations reported in MRC-01165.
MR-1:metabolic ratio in terms of C_{max} in [%]: C_{max} (M-X) / C_{max} (BAY 43-9006)
MR-2:metabolic ratio in terms of AUC(0-24) in [%]: AUC(0-24)_(M-X) / AUC(0-24)_(BAY 43-9006)

Female		BAY 43-9006 *			M-2 (BAY 67-3472)			M-3 (BAY 72-1973)		
Dose: BAY 54-9085 [mg/kg]		0.140	1.40	3.43	0.140	1.40	3.43	0.140	1.40	3.43
Dose: BAY 43-9006 [mg/kg]		0.100	1.00	2.50	0.100	1.00	2.50	0.100	1.00	2.50
AUC(0-24)	[µg·h/L]	1065	12724	41690	n.c.	27.7	111	149	1562	4517
$AUC(0-24)_{norm}$	[kg·h/L]	10.7	12.7	16.7	n.c.	0.0268	0.0427	1.44	1.52	1.74
C_{max}	[µg/L]	74.1	739	2188	n.c.	1.40	5.92	9.89	89.2	249
$C_{max,norm}$	[kg/L]	0.741	0.739	0.875	n.c.	0.00136	0.00228	0.0961	0.0866	0.0963
$C(24)/C_{max}$	[%]	29.7	38.6	55.9	n.c.	66.9	59.0	53.7	52.0	60.6
t_{max}	[h]	4.00	7.00	7.00	n.c.	7.00	7.00	4.00	7.00	7.00
MR_1	[%]				n.c.	0.189	0.270	13.4	12.1	11.4
MR_2	[%]				n.c.	0.217	0.265	14.0	12.3	10.8

n.c. = not calculated t5071052_summary.xls \ AUC_43-9006_M-3_M-4\Müh\04.06.03\mod Bec\06.04.04
* = Parameters were calculated from the geom. mean plasma concentrations reported in MRC-01165.
MR-1:metabolic ratio in terms of C_{max} in [%]: C_{max} (M-X) / C_{max} (BAY 43-9006)
MR-2:metabolic ratio in terms of AUC(0-24) in [%]: AUC(0-24)_(M-X) / AUC(0-24)_(BAY 43-9006)

Tables provided by the sponsor.

- Although the exposure to sorafenib was lower in male than in female rats, the exposure to the metabolites M-1 to M-5 was higher in the males than in the females.
- The exposure (Cmax and AUC) of the 5 metabolites in this study with Wistar rats ranked in the following order (no relevant difference between males and females): M-1 << M-5 <= M-2 < M-4 < M-3
- M-3 was the major metabolite in rat plasma in this study whereas the major human metabolite M-2 contributed only little to the exposure in rat plasma. In total, the measured metabolites M-1 to M-5 contribute to 22 % (males) and 13% (females) of the total AUC(0- 24) which is the sum of the AUCs of BAY 43-9006 and of the 5 metabolites.
- The M-2 to M-5 exposures increased roughly dose-proportionally.
- Tmax at LD was 0.5 h (M-5) and 2-4 h (M-2 to M-4). At MD and HD, tmax was 1-2 h (M-5) and 7 h for the other metabolites indicating a rapid formation of M-5 and slow formations of M-2 through M-4. C(24)/ Cmax of the parent drug was 26 to 56 % and C(24h) of the metabolites M-2 to M-5 was about 50 to 100 % of Cmax indicating a slow elimination.
- The influence of repeated dosing on the metabolite concentrations could not be evaluated since the metabolites were not measured on Day 1 of the study.

Summary of the study
A total of 11 unscheduled deaths occurred in this study: 2 control, 1 LD, 3 MD, and 4 HD animals. Since deaths were not dose or time dependent, the test article-related effect remains unclear.

Daily observations of animals revealed emaciation in 3 HD ♀s females, one of which was sacrificed in moribund condition, as well as labored breathing at MD and HD. Open field and functional observation battery investigations gave no indication of a neurotoxicity.

Food consumption was comparable to controls in both sexes. Water consumption was comparable to control values in all male treatment groups and in females up to and including 1.4 mg/kg. At 3.43 mg/kg females consumed less water.

MD and HD males had up to 10% lower body weights.

Ophthalmology and histopathology gave no indication of ocular toxicity of the test compound.

Changes in the hematology parameters included statistically significantly ↓ platelets at HD (♂s and ♀s). Other changes that were statistically significant consisted of ↑ in hemoglobin and hematocrit in MD and HD ♂s and ♀s, ↑MCV and MCH (♂s and ♀s) and MCHC (♂s; study end) at HD.

Clinical chemistry parameters revealed potential for hepatotoxicity as shown by slight increases in ALP, AST, and ALT (up to 53% increase, at HD). Although statistically significant, increases were not toxicologically significant. There were no histology

correlates in the liver. Histopathology of the liver indicated accumulation of the stains used for processing.

Nephrotoxicity occurred at MD and HD, as indicated by the ↑amount of total protein excreted and the histopathology findings: ↑incidence of tubular dilation, basophilic tubules, and hyaline casts in MD/ HD ♂s and ♀s; ↑incidence of glomerular hyaline in ♂s.

Histology showed effects in bones and teeth as expected from animal studies and from other receptor kinase inhibitors. Those included dentin degeneration in incisors of ♂s and ♀s (MD and HD), osteodystrophy of the jaw (♀s of MD and HD), and fatty replacement of sternum of ♂s (MD and HD). Additionally, an increase of mast cells in mesenteric lymph nodes occurred at MD and HD (both sexes).

Toxicokinetics

- Female plasma concentrations were slightly higher than males (♀/♂: approx. 150%) for sorafenib.
- M-3 is the major metabolite in rats.
- Sorafenib is absorbed relatively slowly, with a t_{max} of approx. 4 hours
- Tmax at LD was 0.5 h (M-5) and 2-4 h (M-2 to M-4). At MD and HD, tmax was 1-2 h (M-5) and 7 h for the other metabolites indicating a rapid formation of M-5 and slow formations of M-2 through M-4. C(24)/ Cmax of the parent drug was 26 to 56 % and C(24h) of the metabolites M-2 to M-5 was about 50 to 100 % of Cmax indicating a slow elimination.
- There was a large increase in exposure to sorafenib from Week 1 to Week 15 at all dose levels (Week 15/Week 1 was approximately 190%), indicating accumulation. There was no significant difference in exposure levels from Week 15 to Week 26.
- Slightly greater than dose proportional increase in exposure to sorafenib from LD to MD (a 13-fold increase for a 10-fold increase in dose) and from MD to HD (a 3-fold increase for a 2.5-fold increase in dose)

Study Title: A 7-Day Oral Dose Pharmacokinetic/Tolerance Study of BAY 54-9085 in the Beagle Dog. A non-GLP study conducted by [redacted]

Key study findings: The oral administration of BAY 54-9085 for 7 consecutive days resulted in treatment related clinical signs, decreased body weight gains, changes in hematology, and biochemistry parameter, and various histological changes in all groups. NOAEL could not be determined.

Report # RMI-00068

Study initiation:	22-Sept-1999
Species:	Beagle dogs (3 groups of 2/sex/group)
Age/Weights:	~7 months/Males: (8.1 to 10.9 kg) Females (7.9 to 9.8 kg)
Test Article:	BAY 54-9085 Lot # 505003
Vehicle:	2-Pyrrolidon (10%), Propyleneglycol (45%) and Cremophor RH 40 (45%)
Dosage:	BAY 54-9085: 41.1 mg/kg (Group 1); 82.2 mg/kg (Group 2); 82.2 (BID) mg/kg (Group 3) for 7 consecutive days (30, 60, 60 BID mg/kg BAY 43-9006)
Route:	oral gavage; dose volume was 3 ml/kg and the actual amount administered was based on the most recent body weight of each animal.

Group No. Identification	Dose Level (mg/kg)	Number of Animals Males	Females
1 BAY 54-9085	41.1	2	2
2 BAY 54-9085	82.2	2	2
3 BAY 54-9085 (BID)	82.2 (BID)	2	2

Doses correspond to	30, 60, and 60 (BID) mg/kg/day of BAY 43-9006; or 600, 1200, 1200 (BID) mg/m2/day of BAY 43-9006
Note: no control group	

Observations

Clinical signs:	Twice a day
Body weights:	Measured at randomization, on Day –1, and on the day of necropsy
Hematology:	Once prior to start of treatment and on Day 8 (approximately 24 hours after last dose)
Clinical chemistry:	Once prior to start of treatment and on Day 8
Gross pathology:	At necropsy (day 8)
Organ weights:	At necropsy (day 8)
Organs weighed	adrenal glands, brain, heart, kidneys, liver, lungs, ovaries/testes, pituitary, prostrate, spleen, thymus, thryroid lobes and parathryroid glands, uterus

Histopathology: At the end of pharmacokinetic sampling period (bone marrow, liver, kidneys, adrenals, gastrointestinal tract, spleen, thymus, testes, lymph nodes.

Toxicokinetics: Blood samples for plasma drug determination were collected on

- Day 1 from Groups 1 and 2 prior to the start of dosing and 0.5, 1, 2, 4, 8, and 24 hours after dosing.
- On Day 1 from Group 3, prior to the first dose and 0.5, 1, 2, 4, 8, and approximately 18 hours after the second dose.
- On Day 7, from Groups 1 and 2 prior to the start of dosing and 0.5, 1, 2, 4, 8, 24, 30, and 48 hours after dosing.
- On Day 7, from Group 3 prior to the start of dosing and 0.5, 1, 2, 4, 8, 24, 30, and 48 hours after the second daily dosing.

Results:

Clinical signs: Soft and/or liquid feces periodically in all groups
Group 3 (82.2 (60) mg/kg/twice daily) also showed slight to moderate tremors from Day 7 until study termination, vomitus, decreased activity, reduced appetite, and increased vocalization.
No mortality was noted in this study.

Body weights: Group 3 (82.2 (60) mg/kg/twice daily) males and one female and one group 2 (82.2 (60) mg/kg daily) female showed decreases in body weight of at least 0.5 kg from the start of treatment to the end of study.

Hematology: No significant changes in RBC, hemoglobin, or hematocrit.

BAY 43-9006 (mg/kg)	♂			♀		
	30	60	60 (BID)	30	60	60 (BID)
*WBC	↑1.2	—	↑2.7	↑1.7	—	↑1.3
*Platelets	↑1.3	↑1.4	↑1.4	—	↑1.3	↑1.5

*Day 8 versus pretreatment

BAY 43-9006 (mg/kg)	Myeloid:Erythroid ratio		
	30	60	60 (BID)
♂	1.33:1.00	↑1.85:1.00	↑3.78:1.00
	1.26:1.00	↑1.87:1.00	↑2.63:1.00
♀	↑2.16:1.00	↑3.43:1.00	↑3.73:1.00
	↑1.83:1.00	↑3.57:1.00	↑2.10:1.00

Individual changes (each row represent changes in one animal)

The increase was attributed to increase in myeloid component. There were no significant findings in the maturation of the hematopoietic cell lines in any animal.

Clinical chemistry: see Table below, the individual animal data (each column represents changes seen in one animal)

mg/kg	♂						♀					
	30		60		60 BID		30		60		60 BID	
*AST	↑1.6	↑1.6	↑1.3	↑1.3	↑1.6	↑2.0	↑1.2	↑1.3	↑1.7	↑2.6	↑7.4	↑5.5
*ALT	—	—	—	—	↑0.6	↑1.9	—	—	↑0.7	↑1.5	↑16.0	↑10.5
*ALP	—	—	—	—	↑1.9	↑2.9	—	—	—	—	↑21.3	↑2.2
*Phos	0.9	↓0.8	↓0.8	↓0.8	↓0.6	↓1.1	—	—	↓0.6	↓0.7	↓0.8	↓0.6

*Day 8 versus pretreatment

All other serum biochemistry parameters, including histamine, were comparable with pretreatment levels and /or within historical laboratory ranges.

Organ Weights: There were no overt differences in absolute or relative organ weights among the groups.

Gross pathology: In all groups, dark areas on the mucosa of the cecum, colon, and/or rectum of some animals. Considered agonal or incidental.

Histopathology:

Findings	BAY 43-9006	30 mg/kg ♂/♀	60 mg/kg ♂/♀	60 mg/kg BID ♂/♀
Bone Marrow	↑ Myelopoiesis	0/0	0/0	1/
Kidney	Tubular basophilia	0/0	0/0	2/0
Liver	Infiltration: mixed cell	0/0	0/0	2/2
Lymph Nodes; Mesenteric	Lymphoid necrosis	1/0	0/1	1/2
	Infiltration (e.g. histocytes or mixed cells)	0/0	0/0	1/2
Spleen	Siderotic plaque	0/0	0/0	1/
	Capsular fibrosis	0/0	0/0	0/1
Stomach	Vasculitis	0/0	1/	0/0
	Necrosis lymph.	0/0	0/1	0/0
	Accumulation foamy histiocyte	0/0	0/0	0/1
Testis	Degeneration: tubular	2	1	2
Thymus	Atrophy: lymphoid	0/1	0/1	0/1

Lesions in the gastrointestinal tract, liver, mesenteric lymph node and possibly thymus, bone marrow, and testis. Lesions were observed in all groups but with a higher frequency in Group 3 (high dose/twice a day) animals.

Sponsor attributes testicular degeneration in all groups to sexual immaturity, and lymphoid atrophy in 4 animals to stress or age-involution.

Note: Toxicitiy is difficult to interpret since samples were collected 1-3 days after dosing.

Toxicokinetics: Method of detection: [ ]

TK parameters	Day 1 BAY 43-9006 (mg/kg)			Day 7 Bay 43-9006 (mg/kg)		
	30 QD	60 QD	60 BID	30 QD	60 QD	60 BID
C_{max} (mg/l)	7.25	7.1	17.7	6.23	7.01	9.82
AUC_{0-inf} (mg*h/l)	85	100	n.d.			
AUC_{0-24} (mg*h/l)	74.7	86.3	228*	79	82.8	114
T_{max} (h)	3.36	2	4	3.36	2.38	2.73
$t_{1/2}$ (h)	6.29	7.51	13.53	7.56	4.85	3.58

(*) $AUC_{(0-18)}$

- Drug exposure in drugs appears to plateau at 60 mg/kg after a single oral dose.
- Plasma concentrations were similar between 30 and 60 mg/kg QD.
- No drug accumulation or autoinduction was observed for 30 and 60 mg/kg QD after multiple dosing for 7 days.
- Increased drug exposure was observed for 60 BID; however, drug exposure decrease 2-fold on day 7, indicating inhibition of absorption or autoinduction after 60 mg/kg BID for 7 days.
- Female dogs showed higher plasma concentrations that males at 60 mg/kg QD.

Summary of the study

The oral administration of 30, 60, 60 BID mg/kg BAY 54-9085 for 7 consecutive days to beagle dogs resulted in treatment related clinical signs, decreased body weight gains, changes in hematology, and biochemistry parameter, and various histological changes in all groups. NOAEL could not be determined. Hematological changes included increased white blood cell counts at 30 mg/kg and 60 mg/kg twice daily; increased platelets at all doses, increased myeloid:erythroid ratio for 60 mg/kg and 60 mg/kg BID. At the higher dose (twice a day), there were increases in AST, ALT, and ALP. Histopathological lesions were observed in the gastrointestinal tract, liver, mesenteric lymph node and possibly thymus, bone marrow, and testis. Lesions were observed in all groups but with a higher frequency at the high dose/twice a day. PK studies show that drug exposure appears to plateau at 60 mg/kg after a single oral dose and there is no drug accumulation or autoinduction at 30 and 60 mg/kg QD after multiple dosing for 7 days. Increased drug exposure was observed for 60 BID; however, drug exposure decrease 2-fold on day 7, indicating inhibition of absorption or autoinduction after 60 mg/kg BID for 7 days.

BAY 54-9085: Subacute Toxicity Study in Beagle Dogs (4 week gavage study and 4 week recovery period). A GLP study conducted by BAYER AG, Wuppertal-Elberfeld.

Key study findings: The 4 week oral treatment of Beagle dogs with BAY 54-9085 yielded no NOAEL at the doses used in the study.

Study Report PH-30221-8 (referred to as MRC-01028 in the IND)
Study # T 3069071

Date of product report: 24-April-2000

Species: Beagle dogs (2/sex/group)
Age/Weights: 18-22 weeks old /weighted between 5.7-9.7 kg

Test Article: BAY 54-9085 (the tosylate salt of sorafenib); Lot # 505003
Vehicle: 2-Pyrrolidon (10%), Propyleneglycol (45%) and Cremophor RH 40 (45%)
Dosage: See table below
Route: oral gavage; dose volume was 3 ml/kg

Group Number	Number of Males/Females	Substance	Dose Level BAY 43-9006		Dose Level BAY 54-9085 mg/kg
			mg/kg	mg/m2	
I	4/4	Tap Water	0	0	0
II	4/4	Vehicle	0	0	0
III	2/2	Vehicle (recovery)*	0	0	0
I	4/4	BAY 54-9085	10 (x 2)	200 (x 2)	14 (x 2)
II	4/4	BAY 54-9085	30 (x 2)	600 (x 2)	41 (x 2)
III	4/4	BAY 54-9085	60 (x 2)	1200 (x 2)	82 (x 2)
IV	2/2	BAY 54-9085 (recovery)*	60 (x 2)	1200 (x 2)	82 (x 2)

*These groups were set on 4 week treatment-free recovery period after the end of dosing.

Due to high toxicities observed in groups II, III, and IV dosing was reduced from twice daily to once daily with the same doses from week 2 of the study onwards.

Observations

Clinical signs: Daily (included test of reflexes and temperature)
Body weights: Weekly
Food/water consumption: Daily
Ophthalmoscopy: Week -2 and week 4 (plus week 8 for recovery group)
ECG and blood pressure: Week -2 and before and 2h after administration in week 1 and 4 (plus week 8 for recovery groups)
Hematology: Week -2 and weeks 2 and 4 (plus week 8 for recovery group)
Clinical chemistry: Week -2 and weeks 2 and 4 (plus week 8 for recovery group)
Urinalysis: Week -2 and weeks 2 and 4 (plus week 8 for recovery group)
Gross pathology: End of study (week 4 and 8)
Organs weighed: Brain, heart, liver, lungs, spleen, adrenals, kidneys, pancreas, thyroid, pituitary, testes, prostate gland, uterus, thymus, ovaries, epididymides, and empty gall bladder
Histopathology: At necropsy (week 4 and 8)
Toxicokinetics: Measured at end of 28 days dosing

Results:

Clinical signs: Reflex tests showed no pathological findings. No difference in body temperature were observed among groups. Feces with bloody admixture was seen in groups II-IV showing reversibility during the recovery period.. Weakness and reduced movements were observed in one group III-male.

Mortality: The death of 1 Group I animal was attributed to intratracheal application and not to the test compound.

Body weights: Mean body weight gain of males was reduced in Group II and III compared to controls (~40%). Body weight gain in Group III and IV females was reduced (%60) compared to controls.

Food/water consumption: There was no difference in food consumption among males; females from group II-IV showed a reduction in feed intake. No differences were noted in water consumption.

Ophthalmoscopy: No ocular changes were detected in any of the groups.

ECG and blood pressure: There were no differences among the groups.

Hematology: No relevant alterations were observed among the groups.

Clinical chemistry: The relevant data was not included in the application, thus these results have been extracted from the summary.

Parameters	Group I	Group II	Group III	Group IV
AST	↑Wk4	↑Wk4	↑Wk2/4	↑Wk2/4
ALT	↑Wk4	↑Wk4	↑Wk2/4	↑Wk2
Aph	—	↑Wk4	↑Wk2	↑Wk2
GLDH	↑Wk4	↑Wk4	↑Wk2/4	↑Wk2
GGT	—	↑Wk4	↑Wk2/4	↑Wk2/4
Bili-t	—	—	↑Wk4	↑Wk2
T3	—	—	↑Wk4	—

Urinalysis: Urinary protein content was slightly increased in Group II and III

Organ Weights: There were no relevant changes among the groups.

Gross pathology: There were no differences in nutritional state among the groups

Treatment-related brown or yellow discoloration of the liver was observed in Group III animals.

Histopathology:

Organ/Tissue	Findings	10 mg/kg ♂/♀	30 mg/kg ♂/♀	60 mg/kg ♂/♀	60 mg/kg ♂/♀ (recovery)
Liver	Bile duct proliferation	—	0 / 1	2 / 2	1 / 1
	Pericholangiolar fibrosis	—	1 / 2	2 / 3	1 / 1
	Infiltration: Granulocytic/Periportal	—	0 / 2	1 / 1	1 / 0
	Infiltration: Mononuclear/Periportal	—	1 / 1	2 / 1	1 / 0
Spleen	↑ hemopoiesis	1 / 1	4 / 4	3 / 1	—
	↑ Megakaryocytes	—	1 / 3	3 / 1	—
	↑ Iron deposits	—	4 / 4	—	1 / 1
Stomach	Hypertrophy/Pyloric region	—	2 / 0	3 / 1	0 / 0
Femoral growth plate	Irregular thickening	—	1 / 2	3 / 3	—
	hypocellularity bone marrow	—	—	2 / 2	—
Teeth	*altered dentin	1 / 0	4 / 4	4 / 4	4 / 4
Kidneys	basophilic tubules	1 / 0	0 / 1	2 / 0	1 / 0

* Not reversible

Toxicokinetics: Method of detection: [redacted]

Doses of BAY 43-9006	10 (mg/kg)		30 (mg/kg)		60 (mg/kg)	
Week 4	Females	Males	Females	Males	Females	Males
AUC $_{(0\text{-}24)}$ (mg*h/l)	19.01	15.33	45.16	34.37	66.2	40.71
Cmax	2.04	2.29	5	3.17	5.67	4.94

- Females appear to have higher exposure (AUC 0-24) than males.
- Increase in exposure was less than dose proportional in both the 10 to 30 mg/kg and 30-60 mg/kg dose ranges, for both sexes.

Summary of the study

The 4-week oral treatment of beagle dogs with 10, 30, 60 mg/kg BAY 43-9006 yielded no NOAEL. Originally, drug administration in this experiment was scheduled for twice a day at the doses above mentioned. One week into the protocol, the dosing schedule was changed to once daily at the same doses due to general poor health of the subjects. Clinical signs included feces with bloody admixture showing reversibility during recovery period. Mean body weight gain was reduced in treated animals compared to controls. Clinical chemistry parameters included increases in AST and ALT. Histopathological changes were observed in liver, stomach, and bone marrow next to the altered growth plate in the high dose group. Dose-dependent alteration in the dentin composition of the teeth observed in all groups and this effect was not reversible in 28 days.

Study title: BAY 54-9-85 Subchronic toxicity study in beagle dogs (13 week gavage study).

Report # PH-31490
Study # T 7069994

Key study findings:

- One ♀ dog was sacrificed moribund. This dog had purulent pleuropneumonia and adhesive pericarditis.
- Clinical chemistry analysis showed signficant changes in liver-associated parameters at doses ≥ 14 mg/kg/d (AST, ALT, ALP, GGT, and GLD).
- Histopathology revealed treatment-related findings predominantly in the liver, kidneys, lymphoreticular and hematopoetic system as well as in the teeth and skin.

Conducting laboratory and location: Bayer AG, Institute of Toxicology, Wuppertal
Date of study initiation: November 20, 2000
GLP compliance: Yes
QA report: yes (x) no ( )
Drug, lot #, radiolabel, and % purity: BAY 54-9085 (batch: 000217); [ ]
Formulation/vehicle: 2-Pyrrolidon (1-%), Propylenglycol (45%), and Cremophor RH 4- (45%).

Dosing:

Species/strain:	beagle dogs
#/sex/group or time point (main study):	4/sex/group
Satellite groups used for toxicokinetics or recovery:	None
Age:	19-20 weeks
Weight:	6.1-8.2 kg

Doses in administered units: 0, 14, 41, 82 mg/kg daily doses of BAY 54-9-85 x 13 weeks
Does of free base: 0, 10, 30, 60 mg/kg/day (0, 200, 600, 1200 mg/m2/day)
Route, form, volume, and infusion rate: orally gavage; 3 ml/kg

Note: Before the start of the study it was assured for a period of 12 days that the test substance is chemically stable within the concentration range used in the study. The stability data were transferred from study T 3069071 to this study. Analytical content checks of the formulation verified that the solution contained the requested amount of test substance (data submitted).

Observations and times

Clinical signs:	Daily
Body weights:	Weekly
Food consumption:	Daily
Ophthalmoscopy:	Before the start of the study (week – 2) and in week 5 and 13 of the study.
EKG:	Electrocardiograms (ECG) and blood pressure measurements were performed once before the start of the study (week – 2) and before and 2h after administration in week 1, 5, and 13 of the study.
Hematology:	Before the start of the study (week – 2) and in week 4, 8, and 13 of the study.
Clinical chemistry:	Before the start of the study (week – 2) and in week 4, 8, and 13 of the study.

Urinalysis:	Before the start of the study (week – 2) and in week 4, 8, and 13 of the study.
Gross pathology:	Necropsies were performed in week 14. The total number of administrations was 91/92.
Organs weighed:	The heart, lung, liver, kidneys, spleen, testes, prostate, ovaries, thyroid, adrenals, thymus, brain, pituitary, pancreas, empty gall bladder, epididymides, and uterus/oviduct were weighed.
Histopathology:	Day 91/92.
Toxicokinetics:	On Day 1 and in Week 4 and 12 of the study, plasma for toxicokinetic measurements was collected before and 1, 3, 7 and 24 h after administration (control group only 1 h after administration). The results of the measurements are presented in a separate toxicokinetic report. As no GLP-approved toxicokinetic data were available when this report was finalized, no toxicokinetic data are contained in this report.
Other:	Testing of each animal's reflexes (pupillary, corneal, patellar, extensor-, postural-, and flexor reflex) was carried out before the start of the study (week -2) and in week 5 and 13 of the study. At the same investigation times, the body temperatures of the animals were measured.

Results:

Mortality:	Animal H 062/♀ low dose (LD: 14 mg/kg) was sacrificed moribund at the end of week 13 of the study (D89). This animal showed findings predominantly affecting the respiratory system (discolorations and solid-firm consistency changes in the lung with pleural adhesions to the chest cavity). Additionally, a thickened pericardium with dark-red areas in the papillary muscle was observed. Microscopically, these findings correlated with a marked to severe purulent pleuropneumonia and a moderate chronic adhesive pericarditis.
Clinical signs:	Animal H 073/control group and H 062/LD showed a reduced health status at the end of the study with strengthened breathing in animal H 062. Both mid dose (MD: 41 mg/kg) and high-dose (HD: 82 mg/kg) animals showed hairless, partly reddish, spots over the whole body up to a nearly complete hair loss and an increased incidence of feces with reddish/bloody, partly foamy, admixtures/mucus.

The hair coat showed a dose dependant reduction in density in all drug-treated groups.

Body weights: Body weight gain was reduced in males at the LD compared to controls. Beginning at group MD (42 mg/kg), body weight gain was reduced in both sexes in comparison to the controls.

Review on the mean body weights per group

Group	Sex	Pretreatment (week –1)	End of treatment (week 13)	Difference week –1/week 13
Contr.	m	6.8 kg	10.1 kg	+ 3.3 kg
	f	6.5 kg	9.2 kg	+ 2.7 kg
	m+f	6.6 kg	9.6 kg	+ 3.0 kg
LD	m	7.4 kg	9.5 kg	+ 2.1 kg
	f	7.2 kg	9.7 kg	+ 2.5 kg
	m+f	7.3 kg	9.6 kg	+ 2.3 kg
MD	m	6.9 kg	8.5 kg	+ 1.6 kg
	f	6.8 kg	8.5 kg	+ 1.7 kg
	m+f	6.8 kg	8.5 kg	+ 1.7 kg
HD	m	7.1 kg	8.4 kg	+ 1.3 kg
	f	6.5 kg	8.2 kg	+ 1.7 kg
	m+f	6.8 kg	8.3 kg	+ 1.5 kg

Food consumption: Feed intake was reduced in HD (82 mg/kg) males compared to control animals whereas in females no significant changes.
Water intake was unremarkable.
The nutritional state showed no changes between the control group and LD group. The nutritional state was slightly reduced in MD and HD groups compared to the control group.

Ophthalmoscopy: Unremarkable

Electrocardiography: Unremarkable

Hematology: Data shows percent difference from controls.

Sex	Dose (mg/kg/day) Free base	Leuco 10^9/L	PTL 10^9/L	Lymph 10^9/L	PT sec	PTT sec
♂	0	16.64	447	4.84	7.6	13.5
	10	↓25	↑43	↓21	↓17	↓16
	30	↓18	↑26	↓10	↓14	-
	60	↓23	↑31	↓29	↓17	↓10
♀	0	12.39	490	5.37	6.6	11.8
	10	↑46	-	↑18	-	-
	30	↑36	↑23	↓9	-	-
	60	-	↑14	↓24	-	-

Clinical chemistry: Data shows percent difference from controls.

Sex	Dose (mg/kg/day) Free base	AST (U/L)	ALT (U/L)	ALP (U/L)	GDH (U/L)	GGT (U/L)
♂	0	33.5	60.4	540	17.6	6
	10	-	-	-	-	-
	30	↑77	↑31	-	↑126	-
	60	↑46	↑35	-	↑38	-
♀	0	26	36.3	261	10.2	3
	10	↑28	↑106	↑26	↑88	↑33
	30	↑68	↑22	↑39	↑58	↑67
	60	↑104	↑178	↑92	↑251	↑100

Urinalysis: Volume, density, pH, protein, glucose, blood, bilirubin, ketone bodies, urobilinogen, and creatinine values were unremarkable.

Organ weights: Data shows percent control difference from controls.

Sex	Dose (mg/kg/day) Free base	BW in kg	Liver	Thymus
♂	0	10.15	378.5	16.8
	10	-	-	↓46
	30	↓16	↓38	↓57
	60	↓18	↓15	↓58
♀	0	9.5	383.3	12.3
	10	-	↓11	-
	30	↓9	↓13	↓37
	60	↓15	↓23	↓16

Gross pathology: Animal H 062/LD sacrificed prematurely showed findings predominantly affecting the respiratory system (discolorations and solid-firm consistency changes in the lung with pleural adhesions to the chest cavity). Additionally, a thickened pericardium with dark-red areas in the papillary muscle were observed.

Microscopically, these findings correlated with a marked to severe purulent pleuropneumonia and a moderate chronic adhesive pericarditis.

Animal H 073/control showed an increased amount of fluid in the body cavities. The Sponsor suggested the reason for this finding is probably a marked liver cirrhosis accompanied by several other findings (including moderate thymic atrophy).

mg/kg/d BAY 43-9006	Males (n=4)				Females (n=4)			
	0	**10**	**30**	**60**	**0**	**10**	**30**	**60**
Lungs-Consistency changes Adhesions	-	-	1	-	-	1 1	-	-
Thymus-diminished	1	-	2	2	-	-	-	-
Skin (↓ density of hair coat)	0	1	4	4	0	0	4	4

Histopathology:

MALES

LUNGS	4	4	4	4
- Atelectasis/(M.)Foc.	1	-	-	-
- Leucostasis	1	1	-	1
- Alveolar Macrophages	2	-	2	2
- Foam Cell Accumul.	-	-	1	-
- Focal Fibrosis	1	1	-	2
- Inflamm.Infiltr.	-	1	1	1
- Purulent Bronchopn.	-	-	-	1
- Debr.Intraal./-bron.	1	-	-	-
- Alveolar Edema	-	-	-	1
TEETH	4	4	4	
- Period.Infl./Inc./LJ	4	4	4	
- Alt.Dent.C./Inc./LJ	-	-	4	
- Period.Infl./Mol./LJ	3	1	3	
- Alt.Dent.C./Mol./LJ	-	-	4	
- Period.Infl./Mol./UJ	-	-	1	
- Alt.Dent.C./Mol./UJ	-	-	2	
LIVER	4	4	4	4
- Cirrhosis	1	-	-	-
- Pigment.Kupffer C.	2	1	2	1
- Pigment.Hepatocytes	1	-	-	-
- Cytoplasm.Vacuol.	1	-	-	-
- Infiltr. Mononuclear	1	-	-	-
- Eosinoph.Cytoplasm	-	-	-	4
- Periportal Fibrosis	-	-	-	4
- Bile Duct Prolif.	-	-	4	4
- Kupffer cell foci	-	4	-	1
- Leucostasis	-	-	2	1
KIDNEYS	4	4	4	4
- Infiltr. Mononuclear	1	-	1	3
- Basophilic Tubules	1	1	3	4
- Single C.Necr./Tub.	-	-	-	1
- Cytopl.Vacuol./DT	1	-	-	-
- Prot.Casts Intrat.	-	-	2	2
- Glomerulopathy	-	-	3	2
- Trans.C.Hyperpl./P.	-	1	-	-
- Juvenile Renal Tiss.	-	1	-	-
- Chron.Inflammation	-	1	-	-
KIDNEYS/PAS	4	4	4	4
- Incr.PAS-Stain./Tub.	-	-	3	3
- Incr.PAS-Stain./Gl.	-	-	3	2
PITUITARY GLAND	4	4	4	4
- Cyst/s/Anterior Lobe	-	1	-	1
- Perivasc.Infiltrat.	-	-	1	-
ADRENAL GLANDS	4	4	4	4
- Cytopl.Vac./Z.Fasc.	-	-	1	2
- Cyst/s	-	1	-	-

FEMALES

LUNGS	4	4	4	4
- Leucostasis	-	-	2	-
- Alveolar Macrophages	-	1	1	1
- Foam Cell Accumul.	-	-	-	2
- Inflamm.Infiltr.	2	1	2	2
- Chron.Prolif.Pneum.	1	-	-	-
- Purulent Bronchopn.	-	1	-	-
- Purulent Vasculitis	-	1	-	-
- Hemorrhage	-	1	-	-
- Purulent Pleuritis	-	1	-	-
TEETH	4	4	4	4
- Period.Infl./Inc./LJ	3	3	4	4
- Alt.Dent.C./Inc./LJ	-	-	2	4
- Period.Infl./Mol./LJ	4	4	4	4
- Alt.Dent.C./Mol./LJ	-	-	4	4
- Molar Retention/LJ	-	1	-	-
LIVER	4	4	4	4
- Pigment.Kupffer C.	1	-	-	3
- Cytoplasm.Vacuol.	1	-	-	-
- Eosinoph.Cytoplasm	-	-	-	3
- Periportal Fibrosis	-	-	2	1
- Bile Duct Prolif.	-	2	3	4
- Kupffer cell foci	2	1	1	2
- Leucostasis	-	2	1	2
- Ballooning Degen.	1	-	1	-
- Congestion	-	1	-	-
- Glycogen Decrease	-	1	-	-
KIDNEYS	4	4	4	4
- Infiltr. Mononuclear	1	2	1	2
- Basophilic Tubules	-	1	1	3
- Single C.Necr./Tub.	-	-	-	1
- Prot.Casts Intrat.	-	-	1	2
- Glomerulopathy	-	-	1	4
- Trans.C.Hyperpl./P.	1	-	-	1
- Chron.Inflammation	-	-	1	-
KIDNEYS/PAS	4	4	4	4
- Incr.PAS-Stain./Tub.	1	-	2	3
- Incr.PAS-Stain./Gl.	-	-	1	2
PITUITARY GLAND	4	4	4	4
- Cyst/s/Anterior Lobe	2	-	1	1
ADRENAL GLANDS	4	4	4	4
- Cytopl.Vac./Z.Fasc.	-	-	1	1
- Cyst/s	-	1	-	-

MALES

SPLEEN	4	4	4	4
- Incr.Hematopoiesis	-	2	4	4
- Incr.Perif.Gran.Inf.	1	1	3	2
- Atrophy	-	-	4	4
- Fibrin Dep./Marg.Z.	-	-	1	-
- Hemorrhage/Marg.Z.	-	2	1	3
BONE MARROW CYLINDER	4	4	4	4
- Incr.Blood Content	1	-	-	-
- Incr.Granulocytes	2	4	4	4
- Incr.Pigmentl.Macr.	-	1	-	-
THYMUS	4	4	4	4
- Atrophy	1	-	3	3
SKIN(MAMMARY REGION)	4	4	4	4
- Cell.Inf./(Sub)Epid.	2	1	1	1
- Alopecia/Deg.Hair F.	-	1	4	4
- (Peri-)Folliculitis	-	-	1	2
- Follicle Cyst/s	-	1	2	1
- Chron.Purul.Dermat.	-	-	1	-
- Hyperkeratosis	-	1	4	2
CECUM	4	4	4	4
- Hemorrhagic Content	1	-	-	-
- Granulocytic Infilt.	1	-	-	-
- Incr.Goblet Cells	-	-	1	3
COLON	4	4	4	4
- Hemorrhagic Content	1	-	-	-
- Incr.Goblet Cells	-	-	2	3
RECTUM	4	4	4	4
- Hemorrhagic Content	1	-	-	-
- Parasitic Granuloma	-	1	-	-
- Incr.Goblet Cells	-	-	4	3

FEMALES

SPLEEN	4	4	4	4
- Incr.Hematopoiesis	-	4	3	4
- Incr.Perif.Gran.Inf.	1	2	4	3
- Atrophy	-	-	-	2
- Hemorrhage/Marg.Z.	3	3	1	1
BONE MARROW CYLINDER	4	4	4	4
- Incr.Granulocytes	1	2	3	2
- Incr.Pigmentl.Macr.	-	1	-	-
THYMUS	4	3	4	4
- Atrophy	1	-	-	1
- Macroph.Accumulation	1	-	-	1
SKIN(MAMMARY REGION)	4	4	4	4
- Cell.Inf./(Sub)Epid.	1	-	1	1
- Alopecia/Deg.Hair F.	-	-	4	4
- (Peri-)Folliculitis	-	-	-	2
- Follicle Cyst/s	-	-	1	-
- Hyperkeratosis	-	-	4	3
CECUM	4	4	4	4
- Granulocytic Infilt.	-	-	1	-
- Incr.Goblet Cells	-	-	2	3
COLON	4	4	4	4
- Incr.Goblet Cells	-	-	2	3
RECTUM	4	4	4	4
- Incr.Goblet Cells	-	-	2	3

- Animal H 062/LD sacrificed prematurely showed marked to severe purulent pleuropneumonia and a moderate chronic adhesive pericarditis (correlating to gross pathology findings).
- Histopathology revealed treatment-related findings predominantly in the liver, kidneys, lymphoreticular and hematopoetic system as well as in the teeth and skin.

Table provided by the sponsor.

Toxicokinetics: Not included in this report

Other: Test of reflexes: Unremarkable

Body temperature: Unremarkable

Summary of individual study findings:

Beagle dogs were treated orally by gavage over 13 weeks with daily doses of BAY 54-9085 (0, 14, 41, or 82 mg/kg). One ♀ dog at 14 mg/kg was sacrificed moribund at the end of week 13 of the study with findings correlating with a marked to severe purulent pleuropneumonia and a moderate chronic adhesive pericarditis. In surviving animals, the nutritional state, food consumption, and body weight gain were reduced at doses ≥ 41

mg/kg in both sexes. Clinical findings included hairless, partly reddish, spots over the whole body up to a nearly complete hair loss and an increased incidence of feces with reddish/bloody, partly foamy, admixtures/mucus.

Hematological changes were unremarkable, whereas clinical chemistry analysis showed signficant changes in liver-associated parameters at doses ≥ 14 mg/kg/d (AST, ALT, ALP, GGT, and GLD). Histopathologically, the liver showed minimal to moderate bile duct proliferation and minimal to slight periportal fibrosis. Other histopatholical changes were observed in the kidneys (increased number of basophilic tubules, proteinaceous casts, glomerulopathy, increased PAS positive reaction of tubules and/or glomerula), the lymphoreticular/hematopoetic system (atrophy of thymus and spleen, increased hematopoiesis and perifollicular granulocytic infiltration in the spleen, necrosis of lymphoid follicles in the tonsils, atrophy of lymphoid follicles of the ileum, increased number of granulocytes in the sternum and in the bone marrow cylinders), teeth (altered dentin composition), large intestine (increased number of goblet cells), and skin (alopecia/degeneration of hair follicles).

Histopathology Inventory for the 13-week rat and dog toxicology studies

Study	PH-29467	T7-69994		
Species	Rat	Dog		
Adrenals	X	X		
Aorta	X	X		
Bone Marrow smear	X	X		
Bone (femur)	X	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			
Ileum	X	X		
Injection site				
Jejunum	X	X		
Kidneys	X	X		
Lachrymal gland				
Larynx	X	X		
Liver	X	X		
Lungs	X	X		
Lymph nodes, cervical	X			
Lymph nodes mandibular		X		
Lymph nodes, mesenteric	X	X		
Mammary Gland	X			
Nasal cavity	X	X		
Optic nerves	X	X		
Ovaries	X	X		
Pancreas	X	X		
Parathyroid	X			
Peripheral nerve				
Pharynx	X	X		
Pituitary	X	X		
Prostate	X	X		
Rectum	X	X		
Salivary gland	X	X		
Sciatic nerve	X			
Seminal vesicles	X			
Skeletal muscle	X	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		
Urinary bladder	X	X		
Uterus	X	X		
Vagina	X	X		
Zymbal gland	X			
Standard List				
Teeth	X	X		

X, histopathology performed;

Study title: Chronic Oral Toxicity Study in Beagle Dogs (52 Weeks Administration by Gavage)

Key study findings: Mortality mainly at HD
Skin: Pustules on body; red/blue skin; peri/folliculitis; acanthosis
Purulent myocarditis, nephritis, and pyemia
Conjunctivitis with mucous coating
GI toxicity
Effects on coagulation parameters: ↑PT and aPTT
Hypothyroidism (↓T3, ↓T4, ↑TSH)
Hemolytic anemia: ↓Fe in circulation and ↑Fe deposit in spleen, ↓erythrocyte/hemoglobin/hematocrit, ↑Heinz bodies
Hepato/ hepatobiliary toxicities: ↑AST, ALT, ALP, GLDH, and GGT, ↓albumin
↑CK
Coagulation parameters: transiently ↑PT and aPTT; ↑platelets

Study Report: PH-33532
Study no.: T 9071362

Volume #, and page #: Module 4 of the NDA (CTD); M4.2.3.2.1.2
Conducting laboratory and location: Bayer HealthCare AG
PH-PD Toxicology International
42096 Wuppertal, Germany
Date of study initiation: January 28, 2002
GLP compliance: Yes; in compliance with the OECD Principles of GLP
QA report: yes (X) no ( )
Drug, lot #, and % purity: BAY 54-9085, batch #s 000217 and 011121, purity of [ ] % and [ ] %
Vehicle: 2-Pyrrolidon, 1,2-Propandiol and Cremophor RH 40 (10 ml: 45 ml: 45 ml; ml was considered equal to gram)

Methods
Doses: daily dosing for 52 weeks; see Table below

Group	Dose of BAY 54-9085		Corresponding dose of BAY 43-9006 (free base)	
	mg/kg/day	mg/m2/day	Mg/kg/day	mg/m2/day
Control (vehicle)	0	0	0	0
Group I/ LD	4	80	3	60
Group II/ LMD	14	280	10	200
Group III/ HMD	41	820	30	600
Group IV/ HD	82	1640	60	1200

BAY54-9085 to BAY43-9006 conversion factor: 1.37
The study was started with doses of 3, 10, 30 and 60 mg/kg BAY 54-9085, which corresponds to 2, 7, 22 and 44 mg/kg BAY 43-9006. The doses were increased from week 3 for the rest of the study period with the above described doses.

Species/strain: dog/ Beagle
Number/sex/group or time point (main study): 4/sex/group
Route, formulation, volume: oral gavage, solution, 3 mL/kg
Toxicokinetics: 4/sex/group
Age: 18-21 weeks on Week -1
Weight: 6.3-9.9 kg on Week -1

Observations and times:
Mortality: Not mentioned
Clinical signs: Daily, several times per day.
Reflexes: Before the start of the study and in the following study Weeks: 6, 13, 26, 39, and 51. Those included papillary, corneal, patellar, extensor, postural, and flexor reflex)

Body weights: Weekly
Food consumption: Daily
Ophthalmoscopy: Before the start of the study (Week -2) and on Weeks 6, 13, 26, 39 and 51 of the study.
EKG and blood pressure: Blood pressure measurements were performed once before the start of the study (Week -2) and before and 2h after administration on Weeks 6, 13, 26, 39 and 51 of the study.

Electrocardiograms (ECG) were performed once before the start of the study (Week – 2) and before and 2h after administration on Weeks 6, 13, 26, 39 and 51 of the study.

Hematology: before the start of the study (Week -2) and on Weeks 6, 13, 26, 39 and 51 of the study.
Clinical chemistry: before the start of the study (Week -2) and on Weeks 6, 13, 26, 39 and 51 of the study.
Except for the electrolytes, the clinical chemistry parameters were determined in the plasma. At necropsy, samples of the liver were taken for the determination of enzymes and the triglyceride content.
Urinalysis: before the start of the study (Week -2) and on Weeks 6, 13, 26, 39 and 51 of the study. Collection was 6 hrs.
Gross pathology: at necropsy; end of treatment, on Week 53
Organ weights: at necropsy
heart, lung, liver, kidneys, spleen, testes, prostate, ovaries, thyroid/parathyroid, adrenals, thymus, brain, pituitary, pancreas, empty gall bladder, epididymides, and uterus/oviduct
Histopathology: Adequate Battery: yes (X), no ( )
Peer review: yes (X), no ()

Table: Organs fixed and evaluated histopathologically.

Adrenal glands	Ovaries
Aorta	Oviducts
Bone marrow cylinder	Pancreas
Brain (cerebrum, cerebellum, brain stem, medulla oblongata)*	Pharynx#
Epididymides	Pituitary gland
Esophagus	Parotis
Eyes	Prostate
Femur with Bone marrow	Sciatic nerve
Gallbladder	Skeletal muscle (thigh)
Heart (2 Papillary Muscles)	Skin (mammary region)
Intestine/Peyer's Patches	Spinal cord (cervical, thoracic, lumbar)*
- Duodenum	Spleen
- Jejunum	Sternum with bone marrow
- Ileum	Stomach
- Caecum	Testes
- Colon	Thymus
- Rectum	Thyroid glands (with parathyroid glands)
Kidneys**	Tonsils
Larynx	Tongue
Liver**	Trachea
Lungs**	Ureters
Lymph nodes, mandibular	Urinary bladder
Lymph nodes, mesenteric	Uterus with uterine cervix
Submandibular and sublingual gland	Vagina
Nose (nasal cavity)#/Teeth	Organs and tissues with macroscopic findings
Optic nerves	Physical identifier *#

* fixation in 10 %-neutral buffered formalin
** additional specimen fixed in 10 % neutral buffered formalin
# no histopathology performed

Table provided by the sponsor.

Toxicokinetics: on Day 1, Weeks 18 and 52

Plasma collected before and 1, 3, 7 and 24 h after administration (control group only 1 h after administration).

Results

Mortality: A total of 6 animals (3♂s and 3 ♀s); either found dead or sacrificed moribund:

- Control:1 ♂ (# I 423) was found dead on Study Week 19,
- HMD (41 mg/kg): 1 ♀(# I 418) was sacrificed in a moribund condition after continuous weight loss on Week 35.
- HD: 1 ♂ (# I 385) was sacrificed on Week 26 showing icteric/jaundice signs and emaciation; 1 ♂ was found dead on Week 28 (# I 391); 1 ♀ died on Week 34 after severe convulsions during the day (# I 396), 1 ♀ died on week 49 (# I 392).

Cause of death:

- 1 ♂ of the control group as well as 1 ♂ and 1 ♀ of the HD group showed a broncho-pneumonia with tracheitis. The female additionally showed a marked alopecia with peri-/folliculitis and a purulent-necrotic inflammation of the intestine.
- 1 ♀ of the HMD group and 1 ♂ of the HD group had a marked alopecia with peri-/folliculitis or focal dermatitis which led to a purulent myocarditis, nephritis and finally pyemia which most probably caused the moribund stage of both animals. Both animals as well as 1 ♀ of the HD group showed a moderate to marked liver cirrhosis or fibrosis.

Clinical signs:

- No effects on the reflexes or body temperature
- Skin, hair and coat: few animas at LMD had sparse haircoat and slight hair loss. In addition, 2 animals had pustules on different body regions (animal No. I 405, 1 420). Starting at HMD, animals were alopecic or nearly alopecic, sometimes reddened or bluish skin areas were seen on the body. Dark skin areas were also visible at the axillar region, mostly in the animals of the HD group.
- GI: ↑incidence of liquid feces and red discoloration at LMD, HMD, and HD. Yellow and red colored mucus also excreted at HMD and HD.

Body weights:

- ↓BW gain starting at LD in ♀s and starting at LMD in ♂s
- Reductions in the BW gains were most evident in ♀s

Group	Sex	Pretreatment (week –1) [kg]	End of treatment (week 52) [kg]	Difference week –1/week 52 [kg]
Ctr.	m	8.6	16.5	+ 7.9
	f	7.7	15.0	+ 7.3
	m+f	8.1	15.6	+ 7.5
I	m	8.2	15.1	+ 6.9
	f	7.9	12.6	+ 4.7
	m+f	8.0	13.8	+ 5.8
II	m	8.5	13.7	+ 5.2
	f	7.6	11.9	+ 4.3
	m+f	8.0	12.8	+ 4.8
III	m	9.0	12.9	+ 3.9
	f	7.7	11.6	+ 3.9
	m+f	8.4	12.3	+ 3.9
IV	m	9.0	12.2	+ 3.2
	f	7.9	9.3	+ 1.4
	m+f	8.4	10.7	+ 2.3

Table provided by the sponsor.

Food/ water consumption:

- ↓Feed intake in HD ♂s in the second half of the study period. ↓Feed intake in ♀ animals starting from Week 8; this was also observed in control ♀s on the second half of the study.

- Water intake was not affected.

Ophthalmoscopy: Conjunctivitis with mucous coating was observed starting at LMD (14 mg/kg group). This could be secondary to the general hair loss (also the hair of the eyelids), resulting in the loss of the barrier for foreign bodies.

EKG: no effect

Hematology:
Changes were mainly in the HD animals on Weeks 26, 39 and 51; therefore, only those results are shown in Table below.

Changes in the mean hematology parameters, compared to the corresponding control

	Week 26	**Week 39**	**Week 51**
Leukocytes	♂: ↑93%	♂:↑58%	♂: ↑20%
Neutrophils	♂: ↑120%	♂: ↑80%	♂: ↑45% ♀: ↑33%
Monocytes	♂: ↑3.5-fold	♂: ↑2-fold	♂: ↑90% ♀: ↑2-fold
Erythrocyte	♂: ↓12%	—	♂: ↓10% ♀: ↓8%
Hemoglobin	♂: ↓10%	—	♂: ↓12% ♀: ↓10%
Hematocrit	♂: ↓10%	—	♂: ↓12% ♀: ↓8%
Reticulocytes	♂: ↑69% ♀:	♀:↑20%	♀:↑100%
Heinz bodies	♂: ↑5-fold ♀: ↑38%	♀:↑80%	—
Platelets	♂: ↑40% ♀:↑23%	♂: ↑50% ♀: ↑20%	♂: ↑75% ♀: ↑40%
ESR-1	♂: ↑100% ♀: ↑5-fold	♂: ↑13-fold ♀: ↑4-fold	♂: ↑6-fold ♀: ↑9-fold
ESR-2	♂: ↑4-fold ♀: ↑5-fold	♂: ↑31-fold ♀: ↑11-fold	♂: ↑19-fold ♀: ↑21-fold
PT	♂: ↑23%	♂: ↑10%	—
aPTT	♂: ↑25%	—	♂: ↑10%

ESR: erythrocyte sedimentation rate

Parameter	Group	Animal no.	Effect
Leuco	III	I 418	increase in week 35
	IV	I 385	increase in week 26
	IV	I 415	increase in week 13,39,40
Neutro	III	I 418	increase in week 35
	IV	I 385	increase in week 26
	IV	I 415	increase in week 39
ERY	III	I 418	decrease in week 35
	IV	I 385	decrease in week 26
	IV	I 415	decrease in week 13
HB	III	I 418	decrease in week 35
	IV	I 385	decrease in week 26
	IV	I 415	decrease in week 13
HCT	III	I 418	decrease in week 35
	IV	I 385	decrease in week 26
	IV	I 415	decrease in week 13
RETI	IV	I 385	increase in week 26
ESR	IV	I 415	increase in week 13 to 17,39,40
	IV	I 400	increase in week 6 to 51
	IV	I 385	increase in week 13 and 26
PT	IV	I 385	increase in week 26
PTT	IV	I 385	increase in week 26

385: HD ♂; 400: HD ♀; 415: HD ♂; 418: HMD ♀
Table provided by the sponsor.

Animal No. I 415 (HD ♂): the high Erythrocyte Sedimentation Rates (ESR) and leucocytes in week 13 and the following weeks were caused by a spontaneous pnemnonia, In week 13 the dog also showed signs of anemia with lower erythrocytes, hemoglobin- and hematocrit-levels. In week 26 all parameters returned to normal 1evels. In week 39 ESR, leucocytes and neutrophils were increased again. In week 40 ESR was slightly reduced compared to the previous week, while leucocytes remained increased.

Animal No. I 400 (HD ♀): also higher Erythrocyte Sedimentation Rates (ESR) were seen between study week 6 and 51. These changes are probably caused by skin lesions with reddening. No distinct differences in other hematological parameters were observed in this animal.

Animal No. I 385 (HD ♂) showed slightly elevated Erythrocyte Sedimentation Rates (ESR) in week 13 and 26. In week 26 this animal showed an increased clotting time (PT, PTT), a high increase of leucocytes with increased neutrophils and was anemic, represented by a decrease in red blood cell parameters (ERY, HB, HCT) together with anisocytosis, macrocytosis, anisochromasia, and hypochromasia and an increase in reticulocyte values, This animal was sacrificed in week 26 with signs of a generalized jaundice.

Animal No. I 418 (HMD ♀) was anemic in week 35 with a decrease in red blood cell parameters (ERY, HB, HCT) and highly increased leucocytes with increased neutrophils. The animal was killed in a moribund stage in study week 35. Necropsy revealed peri/folliculitis or focal dermatitis, purulent myocarditis, nephritis and pyemia.

Clinical chemistry: changes were mostly non-dose-dependent; see the Table. It is not clear whether changes were not statistically significant or the statistical analyses were not reported.

Changes in the mean values, compared to the corresponding control group at the same time point.

Group	Week (# of animals)	Major Findings	
LD (Group I)	—	—	
LMD (Group II)	13		T3: ↓17% (♂s) T4: ↓14% (♂s) TSH: ↑2-fold (♂s)
	26		T3: ↓15% (♂s), ↓20% (♀s) T4: ↓20% (♂s) TSH: ↑100% (♂s), ↑100% (♀s) Fe: ↓30% (♀s)
	39 ♂ (n=4) ♀ (n=4)	CK: ↑18% (♀s)	T3: ↓10% (♂s) T4: ↓20% (♂s) TSH: ↑100% (♂s) Fe: ↓30% (♀s)
	51 ♂ (n=4) ♀ (n=4)	AST: ↑55% (♀s) ALT: ↑60% (♀s) GLDH: ↑ 80% (♀s) GGT: ↑80% (♀s) CK: ↑33% (♀s)	T3: ↓15% (♂s) T4: ↓25% (♂s) TSH: ↑50% (♂s) Fe: ↓20% (♀s)

Group	Week (# of animals)	Major Findings	
HMD (Group III)	6 ♂ (n=4) ♀ (n=4)	AST: ↑2-fold (♀s and ♀s) ALT: ↑2.5-fold (♂s), ↑3.5-fold (♀s) ALP: ↑65% (♀s) GLDH: ↑21-fold (♂s), ↑16-fold (♀s) GGT: ↑2.5-fold (♂s and ♀s)	
	13 ♂ (n=4) ♀ (n=4)	AST: ↑60% (♂s), ↑100% (♀s) ALT ↑125% (♀s) ALP: ↑45% (♀s) GLDH: ↑6-fold (♀s) GGT: ↑75% (♂s), ↑2-fold (♀s) CK: ↑60% (♂s), ↑80% (♀s)	
	26 ♂ (n=4) ♀ (n=4)	AST: ↑80% (♂s), ↑65% (♀s) ALP: ↑40% (♀s) GLDH: ↑55% (♂s), ↑1.4-fold (♀s) GGT: ↑100% (♀s) CK: ↑65% (♂s), ↑70% (♀s)	T3: ↓15% (♂s) T4: ↓35% (♂s) TSH: ↑140% (♂s) Fe: ↓35% (♀s)
	39 ♂ (n=4) ♀ (n=3)	AST: ↑3-fold (♂s), ↑100% (♀s) GLDH: ↑100% (♂s), ↑3.5-fold (♀s) GGT: ↑1.5-fold (♀s), 100% (♀s) CK: ↑85% (♂s), ↑75% (♀s)	T3: ↓15% (♂s), ↓30% (♀s) T4: ↓35% (♂s), ↓40% (♀s) TSH: ↑135% (♂s), ↑150% (♀s) Fe: ↓25% (♀s)
	51 ♂ (n=4) ♀ (n=3)	AST: ↑95%(♂s), ↑65% (♀s) ALT: ↑55% (♂s), ↑70%(♀s) ALP: ↑60% (♀s) GLDH: ↑155% (♂s), ↑2.5-fold (♀s) GGT: ↑40% (♂s), ↑80% (♀s) CK: ↑50% (♂s), ↑30% (♀s)	T4: ↓25% (♂s), ↓20% (♀s) TSH: ↑75% (♂s and ♀s) Fe: ↓25% (♀s)
HD (Group IV)	6 ♂ (n=4) ♀ (n=4)	AST: ↑100% (♂s and ♀s) ALT: ↑3-fold (♂s), 2-fold (♀s) ALP: ↑50% (♂s and ♀s) GLDH: ↑10-fold (♂s), 8-fold (♀s) GGT: ↑2.5-fold (♂s, ↑120% (♀s) CK: ↑1.4-fold (♂s)	
	13 ♂ (n=4) ♀ (n=4)	AST: ↑56% (♂s), ↑100% (♀s) ALT: ↑50% (♂s), ↑80% (♀s) ALP: ↑90% (♂s), ↑95% (♀s) GLDH: ↑7-fold (♀s) GGT: ↑100% (♂s and ♀s) CK: ↑40% (♂s), ↑25% (♀s)	
	26 ♂ (n=4) ♀ (n=4)	AST: ↑ 2-fold (♂s), ↑90% (♀s) ALP: ↑85% (♂s), ↑70% (♀s) GLDH: ↑60% (♀s) GGT: ↑100% (♂s) CK: ↑1.5-fold (♂s), ↑25% (♀s)	Albumin: ↓20% (♂s) T3: ↓25% (♂s), ↓30% (♀s) T4: ↓25% (♂s), ↓30% (♀s) TSH: ↑100% (♂s), ↑3-fold (♀s) Fe: ↓40% (♀s)
	39 ♂ (n=2) ♀ (n=3)	AST: ↑3-fold (♂s), ↑130% (♀s) ALT: ↑40% (♂s), ↑65% (♀s) ALP: ↑1.5-fold (♂s), ↑65% (♀s) GLDH: ↑2-fold (♂s), ↑5-fold (♀s) GGT: ↑1.5-fold (♂s), ↑2.5-fold (♀s) CK: ↑40% (♂s), ↑150% (♀s)	Albumin: ↓20% (♂s), ↓13% (♀s) T3: ↓60% (♂s), ↓15% (♀s) T4: ↓35% (♂s), ↓30% (♀s) TSH: ↑170% (♂s), ↑3.7-fold (♀s) Fe: ↓47% (♀s)
	51 ♂ (n=2) ♀ (n=2)	AST: ↑2.5-fold (♂s), ↑55% (♀s) ALT: ↑3.5-fold (♂s) ALP: ↑3-fold (♂s), ↑25% (♀s) GLDH: ↑6.5-fold (♂s), ↑30% (♀s)	Albumin: ↓13% (♂s), ↓10% (♀s) T3: ↓10% (♂s), ↓30% (♀s) T4: ↓25% (♀s) TSH: ↑150% (♂s), ↑125% (♀s)

Group	Week (# of animals)	Major Findings
		GGT: ↑2-fold (♂s) Fe: ↓48% (♀s) CK: ↑60% (♂s)

GLDH: glutamate dehydrogenase
CK levels were in general higher in dosed groups than in control groups, even before the start of the study.

Urinalysis: no relevant changes

Gross pathology:

- At terminal sacrifice a few animals at 14 mg/kg and all animals at 41 mg/kg and above had a sparse haircoat or were hairless.

Histopathologically the skin of these animals showed a dermatitis and an atrophy/degeneration of the hair follicles. In most of the animals this was accompanied by a peri/folliculitis and in a few animals additionally by an acanthosis of the skin.
A minimal dermatitis as well as a slight alopecia/degeneration of the hair follicles was also seen histologically in males treated at 4 mg/kg.

- Cirrhotic changes in the liver (1 LMD ♀, 1 HMD ♀, and 1 HD ♂)

Organ weights: absolute organ weights consisted mainly of reduction in the weights, which appeared to be mainly secondary to the reduced body weights (except for pancreas in ♂s and kidneys in ♀s.); see below.

Note:

- Interpretation is limited at high-dose, due to the lower number of animals (N=2 at HD, ♂s or ♀s).
- Statistical significance not reported or analysis not done

Relative organ weights (organ weight/ BW) showed hypertrophy in the liver (♂s and ♀s), kidneys (♂s and ♀s), and pancreas (♂s and ♀s), as well as in male reproductive organs, testes/ prostate/ epididymis. The remaining organs had either reduction in weights or had no changes.

Relative organ weight changes showing hypertrophy:

Group	Relative Organ Weight Changes	
	♂	♀
LD ♂: n=4 ♀: n=4	—	Liver: ↑23% Kidneys: ↑23% Adrenals: ↑25%
LMD ♂: n=4 ♀: n=4	Liver: ↑6% Kidneys: ↑13% Testes ↑35% Prostate: ↑14% Pancreas: ↑44%	Liver: ↑15% Kidneys: ↑26% Pancreas: ↑22%

HMD ♂: n=4 ♀: n=3	Liver: ↑20% Kidneys: ↑28% Testes: ↑72% Prostate: ↑28% Adrenals: ↑8% Pancreas: ↑44% Epididymis: ↑25%	Liver: ↑10% Kidneys: ↑50% Adrenals:↑18% Pancreas: ↑7%
HD ♂: n=2 ♀: n=2	Liver: ↑5% Kidneys: ↑25% Testes: ↑21% Adrenals: ↑24% Pancreas: ↑55% Epididymis: ↑25%	Liver: ↑60% Kidneys: ↑100% Pancreas: ↑35%

Table generated by the reviewer

Histopathology: test article- induced findings was seen predominantly in the kidneys, the spleen, the bone marrow, the male reproductive organs and the adrenal glands. There were also findings in the GI tract and in the liver. Inflammation/ mononuclear infiltration was seen in several organs. In addition, hemorrhage and congestion of heart was detected in 1 (out of 4) HD females.

Organ/Tissue	**Major Findings**
Kidneys	• Minimal to moderate glomerulopathy in males at 14 mg/kg and above and in females at 41 mg/kg and above • Minimal to slight tubular dilation in males and females of the same dose groups • Decrease in pigment deposition in males and females at 14 mg/kg and above
Spleen	• Increase in iron deposition in males and females at 14 mg/kg and above
Bone marrow	• Hypocellularity in the bone marrow of the femur in males at 41 mg/kg and above and in females at 14 mg/kg and above, in the bone marrow of the sternum in females at 41 mg/kg and above and in males at 82 mg/kg • Increased amount of fat marrow in the femur of males and females at 41mg/kg and above and in the sternum of males at 41 mg/kg and above.
Bone; femur	• Incomplete epiphyseal closing in 2 unscheduled deaths. The epiphyseal growth plate was normal.
Male reproductive system	• Minimal to moderate tubular degeneration and tubular dilation in the testes of males at 41 mg/kg and above • Minimal to moderate oligospermia in the epididymides of males at 82 mg/kg
Adrenal glands	• Minimal to slight single cell necroses in the zona fasciculata of the cortex in males and females at 41 mg/kg and above • Moderate cell necroses in the zona arcuata in one female at 41 mg/kg
Lymphatic tissue: spleen, tonsils, lymph nodes, thymus, peyer's patches, lymphoid follicles of the cecum and colon	• Depletion, atrophy, cellular necrosis • Predominantly seen in the unscheduled deaths
Teeth	• Slight dentin alteration in 2 unscheduled deaths
GI tract	Stomach, duodenum, jejunum, ileum: • Glandular dilation

	• Inflammation and/or hemorrahge Cecum and colon: • Central necrosis
Liver	• Cirrhosis • Bile duct proliferation

Toxicokinetics: The following is from Report # MRC-01181-13; M 4.4.3.2.13
Plasma concentrations were comparable in female and male dogs. Observed differences appeared to be due to inter-species variability.

Results reported for Weeks 1 and 18 only; see below.

Mean plasma concentrations and PK parameters; ♂s and ♀s combined:

Dose (mg/kg)	Day 1 0 h	1 h	3 h	7 h	24 h	AUC 0-24 (ug*h/l)	AUC 0-24,n (g*h/l)	Cmax (ug/l)	Cmax,n (g/l)	tmax* (h)
3	<LOQ	180.1	297.0	151.1	33.8	2953.9	984.6	304.9	101.6	5.4
10	<LOQ	564.9	661.5	363.8	149.7	7882.3	788.2	737.0	73.7	2.3
30	<LOQ	1678.5	1897.1	1162.6	506.5	26589.1	886.3	2116.1	70.5	7.8
60	<LOQ	3248.5	2928.0	1911.8	1164.2	47008.0	783.5	3381.4	56.4	4.9
	Week 18 0 h	1 h	3 h	7 h	24 h	AUC 0-24 (ug*h/l)	AUC 0-24,n (g*h/l)	Cmax (ug/l)	Cmax,n (g/l)	tmax* (h)
3	65.6	218.9	392.5	277.3	38.3	4286.2	1428.7	408.9	136.3	2.8
10	263.4	819.6	1342.9	882.8	187.2	15128.3	1512.8	1358.3	135.8	3.5
30	234.6	1420.4	2624.2	1750.1	663.1	36300.7	1210.0	3044.3	101.5	3.8
60	506.9	3289.5	3590.6	2213.7	320.3	37632.0	627.2	3757.4	62.6	2.0

Plasma Concentrations in ug/l
* = arithmetic mean used for this parameter

Table provided by the sponsor.

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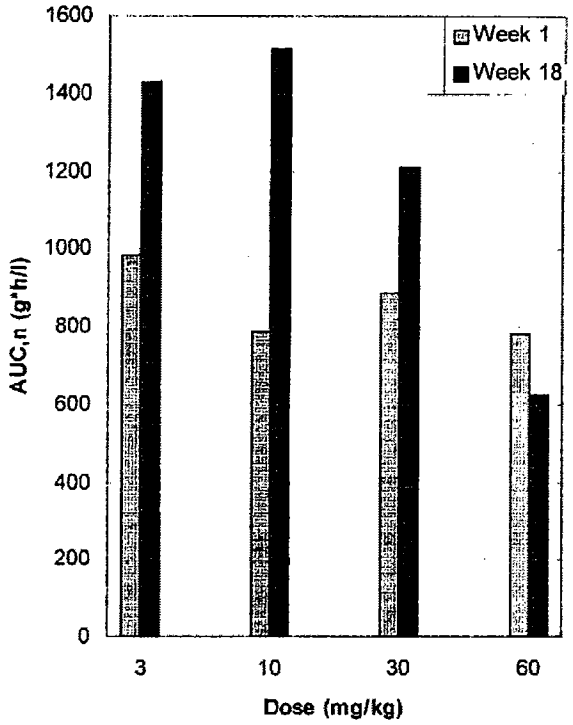
On Original



Graph provided by the sponsor.

The following is from Report PH-33306 TK of metabolites:
Plasma concentrations of BAY 43-9006 and of the metabolites BAY 72-1974 (M-1), BAY 67-3472 (M-2), BAY 72-1973 (M-3), BAY 43-9007 (M-4) and BAY 68-7769 (M-5) of BAY 43-9006 were determined after oral administration of BAY 54-9085 (tosylate salt of BAY 43-9006) to Beagle dogs in a chronic 52 weeks toxicity study at the end of the study in Week 52. Blood samples were collected at 0, 1, 3, 7 and 24 h after administration of the drug and additionally blood was collected from control group animals at 1 h after administration only. The exposure of BAY 43-9006 and the major metabolite M-3 in plasma (geometric means, n = 4 to 8) was as follows:

		BAY 43-9006				M-3 (BAY 72-1973)			
BAY 54-9085 [mg/kg]		4.00	14.0	41.0	82.0	4.00	14.0	41.0	82.0
N		8	8	7	4	8	8	7	4
AUC(0-24)	[µg·h/L]	3938	17424	21679	44825	926	5261	5957	17053
$AUC(0\text{-}24)_{norm}$	[kg·h/L]	1.36	1.71	0.727	0.753	0.309	0.501	0.193	0.277
C_{max}	[µg/L]	391	1470	2120	4900	62.7	300	334	1072
$C_{max,norm}$	[kg/L]	0.135	0.144	0.0711	0.0824	0.0209	0.0286	0.0108	0.0174
$C(24)/C_{max}$	[%]	7.60	17.9	8.83	4.09	32.8	57.6	52.3	32.2
t_{max}	[h]	3.34	2.91	2.56	2.82	5.09	6.72	6.08	7.00
MR_1	[%]					16.0	20.4	15.7	21.9
MR_2	[%]					23.5	30.2	27.5	38.0

t9071362_summary.xls \ AUC_43-9006_M-3_M-4 \ Müh \ 01.08.03

MR-1: metabolic ratio in terms of C_{max} in [%]: C_{max} (M-3) / C_{max} (BAY 43-9006)
MR-2: metabolic ratio in terms of AUC(0-24) in [%]: AUC(0-24)_(M-3) / AUC(0-24)_(BAY 43-9006)
N - number of surviving animals in dosing group

Table provided by the sponsor.

Summary and conclusions:
A total of 6 unscheduled deaths (3 ♂s and 3 ♀s) were observed during this study: 1 control (♂), 1 HMD (♀), and 4 at HD (2 ♂s and 2 ♀s).
The one death in the control was due to bronchopneumonia, likely due to the gavage route of administration (inhalation pneumonia). The deaths at higher doses appeared to be due purulent myocarditis, nephritis, and pyemia, which were most probably caused by alopecia with peri/folliculitis.

↓BW gain was observed in both ♂s (stating at LMD) and ♀s (starting at LD). Changes were more evident in ♀s.

Clinical signs showed that few animas at LMD had sparse haircoat and slight hair loss. In addition, 2 animals had pustules on different body regions. Starting at HMD, animals were alopecic or nearly alopecic, sometimes reddened or bluish skin areas were seen on the body. Dark skin areas were also visible at the axillary region, mostly in the animals of the HD group. ↑incidence of liquid feces and red discoloration was reported at LMD, HMD, and HD. Yellow and red colored mucus was also excreted at HMD and HD. As a result of the general hair loss also the hair of the eyelids was lost and thus the barrier for foreign bodies, such as dust was impaired. Conjunctivitis with mucous coating was observed in animals starting at LMD.

Changes in the hematology parameters were seen mainly at HD and included ↑leukocytes, neutrophils and monocytes, which appear to be due to infections and pyremia as well as due to internal inflammation/injury. Heinz bodies represent oxidized hemoglobin and can contribute to the development of hemolytic anemia. ↑Heinz bodies were observed at HD. ↓Erythrocytes/ hemoglobin/ hematocrit at HD in conjunction with ↑iron deposition in the spleen, suggest the occurrence of hemolytic anemia causing hemochromatosis. The sponsor stated that the ↑Heinz bodies were also observed in the control group and therefore is likely to be formulation-related. Since no historical data was presented on the Heinz bodies in Beagle dogs, the statement cannot be confirmed.

↑platelet levels may be related to the anemic condition of the animals or due to internal injury, e.g. GI ulceration. There was also a tendency for ↑PT and/or aPTT.

Clinical chemistry parameters revealed hepato- and hepatobiliary-toxicities as shown by ↑ALT, AST, GLDH, ALP, and GGT, starting from the LMD level. Although these changes were seen towards the end of the study period in the LMD group, it was seen as early as Week 6 in the HMD and HD animals. Hypothyroidism (↓T3, ↓T4, and ↑TSH) was detected starting at LMD and generally required several weeks of treatment (detected as early as Week 13). The hepato and hepatobiliary toxicities were confirmed by the pathology findings.

Relative organ weights showed hypertrophy in the liver (♂s and ♀s), kidneys (♂s and ♀s), and pancreas (♂s and ♀s), as well as in male reproductive organs, testes/ prostate/ epididymis. The remaining organs had either reduction in weights or had no changes.

Histopathology showed findings in the:

- Kidneys (glomerulopathy, tubular dilation, and reduced pigment deposition) starting at LMD
- Spleen (↑iron deposition) starting at LMD
- Bone marrow (hypocellularity and ↑fat), starting at LMD
- Femoral bone: incomplete epiphyseal closing in 2 unscheduled deaths.
- Male reproductive system (tubular degeneration and dilation, and oligospermia), starting from the HMD
- Adrenal glands (single cell necrosis) starting at HMD
- Teeth (dentin alteration) in 2 unscheduled deaths. From former studies with BAY 54-9085 it is known that the test compound causes dentin alterations in juvenile Beagle dogs before dentition.
- Lymphatic tissues (depletion, atrophy, necrosis), predominately seen in the unscheduled deaths.
- GI tract: inflammation, hemorrhage, glandular dilation
- Liver: cirrhosis, bile duct proliferation

Reflexes, body temperature, blood pressure, heart rate, and ECG measurements (including QT-intervals) showed no adverse effects, under the conditions of this study. CK was increased starting at LMD, on Week 39 of treatment. The CK measured appears to be the total CK (MM/MB/BB), hence it may not be relevant to the heart. Histopathology revealed inflammation and hemorrhage in the heart of 1 female animal at HD.

No relevant changes in urinalysis parameters were noted.

Toxicokinetics:

- There were no gender related differences in plasma concentrations in the parent compound or in the metabolites.

- The parent compound appears to accumulate with chronic dosing, however, ↓AUC/dose is observed at high doses
- There were dose proportional increases in exposure from LD to LMD for both sampling times. Increases in exposure were nearly dose proportional from LMD to HMD and from HMD to HD on Week 1, but less dose proportional on Week 18.
- There were significant increases in exposure from week 1 to week 18 for the LD, LMD, and HMD, but not for the HD. Increases in the AUCs were approximately 145%, 190% and 135%, for LD, LMD, and HMD, respectively, indicating accumulation upon multiple dosing at these levels.
- The exposure (Cmax and AUC) of BAY 43- 9006 and of the 5 metabolites in this study with Beagle dogs ranked in the following order: BAY 43-9006 > M-3 >> M-4 > M-2 > M-5 = M-1. M- 3 was the only major metabolite in dog plasma in this study with an AUC ratio between 23.5 and 38.0 % relative to BAY 43- 9006. The AUC ratio of all other metabolites measured was below 2%. M-5 and M-1 were mostly below LLOQ ([ ]µg/L).
- Exposure to BAY 43- 9006 and M- 3 increased dose- dependently but not always dose- proportionally.
- Tmax was 2.6 to 3.3 h for BAY 43- 9006 and 5.1 to 7.0 h for M- 3. C(24)/ Cmax was 4 to 18 % for BAY 43- 9006 and 32 to 58 % for M- 3 indicating a slightly slower elimination of the metabolite.
- The influence of repeated dosing on the metabolite concentrations could not be evaluated since the metabolites were not measured on Day 1 of the study.

Study Title: BAY 54-9085: Subacute toxicity study in female beagle dogs (4 week gavage study)

Note: This study was conducted mainly to see the effect of treatment on teeth and bone of adult animals.

Report# PH-31108
Study no.: T0069663
Volume #, and page #: Module 4 of the NDA
Conducting laboratory and location: Department for Toxicology-Pharma,
Institute of Toxicology
BAYER AG
Friedrich-Ebert-Straβe 217 – 333
42096 Wuppertal, Germany.
Date of study initiation: May 29, 2000
GLP compliance: Yes
QA report: yes (X) no ( )
Drug, lot #, and % purity: BAY 54-9085, Batch # 000217; [ ]pure
Formulation: Bay 54-9085 solution in 2-Pyrrolidon (10%), propylenglycol (45%), and cremophor RH 40 (45%)

Methods

Doses: 0 and 82 mg/kg of BAY 54-9085 x 4 weeks
Equivalent to:
0 and 60 mg/kg of BAY 43-9006
0 and 1200 mg/m2 of BAY 43-9006
Species/strain: dog/ Beagle
Number/sex/group or time point (main study): 8 ♀/ group
Route, formulation, volume: oral gavage, 3 mL/kg
Age: 61-102 weeks old on Week -1
Weight: 6-8 kg

Observations and times:
Mortality: daily
Clinical signs: daily
Body weights: weekly
Food consumption: daily
Ophthalmoscopy: not done
EKG: not done
Hematology: not done
Clinical chemistry: not done
Urinalysis: not done
Gross pathology: not done
Organ weights: At necropsy (Day 29)
brain, heart, lung, liver, spleen, adrenals, kidneys, pancreas, thyroid, pituitary, uterus, thymus, ovaries, and empty gall bladder
Histopathology: Adequate Battery: yes (X), no ( )
Peer review: yes (X), no ( )

The following Table shows organs/tissues that were fixed and evaluated microscopically.

Adrenal glands	Oviducts
Aorta	Pancreas
Brain (cerebrum, cerebellum, brain stem, medulla oblongata*)	Pharynx''
	Pituitary gland
	Parotis
Esophagus	Sciatic nerve
Eyes	Skeletal muscle (thigh)
Femur	Skin (mammary region)
Gall Bladder	Spinal cord (cervical, thoracal, lumbar)*
Heart	Spleen
Intestine	Sternum
- Duodenum	Stomach
- Jejunum	Teeth
- Ileum	Thymus
- Caecum	Thyroid glands (with parathyroid glands)
- Colon	
- Rectum	Tongue
Kidneys**	Tonsils
Larynx''	Trachea
Liver**	Urinary Bladder
Lungs**	Uterus (with cervix)
Lymph nodes, mandibular	Vagina
Lymph nodes, mesenteric	Organs and tissues with macroscopic findings
Mandibular gland	Physical identifier*''
Nose (nasal cavity)''	
Optic nerves	
Ovaries	

* fixation in 10 % neutral buffered formalin
** additional specimen fixed in 10 % neutral buffered formalin
'' fixed, but not evaluated histopathologically

Table provided by the sponsor.

Toxicokinetics: samples were collected but results not reported under this report

Results

Mortality: 2 unscheduled deaths in the test article-treated group; appear to be gavage-related

Clinical signs: test article-treated group: bloody vomit, ↑salivation, bloody feces

Body weights: ↓BW in the test article-treated group

Group	Sex	Pretreatment (week –1)	End of treatment (week 4)	Difference week –1/week 4
Contr.	♀	7.20 kg	7.61 kg	+ 0.41 kg
I	♀	6.89 kg	6.20 kg	- 0.69 kg

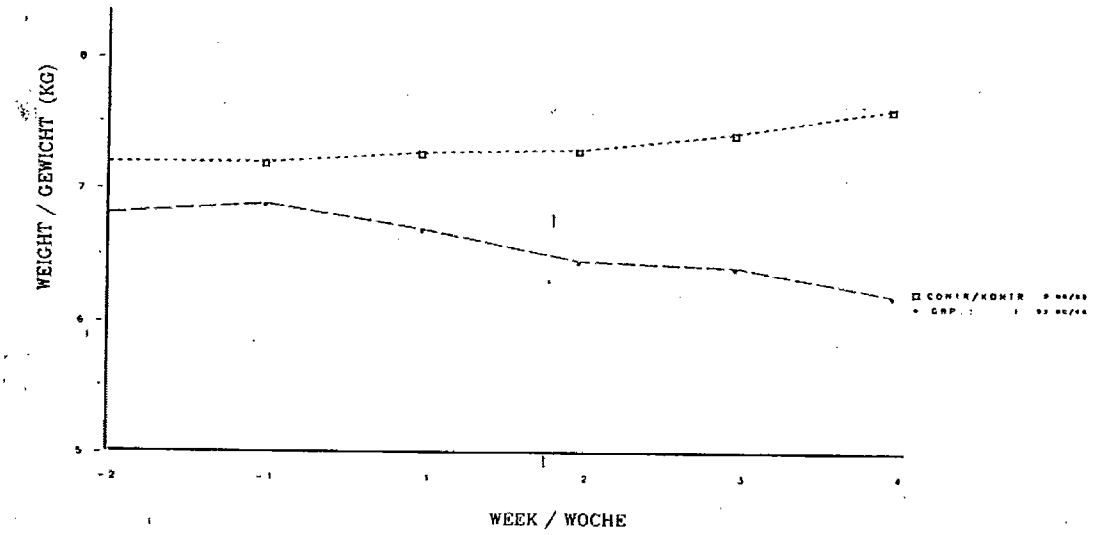


Table and Graph provided by the sponsor.

Food consumption: comparable between the 2 groups

Ophthalmoscopy: not done
EKG: not done
Hematology: not done
Clinical chemistry: not done
Urinalysis: not done

Gross pathology: no relevant changes

Organ weights: no relevant changes

Histopathology:
The following are test article-related findings:

- Hematopoietic system: necrosis of the lymphoid follicles in tonsils; ↑ in follicular atrophy of the germinal center in mesenteric and mandibular lymph nodes. ↑perifollicular granulocytic infiltration and perifollicular necrosis in the spleen. Slight ↑in iron positive pigment in the spleen. Peyer's patch atrophy. ↑thymus atrophy. ↑fatty marrow and ↓cellularity in the sternum marrow.
- Liver: ↑centrilobular fatty change
- Thyroid: ↓amount of colloidal vacuolation in the thyroid gland.

Summary:
This study was conducted to verify the effect of sorafenib on teeth and bones of adult dogs. There were 2 unscheduled deaths in this study that appeared to be aspiration pneumonia caused by intubation error. Test-article-related toxicities were observed in the following tissues/organs: hematopoietic system, including the bone marrow

(hypocellularity and ↑fatty marrow), liver (steatosis), and thyroid (↓colloidal vacuolation).

No effects were seen in the teeth or the femoral bone.

Summary of the single dose toxicity studies

Acute toxicities were observed in the GI tract (vomiting and soft feces) as well as in the liver (↑liver enzymes).

Single dose toxicology studies in mice and rats at doses up to 1460 mg/kg (mice: 4380 mg/m^2; rats: 8760 mg/m^2) of BAY43-9006; free base resulted in only soft feces in rats. No mortality or other signs of toxicities were reported in either species.

Single dose toxicity studies at doses up to 120 mg/kg or 2400 mg/m^2 BAY43-9006 in Beagle dogs, resulted in only vomiting at LD (600 mg/m^2), MD (1200 mg/m2), and HD (2400 mg/m^2). There was no mortality or toxicologically significant effects on hematology or clinical chemistry parameters associated with the treatment. Administration of single oral dose of sorafenib at 500 mg/kg or 10000 mg/m^2 in form of powder, resulted in soft feces, vomiting, red skin, and ↑ALT and AST (1.6-2.7 fold).

Pharmacokinetic data obtained in other studies (see Tabulated PK Summary) indicate that a saturation limit of systemic exposure is achieved after substantially lower oral doses.

Single- dose toxicity studies with parenteral (intravenous) administration were not performed due to the very low solubility of sorafenib or sorafenib tosylate in suitable vehicles.

Summary of the repeat dose toxicity studies

Test article associated toxicities were observed in the liver, kidneys, hematopoietic system, skin, bone, teeth, reproductive system (male and female), GI tract, pancreas, and thyroid/parathyroid. Coagulation parameters were affected and included both ↑ or ↓ in platelet levels and both ↑ or ↓ in PT/aPTT. In a 2- week rat study with focus on pancreas-related effects, serum changes of alpha amylase and morphological changes confirmed this organ as a potential target of toxicity (M4.2.3.7.3.3, PH-33039- study not reviewed).

Open field and functional observation battery investigations gave no indication of a neurotoxicological potential of sorafenib in the chronic studies. However, safety pharmacology studies indicated potential for drug-induced sensory neuropathy.

There appears to be potential for cardiovascular toxicities. Changes in the ECG, heart rate, and blood pressure were not detected in the 52-week dog toxicology study; however, CK was increased in the sorafenib treated groups, mainly at HMD and HD. Although rare, histopathology reports indicated congestion/inflammation and hemorrhage in the

heart, in the repeat dose studies. Moreover, safety pharmacology studies indicated drug-induced effects, e.g. bradycardia, inhibition of K-current and Ca-inward current.

There are no clear gender-dependent differences in the drug-induced toxicities.

Rat Toxicology

Oral doses of up to 250 mg/kg/day (1500 mg/m^2/day x 7) BAY 43-9006 for 7 days were generally tolerated in female rats. There was no mortality or treatment-related changes in body weight observed in this study. Toxicities were seen in the following organs/tissues:

- Hematopoietic system: findings in spleen and bone marrow
- Bone marrow: degeneration of hematopoietic cells within femoral marrow cavity; hypocellularity; normal architecture replaced with fibrin, extravasated RBCs and vacuolated stromal cells.
- Spleen: coagulative/congestive degeneration
- Liver: ↑ALT, AST, ALP; hepatocellular karyomegaly; single cell necrosis
- Kidneys: ↑incidence of tubular dilation; dense protein/hyaline casts

Oral doses of up to 125 mg/kg/day (750 mg/m2/day x 28) BAY 43-9006 for 4 weeks, resulted in abnormal findings in nearly all assessments done. Toxicities were seen in the following organs/tissues, many of which were not reversed after the 4-week recovery period:

- GI: soft feces; abscess-like lesions; necrosis; ulcer; hyperkeratosis; inflammation
- Hematopoietic system: ↓hemoglobin, erythrocytes, and platelets; findings in lymph nodes; findings in spleen (necrosis and depletion); findings in femur (hypocellularity)
- Liver (hepato/ hepatobiliary): ↑AST, ALT, GLDH, cholesterol; multi-focal necrosis; bile duct proliferation
- Kidneys: ↑urinary protein, ↑NAG/creatinine; enlarged; tubular dilations; basophilic tubules; hyaline casts; glomerulopathy
- Adrenals: ↑weight; enlarged/discolored; necrosis
- Femoral bone: thick growth plate; hypocellularity
- Ovaries: retardation; necrosis/corpora lutea
- Testes: diminished in size; tubular degeneration; autolytic changes
- Teeth: dentin degeneration; osteolysis/osteodystrophy
- Pancreas: discoloration; inflammation; atrophy; edema; degeneration/regeneration

In rats, repeat- dose toxicity studies showed mortality at a sorafenib dose of 5 mg/kg (30 mg/m^2/day) in a 3-month study (M4.2.3.3, MRC- 01249). Toxicities in the 3-month rat study were seen in the following tissues/organs (due to the mortality at HD, the study did not contain any recovery phase):

- GI: fecal stains, soft feces, hypertrophic duodenum
- Hematopoietic system: ↓leucocytes and most differentials, ↑hemoglobin, ↑hematocrit, lymphoid depletion, (↑neutrophils appears to be secondary to inflammation/internal injury)

- Liver/ hepatobiliary: ↑liver enzymes, ↑triglycerides, ↑cholesterol, ↓albumin, necrosis; bile duct dilation and hyperplasia
- Kidneys: nephropathy, ↑protein in urine, ↓serum albumin
- Teeth: dysplasia of incisors, dentin not formed
- Bone: thickening of the growth plate (chondrodystrophy); epiphysiolysis
- Adrenal glands: discoloration, enlargement, hemorrhage, necrosis
- Ovaries: arrested follicular development
- Heart: signs of autolysis; degeneration; inflammation
- Parathyroid: ↑incidence of fibrosis

In a chronic 6- month study (M4.2.3.2.5, PH- 32607), doses of BAY-43-9006, up to 2.5 mg/kg/day (15 mg/m2/day x 191) resulted in toxicities in the following tissues/organs:

- Kidneys: basophilis tubules; mononuclear infiltration; tubular dilation; hyaline casts; glomerulus hyaline
- Bone: fatty replacement (sternum)
- Teeth: dentin degeneration; osteodystrophy of jaw
- Liver (minimal): tendency for increased liver enzymes
- Hematopoietic system: ↓platelets, ↑hematopoiesis

Dog Toxicology

The 7-days dosing of sorafenib in beagle dogs was conducted at at does up to 60 mg/kg bid (120 mg/kg/day or 2400 mg/m2/day). The study did not contain a control group. Therefore, magnitude of changes is not well known (values were compared to self on pre-treatment). Toxicities were in the following tissues/organs:

- GI: vomiting; liquid feces; dark areas in cecum, colon and/or rectum; inflammation; lesions (hemorrhage in colon)
- Hematopoietic system: lymphoid necrosis in stomach and mesenteric lymph nodes; Peyer's patch necrosis; ↑WBC and platelets (was attributed to ↑myelopoiesis- could be also in part due to internal injury and inflammation); thymus lymphoid atrophy; findings in spleen (siderotic plaque/↑iron deposits; capsular fibrosis); finding in bone (↑myelopoiesis)
- Liver: ↑AST, ALT, ALP; mixed cell infiltration
- Kidneys: basophilic tubules
- Testes: tubular degeneration
- Bone: ↑myelopoiesis
- Phosphatemia

In a 4- week study in dogs with initial twice- daily administration of 10, 30, or 60 mg/ kg, both 30 mg/ kg bid and 60 mg/ kg bid (60 and 120 mg/kg/day, respectively) of sorafenib exceeded the MTD (M4.2.3.2.8, PH- 30221). Emesis, bloody diarrhea, and reduced body weight gain prevented dosing for more than 1 to 2 weeks under this regimen; dosing was therefore reduced to once daily after one week in this study. Daily dosing at doses up to 60 mg/kg/day or 1200 mg/m2/day of BAY 43-9006 (free base) resulted in toxicities in the following tissues/organs:

- GI: bloody feces, hypertrophy in stomach (pyloric region)

- Liver (hepato/ hepatobiliary): ↑AST, ALT, bile duct proliferation, fibrosis, mononuclear/granulocytic infiltration
- Hematopoietic system: findings in the spleen and bone marrow (hypocellularity)
- Spleen: ↑hematopoiesis and ↑megakaryocytes
- Bone: irregular thickening of the growth plate, hypocellularity
- Teeth: altered dentin (non-reversible)
- Kidneys: basophilic tubules

Once-daily dosing of sorafenib at up to 60 mg/kg/day (free base) or 1200 mg/m2/day, for 3 months resulted in toxicities in the following tissues/organs:

- GI: red/bloody feces, foamy feces
- Hematopoietic system: thymus and spleen atrophy, necrosis of lymphoid follicles in tonsils, atrophy of lymphoid follicles of ileum, perifollicular granulocytic infiltration in the spleen
- Liver (hepato/ hepatobiliary): ↑AST, ↑ALT, ↑ALP, ↑GGT, ↑GLDH; Bile duct proliferation, periportal fibrosis
- Kidneys: ↑basophilic tubules, proteinaceous casts, glomerulopathy
- Skin: alopecia/degeneration of hair follicles, red spots
- Teeth: altered dentin composition
- Bone: ↑granulocytes in the sternum and in the bone marrow cylinders

Once- daily dosing up to 60 mg/kg/day (1200 mg/m2/day) for 12 months resulted in toxicities in the following tissues/organs:

- Skin: alopecia, pustules, red/blue spots on skin, atrophy/degeneration of hair follicles, acanthosis, dermatitis
- GI: liquid feces, red/bloody feces, inflammation, hemorrhage, central necrosis of cecum and colon
- Hematopoietic system: depletion/atrophy/cellular necrosis of lymphatic tissues (spleen, tonsils, lymph nodes, peyer's patches, follicles of cecum and ileum); bone marrow hypocellularity; ↑iron deposition in spleen which appears to be due to hemolytic anemia
- Liver (hepato/hepatobiliary): ↑ALT, AST, GLDH, ALP, GGT; cirrhotic changes, liver hypertrophy, bile duct proliferation
- Kidneys: ↑weight; glomerulopathy, tubular dialation
- ♂ reproductive system: ↑weights of testes/prostate/epididymis; degeneration and tubular dilation of testes; oligospermia
- Bone: incomplete epiphyseal closing; ↑marrow fat (appears to be secondary to hypocellularity)
- Teeth: dentin alteration
- Adrenal glands: cell necroses
- Thyroid: hypothyroidism (↓T3, ↓T4, ↑TSH)
- Pancreas: hypertrophy
- Heart: ↑CK (no findings in ECG, heart rate, blood pressure), hemorrhage and congestion of heart in 1 HD female.
- Coagulation parameters: transiently ↑PT/aPTT, ↑platelets

2.6.6.4 Genetic toxicology
Study title: BAY 54-9085: Salmonella/Microsome test plate incorporation and preincubation method.

Key findings: Under the conditions of this assay, BAY 54-9085 has shown no evidence of mutagenicity in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 in both the presence and absence of metabolic activation.

Study Report PH-29467
Study # T7068427

Conducting laboratory/location: BAYER AG, Wuppertal-Elberfeld.
Date of study initiation: 8-27-1999
GLP/QA compliance: Yes
Drug, lot #, and % purity: BAY 54-9085 Batch # 990722; —
Formulation/vehicle: The test article was dissolved in DMSO

Methods:
Strains: *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, and TA102)
Dose selection criteria:
Basis of dose selection: If not limited by solubility 5000 µg or 5 µl/plate were used as the highest dose.
Range finding studies: Plate incorporation assay: 16, 50, 158, 500, 1581, 2500, and 5000 µg/plate (Due to toxicity, doses ranging from 1 to 64 µg/tube were chosen for the repeat tests).
Test agent stability: Stability tests showed that BAY 54-9085 is stable in the vehicle at room temperature at concentrations ranging from 0.1 mg/ml to 500 mg/ml for at least 24 hours.
Metabolic activation system: Presence and absence of S-9 mix (Aroclor 1254-induced rat liver)
Controls:
Vehicle: DMSO
Negative controls: DMSO
Positive controls: Sodium azide, nitrofurantoin, 4-nitro-1,2-phenylene diamine, cumene hydroperoxide, and 2-aminoanthracene
Exposure conditions:
Incubation and sampling times: Incubation for 2 days at 37°C in the dark
Doses used in definitive study: 16, 50, 158, 500, 1581, 5000 µg BAY 54-9085/plate
Repeat: 1, 2, 4, 8, 16, 32, 64 µg

Study design: Plate incorporation assay followed by independent repeat using preincubation (37°C x 20 min)
Analysis:
No. of replicates: 3 plates for each solvent control; triplicate plates for each treatment group.

Counting method: Automatic colony counter

Criteria for positive results:

- Reproducible statistically significant dose related increase in the number of revertant colonies of at least one strain. For TA1535, TA100, and TA98, this increase should be about twice that of negative controls, whereas for TA1537, alt least a 3-dold increase should be reached. For TA102 an increase of about 100 mutants should reached. Otherwise, the result is evaluated as negative.

Summary of individual study findings:

Study validity:

- Tester strain integrity data was submitted.
- Spontaneous revertant background frequencies were within historical control data.
- Positive control values exhibited the appropriate fold increase over the respective mean vehicle control value for each tester strain.
- Toxicity-A minimum of 3 non-toxic dose levels were provided to evaluate assay data (repeat study).

Study outcome:

- BAY 54-9085 was not toxic to bacteria at doses up to 8 μg/plate.
- Higher doses, starting at 16 μg/plate, had a strong strain specific toxic effect on bacteria.
- BAY 54-9085 precipitated at 5000 μg/plate.
- No indications of mutagenic effects of BAY 54-9085 up to 64 μg/plate in any of the Salmonella typhimurium strains used. None of the 5 strains showed in the plate incorporation test a dose-related and biologically relevant increase in mutant counts over those of the negative controls. This applied both to the tests with and without S9 mix and was confirmed by the results of the pre-incubation trials.
- The positive controls increased mutant counts to well over those of the negative controls demonstrating the system's sensitivity and activity of the S9 mix.

Study title: BAY 54-9085: *In Vitro* Chromosome Aberration Test with Chinese Hamster V79 Cells.

Key findings:

- In the presence of metabolic activation, BAY 54-9085 showed a significant increased numbers of aberrant metaphases. Thus, BAY 54-9085 is clastogenic for mammalian cells *in vitro.*

Study Report PH-29598
Study #: T8068851

Study type: *In Vitro* Chromosome Aberration Test
Conducting laboratory and location: BAYER AG, Wuppertal-Elberfeld.
Date of study initiation: October 5, 1999
GLP compliance: yes

QA reports: yes (x) no ( )
Drug, lot #, and % purity: BAT 54-9085; Batch # 990722 [ ]
Formulation/vehicle: DMSO

Methods:
Strains/species/cell line: Chinese hamster V79 cells
Dose selection criteria:
Basis of dose selection: Cytotoxicity was measured by survival index and mitotic index.
Range finding studies: -S9 mix: 10, 50, 100, 150, 250, 500, 1000, and 1500 µg/ml
Test agent stability:

Nominal Value (mg/ml)	Content as % of nominal value after storage time in hours	
	0 hours	24 hours
0.1 500		

Metabolic activation system: S9 from Aroclor 1254 induced male Sprague Dawley rat livers
Controls:
Vehicle: DMSO
Negative controls: DMSO
Positive controls: Mitomycin C (0.1 µg/ml), Cyclophosphamide (2 µg/ml)
Exposure conditions:
Incubation and sampling times: 4 hr incubation at 37C and harvest time at 18 h and 30 h
Doses used in definitive study: +S9:0, 10, 20, 40, 60, 80 µg/ml (harvest at 18 h)
-S9:0, 5, 10, 20, 40, 60 µg/ml (harvest at 18 h)
+S9:0, 40, 60, 80 µg/ml (harvest at 30 h)
-S9:0, 20, 40, 60 µg/ml (harvest at 30 h)
Study design:
Analysis:
No. of replicates: 2/culture
Counting method: Light microscope; counting 1000 cells/culture; chromosomes of ~200 metaphases/concentration, 100 metaphases from each of 2 parallel cultures. Based on cytotoxicity results, selected for reading of metaphases:
+S9: 10, 20, 40 µg/ml (harvest at 18 h); 40 µg/ml (harvest at 30 h)
-S9: 5, 10, 20 µg/ml (harvest at 18 h); 20 µg/ml (harvest at 30 h)

Criteria for positive results:
- Increased incidence of gaps of both types without concomitant increase of other aberration types was not considered as indication of a clastogenic effect.
- Positive, if there was a relevant and statistically significant increase in the aberration rate.

- Negative, if there was not such increase at any time interval or if there were statistical significant values, which were, however, within the range of historical negative controls.
- Equivocal, if there was an increase above there range of historical negative controls which was statistically significant but not considered relevant, or if an increase occurred, which was considered relevant but which was not statistically significant.

Summary of individual study findings:

Study validity:

- Cell growth and maintenance. Cell growth and maintenance was demonstrated in the cultures evaluated (see table below).
- Spontaneous control data 1994

Metabolic Activation	Solvent or Substance	Time of harves (h)	Metaphases with Aberrations (Median %)		
			Including gaps	Excluding gaps	Exchanges
-S9	DMSO	18	2.8	2.3	0.5
	DMSO	30	2.5	2.5	1
	Mitomycin C	18	44.5	43.5	18
+S9	DMSO	18	2.8	2.5	1.0
	DMSO	30	3.0	2.0	0.5
	Cyclophosphamide	18	32.5	31.0	14.5

- Positive control data. The positive controls, mitomycin C and cyclophosphamide, produced the expected increase in the number of metaphase aberrations, in the absence and presence of metabolic activation.

Study outcome:

Concentration (µg/ml)	Time of harvest (h)	Survival index in %		Mitotic index in %		Metaphases with Aberrations (%)					
						-S9 Mix			+S9 Mix		
		-S9 Mix	+S9 Mix	-S9 Mix	+S9 Mix	Incl gaps	Excl gaps	Exchan ges	Incl gaps	Excl gaps	Exchan ges
solvent control	8	100	100	100	100						
20	8	65.2[A]		38.4*	38.4*						
40	8	55.4[A]	81.7	33.7*	33.7*						
60	8	58.7[A]	93	34.2*	34.2*						
80	8		74.6[A]								
solvent control	18	100	100	100	100	3.5	3	0			
5	18	85.4		82.8*	82.8*	3	3	.5	3	2.5	.5
10	18	74.4[A]	93.9	98.8	98.8	2	2	.5	4	3	1
20	18	58.3[A]	93.9	75.8**	75.8**	3.5	3.5	.5	2	2	0
40	18	48.7[A]	68.3[A]	50.8**	50.8**				12.5**	10**	2
60	18	45.7[A]	51.8[A]	47.1**	47.1**						
80	18		67.7[A]								
positive control											
mitomycin c	18	71.4[A]		100.8	100.8	59.5**	58.5**	34.5**			
cyclophosphamide	18		70.1[A]						57**	55**	30.5**
solvent control		100	100	100	100	1.5	1.5	0	1.5	1.0	0
20	30	45.6[A]		103.3	103.3	2.5	2.5	.5			
40	30	42.9[A]	40.7[A]	99.5	99.5				10**	10**	2
60	30	35.2[A]	37.7[A]	97.8	97.8						
80	30		45.4[A]								

[A] relevant reduction of survival index; *p<0.05 and **p<0.01

- In the presence of S9 mix cultures treated with 40 µg/ml BAY 54-9085 showed biologically relevant and statistically significant increased numbers of aberrant metaphases.
- No clastogenic effects were observed without S9 mix.
- The positive controls, mitomycin C and cyclophosphamide induced clear clastogenic effects.

Study title: BAY 54-9085: Micronucleus-Test on the Male Mouse.

Key study finding: After two intraperitoneal treatment of male mice with doses of BAY 54-9085 up to and including 500 mg/kg show no indication of a clastogenic effect on the mammal ***in vivo***.

Study Report PH-29474
Study # T9068429

Conducting laboratory and location: BAYER AG, Wuppertal-Elberfeld.
Date of study initiation: 11-29-1999
GLP compliance: Yes
QA reports: yes (x) no ( )
Drug, lot #, and % purity: BAY 54-9085 Batch # 990722; [ ]
Formulation/vehicle: BAY 54-9085 was suspended in 0.5% aqueous Cremophor

Methods:

Strains/species/cell line:	♂ mice, [ ] NMRI. Weight/age: 37-44 g/6-12 weeks
Dose selection criteria:	
Basis of dose selection:	Based on a pilot test (groups n=3/sex) where animals received two IP injections (500 mg/kg and 1000 mg/kg BAY 54-9085) separated by 24 h. Starting at 500 mg/kg, apathy, roughened fur, hard abdomen, spasm, difficulty inbreathing and lachrymation were observed. At 1000 mg/kg, 3 of 3 ♂ and 1 of 3 ♀ died; at 500 mg/kg, 1 of 3 ♂ died. Based on these findings, the Sponsor chose 500 mg/kg BAY 54-9085 as MTD for ♂ and since there were no obvious sex differences decided not to include females in the final study.
Range finding studies:	500 mg/kg and 1000 mg/kg BAY 54-9085
Test agent stability:	Approved until 2-5-2000
Metabolic activation system: n/a	
Controls:	
Vehicle:	0.5% aqueous Cremophor
Negative controls:	Vehicle: 0.5% aqueous Cremophor (20 ml/kg)
Positive controls:	Cyclophosphamide (20 mg/kg IP; volume of 10 ml/kg; n=5)

Comments:

Exposure conditions:

Incubation and sampling times: The femoral marrow was prepared 24 h after the last administration.

Doses used in definitive study: 0, 125, 250, and 500 mg/kg BAY 54-9085 IP (n=5); two doses separated by 24 h.

Study design:

Analysis:

No. of replicates: At least one intact femur was prepared from each sacrificed animal

Counting method: Coded slides were evaluated using a light microscope. Normally, 2000 polychromatic erythrocytes were counted/aniamal

Criteria for positive results:

- A test was considered positive if there was no relevant or significant increase in the rate of micronucleated polychromatic erythrocytes.
- A test was also considered negative if there was a significant increase in that rate which, according to the laboratory's experience was within the range of historical negative control.
- A test was considered equivocal if there was an increase of micronucleated polychromatic erythrocytes above the range of attached historical negative controls, provided the increase was not significant than the result of the negative control was not closely related to the respective treatment group. In this case, normally a second test will be performed.

Study validity: Negative and positive controls are within the expected range, in accordance with the laboratory's experience and/or wthe availabe literature.

Study outcome:

- After two IP administrations of 125, 250, and 500 mg/kg BAY 54-9085, treated males showed apathy, roughened fur, hard abdomen, spasm, periodical stretching of body and difficulty breathing.
- No animals died during this study.

Experimental Group	Number of evaluated PCE	Number of NCE/2000 PCE	MNNCE/2000 NDE	MNPCE/2000 PCE
Negative Control	10,000	1873 ± 427	3.2 ± 1.4	2.4 ± 1.1
BAY 54-90852x 125 mg/kg	10,000	1017 ± 333	1.6 ± 1.5	2.8 ± 1.8
BAY 54-90852x 250 mg/kg	10,000	902 ±148	2.3 ± 0.4	2.4 ± 0.9
BAY 54-90852x 500 mg/kg	10,000	1039 ± 304	0.8 ± 1.1	3.2 ± 1.5
Positive Control CP 20 mg/kg	10,000	1638 ± 498	2.3 ± 2.5	32.2 ± 12.2

- The ratio of polychromatic (PCE) to normochromatic (NCE) erythrocytes in males was not altered by BAY 54-9085.

- No difference in the incidence of micronucleated polychromatic erythrocytes (MPCE) in BAY 54-90852-treated compared to negative control.
- No difference in micronucleated normochromatic erythrocytes (MNNCE).
- Positive control, cyclophosphamide, caused a clear increase in MNPCE with micronuclei.

Study title: BAY 67-3472 (M-2 metabolite); Project: BAY 43-9006
Salmonella/microsome test (Ames Test); plate incorporation and pre-incubation method

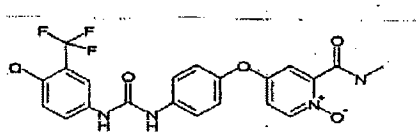
Key findings: BAY 67-3472 was not mutagenic in the Ames Test in the absence of S9.
BAY 67-3472 was not mutagenic in the presence of S9 (the validity of the +S9 assay remains uncertain)

Report# PH-33299
Study # T 0073226

Volume #, and page #: Module 4; M4.2.3.7.5.1
Conducting laboratory and location: Information not provided
Based on high similarities (strains, controls, criteria, ...) to Report PH-31850-1, Study # 6070883, it appears that this study was conducted at:
Rodents and Genotoxicity Unit of Toxicology
BAYER AG,
Friedrich-Ebert-Strabe 217-333, D-42096
Wuppertal, F.R.G.

Date of study initiation: Jan 19, 2004
GLP compliance: Yes; in compliance with OECD Principles of GLP
QA reports: yes (X) no ( )
Drug, lot #, and % purity: BAY 67-3472 (M-2 metabolite of BAY 43-9006); Batch number BXR2F93, [ ] pure
The amount of solvent used was 0.1 mL/plate

Chemical name	:	4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino} carbonyl)amino]phenoxy}-N-methylpyridine-2-carboxamide-1-oxide

Structure : 

Molecular weight : 480.83

Molecular formula : $C_{21}H_{16}ClF_3N_4O_4$

CAS-No. : Not indicated

Methods

Cell line:
Salmonella typhimurium: TA1537, TA1537, TA98, TA100, TA102

TA 1535 and TA 100 bear the base-pair substitution, his G 46, and TA 100 additionally contains the plasmid pKM 101. This R factor, also contained in TA 98 and TA 102, codes for an ampicillin resistance and should raise the sensitivity of the strains. TA 102 carries the ochre mutation his G 428 on the multicopy plasmid pAQ1, which codes in addition for tetracycline resistance. TA 1537 and TA 98 bear frameshift markers. TA 1537 exhibits the +1 mutant, his C 3076, while TA 98 bears the +2 type, his D 3052.

In addition, all strains are partly deficient in lipopolysaccharide side chains of their cell wall. With the exception of TA 102, all strains have reduced capability to repair DNA-damage.

Doses used in definitive study: Doses ranging from 2.5 µg to 80 µg

Basis of dose selection:
Plate incorporation assay:

Standard range of doses routinely used by this laboratory on the basis of a standard protocol.

The following doses of BAY 67-3472 were evaluated in the first test:

	µg per plate	
Negative control	0	
BAY 67-3472	5000	
BAY 67-3472	1581	
BAY 67-3472	500	
BAY 67-3472	158	
BAY 67-3472	50	
BAY 67-3472	16	
Positive control, Na-azide	10	(only TA 1535)
Positive control, NF	0.2	(only TA 100)
Positive control, 4-NPDA	10	(only TA 1537)
Positive control, 4-NPDA	0.5	(only TA 98)
Positive control, MMC	0.2	(only TA 102[1])
Positive control, Cumene	50	(only TA 102[2])
Positive control, 2-AA	3	

Pre-incubation assay:

Doses selected based on the results of the "plate incorporation" assay.

Negative controls: Solvent alone (0.1 mL/plate to match the amount solvent with the test article)

- Mitomycin C was dissolved in deionized water.
- BAY 67-3472 and the other positive controls were dissolved in DMSO.

Positive controls:

Salmonella strains	Compound	Metabolic Activation
TA1535	Sodium azide	-S9
TA100	Nitrofurantoin	-S9
TA1537 and TA98	4-nitro-1,2- phenylene diamine	-S9
TA102	Cumene hydroperoxide and MitomycinC	-S9
All strains	2-aminoanthracene	+S9

Incubation and sampling times:

Plates were counted after incubation for 48 hours at 37°C.

For the pre-incubation assay, pre-incubation was done for 20 min at 37°C.

Counting method:

Colonies were counted automatically using a[ ] counter,[ ] if there were no interference, e.g. by precipitation on the plates or coloration of the plates.

Results

Study validity:

Statistical analysis was not reported.

Replicates:
Results of the plate incorporation assays were verified by the pre-incubation assay, in which pre-incubation was carried out for 20 min at 37°C, then 2 mL of molten soft agar were added to the tube and the content plated.

Number of plates for both "plate incorporation" and "pre-incubation" assays:

- For the mutant count 3 plates were used, with or without S9 mix, for each strain and dose.
- Solvent control: 3 plates with or without S9 mix / strain
- Each positive control also contained 3 plates/strain.

Criteria for test article-induced toxicity:

- The first method was a gross appraisal of background growth on the plates for mutant determination. If a reduction in background growth was observed, it was indicated in the tables by the letter "b" after the mutant count. The "b" represents three plates with reduced background growth.
- Secondly, a toxic effect of the substance was assumed when there was a marked and dose-dependent reduction in the mutant count per plate, compared to the negative controls.
- Thirdly, the titer was determined to define the number of viable cells.

Criteria for positive result:

- A reproducible and dose-related increase in mutant counts of at least one strain is considered to be a positive result.
- For TA 1535, TA 100 and TA 98 this increase should be about twice that of negative controls, whereas for TA 1537, at least a threefold increase should be reached.
- For TA 102 an increase of about 100 mutants should be reached.

Criteria for accepting an assay:

- The negative controls had to be within the expected range, as defined by published data (27) and/ or the laboratories' own historical data
- The positive controls had to show sufficient effects, as defined by the laboratories' experience
- Titer determinations had to demonstrate sufficient bacterial density in the suspension.

Study outcome:
Doses up to and including 16μg/ plate did not cause any toxic effects. Total bacteria counts remained unchanged and no inhibition of growth was observed. A strong toxicity was generally observed at 80 μg/ plate, the highest concentration used in the assays. Substance precipitation occurred at the dose of 5000 μg per plate.

The test article (M-2 metabolite of sorafenib) was non-mutagenic in the absence of S9.

Based on both the OECD Guideline 471 (July 1997) on "Bacterial Reverse Mutation Test" and the CFSAN Red Book, 2-Aminoanthracene should not be used as the sole indicator of the efficacy of the S9-mix. If 2-aminoanthracene is used, each batch of S9 should also be characterized with a mutagen that requires metabolic activation by microsomal enzymes, e.g., benzo(a)pyrene, dimethylbenzanthracene. Therefore, the validity of the genotoxicity study in the presence of S9 remains unclear.

Ratios of mutants in each group/ mutants in the solvent control (plate incorporation assay)

Concentration (µg/plate)	TA1535		TA100		TA1537		TA98		TA102	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
2.5	1.2	1.2	1.0	1.0	1.2	0.6	0.9	1.0	1.1	0.9
5.0	1.2	0.9	1.0	1.0	1.0	1.0	0.9	1.0	1.0	1.0
10.0	1.1	0.9	1.0	1.0	1.0	0.9	1.0	1.0	1.1	0.9
20.0	1.1	0.9	1.0	1.1	1.3	0.9	1.1	1.0	1.0	0.9
40.0	1.1	1.0	1.0	1.1	0.9	1.2	0.7	1.0	0.8	0.8
80.0	0.4	0.8	0.8	0.9	0.5	0.2	0.7	0.7	0.7	0.7
+ control	37.6	16.4	2.5	7.9	10.8	29.9	3.8	26.2	2.5	1.8

Ratios of mutants in each group/ mutants in the solvent control (pre-incubation assay)

Concentration *(µg/tube)	TA1535		TA100		TA1537		TA98		TA102	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
2.5	1.2	0.7	1.0	0.8	0.7	0.8	1.0	1.1	1.0	0.8
5.0	1.3	0.7	1.1	0.9	0.9	0.8	0.8	1.0	1.0	0.8
10.0	1.3	0.8	0.9	0.8	0.5	0.7	0.6	0.9	1.0	0.8
20.0	1.0	0.6	1.0	1.0	0.9	0.8	0.7	0.9	0.6	0.9
40.0	0.6	0.5	0.8	0.9	0.4	1.0	0.7	0.8	0.4	0.7
80.0	0.4	0.5	0.8	0.9	—	0.4	0.6	0.7	0.5	0.6
+ control	55.0	13.7	3.2	9.5	12.1	35.2	8.1	45.4	2.1	1.5

* Synonymous to µg/plate, since all content of the tube was plated.

Study title: [redacted] (impurity); Salmonella/Microsome test; Plate incorporation and pre-incubation method

Key findings: BAY 67-3472 was not mutagenic in the Ames Test in the absence of S9. BAY 67-3472 was non-mutagenic in the presence of S9 (the validity of the +S9 assay remains uncertain)

Report # PH-31850
Study # T 6070883

Volume #, and page #: Module 4; M4.2.3.7.6.1
Conducting laboratory and location: Rodents and Genotoxicity Unit of Toxicology
BAYER AG
Friedrich-Ebert-Strabe 217-333, D-42096
Wuppertal, F.R.G.
Date of study initiation: September 3, 2001

GLP compliance: Yes; in compliance with the OECD Principles of GLP
QA reports: yes (X) no ( )
Drug, lot #, and % purity: BAY [ ] (impurity of BAY 43-9006); Batch# 507114;
[ ] pure

Chemical name

Structure

Molecular weight

Molecular formula

CAS-No.

Other name: [ ]

Methods

cell line:
Salmonella typhimurium: TA1537, TA1537, TA98, TA100, TA102

Doses used in definitive study:
Plate incorporation assay: 16, 50, 158, 500, 1581, and 5000 µg/plate
Pre-incubation assay: 100, 200, 400, 800, 1600, and 3200 µg/plate

Basis of dose selection:
Plate incorporation assay:
Standard range of doses routinely used by this laboratory on the basis of a standard protocol

The following doses of [ ] were evaluated in the first test:

	µg per plate	
Negative control	0	
BAY [ ]	5000	
BAY [ ]	1581	
BAY [ ]	500	
BAY [ ]	158	
BAY [ ]	50	
BAY [ ]	16	
Positive control, Na-azide	10	(only TA 1535)
Positive control, NF	0.2	(only TA 100)
Positive control, 4-NPDA	10	(only TA 1537)
Positive control, 4-NPDA	0.5	(only TA 98)
Positive control, Cumene	50	(only TA 102)
Positive control, 2-AA	3	

Pre-incubation assay:

Doses selected based on the results of the "plate incorporation" assay.
Due to test article precipitation, the doses of 100 µg to 3200 µg/tube were chosen for the pre-incubation assay.

Negative controls: Solvent alone (0.1 mL/plate to match the amount solvent with the test article)

- BAY [ ] and the positive controls were dissolved in DMSO.

Positive controls:

Salmonella strains	Compound	Metabolic Activation
TA1535	Sodium azide	-S9
TA100	Nitrofurantoin	-S9
TA1537 and TA98	4-nitro-1,2- phenylene diamine	-S9
TA102	Cumene hydroperoxide	-S9
All strains	2-aminoanthracene	+S9

Incubation and sampling times:
Plates were counted after incubation for 48 hours at 37°C.
For the pre-incubation assay, pre-incubation was done for 20 min at 37°C.

Counting method:
Colonies were counted automatically using a [ ] counter [ ] if there were no interference, e.g. by precipitation on the plates or coloration of the plates.

Results

Study validity:
Statistical analysis was not reported.

Replicates:
Results of the plate incorporation assays were verified by the pre-incubation assay, in which pre-incubation was carried out for 20 min at 37°C, then 2 mL of molten soft agar were added to the tube and the content plated.

Number of plates for both "plate incorporation" and "pre-incubation" assays:

- For the mutant count 3 plates were used, with or without S9 mix, for each strain and dose.
- Solvent control: 3 plates with or without S9 mix / strain
- Each positive control also contained 3 plates/strain.

Criteria for test article-induced toxicity:

- The first method was a gross appraisal of background growth on the plates for mutant determination. If a reduction in background growth was observed, it

was indicated in the tables by the letter "b" after the mutant count. The "b" represents three plates with reduced background growth.

- Secondly, a toxic effect of the substance was assumed when there was a marked and dose-dependent reduction in the mutant count per plate, compared to the negative controls.
- Thirdly, the titer was determined to define the number of viable cells.

Criteria for positive result:

- A reproducible and dose-related increase in mutant counts of at least one strain is considered to be a positive result.
- For TA 1535, TA 100 and TA 98 this increase should be about twice that of negative controls, whereas for TA 1537, at least a threefold increase should be reached.
- For TA 102 an increase of about 100 mutants should be reached.

Criteria for accepting an assay:

- The negative controls had to be within the expected range, as defined by published data (28) and/ or the laboratories' own historical data
- The positive controls had to show sufficient effects, as defined by the laboratories' experience
- Titer determinations had to demonstrate sufficient bacterial density in the suspension.

Study outcome:
Concentrations of up to 5000 µg/ plate, showed that BAY[ ] was not cytotoxic. However, the test article precipitated starting at 50 µg/ plate level. The sponsor stated that the dose of 5000 µg/plate could not be used for assessment.

BAY[ ] the impurity of sorafenib, was not genotoxic in the Ames assay, in the absence of S9.

Based on both the OECD Guideline 471 (July 1997) on "Bacterial Reverse Mutation Test" and the CFSAN Red Book, 2-Aminoanthracene should not be used as the sole indicator of the efficacy of the S9-mix. If 2-aminoanthracene is used, each batch of S9 should also be characterized with a mutagen that requires metabolic activation by microsomal enzymes, e.g., benzo(a)pyrene, dimethylbenzanthracene. Therefore, the validity of the genotoxicity study in the presence of S9 remains unclear, unless, the S9 fraction was independently shown to be active.

Ratios of mutants in each group/ mutants in the solvent control (plate incorporation assay)

Concentration (µg/plate)	TA1535		TA100		TA1537		TA98		TA102	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
16	0.5	0.8	0.8	1.0	1.0	1.1	1.1	1.0	1.0	1.0
50	0.9	1.1	0.9	1.0	1.0	1.2	1.0	0.9	1.1	1.0
158	0.6	1.3	1.0	1.1	1.0	1.0	1.0	1.0	0.9	1.0
500	0.7	1.2	0.9	1.0	1.1	1.1	1.2	1.5	1.0	0.8
1581	0.8	1.1	1.0	1.0	1.0	0.9	1.1	1.3	0.7	0.8
5000	—	—	0.8	0.8	—	—	—	—	—	—
+ control	66.7	26.1	2.7	15.4	17.1	47.6	7.8	55.3	2.1	1.7

—, not assessed due to precipitation

Ratios of mutants in each group/ mutants in the solvent control (pre-incubation assay)

Concentration *(µg/tube)	TA1535		TA100		TA1537		TA98		TA102	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
100	0.8	1.1	1.1	1.0	0.9	1.1	1.0	1.3	1.0	0.9
200	0.8	1.0	1.1	1.1	0.9	1.1	1.0	0.9	1.0	1.0
400	1.0	0.9	1.1	1.0	0.8	0.8	0.8	1.2	1.0	1.0
800	0.8	1.1	1.0	1.0	0.7	1.0	1.1	0.9	0.9	0.8
1600	0.9	1.2	1.0	1.1	0.7	0.8	0.7	1.4	0.8	0.9
3200	0.6	1.0	0.8	1.0	0.6	1.0	1.1	1.3	0.7	0.9
+ control	75.6	24.8	3.2	15.0	14.1	36.9	9.3	58.6	1.9	1.4

* Synonymous to µg/plate, since all content of the tube was plated.

Study title: [ ] Salmonella/microsome test
Plate incorporation and pre-incubation method

Key findings: [ ] was mutagenic in Salmonella TA 100 and TA 98 in the presence of S9.

Report # PH-33614
Study # T 7074286

Volume #, and page #: Module 4; M4.2.3.7.6.3
Conducting laboratory and location: Rodents and Genotoxicity Unit of Toxicology
BAYER AG,
Friedrich-Ebert-Strabe 217-333, D-42096
Wuppertal, F.R.G.
Date of study initiation: June 7, 2004
GLP compliance: Yes; in compliance with the OECD Principles of GLP
QA reports: yes (X) no ( )
Drug, lot #, and % purity: [ ] Bath # BXROAX5,
[ ] pure

Chemical name [

Structure

Molecular weight

Molecular formula

CAS-No.

Indication]

Other name: [ ]

Methods

cell line:
Salmonella typhimurium: TA1537, TA1537, TA98, TA100, TA102

Doses used in definitive study:
1st study: 50, 158, 500, 1581, and 5000 µg/plate (all strains)
Confirmatory study: 156, 312, 624, 1248, 2496, and 4992 µg/plate (TA 100 and TA 98 only)

Basis of dose selection:
Standard range of doses routinely used by this laboratory on the basis of a standard protocol:

The following doses of [ ]r were evaluated in the first test:

	µg per plate	
Negative control	0	
[	5000	
	1581	
	500	
	158	
	50	
Positive control, Na-azide	10	(only TA 1535)
Positive control, NF	0.2	(only TA 100)
Positive control, 4-NPDA	10	(only TA 1537)
Positive control, 4-NPDA	0.5	(only TA 98)
Positive control, MMC	0.2	(only TA 102)
Positive control, 2-AA	3	

Negative controls: Solvent alone. The amount of solvent for the test substance and for the controls was 0.1 ml/plate.

- Mitomycin C was dissolved in water.
- BAY [illegible] and the other positive controls were dissolved in DMSO.

Positive controls:

Salmonella strains	Compound	Metabolic Activation
TA1535	Sodium azide	-S9
TA100	Nitrofurantoin	-S9
TA1537 and TA98	4-nitro-1,2- phenylene diamine	-S9
TA102	Mitomycin C	-S9
All strains	2-aminoanthracene	+S9

Incubation and sampling times:
Plates were counted after incubation for 48 hours at 37°C.

Counting method:
Colonies were counted automatically using a [illegible] counter, [illegible] if there were no interference, e.g. by precipitation on the plates or coloration of the plates.

Results

Study validity:
Statistical analysis was not reported.

Replicates:
For the positive results, plate incorporation assays were repeated.

Number of plates for both "plate incorporation" and "pre-incubation" assays:
- For the mutant count 3 plates were used, with or without S9 mix, for each strain and dose.
- Solvent control: 3 plates with or without S9 mix / strain
- Each positive control also contained 3 plates/strain.

Criteria for test article-induced toxicity:
- The first method was a gross appraisal of background growth on the plates for mutant determination. If a reduction in background growth was observed, it was indicated in the tables by the letter "b" after the mutant count. The "b" represents three plates with reduced background growth.
- Secondly, a toxic effect of the substance was assumed when there was a marked and dose-dependent reduction in the mutant count per plate, compared to the negative controls.
- Thirdly, the titer was determined to define the number of viable cells.

Criteria for positive result:
- A reproducible and dose-related increase in mutant counts of at least one strain is considered to be a positive result.

- For TA 1535, TA 100 and TA 98 this increase should be about twice that of negative controls, whereas for TA 1537, at least a threefold increase should be reached.
- For TA 102 an increase of about 100 mutants should be reached.

Criteria for accepting an assay:

- The negative controls had to be within the expected range, as defined by published data (29) and/ or the laboratories' own historical data
- The positive controls had to show sufficient effects, as defined by the laboratories' experience
- Titer determinations had to demonstrate sufficient bacterial density in the suspension.

Study outcome:
Although the title of the study mentions plate incorporation and pre-incubation tests, only plate incorporation was conducted.

Doses up to and including 5000 µg/plate did not cause any toxic effects. Total bacteria counts remained unchanged and no inhibition of growth was observed.

The Ames test showed [ ] to have a mutagenic effect. Evidence of mutagenic activity of [ ] was seen in Salmonella TA 100 and TA 98 in the presence of S9. The lowest effective dose was 500 µg/ plate for Salmonella TA 100 and 624 µg/ plate for TA 98.

Ratios of mutants in each group/ mutants in the solvent control (plate incorporation assay)

Concentration (µg/plate)	TA1535		TA100		TA1537		TA98		TA102	
	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9	-S9	+S9
50	1.2	1.1	1.0	1.0	0.9	0.8	1.0	1.0	1.0	0.9
158	1.2	1.0	1.2	1.2	0.7	0.8	0.8	1.3	1.0	1.1
500	1.2	1.0	1.1	1.3	0.6	0.8	1.0	1.4	0.9	1.1
1581	1.1	0.7	1.2	1.4	0.6	0.9	1.0	2.2	0.8	1.0
5000	1.4	0.9	1.1	1.6	0.8	1.3	1.0	3.4	0.7	0.9
+ control	94.7	11.6	2.4	9.3	10.5	26.3	4.0	26.3	2.1	2.6

Ratios of mutants in each group/ mutants in the solvent control (plate incorporation assay)- assay repeated

Concentration (µg/plate)	TA100	TA98
	+S9	+S9
156	1.3	1.4
312	1.2	1.6
624	1.4	2.1
1248	1.6	2.5
2496	1.6	3.4
4992	1.7	4.9
+ control	10.4	31.6

Genetic toxicology summary and conclusions:
The mutagenic potential of BAY 54-9085 was assessed in bacterial mutagenicity studies using selected strains of S. *typhimurium*. BAY 54-9085 did not induce any significant increases in the observed numbers of revertant colonies in the tester strains used, either in the presence or absence of S-9 mix. However, the validity of the +S9 assay remains uncertain, because the positive control used for the +S9 assay was 2-aminoanthracene. Based on the OECD Guideline, this control cannot be used as the sole indicator for the efficacy of the S9 mix. If 2-aminoanthracene is used, each batch of S9 should also be characterized with a mutagen that requires metabolic activation by microsomal enzymes, e.g. benzo(a)pyrene, dimethybenzathracene.

The potential for clastogenicity was assessed *in vitro* using Chinese Hamster V79 cells. This mutagenicity test system is designed to detect structural aberrations in cells at their first post-treatment mitosis. Aberrations of the chromatid type and of the chromosome type are detectable in this assay. Metabolic activation allows the assessment of clastogenic potential of the test substance and of its metabolites. The metaphase chromosomes are stained and analyzed for chromosomal aberrations. In the presence of metabolic activation, BAY 54-9085 showed a significant increased numbers of aberrant metaphases. Thus, BAY 54-9085 is considered to be clastogenic for mammalian cells *in vitro*. BAY 54-9085 was also evaluated *in vivo* using the micronucleus test in male mice. IP administration of BAY 54-9085 (125, 250, and 500 mg/kg; two doses separated by 24 h.) did not increase the incidence of micronucleated polychromatic erythrocytes in the bone marrow. Thus, under the conditions of this assay, BAY 54-9085 tested negative in the *in vivo* micronucleus assay indicating that the substance does not induce micronuclei resulting from chromosomal damage or damage to the mitotic apparatus in the bon marrow erythroblasts.

Additionally, Ames Test was performed to evaluate the genotoxic potential of the major metabolite (N-oxide or M-2 metabolite) as well as specific impurities of sorafenib. The M-2 metabolite was non-genotoxic in the presence or absence of the S9 mix. Similar to the Ames Assay conducted with sorafenib, the validity of the +S9 systems remains uncertain. The micronucleus assay conducted in mice although negative in term of genotoxicity is not supportive of the non-genotoxic characteristics of M-2. Based on the in vitro studies conducted with liver microsomes, the strain of mouse used in the micronucleus assay, NMRI, does not recapitulate the human metabolic profile (see Table below) and the amount of M-2 in the NMRI microsome assay was 72% less than that in human. In vivo metabolism was conducted in rats and dogs only. The in vivo studies showed M-2 metabolite comprised of 0.9% of AUC in rats and was not detected in dogs (M-2 is 16.7% of the AUC in human).

Table 5-1: Metabolite profiles in incubations of [^{14}C]BAY 54-9085 (16 µM) with liver microsomes of different species (protein concentration 0.5 mg/mL, 90 min) (M4.2.2.4.9, PH-32439)

Compound	Man (pool)	Rhesus monkey	Wistar rat	CD-1 mouse	NMRI mouse	Beagle dog	New Zealand rabbit
			% of radioactivity				
M-1	4.9	9.0	1.3	2.4	-	-	-
M-5	-	1.2	-	-	-	-	-
M-2	36.4	29.4	9.6	23.2	10.7	3.8	6.0
M-3	14.2	17.9	16.8	11.0	5.4	19.7	3.2
M-4	1.6	4.6	1.4	1.9	-	2.4	-
Drug	41.0	35.3	70.8	61.5	83.9	74.1	90.8

Table provided by the sponsor.

[redacted]' (BAY[redacted] was subjected to a separate nonclinical experimental qualification procedure because in the early stage of development higher amounts of this potential impurity was expected in the drug product for clinical trials, but according to the sponsor, in most of the batches used for the toxicity program on sorafenib, BAY[redacted] occurred only in minor amounts or was below the detection limit. The qualification program included an Ames test (M4.2.3.7.6.1, PH-31850) and a repeat-dose (4-week) toxicity study in rats (M4.2.3.7.6.2, PH-33379).[redacted] was not genotoxic in the absence or presence of S9. The validity of the assay in the presence of S9 is uncertain.

Another impurity of sorafenib is [redacted] was tested in toxicology studies (e.g. rat 6- month, dog 12- month) at a concentration of[redacted] in batch 000217 of sorafenib tosylate. Batch 990722 of sorafenib tosylate (purity[redacted]) with[redacted] at a concentration of[redacted] was used in the battery of tests to evaluate the genotoxic potential of sorafenib, including the Ames test and the in vitro and in vivo evaluation for clastogenicity (M4.2.3.3.1.1, PH- 9467; M4.2.3.3.1.2, PH- 29598; M4.2.3.3.2.1, PH- 29474). Based on the Ames Assay,[redacted] was genotoxic in TA100 and TA98 in the presence of S9. The mouse micronucleus assay, using sorafenib batch # 99072 (with[redacted] of[redacted] did not reveal any genotoxic potential of this impurity at the levels present.

2.6.6.5 Carcinogenicity

Carcinogenicity studies were not conducted with sorafenib.

2.6.6.6 Reproductive and developmental toxicology

Fertility and early embryonic development

ICH A-B/Segment 1 studies have not been conducted with this product.

Embryofetal development

Study title: BAY 54-9085 (tosylate salt of BAY 43-9006): Developmental toxicity study in rats after oral administration- **Segment 2**

Key study findings: fetal/intrauterine findings:
↓number of ♀s with implantations/ ↑ post-implantation loss/ ↓litter size
↓fetal weight/ ↓placental weight
necrosis of placenta
fetal malformations and skeletal deviations

Study Report PH-33514
Study # T 0063010

Volume #, and page #: Module 4; M4.2.3.5.2
Conducting laboratory and location: Department PH-PD Toxicology International
Experimental Toxicology of Bayer HealthCare AG
42096 Wuppertal, Germany
Date of study initiation: May 14, 2003
GLP compliance: Yes; In compliance with the OECD Principles of GLP

QA reports: yes (X) no ( )
Drug, lot #, and % purity: BAY54-9085, batch # 011121, [ ] pure (free base: [ ])
Formulation: suspension of 0.5% methylhydroxyethyl cellulose (in demineralized water)

Methods

Doses: 0, 0.27, 1.37, and 3.43 mg/kg/day of tosylate salt
Corresponding to: 0, 0.2, 1.0, and 2.5 mg/kg/day of the free base

♀s were dosed from D6 to D17 post coitum

Dose Groups	# of animals	Doses of the tosylate salt		Doses of the free base*		Concentration (mg/mL)
		mg/kg	mg/m2	mg/kg	mg/m^2	
Vehicle control	22	0	0	0	0	0
LD	22	0.27	1.6	0.2	1.2	0.027
MD	22	1.37	8.2	1.0	6.0	0.137
HD	22	3.43	20.6	2.5	15.6	0.343

Vehicle control: 0.5% aqueous [ ] suspension;
* Conversion factor for tosylate salt and free base: 1.37
LD: low-dose; MD: mid-dose; HD: high-dose
Table generated by the reviewer.

Species/strain: Rat/Wistar
Number/sex/group: 22/♀/group
No ♂s treated
Route, formulation, volume, and infusion rate: oral, suspension, 10 mL/kg
Satellite groups used for toxicokinetics: TK done on all ♀s of the LD, MD, and HD groups

Study design:

Mating: 2 females were placed with one male overnight. If the vaginal smear was positive for sperm detection the following morning, that day was recorded as Day 0 of gestation.

C-section: In the main groups, the fetuses were delivered by cesarean section on D20 of gestation.

Parameters and endpoints evaluated: maternal and intra-uterine/fetal parameters

Assessments (♀s)

Clinical examinations:	Day 0 to 20 (main groups) Day 0 to 17 (satellite groups) twice daily (once daily on the weekends)
Body weight:	Day 0, and daily from Day 6 to 20 (main groups) daily from Day 6 to 17 (satellite groups) For main groups, corrected body weight gain was calculated by subtracting the weight of the uterus on Day 20 from the body weight gain from Day 0 to Day 20.
Food consumption:	On gestation days 0-3, 3-6, 6-9, 9-12, 12-15, 15-17, 15-18, 18-20 (main groups) On gestation days 0-3, 3-6, 6-9, 9-12, 12-15, 15-17 (satellite groups)
Toxicokinetics:	From all females of the LD, MD, and HD groups on gestation Day 17, at 1, 2, 4, and 7 hours after administration.
Necropsy:	At the time of cesarean section on Day 20 (main groups) or Day 17 (satellite groups).
Cesarean section:	On gestation day 20 (main groups) or 17 (satellite groups, after the last blood sampling). The following parameters were assessed on Day 20 in the main groups:

- Number of corpora lutea
- Number of implantations (in females without visible implantation sites after staining of the uterus with a solution of 10% of ammonium sulfide)
- Uterine weight, individual weight and appearance of the placenta
- Number of early resorption (only implantation site visible), late resorption (fetal or placental remnant visible), and dead fetuses
- Number, sex, and weight of live fetuses
- External malformations
- Visceral malformations
- Findings in abdominal, pelvic, and thoracic organs as well as skeletal findings

During cesarean section on Day the following data were ascertained in the satellite groups:

- existence of implantations.

Results
Maternal Assessments
Mortality: None

Clinical signs: Red vaginal discharge in 2 ♀s at HD. No other clinical signs.

Body weight: Table provides an overview on the mean body weight gain of the females with viable fetuses during the treatment and gestation periods.

Dose [mg/kg bw/day]	0	0.27	1.37	3.43
mean body weight gain [g]				
days 6 - 17 p.c.	52.3	49.3	50.1	43.6**
days 0 - 20 p.c.	112.0	105.6	107.8	98.1
corrected body weight gain [g]				
days 0 - 20 p.c.	50.2	41.1**	46.5	44.4

Statistically significant difference to control ** = $p < 0.01$

Corrected body weight gain: BW gain over the period from gestation D0 to D20 – weight of uterus on gestation D20.
p.c.: post-coitum

Food consumption: Marginally impaired at the high dose at the end of treatment; statistically significant from day 15-18 post coitum.

Dose [mg/kg bw/day]	0	0.27	1.37	3.43
Mean feed consumption [g/female/day]				
days 0 - 3 p.c.	20.0	18.5	18.9	19.1
days 3 - 6 p.c.	19.9	19.6	20.1	20.5
days 6 - 9 p.c.	20.0	19.7	20.0	20.0
days 9 - 12 p.c.	21.1	20.1	21.1	20.4
days 12 - 15 p.c.	21.8	20.3	21.2	20.6
days 15 - 18 p.c.	24.1	23.0	23.4	22.0**
days 18 - 20 p.c.	25.3	24.2	23.7	23.1

Statistically significant difference to control ** = $p < 0.01$

Necropsy: no treatment related gross pathological alterations

General reproduction data/ Fertility rate: slightly reduced implantation at all dose levels

Dose [mg/kg bw/day]	0	0.27	1.37	3.43
inseminated females	22	22	22	22
inseminated females evaluated	22	22	22	22
females with implantations	22	21	20	20
in % of those inseminated	100.0	95.5	90.9	90.9
mean values per female with implantation sites				
corpora lutea	13.7	13.6	13.2	13.6
preimplantation loss	2.3	1.7	1.3	1.0
implantations	11.4	11.9	11.9	12.6

Fetal/ intrauterine assessments
Gestation rate

The gestation rate (number of females with viable fetuses as a percentage of the number of females with implantations) was reduced at high-dose due to the one resorption

Dose [mg/kg bw/day]	Females with viable fetuses N	Females with viable fetuses in % of females with implantations	Females with total resorption
0	22	100.0	0
0.27	21	100.0	0
1.37	20	100.0	0
3.43	19	95.0	1

Intrauterine parameters

Dose [mg/kg bw/day]	0	0.27	1.37	3.43
number of females				
with implantations (a)	22	21	20	20
with viable fetuses (b)	22	21	20	19
means per female				
placental weight in g (b)	0.65	0.63	0.63	0.58**
number of live fetuses (b)	10.7	11.2	10.8	9.8
postimplantation loss (a)	0.7	0.7	1.1	3.3**
postimplantation loss (b)	0.7	0.7	1.1	2.8**
% males (b)	49.3	51.4	47.4	57.2
fetal weight in g (b)	3.69	3.66	3.61	3.33**

Statistically significant difference to control ** = $p < 0.01$

Placenta weight and appearance

Statistically significant increased incidence of placentas with necrotic placental borders was seen on a fetal and litter basis (40% and 90%, respectively) at high-dose together with 2 pale placentas (in 2 litters) at this dose level. Furthermore statistically significant reduction in placental weight was seen at high-dose.

Post-implantation loss, number of fetuses

One of the females of the high-dose group with red vaginal discharge (# 1731) showed late resorption of 12/12 implants. The other HD female with red vaginal discharge (# 1801) showed late resorption of 7/13 implants.

In the remaining litters of this dose group post-implantation loss (late resorptions) was increased as well and resulted in a slightly reduced mean litter size.

Dose group	**Mean Litter Size**
Control	10.7
LD	11.2
MD	10.8
HD	9.8 (↓8% compared to control)

Sex of Fetuses

Not affected.

Fetal Weight

Slight but dose-dependent reduction in mean fetal weight that was statistically significant at HD (↓10%).

Fetal Malformations

Malformation	Dose [mg/kg bw/day]			
	0	0.27	1.37	3.43
eye rudiment flat/eyeball reduced in size (microphthalmia)	1	1	3 (3)	1
dilation of brain ventricles (hydrocephalus internus)	1	-	-	-
thyroid gland missing, unilateral	-	1	-	1
double aortic arch, left sided descending aorta	-	-	-	1
right-sided retroesophageal aortic arch, left sided descending aorta, pulmonary trunc and ductus arteriosus, left subclavian artery arises from descending aorta	-	-	1	3 (2)
right-sided aortic arch, descending aorta, pulmonary trunc and ductus arteriosus	-	-	-	1
scapula dysplastic	-	-	-	1
scapula and radius dysplastic	-	-	-	1
bifurcation of ribs	-	-	-	1
head of 1st rib missing	1	-	-	-
head of 1st rib missing bilateral; 2nd rib bent, unilateral; shift, fusion or shortage of cartilaginous parts of ribs; cartilaginous end of 1st rib not connected to sternum	-	-	-	1
2nd rib bent, unilateral; shift and fusion of cartilaginous parts of 1st and 2nd rib	-	-	-	2 (1)
combined alterations of thoracic vertebrae	-	-	-	1
combined alterations of lumbar vertebrae	-	-	-	1
malformed vertebral column (kinked) with alteration of thoracic and/or lumbar vertebrae, 1st sacral vertebral arch has the shape of a lumbar vertebral arch unilateral, pelvis shifted caudally right/left	-	-	-	3 (1)
malformed vertebral column (S-shaped), alterations of thoracic and lumbar vertebrae	-	-	-	1
malformed vertebral column (S-shaped), head of 1st rib missing, left, alterations of ribs, thoracic and lumbar vertebrae, 1st sacral vertebral arch has the shape of a lumbar vertebral arch, right; pelvis shifted caudally, right	-	-	-	1
1st sacral vertebral arch has the shape of a lumbar vertebral arch uni- and/or bilateral; pelvis shifted caudally, unilateral	-	-	-	3 (3)
pelvis shift caudally, unilateral	-	-	-	2 (2)
supernumerary lumbar vertebra	-	-	-	1
supernumerary sacral vertebra	-	1	-	-
iliac bone dysplastic (shortened and kinked)	-	-	-	1

Malformation	Dose [mg/kg bw/day]			
	0	0.27	1.37	3.43
number of fetuses per group	235	235	216	186
number of fetuses with malformations	3	3	4	25**
malformed fetuses per group (%)	1.3	1.3	1.9	13.4
number of litters per group	22	21	20	19
number of litters with malformations	3	3	4	11*
malformed litters per group (%)	13.6	14.3	20.0	57.9

( ) number of litters affected; single fetuses and litters show more than one malformation
Statistically significant difference to control * = $p < 0.05$
Statistically significant difference to control ** = $p < 0.01$

Fetal External and Visceral Deviations

Table below gives an overview of external and visceral deviations (findings other than malformations) in live fetuses with percentages referring to the total numbers of fetuses and litters examined in this study.

Deviation	Dose [mg/kg bw/day]			
	0	0.27	1.37	3.43
eye rudiment flat (not confirmed as malformation)	-	-	1	-
slightly edematous (external[e]/visceral[v] finding)	2 (1)[v]	1[v]	-	1[e]
Pale	-	-	-	2 (2)
thyroid gland reduced in size	1	1	2 (2)	-
thymus gland extended cranially	8 (6)	8 (7)	8 (6)	7 (6)
origin of left carotid artery displaced towards left subclavian artery on aortic arch	-	2 (2)	1	1
innominate artery reduced in length	-	1	2 (2)	1
innominate artery missing	-	-	-	2 (2)
pericard filled with reddish brown mass	-	1	1	-
reddish-brown mass in abdominal cavity	5 (4)	1	1	1
reddish-brown spots in liver	12 (7)	5 (5)	3 (2)	4 (4)
uni-/bilateral (slight) dilation of renal pelvis	14 (8)	8 (6)	13 (8)	5 (3)
uni-/bilateral slight dilation of ureter(s)	7 (6)	2 (2)	5 (5)	4 (3)
kidney lying more caudally	-	1	1	-
kidney flat and stretched	1	-	-	-
testicular findings				
uni-/bilateral testi(e)s lying (slightly) more cranially	7 (6)	4 (4)	5 (4)	4 (4)
testi(e)s lying on bladder	2 (2)	4 (4)	2 (2)	-
sum of fetuses (litters) with testicular findings	9 (8)	8 (7)	7 (6)	4 (4)
number of fetuses per group	235	235	216	186
number of fetuses with deviations	40	32	31	25
fetuses with deviations per group (%)	17.0	13.6	14.4	13.4
number of litters per group	22	21	20	19
number of litters with deviations	18	20	14	17
litters with deviations per group (%)	81.8	95.2	70.0	89.5

( ) number of litters affected; single fetuses showed more than one deviation

Fetal Skeletal Deviations

Mid-dose: Statistically significant retarded ossification of bones of phalanges and of 6th sternum. Furthermore, the number of fetuses with flat thoracic vertebral bodies (10th to 13th affected) was increased, also indicating retarded ossification.

High-dose: Statistically significant retarded ossification of phalanges of digits and toes, single metacarpals and sternum, of cervical, thoracic, lumbar and caudal vertebral bodies and skull bones. In addition, there was a statistically significant increase in the incidence of common skeletal variations of ribs (14th rib). Additionally 2 fetuses in 2 litters had a slightly cleft palate (fetus # 89 of female # 1737 and fetus # 575 of female # 1785), indicating retarded ossification.

Toxicokinetics:

The exposure of BAY 43-9006 on gestation Day 17 (geometric means, n=5) are shown in the Table below. Normalization is done by dividing the C_{max} or the AUC by the individual dose.

		BAY 43-9006					
Dose: BAY 54-9085 [mg/kg]		0.270		1.37		3.43	
Dose: BAY 43-9006 [mg/kg]		0.200		1.00		2.50	
		Mean geom.	S.D. geom.	Mean geom.	S.D. geom.	Mean geom.	S.D. geom.
AUC(0-7)	[µg·h/L]	889	1.26	3552	1.23	6027	1.15
$AUC(0-7)_{norm}$	[kg·h/L]	4.44	1.26	3.55	1.23	2.41	1.15
C_{max}	[µg/L]	197	1.51	642	1.30	1055	1.15
$C_{max,norm}$	[kg/L]	0.984	1.51	0.642	1.30	0.422	1.15
t_{max}	[h]	2.95	1.77	4.36	1.68	5.60	1.36

n.c. = not calculated

t0063010_summary.xls/AUC_43-9006 \ FTH \ 20.04.04

Summary of the pharmacokinetic parameters of BAY 43-9006 and its metabolites M-1 to M-5; **LD data**

		BAY 43-9006	M-1	M-2	M-3	M-4	M-5
AUC(0-7)	[µg·h/L]	889	n.c.	n.c.	44.6	11.2	n.c.
$AUC(0-7)_{norm}$	[kg·h/L]	4.44	n.c.	n.c.	0.223	0.0591	n.c.
C_{max}	[µg/L]	197	n.c.	0.788	8.14	2.28	0.837
$C_{max,norm}$	[kg/L]	0.984	n.c.	n.c.	0.0407	0.0120	n.c.
$C(24)/C_{max}$	[%]	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
t_{max}	[h]	2.95	n.c.	n.c.	3.89	2.24	n.c.
MR-1	[%]		n.c.	n.c.	4.14	1.16	n.c.
MR-2	[%]		n.c.	n.c.	5.02	1.26	n.c.

t0063010_summary.xls \ AUCsummary_female \ Müh \ 22.06.04

n.c. = not calculated

MR-1:metabolic ratio in terms of C_{max} in [%]: C_{max} (M-X) / C_{max} (BAY 43-9006)

MR-2:metabolic ratio in terms of AUC(0-7) in [%]: AUC(0-7)_(M-X) / AUC(0-7)_(BAY 43-9006)

Summary of the pharmacokinetic parameters of BAY 43-9006 and its metabolites M-1 to M-5; **MD data**

		BAY 43-9006	M-1	M-2 **	M-3	M-4	M-5
AUC(0-7)	[µg·h/L]	3552	n.c.	25.2	171	61.7	20.1
$AUC(0-7)_{norm}$	[kg·h/L]	3.55	n.c.	0.0245	0.166	0.0636	0.0201
C_{max}	[µg/L]	642	n.c.	18.8	30.2	19.3	12.1
$C_{max,norm}$	[kg/L]	0.642	n.c.	0.0183	0.0294	0.0198	0.0121
$C(24)/C_{max}$	[%]	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
t_{max}	[h]	4.36	n.c.	1.00	3.21	1.48	1.00
MR-1	[%]		n.c.	2.93	4.71	3.00	1.88
MR-2	[%]		n.c.	0.711	4.82	1.74	0.567

t0063010_summary.xls \ AUCsummary_female \ M0h \ 23.06.04

n.c. = not calculated
MR-1:metabolic ratio in terms of C_{max} in [%]: C_{max} (M-X) / C_{max} (BAY 43-9006)
MR-2:metabolic ratio in terms of AUC(0-7) in [%]: AUC(0-7)_(M-X) / AUC(0-7)_(BAY 43-9006)
** = One animal was deactivated, because of limited timepoints above LLOQ, a calculation of AUC was not possible for this animal.
Thus, means and standard deviations were calculated from n=4 animals.

Summary of the pharmacokinetic parameters of BAY 43-9006 and its metabolites M-1 to M-5; **HD data**

		BAY 43-9006	M-1	M-2	M-3	M-4	M-5 **
AUC(0-7)	[µg·h/L]	6027	n.c.	9.40	326	93.0	7.94
$AUC(0-7)_{norm}$	[kg·h/L]	2.41	n.c.	0.00363	0.126	0.0383	0.00316
C_{max}	[µg/L]	1055	n.c.	3.28	60.2	18.1	3.10
$C_{max,norm}$	[kg/L]	0.422	n.c.	0.00127	0.0233	0.00743	0.00124
$C(24)/C_{max}$	[%]	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
t_{max}	[h]	5.60	n.c.	1.74	4.24	2.87	2.00
MR-1	[%]		n.c.	0.311	5.71	1.71	0.294
MR-2	[%]		n.c.	0.156	5.40	1.54	0.132
Fraction of AUC(0-24)_Sum	[%]	93.3		0.145	5.04	1.44	0.123

t0063010_summary.xls \ AUCsummary_female \ M0h \ 23.06.04

n.c. = not calculated
MR-1:metabolic ratio in terms of C_{max} in [%]: C_{max} (M-X) / C_{max} (BAY 43-9006)
MR-2:metabolic ratio in terms of AUC(0-7) in [%]: AUC(0-7)_(M-X) / AUC(0-7)_(BAY 43-9006)
AUC(0-7)_Sum = 6463 µg·h/L : Sum of AUC(0-7) of BAY 43-9006, M-2, M-3, M-4 and M-5
** = One animal was deactivated, because of limited timepoints above LLOQ, a calculation of AUC was not possible for this animal.
Thus, means and standard deviation were calculated from n=4 animals.

Summary and Conclusions

Rationale for Dose Selection:

Doses in this study were selected based on a pilot developmental toxicity study conducted with BAY 54-9085 in rats with dose levels of 0, 0.41, 1.37, and 4.11 mg/kg (Study# T1062995). In addition, a maternal tolerability study was performed in 4 pregnant rats with a dose level of 3.43 mg/kg (Study# T1063002), because 4/ 7 females at

high dose in the range-finding study showed total resorption of the litter. Litter loss was not observed at 3.43 mg/kg dose, therefore, this dose was selected as the highest dose in the pivotal study.

Maternal findings:
Findings were observed in the high-dose group and included red vaginal excretion in two females which revealed either total resorption or a high number of late resorptions, marginally impaired food intake at the end of treatment and slightly impaired body weight gain during the treatment and the overall gestation period.

Statistically significant reduced mean body weights were seen on a single day during treatment (Day 16) at mid-dose and high-dose. Body weight loss was not observed in this study and reduction of body weight gain during treatment (from Day 6-17) was only statistically significant at high-dose. A marginal reduction of overall body weight gain during pregnancy (Day 0-20) was as well observed at high-dose. In summary, treatment with BAY 54-9085 at HD caused impaired absolute weight gain during treatment and gestation probably due to lower litter size and decreased fetal weights while treatment related effects on body weight development were not evident at LD and MD.

Intrauterine
Placenta weight and appearance:
Increased incidence of placental findings (necrotic placental borders, pale placentas) and impaired placental weight were seen after treatment with BAY 54-9085 at high-dose

Post-implantation loss, number of fetuses:
Treatment relationship was evident for the single case of total resorption, increased post-implantation loss and consequently marginally reduced litter size in the remaining females of the 3.43 mg/kg dose group.

Fetal malformation:
The incidence and type of fetal malformations were unaffected by treatment at the 0.27 mg/kg dose level. A treatment-related effect could not be excluded for the single malformation of the aortic arch in the 1.37 mg/kg dose group and was evident for the increased incidence of multiple types of malformations at the 3.43 mg/kg dose level.

Fetal External and Visceral Deviations:
An effect on incidence and type of external and visceral deviations was not evident at a dose level up to and including 1.37 mg/kg but had to be assumed for pale appearance of fetuses and could not be excluded for missing innominate artery at the 3.43 mg/kg dose level due to the malformations of the aorta which were also evident at this dose level.

Fetal skeletal findings:
The treatment-related effect on degree of fetal ossification or occurrence of skeletal variations was at mid-dose included: retarded ossification of several phalangeal bones, 6" sternebra and thoracic vertebral bodies. At high-dose findings consisted of: retarded ossification of bones of forepaws, sternum, vertebral column and skull and for increased incidence of 14" ribs (a common skeletal variation in the rat strain used).

Maternal Findings:

- Statistically significant ↓mean body weights on a single day during treatment (Gestation Day 16) at LD and HD. This finding was not toxicologically significant (↓4% compared to control).
- ↓BW gain was observed in all dose groups as compared to control. This was statistically significant at HD, immediately after the dosing period.
- Red vaginal discharge in 2 HD ♀s. Both these ♀s had late resorptions (resorption of 12/12 implants in one animal and 7/13 in the other animal).
- The gestation rate (percentage of ♀s with viable fetuses on D20 p.c. of those with implantation sites) was decreased at HD, due to the total resorption in 1 ♀.
- No effect on the number of corpora lutea

Fetal/ Intrauterine Findings:

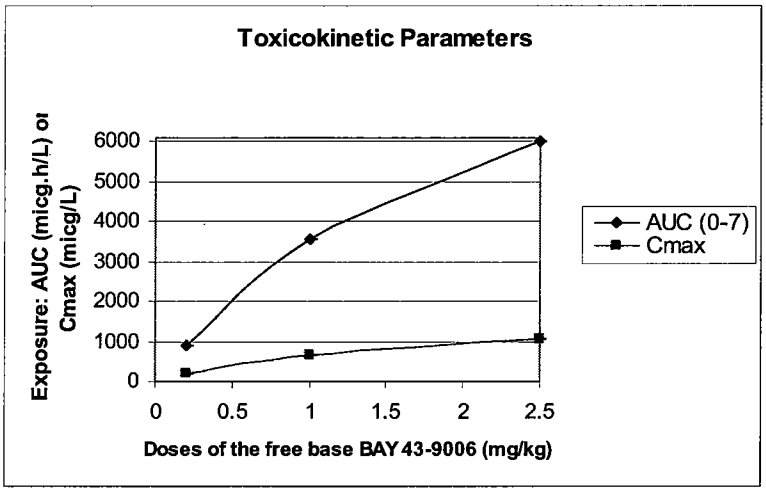
- Slight ↓ in the number of ♀s with implantations; observed at all dose levels (↓5% at LD, ↓10% at MD and HD)
- Slightly ↓ mean litter size (↓8%) and gestation rate (↓5%) at HD due to the resorptions of mainly 1 ♀ which had total resorption of 12/12.
- Dose-dependent ↑ in the post-implantation loss starting at MD (↑57% at MD and ↑3.7-fold at HD)
- Slight but dose-dependent reduction in fetal weight. The ↓fetal weight of 10% was statistically significant at HD.
- Statistically significant ↓placental weight at all at HD (↓12%)
- ↑incidence of placental findings, including necrotic placental borders and pale placentas at HD.
- ↑number of fetuses with malformations at HD (↑7-fold compare to control; statistically significant). Percentage of malformed fetuses at HD was 13.4 as compare to 1.3% in control (1.3% at LD and 1.9% at MD). Malformations at HD were seen in the following organs/tissues: descending aorta (double aortic arch, right-sided aortic arch, ...), scapula (dysplasia), ribs (bifurcation, head missing, bent), thoracic and lumbar vertebrae (alterations), vertebral column (malformed), sacral vertebral arch (shape changed), pelvis (shift caudally), iliac bone (dysplasia)
- Fetal visceral deviations observed at MD and HD: pale appearance of fetuses (MD and HD) and missing artery (HD) due to the malformation of aorta as reported under fetal malformations.
- Fetal skeletal deviations at MD and HD.

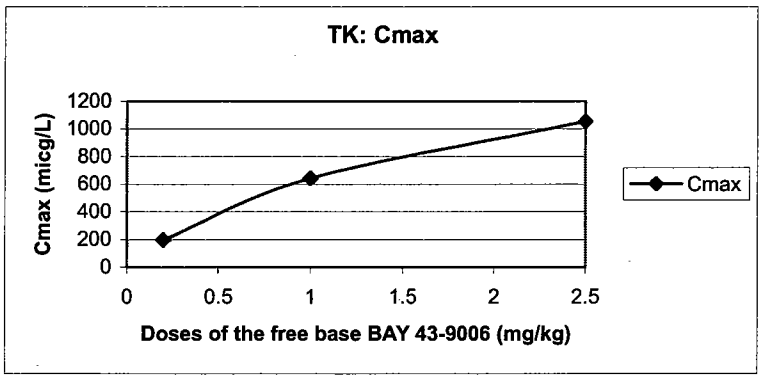
  MD: Retarded ossification of phalangeal, sternebra and thoracic vertebral bones.

  HD: Retarded ossification of bones of forepaws, sternum, vertebral column, and skull, and ↑incidence of variation of 14th ribs (which appears to be a common variation in Wistar rats.

Toxicokinetics:
Note: since the number of time points used are limited and most importantly no termination phase was observed during the collection time, discussions (see below) on TK parameters, i.e. on AUC of sorafenib and its metabolites, are not conclusive.

- Absorption time increased as doses increased
- Increases in the AUC and Cmax were less than dose proportional: a 5-fold increase in the dose from LD to MD resulted in 4-fold increase in the AUC and a 3-fold increase in the Cmax; a 2.5-fold increase in the dose from MD to HD resulted in 1.7-fold increase in the AUC and a 1.6-fold increase in the Cmax.
- Sorafenib was rapidly converted to M-2 metabolite at MD and HD: Tmax of sorafenib was 4.5 hr at MD, the M-2 Tmax was 1 hr; Tmax was 5.6 hr at HD, the M-2 Tmax was 1-hr.
- Metabolic conversion to M-5 was also rapid: Tmax of 1 hr at MD and Tmax of 2 hr at HD.
- M3 appears to be the major metabolite in the species tested, as was also depicted in the in vitro studies conducted with liver microsomes of different species.
- Each M1, M-2, M3, M4, and M-5etabolites contributed < 6% of the sorafenib AUC and Cmax





NOAEL

The sponsor defined the following NOAELs:
Maternal toxicity: 1.37 mg/kg/day of sorafenib tosylate (1.0 mg/kg of the free base)
Developmental toxicity: 0.27 mg/kg/day of sorafenib tosylate (0.2 mg/kg of the free base)

The reviewer concurs.

Study title: Bay54-9085 (tosylate salt of BAY 43-9006)
Developmental toxicity in rabbits after oral administration- **Segment 2**

Key study findings: fetal/ intrauterine findings:
↓mean litter size/ ↑post-implantation loss
necrotic placentas
fetal malformarions/ skeletal deviations

Study Report: PH-33531
Study no.: T4063177

Volume #, and page #: Module 4; M4.2.3.5.2.2
Conducting laboratory and location: Department of Experimental Toxicology
BHC-PH-PD-T
42096 Wuppertal, Germany
Date of study initiation: July 2, 2003
GLP compliance: Yes; in compliance with the OECD Principles of GLP
QA reports: yes (X) no ( )
Drug, lot #, and % purity: BAY 54-9085 (tosylate salt of BAY 43-9006)
Batch# 011121; pure

Vehicle: 0.5% aqueous methylhydroxyethyl cellulose)

Methods

Doses of BAY 54-9085: 0, 0.41, 1.37, and 4.11 mg/kg/day
Daily from D6 to D20 of gestation

Dose Groups	# of animals	Doses of the tosylate salt		Doses of the free base*		Concentration (mg/mL)
		mg/kg	mg/m2	mg/kg	mg/m^2	
Vehicle control	20	0	0	0	0	0
LD	20	0.41	4.92	0.3	3.6	0.082
MD	20	1.37	16.44	1.0	12.0	0.274
HD	20	4.11	49.32	3.0	36.0	0.822

Vehicle control: 0.5% aqueous suspension
* Conversion factor for tosylate salt and free base: 1.37
LD: low-dose; MD: mid-dose; HD: high-dose

Species/strain: rabbits/ Himalayan CHBB:HM (bred by

Number/sex/group: 20 ♀s/dose groups
No ♂ was treated
Route, formulation, volume: P.O. gavage/ suspension/ 5mL/kg
Satellite groups used for toxicokinetics: 3 ♀s/dose group
Study design:
Mating: one ♂ was mated with one ♀
Dosing schedule: daily dosing from Days 6 to 20 of gestation

C-section: on Day 29 of gestation (main groups)

Parameters and endpoints evaluated: Maternal and fetal/intrauterine

Assessments

Clinical examinations (♀s):	Day 0 to 29 (main groups) Day 0 to 21 (satellite groups) twice daily (once daily on the weekends)
Body weight (♀s):	Day and daily from Day 6 to 29 (main groups) daily from Day 6 to 21 (satellite groups) Corrected body weight gain was calculated by subtracting the weight of the uterus on Day 29 from the body weight gain over the period from Day 0 to Day 29.
Food consumption (♀s):	On gestation days 0-3, 3-6, 6-9, 9-12, 12-15, 15-17, 15-18, 18-20, 20-21, 21-24, 24-27, and 27-29 (main groups) On gestation days 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, 18-20, and 20-21 (satellite groups)
Toxicokinetics (♀s):	From all females of the low-dose, mid-dose, and high-dose groups on Days 6 and 20, at 1, 2, 4, 7, and 24 hours after administration
Necropsy (♀s):	At the time of cesarean section on Day 29 (main groups) or on Day 21 (satellite groups)
Cesarean section:	On gestation Day 29 (main groups) or 21 (satellite groups). The following parameters were assessed on Day 29 in the main groups (except for ♀s that showed no implantation sites, uterine anomaly, or which aborted):

- Number of corpora lutea
- Number of implantations (in females without visible implantation sites: after staining of the uterus with a solution of 10% of ammonium sulfide),
- Uterine weight, individual weight and appearance of the placenta,
- Number of early resorption (only implantation site visible), late resorption (fetal or placental remnant visible), and dead fetuses.
- Number, sex, and weight of live fetuses.
- External malformations
- Findings in abdominal, pelvic, and thoracic organs as well as findings in the brain and in the skeletal system

During cesarean section on day 21 the following data were ascertained in the satellite groups:

- existence of implantations.

Results

Maternal

Mortality: None

Clinical signs:

- An increased incidence of females with transient cold ears at HD. This finding, with lower incidence, appears to be commonly observed in rabbits of this strain.
- Abortion: 1 ♀ at high-dose on Day 23 (# 6013).
  This female had slightly ↓food intake (between Days 6-9) and transient body weight loss (↓98g Days 7-8, ↓51g Days 15-17, ↓78g Days 21-22)

Body weight: There was a dose-dependent ↓in BW gain immediately after the dosing period (Day 6-20): ↓4%, ↓22%, ↓60% at LD, MD, and HD, respectively.

Dose (mg/kg b.w./day)	0	0.41	1.37	4.11
absolute body weight gain (g) days 6 - 20 p.c.				
	114.8	109.8	89.0	45.0
absolute body weight gain (g) days 0 - 29 p.c.				
	351.8	379.2	362.4	307.8
corrected body weight gain (g) days 0 - 29 p.c.				
	-73.1	-21.4	-20.2	-15.0

Food consumption: the mean feed intake of the females with viable fetuses at cesarean section was decreased in the HD group between days 12-15 (↓20%).

Dose (mg/kg b.w./day)	0	0.41	1.37	4.11
mean feed intakes (g/animal/day)				
days 0 - 3 p.c.	99.0	101.8	95.0	96.7
days 3 - 6 p.c.	98.4	106.5	102.5	108.5
days 6 - 9 p.c.	109.1	102.3	106.9	107.6
days 9 - 12 p.c.	103.0	92.6	95.6	92.0
days 12 - 15 p.c.	89.7	92.4	83.7	70.1
days 15 - 18 p.c.	89.8	94.3	84.1	82.7
days 18 - 20 p.c.	89.1	94.3	92.9	93.8
days 20 - 21 p.c.	90.7	93.7	98.0	102.7
days 21 - 24 p.c.	93.4	95.0	96.5	100.6
days 24 - 27 p.c.	93.3	87.7	96.4	102.1
days 27 - 29 p.c.	92.1	92.0	97.5	99.6

Gross pathology: no treatment related gross pathological findings were observed

General reproduction data/ Fertility rate

The number of females mated and the fertility rate (percentage of mated females with implantations) were not affected.

- There was a slight reduction in the number of corpora lutea at MD (↓11%) and HD (↓11%).
- There was an increase in the pre-implantation loss at MD (↑75%) and HD (↑75%). However, since the test article was administered on gestation Day 6 (the presumed implantation time), this effect does not appear to be drug related.

Dose (mg/kg b.w./day)	0	0.41	1.37	4.11
mated females	20	20	20	20
mated females evaluated	20	20	19+	20
females with implantations	19	18	18	20
in % of those mated	95.0	90.0	94.7	100.0
mean values (without females displaying abortions) per female with implantation sites				
corpora lutea	9.0	8.7	8.0	8.0
preimplantation loss	0.4	0.4	0.7	0.7
implantations	8.6	8.3	7.3	7.3

+ one female with an uterine anomaly was excluded

Fetal/ intrauterine assessments

Gestation rate

The gestation rate (percentage of females with viable fetuses on Day 29 of those with implantation sites) in the main groups was decreased in the high-dose group. This was due to the abortion in 1 ♀ and total resorptions in 3 ♀s.

Intrauterine parameters

Dose (mg/kg b.w./day)	0	0.41	1.37	4.11
number of females (without females displaying abortions)				
with implantations (a)	19	18	18	19
with viable fetuses (b)	19	18	18	16
mean values per female				
placental weight in g [b]	4.23	4.31	4.53	4.69
number of fetuses [b]	8.2	7.7	6.9	5.6**
postimplantation loss [a, b]	0.4, 0.4	0.7, 0.7	0.4, 0.4	2.5**, 1.7*
males in % [b]	55.7	43.8	50.5	40.4
fetal weight in g [b]	36.92	37.14	38.90	38.33

Statistically significant difference to control * = $p < 0.05$
Statistically significant difference to control ** = $p < 0.01$

Placenta weight and appearance

Partly necrotic placentas, statistically significant at high-dose (see Table next page for the incidence).

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SUMMARY OF PLACENTAL OBSERVATIONS

		0 MG/KG	0.41 MG/KG	1.37 MG/KG	4.11 MG/KG
Litters Evaluated	N	19	18	18	16
Fetuses Evaluated	N	156	138	125	90
Live	N	156	138	125	90
Dead	N	0	0	0	0
PLACENTA					
SEVERAL BLACK VESICLES					
Fetal Incidence	N	0 f	1	0	0
	%	0.0	0.7	0.0	0.0
	p-value	0.441			
Litter Incidence	N	0 f	1	0	0
	%	0.0	5.6	0.0	0.0
	p-value	0.394			
Affected Fetuses/Litter	MEAN%	0.00 k	0.51	0.00	0.00
	S.D.	0.000	2.143	0.000	0.000
	p-value	0.400			
PLACENTA PARTLY NECROTIC					
Fetal Incidence	N	1 f	2	4	19**
	%	0.6	1.4	3.2	21.1
	p-value	0.000	1.000	0.526	0.000
Litter Incidence	N	1 f	2	4	8*
	%	5.3	11.1	22.2	50.0
	p-value	0.007	1.000	0.539	0.015
Affected Fetuses/Litter	MEAN%	0.66 k	1.81	5.94	27.21*
	S.D.	2.868	5.410	13.838	39.118
	p-value	0.004	1.000	1.000	0.044
TOTAL PLACENTAL OBSERVATIONS					
Fetal Incidence	N	1 f	3	4	19**
	%	0.6	2.2	3.2	21.1
	p-value	0.000	1.000	0.526	0.000
Litter Incidence	N	1 f	3	4	8*
	%	5.3	16.7	22.2	50.0
	p-value	0.015	1.000	0.539	0.015

Statistical key: f=Fisher's Exact k=Kruskal-Wallis * = p<0.05 ** = p<0.01

Post-implantation loss, number of fetuses

Three females (no. 6025, 6037, 6044) of the high-dose group showed total resorptions. Additionally, the post-implantation loss in females with viable fetuses was statistically significantly increased at HD, mainly caused by late resorptions. As a result, the mean number of fetuses was decreased statistically significantly at high-dose.

Sex of Fetuses

Fetal sex distribution was shifted to 40.4 % males at high-dose. This finding was not statistically significant. Fetal sex distribution was unaffected at low-dose and mid-dose.

Fetal weight

Not affected

Fetal malformation

The incidence of some malformations commonly seen in the strain of rabbits used was increased at HD. Those included increased incidence of malformations of kidneys, vertebrae, and ribs at HD.

Some fetuses revealed more than one malformation.

Malformation	Dose (mg/kg b.w./day)			
	0	0.41	1.37	4.11
malposition of forelimb(s) with/without narrowed thorax	1	2 (2)	3 (2)	2 (2)
malformation of the heart with/without malformations of the major vessels	1	2 (2)	1	1
kidney and ureter are missing				5* (3)
right kidney displaced, lying at right testis, dilation of renal pelvis, right ureter shortened without connection to urinary bladder				2(2)
one supernumerary sternal segment above 1st sternal segment (fused with it), cervical ribs at 7th cervical vertebra bilateral, 7th cervical vertebral arches look like thoracic vertebral arches bilateral	1			
one supernumerary presacral vertebra with anomalies of the sacral vertebrae				2 (2)
supernumerary presacral vertebra			1	3 (1)
1st sacral vertebral arch left looks like a lumbar vertebral arch, pelvis left shift to caudal				2 (2)
fusion of caudal vertebral body(ies)				1
malformations of thoracic and lumbar vertebrae and ribs				2 (2)
fusion of ribs in the cartilaginous part	1			
bifurcation of ribs in the osseous part	1			
all bones reddish-black discolored		1		
number of fetuses per group	156	138	125	90
number of fetuses with malformations	3	5	5	16**
malformed fetuses per group (%)	1.9	3.6	4.0	17.8
number of litters per group	19	18	18	16
number of litters with malformations	2	4	4	7
malformed litters per group (%)	10.5	22.2	22.2	43.8

() number of litters affected
Statistically significant difference to control * = $p < 0.05$
Statistically significant difference to control ** = $p < 0.01$

Fetal External and Visceral Deviations

The only external or visceral deviations consisted in one fetus of the mid-dose group with an abdominal cavity, filled with reddish fluid, and one fetus each of the low-dose and high-dose with white discoloration of the liver. A treatment related effect was not assumed for these, because the values were within the range of historical control data, and findings were not dose dependent.

Deviation	Dose (mg/kg b.w./day)			
	0	0.41	1.37	4.11
abdominal cavity filled with reddish fluid			1	
whitish discoloration of the liver		1		1
number of fetuses per group	156	138	125	90
number of fetuses with deviations	0	1	1	1
fetuses with deviat. per group (%)	0.0	0.7	0.8	1.1
number of litters per group	19	18	18	16
number of litters with deviations	0	1	1	1
litters with deviat. per group (%)	0.0	5.6	5.6	6.3

Fetal Skeletal findings

Statistically significant ↑incidence of fused sternebrae and retarded ossification of the cervical vertebral bodies (1st, 3rd- 5th) and frontal bones (bilateral) occurred at the high-dose. These values were above the range of the historical data.

Thus, skeletal development (retardations/ variations) revealed an increased incidence of fused sternebrae and retarded ossification of cervical vertebral bodies and frontal bones at the 4.11 mg/kg level.

Toxicokinetics:

The metabolites M-1, M-2 M-3 and M-5 contributed less than 10 % to the exposure, compared to BAY 43-9006 and were regarded as minor metabolites. The contribution of M-4 to the overall exposure ranged between 10 to 20 % on Day 6. and 25 to 40 % on Day 20. Thus, M-4 was considered a major metabolite in this species.

After repeated dosing of BAY 54-9085 a slight increase in $AUC_{(0-24)}$ and C_{max} of BAY 43-9006 by a factor of approximately 1.3 was observed for all dose groups comparing Day 20 p.c. to Day 6 p.c. For BAY 43-9007 (M-4) a marked increase in exposure after repeated dosing was observed with regard to both C_{max} and $AUC_{(0-24)}$. Accumulation factors in terms of $AUC_{(0-24)}$ were 2.87 to 3.45-fold for all doses administered. C_{max} values increased by a factor of about 2.47 to 3.24 when Day 20 to Day 6 values were compared.

PK parameters on gestation Day 20

		BAY 43-9006						M-4 (BAY 43-9007)					
Dose: BAY 54-9085 [mg/kg]		0.410		1.37		4.11		0.410		1.37		4.11	
Dose: BAY 43-9006 [mg/kg]		0.300		1.00		3.00		0.300		1.00		3.00	
		Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.	Mean	S.D.
AUC(0-24)	[µg·h/L]	976	1.23	3413	1.20	12321	1.12	319	1.16	1041	1.21	5240	1.29
$AUC(0-24)_{norm}$	[kg·h/L]	3.25	1.23	3.41	1.20	4.11	1.12	1.10	1.16	1.07	1.21	1.80	1.29
C_{max}	[µg/L]	58.8	1.38	207	1.24	722	1.06	14.8	1.16	50.4	1.14	258	1.37
$C_{max,norm}$	[kg/L]	0.196	1.38	0.207	1.24	0.241	1.06	0.0511	1.16	0.0520	1.14	0.0886	1.37
$C(24)/C_{max}$	[%]	55.4	1.29	51.1	1.20	47.5	1.16	99.6	1.01	94.3	1.06	80.2	1.08
t_{max}	[h]	3.17	1.49	2.52	1.49	5.81	1.38	15.9	2.04	7.27	2.61	3.17	1.49
MR-1	[%]							25.2		24.4		35.7	
MR-2	[%]							32.7		30.5		42.5	
R_{A1}	[%]	133		127		139		267		247		324	
R_{A3}	[%]	130		132		145		318		287		345	

t4063177_summary_FTH.xls \ AUC_43-9006_M-4 \ FTH \ 05.03.04

n.c. = not calculated
MR-1:metabolic ratio in terms of C_{max} in [%]: C_{max} (M-X) / C_{max} (BAY 43-9006)
MR-2:metabolic ratio in terms of AUC(0-24) in [%]: AUC(0-24)_(M-X) / AUC(0-24)_(BAY 43-9006)
$R_{A1} = C_{max,Day\ 20\ p.c.}/C_{max,Day\ 6\ p.c.}$
$R_{A3} = AUC(0-24)_{Day\ 20\ p.c.}$ / $AUC(0-24)_{Day\ 6\ p.c.}$

PK parameters of BAY 43-9006 and its metabolites; **LD, gestation D20**

		BAY 43-9006	M-1	M-2	M-3	M-4	M-5
AUC(0-24)	[µg·h/L]	976	n.c.	n.c.	11.6	319	n.c.
$AUC(0-24)_{norm}$	[kg·h/L]	3.25	n.c.	n.c.	0.0373	1.10	n.c.
C_{max}	[µg/L]	58.8	n.c.	n.c.	0.763	14.8	n.c.
$C_{max,norm}$	[kg/L]	0.196	n.c.	n.c.	0.00246	0.0511	n.c.
$C(24)/C_{max}$	[%]	55.4	n.c.	n.c.	n.c.	99.6	n.c.
t_{max}	[h]	3.17	n.c.	n.c.	2.00	15.9	n.c.
MR-1	[%]		n.c.	n.c.	1.30	25.2	n.c.
MR-2	[%]		n.c.	n.c.	1.19	32.7	n.c.
R_{A1}	[%]	133	n.c.	n.c.	n.c.	267	n.c.
R_{A3}	[%]	130	n.c.	n.c.	n.c.	318	n.c.

t4063177_summary.xls \ AUCsummary_d20 \ Müh \ 01.10.04

n.c. = not calculated
MR-1: metabolic ratio in terms of C_{max} in [%]: C_{max} (M-X) / C_{max} (BAY 43-9006)
MR-2: metabolic ratio in terms of AUC(0-24) in [%]: AUC(0-24)_(M-X) / AUC(0-24)_(BAY 43-9006)
R_{A1} = C_{max}_Day 20 / C_{max}_Day 6 in [%]
R_{A3} = AUC_Day 20 / AUC_Day 6 in [%]

PK parameters of BAY 43-9006 and its metabolites; **MD, gestation D20**

		BAY 43-9006	M-1	M-2	M-3	M-4	M-5
AUC(0-24)	[µg·h/L]	3413	n.c.	40.1	63.1	1041	38.7
$AUC(0-24)_{norm}$	[kg·h/L]	3.41	n.c.	0.0390	0.0612	1.07	0.0387
C_{max}	[µg/L]	207	n.c.	3.75	3.83	50.4	3.37
$C_{max,norm}$	[kg/L]	0.207	n.c.	0.00364	0.00372	0.0520	0.00337
$C(24)/C_{max}$	[%]	51.1	n.c.	35.4	56.1	94.3	46.2
t_{max}	[h]	2.52	n.c.	2.00	2.00	7.27	2.00
MR-1	[%]		n.c.	1.82	1.85	24.4	1.63
MR-2	[%]		n.c.	1.18	1.85	30.5	1.13
R_{A1}	[%]	127	n.c.	n.c.	165	247	n.c.
R_{A3}	[%]	132	n.c.	n.c.	161	287	n.c.

t4063177_summary.xls \ AUCsummary_d20 \ Müh \ 01.10.04

n.c. = not calculated
MR-1: metabolic ratio in terms of C_{max} in [%]: C_{max} (M-X) / C_{max} (BAY 43-9006)
MR-2: metabolic ratio in terms of AUC(0-24) in [%]: AUC(0-24)_(M-X) / AUC(0-24)_(BAY 43-9006)
R_{A1} = C_{max}_Day 20 / C_{max}_Day 6 in [%]
R_{A3} = AUC_Day 20 / AUC_Day 6 in [%]

PK parameters of BAY 43-9006 and its metabolites; **HD, gestation D20**

		BAY 43-9006	M-1	M-2	M-3	M-4	M-5
AUC(0-24)	[µg·h/L]	12321	n.c.	178	258	5240	164
$AUC(0-24)_{norm}$	[kg·h/L]	4.11	n.c.	0.0575	0.0831	1.80	0.0545
C_{max}	[µg/L]	722	n.c.	10.6	15.9	258	8.50
$C_{max,norm}$	[kg/L]	0.241	n.c.	0.00344	0.00513	0.0886	0.00283
$C(24)/C_{max}$	[%]	47.5	n.c.	52.5	42.6	80.2	72.6
t_{max}	[h]	5.81	n.c.	3.17	3.04	3.17	3.83
MR-1	[%]		n.c.	1.47	2.20	35.7	1.18
MR-2	[%]		n.c.	1.45	2.09	42.5	1.33
R_{A1}	[%]	139	n.c.	96.5	124	324	98.0
R_{A3}	[%]	145	n.c.	166	175	345	292

t4063177_summary.xls \ AUCsummary_d20 \ Müh \ 04.10.04

n.c. = not calculated
MR-1: metabolic ratio in terms of C_{max} in [%]: C_{max} (M-X) / C_{max} (BAY 43-9006)
MR-2: metabolic ratio in terms of AUC(0-24) in [%]: AUC(0-24)_(M-X) / AUC(0-24)_(BAY 43-9006)
R_{A1} = C_{max}_Day 20 / C_{max}_Day 6 in [%]
R_{A3} = AUC_Day 20 / AUC_Day 6 in [%]

Summary and Conclusions

Maternal

- An increased incidence of females with transient cold ears at HD. This finding, with lower incidence, is commonly observed in rabbits of this strain.
- Abortion: 1 ♀ at high-dose on Day 23 (animal # 6013). This female had slightly ↓food intake between Days 6-9) and transient body weight loss (↓98g Days 7-8, ↓51g Days 15-17, ↓78g Days 21-22).
- There was a dose-dependent ↓in BW gain immediately after the dosing period (Day 6-20): ↓4%, ↓22%, ↓60% at LD, MD, and HD, respectively
- The mean feed intake was decreased at MD and HD and was most evident at HD between days 12-15 (↓20%).
- There was a slight reduction in the number of corpora lutea at MD (↓11%) and HD (↓11%).

- The gestation rate (percentage of females with viable fetuses on Day 29 vs those with implantation sites) was decreased at HD (↓16% compared to control), due to the abortion in 1 ♀ and total resorptions in 3 ♀s.
- No treatment related gross pathological findings were found.

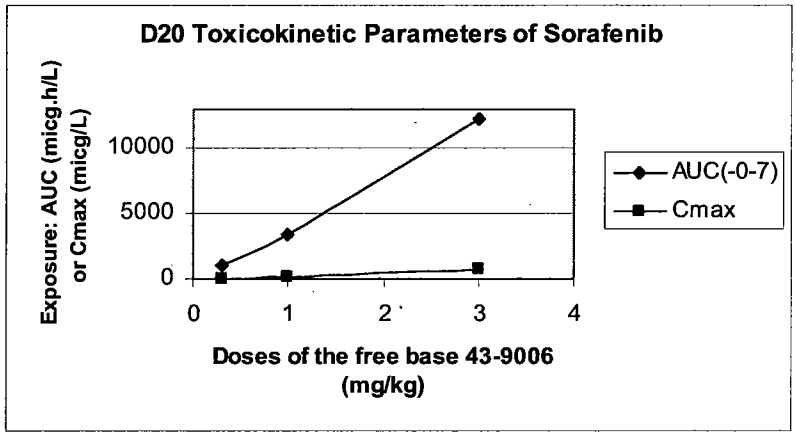
Intrauterine/ Fetal

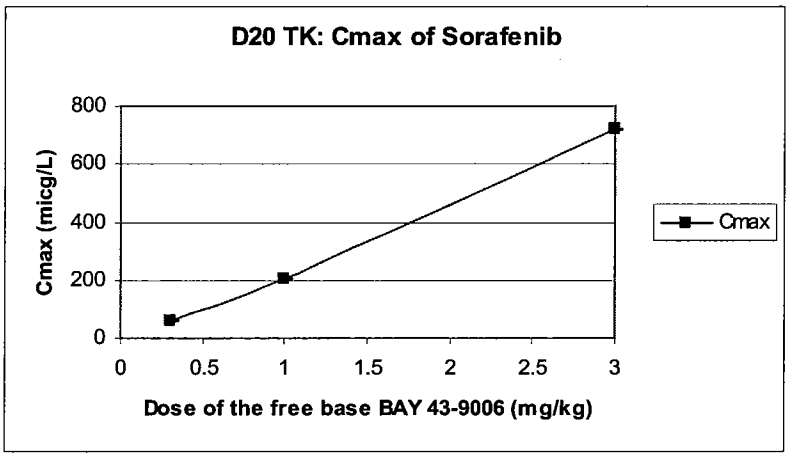
- There was an increase in the pre-implantation loss at MD (↑75%) and HD (↑75%). Since dosing started from the presumed implantation, this finding does not appear to be drug-related.
- The mean litter size decreased dose-dependently at all doses of the test article and was statistically significantly ↓ at the HD (↓6%, ↓16%, and ↓32%, at LD, MD, and HD, respectively).
- Statistically significant ↑ in post-implantation loss at HD, due to one abortion and 3 total resorptions.
- The gestation rate (percentage of females with viable fetuses on Day 29 vs those with implantation sites) was decreased at HD (↓16% compared to control), due to the abortion in 1 ♀ and total resorptions in 3 ♀s.
- The incidence of partly necrotic placentas increased and was statistically significant at HD. The placental weights in all dose groups were unaffected by treatment with BAY 54-9085.
- The fetal weights in all dose groups were comparable to the control value.
- Increased incidence of fetal malformations (mainly malformations of kidneys, vertebrae, and ribs) at HD. These are malformations common in the rabbit strain used.
- No clear treatment related effect was seen on external and visceral deviations (other than malformations mentioned above).
- Skeletal development (retardations/variations) revealed an increased incidence of fused sternabrae and retarded ossification of cervical vertebral bodies and frontal bones at HD.

Toxicokinetics:

- M-4 appears to be the major metabolite in this species.
- AUC and C_{max} of the metabolites M-1, M-2, M-3, and M-5 were each less than 10% of the sorafenib exposure. The concentration of M-4 relative to sorafenib ranged between 10 to 20% on Day 6 p.c. and 25 to 40% on Day 20.
- Sorafenib: Dose proportional increase in exposure for LD and MD. The increase in $AUC_{(0-24)}$ and C_{max} was slightly more than dose-proportional, when the dose was increased from MD to HD.
- M-4 metabolite: a dose proportional increase in $AUC_{(0-24)}$ and C_{max} at LD and MD. Further increase in dose to HD resulted in a moderately more than dose-proportional increase in $AUC_{(0-24)}$ and C_{max}.
- Peak plasma concentrations for BAY 43-9006 and M-4 on Day 20 were reached in a time interval between 2 and 7 hrs for BAY 43-9006 and between 2 and 24 h for M-4, for the 3 doses. This suggests that conversion of sorafenib to M-4 was rather slow.

- A slight increase in $AUC_{(0-24)}$ and C_{max} of BAY 43-9006 by 30% was observed for all dose groups comparing Day 20 to Day 6.
- Approximately 3-fold increase in the M-4 blood levels, when comparing D20 to D6.





NOAEL:

The sponsor determined the NOAEL to be < 0.41 mg/kg/day of sorafenib tosylate for maternal toxicity, because an increased incidence of females with cold ears was observed at LD, which might be possibly related to the treatment.

Reviewer's comment: since the cold ears may not necessarily consist of an adverse event and as mentioned by the sponsor, it is commonly seen in this strain of rabbit used, we suggest the NOAEL of 0.41 mg/kg for sorafenib tosylate (0.3 mg/kg or 3.6 mg/m^2 of the free base).

The sponsor determined the NOAEL to be 1.37 mg/kg/day of sorafenib tosylate for intrauterine/fetal toxicity. However, since the mean litter size decreased dose-dependently, starting from the LD and the number of litters with malformations increased starting from the LD, the NOAEL for intrauterine/fetal development appears to be < 0.41 mg/kg/day (<0.3 mg/kg or 3.6 mg/m^2 of the free base).

OVERALL SUMMARY OF REPRODUCTIVE TOXICITY STUDIES

Developmental toxicity studies were conducted in rats and rabbits.

In general, except for the fetal and placental weights, the extent of maternal and fetal toxicities was higher in rabbits, which appears to be due to the higher doses employed in rabbits on the basis of the body surface area:

Rats:	0	1.2	6.0	15.6	(mg/m2/day of the free base)
Rabbits:	0	3.6	12.0	36.0	(mg/m2/day of the free base)

Maternal:

- ↓BW gain immediately after the end of the dosing period (rats and rabbits)
- ↓Number of corpora lutea at 12 and 36 mg/m2/day of the free base (rabbits)
- ↓Number of females with implantations (rats and rabbits), due to total resorptions (rats and rabbits), and abortion (rabbits).

Fetal:

- Total resorptions with higher incidence in rabbits (rats and rabbits)
- ↓Mean litter size (rats and rabbits)
- ↑Incidence of necrotic placentas (rats and rabbit)
- ↓Weights of placentas (rats)
- ↓Fetal weight (rats)
- Fetal sex distribution shifted to 40% ♂s (rabbits)- not statistically significant
- ↑Incidence of fetal malformations (rats and rabbits), e.g. seen in the ribs, verterbrae, kidndeys, aorta, pelvis
- Skeletal deviations, mainly retarded ossifications of various bones (rats and rabbits)

NOAEL:

- For both rats and rabbits the fetal toxicities occurred at doses that were not toxic to the dams/does (maternal NOAEL > fetal NOAEL).

Toxicokinetics:

- TK parameters were not conclusive in rats due to the limited sampling (n=4). The terminal phase was not observed during the 7-hr collection time.
- M-3 was the major metabolite in rats (<10% of sorafenib exposure) and M-4 the major metabolite in rabbits (>10% of sorafenib exposure).
- Repeated dosing resulted in a slight increase in the sorafenib exposure in rabbits on D20 (↑30% as compared to D6).
- Repeated dosing resulted in a moderate increase in the exposure of M-4 metabolite on D20 (↑approx. 3-fold compared to D6).
- Developmental toxicities observed in rats and rabbits appear to be related to sorafenib and not to the metabolites, since toxicities were similar in the 2 species, however, major metabolites are different.

In rats, embryo-fetal toxicities were manifested starting at the LD (1.2 mg/m^2 of the free base). Based on the limited blood sampling the steady state AUC(0-7) at LD in rats was 889 µg.h/L. In rabbits embryo-fetal toxicities were observed at the LD (3.6 mg/m2 of the free base, corresponding to the AUC(0-24) of 976 µg.h/L). Based on the summary table provided by the sponsor, the 400 mg/kg dose of sorafenib, when given bid will result in AUC(0-24) of 128600 µg.h/L.

Based on the ratios of exposures in the animal species vs human, the embryo-fetal toxicities appear to occur at sub-therapeutic doses of sorafenib in human (see Tables below).

The lowest dose (mg/m2/day of the free base) and *AUC (µg.h/L) causing embryo-fetal toxicities				**Ratio of *AUCs**	
Rat (Day 17 data)		**Rabbit (Day 20 data)**		**Human/ rat**	**Human/ rabbit**
Dose: 1.2 mg/m^2	AUC: 889 µg.h/L	Dose: 3.6 mg/m^2	AUC: 976 µg.h/L	145 (rat/human: 0.007)	132 (rabbit/human: 0.008)

* AUC(0-7) for rats, AUC(0-24) for rabbits, and AUC(0-24) for humans are used.
Note: limited sampling in rats, with the last timepoint at Hr 7.

Plasma exposure (geometric mean) at steady state of sorafenib and metabolites following continuous daily oral administration in cancer patients

Dose [mg/day]	**Dose** [a] [mg/m^2/day]	**Plasma Exposure** [b]		**Sorafenib** (n=27)	**M-2** (n=8)	**M-4** (n=8)	**M-5** (n=3)
2 x 400	500	$AUC_{0\text{-}12\,h}$	[mg · h/L]	64.3	7.7	3.2	3.3
		$AUC_{0\text{-}24\,h}$	[mg · h/L]	128.6	15.4	6.4	6.6
		C_{max}	[mg/L]	7.7	0.9	0.4	0.5

a: based on 60 kg person, b: $AUC_{0\text{-}24h}$ extrapolated
Reference: Studies 10164, 100277, 100283 and 100342 (Modules 5.3.5.2.3, 5.3.5.2.5, 5.3.5.2.1, 5.3.5.2.7)

Specific fertility and early embryonic development or pre/post-natal development studies including maternal function have not been conducted. Repeat-dose toxicity studies and pharmcokinetic investigations on secretion of sorafenib into breast milk indicate a potential to adversely affect fertility and post-natal development. Histopathology assessments in the repeat-dose toxicity studies demonstrated a potential of sorafenib to impair reproductive function by affecting male and female reproductive organs. Various effects including retardation and degradation were observed in reproductive organs of male (tubular degeneration in the testes, epididymidal oligospermia) and female animals (retarded ovaries, central necrosis of corpora lutea). Some of these effects were seen at doses of the free base as low as 5 mg/kg/day (30 mg/m2/day x 28) in the 4-week rat toxicology, however, the clear test article-induced effect was observed at 25 mg/kg of BAY43-9006 (rat 4 week toxicology; 150 mg/m2/day x 28). In dogs, toxicities to the reproductive organs were seen in the 1-year toxicity study, as low as 30 mg/kg/day or 600 mg/m2/day of sorafenib as the free base.

2.6.6.7 Local tolerance

- BAY 43-9006 was not an irritant to the skin. There were no systemic intolerance reactions.
- BAY 43-9006 was not irritating to eyes. There were no relevant systemic intolerance reactions.
- BAY 43-9006 had neither an irritating nor a sensitizing potential in mice after dermal application.

2.6.6.8 Special toxicology studies

None

2.6.6.9 Tables and Figures

See Tables and Figures within the review of each study or under "Tabulated Summary" sections.

2.6.7 TOXICOLOGY TABULATED SUMMARY

See below selected Tables of summary, excerpted from the submission.

Report Title: Acute Toxicity in the Mouse and Rat after Oral Administration (Study T9069220 and T5069226)
Report No.: PH-29961
Test Article: Sorafenib Tosylate (BAY 43-9006 Tosylate, BAY 54-9085) GLP Compliance: Yes
Location in CTD: M4.2.3.1.1

Single-Dose Toxicity **Test Article:** **BAY 54-9085** **Report No.: PH-29961**

Species / Strain	Method of Administration (Vehicle/ Formulation) [b]	Doses [a] [mg/kg]	Gender and No. per Group	Observed Maximum Non-Lethal Dose [a] [mg/kg]	Approximate Lethal Dose [a] [mg/kg]	Noteworthy Findings	Study Number
Rat / Wistar	Oral (suspension)	Up to 1460	5M, 5F	1460	> 1460	No clinical signs of toxicity	T9069220
Mouse / NMRI	Oral (suspension)	Up to 1460	5M, 5F	1460	> 1460	No clinical signs of toxicity	T5069226

a doses as free base (sorafenib, BAY 43-9006)
b vehicle: Pluronic® F68 / propylene glycol / polyethylene glycol 400 (15:42.5:42.5 w:w:w)

Report Title: A Single Oral Dose Pharmacokinetic/Tolerance Study of BAY 54-9085 in the Beagle Dog;
A Single Oral Dose Pharmacokinetic/Tolerance Study of BAY 54-9085 (Powder and Solution) in the Beagle Dog
Report No.: RMI-00069, RMI-00070
Test Article: Sorafenib Tosylate (BAY 43-9006 Tosylate, BAY 54-9085) GLP Compliance: No
Location in CTD: M4.2.3.1.2, M4.2.3.1.3

Single-Dose Toxicity **Test Article: BAY 54-9085** **Report No.: RMI-00069, RMI-00070**

Species / Strain	Method of Administration (Vehicle/ Formulation) [b]	Doses [a] [mg/kg]	Gender and No. per Group	Observed Maximum Non-Lethal Dose [a] [mg/kg]	Approximate Lethal Dose [a] [mg/kg]	Noteworthy Findings	Study Number
Dog / Beagle	Oral (solution)	30, 60, 120	2M, 2F	120	> 120	No clinical signs of significant toxicity, vomiting,	88999
Dog / Beagle	Oral (solution)	30, 60	2M, 2F	120	> 120	No clinical signs of significant toxicity, vomiting	89105
	(powder)	1000	2M, 2F	1000	> 1000		

a doses as free base (sorafenib, BAY 43-9006)
b vehicle: Pluronic® F68 / propylene glycol / polyethylene glycol 400 (15:42.5:42.5 w:w:w)

Report Title:	**BAY 54-9085 (Tosylate Salt of BAY 43-9006). Study on Subchronic Toxicity in CD-1 Mice. Administration by Gavage for 3-Months**
Report No.:	PH-32953
Test Article:	Sorafenib Tosylate (BAY 43-9006 Tosylate, BAY 54-9085)
Location in CTD:	M4.2.3.7.7.1
Species/Strain:	Mice, CD-1(ICR)BR
Initial age:	About 7 weeks
Duration of Dosing:	males: 91 days, females: 92 days
Duration of Postdose	-
Method of Administration:	Oral, Gavage
Vehicle/Formulation:	Pluronic®F68 / Propylene Glycol / Polyethylene Glycol 400 (15:42.5:42.5 w:w:w)
Special Features:	-
NOAEL:	Not established
Study No.:	T5071881
GLP Compliance:	Yes
Date of 1st Dose:	July 2002

Repeat-Dose Toxicity - 3-Months Toxicity Study in Mice				Test Article: Sorafenib Tosylate			Report No.: PH-32953	
Daily Dose - Sorafenib [mg/kg]	**0 Control**	**30**	**100**	**300**	**0 Control**	**30**	**100**	**300**
Gender	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**
Number of Animals	10	10	10	10	10	10	10	10
Toxicokinetics (males and females pooled)								
Scheduled number of animals / sex / /timepoint		3	3	3				
AUC [mg*h/L] Week 13 (Sorafenib)		58.7	147	254				
Cmax [mg/L] Week 13 (Sorafenib)		12.0	25.2	30.7				
Noteworthy Findings								
Died/Sacrificed Moribund	0	1	0	3	0	0	1	5
Body Weight (%[a])	36.0 g	-1.4	-5	-13.3	31.1 g	-7.7	-8.7	21.9
Food Intake (%[b])	5.83 g/d	+1.7	+2.2	+0.3	5.76 g/d	+0.3	+4.7	-22.9
Food Intake (%[a])	168.07 g/kg/d	+5.4	+9.6	+13.6	199.63 g/kg/d	+6.1	+10.1	-11.4
Water Intake (%[b])	6.02 g/d	+3.3	-5.6	-12.0	6.64 g/d	-5.4	-11.1	-23.8
Water Intake (%[a])	173.87 g/kg/d	+6.6	+0.8	-1.1	230.07 g/kg/d	+0.1	-7.2	-11.8

Repeat-Dose Toxicity - 3-Months Toxicity Study in Mice				Test Article: Sorafenib Tosylate			Report No.: PH-32953	
Daily Dose - Sorafenib [mg/kg]	**0 Control**	**30**	**100**	**300**	**0 Control**	**30**	**100**	**300**
Gender	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**
Hematology (Day 79/80)								
ERY [10E12/l]	8.84	9.04	8.70	7.23**	9.23	8.60	8.05**	7.28**
HB [g/l]	142	155	155	131	145	144	138	129**
HCT [l/l]	0.470	0.506	0.514	0.452	0.499	0.489	0.473	0.442**
MCV [fl]	53.4	56.0*	59.0**	63.1**	54.1	57.0*	58.9**	61.2**
MCH [pg]	16.1	17.2**	17.8**	18.2**	15.8	16.7**	17.2**	17.7**
MCHC [g/l ERY]	301	307	301	288*	291	294	292	290
RETI [‰]	30	26	27	80	32	29	26	65
LYM [%]	76.0	78.0	74.1	67.6*	74.8	83.3	75.4	71.8
SEGM [%]	20.2	16.4	19.9	26.8*	20.8	13.3	19.2	25.2
BAND [%]	0.2	0.0	0.2	1.0*	0.2	0.1	0.5	0.1
Serum Chemistry (Day 86/87)								
AST [U/l]	53.3	60.1	73.0**	85.5**	60.6	79.5*	95.0**	153.4
ALT [U/l]	41.6	59.0**	63.1**	78.0*	45.0	54.5	55.1	98.2
Organ Weights[a, b] (%)								
Spleen weights, abs.	122 mg	-18	-29	-26	132 mg	-18	-17	-51**
Spleen weights, rel.	338 mg/100g	-17	-25	-16	431 mg/100g	-14	-11	-40**
Liver weights, abs.	2033 mg	-9	-12*	-23**	1602 mg	-10	-8	-21**
Liver weights, rel.	5648 mg/100g	-7	-8	-12*	5267 mg/100g	-6	-4	-1
Testes weights, abs.	245 mg	+5	-12	-29**				
Testes weights, rel.	683 mg/100g	+5	-8	-17*				

Repeat-Dose Toxicity - 3-Months Toxicity Study in Mice				Test Article: Sorafenib Tosylate			Report No.: PH-32953	
Daily Dose - Sorafenib [mg/kg]	**0 Control**	**30**	**100**	**300**	**0 Control**	**30**	**100**	**300**
Gender	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**
Histopathology								
Number of animals examined (except otherwise indicated)	10	10	10	10	10	10	10	10
Stomach								
squamous hyperplasia	0	1	5	10	0	2	8	9
Average grading		1.0	1.6	3.0		2.0	1.8	2.4
Teeth / upper jaw:								
fracture/inflammation [n]	0	0	0	2	0	0	0	3
altered dentin composition [n]	0	0	5	10	0	0	8	9
focal necrosis/pulp [n]	0	0	0	4	1	0	2	5
edema/hyperemia/PLP [n]	0	0	1	8	0	0	0	6
flattening/ameloblast [n]	1	0	0	4	0	0	2	6
granulocytic infiltration. [n]	0	0	0	3	0	0	0	0
degeneration/odontoblast [n]	0	0	0	0	0	0	0	2
osteomyelitis/alv. [n]	0	0	0	0	0	0	0	1
Teeth / lower jaw:								
fracture/inflammation [n]	0	0	0	1	0	0	1	1
altered dentin composition[n]	0	0	3	8	0	0	6	8
focal necrosis/pulp [n]	0	0	0	2	0	0	1	4
granulocytic infiltration [n]	0	0	2	2	0	0	3	2
degeneration/odontoblast [n]	0	0	0	0	0	0	0	1
degeneration/ameloblast [n]	0	0	0	2	0	0	0	4
Adrenal glands								
cortical eosinophilia [n]	0	0	0	5	0	0	2	5
Spleen								
Increased Pigment [n]	0	0	5	6	1	0	3	4
Extramed. Hematopoiesis [n]	10	9	10	9	10	10	9	5
Uterus								
atrophy [n]					0	0	1	10

Repeat-Dose Toxicity - 3-Months Toxicity Study in Mice				Test Article: Sorafenib Tosylate				Report No.: PH-32953
Daily Dose - Sorafenib [mg/kg]	**0 Control**	**30**	**100**	**300**	**0 Control**	**30**	**100**	**300**
Gender	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**
Ovaries								
no/few corpora lutea glands [n]					1	1	6	9
Testes								
tubular atrophy [n]	0	0	1	7				
Epididymides								
atrophy/adjacent. adipose. tissue [n]	0	0	0	3				
Liver								
atrophy/reduced glycogen [n]	0	2	1	8	2	2	5	7
Femur/bone marrow								
hypocellularity/BM [n]	0	2	6	5	0	0	4	6
Sternum/bone marrow								
hypocellularity/BM [n]	0	1	4	5	0	0	1	6
atrophy/adjacent adipose. tissue [n]	0	1	0	4	0	0	0	3
Spinal cord								
atrophy/adjacent adipose. tissue [n]	0	0/1		4	0		0/1	3
Sciatic nerve					0			0
atrophy/adjacent adipose. tissue [n]	0	0/1		1				
Heart								
atrophy/adipose tissue [n]	0	0/1		0	0		0/1	3
Aorta								
atrophy/adipose tissue [n]	0	0/1		1	0		1/1	5
Kidneys								
atrophy/adipose tissue [n]	0	1	0	1	0	0	1	5
Ureters								
atrophy/adipose tissue.	0			0	0		0/1	4
Adrenal glands [n]								
atrophy/adjacent tissue [n]	0	1	0	4	0	0	0	4

Repeat-Dose Toxicity - 3-Months Toxicity Study in Mice				Test Article: Sorafenib Tosylate			Report No.: PH-32953	
Daily Dose - Sorafenib [mg/kg]	**0 Control**	**30**	**100**	**300**	**0 Control**	**30**	**100**	**300**
Gender	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**
Thymus								
atrophy/ adjacent tissue [n]	0	0	0	3	0	0	1	4
Skin								
reduced adipose/sub-cutaneous tissue [n]	1	1/2		3	0		1/1	5
Body cavities								
atrophy/adipose tissue [n].	0	1	0	2	0	0	2	5
Pancreas								
atrophy/acinar cell [n].	0	0/1		1	0	0	0	4
Additional Examinations	-	-	-	-	-	-	-	-

- No noteworthy finding + Mild ++ Moderate +++ Marked n = number of animals affected

Statistical analysis: * $p \leq 0.05$, ** $p \leq 0.01$

Analysis of variance followed by a Dunnett test	body weights, organ weights
Kruskal-Wallis test with a Steel-Test	food and water intake
Analysis of variance followed by Dunnett test	ERY, HB, HCT, MCH, MCHC, MCV
Kruskal-Wallis test followed by adjusted U-test	RETI, LYM, SEGM, BAND,
Adjusted Welsh test	ALT, AST

a At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)

b Both absolute and relative weights differed from controls in the direction indicated. Number indicate percent difference for the absolute organ weights

Repeat-Dose Toxicity – 7-Day Pharmacokinetics / Tolerance Study in Rats **Test Article: Sorafenib Tosylate** **Report No.: RMI-00067**

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Test Compound	Duration of Dosing	Doses Sorafenib [mg/kg]	Gender and No. per Group	NOAEL[a] [mg/kg]	Noteworthy Findings	Study Number
Rat / Sprague -Dawley	oral by gavage	BAY 54-9005	7 days	0, 25, 125, 250	8 F	not established	No deaths, generally well tolerated. No statistically significant hematological or serum chemistry findings, no treatment related macroscopic findings. Clinical chemistry and histopathology: Dose-dependent bone marrow degeneration and a decrease in red cell counts and hematocrit in treated animals from all treatment groups. Increased incidence of hepatocellular karyomegaly and apoptosis and elevated liver enzymes in animals from all treatment groups. Increased incidence of renal tubular dilatation and protein/hyaline casts in animals from all treatment groups. Increased incidence of splenic coagulative / congestive degeneration in animals from all treatment groups.	— QEAW-19

a No Observed Adverse Effect Level

Report Title:	**Subacute Oral Toxicity Study in Female Wistar Rats (2-Weeks Administration by Gavage) Special Study to Investigate Potential Effects on Pancreas**
Report No.:	PH-33039
Test Article:	Sorafenib Tosylate (BAY 43-9006 Tosylate, BAY 54-9085)
Location in CTD	M4.2.3.7.3.3
Special Features:	Study parameter focused on pancreas histopathology (necropsy on Day 16) and serial analysis of serum levels of alpha amylase and lipase (prior to treatment, then 5 hours and 24 hours on days 2/3, 4/5, 8/9, 15/16). Vehicle: Pluronic®F68 / Propylene Glycol / Polyethylene Glycol 400 (15:42.5:42.5 w:w:w)

Repeat-Dose Toxicity – 2-week rat toxicity study (pancreas) **Test Article:** **Sorafenib Tosylate** **Report No.:** **PH-33039**

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Test Compound	Duration of Dosing	Doses Sorafenib [mg/kg]	Gender and No. per Group	NOAEL[a] [mg/kg]	Noteworthy Findings	Study Number
Wistar — WI) BR	oral by gavage	BAY 54-9085	15 days	0, 5, 25	6 F	not established	Serial serum analysis of alpha amylase and lipase: Increase in alpha amylase activity after few administrations and generally a decrease thereafter. At day 15/16, values slightly higher than pre-treatment. Increase more pronounced at blood sampling 24 hourspost administration than after 5 hours. Only at this time point a dose dependency could be shown. Lipase activity not changed by the treatment. Histopathology (pancreas): At 25 mg/kg, degenerative changes. Atrophy, vacuolation of the acinar cells and an interstitial edema. At 5 mg/kg, some of these changes were noted with lower incidence and degree indicating a borderline dose for morphological changes.	T8073734

a No Observed Adverse Effect Level

Repeat-Dose Toxicity – 7-Day Pharmacokinetics / Tolerance Study in Dogs **Test Article:** **Sorafenib Tosylate** **Report No.:** **RMI-00068**

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Test Compound	Duration of Dosing	Doses Sorafenib [mg/kg]	Gender and No. per Group	NOAEL[a] [mg/kg]	Noteworthy Findings	Study Number
Dog / Beagle	oral by gavage	BAY 54-9005	7 days	30, 60, 60 bid	2 F, 2 M	not established	No mortality. At 30 and 60 mg/kg, soft and/or liquid feces. At 60 mg/kg bid, soft and/or liquid feces, slight to moderate tremors from Day 7 until study termination. Emesis, decreased activity, reduced appetite and increased vocalization in some 60 mg/kg bid animals. Decreases in body weight (2 males and 1 female at 60 mg/kg bid, 1 female at 60 mg/kg. Increased white blood cell counts at 30 mg/kg. Platelet counts increased in all dose groups. Increased myeloid:erythroid ratio in bone marrow. At 60 mg/kg bid, slight increase in AST, ALT, ALP. Histopathology: Degenerative lesions in GI tract, liver, lymph node, thymus, bone marrow and testis	[redacted] 89149

a No Observed Adverse Effect Level

Report Title:	**Subacute toxicity study in Beagle dogs (4 week gavage study). Study No. T0069663. (Special study to investigate bone and teeth effects in aged female animals)**
Report No.:	PH-31108
Test Article:	Sorafenib Tosylate (BAY 43-9006 Tosylate, BAY 54-9085)
Location in CTD:	M4.2.3.7.3.1

Species/Strain:	Beagle dogs	Study No.:	T0069663
Initial age:	61-102 weeks	GLP Compliance:	yes
Duration of Dosing:	4 weeks	Date of 1st Dose:	May 29, 2000
Duration of Postdose:	-		
Method of Administration:	oral (gavage) Once daily		
Vehicle/Formulation:	3 ml/kg; mixture of 10% 2-Pyrrolidone, 45% Propylene glycol, 45% Cremophor RH 40		
Special Features:	Only one dose applied, equivalent to high-dose in pivotal 4-week dog study		
NOAEL:	Not established		

Repeat Dose Toxicity – 4-week Toxicity Study in Aged Dogs **Test Article: Sorafenib Tosylate** **Report No.: PH-31108**

Daily Dose Sorafenib [mg/kg]	**0**	**60**
	Control	
Gender	**F**	**F**
Number of Animals	8	8
Toxicokinetics		
Number of animals	8	8
AUC [mg·h/L], week 4 Sorafenib	-	67
Cmax [mg/L], week 4 Sorafenib	-	7
Noteworthy Findings		
Died/Sacrificed Moribund	-	2
Body Weight	-	-
Food Intake	-	-
Water Intake	-	-
Histopathology		
Number examined	8	8
Bone:		
Any change [n]	-	-
Teeth		
Any change [n]	-	-
Liver:		
Centrilobular fatty change [n]	2	7
Thyroid gland		
Decrease of colloidal vacuolation [n]	8	7
Average Grading	1.9	1.0
Spleen		
Perifollicular necrosis [n]	0	5
Iron deposition [n]	8	8
Average Grading	2.5	3.0
Increased perifollicular granulocytic infiltration [n]	0	6

Repeat Dose Toxicity – 4-week Toxicity Study in Aged Dogs **Test Article: Sorafenib Tosylate** **Report No.: PH-31108**

Daily Dose Sorafenib [mg/kg]	**0**	**60**
	Control	
Gender	**F**	**F**
Thymus		
Atrophy [n]	2	5
Average Grading	1.5	2.2
Tonsils		
Necrosis/lymphoid follicles [n]	0	7
Ileum		
Atrophy of Peyer's patches [n]	0	6
Mandibular. Lymph Nodes		
Follicular atrophy of germinal center [n]	0	3
Necrosis/Germinal center [n]	0	1
Mesenteric. Lymph Nodes		
Follicular atrophy of germinal center [n]	1	3
Necrosis/Germinal center [n]	0	2
Sternum, Marrow		
Fat Marrow [n]	1	6
Reduced cellularity [n]	0	5

- No noteworthy finding + Mild ++ Moderate +++ Marked n = number of animals affected

Rat 4-Week Toxicity Study (+ 4-Week Recovery) **Test Article: Sorafenib Tosylate** **Report No.: PH-30261**

Daily Dose Sorafenib [mg/kg]	**0 Con-trol**	**1**	**5**	**25**	**125**	**0 Con-trol**	**1**	**5**	**25**	**125**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Number of Animals	10	10	10	10	10	10	10	10	10	10
Recovery groups	10				10	10				10
Toxicokinetics										
Number of animals per timepoint	3	3	3	3	3	3	3	3	3	3
AUC (mg·h/L) week 3 or 4 Sorafenib	0	10.3	60.9	283	205	0	13.0	73.2	261	220
Cmax (mg/L) week 3 or 4 Sorafenib	0	0.727	3.72	15.2	12.4	0	0.854	4.72	13.5	10.2
Noteworthy Findings (main groups)										
Died/Sacrificed Moribund	0	0	0	1	3	0	0	0	9	1
Body Weight (g) /week 4	297	282	277	134**	157**	180	177	179	118nc	136**
Food Intake(g/d) /week 4	19.9	19.3	17.7*	6.6**	7.8**	12.9	12.8	12.0	5.2**	6.9**
Water Intake (g/d) /week 4	32.8	32.7	27.5*	14.6**	14.0**	22.1	21.7	21.3	9.7**	12.8**
Hematology /week 4										
LEUCO (10E9/l)	10.94	11.99	12.22	7.22**	7.54**	8.59	8.13	8.20	7.27	7.22
ERY (10E12/l)	7.73	7.93	8.04	5.12**	6.14**	7.99	8.07	8.19	2.37**	5.33**
HB (g/l)	147	151	158	107**	124**	146	151	153	52**	110**
HCT (l/l)	0.457	0.463	0.484	0.31**	0.36**	0.441	0.453	0.451	0.16**	0.33**
MCV (fl)	59.1	58.5	60.2	61.2	59.3	55.2	56.1	55.2	67.1**	62.5**
MCH (pg)	19.1	19.0	19.6	21.0**	20.3**	18.2	18.7	18.7	21.9**	20.8**
MCHC (g/l ERY)	323	325	326	343**	333	330	334	339*	327	333
RETI (o/oo)	26	26	18**	49	33	14	18	12	151**	98**
THRO (10E9/l)	1247	1135	1007*	494**	563**	1105	1114	936	479**	804**
HQUICK (sec)	29.6	29.4	28.8	27.3*	27.6	29.3	29.1	28.1	27.1	27.0*

Rat 4-Week Toxicity Study (+ 4-Week Recovery)					Test Article: Sorafenib Tosylate			Report No.: PH-30261		
Daily Dose Sorafenib [mg/kg]	**0 Con-trol**	**1**	**5**	**25**	**125**	**0 Con-trol**	**1**	**5**	**25**	**125**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Serum Chemistry /week 4										
AST (u/l)	38.0	42.6**	60.9**	146.6**	99.7**	40.7	43.0	63.9**	192.3**	114.5**
ALT (u/l)	39.6	46.8**	74.6**	129.6**	95.3**	33.6	39.2*	76.6**	162.1**	90.4**
ALP (u/l)	524	579	690**	175**	218**	331	326	459**	186**	158**
LDH (u/l)	67	58	71	664	418	62	73	67	584	332*
GLDH (mmol/l)	2.2	1.8	1.6	36.5	11.2	3.7	2.4	2.8	19.3*	9.9*
GLUC (mmol/1)	6.28	5.54**	5.51**	5.46**	5.29**	5.29	4.99	5.11	5.43	4.99
Chol (mmol/l)	1.96	1.84	2.07	4.44**	4.43**	1.50	1.60	2.21**	3.07	3.36**
Trigl (mmol/l)	2.17	1.52	1.08**	1.49	1.28*	0.99	0.79	0.51	2.23**	1.46
Crea (mcmol/l)	41	51	53	38	38	49	39	40	33*	37
Urea (mmol/l)	6.92	6.88	7.44	8.78**	7.39	6.87	6.25	7.03	13.59**	8.35
Bili-t (mcmol/l)	1.2	1.2	1.6**	5.1**	4.7**	1.0	1.1	1.5**	3.4**	3.9**
Prot (g/l)	64.4	64.6	63.7	46.3**	52.7**	62.2	63.7	63.5	42.8**	50.0**
Urinalysis /week 4										
Vol (ml)	11.3	18.2	11.3	3.8**	3.7**	16.0	14.4	10.6**	3.3**	3.7**
Density (g/l)	1020	1010**	1021	1038**	1033**	1008	1010	1016**	1035**	1028**
Prot (g/l)	1.02	0.56**	1.18	9.57*	6.04**	0.15	0.15	0.22	4.23**	1.47**
Crea (mmol/l)	5.24	2.83**	5.53	5.89	5.52	2.21	2.54	3.93*	4.74*	5.66**
NAG (u/l)	19.55	9.47**	23.38	68.12**	104.94*	7.20	8.48	16.60**	47.14**	32.34**
GGT (u/l)	890	492**	867	365**	319**	135	143	203	198	219
AAP (u/l)	59.6	31.5**	57	24.6**	18.6**	7.3	7.9	11.5	11.0	12.6
LDH (u/l)	12	6**	11	234**	68**	4	5	8*	146**	71**
Organ Weights absolute (mg)										
Brain	1864	1882	1884	1614**	1763	1743	1631**	1767	1678nc	1637**
Adrenals	52	50	50	101**	90**	60	58	61	153nc	143**
Heart	1159	1055	964*	709**	732**	808	796	718*	755nc	735
Liver	13223	12276	10837*	5231**	6163**	7528	7473	6556**	5030nc	5751**
Spleen	624	640	639	252**	377**	470	474	444	289nc	376**
Thymus	580	554	496	94**	114**	435	369	315**	85nc	143**
Kidneys	2097	1885	1929	1693**	1532**	1228	1216	1279	1260nc	1409*
Testes	3150	2976	2984	1201**	1809**					

Rat 4-Week Toxicity Study (+ 4-Week Recovery)					Test Article:	Sorafenib Tosylate		Report No.:		PH-30261
Daily Dose Sorafenib [mg/kg]	**0 Control**	**1**	**5**	**25**	**125**	**0 Control**	**1**	**5**	**25**	**125**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Epididymides	1023	916	902	346**	535**					
Histopathology										
Number examined	10	10	10	10	10	10	10	10	10	10
Adrenal glands										
Peliosis [n]	0	0	0	10	8	0	0	0	10	10
Necrosis [n]	0	0	0	6	8	0	0	0	7	6
Increased intracytoplasm. Vacuolation [n]	4	2	2	10	8	0	0	0	10	10
Average Grading	1.0	1.5	1.0	3.6	3.4	0	0	0	4.1	4.0
Thyroid gland										
Flattened follicular epithelium [n]	0	0	0	8	9	0	0	0	5	10
Liver										
Bile duct proliferation [n]	0	0	0	7	8	0	0	0	7	9
Glycogen decrease [n]	0	0	0	10	10	0	0	0	10	8
Diffuse Kupffer cell activation [n]	0	0	0	7	4	0	0	0	10	7
Pigment. Kupffer cells	0	0	0	6	10	0	0	0	9	9
Nuclear activation of hepatocytes [n]	0	0	0	8	5	0	0	0	8	7
Single cell necroses [n]	0	0	0	4	2	0	0	0	7	2
(Multi-)Focal necroses [n]	0	0	0	2	1	0	0	0	6	1
Pancreas										
Atrophy [n]	0	0	0	9	10	0	0	0	5	7
Interstitial edema [n]	0	0	0	9	9	0	0	0	7	8
Degeneration/ regeneration [n]	0	0	0	9	10	0	0	0	10	10
Tongue										
Vacuolation serous parts of sublingual glands [n]	1	0	2	9	10	1	0	7	7	10
Intramuscular edema [n]	1	0	1	8	8	0	0	4	10	7

Rat 4-Week Toxicity Study (+ 4-Week Recovery) **Test Article: Sorafenib Tosylate** **Report No.: PH-30261**

Daily Dose Sorafenib [mg/kg]	0 Control	1	5	25	125	0 Control	1	5	25	125
Gender	M	M	M	M	M	F	F	F	F	F
Decrease of interstitial mast cells [n]	0	0	10	10	10	0	0	10	10	10
Average Grading	0	0	2.7	5.0	5.0	0	0	3.5	5.0	5.0
Salivary glands										
Acinar atrophy [n]	0	0	1	1	0	0	0	0	1	0
Average Grading	0	0	1.0	3.0	0	0	0	0	3.0	0
Ductular atrophy [n]	0	0	0	9	7	3	0	2	3	9
Average Grading	0	0	0	2.4	1.9	1.0	0	1.0	2.7	2.0
Single cell necroses [n]	0	0	0	2	1	0	0	0	1	1
Stomach										
Hyperkeratosis [n]	0	0	1	7	10	0	0	2	2	8
Erosion limiting ridge [n]	0	0	0	0	3	0	0	0	0	0
Cellular hypertrophy pyloric region [n]	0	0	0	7	8	0	0	0	3	10
Duodenum										
Hypertrophy mucosa [n]	0	0	5	9	7	0	0	1	5	9
Hypertrophy muscularis [n]	0	0	0	4	7	0	0	0	1	7
Degeneration /regeneration [n]	0	0	0	4	5	0	0	0	4	8
Inflammatory Infiltration [n]	0	0	0	6	8	0	0	0	4	9
Bile duct necrosis	0	0	0	0	4	0	0	0	2	1
Kidneys										
Basophilic tubules [n]	6	5	6	9	10	2	2	5	4	10
Average Grading	1.0	1.0	1.3	2.4	2.0	1.0	1.0	1.4	2.5	2.3
Dilation of cortical tubules [n]	1	0	4	9	5	1	0	2	5	7
Average Grading	1.0	0	1.3	2.2	1.6	2.0	0	1.0	1.8	2.6
Hyaline casts	1	0	1	8	7	0	0	2	5	7
Average Grading	1.0	0	1.0	2.4	1.7	0	0	1.0	1.6	1.7
Pigment deposition [n]	0	0	0	8	5	0	0	0	8	10

Rat 4-Week Toxicity Study (+ 4-Week Recovery)				Test Article:	Sorafenib Tosylate			Report No.:	PH-30261	
Daily Dose Sorafenib [mg/kg]	**0 Control**	**1**	**5**	**25**	**125**	**0 Control**	**1**	**5**	**25**	**125**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Glomerulopathy [n]	0	0	2	5	7	0	0	0	2	10
Intraglomerular Macrophages [n]	0	0	0	2	5	0	0	0	1	1
Bone (Femur)										
Thickening of the growth plate [n]	0	0	6	10	10	0	0	6	10	10
Hypocellularity adjacent to the growth plate [n]	0	0	0	10	10	0	0	1	10	10
Bone marrow										
Hypocellularity/sternum [n]	0	0	0	10	10	0	0	0	10	8
Fat marrow/femur [n]	10	10	10	10	6	10	10	10	4	9
Average Grading	1.5	1.6	2.4	3.1	3.5	1.5	1.4	2.5	3.5	2.8
Fat marrow/sternum [n]	2	5	9	8	6	4	5	10	4	9
Average Grading	1.0	1.0	1.7	3.3	2.8	1.0	1.0	1.5	2.0	1.8
Incr. Blood content/femur [n]	0	0	1	8	7	0	0	0	10	9
Incr. Blood content/sternum [n]	0	0	0	2	3	0	0	0	5	2
Teeth										
Dentin degeneration [n]	0	0	10	10	10	0	0	10	10	10
Average Grading	0	0	1.9	2.9	2.9	0	0	3.6	2.4	2.9
Ameloblast degeneration [n]	0	0	8	10	10	0	0	8	10	10
Single cell necroses/Strat. intermedium [n]	1	3	9	10	8	0	2	9	10	10
Angiectasis/Periodontal Ligament [n]	0	0	0	3	6	0	0	8	1	5
Hyperostosis jawbone [n]	0	0	0	0	3	0	0	0	0	0
Spleen										
Decreased hematopoiesis [n]	0	0	0	8	4	0	0	0	9	0
Average Grading	0	0	0	2.1	2.8	0	0	0	3.3	0

Rat 4-Week Toxicity Study (+ 4-Week Recovery)				Test Article:	Sorafenib Tosylate			Report No.:	PH-30261	
Daily Dose Sorafenib [mg/kg]	**0 Con-trol**	**1**	**5**	**25**	**125**	**0 Con-trol**	**1**	**5**	**25**	**125**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Necrosis white pulp [n]	0	0	0	1	3	0	0	0	8	0
Necrosis red pulp [n]	0	0	0	1	2	0	0	0	6	0
Lymphoid depletion [n]	0	0	0	1	1	0	0	0	8	1
Iron deposition [n]	1	1	9	10	10	10	8	10	10	10
Average Grading	1.0	1.0	1.0	2.8	2.4	1.1	1.3	1.5	3.2	2.8
Thymus										
Atrophy [n]	0	0	0	10	6	1	0	0	8	8
Single cell necroses [n]	0	0	0	7	6	0	0	0	5	5
Mesenteric Lymph nodes										
Atrophy [n]	0	0	0	6	6	0	0	0	3	6
Follicular necroses [n]	0	0	4	2	4	5	0	7	4	5
Average Grading	0	0	1.0	1.5	1.5	1.0	0	1.3	1.8	1.8
Mandibular Lymph nodes										
Atrophy [n]	0	0	0	2	0	0	0	0	0	0
Follicular necroses [n]	0	0	0	2	1	0	0	3	3	1
Testes										
Tubular degeneration [n]	0	1	1	10	10					
Average Grading	0	5.0	5.0	3.8	2.3					
Epididymides										
Oligospermia [n]	0	0	0	1	5					
Single cell necroses [n]	0	0	0	1	0					
Prostate										
Retardation [n]	0	0	0	10	10					
Seminal vesicles										
Retardation [n]	0	0	0	10	10					
Ovaries										
Retardation [n]						0	0	0	10	10
Corpora lutea [n]						10	10	10	10	10
Average Grading						2.0	1.8	3.2	1.4	1.2
Central necroses corpora lutea [n]						0	1	9	6	6

Rat 4-Week Toxicity Study (+ 4-Week Recovery) **Test Article: Sorafenib Tosylate** **Report No.: PH-30261**

Daily Dose Sorafenib [mg/kg]	0 Control	1	5	25	125	0 Control	1	5	25	125
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Average Grading						0	1.0	2.0	1.7	1.3
Uterus										
retardation [n]						0	0	0	10	10
Vagina										
Exfoliating cells [n]						3	2	3	9	8
Average Grading						1.3	1.5	1.0	2.1	2.9
Intraluminal mucous [n]						3	0	0	4	8
Average Grading						1.7	0	0	2.5	2.6
Keratinization [n]						2	2	4	1	0
Harderian glands										
porphyrin deposition [n]	2	0	1	9	10	1	0	3	10	10
Lacrimal glands										
Atrophy [n]	0	0	0	9	10	0	0	0	10	10
Single cell necroses [n]	0	0	0	3	4	1	0	0	3	1
Heart										
Degeneration /inflammation [n]	0	0	0	3	1	0	0	0	0	1
Skin										
Hyperkeratosis [n]	0	0	0	10	9	2	0	1	10	9
Reduction of submucosal fat tissue [n]	0	0	0	7	5	0	0	0	5	4

Rat 4-Week Toxicity Study (+ 4-Week Recovery)					Test Article: Sorafenib Tosylate				Report No.:	PH-30261
Daily Dose Sorafenib [mg/kg]	**0 Control**	**1**	**5**	**25**	**125**	**0 Control**	**1**	**5**	**25**	**125**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Postdose Evaluation [a]										
Histopathology										
Number Examined	10				10	10				10
Adrenal glands										
Peliosis [n]	0				0	0				1
Necrosis [n]	0				0	0				1
Incr. Intracytopl.Vacuol. [n]	6				8	0				8
Average Grading	1.5				1.6	0				1.9
Pigment-loaded Macrophages [n]	0				6	0				2
Fibrotic tissue [n]	0				6	0				3
Thyroid gland										
Flattened follicular epithelium [n]	0				5	0				0
Liver										
Bile duct proliferation [n]	0				7	0				9
Glycogen decrease [n]	0				8	0				2
Diffuse Kupffer cell activation [n]	0				6	0				6
Pigment. Kupffer cells	0				1	0				1
Nuclear activation of hepatocytes [n]	0				7	0				1
Single cell necroses [n]	0				5	0				1
(Multi-)Focal necroses [n]	0				1	0				0
Periportal fibrosis [n]	0				2	0				1
Pancreas										
Atrophy [n]	0				1	0				2
Interstitial edema [n]	0				3	0				1
Degeneration /regeneration [n]	0				8	1				3

Rat 4-Week Toxicity Study (+ 4-Week Recovery)					Test Article: Sorafenib Tosylate				Report No.: PH-30261	
Daily Dose Sorafenib [mg/kg]	**0 Control**	**1**	**5**	**25**	**125**	**0 Control**	**1**	**5**	**25**	**125**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Tongue										
Vacuolation serous parts of sublingual glands [n]	0				3	0	1			1
Average Grading	0				1.0	0	1.0			2.0
Intramuscular edema [n]	0				0	0				1
Decrease of interstitial mast cells [n]	0				10	0				8
Salivary glands										
Ductular atrophy [n]	0				8	0				9
Acinar atrophy [n]	0				1	0				0
Single cell necroses [n]	0				1	0				0
Stomach										
Hyperkeratosis [n]	0				1	0				1
Edema [n]	0				1	0				0
Duodenum										
Degener./Regener. [n]	0				1	0				1
Chronic Inflammation [n]	0				1	0				0
Hypertrophy of muscular layer [n]	0				0	0				1
Kidneys										
Basophilic tubules [n]	10				8	3				8
Average Grading	1.2				2.4	1.0				2.1
Dilation of cortical tubules [n]	2				6	0				5
Average Grading	1.0				1.8	0				1.6
Hyaline casts	0				5	0				2
Pigment deposition [n]	0				6	0				9
Glomerulopathy [n]	0				5	0				4
Intraglomerular Macrophages [n]	0				3	0				3

Rat 4-Week Toxicity Study (+ 4-Week Recovery)					Test Article: Sorafenib Tosylate				Report No.:	PH-30261
Daily Dose Sorafenib [mg/kg]	**0 Control**	**1**	**5**	**25**	**125**	**0 Control**	**1**	**5**	**25**	**125**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Bone (Femur)										
Thickening of the growth plate [n]	0				4	0				4
Bone formation/Growth plate [n]	0				9	0				6
Malformation [n]	0				2	0				0
Epiphysiolysis [n]	0				1	0				1
Hypocellularity adjacent to the growth plate [n]	0				4	0				1
Bone marrow										
Hypocellularity/sternum [n]	0				2	0				1
Fat marrow/femur [n]	10				8	9				8
Average Grading	2.2				2.8	1.3				1.8
Fat marrow/sternum [n]	7				8	6				4
Average Grading	1.3				2.1	1.2				1.8
Incr. Blood content/femur [n]	0				4	0				1
Incr. Blood content/sternum [n]	0				3	0				0
Incr. Granulocytes/femur [n]	0				7	3				7
Incr. Granulocytes /sternum [n]	0				5	0				1
Teeth										
Dentin degeneration [n]	0				10	0				9
Ameloblast degeneration [n]	0				10	0				9
Hyperplasia/Periodontal Ligament [n]	0				10	0				10
Hyperostosis jawbone [n]	0				8	0				6
Osteolysis/ Osteodystrophy [n]	0				6	0				3

Rat 4-Week Toxicity Study (+ 4-Week Recovery)				Test Article:	Sorafenib Tosylate		Report No.:	PH-30261	
Daily Dose Sorafenib [mg/kg]	**0 Control**	**1**	**5**	**25**	**125**	**0 Control**	**1**	**5**	**25**	**125**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Angiectasis/Periodontal Ligament [n]	0				0	0				7
Spleen										
Decreased hemopoiesis [n]	0				7	0				2
Atrophy red pulp [n]	0				0	0				1
Lymphoid depletion [n]	0				2	0				1
Iron deposition [n]	10				10	10				10
Average Grading	1.7				2.0	2.5				1.3
Thymus										
Atrophy [n]	0				5	0				1
Single cell necroses [n]	0				3	0				1
Mesenteric Lymph nodes										
Atrophy [n]	0				5	0				1
Mandibular Lymph nodes										
Atrophy [n]	0				1	0				1
Single cell necroses [n]	0				1	0				0
Testes										
Tubular degeneration [n]	5				8					
Average Grading	1.0				1.8					
Epididymides										
Oligospermia [n]	0				4					
Single cell necroses [n]	0				2					
Prostate										
Retardation [n]	0				8					
Seminal vesicles										
Retardation [n]	0				8					
Ovaries										
Central necroses corpora lutea [n]						0				1
Uterus										
retardation [n]						0				1

Rat 4-Week Toxicity Study (+ 4-Week Recovery) **Test Article: Sorafenib Tosylate** **Report No.: PH-30261**

Daily Dose Sorafenib [mg/kg]	0 Control	1	5	25	125	0 Control	1	5	25	125
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Vagina										
Exfoliating cells [n]						0				2
Average Grading						0				1.0
Harderian glands										
Porphyrin deposition [n]	2				2	0				5
Lacrimal glands										
Atrophy [n]	0				8	0				0
Skin										
Hyperkeratosis [n]	1				7	4				7
Reduction of submucosal fat tissue [n]	0				5	0				1

- No noteworthy finding + Mild ++ Moderate +++ Marked
Statistical analysis: * $p < 0.05$, ** $p < 0.01$

a Noteworthy findings during the treatment period, which were not listed under 'Postdose Evaluation' were fully reversible
nc not calculated (low number of animals)

Rat 6-Month Toxicity Study				Test Article:	Sorafenib Tosylate		Report No.:	PH-32607
Daily Dose Sorafenib [mg/kg]	**0**	**0.1**	**1**	**2.5**	**0**	**0.1**	**1**	**2.5**
	Control				**Control**			
Gender	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**
Number of Animals	20	20	20	20	20	20	20	20
Toxicokinetics								
Number of animals/timepoint		6	6	6				
AUC_{0-24h} [mg*h/L] Week 26 Sorafenib		0.7	10	28		1.1	13	42
Cmax [mg/L], Week 26 Sorafenib		0.049	0.72	1.9		0.074	0.74	2.2
Noteworthy Findings								
Died/Sacrificed Moribund	1	1	1	2	1	1	2	2
Body Weight (%[a])	480 g	- 0.25	-8	-9	263 g	+1	-2	-1
Food Intake (%[a])	21.3 g/d	0	-1	-5	15.7 g/d	+1	+1	-6
Water Intake (%[a])	24.8 g/d	-4	-4	-7	21.2 g/d	+6	-3	-13
Ophthalmoscopy	-	-	-	-	-	-	-	-
Hematology								
HB [g/L] Day 90	153	157	159*	170**	156	159	163*	166**
HB [g/L] Day 181	150	154	157**	169**	151	155	156	161**
HCT [L/L] Day 90	0.466	0.476	0.484*	0.510**	0.467	0.471	0.483	0.490*
HCT [L/L] Day 181	0.477	0.482	0.492*	0.519**	0.458	0.470	0.471	0.486*
MCV [fl] Day 90	52.0	52.5	52.3	54.7**	52.0	52.5	52.3	54.7**
MCH [pg] Day 90	17.1	17.3	17.2	18.3**	17.9	18.2	18.5	18.6*
MCH [pg] Day 181	16.4	16.7	16.6	17.8**	18.0	18.0	18.5	18.7*
MCHC [g/L ERY] Day 181	315	320	320	325**	329	331	331	332
THRO [10^9/L] Day 90	1386	1226*	1253	1117**	1307	1182	1238	1140*
THRO [10^9/L] Day 181	1403	1260	1303	1171**	1223	1192	1097	998**
EOS [10^9/L] Day 90	0.19	0.14	0.12*	0.13*	0.09	0.09	0.09	0.08
BASO [10^9/L] Day 181	0.03	0.03	0.03	0.03	0.01	0.02*	0.02	0.02*

Rat 6-Month Toxicity Study				Test Article: Sorafenib Tosylate				Report No.: PH-32607
Daily Dose Sorafenib [mg/kg]	**0 Control**	**0.1**	**1**	**2.5**	**0 Control**	**0.1**	**1**	**2.5**
Gender	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**
Serum Chemistry								
AST [U/L] Day 90	69.4	69.5	72.3	78.0	68.4	70.5	78.5	86.8**
ALT [U/L] Day 90	30.4	32.4	35.0	42.7**	26.6	25.7	29.9	39.8**
ALT [U/L] Day 181	30.8	32.5	35.8	46.3**	45.4	35.0	41.1	47.8
Glucose [mmol/L] Day 90	4.32	4.06	3.82**	3.51**	3.96	4.19	3.95	3.93
Glucose [mmol/L] Day 181	4.66	4.21	4.12*	4.08*	4.27	4.25	4.18	3.95
Bili-t [µmol/L] Day 90	1.6	1.6	1.7	1.7	1.5	1.5	1.6	1.8*
Bili-t [µmol/L] Day 181	1.3	1.2	1.4	1.3	1.6	2.1*	2.0*	2.0*
Urinalysis								
pH Day 90	8.0	7.6	7.7	7.3*	7.1	7.1	6.9	6.9
Organ Weights [a, b] (%)								
Heart weights, abs.	1467 mg	-7	-12**	-8	937 mg	+2	-3	-6
Liver weights, abs.	16445 mg	-2	-10	-7	9049 mg	+2	-11*	-8
Thymus weights, abs.	328 mg	-5	-18	-32**	270 mg	-6	-10	-17
Kidney weights, abs.	2722 mg	-0	-12 **	-5	1657 mg	+0	-7	-2
Histopathology								
Number examined	20	20	20	20	20	20	20	20
Liver								

Rat 6-Month Toxicity Study				Test Article: Sorafenib Tosylate				Report No.: PH-32607
Daily Dose Sorafenib [mg/kg]	**0 Control**	**0.1**	**1**	**2.5**	**0 Control**	**0.1**	**1**	**2.5**
Gender	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**
Pigment storage in Kupffer cells [n]	1	1	2	8	0	1	0	6
Kidneys								
Basophilic tubules [n]	14	16	17	19	4	3	4	14
Average Grading	1.2	1.4	1.6	2.2	1.3	1.0	1.0	1.5
Tubular dilation [n]	9	10	11	17	1	1	1	8
Average Grading	1.1	1.2	1.4	1.5	2.0	1.0	1.0	1.6
Hyaline casts [n]	6	7	9	16	2	2	2	13
Average Grading	1.0	1.7	1.9	1.7	1.5	1.5	1.0	1.8
Teeth								
Dentin degeneration [n]	0	0	3	10	0	4	4	12
Mesenteric. Lymph node								
Increased mast cells [n]	2	1	9	11	2	1	7	10
Sternum								
Fatty Replacement [n]	18	19	20	20	20	20	20	20
Average Grading	1.6	1.6	2.0	2.4	2.3	2.2	2.4	2.4

- No noteworthy finding + Mild ++ Moderate +++ Marked n = number of animals affected abs. = absolute

Statistical analysis: * $p < 0.05$, ** $p < 0.01$
Dunnett test
Analysis of variance followed by Dunnett test
Kruskal-Wallis test followed by adjusted U-test
Adjusted Welsh test

Food intake, water intake, body weights, organ weights
Hematology, blood chemistry

a At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)
b Both absolute and relative weights differed from controls in the direction indicated. Number indicate percent difference for the absolute organ weights

Report Title:	**Subacute toxicity study in Beagle dogs (4 week gavage study + 4 week recovery period)**
Report No.:	PH-30221 (Toxicokinetics MRC-01053)
Test Article:	Sorafenib Tosylate (BAY 43-9006 Tosylate, BAY 54-9085)
Location in CTD:	M4.2.3.2.8, M4.2.3.2.9

Species/Strain:	Beagle dogs	Study No.:	T 3069071
Initial age:	18-22 weeks	GLP Compliance:	yes
Duration of Dosing:	4 weeks	Date of 1st Dose:	Nov 1999
Duration of Postdose:	4 weeks		
Method of Administration:	Oral (gavage)		
Vehicle/Formulation:	3 ml/kg; mixture of 10% 2-Pyrrolidone, 45% Propylene glycol, 45% Cremophor RH 40		
Special Features:	Dosing reduced from twice daily to once daily from week 2 onwards; two control groups (dosed with tap water or vehicle, respectively) + control recovery		
NOAEL:	Not established		

Dog 4-week Toxicity Study (with 4-week recovery) **Test Article: Sorafenib Tosylate** **Report No.: PH-30221**

Daily Dose [mg/kg] Sorafenib	**0 Control I**	**0 Control II**	**2x10/10**	**2x30/30**	**2x60/60**	**0 Control I**	**0 Control II**	**2x10/10**	**2x30/30**	**2x60/60**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Number of Animals	4	4	4	4	4	4	4	4	4	4
Toxicokinetics (males and females pooled)										
Number of animals	4	4	4	4	4	4	4	4	4	4
$AUC_{0\text{-}24h}$ [mg*h/L] week 4 Sorafenib		17	39	52						
Cmax [mg/L] week 4 Sorafenib		2.2	4.0	5.3						
Noteworthy Findings (main groups)										
Died/Sacrificed Moribund	-	-	1	-	-	-	-	-		
Body weight gain[a]	-	-	-	-	reduced	-	-	-	-	reduced
Food Intake	-	-	-	-	-	-	-	-	reduced	reduced
Water Intake	-	-	-	-	-	-	-	-	-	-
Clinical Observations:										
Feces, bloody admixture [n]	0	0	3	4	4	1	2	1	3	4
Ophthalmoscopy	-	-	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-	-	-
Hematology	-	-	-	-	-	-	-	-	-	-
Serum Chemistry										
AST increase [n]	0	0	1	0	1	0	0	0	2	3
ALT increase [n]	0	0	1	0	1	0	0	0	4	4
ALP increase [n]	0	0	0	0	1	0	0	0	1	4
GLDH increase [n]	0	0	1	0	1	0	0	0	4	4
GGT increase [n]	0	0	0	0	1	0	0	0	2	4
Bili-t increase [n]	0	0	0	0	0	0	0	0	0	1
T3, decrease [n]	0	0	0	0	1	0	0	0	0	0

Dog 4-week Toxicity Study (with 4-week recovery) **Test Article: Sorafenib Tosylate** **Report No.: PH-30221**

Daily Dose [mg/kg] Sorafenib	**0 Control I**	**0 Control II**	**2x10/10**	**2x30/30**	**2x60/60**	**0 Control I**	**0 Control II**	**2x10/10**	**2x30/30**	**2x60/60**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Urinalysis										
Slight increase in protein [n]	0	0	0	1	1	0	0	0	1	2
Organ Weights	-	-	-	-	-	-	-	-	-	-
Histopathology										
Number examined	4	4	4	4	4	4	4	4	4	4
Liver										
Bile duct proliferation [n]	0	0	0	0	2	0	0	0	1	2
Pericholangiolar fibrosis [n]	0	0	0	1	2	0	0	0	2	3
Granulocytic periportal infiltration [n]	0	0	0	0	1	0	0	0	2	1
Average Grading	0	0	0	0	1.0	0	0	0	1.5	2.0
Mononuclear periportal infiltration [n]	0	0	0	1	2	0	0	0	1	1
Stomach										
Cellular hypertrophy/pyloric region [n]	0	0	0	2	3	0	0	0	0	1
Bone (Femur)										
Thickening of the growth plate [n]	0	0	0	1	3	0	0	0	2	3
Hypocellularity adjacent to the growth plate [n]	0	0	0	0	2	0	0	0	0	2
Teeth										
Dentin alteration [n]	1	0	1	4	4	0	0	0	4	4
Average Grading	1.0	0	2.0	2.0	1.8	0	0	0	2.5	2.5
Spleen										
Increased hemopoiesis [n]	0	0	1	4	3	0	1	1	4	1
Average Grading	0	0	1.0	2.0	2.0	0	1.0	2.0	2.5	1.0
Increased number of megakaryocytes [n]	0	0	0	1	3	0	1	0	3	1

Dog 4-week Toxicity Study (with 4-week recovery) **Test Article: Sorafenib Tosylate** **Report No.: PH-30221**

Daily Dose [mg/kg] Sorafenib	**0 Control I**	**0 Control II**	**2x10/10**	**2x30/30**	**2x60/60**	**0 Control I**	**0 Control II**	**2x10/10**	**2x30/30**	**2x60/60**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Average Grading	0	0	0	2.0	1.3	0	1.0	0	1.7	2.0
Iron deposition [n]	1	3	3	3	4	3	2	4	4	4
Average Grading	2.0	1.7	1.7	2.0	2.0	1.0	1.5	2.0	2.0	3.0
Postdose Evaluation[c]										
Number Evaluated		2			2		2			2
Clinical Observations:										
Feces with bloody admixture, (week 5) [n]	-	-	-	-	1	-	-	-	-	2
Histopathology										
Liver										
Bile duct proliferation [n]		0			1		0			1
Pericholangiolar fibrosis [n]		0			1		0			1
Granulocytic periportal infiltration [n]		0			1		0			0
Spleen:										
Iron deposition [n]		2			1		2			1
Average Grading		1.0			2.0		1.0			2.0
Teeth										
Dentin alteration [n]		0			2		0			2

- No noteworthy finding + Mild ++ Moderate +++ Marked n = number of animals affected

a At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)

b Both absolute and relative weights differed from controls in the direction indicated. Number indicate percent difference for the absolute organ weights

c Noteworthy findings during the treatment period, which were not listed under 'Postdose Evaluation' were fully reversible

Report Title:	Study on Chronic Toxicity in Beagle Dogs. Administration by Gavage over 52 Weeks.
Report No.:	PH-33532 (Toxicokinetics MRC-01181, PH-33306)
Test Article:	Sorafenib Tosylate (BAY 43-9006 Tosylate, BAY 54-9085)
Location in CTD:	M4.2.3.2.12, M4.2.3.2.13, M4.2.3.2.14

Species/Strain:	Beagle dogs	Study No.:	T9071362
Initial age:	18-22 weeks	GLP Compliance:	Yes
Duration of Dosing:	52 weeks	Date of 1st Dose:	Jan 2001
Duration of Postdose:	-		
Method of Administration:	Oral (gavage)		
Vehicle/Formulation:	3 ml/kg; mixture of 10% 2-Pyrrolidone, 45% Propylene glycol, 45% Cremophor RH 40		
Special Features:	-		
NOAEL:	Not established		

Dog 12-Month Toxicity Study					Test Article:	Sorafenib Tosylate			Report No.:	PH-33532	
Daily Dose [mg/kg] sorafenib		**0 Control**	**3**	**10**	**30**	**60**	**0 Control**	**3**	**10**	**30**	**60**
Gender		**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Number of Animals		4	4	4	4	4	4	4	4	4	4
Toxicokinetics **(males and females pooled):**											
Number of animals			8	8	7	4					
$AUC_{0\text{-}24h}$ [mg*h/L] week52 Sorafenib		-	3.9	17	22	45					
Cmax [mg/L] week 52 Sorafenib		-	0.39	1.5	2.1	4.9					
Noteworthy Findings											
Died/Sacrificed Moribund		1	0	0	0	2	0	0	0	1	2
Body Weight gain (kg)		+7.9	+6.9	+5.2	+3.9	+3.2	+7.3	+4.7	+4.3	+3.9	+1.4
Ophthalmoscopy		-	-	-	-	-	-	-	-	-	-
Electrocardiography		-	-	-	-	-	-	-	-	-	-
Serum Chemistry											
AST (U/L)	week -2	18.6	22.3	17.8	20.8	20.7	20.3	20.2	18.0	20.3	19.7
	week 6	21.6	26.0	30.5	60.9	54.0	25.8	23.7	32.9	76.5	52.8
	week 13	30.2	33.1	33.5	48.7	47.7	25.7	29.6	44.0	50.1	51.3
	week 26	25.0	37.1	45.3	45.3	70.0	24.4	29.9	37.8	40.5	46.2
	week 39	23.7	41.9	47.3	84.1	94.4	26.4	27.9	32.7	51.0	59.2
	week 51	26.9	31.8	35.6	53.0	95.8	27.4	26.6	42.1	44.9	41.8
ALT (U/L)	week -2	35.7	25.5	33.9	27.3	32.4	31.5	27.2	29.4	25.5	28.4
	week 6	33.0	32.4	58.6	119.5	143.5	34.9	31.4	68.0	167.9	107.1
	week 13	66.2	43.8	38.4	80.5	99.7	36.4	36.5	95.0	79.3	95.6
	week 26	73.3	78.3	57.0	73.9	68.5	45.1	40.9	92.1	50.3	36.7
	week 39	81.9	83.9	69.6	99.7	117.3	56.3	50.6	97.3	75.4	93.2
	week 51	72.3	72.6	73.5	112.7	317.6	59.6	49.3	97.1	102.6	35.4

Dog 12-Month Toxicity Study					Test Article:	Sorafenib Tosylate			Report No.:	PH-33532
Daily Dose [mg/kg] sorafenib	**0 Control**	**3**	**10**	**30**	**60**	**0 Control**	**3**	**10**	**30**	**60**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Histopathology										
Number examined	4	4	4	4	4	4	4	4	4	4
Liver										
Bile duct proliferation [n]	0	2	2	3	3	2	2	2	3	3
Average Grading		1.5	2.0	1.7	2.3	1.5	2.5	1.5	2.7	1.3
Interlobular fibrosis [n]	1	2	2	3	3	3	2	3	3	2
Average Grading	2.0	2.0	2.5	2.3	2.7	2.0	1.5	1.3	2.3	2.5
Mixed cell infiltration [n]	0	2	1	1	3	2	1	2	3	2
Average Grading		1.0	2.0	1.0	1.7	1.5	2.0	1.5	1.3	1.0
Vacuolar degeneration/ hepatocytes [n]	1	1	2	1	1	2	3	2	3	1
Average Grading	1.0	2.0	1.5	2.0	2.0	2.5	1.3	1.5	1.7	1.0
Cirrhosis [n]	0	0	0	0	1	0	0	1	1	0
Pigment deposition [n]	3	1	4	3	4	3	3	2	4	2
Average Grading	1.3	2.0	2.0	1.7	1.8	1.7	1.3	2.5	1.8	1.5
Kidneys										
Glomerulopathy [n]	1	1	3	4	2	1	0	1	3	3
Average Grading	1.0	1.0	2.3	1.3	2.0	2.0	0	1.0	1.3	1.3
Tubular dilation [n]	0	0	3	3	1	1	0	1	2	4
Pigment deposition/ Cortical tubules [n]	3	4	3	2	2	4	2	3	3	1
Average Grading	2.7	2.0	1.7	1.5	1.5	1.8	2.5	1.3	1.0	1.0
Spleen										
Iron deposition [n]	4	4	4	4	4	4	4	4	4	4
Average Grading	1.8	1.5	3.0	2.8	2.8	1.5	1.8	2.8	3.0	2.5
Follicle necrosis [n]	0	0	0	0	1	0	0	0	0	2
Testes										
Tubular degeneration [n]	0	0	0	3	3					
Average Grading				1.3	2.3					
Tubular dilation [n]	0	0	0	3	1					
Average Grading				1.3	2.0					

Dog 12-Month Toxicity Study				Test Article: Sorafenib Tosylate				Report No.: PH-33532		
Daily Dose [mg/kg] sorafenib	0 Control	3	10	30	60	0 Control	3	10	30	60
Gender	M	M	M	M	M	F	F	F	F	F
Epididymides										
Oligospermia [n]	0	0	0	0	2					
Adrenal glands										
Single cell necroses/ Z. fasciculata [n]	0	0	0	1	2	0	0	0	1	1
Single cell necroses/ Z. arcuata [n]	0	0	0	0	0	0	0	0	1	0
Bone marrow										
Hypocellularity/femur [n]	0	0	0	4	3	0	0	3	2	3
Average Grading				1.3	2.0			1.3	3.0	1.3
Incr. Fat marrow/femur [n] [n]	0	0	0	4	3	1	3	4	3	3
Average Grading				2.0	2.0	2.0	1.0	1.8	2.3	2.3
Hypocellularity/sternum [n]	0	0	0	0	1	0	0	0	1	1
Average Grading					1.0				3.0	1.0
Incr. Fat marrow/sternum [n]					2	1	0	4	2	3
Average Grading				1.5	1.5	1.0		1.5	1.0	1.3
Teeth										
Dentin alteration [n]	0	0	0	0	0	0	0	0	1	1
Skin										
Dermatitis [n]	0	2	2	3	1	1	1	0	1	3
Average Grading		1.0	1.0	2.0	2.0	1.0	1.0		4.0	3.0
Alopecia/Degener. Hair follicles [n]	0	2	4	4	4	1	1	3	4	4
Average Grading		2.0	1.5	2.5	3.0	1.0	1.0	1.3	2.8	3.0
Peri-/Folliculitis [n]	1	0	0	4	3	0	1	2	3	3
Average Grading	1.0			2.3	1.3		1.0	1.0	2.3	2.7
Acanthosis [n]	0	0	0	2	1	0	0	0	1	4

Dog 12-Month Toxicity Study					Test Article: Sorafenib Tosylate				Report No.: PH-33532	
Daily Dose [mg/kg] sorafenib	**0 Control**	**3**	**10**	**30**	**60**	**0 Control**	**3**	**10**	**30**	**60**
Gender	**M**	**M**	**M**	**M**	**M**	**F**	**F**	**F**	**F**	**F**
Tonsils										
Atrophy [n]	0	0	0	4	3	0	0	0	1	2
Average Grading				1.0	2.3				3.0	1.0
Follicular necroses [n]	1			1	1				1	3
Average Grading	1.0			1.0	3.0				3.0	1.3
Thymus										
Atrophy/ involution [n]	0	2	0	2	3	1	0	1	1	3
Average Grading		2.0		2.5	3.3	2.0		2.0	4.0	3.0
Mesenteric Lymph nodes										
Lymphatic depletion [n]	0	0	0	0	0	0	0	0	1	2
Follicular necroses [n]	0	0	0	0	2	0	0	0	1	1
Average Grading					2.0				2.0	3.0
Mandibular Lymph nodes										
Lymphatic depletion [n]	0	0	0	0	0	0	0	0	1	0
Follicular necroses [n]	0	0	0	0	0	0	0	0	1	1
Average Grading									2.0	1.0
Peyer's Patches										
Atrophy [n]	0	0	0	0	1	0	0	0	1	0
Central necroses [n]	0	0	0	0	0	0	0	0	0	2
Colon										
Necroses of lymphoid follicles [n]	0	0	0	0	1	0	0	0	0	1
Cecum										
Necroses lymphoid follicles	0	0	0	0	1	0	0	0	0	0

- No noteworthy finding
n = number of animals affected

Report Title:	**Developmental Toxicity Study in Rats after Oral Administration**
Report No.:	PH-33514
Test Article:	Sorafenib Tosylate (BAY 43-9006 Tosylate, BAY 54-9085)
Location in CTD:	M4.2.3.5.2.1

Design similar to ICH 4.1.3?	Yes	Study No.:	T0063010
Species/Strain:	Rat; Wistar — Cpb:WU		
Initial Age:	13 - 20 weeks	GLP Compliance:	Yes
Date of First dose	May 27, 2003		
Duration of Dosing: (G)	days 6-17		
Day of Mating[a]: (G)	day 0		
Day of First Dose: (G)	day 6		
Day of C-Section: (G)	day 20		
Method of Administration:	orally by gavage		
Vehicle/Formulation:	0.5% aqueous methyl-hydroxyethylcellulose [ ]		

G = Gestation day
[a] : day 0 is the day when sperm was found in vaginal swab

Special Features: -

No Observed Adverse Effect Level (NOAEL):

F_0 Females:	1.0 mg/kg/day Sorafenib
F_1 Litters:	0.2 mg/kg/day Sorafenib

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rats **Test Article: Sorafenib Tosylate** **Report No.: PH-33514**

Dams Daily Dose Sorafenib [mg/kg]	0 (Control)	0.2	1.0	2.5
Toxicokinetics:(day 17 p.c.)				
Sorafenib AUC (0-7) (µg·h/L)	not done	889	3552	6027
Sorafenib Cmax (mg/L)	not done	197	642	1055
No. Pregnant (with implantation sites)	22	21	20	20
No. Aborted or with Total Resorption of Litter	0	0	0	1
Clinical Observations (total no. of days observed / total no. of animals affected)				
reddish vaginal discharge	-	-	-	4/2
Necropsy Observations	-	-	-	-
Body Weight Gain. Gestation Period (%)[a]	112.0 g	-5.71	-3.75	-12.41
Body Weight Gain. Treatment Period (%)[a]	52.3 g	-5.74	-4.21	-16.63**
Food Consumption. Treatment Period (%)[a]	87.0 g	-4.48	-1.49	-4.60
Day G 15-18 (%)[a]	24.1 g	-4.56	-2.90	-8.71**
Mean No. Corpora Lutea	13.7	13.6	13.2	13.6
Mean No. Implantations	11.4	11.9	11.9	12.6
Mean Preimplantation Loss per Female in Females with Implantation Sites	2.3	1.7	1.3	1.0

- No noteworthy finding G = Gestation day

a For controls group means are shown. For treated groups percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)
* $p < 0.05$. ** $p < 0.01$;
Statistical methods: body weight; feed consumption: ANOVA and Dunnett's test
preimplantation loss: Kruskal-Wallis and Dunn's test

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rats **Test Article: Sorafenib Tosylate** **Report No.: PH-33514**

Litters Daily Dose Sorafenib [mg/kg]	0 (Control)	0.2	1.0	2.5
No. Live Fetuses (Litters)	235 (22)	235 (21)	216 (20)	186 (20)
Mean No. Live Fetuses	10.7	11.2	10.8	9.8
Mean No. Early Resorptions in Females with Implantation Sites	0	0	0	0
Mean No. Early Resorptions in Females with Live Fetuses	0	0	0	0
Mean No. Late Resorptions in Females with Implantation Sites	0.7	0.7	1.1	3.3**
Mean No. Late Resorptions in Females with Live Fetuses	0.7	0.7	1.1	2.8**
No. Of Litters with Dead Fetuses	0	0	0	0
Mean Postimplantation Loss per Female in Females with Implantation Sites	0.7	0.7	1.1	3.3**
Mean Postimplantation Loss per Female in Females with Live Fetuses	0.7	0.7	1.1	2.8**
Mean Fetal Body Weight (g)	3.69	3.66	3.61	3.33**
Fetal Sex Ratio (% Males/Litter)	49.3	51.4	47.4	57.2
Mean Placental Weight (g)	0.65	0.63	0.63	0.58**
Noteworthy Placental Findings [Fetuses (Litters)]				
Necrotic placental borders	17 (6)	9 (4)	16 (7)	76** (17)**
Placenta pale	0	0	0	2 (2)

- No noteworthy finding.
* $p < 0.05$. ** $p < 0.01$
Statistical methods: postimplantation loss, placental findings: Kruskal-Wallis and Dunn's test
placental weight: ANOVA and Dunnett's test

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rats **Test Article: Sorafenib Tosylate** **Report No.: PH-33514**

Litters Daily Dose Sorafenib [mg/kg]	0 (Control)	0.2	1.0	2.5
Fetal Malformations				
[Fetuses (Litters) evaluated]	235 (22)	235 (21)	216 (20)	186 (19)
Gross External Malformations				
Eye rudiment flat (confirmed as malformation)	0	0	1 (1)	1 (1)
Total No. of Fetuses (%) affected	0	0	1 (0.5)	1 (0.5)
Total No. of Litters (%) affected	0	0	1 (5.00)	1 (5.3)
Visceral Malformations				
Eyeball reduced in size (micophthalmia)	1	1	3 (3)	1
Dilation of brain ventricles (hydrocephalus internus)	1	0	0	0
Thyroid gland missing, unilateral	0	1	0	1
Double aortic arch, left-sided descending aorta	0	0	0	1
Right-sided retroesophageal aortic arch, left-sided descending aorta, pulmonary trunc and ductus arteriosus; left subclavian artery arises from descending aorta	0	0	1	3 (2)
Right-sided aortic arch, descending aorta, pulmonary trunc and ductus arteriosus	0	0	0	1
Total No. of Fetuses (%) affected	2 (0.9)	2 (0.9)	4 (1.9)	6 (3.2)
Total No. of Litters (%) Affected	2 (9.1)	2 (9.5)	4 (20.0)	3 (15.8)
Skeletal Malformations				
Scapula dysplastic / dysplastic forelimb bones	0	0	0	1
Scapula and radius dysplastic	0	0	0	1
Bifurcation of ribs	0	0	0	1
Head of 1st rib missing	1	0	0	0

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rats **Test Article: Sorafenib Tosylate** **Report No.: PH-33514**

Litters Daily Dose Sorafenib [mg/kg]	0 (Control)	0.2	1.0	2.5
Head of 1st rib missing bilateral; 2nd rib bent, unilateral; shift. Fusion or shortage of cartilaginous parts of ribs; cartilaginous end of 1st rib not connected to sternum	0	0	0	1
2nd rib bent, unilateral; shift and fusion of cartilaginous parts of 1st and 2nd rib	0	0	0	2 (1)
Combined alterations of thoracic vertebrae	0	0	0	1
Combined alterations of lumbar vertebrae	0	0	0	1
Malformed vertebral column (kinked) with alteration of thoracic and/or lumbar vertebrae, 1st sacral vertebral arch has the shape of a lumbar vertebral arch unilateral. pelvis shifted caudally right/left	0	0	0	3 (1)
Malformed vertebral column (S-shaped), alterations of thoracic and lumbar vertebrae	0	0	0	1
Malformed vertebral column (S-shaped), head of 1st rib missing, left, alterations of ribs, thoracic and lumbar vertebrae, 1st sacral vertebral arch has the shape of a lumbar vertebral arch, right; pelvis shifted caudally, right	0	0	0	1
1st sacral vertebral arch has the shape of a lumbar vertebral arch uni- and/or bilateral; pelvis shifted caudally, unilateral	0	0	0	3 (3)
Pelvis shift caudally, unilateral	0	0	0	2 (2)
Supernumerary lumbar vertebra	0	0	0	1
Supernumerary sacral vertebra	0	1	0	0
Iliac bone dysplastic	0	0	0	1
Total No. of Fetuses (%) affected	1 (0.4)	1 (0.4)	0	20 (10.8)
Total No. of Litters (%) affected	1 (4.5)	1 (4.8)	0	10 (52.6)

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rats **Test Article: Sorafenib Tosylate** **Report No.: PH-33514**

Litters Daily Dose Sorafenib [mg/kg]	0 (Control)	0.2	1.0	2.5
Overall No. (%) of Fetuses with Malformations[b]	3 (1.3)	3 (1.3)	4 (1.9)	25** (13.4)
Overall No. (%) of Litters with Malformations[b]	3 (13.6)	3 (14.3)	4 (20.0)	11* (57.9)

- No noteworthy finding
* $p < 0.05$, ** $p < 0.01$;
Statistical method: 2*N-Chi^2 and Fisher's Exact
b Statistical significance is based on actual data (not on percent values)
Single fetuses and litters show more than one malformation

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rats **Test Article: Sorafenib Tosylate** **Report No.: PH-33514**

Litters Daily Dose Sorafenib [mg/kg]	0 (Control)	0.2	1.0	2.5
Noteworthy External and Visceral Fetal Findings (others than malformations) [Fetuses (Litters) evaluated]	235 (22)	235 (21)	216 (20)	186 (19)
External Findings				
Pale				
Total No. of Fetuses (%) affected	0	0	0	2 (1.1)
Total No. of Litters (%) affected	0	0	0	2 (10.5)
Visceral Findings				
Innominate artery missing				
Total No. of Fetuses (%) Affected	0	0	0	2 (1.1)
Total No. of Litters (%) Affected	0	0	0	2 (10.5)
Noteworthy Skeletal Fetal Findings (others than malformations) [Fetuses (Litters)] evaluated	121 (22)	121 (21)	113 (20)	98 (19)
Skeletal Variations				
14^{th} ribs sum				
Total No. of Fetuses (%) affected[b]	18 (14.9)	30 (24.8)	13 (11.5)	40** (40.8)
Total No. of Litters (%) affected[b]	9 (40.9)	15 (71.4)	10 (50.0)	15 (78.9)
Degree of Ossification				
Phalangeal bones of forepaws (1^{st} – 5^{th}, incompletely ossified and/or unossified)	-	-	+ / ++	+++
Metacarpals (5^{th}, unossified)	-	-	-	+++
Sternebrae (3^{rd}, 5^{th} and/or, 6^{th}, incompletely ossified)	-	-	+	++ / +++

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rats **Test Article: Sorafenib Tosylate** **Report No.: PH-33514**

Litters Daily Dose Sorafenib [mg/kg]	0 (Control)	0.2	1.0	2.5
Cervical vertebral bodies (1st, 5th, 6th and/or 7th, incompletely ossified)	-	-	-	++ /+++
Thoracic vertebral bodies (2nd – 13th, dumbbell shaped, flat and/or bipartite)	-	-	+ / ++	+++
Lumbar vertebral bodies (1st, dumbbell shaped and/or flat)	-	-	-	+++
Caudal vertebral bodies (4th, 5th, reduced no. present)	-	-	-	++
Nasal bones (incompletely ossified)	-	-	-	++
Supraoccipital bone (incompletely ossified)	-	-	-	++
Basioccipital bone (incompletely ossified)	-	-	-	+++
Sphenoid bone (incompletely ossified)	-	-	-	+

- No noteworthy finding + mild ++ moderate +++ marked
Evaluation for degree of ossification represents a compilation of fetal and litter data
* $p < 0.05$ ** $p < 0.01$ Statistical method: 2*N-Chi^2 and Fishers's Exact
b Statistical significance is based on actual data (not on percent values)

Report Title:	**Developmental Toxicity Study in Rabbits after Oral Administration**
Report No.:	PH-33531
Test Article:	Sorafenib Tosylate (BAY 43-9006 Tosylate, BAY 54-9085)
Location in CTD:	M4.2.3.5.2.2

Design similar to ICH 4.1.3?	Yes	Study No.:	T4063177
Species/Strain:	Rabbit, strain CHBB:HM		
Initial Age:	119-206 days	GLP Compliance:	Yes
Date of First dose	July 13, 2003		
Duration of Dosing: (G)	days 6-20		
Day of Mating: (G)	day 0		
Day of First Dose: (G)	day 6		
Day of C-Section: (G)	day 29		
Method of Administration:	orally by gavage		
Vehicle/Formulation:	0.5% aqueous methylhydroxyethylcellulose [ ]		
			G = Gestation day
Special Features:	-		

No Observed Adverse Effect Level (NOAEL):

F_0 Females:	< 0.25 mg/kg/day Sorafenib
F_1 Litters:	1.0 mg/kg/day Sorafenib

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rabbits **Test Article: Sorafenib Tosylate** **Report No.: PH-33531**

Dams Daily Dose Sorafenib [mg/kg]	0 (Control)	0.3	1	3
Toxicokinetics:(day 20 p.c.)				
Sorafenib AUC (0-24) (µg·h/L)	not done	976	3413	12321
Sorafenib Cmax (µg/L)	not done	58.8	207	722
No. Pregnant (with implantation sites)	19	18	18	20
No. Aborted or with Total Resorption of Litter	0	0	0	1/3
Clinical Observations (total no. of days observed/ total no. of animals affected)				
cold ears	3/3	17/6	17/10	33/15
Necropsy Observations	-	-	-	-
Body Weight Gain. Gestation Period (%)[a]	351.8 g	+7.79	+3.01	-12.51
Body Weight Gain. Treatment Period (%)[a]	114.8 g	-4.36	-22.47	-60.80
Body Weight Gain. Day G 6-7 (%)[a]	16.4 g	-112.20*	-67.68	-173.78**
Food Consumption. Treatment Period (%)[a]	480.7 g	-1.00	-3.64	-7.18
Food Consumption. Day G 12-15	89.7 g	+3.01	-6.69	-21.85
Mean No. Corpora Lutea	9.0	8.7	8.0	8.0
Mean No. Implantations	8.6	8.3	7.3	7.3
Mean Preimplantation Loss per Female in Females with Implantation Sites	0.4	0.4	0.7	0.7

- No noteworthy finding G = Gestation day

a For controls group means are shown. For treated groups percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences)
* $p < 0.05$, ** $p < 0.01$
Statistical methods: Body weight: ANOVA and Dunnett's test

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rabbits **Test Article: Sorafenib Tosylate** **Report No.: PH-33531**

Litters Daily Dose Sorafenib [mg/kg]	0 (Control)	0.3	1	3
No. Live Fetuses (Litters)	156 (19)	138 (18)	125 (18)	90 (16)
Mean No. Live Fetuses	8.2	7.7	6.9	5.6**
Mean No. Early Resorptions in Females with Implantation Sites	0.0	0.0	0.0	0.4
Mean No. Early Resorptions in Females with Live Fetuses	0.0	0.0	0.0	0.0
Mean No. Late Resorptions in Females with Implantation Sites	0.4	0.7	0.4	2.2*
Mean No. Late Resorptions in Females with Live Fetuses	0.4	0.7	0.4	1.7*
No. Of Litters with Dead Fetuses	0	0	0	0
Mean Postimplantation Loss per Female in Females with Implantation Sites	0.4	0.7	0.4	2.5**
Mean Postimplantation Loss per Female in Females with Live Fetuses	0.4	0.7	0.4	1.7*
Mean Fetal Body Weight (g)	36.92	37.14	38.90	38.33
Fetal Sex Ratio (% Males/Litter)	55.7	43.8	50.5	40.4
Mean Placental Weight (g)	4.23	4.31	4.53	4.69
Noteworthy Placental Findings [Fetuses (Litters)]				
Placenta partly necrotic	1 (1)	3 (3)	4 (4)	19** (8)*

- No noteworthy finding.
* $p < 0.05$. ** $p < 0.01$
Statistical methods: Live fetuses per female: ANOVA and Dunnett's test
Postimplantation loss, late resorptions: Kruskal-Wallis test and Dunn's test
Placental findings: 2*N-Chi^2 and Fisher's Exact

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rabbits **Test Article: Sorafenib Tosylate** **Report No.: PH-33531**

Litters Daily Dose Sorafenib [mg/kg]	0 (Control)	0.3	1	3
Fetal Malformations				
[Fetuses (Litters) evaluated]	156 (19)	138 (18)	125 (18)	90 (19)
Gross External Malformations				
malposition of forelimb(s) with/without narrowed thorax	1	2 (2)	3 (2)	2 (2)
Total No. of Fetuses (%) affected	1 (0.6)	2 (1.4)	1 (0.8)	2 (2.2)
Total No. of Litters (%) affected	1 (5.3)	2 (11.1)	1 (5.6)	1 (12.5)
Visceral Malformations				
malformation of the heart with/without malformations of the major vessels	1	2 (2)	1	1
kidney and ureter are missing	-	-	-	5* (3)
right kidney displaced, lying at right testis, dilation of renal pelvis, right ureter shortened without connection to urinary bladder	-	-	-	2(2)
Total No. of Fetuses (%) affected	1 (0.6)	2 (1.4)	1 (0.8)	8 (8.9)
Total No. of Litters (%) Affected	1 (5.3)	2 (11.1)	1 (5.6)	5 (31.3)
Skeletal Malformations				
one supernumerary sternal segment above 1st sternal segment (fused with it), cervical ribs at 7th cervical vertebra bilateral, 7th cervical vertebral arches look like thoracic vertebral arches bilateral	1	-	-	-
one supernumerary presacral vertebra with anomalies of the sacral vertebrae	-	-	-	2 (2)
supernumerary presacral vertebra	-	-	1	3 (1)
1st sacral vertebral arch left looks like a lumbar vertebral arch, pelvis left shift to caudal	-	-	-	2 (2)
fusion of caudal vertebral body(ies)	-	-	-	1

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rabbits **Test Article: Sorafenib Tosylate** **Report No.: PH-33531**

Litters Daily Dose Sorafenib [mg/kg]	0 (Control)	0.3	1	3
malformations of thoracic and lumbar vertebrae and ribs	-	-	-	2 (2)
fusion of ribs in the cartilaginous part	1	-	-	-
bifurcation of ribs in the osseous part	1	-	-	-
all bones reddish-black discolored	-	1	-	-
Total No. of Fetuses (%) affected	3 (1.9)	1 (0.4)	1 (0.8)	10 (11.1)
Total No. of Litters (%) affected	2 (10.5)	1 (4.8)	1 (5.6)	5 (31.3)
Overall No. (%) of Fetuses with Malformations[b]	3 (1.9)	5 (3.6)	5 (4.0)	16** (17.8)
Overall No. (%) of Litters with Malformations[b]	2 (10.5)	4 (22.2)	4 (22.2)	7 (43.8)

- No noteworthy finding
* $p < 0.05$, ** $p < 0.01$;
Statistical methods: Malformations: 2*N-Chi^2 and Fisher's Exact
b Statistical significance is based on actual data (not on percent values)
Single fetuses and litters show more than one malformation

Reproductive and Developmental Toxicity - Study for effects on embryo-fetal development in rabbits	**Test Article: Sorafenib Tosylate**		**Report No.: PH-33531**	
Litters **Daily Dose Sorafenib [mg/kg]**	**0 (Control)**	**0.3**	**1**	**3**
Noteworthy External and Visceral Fetal Findings (others than malformations) [Fetuses (Litters) evaluated]	156 (19)	138 (18)	125 (18)	90 (16)
External Findings	-	-	-	-
Total No. of Fetuses (%) affected	-	-	-	-
Total No. of Litters (%) affected	-	-	-	-
Visceral Findings				
Total No. of Fetuses (%) Affected	-	-	-	-
Total No. of Litters (%) Affected	-	-	-	-
Noteworthy Skeletal Fetal Findings (others than malformations)				
[Fetuses (Litters)] evaluated	156 (19)	138 (18)	125 (18)	90 (16)
Degree of Ossification				
fusion of sternebrae	+	+	+	+++
cervical vertebral bodies incompletely ossified (control 1st , 3rd-4th, 0.41 mg/kg group 1st and 3rd, 1.37 mg/kg group 1st , 3rd-4th, and 4.11 mg/kg group 1st, 3rd-5th)	+	+	+	+++
frontal bones bilateral incompletely ossified	+	+	++	+++

- No noteworthy finding + mild ++ moderate +++ marked
Evaluation for degree of ossification represents a compilation of fetal and litter data

Report No.: PH-33574
Test Article: BAY 43-9006 (batch 05863619)
Location in CTD M4.2.3.6.1
Special Features: Test for irritation (DRAIZE-Score)
Guidelines: OECD 404, EEC B.4, EPA OPPTS 870.2500

Acute Skin Irritation / Corrosion on Rabbits **Test Article:** **BAY 43-9006** **Report No.:** **PH-33574**

Species/ Strain	Method of Administration (Vehicle/ Formulation)	Test Compound	Duration of Dosing	Doses	Gender and No. per Group	NOAEL[a] [mg/kg]	Noteworthy Findings	Study Number
Rabbit / NZW	dermal	BAY 43-9006	4 hours	0.5 g	3 F	-	No irritation	T6074393

a No Observed Adverse Effect Level

2.6.8 OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:
Sorafenib is a multi-kinase inhibitor, targeting the following serine/threonine or tyrosine kinases: RAF (CRAF, BRAF, and the mutant V600E BRAF), KIT, LT-3, VEGFR-2, VEGFR-3, and PDGF-β.

The sponsor is seeking the marketing approval for sorafenib in patients with refractory and/or metastatic renal cell carcinoma at a dose of 400 mg bid (approx. 500 mg/m^2/day considering a 60 kg body weight).

Based on the safety pharmacology studies, sorafenib has the potential to cause cardiac toxicity by blocking the K-channel and the Ca- inward channel, sensory neuropathy, and hypoglycemia.

Acute toxicity studies determined the GI tract and the liver to be target organs/tissues of toxicity. In the pivotal repeat-dose toxicology studies, conducted in rats and dogs, clear signs of toxicities were observed in the following organs/tissues: liver, kidneys, hematopoietic system, skin, bone, teeth, reproductive system, GI tract, and pancreas. In addition, hypothyroidism was noted in the chronic dog toxicity study. Although clear adverse cardiovascular effects were not seen in the dog telemetry studies (no relevant changes in the QTc intervals, blood pressure, and heart rate at toxic doses), there is a high potential for cardiovascular toxicity, based on the limited histopathological findings in few toxicology studies, the positive finding in the in vitro hERG and action potential assays, the ↑CK in the chronic dog toxicity study, and the general knowledge on the family of compounds directly or indirectly targeting tyrosine kinase receptors, especially targeting the VEGFR.

- Bevacizumab/ VEGF inhibitor: Arterial thromboembolic events
- Trastuzumab/ her2-neu inhibitor: cardiomyopathy, ↓ejection fraction, ventricular dysfunction, hypotension
- Cetuximab/ EGFR inhibitor: hypotension
- Gleevec/ bcr-abl: cardiac failure, tachycardia, hypertension, hypotension (infrequent); thrombosis/ embolism (rare)

The clinical data with sorafenib also demonstrated the potential for cardiovascular toxicity, e.g. hypertension (all grades 8% in sorafenib arm vs. <1% in the placebo arm). Although rare, cases of heart valvular disease and heart failure were reported as cause of death in the sorafenib arm.

Growth plate suppression, as was seen with sorafenib, is a characteristic of many receptor kinase inhibitors, including VEGFR, PDGFR, and FGFR inhibitors.

Sorafenib was genotoxic in the CHO chromosome aberration test, in the presence of S9. Sorafenib is teratogenic and can cause embryo-fetal toxicities at sub-therapeutic doses.

M-2 appears to be the major metabolite in human. Since the metabolic profile of rats and dogs differed from that in human, the sponsor conducted a 4-week toxicology study with M-2 metabolite in rats. The Ames test was also conducted with the M-2 metabolite. The M-2 metabolite appears to be an active metabolite, since the pattern of toxicity obtained with M-2 is similar to that observed with the parent compound. Treatment with M-2 resulted in ↓platelet counts, dentin alteration, ↑liver enzymes, and ↑adipocytes in bone marrow in the general toxicology study. The M-2 metabolite was not genotoxic in the Ames assay.

The main impurity [ ] , was shown to be genotoxic in the Ames (+S9) assay.

Sorafenib can cross the blood-brain barrier. In addition, the single dose safety pharmacology revealed the potential for sorafenib to cause sensory neuropathy. Sensory neuropathy (mostly low grade) was observed in the Phase 2 clinical trial conducted with sorafenib.

In vitro data indicate that sorafenib is metabolized by CYP3A4 and UGT1A9 pathways. Sorafenib inhibits glucuronidation by the UGT1A1 (K_i = 1 μM) and UGT1A9 pathways (K_i = 2 μM). In clinical studies, when administered with irinotecan, whose active metabolite SN-38 is further metabolized by the UGT1A1 pathway, there was a 67-120% increase in the AUC of SN-38 and a 26-42% increase in the AUC of irinotecan. Protein binding of sorafenib appears to be high: 0.5% in mouse, rat, and human, 0.9% in dogs, and 2% in rabbits. Sorafenib showed the potency to inhibit CYPs 2B6 and 2C8 (ki= 1-2 μM), and 2C9 (ki= 7-8 μM). The excretion in rats and dogs was mainly through the biliary/fecal route. The urinary route of excretion was minimal (1-3%) in rats and dogs. The urinary excretion appears to be more pronounced in human (about 20%).

Unresolved toxicology issues: None

Recommendations:

To be communicated to the sponsor:

1. Please identify test-article BAY[ ] used in study MRC-01019 in the xenograft models.
2. In the one year toxicity study in dogs, please identify the CK parameter assayed, i.e. MM, MB, BB or the total CK.
3. For your future genotoxicity studies, if using 2-aminoanthracene as the positive control for the +S9 system, we encourage you to qualify each batch of S9 with chemicals such as benzo(a)pyrene or dimethylbenzanthracene.
4. Please provide the historical data for the strain of rabbit used in the reproductive toxicology (CHBB:HM) with regard to embryo-fetal malformations. Please send an electronic version of the data for the past 3-5 years, as observed within the test facility where the studies were conducted.

Signatures:

Reviewer Signature /S/

Haleh Saber-Mahloogi, Ph.D.
Pharmacology/ Toxicology Reviewer

Supervisor Signature /S/ Concurrence Yes _X_ No ___

David E. Morse, Ph.D.
Supervisory Pharmacologist

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2.6.9 APPENDIX/ ATTACHMENTS

The sponsor's response to the pharmacology/toxicology comments:

FDA Comment:

1. Please identify test-article BAY [ ] used in study MRC-01019 in the xenograft models.

Bayer Response

BAY [ ] was an early reference compound in the sorafenib discovery project. In Report MRC-01019, it was used as a positive control on the responsiveness of the tumor models. Its chemical name is [ ] BAY [ ] has a molecular weight of [ ] and the chemical structure is illustrated below:

[ ]

FDA Comment:

2. In the one year toxicity study in dogs, please identify the CK parameter assayed, i.e. MM, MB, BB or the total CK.

Bayer Response

Total CK-activity has been determined in this study.

FDA Comment:

3. For your future genotoxicity studies, if using 2-aminoanthracene as the positive control for the +S9 system, we encourage you to qualify each batch of S9 with chemicals such as benzo(a)pyrene or dimethylbenzanthracene.

Bayer Response

The agency's comment is in line with OECD-guideline No. 471 (adopted: 21 July 1997). The guideline states for the Bacterial Reverse Mutation Test: "2-Aminoanthracene should not be used as sole indicator of the efficacy of the S9-mix. If 2-aminoanthracene is used, each batch of S9 should also be characterized with a mutagen that requires metabolic activation by microsomal enzymes, e.g. benzo(a)pyrene, dimethylanthracene". Bayer's standard procedure in the Salmonella/microsome test follows this guidance, please see statement in the last paragraph of Section 4.3 "S9 Mix" page 18 of Bayer report PH-29467: "Prior to first use, each batch was checked for its metabolizing capacity by using reference mutagen(s); appropriate activity was demonstrated." For the test of metabolizing capacity, Bayer is using 2-aminoanthracene and additionally cylophosphamide, which is also named as positive control in Guideline No. 471.

FDA Comment:

4. Please provide the historical data for all endpoints from the strain of rabbit used in the reproductive toxicology (CHBB:HM). Please send an electronic version of the data, as observed within the test facility where the studies were conducted, for the past 3-5 years.

Bayer Response

The developmental toxicity study in rabbits with BAY 54-9085 (tosylate salt of BAY 43-9006) has been conducted in 2003, experimental starting date 7 July 2003.

Historical control data covering the years 1998 to 2002 are included in the Annex of study report PH-33531 on pages 398 to 728 (see Table of Content on page 58 to 60). This report has been submitted with the NDA electronically (CTD Module 4.2.3.3.1). Historical control data for the year 2003 are available in the meantime and are submitted with this response as a pdf-file.

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

/s/

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10/28/2005 12:03:25 PM
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David Morse
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