Gross pathology:

There were few macroscopic findings in the unscheduled deaths and in the scheduled deaths, only one MD male mouse exhibited any gross pathology. This mouse was the same mouse that hematology parameters showed severe anemia. The sponsor's tables below present these data.

Incidence of Macroscopic Findings in Unscheduled Deaths

Sex	Male				Female			
Dose (mg/kg/day)	0	100	300	1000	0	100	300	1000
Number examined	0	0	0	10	0	0	0	10
Cecum								
Soft red material	0	0	0	1	0	0	0	1
Kidneys								
Pale discoloration	0	0	0	4	0	0	0	2
Liver								
Pale discoloration	0	0	0	4	0	0	0	2
Stomach								
Soft yellow material	0	0	0	9	0	0	0	10
General (whole body)								
Mild yellow discoloration	0	0	0	3	0	0	0	1

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Incidence of Macroscopic Findings in Scheduled Deaths

Sex	Male				Female			
Dose (mg/kg/day)	0	100	300	1000	0	100	300	1000
Number examined	10	10	10	0	10	10	10	0
Adrenals								
Pale discoloration	0	0	1	0	0	0	0	0
Cecum								
Red-brown material	0	0	1	0	0	0	0	0
Epididymides								
Pale discoloration	0	0	1	0	0	0	0	0
Kidneys								
Pale discoloration	0	0	1	0	0	0	0	0
Lungs								
Pale discoloration	0	0	1	0	0	0	0	0
Mesenteric lymph node								
Pale discoloration	0	0	1	0	0	0	0	0
Pancreas								
Pale discoloration	0	0	1	0	0	0	0	0
Spleen								
Enlarged (increased)	0	0	1	0	0	0	0	0
Testes								
Pale discoloration	0	0	1	0	0	0	0	0
Thymus/thymic area								
Pale discoloration	0	0	1	0	0	0	0	0

Organ weights: Not conducted

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

Several tissues were preserved from the unscheduled and scheduled deaths, but none of them were examined for histopathological changes.

Toxicokinetics:

The sponsor's table below presents the toxicokinetic data for Days 1 and 14 (HD mice have only Day 1 data as all were euthanized moribund on Day 8). Increasing doses of GW572016 led to increases in both AUC and C_{max}, though not in a dose-proportional manner. Half-lives were relatively comparable between the LD and MD but much longer on Day 1 in the HD group.

Toxicokinetic Parameters of GW572016X in CD-1 Mice

Sex	Dose (mg/kg/day)	Day	AUC[1] (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	Dose-Normalized AUC (h*ng/mL)	Dose-Normalized C_{max} (ng/mL)
F	100	1	58752	14057	1	2.04	58752	14057
		14	48836	9024	1	1.36	48836	9024
	300	1	251379	23224	8	1.54	83793	7741
		14	150283	13072	4	2.30	50094	4357
	1000	1	806704	29924	8	14.6	80670	2992
M	100	1	123343	15220	1	1.95	123343	15220
		14	53440	10583	1	2.54	53440	10583
	300	1	272380	27077	8	1.37	90793	9026
		14	173473	14901	4	2.88	57824	4967
	1000	1	540545	23788	4	10.1	54054	2379

[1] AUC_{∞} on Day 1 and AUC_{24h} on Day 14.
n= 3 males and females per timepoint per dose group per day.

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Study title: GW572016F: 13-Week oral gavage pilot carcinogenicity study in mice.

Key study findings:

- Doses up to 200 mg/kg/day well tolerated in mice for 13 weeks
- Indication of liver toxicity – centrilobular hypertrophy, increased liver weights
- GI effects seen as indicated by mucosal hyperplasia in the cecum and colon
- Chronic inflammation of the preputial gland seen in the male mice

Study no.: RD2002/01283/00
Volume #, and page #: Module 4.2.3.2.2
Conducting laboratory and location:

Date of study initiation: 5 February 2002
GLP compliance: Compliance letter included and signed.
QA reports: yes (X) no ( )
Drug, lot #, and % purity: GW572016F; Lot# R5361/44/1, purity

Methods

Doses:	50, 100 and 200 mg/kg/day
Species/strain:	Mouse CD-1® (ICR) BR
Number/sex/group or time point (main study):	28/sex/dose
Route, formulation, volume, and infusion rate:	PO, in 0.5% hydroxypropyl methylcellulose + 0.1% Tween 80, 10 mL/kg
Satellite groups for toxicokinetics or recovery:	6/sex/dose
Age:	Approximately 6 weeks
Weight:	Male: 24.5-31.0 g Female: 20.6-26.0 g
Sampling times:	Weeks 4 and 13 at 0, 0.5, 2, 4, 8 and 12 hrs post treatment.

Observation times and results

Mortality: Twice daily

One control mouse found dead (Day 63), no known cause of death, no histopathological changes

One male MD mouse euthanized (Day 74) due to marked ulcerations of pinnae
As this clinical sign was seen in control mice, and in this study no difference in severity of skin reddening and scabbing, the sponsor proposes that this death was not drug related. Given that redness and scabbing has been shown in other studies to be treatment-related, attribution of this morbidity to GW572016 can not be ruled out.

Clinical signs: Twice daily
Clinical signs were generally not seen with increased frequency or severity in GW572016 treated mice compared to control. Skin scabs were seen in all dose groups.

Clinical Signs During 13 Week GW572016 Administration in Mice								
	Males				Females			
	Control	LD	MD	HD	Control	LD	MD	HD
Skin, scabs	5/28	3/28	2/28	8/28	2/28	1/28	1/28	0/28

Body weights: Weekly
No treatment related body weight changes

Food consumption: Weekly
No treatment related food consumption changes

Ophthalmoscopy: Not conducted

EKG: Not conducted

Hematology: Week 5 on 6/sex/dose and at termination on 6/sex/dose
No treatment related hematology changes

Clinical chemistry: Week 5 on 6/sex/dose and at termination on 6/sex/dose
44% ↑ total bilirubin in HD females at Week 5
48% ↑ total bilirubin in HD males at Week 5
No concomitant histopath changes

Urinalysis: Not conducted

Gross pathology:
2/16 HD males enlargement/mass in the preputial glands – correlated with chronic inflammation

Organ weights:
11% ↑ in liver relative to body weight in HD males

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

Significant Histopathological Changes Compared to Control 13 Week GW572016 Administration in Mice		
Organ/Tissue Finding	**MD**	**HD**
Liver		
Centrilobular hypertrophy, minimal	1/16 ♂	6/16 ♂
Cecum		
Mucosal hyperplasia	3/16 ♂	2/16 ♂
Colon		
Mucosal hyperplasia	---	5/16 ♂ 4/16 ♀
Preputial glands		
Chronic inflammation	4/16 ♂	5/16 ♂
Bone Marrow		
Hypercellularity, hematopoietic	----	2/16 ♂
Hypercellularity, myeloid	---	2/16 ♂

Toxicokinetics:

Toxicokinetic Parameters In Mice Following Administration Of GW572016						
Dose (mg/kg/day)	**Males**			**Females**		
	50	**100**	**200**	**50**	**100**	**200**
AUC_{24} (h*ng/mL)						
Day 28	20621	57683	116278	15092	38215	85981
Day 89	24036	63534	130961	15452	54349	100349
C_{max} (ng/mL)						
Day 28	5324	7901	10675	4611	7127	8638
Day 89	5334	10092	10503	5189	8855	8789

Study title: GW572016B and GW574783B: Non-audited 7-day toxicity study in male Han Wistar rats.

Key study findings:

- Two ErbB2/EGF inhibitors were tested, the results for lapatinib ditosylate (GW572016B) are presented
- No lethality seen at doses up to 240 mg/kg
- AUC and C_{max} show the rats were clearly exposed to GW572016
- Minor changes in adrenal (↑) and prostate (↓) weights
- Some histopathological changes that did not correlate to any gross pathology changes

Study no.: RD1999/01207/00

Volume #, and page #:	Module 4.2.3.2.3
Conducting laboratory and location:	Glaxo Wellcome Inc. Medicines Safety Evaluation Five Moore Drive Research Triangle Park, NC 27709
Date of study initiation:	22 June 1999
GLP compliance:	No
QA reports:	Yes ( ) no (X)
Drug, lot #, and % purity:	GW572016B, lot # U15469/11/1, purity — GW574783B, lot # U12816/179/1, purity —

Methods

Doses:	0, 60, 120 and 240 mg/kg/day
Species/strain:	Rat/Wistar Han — WI(Glx/BRL/Han)IGS BR]
Number/sex/group or time point (main study):	3 males/dose – 4 males for control group
Route, formulation, volume, and infusion rate:	PO, 0.5% hydroxypropyl methylcellulose + 0.1% Tween 80, 10 mL/kg volume
Satellite groups for toxicokinetics or recovery:	4 rats/dose for TK, 2 controls for TK
Age:	≈ 9 weeks
Weight:	244-298 g
Sampling times:	Days 1 then 7 of dosing at 0.5, 1, and 4 hours after administration

Observation times and results

Mortality: Monitored twice daily

No unscheduled deaths

Clinical signs: Monitored twice daily, with detailed examinations once pre-treatment and prior to necropsy

No treatment-related clinical signs were noted.

Body weights: Day 1 prior to treatment then Day 8

Not treatment-related changes in body weights were noted.

Food consumption: Not measured

Ophthalmoscopy: Not measured

EKG: Not measured

Hematology: Measured at end of treatment period

No treatment-related changes in hematological parameters were noted.

Clinical chemistry: Measured at end of treatment period

No treatment-related changes in clinical chemistry were noted.

Urinalysis: Not conducted

Gross pathology:

No macroscopic changes that were treatment-related were noted.

Organ weights:

The table below presents the few changes in organ weights seen with GW572016B treatment. Increased adrenal glands and decreased prostate glands were noted with GW572016 administration. No dose-response relationship was seen in the adrenal gland changes and no correlating histopathological changes were noted in this organ. The prostate changes also did not show a dose-response relationship and although there were histopathological changes to the prostate, they did not correlate to the changes in organ weights.

Organ Weight Changes in Male Rats Following 7-Day GW572016 Administration Percent Change From Control

	LD 60 mg/kg	MD 120 mg/kg	HD 240 mg/kg
Adrenal Gland			
Absolute	↑ 17%	↑ 9%	↑ 22%
Relative to BW	↑ 17%	↑ 15%	↑ 30%
Prostate			
Absolute	↓ 22%	↓ 8%	↓ 24%
Relative to BW	↓22%	↓ 4%	↓ 19%

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

Histopathological changes noted in the rats, both main and toxicokinetic groups, are presented below. For the most part, unless there was gross pathology indicating a problem, only the control and HD tissues were analyzed. The prostate changes were not always seen in the same rats that had increased prostate weights. The histopathology doesn't show a clear definitive effect of GW572016 treatment.

Incidence of Histopathological Changes in Rats After 7 Days of GW572016 Administration

	Control	LD 60 mg/kg	MD 120 mg/kg	HD 240 mg/kg
Prostate gland				
Infiltrate, lymphohistiocytic	1/6	3/7	5/7	0/7
Atrophy	0/6	1/7	0/7	1/7
Lymph Nodes				
Hemorrhage, mesenteric	3/6	0/0	0/0	5/7
Hemorrhage, mandibular	2/6	0/0	0/0	4/7
Lungs				
Infiltrate, eosinophilic, perivascular	2/6	0/0	0/0	1/7
Infiltrate, macrophage, alveolar	0/6	0/0	0/0	2/7
Hemorrhage	0/6	0/0	0/0	2/7
Mineralization, vascular	0/6	0/0	0/0	1/7
Esophagus				
Fibrosis, skeletal muscle	1/6	0/0	0/0	1/7
Degeneration, skeletal muscle	0/6	0/0	0/0	3/7
Hemorrhage	0/6	0/0	0/0	1/7
Tongue				
Degeneration, skeletal muscle	0/6	0/0	0/0	1/7
Liver				
Infiltrate, lymphohistiocytic	2/6	0/0	0/0	7/7
Kidney				
Regeneration, tubular	2/6	0/0	0/0	2/7
Dilatation, pelvis	1/6	0/0	0/0	2/7

Toxicokinetics:

The sponsor's table presenting toxicokinetic parameters is presented below. Regarding GW572016B, it is evident that all dose groups were exposed to measurable levels, though on Day 1, the 120 mg/kg dose group had lower C_{max} and AUC levels than the 60 mg/kg group. On Day 7, there is evidence of some accumulation and the C_{max} and AUC are increasing in a near dose-proportional fashion.

Mean Toxicokinetic Parameters for GW572016B and GW574783B

Test Material			GW572016B			GW574783B		
Daily Dose (mg/kg/day)		0	60	120	240	60	120	240
AUC_{0-4h} (ng h/mL)	Day 1	----	11482	9221	20661	2767	8273	7207
	Day 7	----	14856	23436	51034	1986	3283	15798
C_{max} (ng/mL)	Day 1	<10	3719	2870	6329	1014	4164	3008
	Day 7	<10	5352	7630	24168	673	1030	8205
T_{max} (hour)	Day 1	----	1	1	4	0.5	1	4
	Day 7	----	1	4	0.5	0.5	4	4

—not calculated.

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Study title: GW572016F: 14-Day oral gavage toxicity study in Wistar Han rats

Key study findings:

- Mortality was seen at 1000 mg/kg
- Body weights and food consumption adversely affected by the HD in males and MD and HD in females
- Elevated white blood cell parameters seen in MD and HD groups
- Increased adrenal gland weights and decreased prostate and thymus weights
- Histopathology changes on GI system, adrenal glands, spleen, thymus, lymph nodes, prostate, skeletal muscle, liver, pancreas, lungs

Study no.: RD1999/02391/00

Volume #, and page #:	Module 4.2.3.2.4
Conducting laboratory and location:	Glaxo Wellcome Inc. Medicines Safety Evaluation Five Moore Drive Research Triangle Park, NC 27709
Date of study initiation:	15 March 2000
GLP compliance:	Letter included and signed
QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	GW572016F, lot # U14572/39/3, purity —

Methods

Doses:	0, 60, 240, 1000 mg/kg/day
Species/strain:	Rat/Wistar Han ~ WI(Glx/BRL/Han)IGS BR]
Number/sex/group or time point (main study):	10/sex/ dose with additional 5/sex for control and HD recovery
Route, formulation, volume, and infusion rate:	PO, in 0.5% hydroxypropyl methylcellulose + 0.1% Tween 80, 10 mL/kg volume
Satellite groups for toxicokinetics or recovery:	9/sex/dose for drug groups and 3/sex for control
Age:	≈ 10 weeks
Weight:	Males – 266-333 g Females – 180-225 g
Sampling times:	Days 1 and 14 (Day 10 for HD ♀) taken at 0. 0.5, 2, 4, 8, and 24 hours post dosing

Observation times and results

Mortality: Monitored twice daily

Mortality was seen in 5 of the HD rats including the toxicokinetic animals

Main rats

1/15 HD male rats died

2/15 HD female rats died

Toxicokinetic rats

2/9 HD female rats died

Clinical signs: Monitored twice daily, with detailed examinations once pre-treatment and prior to necropsy

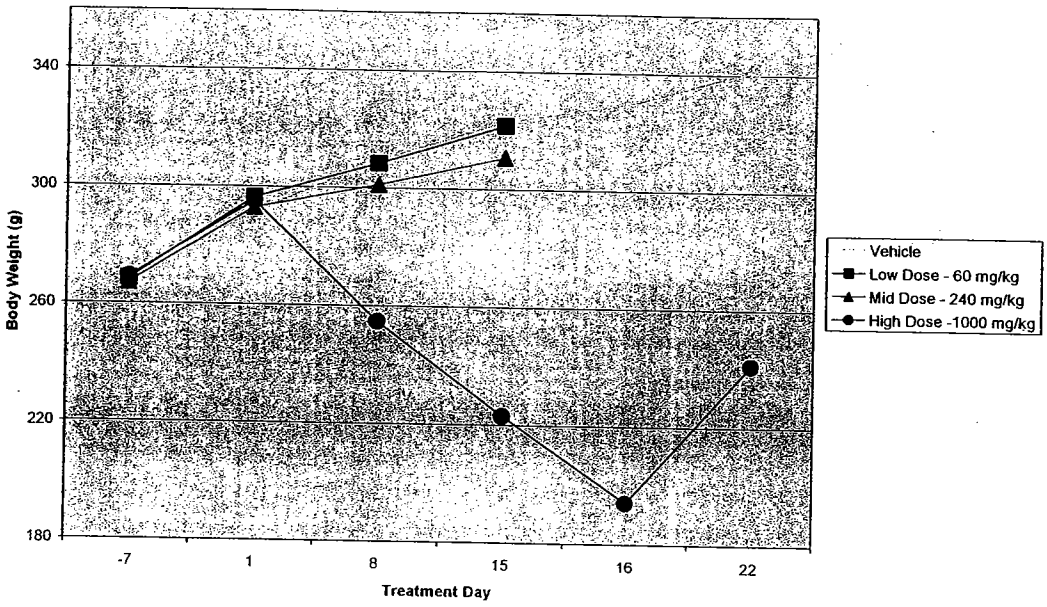
The sponsor's table below shows the clinical signs that were noted after 14 days of GW572016 treatment. GI toxicity is evident as is a general malaise (decreased activity, hunched posture and piloerection). Dehydration and decreased activity were dose-related in both frequency and degree.

Treatment-Related Clinical Observations - Number of Rats Affected						
Clinical Observation	**Males**			**Females**		
Dose (mg/kg/day)	**60**	**240**	**1000**	**60**	**240**	**1000**
N	**10**	**10**	**15**	**10**	**10**	**15**
loose/mucoid feces	1	2	12	0	6	14
dehydration (slight to extreme)	0	0	12	0	7	15
red discoloration of fur (around eyes, snout, forelimbs, mouth, penis)	0	0	8	0	5	14
decreased activity	0	0	9	0	2	8
piloerection	0	0	0	0	8	14
hunched posture	0	0	3	0	0	8
yellow feces	0	0	0	0	1	7
yellow staining of urogenital area	0	0	0	0	0	5

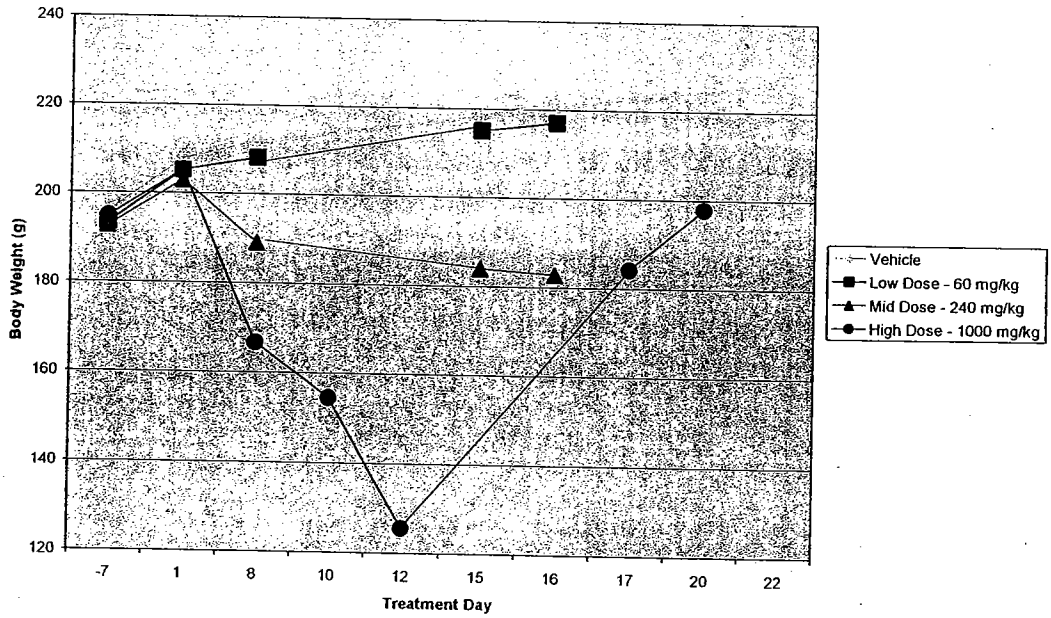
Body weights: twice pre-treatment including Day 1 prior to treatment then weekly until necropsy

The graphs below show the body weights of the male and female rats over the course of the 14-day drug administration and then control and HD rats during recovery. Additional weights were taken of the HD females at Days 10 and 12 during treatment and Days 17 and 20 during recovery, because of the weight losses noted during the study. Weight loss was noted in the HD male and MD and HD female rats, starting on Day 8. The HD rats of both genders were recovering from this toxicity, as weights were increasing at a rate far greater than the weights in the control recovery rats.

Male Rat Body Weights
14-day GW572016 Administration

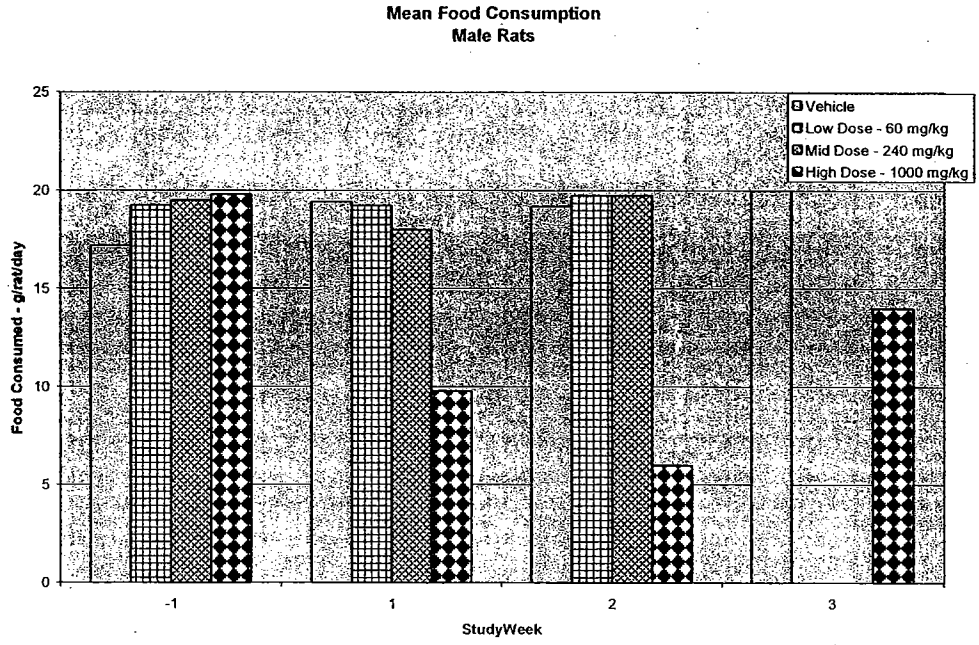


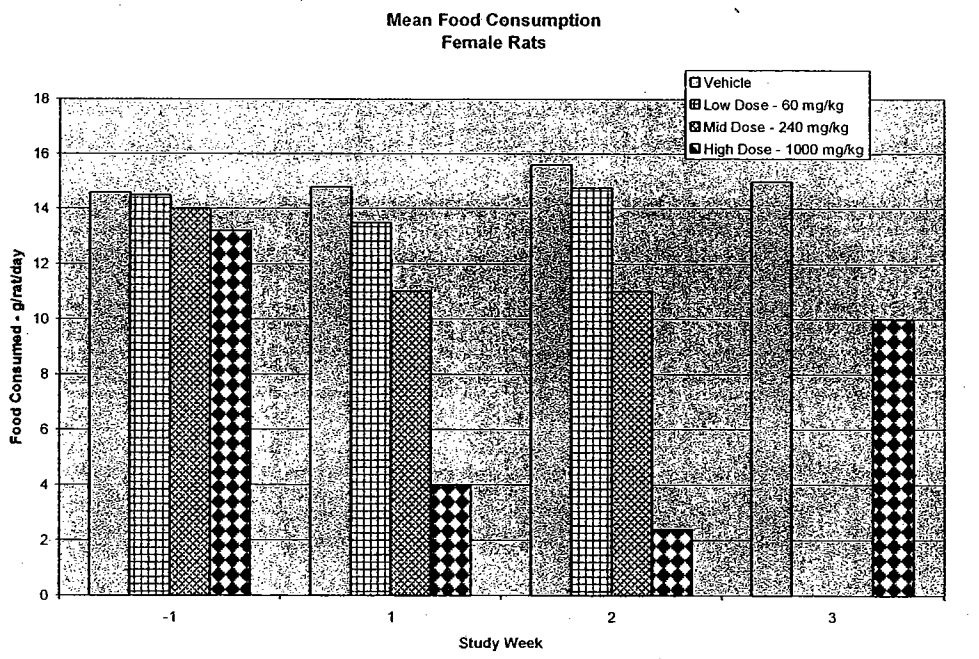
Female Rat Body Weights
14-day GW572016 Administration



Food consumption: One week prior to treatment then weekly until necropsy

Significant decreases in food consumption were seen in the HD male rats and the MD and HD female rats. The food consumption was increasing during the recovery period, although not equal to control it was not significantly different from control.





Ophthalmoscopy: Once pre-treatment, Day 13 for all groups and then Day 20 for recovery groups

No treatment-related ophthalmological changes were seen.

EKG: Not measured

Hematology: Measured at end of treatment or recovery period (euthanized moribund animals measured, but not animals found dead)

The table below presents the statistically significant changes in hematological parameters seen in this study. The HD female rat data are presented, but no statistical tests were conducted on these animals, so statistical significance only applies to the male rat data and the LD and MD female rats. Changes from control are presented in the table to give a broader picture of the hematological changes, but it should be noted that the day the blood was taken from the control recovery females was Day 22 but the HD female recovery blood was taken on Day 20 and the end of treatment samples were taken on Day 10 in the HD females and Day 16 in the control females. The different days of sampling make comparison between HD and control less valid which is why statistical analyses were not conducted.

The major significant hematological effects were all white blood cell parameters. While several red blood cell parameters were significantly decreased, the magnitude was low (6-17% of control), other than the increase in platelets seen in the female rats, significant at the MD at 37% above control. The majority of the parameters, though not back to control levels at recovery, were returning to normal on Day 20/22.

Hematology Parameters
Given 14-Day Treatment With GW572016
Percent Changes from Control

	Males		Females		
Dose Mg/kg/day	MD 240	HD 1000	LD 60	MD 240	HD 1000
WBC					
End of treatment	↑ 28%	↑ 141%	--	↑ 116%	↑ 105%
End of recovery		--			↑ 34%
Lymphocytes					
End of treatment	--	↑ 70%	--	↑ 49%	↑ 16%
End of recovery		--			↓ 21%
Lymphocyte %					
End of treatment	↓ 10%	↓ 28%	↓ 8%	↓ 30%	↓ 42%
End of recovery		↓ 29%			↓ 38%
Neutrophils					
End of treatment	↑ 141%	↑ 631%	↑ 56%	↑ 531%	↑ 639%
End of recovery		↑ 358%			↑ 356%
Neutrophils %					
End of treatment	↑ 77%	↑ 188%	↑ 53%	↑ 181%	↑ 243%
End of recovery		↑ 223%			↑ 225%
Monocytes					
End of treatment	↑ 110%	↑ 810%	--	↑ 523%	↑ 762%
End of recovery		↑ 381%			↑ 198%
Monocytes %					
End of treatment	--	↑ 264%	--	↑ 184%	↑ 311%
End of recovery		↑ 257%			↑ 114%
Basophils					
End of treatment	--	--	--	↑ 124%	↑ 152%
End of recovery		--			↑ 108%
Platelets					
End of treatment	--	--	--	↑ 37%	↑ 47%
End of recovery		--			↑ 38%

HD females – blood taken on Day 10, others taken on Days 15/16
Recovery rats are HD only
-- represents that the data were not statistically significant

Clinical chemistry: Measured at end of treatment or recovery period (euthanized moribund animals measured, but not animals found dead)

The table below presents the statistically significant changes in clinical chemistry parameters seen in this study. The HD female rat data are presented, but no statistical tests were conducted on these animals, so statistical significance only applies to the male rat data and the LD and MD female rats. Changes from control are presented in the table to give a broader picture of the hematological changes, but it should be noted that the day the blood was taken from the control recovery females was Day 22 but the HD female recovery blood was taken on Day 20 and the end of treatment samples were taken on Day 10 in the HD females and Day 16 in the control females. The different days of sampling make comparison between HD and control less valid which is why statistical analyses were not conducted.

Clinical pathology shows liver toxicity from GW572016 administration. Increases in liver enzymes show a dose-response effect and appear to be recovering. Decreases in albumin were still noticeable at recovery.

Clinical Chemistry Parameters in Rats Given 14-Day Treatment With GW572016 Percent Changes from Control

	Males		Females		
Dose Mg/kg/day	MD 240	HD 1000	LD 60	MD 240	HD 1000
A/G ratio					
End of treatment	--	↓ 16%	--	↓ 25%	↓ 23%
End of recovery		--			↓25%
Albumin					
End of treatment	--	↓ 22%	--	↓ 19%	↓ 23%
End of recovery		↓ 16%			↓ 13%
ALT					
End of treatment	↑ 65%	↑ 262%	↑ 26%	--	↑ 162%
End of recovery		--			↑ 58%
AST					
End of treatment	↑ 39%	↑ 201%	--	↑ 24%	↑ 692%
End of recovery		↑ 59%			↑ 5%
Alkaline phosphatase					
End of treatment	--	↓ 49%	--		↓ 47%
End of recovery		--			↑ 38%
Total bile acids					
End of treatment	--	↑ 82%	--	↑ 106%	↑ 47%
End of recovery		↑ 147%			↑ 608%
Calcium					
End of treatment	--	↓ 11%	--	↓ 5%	↓ 13%
End of recovery		↓ 5%			↑ 8%
Cholesterol					
End of treatment	--	↑ 46%	↑ 15%	↑ 31%	↑ 42%
End of recovery		↑ 52%			↑ 64%
Glucose					
End of treatment	--	↓ 29%	--	↓ 26%	↓ 40%
End of recovery		--			↓ 16%
Total protein					
End of treatment		↓ 16%	--	↓ 15%	↓ 16%
End of recovery					↓ 5%
Triglycerides	(LD ↓ 40%)				
End of treatment	↓ 43%	↓ 41%	--	--	↓ 59%
End of recovery					↑ 9%

HD females – blood taken on Day 10, others taken on Days 15/16
Recovery rats are HD only
-- represents that the data were not statistically significant

Urinalysis: Day 13 during treatment then Day 21 in recovery animals. No urine taken from HD females on Day 13

The significant urinalysis effect is presented in the table below. Urine was not collected from the HD female rats due to morbidity. These results are consistent with the clinical sign of dehydration seen in the HD male rats. Blood was present in 3 of the HD male rats at the Day 14 analysis, though RBCs were not seen microscopically in the urine. One HD male also had a large amount of protein in the urine at Day 14.

Urinalysis Parameters
14 Day GW572016 Administration in Rats
Percent Changes from Control

	Males	Males	Females	Females
Dose Mg/kg/day	MD 240	HD 1000	LD 60	MD 240
Urine Volume				
Day 14	↓ 20%	↓ 7%	↓ 40%	↑ 8%
Day 21	---	↓ 75%*	---	---

* - statistically significant

Gross pathology:

Macroscopic changes in rats with both scheduled and unscheduled deaths are presented in the table below.

Macroscopic Findings in the Rat
Following 14 Days of GW572016 Treatment

	Males		Females		
	MD 240 mg/kg	HD 1000 mg/kg	LD 60 mg/kg	MD 240 mg/kg	HD 1000 mg/kg
General					
Yellow tissues throughout	--	5/10	--	10/10	10/10
Stomach					
Yellow material	--	5/10	--	2/10	8/10
Yellow granular material	2/10	4/10	1/10	1/10	1/10
Cecum					
Watery material	2/10	6/10	1/10	9/10	8/10
Thymus					
Reduced size	--	3/10	--	--	--
Prostate					
Reduced size	--	3/10			

Organ weights: Not measured for unscheduled deaths

The significant organ weight changes that are likely-drug related include increases in adrenal weights and decreases in prostate and thymus weights.

Organ Weight Changes in Rats Following 14-Day GW572016 Administration Percent Change From Control

	Males		Females		
Dose – mg/kg	**HD 1000**	**HD Recovery**	**MD 240**	**HD 1000**	**HD Recovery**
Adrenal Gland					
Absolute	↑ 39%	--	--	↑ 42%	↓ 6%
Relative to BW	↑ 99%	↑ 66%	↑ 46%	↑ 104%	↑ 8%
Prostate					
Absolute	↓ 58%	↓ 61%			
Relative to BW	↓ 44%	--			
Thymus					
Absolute	↓ 53%	↓ 70%	--	↓ 66%	↓ 18%
Relative to BW	↓ 40%	↓ 58%	--	↓ 53%	↓ 7%

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

Two tables below show the histopathological changes seen in the 14 day study with GW572016. The first table presents the scheduled deaths while the second table presents the control and HD recovery animals, as well as the unscheduled HD rats. Major changes included effects on rapidly dividing cells. These changes included erosion, ulceration, atrophy, dilatation and degeneration/necrosis of the organs of the GI system. Accessory digestive organs such as the liver, pancreas and salivary glands showed treatment-related changes in the HD males and MD and HD female rats. Lymphoid depletion and foamy macrophage infiltration were seen in the thymus, spleen and lymph nodes. The adrenal glands of MD and HD rats showed cortical vacuolation or cortical hypertrophy. Degeneration, necrosis, hyperplasia and atrophy were noted in the rat prostate in the HD group. Foamy macrophages were also seen in the lungs of all HD rats and also in all MD females. Skeletal muscle degeneration was noted in several sites, including the eye and tongue.

GI histological changes that could resolve over time were mostly not seen upon recovery. Prostate, lung and mammary changes persisted throughout recovery.

Incidence of Histopathological Changes in Rats After 14 Days of GW572016 Administration								
	Control		LD 60 mg/kg		MD 240 mg/kg		HD 1000 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
Stomach								
Focal forestomach erosion	--	--	--	--	--	--	--	1/10
Focal chronic active forestomach ulcer	--	--	--	--	--	3/10	--	--
Focal glandular stomach erosion	--	--	--	--	--	4/10	--	1/10
Multifocal glandular stomach erosion	--	--	--	--	--	--	1/10	--
Diffuse glandular stomach erosion	--	--	--	--	--	--	--	1/10
Focal glandular atrophy	--	--	--	--	--	--	2/10	--
Multifocal glandular atrophy	--	--	--	--	--	1/10	--	1/10
Diffuse glandular atrophy	--	--	--	--	--	--	5/10	4/10
Multifocal glandular dilatation	--	--	--	--	--	1/10	--	5/10
Diffuse glandular dilatation	--	--	--	--	--	5/10	5/10	5/10
Duodenum								
Multifocal mucosal epithelial degen/necrosis	--	--	--	--	--	--	--	5/10
Diffuse mucosal epithelial degen/necrosis	--	--	--	--	--	1/10	--	--
Multifocal erosion	--	--	--	--	--	--	3/10	--
Diffuse erosion	--	--	--	--	--	--	1/10	--
Diffuse lamina propria foamy macrophages	--	--	--	--	--	--	2/10	6/10
Multifocal villous atrophy	--	--	--	--	--	--	1/10	--
Diffuse villous atrophy	--	--	--	--	--	--	--	1/10
Jejunum								
Multifocal mucosal epithelial degen/necrosis	--	--	--	--	--	--	--	3/10
Diffuse mucosal epithelial degen/necrosis	--	--	--	--	--	--	--	3/10
Multifocal erosion	--	--	--	--	--	--	3/10	--
Diffuse erosion	--	--	--	--	--	--	1/10	--
Diffuse lamina propria foamy macrophages	--	--	--	--	--	--	2/10	4/10
Multifocal villous atrophy	--	--	--	--	--	--	2/10	--
Diffuse villous atrophy	--	--	--	--	--	--	3/10	5/10
Ileum								
Multifocal mucosal epithelial degen/necrosis	--	--	--	--	--	--	--	4/10
Diffuse mucosal epithelial degen/necrosis	--	--	--	--	--	--	--	1/10
Multifocal erosion	--	--	--	--	--	--	3/10	--
Diffuse erosion	--	--	--	--	--	--	2/10	--
Diffuse lamina propria foamy macrophages	--	--	--	--	--	--	3/10	9/10
Multifocal villous atrophy	--	--	--	--	--	--	1/10	--
Diffuse villous atrophy	--	--	--	--	--	--	2/10	7/10
Cecum								
Multifocal acute erosion	--	--	--	--	--	--	1/10	--
Multifocal subacute erosion	--	--	--	--	6/10	6/10	1/10	7/10
Diffuse subacute erosion	--	--	--	--	1/10	3/10	3/10	1/10
Multifocal epithelial regener/hyperplasia	--	--	--	--	--	--	1/10	1/10
Diffuse epithelial regeneration/hyperplasia	--	--	--	--	7/10	9/10	5/10	7/10
Colon								
Multifocal subacute erosion	--	--	--	--	--	9/10	1/10	8/10
Diffuse subacute erosion	--	--	--	--	--	--	1/10	1/10
Diffuse subacute inflammation	--	--	--	--	5/10	1/10	--	--
Multifocal epithelial regener/hyperplasia	--	--	--	--	1/10	8/10	1/10	4/10

Diffuse epithelial regeneration/hyperplasia	--	--	--	--	--	1/10	--	--
Rectum								
Focal subacute erosion	--	--	--	--	--	--	--	1/10
Multifocal subacute erosion	--	--	--	--	--	3/10	2/10	5/10
Diffuse subacute erosion	--	--	--	--	1/10	1/10	1/10	--
Diffuse subacute inflammation	--	--	--	--	--	2/10	3/10	--
Multifocal epithelial regener/hyperplasia	--	--	--	--	--	--	--	2/10
Diffuse epithelial regeneration/hyperplasia	--	--	--	--	1/10	4/10	2/10	1/10
Liver								
Multifocal necrotizing granulomatous inflam	--	--	--	--	--	5/10	4/10	10/10
Pancreas								
Multifocal acinar-cell degranulation	--	--	--	--	--	1/10	--	6/10
Salivary glands								
Multifocal serous gland acinar atrophy	--	--	--	--	--	--	--	2/10
Diffuse serous gland acinar atrophy	--	--	--	--	--	--	4/10	8/10
Multifocal ductal epithelial degeneration	--	--	--	--	--	--	5/10	--
Lymph Nodes – mandibular								
Multifocal foamy macrophages	--	--	--	--	--	--	1/10	--
Diffuse foamy macrophages	--	--	--	--	--	7/10	4/10	10/10
Lymph Nodes – mesenteric								
Multifocal foamy macrophages	--	--	--	--	--	--	1/10	--
Diffuse foamy macrophages	--	--	--	--	--	10/10	8/10	10/10
Spleen								
Multifocal ↑ extramedullary hematopoiesis	--	--	--	--	--	1/10	--	--
Diffuse foamy macrophages	--	--	--	--	--	10/10	9/10	10/10
Thymus								
Diffuse lymphoid depletion	--	--	--	--	--	1/10	2/10	3/10
Multifocal lymphoid depletion	--	--	--	--	--	--	1/10	4/10
Multifocal foamy macrophages	--	--	--	--	--	9/10	4/10	8/10
Diffuse foamy macrophages	--	--	--	--	--	--	2/10	2/10
Adrenal glands								
Diffuse bilateral ↑ cortical vacuolation	--	--	--	--	2/10	4/10	--	3/10
Diffuse bilateral cortical hypertrophy	--	--	--	--	1/10	--	5/10	5/10
Prostate gland								
Focal epithelial degeneration/necrosis	--		--		--		1/10	
Multifocal epithelial degeneration/necrosis	--		--		--		1/10	
Multifocal glandular epithelial hyperplasia	--		--		--		2/10	
Diffuse atrophy	--		--		--		5/10	
Skeletal muscle								
Multifocal muscle degeneration/necrosis	--	--	--	--	--	--	4/10	5/10
Diffuse muscle degeneration/necrosis	--	--	--	--	--	--	1/10	--
Tongue								
Focal muscle degeneration/necrosis	--	--	--	--	--	1/10	--	--
Multifocal muscle degeneration/necrosis	--	--	--	--	--	--	2/10	5/10
Eye – extrinsic skeletal muscle								
Multifocal muscle degeneration/necrosis	--	--	--	--	--	--	4/10	10/10
Lungs								
Diffuse alveolar histocytosis	--	--	--	--	--	10/10	10/10	10/10
Multifocal perivascular mononuclear-cell infiltrate	--	--	--	--	--	1/10	--	2/10
Mammary glands								
Diffuse epithelial ballooning degeneration	--	--	--	--	--	--	4/10	--
Diffuse epithelial pigment deposits	--	--	--	--	--	--	4/10	10/10

Incidence of Histopathological Changes in Rats After 14 Days of GW572016 Administration Unscheduled Deaths and Recovery Animals	Control Recovery		HD 1000 mg/kg Recovery		HD 1000 mg/kg Unscheduled Deaths	
	♂	♀	♂	♀	♂	♀
Stomach						
Multifocal glandular stomach ulceration	--	--	--	1/3	--	1/2
Multifocal glandular stomach erosion	--	--	--	--	--	--
Diffuse glandular dilatation	--	--	--	--	1/1	--
Duodenum						
Diffuse erosion	--	--	--	--	1/1	1/2
Diffuse lamina propria foamy macrophages	--	--	--	--	1/1	1/2
Jejunum						
Diffuse erosion	--	--	--	--	1/1	1/2
Diffuse lamina propria foamy macrophages	--	--	--	--	1/1	1/2
Ileum						
Diffuse erosion	--	--	--	--	1/1	1/2
Diffuse lamina propria foamy macrophages	--	--	--	--	1/1	1/2
Cecum						
Diffuse acute erosion	--	--	--	--	1/1	2/2
Multifocal subacute erosion	--	--	--	--	--	1/2
Colon						
Diffuse acute erosion	--	--	--	--	1/1	2/2
Rectum						
Multifocal acute erosion	--	--	--	--	--	1/2
Diffuse acute erosion	--	--	--	--	1/1	1/2
Liver						
Multifocal necrotizing granulomatous inflam	--	--	--	--	--	2/2
Diffuse necrotizing granulomatous inflam	--	--	--	--	1/1	--
Pancreas						
Multifocal acinar-cell degranulation	--	--	2/4	--	--	1/2
Salivary glands						
Diffuse serous gland acinar atrophy	--	--	--	--	1/1	--
Multifocal ductal epithelial degeneration	--	--	--	--	1/1	2/2
Lymph Nodes – mandibular						
Focal lymphoid necrosis	--	--	--	--	1/1	--
Multifocal foamy macrophages	--	--	1/4	2/3	--	2/2
Diffuse foamy macrophages	--	--	--	--	1/1	--
Lymph Nodes – mesenteric						
Focal granulomatous inflammation	--	--	2/4	--	--	--
Multifocal foamy macrophages	--	--	4/4	2/3	--	--
Diffuse foamy macrophages	--	--	--	1/3	1/1	2/2
Spleen						
Multifocal ↑ extramedullary hematopoiesis	--	--	--	1/3	--	--
Diffuse ↑ extramedullary hematopoiesis	--	--	--	2/3	--	--
Multifocal foamy macrophages	--	--	1/4	--	--	--
Diffuse foamy macrophages	--	--	1/3	--	1/1	2/2
Thymus						
Multifocal lymphoid depletion	--	--	2/4	--	--	--
Diffuse lymphoid depletion	--	--	--	--	--	1/2
Multifocal foamy macrophages	--	--	3/4	--	--	--

Diffuse foamy macrophages	--	--	1/4	--	1/1	1/2
Adrenal glands						
Multifocal bilateral cortical cell necrosis	--	--	--	--	1/1	--
Diffuse bilateral ↑ cortical vacuolation	2/5	--	4/4	3/3	--	--
Diffuse bilateral cortical hypertrophy	--	--	--	--	1/1	2/2
Prostate gland						
Diffuse atrophy	--		3/4		1/1	
Skeletal muscle						
Multifocal muscle degeneration/necrosis	--	--	--	--	1/1	2/2
Diffuse muscle regeneration	--	--	4/4	--	--	--
Tongue						
Multifocal muscle regeneration	--	--	4/4	--	--	--
Multifocal muscle degeneration/necrosis	--	--	--	--	1/1	2/2
Eye – extrinsic skeletal muscle						
Multifocal muscle degeneration/necrosis	--	--	--	--	1/1	1/2
Multifocal muscle regeneration	--	--	2/4	--	--	--
Lungs						
Diffuse alveolar histocytosis	--	--	4/4	3/3	1/1	1/2
Mammary glands						
Diffuse epithelial ballooning degeneration	--	--	--	--	1/1	--
Multifocal epithelial pigment deposits	--	--	3/4	--	--	--
Diffuse epithelial pigment deposits	--	--	--	3/3	1/1	2/2

Toxicokinetics:

Toxicokinetics are presented in the sponsor's table below. All treatment groups had measurable levels of GW572016, but female rats showed higher exposures, with higher AUC and C_{max} values at each dose. Only the HD male rats showed any signs of drug accumulation over the 14-day administration.

Mean Toxicokinetic Parameters for GW572016X							
Sex		**Males**			**Females**		
Daily dose (mg/kg/day)		**60**	**240**	**1000**	**60**	**240**	**1000**
AUC[1] (h µg/mL)	Day 1	39.7	178.3	297.9	219.9	2015.0	1131.0
	Day 14[2]	16.1	116.9	773.3	204.3	1418.6	946.5
C_{max} (µg/mL)	Day 1	4.8	5.6	7.5	14.0	46.2	37.0
	Day 14[2]	2.1	9.6	37.4	14.9	86.9	114.8
t_{max} (h)	Day 1	2	4	4	8	8	8
	Day 14[2]	2	2	4	8	8	0
$t_{1/2}$ (h)	Day 1	1.9	22.0	15.2	4.7	27.0	17.9
	Day 14[2]	2.6	4.6	20.7	2.7	13.0	17.3

[1] AUC on Day 1 = AUC_{∞}; on Day 14 = AUC_{τ}

[2] Day 10 for females at 1000 mg/kg/day

Study title: GW572016F: 13 Week oral toxicity study in Wistar Han rats

Key study findings:

- Female rats were more sensitive to GW572016 toxicity
- Mortality (30%) and ↓ body weights seen in HD ♀ rats, and trend toward decrease food consumption, though mortality of 5/6 rats was likely gavage error
- HD ♀ rats ↑ WBC parameters
- Yellow discoloration main macroscopic finding with scabbing also noted
- Organ weight effects, primarily seen in HD females, include ↑ adrenals, lung and spleen and ↓ uterine weights
- Histological changes also predominantly seen in females, though HD males had cecum and heart lesions
- Most histological changes were in lymphoid tissue, GI organs, skin, as well as the lungs, bone and endocrine organs

Study no.: RD2000/01171/01

Volume #, and page #:	Module 4.2.3.2.5
Conducting laboratory and location:	Glaxo Wellcome Inc. Medicines Safety Evaluation Five Moore Drive Research Triangle Park, NC 27709
Date of study initiation:	19 July 2000
GLP compliance:	Letter included and signed
QA reports:	yes (X) no ( )
Drug, lot #, and % purity:	GW572016F, lot # U14572/36/3, purity —

Methods

Doses:	0, 20, 60 and 180 mg/kg/day
Species/strain:	Rat/Wistar Han ~ WI(Glx/BRL/Han)IGS BR]
Number/sex/group or time point (main study):	12/sex/dose (16 HD ♀) 8/sex control and ♂ HD for recovery 4 HD ♀ for recovery
Route, formulation, volume, and infusion rate:	PO, in 0.5% hydroxypropyl methylcellulose + 0.1% Tween 80, 10 mL/kg volume
Satellite groups for toxicokinetics or recovery:	12/sex/dose drug groups, 3/sex controls
Age:	≈ 9 weeks
Weight:	Male – 233.3 – 285.9 g
Sampling times:	Female – 161.4 – 221.8 g

Observation times and results

Mortality: Monitored twice daily

HD females – 6/20 died on study though histopathology indicated that 5 of the rats suffered a gavage error which likely contributed to or accounted for their deaths. These

rats also had histological changes similar to the other GW572016-treated rats, and one had significant renal lesions in addition to the gavage error

Clinical signs: Monitored twice daily (once daily during recovery), with detailed examinations once during treatment, once Week 4 and prior to necropsy

HD ♀ ↑ incidence of
- Hair loss
- Bruising
- Loose feces
- Piloerection
- Red staining (muzzle, mouth, eyes)
- Scabs
- Yellow skin
- Labored breathing
- Dehydration
- Hunched posture
- ↓ activity

HD ♂ and ♀ ↑ incidence of
- Clipped incisors
- Salivation

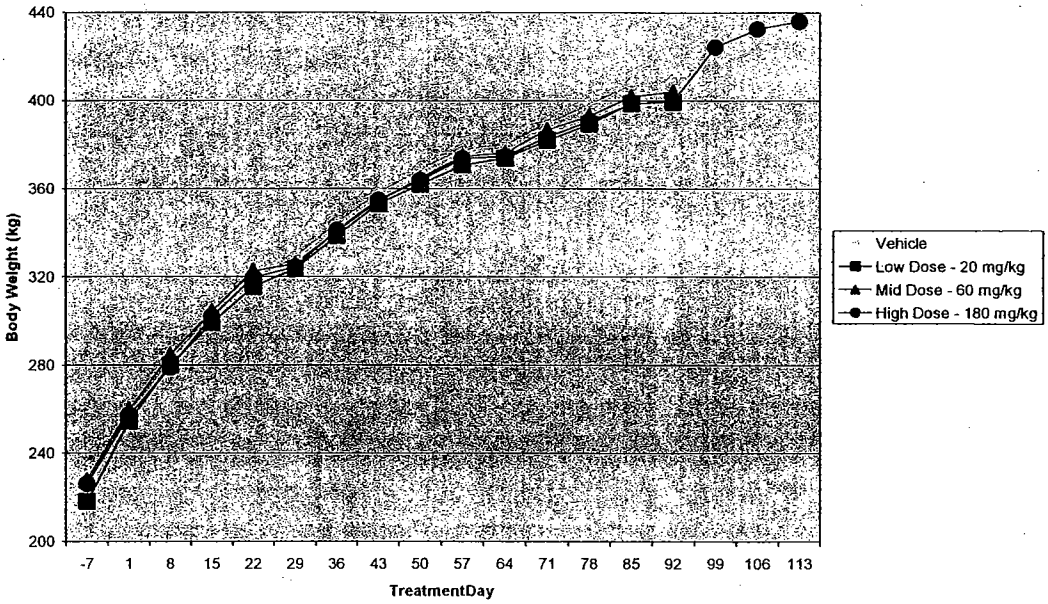
MD ♀ ↑ incidence of
- Hair loss

All ♂ rats
- Dose-dependant salivation

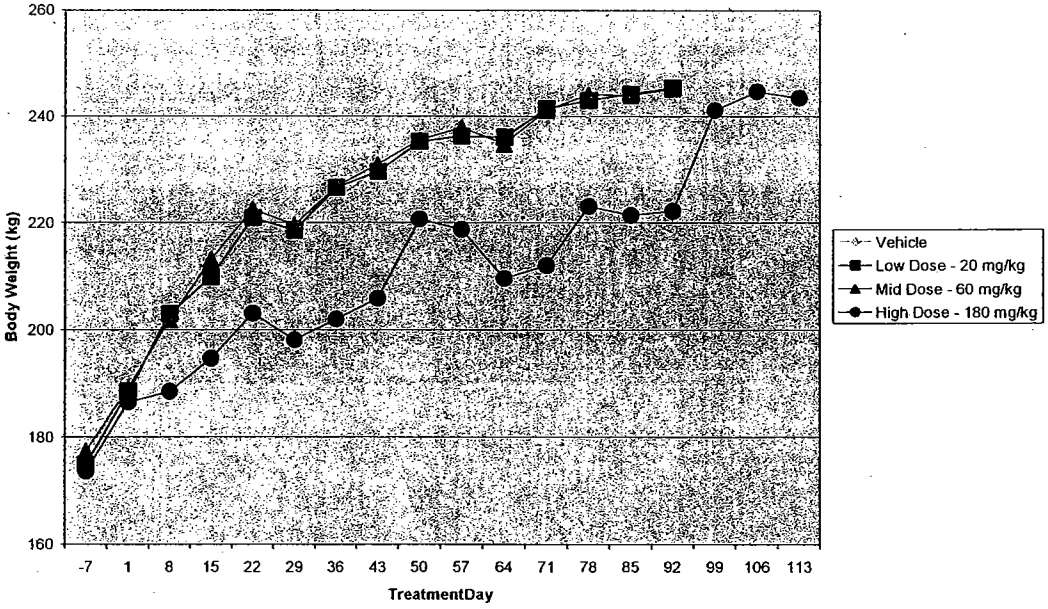
Body weights: Day -7 and 1 prior to treatment then Day 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, 78, 85, and at necropsy. Also Days 99, 106 and at necropsy in recovery rats

The graphs below show the effects of 13 weeks of GW572016 treatment n the body weights of male and female rats. Only the female rats showed an adverse effect of GW572016 administration on weights. The HD female rats had significantly lower body weights than controls from Day 8 until Day 92. The difference was no longer significant during the recovery period, where although the female HD rat weights were lower than the controls, the HD group were increasing in weight greater than was the control group.

Male Rat Body Weights
13-Week GW572016 Administration

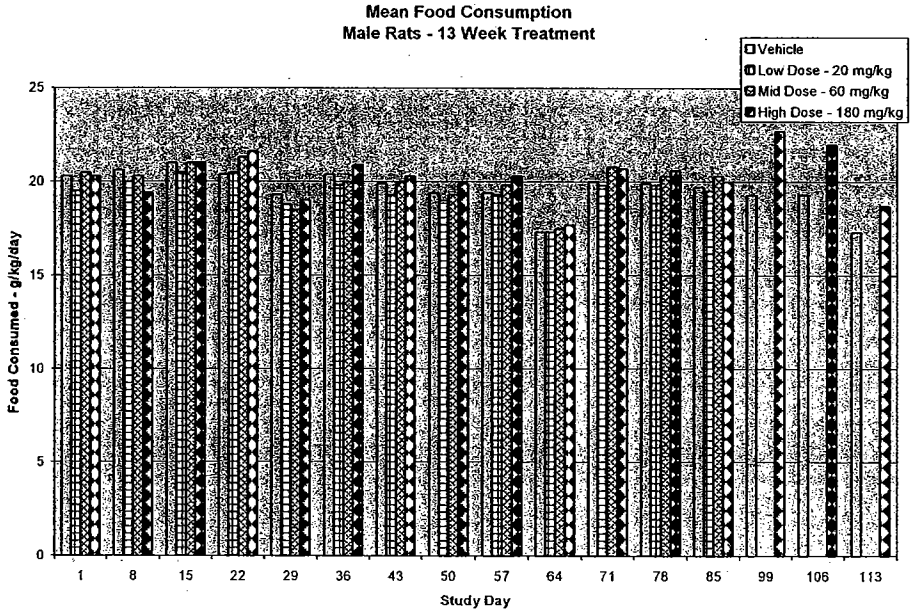


Female Rat Body Weights
13-Week GW572016 Administration



Food consumption: Measured for 1 week prior to treatment and then weekly until Day 85 and weekly during recovery

The tables below show the food consumption of male and female rats throughout the 13 weeks of GW572016 administration and during recovery for control and HD rats. No differences in food consumption were noted in the male rats. In the female rats, the HD group ate less food, although not statistically significant, than control. During recovery the HD male and female rats ate more food than the control rats.



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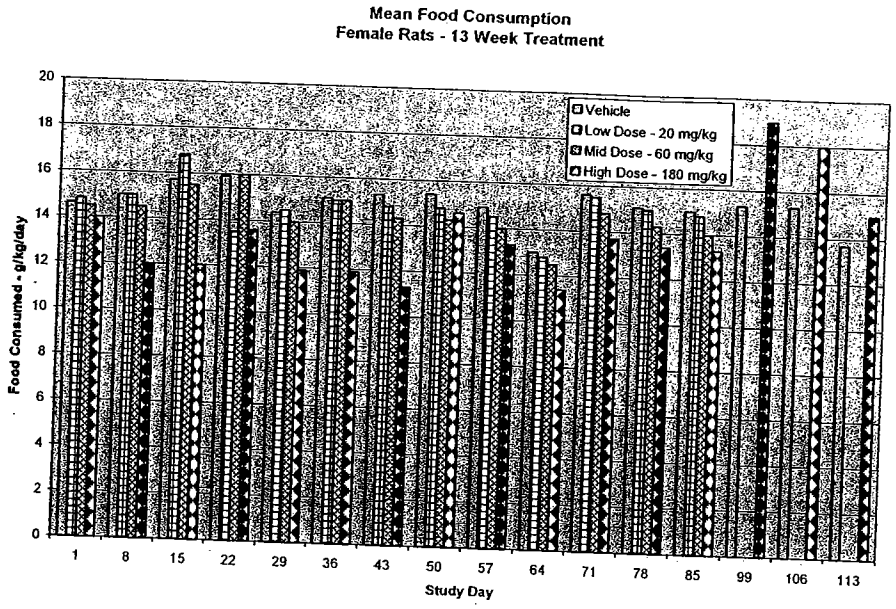

Ophthalmoscopy: Day -9 and Day 90

No ophthalmologic changes related to treatment were noted

EKG: Not measured

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Hematology: Measured once during Week 4 and Week 9 and then at necropsy for main and recovery animals (euthanized moribund animals measured, but not animals found dead)

The table below shows the significant hematological changes in the rats at two points during the study, then at the end of treatment and recovery.

Hematology Parameters
Given 13-Week Treatment With GW572016
Percent Changes from Control

	Males		Females		
Dose Mg/kg/day	MD 60	HD 180	LD 20	MD 60	HD 180
WBC					
Day 27/28	--	↑ 17%	--	--	↑ 95%
Day 58/59	--	↑ 18%	↑ 19%	↑ 31%	↑ 169%
End of Treatment	--	↑ 21%	--	--	↑ 138%
End of recovery		↓ 21%			--
Lymphocytes					
Day 27/28	--	↑ 17%	--	--	↑ 54%
Day 58/59	--	↑ 19%	--	--	↑ 96%
End of Treatment	--	--	--	--	↑ 70%
End of recovery		↓ 20%			--
Lymphocyte %					
Day 27/28	--	--	--	↓ 6%	↓ 22%
Day 58/59	--	--	--	↓ 5%	↓ 27%
End of Treatment	--	--	--	↓ 8%	↓ 27%
End of recovery		--			↓ 7%
Neutrophils					
Day 27/28	--	--	--	--	↑ 267%
Day 58/59	--	--	--	--	↑ 508%
End of Treatment	--	--	--	↑ 62%	↑ 495%
End of recovery		↓ 27%			↑ 77%
Neutrophils %					
Day 27/28	--	--	--	↑ 24%	↑ 99%
Day 58/59	--	--	--	--	↑ 129%
End of Treatment	--	--	--	↑ 43%	↑ 138 %
End of recovery		--			↑ 46%
Monocytes					
Day 27/28	--	--	--	--	↑ 154%
Day 58/59	--	--	--	↑ 52%	↑ 366%
End of Treatment	--	--	--	--	↑ 348%
End of recovery		↓ 41%			--

Monocytes %					
Day 27/28	--	--	--	--	↑ 35%
Day 58/59	--	--	--	--	↑ 77%
End of Treatment	--	--	--	--	↑ 79%
End of recovery		--			--
Eosinophils					
Day 27/28	--	--	--	↑ 46%	↑ 81%
Day 58/59	--	--	--	--	↑ 47%
End of Treatment	--	--	--	--	--
End of recovery		--			--
Eosinophils %					
Day 27/28	--	--	--	--	--
Day 58/59	--	--	--	--	↓ 45%
End of Treatment	--	--	↓ 31%	↓ 24%	↓ 60%
End of recovery		--			--
Basophils					
Day 27/28	--	--	--	--	↑ 112%
Day 58/59	--	--	--	--	↑ 207%
End of Treatment	--	--	--	--	↑ 190%
End of recovery		--			--
Hematocrit					
Day 27/28	--	--	--	--	↓ 5%
Day 58/59	--	--	--	--	↓ 3%
End of Treatment	--	--	--	--	--
End of recovery		--			--
Hemoglobin					
Day 27/28	--	--	--	--	↓ 5%
Day 58/59	--	--	--	--	↓ 4%
End of Treatment	--	--	--	--	↓ 10%
End of recovery		--			--
MCH					
Day 27/28	--	--	--	--	↓ 3%
Day 58/59	--	--	--	--	↓ 6%
End of Treatment	--	--	--	--	↓ 9%
End of recovery		--			↓ 4%
MCV					
Day 27/28	--	--	--	--	↓ 3%
Day 58/59	--	--	--	--	↓ 5%
End of Treatment	--	--	--	--	↓ 7%
End of recovery		--			↓ 4%
Reticulocytes					
Day 27/28	--	↑ 16%	--	--	↑ 45%
Day 58/59	↑ 12%	↑ 20%	--	--	--
End of Treatment	--	--	--	--	↑ 50%
End of recovery		--			--

Reticulocytes %					
Day 27/28	--	↑ 15%	--	--	↑ 46%
Day 58/59	--	↑ 17%	--	--	--
End of Treatment	--	--	--	--	↑ 55%
End of recovery		--			--
RDW					
Day 27/28	--	--	--	--	↑ 7%
Day 58/59	--	--	--	--	↑ 10%
End of Treatment	--	--	--	--	↑ 15%
End of recovery		↑ 9%			↑ 23%
Platelets					
Day 27/28	--	--	--	--	↑ 36%
Day 58/59	--	↑ 11%	--	--	↑ 47%
End of Treatment	--	↑ 13%	--	--	↑ 46%
End of recovery		--			--
Prothrombin Time					
End of Treatment	↑ 5%	↑ 5%	--	--	--
End of recovery		↑ 7%			--

Recovery rats are HD only
-- represents that the data were not statistically significant

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Clinical chemistry: Measured once during Week 4 and Week 9 and then at necropsy for main and recovery animals (euthanized moribund animals measured, but not animals found dead)

The table below presents the significant clinical chemistry changes seen

Clinical Chemistry Parameters in Rats Given 13-Week Treatment With GW572016 Percent Changes from Control

	Males			Females		
Dose Mg/kg/day	LD 20	MD 60	HD 180	LD 20	MD 60	HD 180
A/G ratio						
Day 27/28	--	--	--	--	--	↓ 27%
Day 58/59	--	--	--	↓ 10%	--	↓ 37%
End of Treatment	--	--	--	--	--	↓ 37%
End of recovery			--			↓ 31%
Albumin						
Day 27/28	--	--	--	--	--	↓ 9%
Day 58/59	--	--	--	--	--	↓ 18%
End of Treatment	--	--	↓ 5%	--	--	↓ 22%
End of recovery			--			--
ALT						
Day 27/28	--	--	--	--	↑ 29%	↑ 81%
Day 58/59	--	↑ 34%	↑ 33%	--	↑ 32%	↑ 70%
End of Treatment	--	--	--	--	--	↑ 47%
End of recovery			--			--
AST						
Day 27/28	↓ 9%	--	--	--	--	↑ 13%
Day 58/59	--	↑ 17%	↑ 17%	--	↑ 21%	↑ 41%
End of Treatment	--	--	--	--	--	↑ 35%
End of recovery			--			--
Total bile acids						
Day 27/28	--	--	--	--	--	↑ 49%
Day 58/59	↑ 99%	--	↑ 89%	--	↑ 81%	↑ 112%
End of Treatment	--	--	↑ 53%	--	--	--
End of recovery			--			--
Cholesterol						
Day 27/28	--	--	--	--	↑ 30%	↑ 66%
Day 58/59	--	--	--	--	--	↑ 50%
End of Treatment	--	--	--	--	--	↑ 33%
End of recovery			--			--

Creatinine						
Day 27/28	--	--	--	--	--	↓ 16%
Day 58/59	--	--	--	--	--	--
End of Treatment	--	--	--	--	↓ 23%	↓ 29%
End of recovery			--			--
Globulin						
Day 27/28	--	--	--	--	↑ 5%	↑ 19%
Day 58/59	--	--	--	--	--	↑ 32%
End of Treatment	--	--	--	--	--	↑ 15%
End of recovery						↑ 35%
Total protein						
Day 27/28	--	--	--	--	--	--
Day 58/59	--	--	--	--	--	↓ 5%
End of Treatment	--	↓ 4%	↓ 5%	--	--	↓ 12%
End of recovery			--			--
Triglycerides						
Day 27/28	--	↓ 32%	↓ 27%	--	--	↑ 61%
Day 58/59	--	--	--	↑ 30%	↑ 45%	↑ 66%
End of Treatment	--	--	--	--	--	--
End of recovery			--			--

HD females – blood taken on Day 10, others taken on Days 15/16
Recovery rats are HD only
-- represents that the data were not statistically significant

Urinalysis: Measured once during Weeks 4, 9, 13 and 16 (recovery animals)

While there were a handful of significant urinary parameters, there was no clear treatment related effect as the significant points were very sporadic with no dose-response effect and no consistency over the several time points when urine was analyzed.

Gross pathology:

Macroscopic findings following GW572016 administration are presented in the table below. The preponderance of gross pathology findings were found in the female rat and included yellow discoloration of tissues and skin and fur changes. The only noteworthy macroscopic findings in the male rat included yellow discoloration of the skin in one male MD rat and hair loss in 2 LD rats.

Macroscopic Findings in the Rat Following 13 Weeks of GW572016

	Females		
	LD 20 mg/kg	MD 60 mg/kg	HD 180 mg/kg
Whole carcass			
Yellow discoloration	--	--	8/10
Liver			
Yellow areas	--	--	1/10
Increase in size	--	--	1/10
Spleen			
Increase in size	--	--	1/10
Adrenals			
Increase in size	--	--	1/10
Skin			
Scabs (varying locations)	1/12	--	4/10
Hair loss (varying locations)			

APPEARS THIS WAY
ON ORIGINAL

Organ weights: Not measured for unscheduled deaths

The table below presents the significant changes in organ weights, either absolute weight or relative to body weight, at terminal sacrifice either on Day 91/92 or after recover on Day 113. Many of the changes are spurious, either occurring in only one dose group or being seen in only the absolute organ weight or the relative organ weight. It appears that the several changes in the female rats may be treatment-related, including the increase in lung, liver and spleen weights and decreased uterus weights.

*** Organ Weight Changes in Rats Following 13-Week GW572016 Administration Percent Change From Control**

	Males				Females			
Dose – mg/kg	LD 20	MD 60	HD 180	HD Recov.	LD 20	MD 60	HD 180	HD Recov.
Adrenal Gland								
Absolute	↓ 24%	--	--	--	--	--	↑ 28%	--
Relative to BW	--	--	--	--	--	--	↑ 41%	--
Testes								
Absolute	--	--	--	↓ 5%				
Relative to BW	--	--	--	--				
Thymus								
Absolute	--	↓ 14%	--	--	--	--	--	--
Relative to BW	--	--	--	--	--	--	--	--
Thyroid								
Absolute	--	--	--	↑ 25%	--	↓ 27%	--	--
Relative to BW	--	--	--	↑ 21%	--	--	--	--
Lung								
Absolute	--	--	--	--	--	--	↑ 66%	--
Relative to BW	--	--	--	--	--	--	↑ 80%	↑ 10%
Spleen								
Absolute	--	--	--	--	--	--	↑ 33%	--
Relative to BW	--	--	--	--	--	--	↑ 66%	--
Liver								
Absolute	--	--	--	--	--	--	--	↑ 12%
Relative to BW	--	--	--	--	--	--	↑ 25%	↑ 18%
Brain								
Absolute	--	--	--	--	↑ 6%	--	--	--
Relative to BW	--	--	--	--	--	--	↑ 11%	--
Kidney								
Absolute	--	--	--	--	--	--	--	--
Relative to BW	--	--	--	--	--	--	--	↑ 10%
Uterus								
Absolute					--	--	↓ 44%	--
Relative to BW					--	--	↓ 38%	--

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

The table below presents the organs where increased incidence of drug-related lesions was noted in the 13-week GW572016 study in rats.

Incidence of Histopathological Changes in Rats After 13 Weeks of GW572016 Administration – Scheduled Deaths

	Control		LD 20 mg/kg		MD 60 mg/kg		HD 180 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
Stomach								
Fundus, epithelium, degeneration and apoptotic necrosis (total)	0/12	0/12		0/12		0/12	0/12	2/10
Minimal								1/10
Slight/mild								1/10
Fundus, glandular dilation (total)	1/12	3/12		0/12		0/12	2/12	8/10
Minimal	1/12	3/12					2/12	4/10
Slight/mild								4/10
Nonglandular, ulcer, focal (total)	0/12	0/12		0/12		0/12	0/12	3/10
Minimal								2/10
Slight/mild								1/10
Pylorus, epithelium, degeneration and apoptotic necrosis (total)	0/12	0/12		0/12		0/12	0/12	1/10
Slight/mild								1/10
Duodenum								
Villi, atrophy (total)	0/11	0/12					0/12	1/10
Minimal								1/10
Jejunum								
Villi, atrophy (total)	0/12	0/12					0/12	1/10
minimal								1/10
Ileum								
Villi, atrophy (total)	0/12	0/12					0/12	1/10
minimal								1/10
Cecum								
Glandular dilation and intraluminal cellular debris (total)	0/12	0/12	0/12	0/12	0/12	0/12	0/12	2/10
Minimal								2/10
Typhlitis, proliferative (total)	2/12	1/12	2/12	1/12	5/12	2/12	5/12	7/10
Minimal	2/12	1/12	1/12	1/12		2/12		4/10
Slight/mild			1/12		5/12		5/12	3/10
Liver								
Hepatocellular necrosis, focal (total)	0/12	1/12		0/12		0/12	1/12	1/10
Minimal		1/12					1/12	
Moderately severe								1/10
Hepatocytes, hypertrophy, diffuse (total)	0/12	0/12		0/12		0/12	0/12	7/10
Minimal								3/10
Slight/mild								3/10
Moderate								1/10
Infiltration, mononuclear cell, focal (total)	3/12	4/12		2/12		1/12	4/12	6/10
Minimal	3/12	3/12		2/12		1/12	3/12	2/10
Slight/mild		1/12					1/12	3/10

Moderate								1/10
Kupffer cells, pigment accumulation and hyperplasia (total)	0/12	0/12		0/12		0/12	0/12	4/10
Minimal								3/10
Moderate								1/10
Pyogranulomas, multiple (total)	0/12	0/12		0/12		0/12	0/12	1/10
Moderately severe								1/10
Pancreas								
Acini, zymogen granule depletion (total)	0/12	0/12		0/12		0/12	0/12	2/10
minimal								2/10
Salivary glands								
Acini, atrophy (total)	1/12	0/12		0/12		0/12	0/12	3/10
Minimal	1/12							2/10
Moderate								1/10
Lymph Nodes – mandibular								
Lymphoid hyperplasia (total)	2/12	3/11	0/1	0/12		3/12	4/11	4/10
Minimal		3/11				3/12	4/11	3/10
Slight/mild	2/12							1/10
Macrophage infiltration (total)	1/12	0/11	0/1	0/12		0/12	0/11	1/10
Minimal	1/12							1/10
Plasma cell infiltrate (total)	3/12	4/11	0/1	4/12		1/12	7/11	9/10
Minimal	3/12	4/11		3/12		1/12	6/11	4/10
Slight/mild				1/12			1/11	3/10
Moderate								2/10
Lymph Nodes – mesenteric								
Lymphoid hyperplasia (total)	0/12	0/12		0/12		0/12	2/12	6/10
Minimal							2/12	4/10
Slight/mild								2/10
Macrophage infiltration (total)	10/12	9/12		7/12		10/12	12/12	10/10
Minimal	9/12	8/12		5/12		4/12	3/12	
Slight/mild	1/12	1/12		1/12		2/12	6/12	4/10
Moderate				1/12		4/12	3/12	5/10
Moderately severe								1/10
Spleen								
Red pulp, extramedullary hematopoiesis (total)	0/12	0/12		0/12		0/12	0/12	3/10
Minimal								2/10
Moderately severe								1/10
Red pulp, pigmented macrophage infiltrate (total)	12/12	12/12		12/12		12/12	12/12	10/10
Minimal	12/12	12/12		8/12		8/12	12/12	2/10
Slight/mild				4/12		4/12		3/10
Moderate								5/10
Thymus								
Atrophy (total)	0/12	0/12	0/1	0/12		0/12	0/12	1/10
Minimal								1/10
Adrenal glands								
Cortex, hypertrophy (total)	0/12	0/12		1/12		0/12	0/12	4/10
Minimal				1/12				3/10
Slight/mild								1/10
Bone, femur joint								
Trabecular atrophy (total)	0/12	0/12		0/12		0/12	0/12	5/10
Minimal								4/10
Slight/mild								1/10
Heart								

Fibrosis, focal (total)	0/12	0/12	0/12	0/12	0/12	0/12	2/12	0/10
Minimal							2/12	
Infiltration, mononuclear cell, focal (total)	0/12	0/12	0/12	0/12	0/12	0/12	2/12	0/10
Minimal							1/12	
Slight/mild							1/12	
Myocyte degeneration, focal (total)	0/12	0/12	0/12	0/12	0/12	0/12	1/12	1/10
Minimal							1/12	1/10
Kidney								
Renal tubules, pigment accumulation, bilateral (total)	0/12	0/12		2/12		1/12	0/12	6/10
Minimal				2/12		1/12		3/10
Slight/mild								3/10
Lungs								
Alveoli, histiocytosis (total)	5/12	1/12		1/12			4/12	10/10
Minimal	4/12	1/12		1/12			3/12	
Slight/mild	1/12						1/12	2/10
Moderate								7/10
Moderately severe								1/10
Uterine horns								
Endometrium, atrophy (total)		0/12		0/12		0/12		7/10
Minimal								4/10
Slight/mild								3/10
Mammary glands								
Epithelium, vacuolar degeneration and pigment accumulation (total)	0/6	0/12		0/12		1/10	0/9	7/8
Minimal						1/10		4/8
Slight/mild								3/8
Skin								
Dermis, fibrosis, focal (total)	0/12	0/12		0/12	0/1	0/12	0/12	1/10
Slight/mild								1/10
Dermis, furunculosis and folliculitis, granulomatous (total)	0/12	0/12		0/12	0/1	0/12	0/12	8/10
Minimal								1/10
Slight/mild								5/10
Moderate								2/10
Epidermis, hyperplasia, focal (total)	0/12	0/12		0/12	0/1	0/12	0/12	2/10
Minimal								1/10
Slight/mild								1/10
Epidermis, keratinocytes, degeneration and apoptotic necrosis (total)	0/12	0/12		0/12	0/1	0/12	0/12	1/10
Minimal								1/10
Follicular, epithelium, degeneration and apoptotic necrosis (total)	0/12	0/12		0/12	0/1	0/12	0/12	1/10
Minimal								1/10
Hair follicles, atrophy (total)	0/12	0/12		0/12	1/1	0/12	0/12	0/10
Minimal					1/1			
Hair follicles, folliculitis, focal (total)	0/12	0/12		1/12	1/1	3/12	0/12	0/10
Minimal				1/12	1/1	2/12		
Slight/mild						1/12		
Skin of muzzle								
Hair follicles, atrophy (total)			1/1					
Moderate			1/1					
Hair follicles, folliculitis, focal (total)			1/1					
Moderately severe			1/1					
Skin of cheeks								

Bilateral, dermis, furunculosis and foliculitis, granulomatous (total)				0/2		1/2		
Minimal						1/2		
Epidermis, hyperplasia, focal (total)				1/2		0/2		
Minimal				1/2				
Hair follicles, atrophy (total)				1/2		1/2		
Minimal				1/2		1/2		
Hair follicles, folliculitis, focal (total)				1/2		1/2		
Minimal				1/2		1/2		
Moderate								
Right, dermis, dermatitis, chronic-active, focal (total)				1/2		0/2		
Slight/mild				1/2				
Right, dermis, furunculosis and foliculitis, granulomatous (total)				1/2		0/2		
Minimal				1/2				
Right, epidermis, hyperplasia, focal (total)				1/2		0/2		
Minimal				1/2				
Right, epidermis, ulcer, focal (total)				1/2		0/2		
Slight/mild				1/2				
Skin of head								
Dermis, furunculosis and foliculitis, granulomatous (total)						1/2		
Minimal						1/2		
Hair follicles, atrophy (total)						1/2		
Minimal						1/2		
Hair follicles, folliculitis, focal (total)						1/2		
Moderate						1/2		
Skin of left side								
Epidermis, hyperplasia, focal (total)				1/1				
Minimal				1/1				
Hair follicles, folliculitis, focal (total)				1/1				
Minimal				1/1				
Skin of shoulder								
Dermis, furunculosis and foliculitis, granulomatous (total)	0/1		0/2	0/4		1/4		3/3
Minimal								1/3
Slight/mild						1/4		1/3
moderate								1/3
Hair follicles, atrophy (total)	0/1		1/2	4/4		2/4		0/3
Minimal			1/2	3/4		2/4		
Slight/mild	0/1			1/4				
Hair follicles, folliculitis, focal (total)			2/2	2/4		4/4		0/3
Minimal			2/2	2/4		1/4		
Slight/mild						2/4		
Moderate						1/4		
Skin of upper lip								
Dermatitis, chronic-active, focal (total)								1/1
Moderately severe								1/1
Dermis, furunculosis and foliculitis, granulomatous (total)								1/1
Moderately severe								1/1
Epidermis, hyperplasia, focal (total)								1/1
Slight/mild								1/1
Skin of ventral abdomen								

Hair follicles, atrophy (total)			1/1					
Moderate			1/1					
Hair follicles, folliculitis, focal (total)			1/1					
Moderately severe			1/1					
Skin , neck								
Dermis, dermatitis, chronic-active, focal (total)			0/1					1/3
Minimal								1/3
Dermis, furunculosis and foliculitis, granulomatous (total)			0/1					3/3
Minimal								1/3
Slight/mild								1/3
Moderate								1/3
Epidermis, hyperplasia, focal (total)			0/1					2/3
Minimal								2/3
Follicular epithelium, degeneration and apoptotic necrosis (total)			0/1					1/3
Slight/mild								1/3
Hair follicles, atrophy (total)			1/1					0/3
Minimal			1/1					
Hair follicles, folliculitis, focal (total)			1/1					0/3
Minimal			1/1					

Blocks are left blank if no tissues from a dose/sex group were examined

The table below presents the organs where increased incidence of drug-related lesions was noted in the 13-week GW572016 study in rats.

Incidence of Histopathological Changes in Rats After 13 Weeks of GW572016 Administration – Recovery Animals				
	Control		**HD 180 mg/kg**	
	♂	♀	♂	♀
Liver				
Infiltration, mononuclear cell, focal (total)		1/8		0/4
Minimal		1/8		
Kupffer cells, pigment accumulation and hyperplasia (total)		0/8		3/4
Minimal				1/4
Slight/mild				2/4
Salivary glands				
Acini, atrophy (total)		0/8		1/4
Slight/mild				1/4
Inflammation, chronic (total)		0/8		1/4
Moderate				1/4
Lymph Nodes – mandibular				
Lymphoid hyperplasia (total)		0/8		1/4
Minimal				1/4
Plasma cell infiltrate (total)		1/8		2/4
Minimal		1/8		2/4
Lymph Nodes – mesenteric				
Macrophage infiltration (total)		7/8		4/4
Minimal		5/8		1/4
Slight/mild		2/8		1/4

Moderate				2/4
Spleen				
Red pulp, pigmented macrophage infiltrate (total)		8/8		4/4
Minimal		8/8		1/4
Slight/mild				3/4
Adrenal glands				
Cortex, hypertrophy (total)		3/8		1/4
Minimal		2/8		
Slight/mild		1/8		1/4
Cortex, pigment accumulation (total)		0/8		3/4
Minimal				3/4
Heart				
Myocyte degeneration, focal (total)	0/8	0/8	1/8	0/4
Minimal			1/9	
Kidney				
Renal tubules, pigment accumulation, bilateral (total)		0/8		2/4
Slight/mild				2/4
Lungs				
Alveoli, histiocytosis (total)		1/8		1/4
Minimal				1/4
Slight/mild		1/8		
Mammary glands				
Epithelium, vacuolar degeneration and pigment accumulation (total)		0/7		2/4
Minimal				2/4
Skin				
Dermis, fibrosis, focal (total)	0/2	1/7		0/3
Slight/mild		1/7		
Dermis, furunculosis and folliculitis, granulomatous (total)	0/2	0/7		1/3
Slight/mild				1/3
Skin of cheeks				
Hair follicles, atrophy (total)	1/2			
Minimal	1/2			
Hair follicles, folliculitis, focal (total)	1/2			
Slight/mild	1/2			
Skin of shoulder				
Dermis, furunculosis and folliculitis, granulomatous (total)	0/1	0/2	0/1	1/1
Moderate				1/1
Hair follicles, atrophy (total)	0/1	1/2	1/1	0/1
Minimal		1/2	1/1	
Slight/mild				
Hair follicles, folliculitis, focal (total)	0/1	0/2	0/1	0/1
Minimal				
Skin , neck				
Dermis, furunculosis and folliculitis, granulomatous (total)		0/4		2/2
Slight/mild				1/2
Moderate				1/2

Blocks are left blank if no tissues from a dose/sex group were examined

The histopathological findings in the female rats that died while on study are presented in the table below.

Incidence of Histopathological Changes in Rats After 13 Weeks of GW572016 Administration – Unscheduled Deaths	
	Females
	HD 180 mg/kg
Stomach	
Fundus, epithelium, degeneration and apoptotic necrosis (total)	4/6
Minimal	1/6
Slight/mild	1/6
Moderate	2/6
Fundus, glandular dilation (total)	3/6
Minimal	1/6
Slight/mild	1/6
Moderate	1/6
Ileum	
Gut associated lymphoid tissue, apoptotic necrosis (total)	1/6
Minimal	1/6
Cecum	
Typhlitis, proliferative (total)	3/6
Slight/mild	3/6
Colon	
Gut associated lymphoid tissue, apoptotic necrosis (total)	1/6
Minimal	1/6
Epithelium, apoptotic necrosis (total)	3/6
Minimal	2/6
Slight/mild	1/6
Bone, femur joint	
Trabecular atrophy (total)	3/6
Slight/mild	3/6
Liver	
Kupffer cells, pigment accumulation and hyperplasia (total)	2/6
Minimal	1/6
Slight/mild	1/6
Salivary gland	
Parotid, acini, apoptotic necrosis (total)	2/6
Minimal	2/6
Lymph Nodes – mandibular	
Plasma cell infiltrate (total)	2/6
Minimal	1/6
Moderate	1/6
Lymph Nodes – mesenteric	
Macrophage infiltration (total)	6/6
Slight/mild	1/6
Moderate	4/6
Moderately severe	1/6
Lymphoid depletion (total)	5/6
Slight/mild	4/6
Moderate	1/6
Spleen	
Red pulp, pigmented macrophage infiltrate (total)	6/6
Slight/mild	2/6

Moderate	4/6
White pulp, lymphoid depletion (total)	1/6
Moderately severe	1/6
Adrenal glands	
Cortex, hypertrophy (total)	5/6
Minimal	1/6
Slight/mild	4/6
Heart	
Myocyte degeneration, focal (total)	1/6
Slight/mild	1/6
Infiltration, mononuclear cell, focal (total)	1/6
Slight/mild	1/6
Thymus	
Apoptotic necrosis and lymphoid depletion (total)	2/4
Moderate	2/4
Lymphoid depletion and atrophy (total)	2/4
Moderately severe	2/4
Lungs	
Alveoli, histiocytosis (total)	5/6
Moderate	4/6
Moderately severe	1/6
Pancreas	
Acini, zymogen granule depletion (total)	5/6
Minimal	4/6
Moderate	1/6
Skin	
Hair follicles, folliculitis, focal (total)	1/6
Minimal	1/6
Skin of shoulder	
Hair follicles, atrophy (total)	1/2
Slight/mild	1/2
Skin, dorsal neck	
Dermis, furunculosis and foliculitis, granulomatous (total)	1/1
Slight/mild	1/1
Skin, left neck	
Dermis, furunculosis and foliculitis, granulomatous (total)	1/1
Slight/mild	1/1

Toxicokinetics:

Toxicokinetic Parameters of GW572016X in Wistar Han Rats								
Sex	Dose (mg/kg/day)	Day	AUC[1] (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$[2] (h)	Dose-Normalized AUC (h*ng/mL)	Dose-Normalized C_{max} (ng/mL)
F	20	1	61621	7275	4	1.43	61621	7275
		22	56682	6646	2	2.65	56682	6646
		78	94549	12477	4	2.96	94549	12477
	60	1	278023	21688	2	2.99	92674	7229
		22	318476	23355	4	2.96	106159	7785
		78	342063	28771	2	3.72	114021	9590
	180	1	988443	41891	4	10.4	109827	4655
		22	692018	40306	12	8.58	76891	4478
		78	720320	46735	4	12.3	80036	5193
M	20	1	5628	1209	2	2.42	5628	1209
		22	5796	1026	2	3.24	5796	1026
		78	11984	1651	2	2.38	11984	1651
	60	1	24005	3062	2	2.29	8002	1021
		22	28417	4234	2	2.43	9472	1411
		78	40524	5378	2	2.23	13508	1793
	180	1	86493	6981	4	5.14	9610	776
		22	117966	7983	4	3.33	13107	887
		78	103859	8289	2	3.79	11540	921

n= 2-3 males or females per timepoint per dose group per day

1 AUC_{-} on Day 1 and AUC_{24h} on Days 22 and 78.

2 The half-life for female rats was determined from 2 points.

Study title: GW572016F: A 26-week oral gavage toxicity study in Wistar Han rats

Key study findings:

- Mortality seen in HD male and MD and HD females, several deaths could likely be attributed to technique during the blood draw
- Most toxicities more prominent in the female rats
- Increases in white blood cells, bile acids, cholesterol and ALT
- Increased pigmentation in macrophages seen in ovaries, uterus, spleen and the zona reticularis of the adrenal glands

Study no.: RD2001/01306/00
Volume #, and page #: Module 4.2.3.2.6
Conducting laboratory and location:

Date of study initiation: 28 August 2001
GLP compliance: Letter included and signed
QA reports: yes (X) no ( )
Drug, lot #, and % purity: GW572016F, Lot # R5361/143/1,

Methods

Doses:	20, 60, 180 mg/kg/day – ♂ 10, 60, 120 mg/kg/day ♀
Species/strain:	Rat/Wistar Han [WI(Glx/BRL/Han)IGS BR]
Number/sex/group or time point (main study):	20/sex/dose
Route, formulation, volume, and infusion rate:	PO, in 0.5% hydroxypropyl methylcellulose + 0.1% Tween 80, 10 mL/kg volume
Satellite groups for toxicokinetics or recovery:	8/sex/dose for LD, MD and HD 3/sex/dose for control
Age:	≈ 13 weeks
Weight:	278-350 g ♂ 182-228 g ♀
Sampling times:	Day 1 and during Weeks 13 and 25 At 0, 0.5, 2, 4, 8, 12, and 24 hrs post-administration

Observation times and results

Mortality: Examined twice daily at 1-2 and 4-5 hrs post dose
There were 4 deaths in the main study rats over the course of the study

- 1 MD female
- 3 HD females

Histopathological exams in 3 of the 4 rats showed that the deaths were likely due to the blood draws. There was extensive hemorrhage in the subcutaneous, thoracic and/or

ventral thoracic muscles. The 4th rat did not show these histopathological signs but did die in close association with the blood sampling procedure

In the toxicokinetic rats, 1 HD male and 1 MD female also died while on study. The female rat died the same days as the blood sampling. The male rat did not die in association with the blood sampling procedure. This rat showed clinical signs of:

- labored breathing
- liquid feces
- thinning fur
- red and scabbing skin lesions.

Clinical signs: Weekly detailed exams in addition to the twice daily observations and full physical examination by a veterinarian on Weeks -1, 4, 13 and 26

Thin fur, red skin, dry skin, skin scab and/or flaking on the tail and red muzzle. Noted in both genders at MD and HD, with increased incidence and severity in the HD females.

Red skin
Thin fur
Dry skin
Fur staining
Skin scab
Flaking on the tail

Body weights: Measured weekly
No treatment related body weight changes

Food consumption: Measured weekly
No treatment related food consumption changes

Ophthalmoscopy: Examined once prior to treatment, during Weeks 13 and 26 and at the end of the recovery period
No treatment related changes

EKG: Not conducted

Hematology: During Weeks 4, 13, 26 and at end of recovery period

Hematology Parameters 26 Week GW572016 Administration in Rats Percent Changes from Control				
	Males		Females	
Dose Mg/kg/day	MD 60	HD 180	MD 60	HD 120
WBC				
Week 4	---	↑ 22%	↑ 27%	↑ 57%
Week 13	---	↑ 18%	---	↑ 119%
Week 26	---	---	↑ 44%	↑ 142%
Week 30	---	---	---	↑ 44%
Neutrophils				
Week 4	---	↑ 58%	↑ 84%	↑ 321%
Week 13	---	↑ 52%	↑ 100%	↑ 407%
Week 26	---	---	↑ 167%	↑ 558%
Week 30	---	---	NA	↑ 100%
Monocytes				
Week 4	---	↑ 60%	↑ 70%	↑ 130%
Week 13	---	↑ 44%	---	↑ 213%
Week 26	---	---	↑ 117%	↑ 300%
Week 30	---	---	NA	↑ 177%
Lymphocytes				
Week 4	---	---	---	---
Week 13	---	---	---	↑ 51%
Week 26	---	---	---	↑ 57%
Week 30	---	---	---	---

Clinical chemistry: During Weeks 4, 13, 26 and at end of recovery period

Clinical Chemistry Parameters 26 Week GW572016 Administration in Rats Percent Changes from Control				
	Males		Females	
Dose Mg/kg/day	MD 60	HD 180	MD 60	HD 120
ALT				
Week 4	↑ 15%	↑ 20%	↑ 25%	↑ 40%
Week 13	↑ 18%	↑ 27%	↑ 17%	↑ 36%
Week 26	---	↑ 21%	↑ 26%	↑ 45%
Week 30	---	---	NA	---
Cholesterol				
Week 4	---	---	↑ 24%	↑ 32%
Week 13	---	---	↑ 29%	↑ 37%
Week 26	---	↑ 15%	↑ 42%	↑ 33%
Week 30	---	↑ 21%	---	---
Bile Acids				
Week 4	---	↑ 160%	↑ 24%	↑ 32%
Week 13	↑ 139%	↑ 81%	↑ 29%	↑ 37%
Week 26	---	↑ ---	↑ 42%	↑ 33%
Week 30	NA	↑ 71%	---	---

Urinalysis: During Weeks 4, 13, 26 and at end of recovery period
No treatment related changes

Gross pathology:

Enlarged mandibular lymph nodes
- 10/12 HD females at termination
- 4/11 MD females at termination
- 4/5 HD females at end of recovery
- 2/2 recovery HD females that died on day 205

Scabs on skin of tail
- 12/12 HD females at termination
- 6/11 MD females at termination
- 4/5 HD females at end of recovery

Scab on muzzle
- 1 HD female rat that died on day 24

Organ weights:

Female HD rats

Adrenal gland – ↑ 33% from control
Liver – ↑ 138% from control
Kidneys – ↑ 14% from control

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

The table below shows the histopathology changes, seen predominantly in the female rats.

Significant Histopathological Changes Compared to Control 26 Week GW572016 Administration in Rats

Organ/Tissue Finding	MD	HD
Skin Granulomatous follicular inflammation, destruction of follicular integrity, epidermal hyperplasia	5/12 ♀	8/12 ♀
Adrenal glands Cytoplasmic eosinophilla	---	3/12 ♀
Cecum Mucosal hyperplasia	---	3/12 ♂ 6/12 ♀
Colon Mucosal hyperplasia	---	3/12 ♀
Duodenum Inflammation	---	3/12 ♀
Lymph nodes Lymphoid hyperplasia Pigmented macrophages	8/11 ♀ 8/11 ♀	12/12 ♀ 12/12 ♀
Ovaries Pigmented macrophages	11/11	12/12
Uterus Pigmented macrophages	8/11	12/12
Spleen Pigmented macrophages	2/8 ♀	812 ♀

Toxicokinetics:

Toxicokinetic Parameters in Rats Following 26 Weeks of GW572016 Administration						
Dose (mg/kg/day)	**Males**			**Females**		
	20	**60**	**180**	**10**	**60**	**120**
AUC_{24} (h*ng/mL)						
Day 1	5117	20424	68118	12745	134044	369941
Day 85	7621	23765	92604	21124	195282	384908
Day 169	10455	24705	71680	25052	207267	414998
C_{max} (ng/mL)						
Day 1	1411	3998	8213	1916	12616	38329
Day 85	2327	3401	10607	3320	20976	24949
Day 169	2435	3854	7236	3710	22733	24631

Other:

Study title: GW572016B:Non-audited 7-day oral toxicity study in male Beagle dogs

Key study findings:

- Doses up to 120 mg/kg were well tolerated by male dogs for 7 daily doses

Study no.: RD1999/01838/01
Volume #, and page #: Module 4.2.3.2.7
Conducting laboratory and location: Glaxo Wellcome Inc.
Medicines Safety Evaluation
Five Moore Drive
Research Triangle Park, NC 27709
Date of study initiation: 15 September 1999
GLP compliance: Non-GLP
QA reports: yes () no (X)
Drug, lot #, and % purity: GW572016B, lot # U15602/154/1, purity unknown

Methods

Doses: 30, 60, and 120 mg/kg
Species/strain: Dog/ Beagle
Number/sex/group or time point (main study): 3/dose in main study
Route, formulation, volume, and infusion rate: Oral/gelatin capsule
Satellite groups used for toxicokinetics or recovery: TK from main study dogs
Age: ≈ 12 months
Weight: 8.58 – 9.89 kg
Sampling times: Days 1 and 7 taken at predose, 1, 2, 4, 8, 12 and 24 hrs post-dose

Observation times and results

Mortality: Monitored twice daily

No mortality seen in the study

Clinical signs: Monitored at least twice daily, with detailed exam during pretreatment and at necropsy

Loose feces were seen in the GW572016 dogs with increasing frequency and in increasing numbers of dogs as the GW572016 dose increased.

One HD dog had scabs first noted on the last day of dosing.

Body weights: Days -7, -1 and 8

No treatment-related changes in body weights were noted

Food consumption: One week prior and then weekly during treatment

No treatment-related changes in food consumption were noted

Ophthalmoscopy: Not conducted

EKG: Not conducted

Hematology: Prior to treatment and then on Day 7

No treatment-related changes in hematology were noted

Clinical chemistry: Prior to treatment and then on Day 7

No treatment-related changes in body weights were noted

Urinalysis: Not conducted

Gross pathology:
No significant treatment-related changes in gross pathology were noted
Skin lesions were noted in one dog
Enlarged spleens noted in several dogs, likely not a treatment-related effect but may be a stress reaction.
Enlarged Spleens
Control 1/3
LD 1/3
MD 0/3
HD 2/3

Organ weights:

No treatment-related changes in organ weights were noted

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

No treatment-related histopathological findings

Toxicokinetics: Days 1 and 7

The sponsor's table below presents the toxicokinetic parameters in male dogs over a 7-day period of drug administration. AUC increased with increasing doses on a nearly dose-proportional level. Some increase in drug half-life is seen over the course of a week of daily dosing. Indication of drug accumulation as the AUC increased from Day 1 to Day 7 over the week of dosing.

Parameter	Day	Daily Dose[1]		
		30 mg/kg/day (600 mg/m^2/day)	60 mg/kg/day (1200 mg/m^2/day)	120 mg/kg/day (2400 mg/m^2/day)
AUC (ng h/mL)[2]	1	8084	12478	38686
	7	16436	30876	85961
C_{max} (ng/mL)	1	1254	1463	3250
	7	1470	2092	6225
T_{max} (h)	1	2.67	10.70	4.00
	7	4.33	16.67	6.67
$t_{½}$ (h)	1	3.43	4.50[3]	9.23
	7	5.70	ND[4]	11.70

1 N=3, unless otherwise noted
2 AUC_{∞} on Day 1; AUC_{24} on Day 7
3 N=2
4 Not determined

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Study title: GW572016 F: 14-Day oral toxicity study in Beagle dogs

Key study findings:

- HD of 360 mg/kg not well-tolerated, especially in female dogs
- GW572016 adversely affected body weights and food consumption
- Histopathological changes most notable in the GI tract and lymphoid tissues

Study no.: RD1999/02634/00
Volume #, and page #: Module 4.2.3.2.8
Conducting laboratory and location:

Date of study initiation: 11 April 2000
GLP compliance: Letter included and signed
QA reports: yes (X) no ()
Drug, lot #, and % purity: GW572016F; Lot #U14572/31/15; purity unknown

Methods

Doses:	10, 60, and 360 mg/kg
Species/strain:	Dog/ Beagle
Number/sex/group or time point (main study):	5/sex/dose Control and HD 3/sex/dose LD and MD 2 of the Control and HD of each gender used as recovery animals
Route, formulation, volume, and infusion rate:	Oral/gelatin capsule
Satellite groups used for toxicokinetics or recovery:	TK from main study dogs
Age:	≈ 12 months
Weight:	7.12 – 8.93 kg ♂ 5.56 -7.58 kg ♀
Sampling times:	Days 1 and 15 taken at predose, 0.5, 2, 4, 8, 12 and 24 hrs post-dose

Observation times and results

Mortality: Monitored twice daily

2/5 HD ♀ dogs were euthanized one day prior to termination due to morbidity.

Clinical signs: Monitored at least twice daily (prior to and after dosing). Detailed clinical examinations given prior to study, prior to necropsy and twice during recovery (Day 21 and 35).

The sponsor's table below shows that loose feces, salivation, decreased activity and dehydration were more prevalent in with increasing doses of GW572016. Loose feces, decreased activity and dehydration were still noticeable during the recovery period. The

two dogs that were euthanized moribund both had noted cold extremities, with one dog exhibiting tremors and the other having abdominal discoloration.

Group Incidence[1] of Clinical Observations

Sex	Male				Female			
Daily Dose[2] (mg/kg/day)	0	10	60	360	0	10	60	360
Numbers of animals:								
Main	3	3	3	3	3	3	3	3
Recovery	2	0	0	2	2	0	0	2
Treatment								
Salivation (Days 1-16)								
slight to extreme	1	2	1	4	-	-	-	5
Loose feces (Days 1-16)	2	1	2	5	5	1	3	5
Vomiting (Days 1-16)	1	2	-	5	-	2	1	5
Decreased Activity (Days 3-16)								
slight to extreme	-	-	1	5	-	-	1	5
Dehydration (Days 7-16)								
slight to extreme	-	-	-	5	-	-	-	4
Lacrimation (Days 1-16)	-	1	-	-	1	1	1	2
Recovery								
Loose feces (Days 17-35)	-	-	-	2	-	-	-	2
Vomiting (Day 19)	-	-	-	-	1	-	-	-
Decreased Activity (Days 17-25)								
slight to extreme	-	-	-	1	-	-	-	1
Dehydration (Days 17-27)								
slight to extreme	-	-	-	2	-	-	-	2
Lacrimation (Days 17-29)	-	-	-	1	-	-	-	1

[1] Indicates number of animals in the group exhibiting the symptom.

[2] All doses were expressed as the free base, GW572016X.

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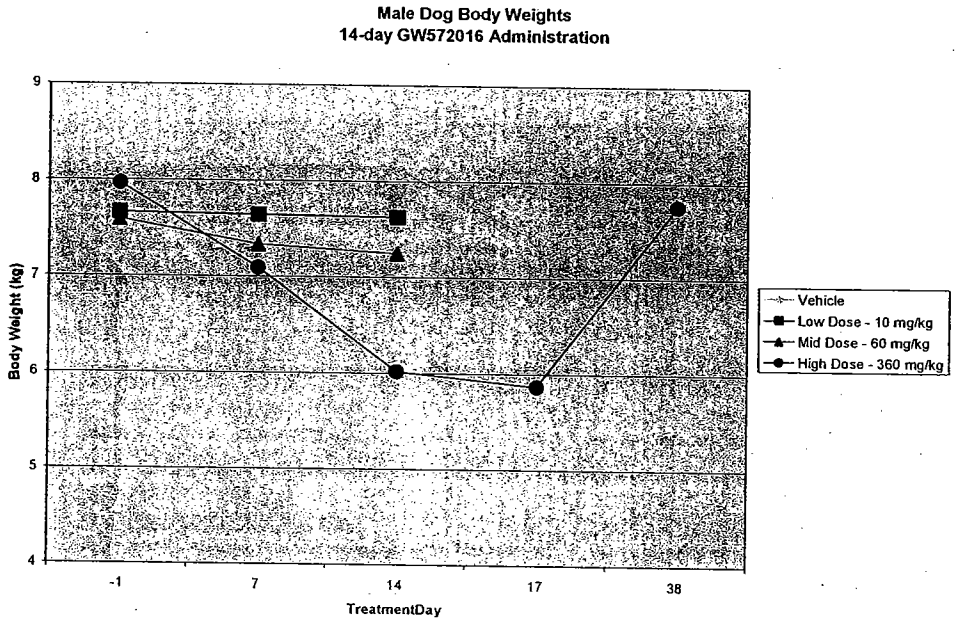
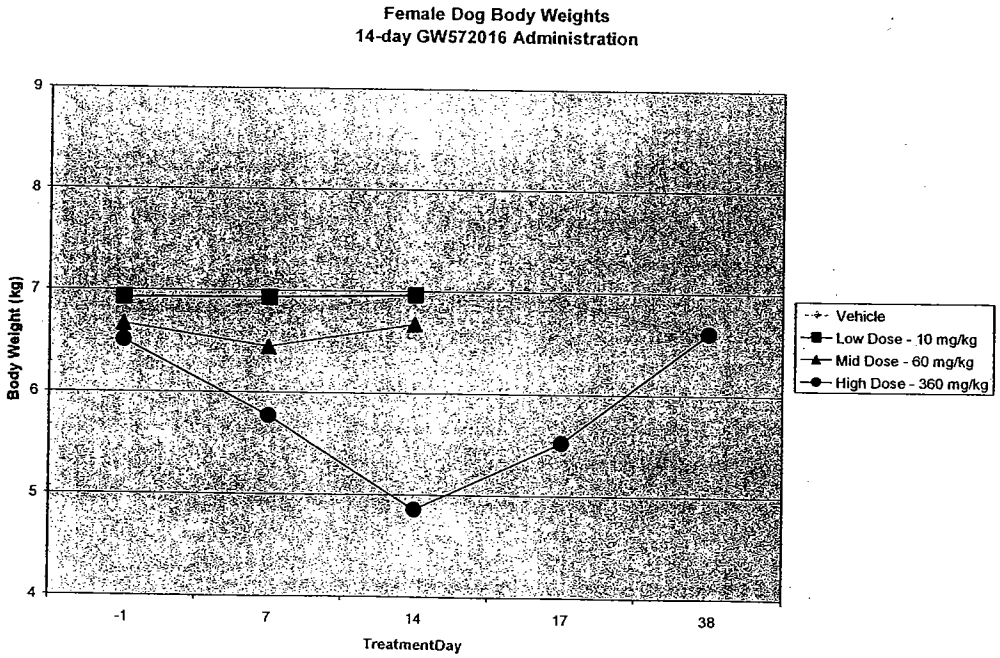
Body weights: Taken 4 times prior to the start of the study and then on Days 7, 14, 16 and 17 and Days 24, 31 and 38 for the recovery dogs.

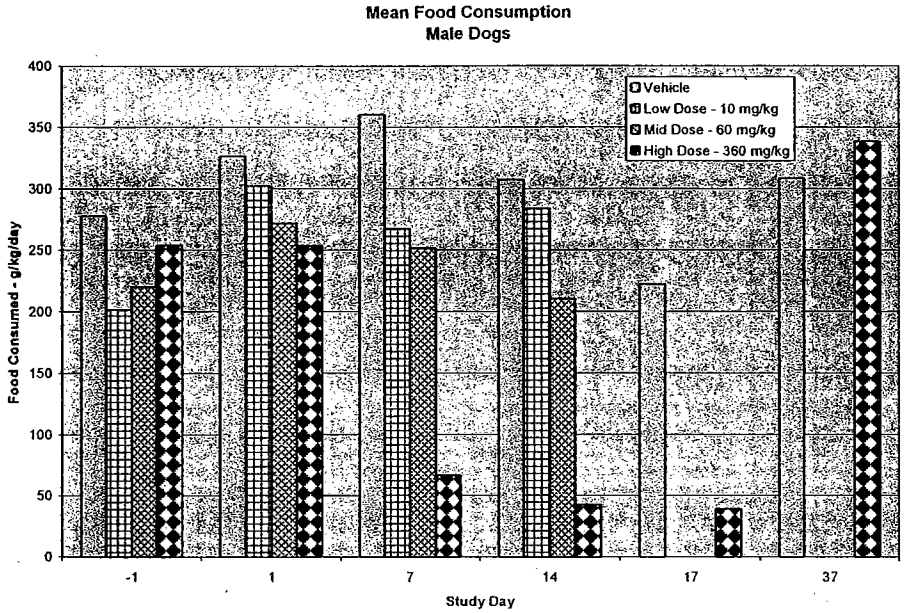
The figures below show the body weights of the dogs over the course of the treatment period and recovery. The toxicity of GW572016 is evident at the HD by the decrease in the dogs' body weights.

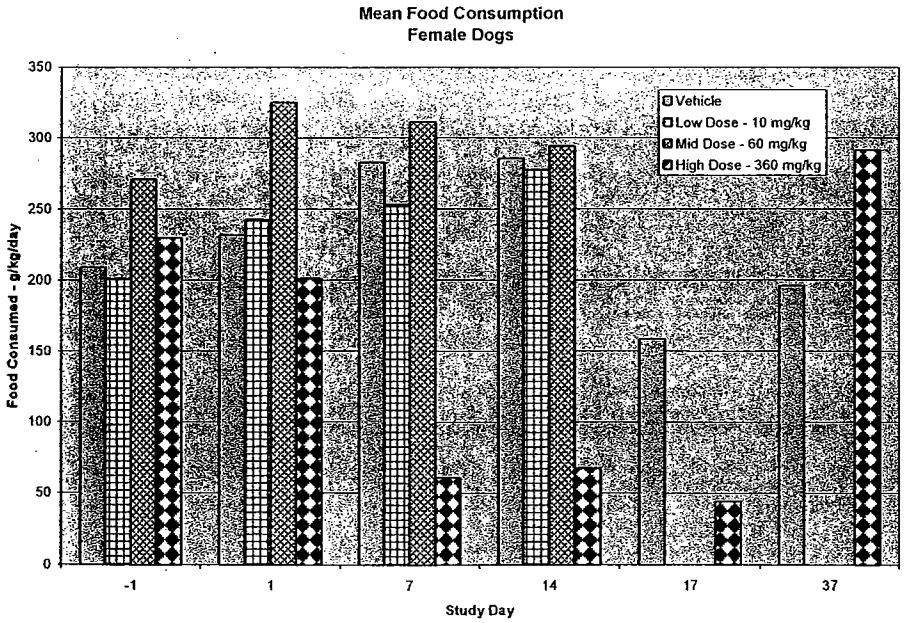




Food consumption: Measured daily during treatment and also days -27 until -21 and Days -7 until Day -1.

The charts below show the food consumption during treatment and recovery. The toxicity of GW572016 can be seen in the decreased food consumption at the HD, which had rebounded by the end of the recovery period.





Hematology: Blood taken on Days -22 and -4, then on Day 16 during treatment period and then Days 22, 29 and 36 during recovery

The table below shows significant changes in hematology parameters at the end of the dosing period, Day 16. Other than persistent increases in total WBCs, the parameters were returning to control levels by Day 36, the end of the recovery period. HD values were not analyzed statistically due to the decreased food consumption and fluid intervention with these dogs.

Hematology Parameters
14 Day GW572016 Administration in Dogs
Percent Changes from Control

	Males		Females	
Dose Mg/kg/day	MD 60	HD 360	MD 60	HD 360
WBCs				
Day 16	↑ 55%	↑ 121%	↑ 33%	↑ 45%
Day 36		↑ 3%		↑ 22%
Lymphocytes - %				
Day16	↓ 18%	↓ 38%	↓ 20%	↓ 44%
Neutrophils				
Day 16	↑ 77%	↑ 196%	↑ 48%	↑ 100%
Monocytes				
Day 16	↑ 100%	↑ 130%	↑ 67%	↑ 46%
Eosinophils				
Day 16	↓ 65%	↓ 57%	↓ 47%	↓ 47%
Eosinophils - %				
Day 16	↓ 75%	↓ 79%	↓ 58%	↓ 68%
Hemoglobin				
Day 16	---	↑ 24%	---	↑ 40%
RBCs				
Day 16	---	↑ 26%	---	↑ 38%
Reticulocytes				
Day 16	---	↓ 76%	---	↓ 61%

Clinical chemistry: Blood taken on Days -22 and -4, then on Day 16 during treatment period and then Days 22, 29 and 36 during recovery

The table below shows significant changes in hematology parameters at the end of the dosing period, Day 16. Parameters were recovered or returning to control values in the HD dogs that survived to Day 36 during the recovery period. HD values were not analyzed statistically due to the decreased food consumption and fluid intervention with these dogs.

Clinical Chemistry Parameters
14 Day GW572016 Administration in Dogs
Percent Changes from Control

	Males		Females	
Dose Mg/kg/day	MD 60	HD 360	MD 60	HD 360
Alkaline Phosphatase Day16	---	↑ 6%	↑ 78%	↑ 20%
Total Bilirubin Day 16	---	↑ 260%	---	↑ 780%
Total Bile Acids Day 16	↑ 33%	↑ 251%	↑ 42%	↑ 371%
Total Protein Day 16	↓ 9%	↓ 34%	↓ 5%	↓ 34%
Albumin Day 16	↓ 17%	↓ 48%	↓ 14%	↓ 47%
A/G Ratios Day 16	↓ 21%	↓ 41%	↓ 22%	↓ 39%
Calcium Day 16	↓ 5%	↓ 20%	↓ 4%	↓ 22%
ALT Day 16	↑ 30%	↑ 1%	↑ 104%	↑ 66%

Urinalysis: Urine collected on Days -25 and -5, then at necropsy, either Day 16 for main study dogs or Day 38 for recovery dogs

There were lowered levels of several electrolytes in the urinalysis of the MD and mostly the HD dogs. This was likely secondary to dehydration and fluid imbalance and not a direct drug effect. The moribund state of the HD dogs required fluid intervention and would likely have interfered with electrolyte levels.

Urine Electrolytes
14 Day GW572016 Administration in Dogs
Percent Changes from Control

	Males		Females	
Dose Mg/kg/day	MD 60	HD 360	MD 60	HD 360
Chloride				
Day16-17	---	↓ 82%	↓ 40%	↓ 85%
Day 38		↓ 63%		↓ 21%
Potassium				
Day 16-17	↓ 35%	↓ 81%	---	↓ 60%
Day 38		↓ 18%		↓69%
Sodium				
Day 16-17	---	↓ 90%	↓ 61%	↓ 93%
Day 38		↓ 32%		↓ 33%

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Gross pathology:

Macroscopic findings are presented in the table below. In addition to reduced contents in all the GI organs in the unscheduled death dogs, the primary macroscopic findings are yellow and red discoloration, primarily of the GI organs. The gall bladder also shows macroscopic signs of toxicity.

Macroscopic Findings Following 14 Days of GW572016 in Dogs Including Unscheduled Deaths

	HD Males	HD Females Scheduled Deaths	HD Females Unscheduled Deaths
Stomach			
Yellow mucosa	1/3	0/1	2/2
Duodenum			
Red mucosa	2/3	1/1	0/2
Jejunum			
Red mucosa	2/3	1/1	1/2
Ileum			
Red mucosa	1/3	1/1	0/2
Cecum			
Red mucosa	0/3	0/1	1/2
Colon			
Red mucosa	0/3	0/1	1/2
Thymus			
Reduction in size	0/3	1/1	0/2
Gall Bladder			
Distended, dark bile	1/3	1/1	2/2
Gingiva			
Depressed area, multifocal	1/3	1/1	2/2
Lymph Nodes			
Increased in size	1/1	1/1	1/2
Tongue			
Depressed focus	1/3	0/1	1/2
Brown multifocal discoloration	0/3	1/1	0/2
Focal brown discoloration	1/3	0/1	1/2
Carcass			
Yellow discoloration	1/3	1/1	1/2

Organ weights: Not conducted for unscheduled deaths

Relevant changes in absolute organ weights and organ weights relative to BW are presented in the table below. The liver findings are not consistent or with related histopathological findings, so are likely not drug-related. Increased adrenal glands are seen in the HD dogs and likely due to the stress of the toxicity at this dose. Persistent and consistent decreases in spleen and thymus were also associated with lymphoid depletion of these organs. The reproductive organ weight changes were not accompanied by histopathological changes.

Organ Weights Following 14 Days of GW572016 Including Recovery Animals Percent Changes from Control

	Males			Females		
Dose Mg/kg/day	MD 60	HD 360	Recovery	MD 60	HD 360	Recovery
Adrenal Glands						
Absolute	---	↑23%	↑ 23%	---	↑ 12%	↑ 33%
Relative to BW		↑ 88%	↑ 21%		↑ 74%	↑ 33%
Spleen						
Absolute	↓ 29%	↓ 50%	↓ 20%	↓ 16%	↓ 67%	↓ 31%
Relative to BW	↓ 18%	↓ 25%	↓ 22%	↓ 6%	↓ 47%	↓ 31%
Thymus						
Absolute	↓ 39%	↓ 66%	↑ 34%	↓ 37%	↓ 76%	↓ 32%
Relative to BW	↓ 28%	↓ 48%	↑ 35%	↓ 35%	↓ 64%	↓ 32%
Prostate						
Absolute	↓ 17%	↓ 46%	↓ 38%			
Relative to BW	↓ 4%	↓ 18%	↓ 38%			
Uterus						
Absolute				↓ 15%	↓ 56%	↑ 29%
Relative to BW				↓ 11%	↓ 31%	↑ 27%
Ovaries						
Absolute				↓ 21%	↓ 44%	↓ 27%
Relative to BW				↓ 17%	↓ 14%	↓ 28%
Liver						
Absolute	↓ 12%	↓ 23%	↑ 28%	↓ 10%	↓ 42%	↑ 41%
Relative to BW	↑ 4%	↑ 18%	↑ 26%	↓ 5%	↓ 11%	↑ 42%

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

Microscopic Findings Following 14 Days of GW572016 Including Recovery Animals			
	HD Males	HD Females Scheduled Deaths	HD Females Unscheduled Deaths
Stomach, fundus			
Atrophy/degen mucosal glands, minimal	-	-	-
Slight/mild	-	-	-
moderate	3/3	-	-
moderately severe	-	1/1	2/2
Duodenum			
Degen/necrosis, mucosal glands, moderate	2/3	-	-
moderately severe	1/3	1/1	2/2
Villous atrophy, slight/mild	1/3	-	-
Moderate	1/3	-	2/2
Moderately severe	1/3	1/1	-
Jejunum			
Degen./necrosis, mucosal glands, minimal	1/3	-	-
Slight/mild	2/3	1/1	-
moderate	-	-	2/2
Villous atrophy, minimal	-	1/1	-
slight/mild	1/3	-	1/2
moderate	1/3	-	1/2
Ileum			
Degen./necrosis, mucosal glands, minimal	2/3	-	-
slight/mild	-	-	2/2
moderate	-	1/1	-
Villous atrophy, minimal	1/3	-	-
slight/mild	1/3	-	1/2
Moderate	-	1/1	1/2
Ileum, Peyer's Patches			
Lymphoid depletion, slight mild	1/3	-	-
moderate	2/3	-	1/2
Moderately severe	-	1/1	1/2
Macrophage infiltrate, minimal	-	-	-
Slight/mild	-	-	-
moderate	3/3	1/1	2/2
Cecum			
Dilated mucosal glands, minimal	1/3	-	1/2
Slight/mild	1/3	-	-
Colon			
Dilated mucosal glands, minimal	1/3	-	2/2
Rectum			
Dilated mucosal glands, minimal	-	1/1	1/2
Slight/mild	1/3	-	1/2
Spleen			
Lymphoid depletion, slight/mild	3/3	-	-
moderate	-	1/1	2/2
Macrophage infiltrate, minimal	-	-	1/2
Slight/mild	3/3	1/1	1/2

Thymus			
Lymphoid depletion, minimal	-	(1/2)	-
moderate	-	(1/2)	-
moderately severe	3/3 (2/2)	1/1	1/2
severe	-	-	1/2
Macrophage infiltrate, slight/mild	-	-	1/2
moderate	3/3	1/1	1/2
Pancreas			
Zymogen depletion, minimal	3/3	1/1	-
slight/mild	-	-	1/2
moderate	-	-	1/2
Liver, hepatocytes			
Cytoplasmic vacuolization, focal, slight/mild	-	-	1/2
Glycogen depletion, minimal	-	1/1	1/2
Slight/mild	1/3	-	-
moderate	-	-	1/2
Lymph Nodes			
Lymphoid depletion, slight/mild	1/3	1/1	-
moderate	2/3	-	2/2
Macrophage infiltrate, slight/mild	2/3	1/1	1/2
moderate	1/3	-	1/2
Tongue			
Inflammation, ulcerative, focal, moderate	-	-	1/2
Inflammation, chronic-active, focal, slight/mild	-	1/1	
Gingiva			
Inflam, ulcerative, chronic-active, focal, moderate	1/3	-	-
Slight/mild	-	1/1	-
Skeletal muscle			
Atrophy, minimal	2/3 (1/2)	-	-

( ) represent incidences in recovery animals

Toxicokinetics:

The sponsor's table below presents the toxicokinetic data for Days 1 and 15.

Mean Plasma Toxicokinetic Parameters of GW572016X

Sex		Male				Female			
Daily Dose[1] (mg/kg/day)		0[2]	10[2]	60[2]	360[2]	0[2]	10[2]	60[2]	360[2]
AUC[3] (h*ng/mL)	Day 1	-	4206	60253	145880	-	8685	46256	352644
	Day 15	-	5147	57621	153186	-	11851	56099	143825
C_{max} (ng/mL)	Day 1	BQL	663	3239	6629	BQL	972	3716	9083
	Day 15	BQL	770	3870	7467	BQL	1246	4384	6518
$t_{1/2}$ (h)	Day 1	-	4.31	8.67	11.7	-	4.37	4.61	21.1
	Day 15	-	3.05	15.7	88.9	-	5.62	12.0	200

1 All doses were expressed as the free base, GW572016X
2 n of 3 to 5 males or females,
3 AUC_∞ on Day 1 and AUC_τ on Day 15,
- = not applicable, BQL = Below Quantitation Limit, 10 ng/mL

Study title: GW572016F: 13-Week oral toxicity study in Beagle dogs

Key study findings:

- 2 HD ♂ dogs euthanized moribund
- Clinical signs included dehydration, salivation, loose feces, ulcerations, scabs, vomiting
- Body weights decreased in HD dogs, and that continued during recovery with HD ♀ dogs but not ♂ dogs
- Decreased food consumption in HD dogs, significant in the first week of dosing
- Increased WBCs, neutrophils and monocytes, and decreased basophils - more prominent in female dogs
- Increases in bilirubin, total bile acids, alkaline phosphatase, ALT
- Histological changes in lymphoid tissue, liver, GI, spleen, thymus, muscle, pancreas, skin, mammary glands, bone marrow as well as increased pigment deposition in numerous tissues

Study no.: RD2000/01600/01

Volume #, and page #:	Module 4.2.3.2.9
Conducting laboratory and location:	Glaxo Wellcome Inc. Medicines Safety Evaluation Five Moore Drive Research Triangle Park, NC 27709
Date of study initiation:	2 September 2000
GLP compliance:	Letter included and signed
QA reports:	yes (X) no ()
Drug, lot #, and % purity:	GW572016F, lot # R5361/44/1, purity not given though other studies have shown this Lot # with a purity around —

Methods

Doses:	10, 40, and 160 mg/kg
Species/strain:	Dog/ Beagle
Number/sex/group or time point (main study):	4/sex/dose in main study Additional 2/sex in Control and HD for recovery
Route, formulation, volume, and infusion rate:	Oral/gelatin capsule
Satellite groups used for toxicokinetics or recovery:	TK from main study dogs
Age:	≈ 11-12 months
Weight:	9.11 – 12.5 kg ♂ 7.25 -9.64 kg ♀
Sampling times:	Days 1, 29 and 85 taken at predose, 0.5, 2, 4, 8, 12 and 24 hrs post-dose

Observation times and results

Mortality: Monitored twice daily

2/6 HD ♂ dogs were euthanized moribund, one on Day 31 and one on Day 86

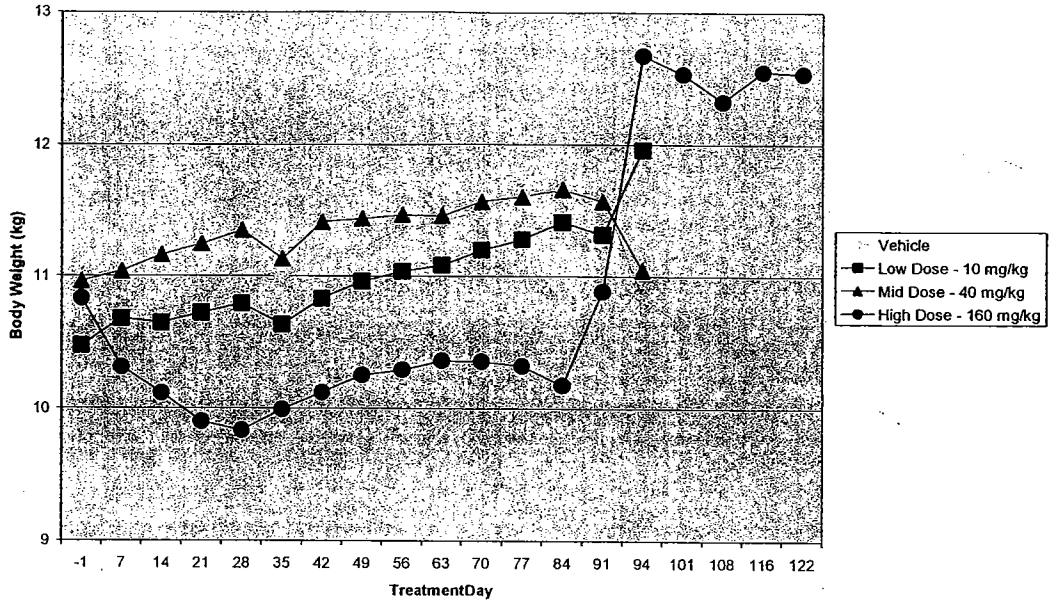
Clinical signs: Monitored at least twice daily (prior to and after dosing) during treatment and once daily during recovery. Detailed clinical examinations given prior to study, Week 5 and prior to necropsy (terminal and recovery).

The following clinical signs were seen with increasing incidence and frequency with GW572016 exposure: Decreased activity, dehydration, loose feces, scabs/raw area, red paws, red gums/mouth, red in feces, yellow feces, vomiting, salivation, swollen footpads, ulcerations (paw, mouth), and yellow sclera/skin.

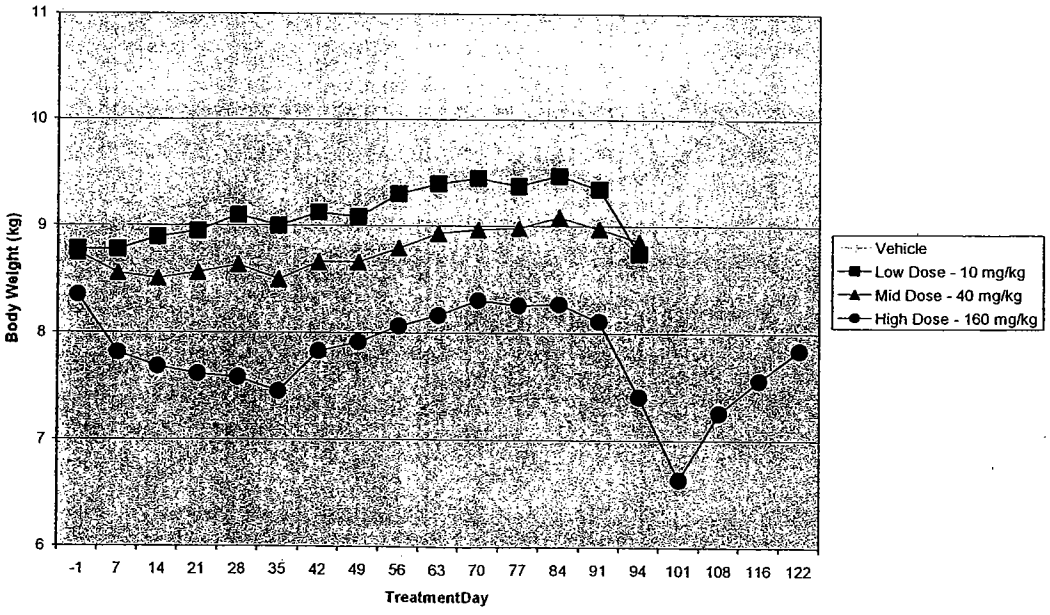
Body weights: Taken 2 times prior to the start of the study and then weekly and on day of necropsy (terminal and recovery).

The graphs below show the effect of GW572016 treatment on body weights. The HD dogs had lower body weights at the end of the treatment period in both genders. In the female dogs, this lowered body weight persisted during the recovery period. In the male HD dogs, the food weights increased during recovery and by the end of the recovery period, male HD dogs weighed more than control dogs. The female HD recovery animals were gaining weight however, indicative of some degree of recovery of the toxicity of GW572016 on body weights.

Male Dog Body Weights
13-Week GW572016 Administration

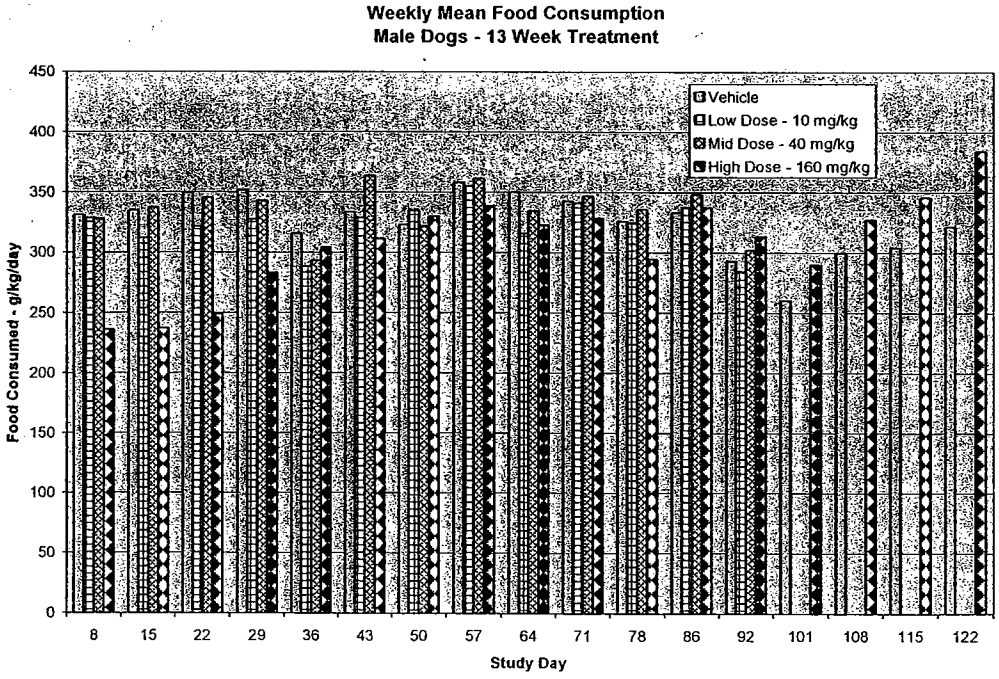


Female Dog Body Weights
13-Week GW572016 Administration



Food consumption: Measured once prior to treatment and then weekly during treatment and recovery period.

The graphs below present the food consumption during the 13 week drug treatment for all 4 groups and during recovery for the control and HD groups. HD male and female dogs had statistically significant decreases in food intake in the first week of dosing. Though not significant, the GW572016 HD dogs continued to eat less food throughout dosing than did the control dogs. During recovery, the HD dogs had increased food consumption compared to control dogs.



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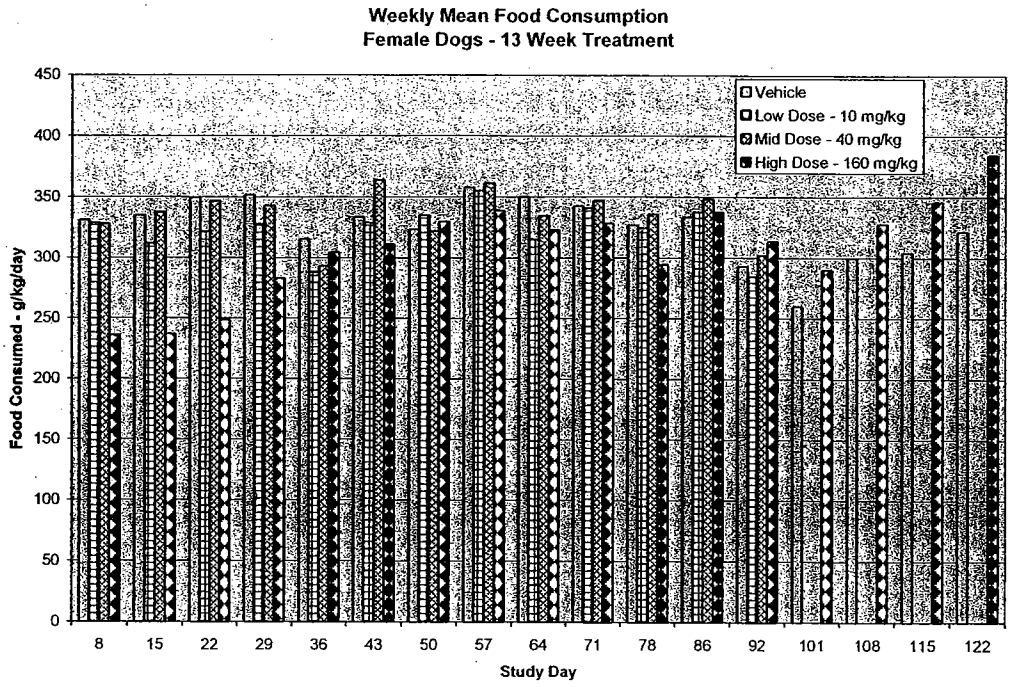

Ophthalmoscopy: Examined Days -16 and Day 90

No treatment-related effects on ophthalmologic evaluations were noted.

EKG: Examined Days -15, -7 and Days 28 and 91 during treatment and Day 119 during recovery, 2-6 hrs post-dose on treatment days

No treatment-related effects on electrographic data were seen

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Hematology: Blood taken on Days -6 then on Days 30 and 90 during treatment period and then Day 121 during recovery

The table below shows significant changes in hematology parameters at Day 30 and at the end of the dosing period, Day 90. Absolute monocytes and monocyte percentage were elevated at Day 30 and Day 90 in the HD and at Day 90 in the MD. These numbers were returning to normal at the recovery time point, though still decreased from the control. Total WBCs and absolute neutrophils were elevated in the female dogs, with significance seen at Day 30. These same dogs had significantly decreased basophil levels as well. GW572016 effects on hematology were more prominent in the female dogs. The hematological changes could likely have been due to inflammation and damage seen in the GI tract.

Hematology Parameters
13 Week GW572016 Administration in Dogs
Percent Changes from Control

	Males		Females	
Dose Mg/kg/day	MD 40	HD 160	MD 40	HD 160
WBCs				
Day 30	↓ 13%	↓ 6%	↑ 15%	↑ 47%*
Day 90	↑ 2%	↑ 2%	↑ 1%	↑ 23%
Recovery		↑ 4%		↑ 13%
Neutrophils				
Day 30	↓ 18%	↓ 10%	↑ 15%	↑ 53%*
Day 90	↑ 4%	0	↓ 5%	↑ 22%
Recovery		↑ 4%		↑ 14%
Monocytes				
Day 30	↑ 3%	↑ 66%*	↑ 44%	↑ 128%*
Day 90	↑ 28%	↑ 24%	↑ 50%*	↑ 83%*
Recovery		↑ 17%		↑ 52%
Monocytes - %				
Day 30	↑ 21%	↑ 80%*	↑ 22%	↑ 53%*
Day 90	↑ 25%	↑ 21%	↑ 46%*	↑ 49%*
Recovery		↑ 16%		↑ 36%
Basophils - %				
Day 30	↓ 10%	↓ 40%	↓ 34%	↓ 44%*
Day 90	↓ 22%	↓ 54%	↓ 23%	↓ 33%*
Recovery		↓ 38%		↑ 56%

* - statistically significant

Clinical chemistry: Blood taken on Days -6 then on Days 30 and 90 during treatment period and then Day 121 during recovery

The table below shows the effects of GW572016 administration on clinical chemistry parameters. Significant increases in bilirubin, bile acids, alkaline phosphatase, and ALT is seen in dogs of both genders at the MD and HD levels, indicative of toxicity to the hepatobiliary and/or GI systems. Additional changes of this toxicity include decreases in total protein, albumin and A/G ratios and increased globulin in several of the treatment groups. At recovery, the male dogs show that the toxicity is recovering and the numbers are returning to control levels. The female dogs show similar recovery though the numbers are slightly skewed by one of the two recovery females still having numbers different from control, though returning to normal levels showing signs of ongoing recovery.

Clinical Chemistry Parameters
13 Week GW572016 Administration in Dogs
Percent Changes from Control

	Males		Females	
Dose Mg/kg/day	MD 40	HD 160	MD 40	HD 160
Alkaline Phosphatase				
Day30	↑ 57%	↑ 111%*	↑ 36%	↑ 264%*
Day 90	↑ 137%*	↑ 312%*	↑ 106%*	↑ 565%*
Recovery		↑ 68%		↑ 231%
Total Bilirubin				
Day30	↑ 50%	↑ 117%	0	↑ 100%
Day 90	↑ 26%	↑ 67%	↑ 200%*	↑ 1600%*
Recovery		↓ 50%		↑ 100%
Total Bile Acids				
Day30	↑ 29%*	↑ 82%*	↑ 26%	↑ 159%*
Day 90	↑ 54%*	↑ 88%*	↑ 30%*	↑ 383%*
Recovery		↑ 20%		↓ 30%
Total Protein				
Day30	↓ 5%	↓ 12%*	↓ 10%*	↓ 17%*
Day 90	↑ 2%	↑ 15%*	↓ 2%	↑ 3%
Recovery		↑ 11%		↑ 9%
Albumin				
Day30	↓ 3%	↓ 24%*	↓ 15%*	↓ 10%*
Day 90	↓ 3%	↓ 28%	↓ 35%*	↓ 27%*
Recovery		↑ 4%		↓ 12%
A/G Ratios				
Day30	↑ 4%	↓ 27%\	↓ 13%	↓ 44%*
Day 90	↓ 11%	↓ 60%	↓ 19%*	↓ 53%*
Recovery		↓ 15%		↓ 39%
Calcium				
Day30	↓ 1%	↓ 8%	↓ 7%*	↓ 10%*
Day 90	0	↓ 3%	↓ 3%	↓ 5%*
Recovery		↓ 1%		0

ALT				
Day30	0	↑ 8%	↑ 50%*	↑ 112%*
Day 90	↑ 34%*	↑ 44%*	↑ 22%	↑ 68%*
Recovery		↑ 11%		↑ 173%
Cholesterol				
Day30	↑ 19%	↑ 40%*	↓ 8%	↓ 3%
Day 90	↑ 30%*	↑ 43%*	↓ 4%	↑ 7%
Recovery		↑ 19%		↓ 35%
Globulin				
Day30	↓ 7%	↑ 5%	↓ 2%	↑ 15%
Day 90	↑ 9%	↑ 82%*	↑ 12%*	↑ 56%*
Recovery		↑ 22%		↑ 44%
Glucose				
Day30	↑ 15%*	↑ 12%*	↑ 7%	↑ 12%
Day 90	0	↑ 4%	↑ 2%	↓ 6%
Recovery		↑ 2%		↓ 2%

* - statistically significant

Urinalysis: Urine collected on Days -7 then on Days 31 and 91 during treatment and Day 120 during recovery.

Urinalysis showed female dogs had significantly higher levels of urobilinogen at both Day 41 and Day 91. This was not seen at the recovery period.

Urinalysis Parameters 13 Week GW572016 Administration in Dogs Percent Changes from Control		
	Males	**Females**
Dose	HD	HD
Mg/kg/day	160	160
Urobilinogen		
Day 31	↑ 108%	↑ 377%*
Day 91	↑ 111%	↑ 539%*
Recovery	↓ 92%	0

* - statistically significant

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Gross pathology:

Gross pathology findings are presented in the table below. Most notable treatment-related events included red discoloration, primarily of the GI tract, scabs on the skin, and several gall bladder findings.

Macroscopic Findings Following 13 Weeks of GW572016 in Dogs Including Recovery Animals

	MD 40 mg/kg	HD 160 mg/kg			MD 40 mg/kg	HD 160 mg/kg	
		Main	Recov	Unsched		Main	Recov
	♂	♂	♂	♂	♀	♀	♀
Stomach							
Fundic glandular depressed area			-	1/2			-
Duodenum							
Multifocal red discoloration			-	1/2			-
Jejunum							
Multifocal red discoloration			-	1/2			-
Colon							
Multifocal red discoloration			-	1/2			-
Gall Bladder							
Distended	1/4	1/2	-	1/2	-	2/4	-
Abnormal contents – viscous	-	1/2	-	1/2	-	1/4	-
Slightly flocculent bile	-	-	-	1/2	-	-	-
Granular contents	1/4	-		-	1/4	1/4	-
Skin							
Hair loss	-	2/2	1/2	1/2	-	3/4	1/2
Red area	-	-	-	1/2	-	-	-
Scabs	-	-	1/2	-	-	-	-
Discoloration	-	-	-	-	-	4/4	1/2
Aorta							
Yellow discoloration	-	-	-	1/2	-	-	-
Lungs							
Adhesions	-	-	-	-	1/4	-	-
Dark discoloration	-	-	-	-	-	1/4	-
Yellow discoloration	-	1/2	-	-	-	1/4	-
Tongue							
Depressed areas	-	-	-	1/2	-	-	1/2
Depressed areas, multifocal	-	-	-	1/2	-	2/4	-
Red multifocal areas	-	-	-	-	-	1/4	-
Oral cavity							
Depressed area	-	-	-	1/2	-	-	-
Red discoloration	-	-		-	-	1/4	-
Focal red discoloration	-	1/2		-	-	-	-
Mouth							
Raw area/ulceration			-	1/2			-
Tonsil							
Bilateral enlargement	-	1/2	-	-	-	-	-
Vagina							
Yellow discoloration					-	1/4	-
Paw							
Red discoloration	-	-	-	1/2	-	-	-

Interdigital thickening	2/4	2/2	1/2	1/2	3/4	4/4	2/2
Interdigital scabs	-	1/2	-	-	-	-	1/2
Hair loss	4/4	1/2	-	1/2	4/4	4/4	-
General							
Yellow discoloration	-	1/2	-	-	-	2/4	1/2

Organ weights:

Relevant changes in absolute organ weights and organ weights relative to BW are presented in the table below. Significant changes in organ weights were seen in the male dogs, with the only significant finding in the female dogs seen in the recovery dogs. Increases were seen in pituitary weights in the HD, both absolute and relative. Increases were seen in the relative liver weights and adrenal gland weights at the HD and the lungs at the MD and HD.

Organ Weight Following 13 Weeks of GW572016 in Dogs Including Recovery Animals Percent Changes from Control

	Males			Females		
Dose Mg/kg/day	MD 60	HD 360	HD Recovery	MD 60	HD 360	HD Recovery
Adrenal Glands						
Absolute	↑ 17%	↑ 10%	↑ 52%*	↑ 3%	↓ 1%	↓ 2%
Relative to BW	↑ 23%	↑ 51%*	↑ 30%	↑ 4%	↓ 7%	↑ 25%
Thymus						
Absolute	↓ 23%	↓ 57%	↑ 8%	↓ 14%	↑ 10%	↓ 36%
Relative to BW	↓ 22%	↓ 42%	↓ 10%	↓ 12%	↑ 16%	↓ 21%
Liver						
Absolute	0	↑ 2%	↑ 50%*	↑ 7%	↑ 18%	↓ 15%
Relative to BW	↑ 5%	↑ 39%*	↑ 28%	↑ 9%	↑ 25%	↑ 8%
Lung						
Absolute	↑ 11%	↑ 3%	↑ 7%	↑ 2%	↑ 14%	↑ 10%*
Relative to BW	↑ 17%*	↑ 39%*	↓ 8%	↑ 4%	↑ 22%	↑ 40%
Brain						
Absolute	↓ 7%	↓ 23%*	↑ 1%	↑ 3%	↓ 3%	↓ 10%
Relative to BW	↓ 4%	↑ 4%	↓ 14%	↑ 6%	↑ 4%	↑ 14%
Pituitary						
Absolute	↓ 6%	↑ 92%*	↓ 3%	↓ 29%	↓ 29%	↓ 31%
Relative to BW	↓ 5%	↑ 180%*	↓ 18%	↓ 27%	↓ 23%	↓ 14%

* - statistically significant

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

The table below recreates the sponsor's histopathology incidence for all main study animals with scheduled termination.

Incidence of Histopathological Changes in Dogs After 13 Weeks of GW572016 Administration – Scheduled Deaths								
	Control		LD 10 mg/kg		MD 40 mg/kg		HD 160 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
Stomach								
Fundus, mucosa, atrophy/degeneration (total)	-	-	-	-	-	-	2/2	4/4
Minimal	-	-	-	-	-	-	-	2/4
Slight/mild	-	-	-	-	-	-	-	1/4
Moderate	-	-	-	-	-	-	2/2	1/4
Pigment deposition (total)	-	-	-	1/4	1/4	2/4	2/2	4/4
Minimal	-	-	-	1/4	1/4	2/4	2/2	1/4
Slight/mild	-	-	-	-	-	-	-	3/4
Lymphoid nodules, depletion (total)	-	-	-	-	-	-	2/2	1/4
Minimal	-	-	-	-	-	-	2/2	1/4
Duodenum								
Pigment deposition (total)	-	-	-	-	-	-	1/2	-
Minimal	-	-	-	-	-	-	1/2	-
Peyer's Patches, lymphoid depletion (total)	-	-	-	-	-	-	2/2	-
Minimal	-	-	-	-	-	-	2/2	-
Jejunum								
Pigment deposition (total)	-	-	-	-	-	-	-	1/4
Minimal	-	-	-	-	-	-	-	1/4
Peyer's Patches, lymphoid depletion (total)	-	-	-	-	-	-	-	1/4
Slight/mild	-	-	-	-	-	-	-	1/4
Ileum								
Pigment deposition (total)	-	-	-	-	-	2/4	2/2	3/4
Minimal	-	-	-	-	-	2/4	2/2	2/4
Slight/mild	-	-	-	-	-	-	-	1/4
Peyer's Patches, lymphoid depletion (total)	-	-	-	-	-	-	2/2	3/4
Slight/mild	-	-	-	-	-	-	-	2/4
Moderate	-	-	-	-	-	-	2/2	1/4
Cecum								
Pigment deposition (total)	-	-	-	-	-	3/4	2/2	4/4
Minimal	-	-	-	-	-	3/4	1/2	3/4
Slight/mild	-	-	-	-	-	-	1/2	1/4
Peyer's Patches, lymphoid depletion								

(total)	-	-	-	-	-	-	2/2	4/4
Minimal	-	-	-	-	-	-	-	1/4
Slight/mild	-	-	-	-	-	-	2/2	3/4
Colon								
Pigment deposition (total)	-	-	-	-	-	-	2/2	3/4
Minimal	-	-	-	-	-	-	2/2	3/4
Peyer's Patches, lymphoid depletion (total)	-	-	-	-	-	-	2/2	4/4
Minimal	-	-	-	-	-	-	2/2	-
Slight/mild	-	-	-	-	-	-	-	3/4
Moderate	-	-	-	-	-	-	-	1/4
Rectum								
Mucosa, gland degeneration (total)	-	-	-	-	-	-	-	1/4
Minimal	-	-	-	-	-	-	-	1/4
Pigment deposition (total)	-	-	-	-	-	2/4	2/2	4/4
Minimal	-	-	-	-	-	2/4	2/2	2/4
Slight/mild	-	-	-	-	-	-	-	2/4
Peyer's Patches, lymphoid depletion (total)	-	-	-	-	-	-	2/2	4/4
Minimal	-	-	-	-	-	-	1/2	1/4
Slight/mild	-	-	-	-	-	-	1/2	2/4
Moderate	-	-	-	-	-	-	-	1/4
Tongue								
Lamina propria, inflamm, chronic (total)	-	-	-	-	-	-	-	1/4
Slight/mild	-	-	-	-	-	-	-	1/4
Mucosa, inflammation, acute (total)	-	-	-	-	-	-	-	2/4
Minimal	-	-	-	-	-	-	-	2/4
Mucosa, erosion/ulceration (total)	-	-	-	-	-	-	-	1/4
Minimal	-	-	-	-	-	-	-	1/4
Pigment deposition (total)	-	-	-	-	-	-	-	1/4
Minimal	-	-	-	-	-	-	-	1/4
Liver								
Hepatocytes, glycogen depletion (total)	-	-	-	-	-	-	-	1/4
Severe/high	-	-	-	-	-	-	-	1/4
Hepatocytes, vacuolization (total)	-	-	-	-	-	-	1/2	2/4
Minimal	-	-	-	-	-	-	-	2/4
Slight/mild	-	-	-	-	-	-	1/2	-
Inflammation, chronic (total)	4/4	4/4	4/4	4/4	4/4	4/4	2/2	4/4
Minimal	4/4	4/4	4/4	4/4	2/4	2/4	1/2	-
Slight/mild	-	-	-	-	2/4	2/4	-	2/4
Moderate	-	-	-	-	-	-	1/2	1/4
Moderately severe	-	-	-	-	-	-	-	1/4
Pigment deposition (total)	2/4	2/4	1/4	2/4	2/4	3/4	2/2	3/4
Minimal	2/4	2/4	1/4	2/4	2/4	3/4	-	-
Slight/mild	-	-	-	-	-	-	2/2	2/4
Moderate	-	-	-	-	-	-	-	1/4

Bile ducts, hyperplasia (total)	-	-	-	-	-	-	-	1/4
Minimal	-	-	-	-	-	-	-	1/4
Salivary glands								
Atrophy (total)	1/4	-	2/4	-	1/4	-	-	2/4
Minimal	1/4	-	1/4	-	1/4	-	-	2/4
Slight/mild	-	-	1/4	-	-	-	-	-
Pigment deposition (total)	-	-	-	-	-	-	-	2/4
Minimal	-	-	-	-	-	-	-	2/4
Lymph Nodes – mandibular								
Infiltrate, macrophage, increased (total)	-	-	-	-	3/4	-	2/2	3/4
Minimal	-	-	-	-	3/4	-	1/2	2/4
Slight/mild	-	-	-	-	-	-	-	1/4
Moderate	-	-	-	-	-	-	1/2	-
Lymphoid depletion (total)	-	-	-	-	-	-	2/2	4/4
Slight/mild	-	-	-	-	-	-	2/2	3/4
Moderate	-	-	-	-	-	-	-	1/4
Pigment deposition (total)	-	2/4	4/4	4/4	2/4	4/4	2/2	4/4
Minimal	-	2/4	4/4	3/4	2/4	4/4	-	1/4
Slight/mild	-	-	-	1/4	-	-	2/2	3/4
Lymph Nodes – mesenteric								
Infiltrate, macrophage, increased (total)	-	-	-	-	1/4	-	1/2	-
Minimal	-	-	-	-	1/4	-	-	-
Slight/mild	-	-	-	-	-	-	1/2	-
Lymphoid depletion (total)	-	-	-	-	-	-	2/2	4/4
Minimal	-	-	-	-	-	-	-	3/4
Slight/mild	-	-	-	-	-	-	2/2	-
Moderate	-	-	-	-	-	-	-	1/4
Pigment deposition (total)	-	-	-	2/4	1/4	4/4	2/2	4/4
Minimal	-	-	-	2/4	1/4	4/4	-	2/4
Slight/mild	-	-	-	-	-	-	2/2	2/4
Tonsil								
Lymphoid depletion (total)	-	-	-	-	-	-	1/2	-
Slight/mild	-	-	-	-	-	-	1/2	-
Pigment deposition (total)	-	-	-	-	-	-	1/2	-
Minimal	-	-	-	-	-	-	1/2	-
Spleen								
Lymphoid depletion (total)	-	-	-	-	-	-	2/2	-
Minimal	-	-	-	-	-	-	1/2	-
Moderate	-	-	-	-	-	-	1/2	-
Pigment Deposition (total)	4/4	4/4	4/4	4/4	4/4	4/4	2/2	4/4
Minimal	2/4	1/4	2/4	1/4	3/4	1/4	1/2	2/4
Slight/mild	2/4	3/4	2/4	2/4	1/4	3/4	-	1/4
Moderate	-	-	-	1/4	-	-	1/2	1/4
Thymus								
Lymphoid depletion (total)	2/4	3/4	4/4	4/4	4/4	3/4	2/2	3/4

Minimal	1/4	1/4	2/4	2/4	2/4	2/4	-	1/3
Slight/mild	1/4	2/4	1/4	2/4	1/4	1/4	1/2	1/3
Moderate	-	-	1/4	-	1/4	-	-	-
Moderately severe	-	-	-	-	-	-	1/2	1/3
Pigment Deposition (total)	-	-	-	-	-	2/4	2/2	4/4
Minimal	-	-	-	-	-	2/4	1/2	4/4
Slight/mild	-	-	-	-	-	-	1/2	-
Adrenal glands								
Cortex, cytoplasmic alteration (total)	-	-	-	-	-	-	2/2	3/4
Minimal	-	-	-	-	-	-	1/2	3/4
Moderate	-	-	-	-	-	-	1/2	-
Cortico-medullary junction, pigment deposits (total)	1/4	-	2/4	-	-	-	-	-
Minimal	1/4	-	2/4	-	-	-	-	-
Medulla, pigment deposition (total)	-	-	-	1/4	1/4	1/4	-	-
Minimal	-	-	-	1/4	1/4	1/4	-	-
Kidney								
Cortex, tubules, pigment deposition (total)	3/4	2/4	4/4	1/4	4/4	2/4	2/2	3/4
Minimal	3/4	1/4	4/4	1/4	3/4	-	1/2	-
Slight/mild	-	1/4	-	-	1/4	2/4	1/2	2/4
Moderate	-	-	-	-	-	-	-	1/4
Lungs								
Pigment deposition (total)	1/4	4/4	3/4	3/4	4/4	4/4	2/2	4/4
Minimal	1/4	3/4	3/4	3/4	4/4	3/4	-	-
Slight/mild	-	1/4	-	-	-	1/4	2/2	2/4
Moderate	-	-	-	-	-	-	-	2/4
Lacrimal gland								
Pigment deposition (total)	-	-	-	-	-	1/4	1/2	-
Minimal	-	-	-	-	-	1/4	1/.2	-
Ovary								
Pigment deposition (total)		-		-		1/4		2/4
Minimal		-		-		1/4		2/4
Uterus								
Pigment deposition (total)		4/4		2/4		3/4		4/4
Minimal		2/4		1/4		2/4		-
Slight/mild		2/4		1/4		1/4		4/4
Mammary glands								
Reduced proliferation (total)		-		-		1/4		2/4
Present		-		-		1/4		2/4
Pigment deposition (total)		3/4		2/4		3/4		4/4
Minimal		3/4		1/4		1/4		-
Slight/mild		-		1/4		1/4		-
Moderate		-		-		1/4		2/4
Moderately severe		-		-		-		2/4
Skin								
Dermis, inflammation, chronic (total)	1/4	-	1/4	-	-	-	1/2	2/4
Minimal	1/4	-	1/4	-	-	-	1/2	2/4
Epidermis, hyperplasia (total)	-	-	-	-	-	-	-	1/4
Minimal	-	-	-	-	-	-	-	1/4

Parasite, acarid (total)	-	-	1/4	-	-	-	-	-
Present	-	-	1/4	-	-	-	-	-
Skin , paw, interdigital								
Dermatophyte (total)	-	-	-	-	-	-	1/2	2/4
Present	-	-	-	-	-	-	1/2	2/4
Dermis, inflammation, chronic (total)	3/4	4/4	4/4	3/4	3/4	4/4	1/2	3/4
Minimal	3/4	4/4	4/4	2/4	2/4	3/4	-	1/4
Slight/mild	-	-	-	1/4	1/4	1/4	-	1/4
Moderately severe	-	-	-	-	-	-	1/2	1/4
Dermis, inflamm, chronic active (total)	1/4	-	-	-	1/4	-	2/2	1/4
Mild	-	-	-	-	-	-	-	-
Moderate	1/4	-	-	-	-	-	1/2	1/4
Moderately severe	-	-	-	-	1/4	-	-	-
Severe/high	-	-	-	-	-	-	1/2	-
Dermis, pigment deposition (total)	1/4	-	1/4	-	1/4	-	2/2	1/4
Minimal	1/4	-	1/4	-	1/4	-	2/2	1/4
Epidermis, erosion/ulceration (total)	-	-	-	-	-	-	-	1/4
Minimal	-	-	-	-	-	-	-	1/4
Epidermis, hyperplasia (total)	-	-	-	-	1/4	-	2/2	1/4
Slight/mild	-	-	-	-	1/4	-	2/2	1/4
Epidermis, inflamm, suppurative (total)	-	-	-	-	-	1/4	-	-
Slight/mild	-	-	-	-	-	1/4	-	-
Parasite, acarid (total)	-	-	-	-	-	1/4	-	-
Present	-	-	-	-	-	1/4	-	-
Skin, paw, dorsal								
Dermatophyte (total)	-	-	-	-	-	-	-	1/4
Present	-	-	-	-	-	-	-	1/4
Dermis, inflamm, chronic active (total)	-	-	-	-	-	-	-	1/4
Slight/mild	-	-	-	-	-	-	-	1/4
Epidermis, hyperplasia (total)	-	-	-	-	-	-	-	1/4
minimal	-	-	-	-	-	-	-	1/4
Skin , footpad								
Dermatophyte (total)	-	-	-	-	-	-	1/2	-
Present	-	-	-	-	-	-	1/2	-
Dermis, inflammation, chronic (total)	4/4	3/4	4/4	3/4	3/4	2/4	-	3/4
Minimal	1/4	3/4	1/4	-	1/4	1/4	-	1/4
Slight/mild	1/4	-	2/4	3/4	1/4	-	-	-
Moderate	2/4	-	1/4	-	1/4	1/4	-	1/4
Severe/high	-	-	-	-	-	-	-	1/4
Dermis, inflamm, chronic active (total)	-	-	-	-	1/4	2/4	2/2	1/4
Moderate	-	-	-	-	1/4	2/4	-	1/4
Severe/high	-	-	-	-	-	-	2/2	-
Dermis, pigment deposition (total)	1/4	1/4	2/4	1/4	2/4	3/4	2/2	4/4

Minimal	1/4	1/4	2/4	1/4	2/4	3/4	1/2	2/4
Slight/mild	-	-	-	-	-	-	1/2	2/4
Epidermis, erosion/ulceration (total)	-	-	-	-	-	-	1/2	-
Slight/mild	-	-	-	-	-	-	1/2	-
Epidermis, hyperplasia (total)	-	-	-	-	1/4	-	-	-
Slight/mild	-	-	-	-	1/4	-	-	-
Parasite, acarid (total)	-	-	1/4	-	-	1/4	-	1/4
Present	-	-	1/4	-	-	1/4	-	1/4
Skin , other								
Dermatophyte (total)	-	-	-	-	-	-	-	2/4
Present	-	-	-	-	-	-	-	2/4
Dermis, inflammation, chronic (total)	1/4	-	-	-	-	-	1/2	3/4
Minimal	1/4	-	-	-	-	-	-	3/4
Slight/mild	-	-	-	-	-	-	1/2	-
Dermis, pigment deposition (total)	-	-	-	-	-	-	-	1/4
Minimal	-	-	-	-	-	-	-	1/4
Epidermis, hyperplasia (total)	-	-	-	-	-	-	1/2	3/4
Minimal	-	-	-	-	-	-	1/2	2/4
Slight/mild	-	-	-	-	-	-	-	1/4
Parasite, acarid (total)	-	-	-	-	-	-	-	1/4
Present	-	-	-	-	-	-	-	1/4

Blocks are left blank if no tissues from a dose/sex group were examined

Incidence of Histopathological Changes in Dogs After 13 Weeks of GW572016 Administration – Recovery Animals				
	Control		**HD 160 mg/kg**	
	♂	♀	♂	♀
Stomach				
Pigment deposition (total)	-	-	2/2	2/2
Minimal	-	-	2/2	1/2
Slight/mild	-	-	-	1/2
Duodenum				
Pigment deposition (total)	-	-	1/2	-
Minimal	-	-	1/2	-
Jejunum				
Pigment deposition (total)	-	-	-	1/2
Minimal	-	-	-	1/2
Ileum				
Pigment deposition (total)	-	-	2/2	2/2
Minimal	-	-	2/2	2/2
Cecum				
Pigment deposition (total)	-	-	2/2	2/2
Minimal	-	-	2/2	1/2
Slight/mild	-	-	-	1/2
Colon				

Pigment deposition (total)	-	-	-	1/2
Minimal	-	-	-	1/2
Rectum				
Pigment deposition (total)	-	-	2/2	2/2
Minimal	-	-	2/2	1/2
Slight/mild	-	-	-	1/2
Liver				
Hepatocytes, glycogen depletion (total)	-	-	-	2/2
Slight/mild	-	-	-	1/2
Moderate	-	-	-	1/2
Inflammation, chronic (total)	2/2	2/2	2/2	2/2
Minimal	2/2	2/2	2/2	-
Slight/mild	-	-	-	2/2
Pigment deposition (total)	1/2	1/2	2/2	2/2
Minimal	1/2	1/2	1/2	-
Slight/mild	-	-	1/2	1/2
Moderate	-	-	-	1/2
Salivary glands				
Pigment deposition (total)	-	-	-	1/2
Minimal	-	-	-	1/2
Lymph Nodes – mandibular				
Infiltrate, macrophage, increased (total)	-	-	1/2	1/2
Minimal	-	-	1/2	-
Slight/mild	-	-	-	1/2
Pigment deposition (total)	-	1/2	2/2	2/2
Minimal	-	1/2	-	-
Slight/mild	-	-	2/2	1/2
Moderate	-	-	-	1/2
Lymph Nodes – mesenteric				
Pigment deposition (total)	1/2	-	2/2	2/2
Minimal	1/2	-	-	1/2
Slight/mild	-	-	2/2	1/2
Spleen				
Pigment Deposition (total)	2/2	2/2	2/2	2/2
Minimal	2/2	-	2/2	1/2
Slight/mild	-	2/2	-	1/2
Thymus				
Lymphoid depletion (total)	1/2	1/2	2/2	2/2
Minimal	-	1/2	-	1/2
Slight/mild	1/2	-	-	-
Moderate	-	-	1/2	1/2
Moderately severe	-	-	1/2	-
Pigment Deposition (total)	-	-	1/2	2/2
Minimal	-	-	1/2	1/2
Slight/mild	-	-	-	1/2
Adrenal glands				
Cortex, pigment deposition (total)	-	-	-	1/2
Minimal	-	-	-	1/2
Cortico-medullary junction, pigment deposition (total)	-	-	-	1/2

Minimal	-	-	-	1/2
Medulla, pigment deposition (total)	1/2	-	1/2	2/2
Minimal	1/2	-	1/2	2/2
Kidney				
Cortex, tubules, pigment deposition (total)	1/2	1/2	2/2	1/2
Minimal	1/2	1/2	-	1/2
Slight/mild	-	-	2/2	-
Lungs				
Interstitium, inflammation, chronic (total)	-	1/2	1/2	-
Minimal	-	-	1/2	-
Slight/mild	-	1/2	-	-
Pigment deposition (total)	2/2	1/2	2/2	2/2
Minimal	1/2	-	-	-
Slight/mild	1/2	-	2/2	1/2
Moderate	-	1/2	-	1/2
Ovary				
Pigment deposition (total)		-		2/2
Slight/mild		-		2/2
Uterus				
Pigment deposition (total)		2/2		2/2
Minimal		2/2		-
Slight/mild		-		2/2
Mammary glands				
Pigment deposition (total)		1/2		2/2
Minimal		1/2		-
Moderate		-		2/2
Skin				
Dermis, inflammation, chronic (total)	-	-	-	1/2
Minimal	-	-	-	1/2
Skin , paw, interdigital				
Dermis, inflammation, chronic (total)	1/2	1/2	2/2	-
Minimal	1/2	1/2	1/2	-
Slight/mild	-	-	1/2	-
Dermis, inflamm, chronic active (total)	-	-	-	2/2
Severe/high	-	-	-	2/2
Dermis, necrosis (total)	-	-	1/2	-
Moderate	-	-	1/2	-
Dermis, pigment deposition (total)	-	-	-	2/2
Slight/mild	-	-	-	1/2
Moderate	-	-	-	1/2
Epidermis, erosion/ulceration (total)	-	-	-	1/2
Slight/mild	-	-	-	1/2
Epidermis, hyperplasia (total)	-	-	1/2	2/2
Minimal	-	-	1/2	-
Moderate	-	-	-	2/2
Parasite, acarid (total)	-	-	-	1/2
Present	-	-	-	1/2

Skin , footpad				
Dermis, inflammation, chronic (total)	-	-	1/2	1/2
Minimal	-	-	-	1/2
Slight/mild	-	-	1/2	-
Dermis, inflamm, chronic active (total)	-	-	-	1/2
Moderate	-	-	-	1/2
Dermis, pigment deposition (total)	-	-	1/2	1/2
Minimal	-	-	1/2	-
Slight/mild	-	-	-	1/2
Skin , other				
Dermis, inflammation, chronic (total)	-	-	1/2	1/2
Minimal	-	-	1/2	1/2
Epidermis, hyperplasia (total)	-	-	1/2	1/2
Minimal	-	-	-	1/2
Moderate	-	-	1/2	-

Blocks are left blank if no tissues from a dose/sex group were examined

The table below presents the histopathological findings in the two male rats that died while on study.

Incidence of Histopathological Changes in Dogs After 13 Weeks of GW572016 Administration Two Male Unscheduled Deaths

	HD 160 mg/kg
	♂
Stomach	
Fundus, mucosa, atrophy/degeneration (total)	2/2
Moderate	1/2
Moderately severe	1/2
Lymphoid nodules, depletion (total)	2/2
Minimal	1/2
Slight/mild	1/2
Pigment deposition (total)	2/2
Minimal	1/2
Slight/mild	1/2
Pylorus, mucosa, atrophy/degeneration (total)	1/2
Slight/mild	1/2
Duodenum	
Mucosa, congestion (total)	1/2
Slight/mild	1/2
Mucosa, gland, degeneration (total)	2/2
Minimal	1/2
Slight/mild	1/2
Mucosa, villous atrophy (total)	2/2

Minimal	1/2
Moderate	1/2
Peyer's Patches, lymphoid depletion (total)	1/2
Minimal	1/2
Jejunum	
Mucosa, congestion (total)	1/2
Slight/mild	1/2
Mucosa, villous atrophy (total)	2/2
Minimal	1/2
Moderate	1/2
Ileum	
Mucosa, villous atrophy (total)	2/2
Moderate	2/2
Peyer's Patches, lymphoid depletion (total)	2/2
Moderate	2/2
Cecum	
Lymphoid nodules, depletion (total)	2/2
Moderate	2/2
Mucosa, gland, degeneration (total)	2/2
Slight/mild	2/2
Pigment deposition (total)	1/2
Minimal	1/2
Colon	
Lymphoid nodules, depletion (total)	2/2
Slight/mild	2/2
Mucosa, congestion (total)	1/2
Slight/mild	1/2
Rectum	
Lymphoid nodules, depletion (total)	2/2
Slight/mild	2/2
Mucosa, gland, degeneration (total)	1/2
Slight/mild	1/2
Pigment deposition (total)	1/2
Minimal	1/2
Liver	
Hepatocytes, glycogen depletion (total)	2/2
Moderate	1/2
Moderately severe	1/2
Hepatocytes, vacuolization (total)	2/2
Minimal	1/2
Moderate	1/2
Inflammation, chronic (total)	2/2
Minimal	1/2
Moderate	1/2

Pigment deposition (total)	1/2
Minimal	1/2
Pancreas	
Acinar cells, zymogen depletion (total)	2/2
Minimal	1/2
Moderate	1/2
Gallbladder	
Intraluminal basophilic material (total)	2/2
Present	2/2
Oral cavity	
Lamina propria, inflammation, acute (total)	1/2
Minimal	1/2
Mucosa, erosion/ulceration (total)	1/2
Slight/mild	1/2
Tongue	
Lamina propria, inflammation, acute (total)	2/2
Minimal	2/2
Mucosa, erosion/ulceration (total)	2/2
Slight/mild	2/2
Lymph Nodes – mandibular	
Infiltrate, macrophage, increased (total)	2/2
Minimal	1/2
Slight/mild	1/2
Infiltrate, neutrophil (total)	1/2
Slight/mild	1/2
Lymphoid depletion (total)	2/1
Slight/mild	1/2
Moderate	1/2
Pigment deposition (total)	2/2
Slight/mild	2/2
Lymph Nodes – mesenteric	
Infiltrate, macrophage, increased (total)	1/2
Minimal	1/2
Lymphoid depletion (total)	2/1
Slight/mild	1/2
Moderate	1/2
Pigment deposition (total)	2/2
Slight/mild	2/2
Spleen	
Lymphoid depletion (total)	2/2
Slight/mild	2/2
Pigment Deposition (total)	2/2
Moderate	2/2
Thymus	
Lymphoid depletion (total)	2/2
Severe/high	2/2

Pigment Deposition (total)	2/2
Minimal	2/2
Adrenal glands	
Cortex, cytoplasmic alteration (total)	1/2
Moderate	1/2
Cortex, hyperplasia (total)	2/2
Slight/mild	2/2
Medulla, pigment deposition (total)	2/2
Minimal	2/2
Lungs	
Interstitium, inflammation, chronic (total)	2/2
Minimal	2/2
Pigment deposition (total)	2/2
Minimal	2/2
Epididymis	
Epithelium, vacuolization (total)	1/2
Moderate	1/2
Intraluminal debris, increased (total)	1/2
Moderate	1/2
Bone marrow, sternum	
Hypocellularity (total)	1/2
Moderate	1/2
Necrosis (total)	1/2
Slight/mild	1/2
Skeletal muscle	
Myofiber, atrophy (total)	2/2
Slight/mild	2/2
Skin , paw, interdigital	
Dermis, inflammation, chronic active (total)	1/2
Severe/high	1/2
Skin , paw, footpad	
Dermis, inflammation, chronic active (total)	1/2
Severe/high	1/2
Pigment deposition (total)	1/2
Minimal	1/2
Skin , dorsal	
Dermis, inflammation, chronic active (total)	1/2
Severe/high	1/2
Epidermis, hyperplasia (total)	1/2
Minimal	1/2
Skin , other	
Dermis, inflammation, chronic active (total)	1/2
Slight/mild	1/2

Toxicokinetics:

The sponsor's tables are presented below depicting the toxicokinetic parameters of GW572016 in male and female dogs. GW572016 levels were measurable in all the drug-treated dogs. The C_{max} increased dose-proportionally in the male dogs over the study, but in the female dogs only on Day 1. The increase in C_{max} was less than dose-proportional in the female dogs on the two later days of dosing. AUC values increased dose-proportionally in both genders on all 3 dosing days tested. There is a trend to lower C_{max} and AUC levels in the male dogs than the female dogs. Accumulation of drug over the testing period is not seen.

Mean Plasma Toxicokinetic Parameters of GW572016X in Male Beagle Dogs

Dose (mg/kg/day)	Day		AUC[1] (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	Dose-Normalized AUC (h*ng/mL)	Dose-Normalized C_{max} (ng/mL)
10	1	Mean	3152	452	2-4	2.76	3152	452
		SD	1118	112		0.52	1118	112
	29	Mean	3748	451[2]	2-4	4.00	3748	451
		SD	3423	371		1.61	3423	371
	85	Mean	5238	611	2-4	3.77	5238	611
		SD	3315	306		1.29	3315	306
40	1	Mean	32540	2150	4-8	7.91	8135	538
		SD	26144	1187		4.03	6536	297
	29	Mean	20767	1640	0-4	11.0	5192	410
		SD	11560	851		5.99	2890	213
	85	Mean	32439	2539	2-4	10.4	8110	635
		SD	16482	1365		1.38	4120	341
160	1	Mean	127716	6098	4-24	9.13	7982	381
		SD	110092	4580		2.53	6881	286
	29	Mean	79204	4183	4-12	27.2	4950	261
		SD	56398	2211		24.4	3525	138
	85	Mean	98247	5535	0-8	36.7	6140	346
		SD	49893	1950		41.3	3118	122

n= 4-6

[1] AUC_{∞} on Day 1 and AUC_{τ} on Days 29 and 85

[2] Statistical difference ($p<0.05$) between male and female values.

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Mean Plasma Toxicokinetic Parameters of GW572016X in Female Beagle Dogs								
Dose (mg/kg/day)	Day		AUC[1] (h*ng/mL)	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	Dose-Normalized AUC (h*ng/mL)	Dose-Normalized C_{max} (ng/mL)
10	1	Mean	5525	723	2-4	3.06[3]	5525	723
		SD	1814	216		0.44	1814	216
	29	Mean	8182	1008[2]	2-4	4.38[3]	8182	1008[4]
		SD	2709	239		0.51	2709	239
	85	Mean	10119	1074	4	5.70[3]	10119	1074[4]
		SD	3286	397		0.27	3286	397
40	1	Mean	46768	2735	4-8	9.84	11692	684
		SD	35547	882		4.70	8887	221
	29	Mean	36302	2525	0-8	10.0	9075	631[4]
		SD	30477	1735		2.64	7619	434
	85	Mean	31210	2330	2-4	8.90	7803	583[4]
		SD	32048	2085		2.71	8012	521
160	1	Mean	253600[3]	8480	4-24	14.1[3]	15850	530
		SD	163336	4842		8.71	10209	303
	29	Mean	107409[3]	5560	4-8	34.1[3]	6713	348[4]
		SD	53052	2263		20.0	3316	141
	85	Mean	117174[3]	6157	0-12	44.3[3]	7323	385[4]
		SD	21979	1683		16.9	1374	105

n= 4-6

[1] AUC_{∞} on Day 1 and AUC_{τ} on Days 29 and 85

[2] Statistical difference ($p<0.05$) between male and female values.

[3] Statistical difference ($p<0.05$) between values from groups based dosing day.

[4] Statistical difference ($p<0.05$) between values from groups based dose level.

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Study title: GW572016F: 39-Week oral capsule toxicity study in beagle dogs

Key study findings:

- Two HD male dogs euthanized moribund
- Decreased body weights in the HD dogs and decreased food consumption, occasionally statistically significant
- Hematology parameter changes seen in HD female dogs, decreased RBC parameters and increased platelets
- Clinical chemistry changes include increases in ALT, ALP, bilirubin, bile acids
- Large levels of bilirubin in urine seen in some HD dogs
- Microscopic and macroscopic effects of drug seen in the GI, liver, skin, lymphoid tissue and adrenals, most resolved during recovery

Study no.: RD2001/00926/01
Volume #, and page #: Module 4.2.3.2.10
Conducting laboratory and location:

Date of study initiation: 28 August 2001
GLP compliance: Letter included and signed
QA reports: yes (X) no ( )
Drug, lot #, and % purity: GW572016F, Lot # R5361/144/1, —

Methods

Doses:	10, 40, and 100 mg/kg
Species/strain:	Dog/ Beagle
Number/sex/group or time point (main study):	4/sex/dose in main study Additional 2/sex in Control and HD for recovery
Route, formulation, volume, and infusion rate:	Oral/gelatin capsule
Satellite groups used for toxicokinetics or recovery:	TK from main study dogs
Age:	≈ 10-11 months
Weight:	9.5 – 13.2 kg ♂ 6.1 -7.5 kg ♀
Sampling times:	Day 1 and Weeks 13, 26 and end of treatment taken at predose, 0.5, 2, 4, 8, 12 and 24 hrs post-dose

Observation times and results:

Mortality: Twice daily

2 ♂ HD dogs euthanized moribund – one on Day 212 and one on Day 228
Histopathology findings in these dogs were consistent with treatment effects

Clinical signs: Weekly detailed exams in addition to the twice daily observations and full physical examination by a veterinarian on Weeks -1, 4, 13, 26, 39 and 43

Dosing had to be suspended temporarily in 2 ♂ and 2 ♀ dogs due to severe body weight losses – the two ♂ dogs were later euthanized moribund

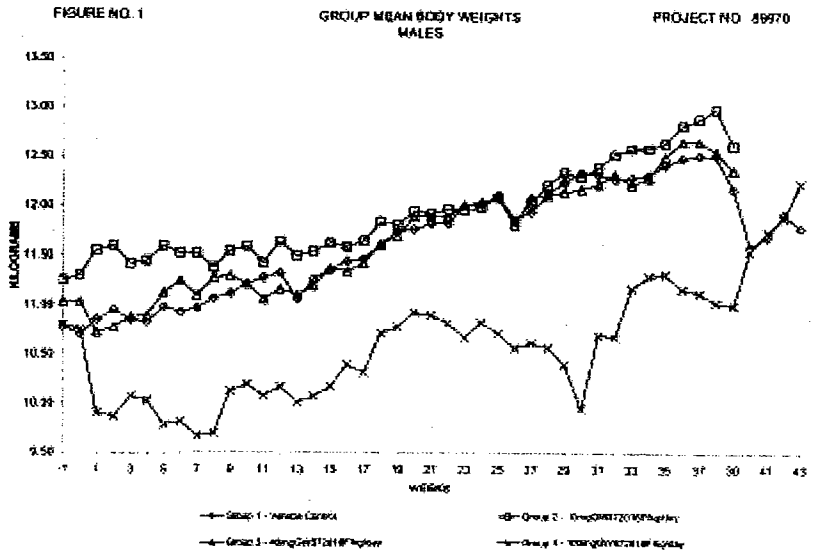
Dog	Dosing suspended	Dosing restarted
HD ♂	85	148
HD ♂	53	92
HD ♀	172	263
HD ♀	85	148

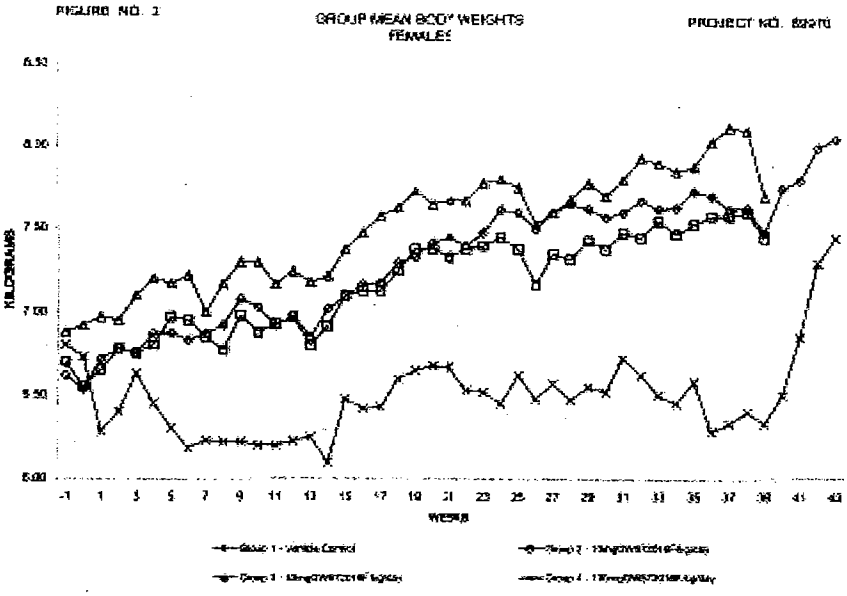
The main clinical signs noted with more frequency or severity in the GW572016 dogs are noted in the table below, with only the HD dogs listed, though the signs were sometimes evident to a lesser degree in the other dose groups.

Clinical Sign	HD dogs 100 mg/kg
Poor body condition	2/6 ♂ 4/6 ♀
Dehydration	1/6 ♂ 4/6 ♀
Swollen lymph nodes	2/6 ♀
Soft/liquid feces	6/6 ♀ 6/6 ♀
Yellow discoloration of feces	6/6 ♂ 5/6 ♀
Paw lesions	6/6 ♂ 6/6 ♀
Skin lesions and redness	4/6 ♂ 6/6 ♀
Orange/yellow discoloration of skin/mucous membranes/eyes	2/6 ♂ 4/6 ♀

Body weights: Weekly

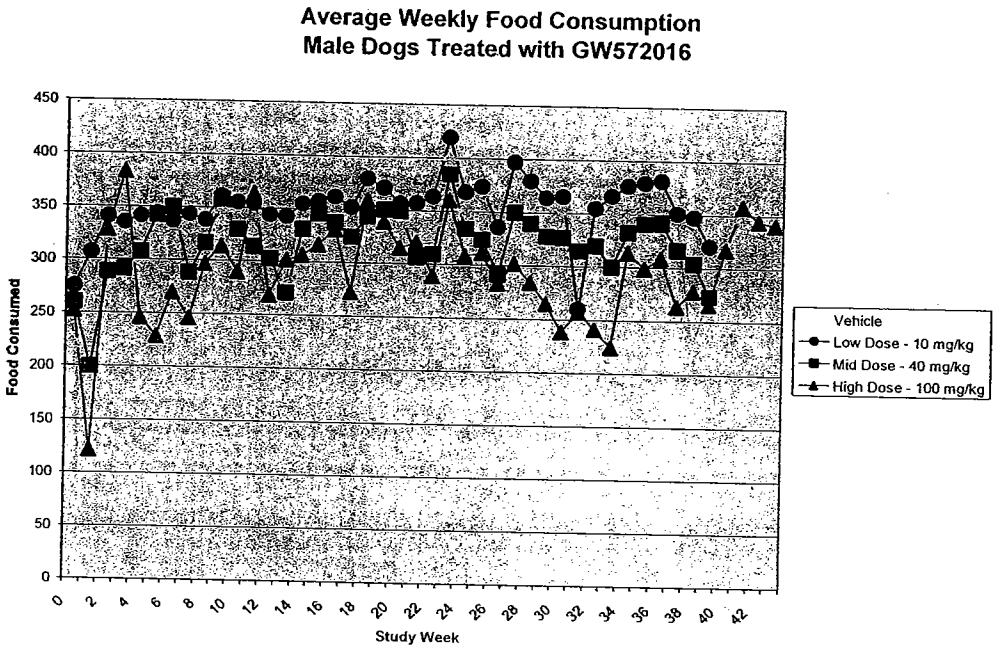
The sponsor's graph below show that the administration of GW572016 adversely affected the body weight gains in both the male and female dogs at the HD level. Both the control groups and the HD dogs gained weight during the recovery period.





Food consumption: Daily

The following graphs show the average food intake weekly throughout the study, and during the recovery period. The HD of GW572016 led to decreased food intake, although this only reached statistical significance in the male dogs during Weeks 1, 3, 7, 28 and 30 and in the female dogs during Weeks 1 and 3.



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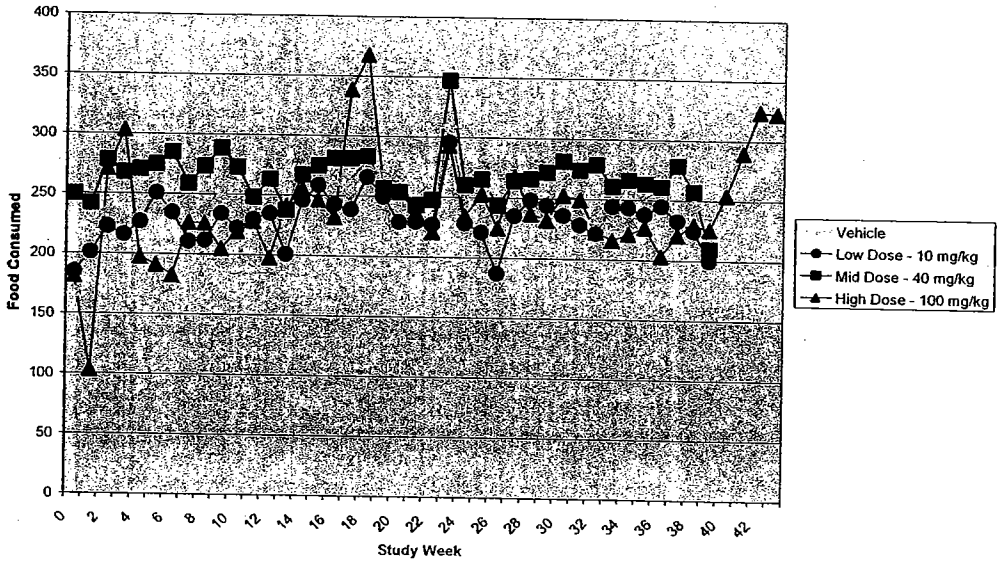
Average Weekly Food Consumption
Female Dogs Treated with GW572016



Ophthalmoscopy: Prior to treatment, Weeks 13, 26 and 39 and at the end of recovery

Evidence of jaundice was noted by yellow discoloration of the sclera in some of the HD dogs. No other ocular findings were noted in the study.

EKG: Twice prior to treatment, Weeks 13, 26 and 39 and at the end of recovery

No evidence of a treatment related effect on the electrocardiogram was seen.

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Hematology: Once prior to treatment, Weeks 9, 13, 26, 39, and at the end of recovery

The table below shows the significant changes in hematology parameters seen over the c course of the study. The results are indicative of an anemia and immune response following drug administration. All changes in hematology parameters were not significantly different from control during the recovery period.

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Hematology Parameters 39 Week GW572016 Administration in Dogs Percent Changes from Control				
	Males		Females	
Dose Mg/kg/day	MD 40	HD 100	MD 40	HD 100
RBC				
Week 9	---	---	---	↓ 13%
Week 13	---	---	---	↓ 17%
Week 26	---	---	---	↓ 13%
Week 39	↑ 12%	---	---	---
Hemoglobin				
Week 9	---	---	---	↓ 12%
Week 13	---	---	---	↓ 16%
Week 26	---	---	---	↓ 14%
Week 39	---	---	---	---
Hematocrit - %				
Week 9	---	---	---	↓ 14%
Week 13	---	---	---	↓ 16%
Week 26	---	---	---	↓ 14%
Week 39	---	---	---	---
Platelets				
Week 9	---	---	↑ 54%	↑ 114%
Week 13	---	---	---	↑ 90%
Week 26	---	↑ 32%	---	↑ 67%
Week 39	---	---	---	↑ 89%
WBC				
Week 9	---	---	↑ 48%	↑ 44%
Week 13	---	---	---	---
Week 26	---	---	---	---
Week 39	---	---	---	↑ 57%
Monocytes - %				
Week 9	---	---	↑ 84%	↑ 56%
Week 13	---	---	---	↑ 83%
Week 26	---	---	---	---
Week 39	---	---	---	↑ 156%
Monocytes – Absolute				
Week 9	---	---	---	↑ 132%
Week 13	---	---	---	---
Week 26	---	---	---	↑ 153%
Week 39	---	---	---	↑ 33%
Lymphocytes - Absolute				
Week 9	---	---	↑ 41%	---
Week 13	---	---	---	---
Week 26	---	---	---	---
Week 39	---	---	---	---

Clinical chemistry: Once prior to treatment, Weeks 9, 13, 26, 39, and at the end of recovery

The table below shows the significant changes in clinical chemistry parameters seen over the course of the study. Although none of the parameters at the recovery period in the HD dogs were significantly different from the control group, there was still an indication of increased ALP in both the male and female dogs, and decreased albumin and increased globulin in the female dogs.

Clinical Chemistry Parameters 39 Week GW572016 Administration in Dogs Percent Changes from Control				
	Males		Females	
Dose Mg/kg/day	MD 40	HD 100	MD 40	HD 100
Total Bilirubin				
Week 9	---	↑ 146%	---	↑ 143%
Week 13	---	---	---	---
Week 26	---	↑ 206%	---	↑ 94%
Week 39	---	↑ 136%	---	---
ALT				
Week 9	---	---	---	---
Week 13	---	---	---	↑ 128%
Week 26	---	↑ 127%	↑ 205%	↑ 185%
Week 39	---	↑ 80%	↑ 231%	↑ 184%
ALP				
Week 9	---	↑ 170%	---	---
Week 13	---	---	---	---
Week 26	---	↑ 268%	---	---
Week 39	---	↑ 291%	---	↑ 245%
Total Bile Acids				
Week 9	---	↑ 540%	---	---
Week 13	---	---	---	↑ 261%
Week 26	---	---	---	↑ 91%
Week 39	---	---	---	↑ 165%
Albumin				
Week 9	---	↓ 31%	---	↓ 26%
Week 13	---	↓ 20%	---	↓ 23%
Week 26	---	↓ 23%	---	↓ 26%
Week 39	---	↓ 20%	---	↓ 31%
Globulin				
Week 9	---	---	---	↑ 26%
Week 13	---	---	---	↑ 28%
Week 26	---	---	---	↑ 35%
Week 39	---	---	---	↑ 44%
A/G Ratio				
Week 9	---	↓ 36%	↓ 23%	↓ 40%
Week 13	---	↓ 32%	---	↓ 39%
Week 26	---	↓ 34%	↓ 26%	↓ 46%
Week 39	---	↓ 33%	↓ 27%	↓ 52%
Calcium				
Week 9	---	---	---	↓ 7%
Week 13	---	---	---	---
Week 26	---	↓ 5%	---	↓ 7%
Week 39	---	---	---	---

Urinalysis: Once prior to treatment, Weeks 9, 13, 26, 39, and at the end of recovery

2 HD ♀ showed large amounts of bilirubin in the urine at Week 39
2 HD ♂ that were euthanized prior to the end of the study also showed large amounts of bilirubin in the urine at termination. One of these rats also had a large bilirubin level in the urine at Week 26.

Gross pathology:

Macroscopic Findings Following 39 Weeks of GW572016 in Dogs Including Unscheduled Death Males

	Control		LD 10 mg/kg		MD 40 mg/kg		HD 100 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
Stomach								
Foci dark	-	-	-	-	-	-	2/4	1/4
Thickening	-	-	-	-	-	-	1/4	-
Duodenum								
Area dark	1/4	-	-	1/4	-	1/4	-	-
Foci dark	-	-	-	-	-	-	1/4	-
Jejunum								
Area dark	-	-	-	-	-	1/4	-	-
Ileum								
Area dark	-	-	-	-	-	1/4	1/4	-
Colon								
Foci dark	-	-	-	-	-	-	1/4	-
Rectum								
Area dark	-	-	-	-	-	-	1/4	-
Salivary gland – mandibular								
Discoloration pale	-	-	-	-	-	-	2/4	3/4
Salivary gland – parotid								
Discoloration pale	-	-	-	-	-	-	2/4	3/4
Gall Bladder								
Area dark	-	-	-	-	-	-	1/4	-
Area raised	-	-	1/4	-	-	-	-	1/4
Dilatation	-	-	-	-	-	-	2/4	-
Material dark	-	-	1/4	-	-	-	3/4	1/4
Bile duct								
Dilatation	-	-	-	-	-	-	1/4	-
Liver								
Firm	-	-	-	-	-	-	1/4	-
Prominent lobular architecture	-	-	-	-	-	-	1/4	-
Heart								
Area dark	-	-	-	-	-	-	1/4	-
Area raised	-	-	-	1/4	-	-	-	-
Lungs								
Area pale	-	1/4	-	2/4	2/4	2/4	2/4	4/4
Nodule	-	-	-	-	1/4	-	-	-
Area dark	-	-	-	-	-	-	-	2/4
Area depressed	-	-	-	-	-	1/4	-	1/4
Adrenal								
Enlargement	-	-	1/4	-	1/4	-	2/4	-

Lymph node								
Area dark	-	-	-	-	-	-	1/4	-
Discoloration dark	2/4	-	-	-	-	1/4	2/4	2/4
Foci dark	-	-	-	-	-	-	1/4	-
Mottled	1/4	-	1/4	1/4	2/4	2/4	1/4	2/4
Enlargement	-	-	-	-	-	1/4	-	3/4
Lymph node - mandibular								
Discoloration dark	-	-	-	-	-	-	-	1/4
Enlargement	-	-	-	-	-	-	-	2/4
Lymph node - mesenteric								
Area dark	-	-	-	-	-	-	1/4	-
Mottled	-	-	-	-	1/4	-	1/4	1/4
Spleen								
Area raised	-	-	1/4	-	-	-	-	-
Area pale	-	1/4	-	1/4	-	1/4	-	1/4
Enlargement	-	1/4	-	-	-	-	-	-
Thymus								
Foci dark	-	-	-	-	1/4	-	-	-
Small	-	1/4	-	-	-	-	2/4	3/4
Discoloration dark	-	-	-	-	-	-	-	1/4
Pituitary								
Cyst	1/4	1/4	1/4	-	-	-	1/4	1/4
Prostate								
Enlargement	1/4		-		2/4		-	
Ovary								
Area raised		-		-		-		1/4
Vagina								
Mass		1/4		-		-		-
Uterus								
Mass		-		1/4		-		-
Urinary bladder								
Area raised	-	-	-	-	-	-	-	1/4
Thickening	-	-	-	-	-	-	1/4	-
Skin								
Scab	-	-	-	-	-	-	1/4	-
Thin haircoat	-	-	-	-	-	1/4	1/4	1/4
Ulceration	-	-	-	-	-	-	1/4	-
Carcass								
Discoloration pale	-		-		-		2/4	
Emaciation	-		-		-		2/4	

Macroscopic Findings Following 39 Weeks of GW572016 in Dogs Recovery Animals				
	Control		HD 100 mg/kg	
	♂	♀	♂	♀
Abdomen				
Hernia	-	-	-	1/2
Duodenum				
Area dark	-	-	1/2	-
Jejunum				
Area dark	-	-	1/2	-
Ileum				
Area dark	-	-	1/2	-
Cecum				
Area dark	-	-	1/2	-
Rectum				
Area raised	-	-	1/2	-
Gall Bladder				
Foci dark	-	-	-	1/2
Foci pale	-	-	-	1/2
Material dark	-	-	-	1/2
Lungs				
Area pale	-	-	-	1/2
Area raised	1/2	-	-	1/2
Area dark	1/2	-	-	-
Area depressed	-	-	-	1/2
Foci dark	-	-	-	2/2
Adrenal				
Area depressed	-	-	1/2	-
Lymph node				
Discoloration dark	1/2	-	1/2	-
Mottled	-	-	1/2	2/2
Lymph node - mandibular				
Mottled	-	1/2	1/2	2/2
Lymph node - mesenteric				
Mottled	-	-	-	2/2
Spleen				
Enlargement	-	-	1/2	-
Pituitary				
Cyst	1/2	-	1/2	1/2
Skin				
Alopecia	-	-	-	1/2

Organ weights:
The table below shows changes in organ weights in organs where significant changes were seen, either absolute or relative to body weight.

Organ Weight Following 39 Weeks of GW572016 in Dogs Including Recovery Animals Percent Changes from Control

	Males				Females		
Dose Mg/kg/day	LD 10	MD 40	HD 100	HD Recov	MD 40	HD 100	HD Recov
Heart							
Absolute	↑ 16%*	↑ 4%	↓ 12%	↓ 5%	↓ 11%	↓ 6%	↓ 14%
Relative to BW	↑ 15%*	↑ 4%	↑ 5%	↓ 6%	↓ 17%	↑ 8%	↓ 8%
Thymus							
Absolute	↓ 13%	↑ 2%	↓ 65%	↑ 39%	↓ 1%	↓ 48%	↓ 33%
Relative to BW	↓ 15%	↑ 1%	↓ 60%*	↑ 27%	↓ 5%	↓ 37%	↓ 29%
Liver							
Absolute	↑ 12%	↑ 17%*	↑ 22%*	↑ 12%	↑ 5%	↑ 27%*	↑ 18%
Relative to BW	↑ 10%	↑ 15%	↑ 46%*	↑ 12%	↓ 2%	↑ 47%*	↑ 27%
Lung							
Absolute	↑6%	↑ 14%	↑ 4%	↑ 0.4%	↑ 13%	↑ 9%	↑ 9%
Relative to BW	↑ 5%	↑ 13%	↑ 24%*	↑ 0.5%	↑ 7%	↑ 26%	↑ 18%
Brain							
Absolute	↓ 0.9%	↑ 1%	↑ 2%	↓ 5%	↓ 3%	↑ 0.8%	↓ 5%
Relative to BW	↓ 3%	↑ 0.7%	↑ 22%*	↓ 5%	↓ 9%	↑ 16%	↑ 3%
Pituitary							
Absolute	↑ 6%	↑ 17%	↑ 20%	↑ 22%	↓ 2%	↓ 7%	↑ 16%
Relative to BW	↑ 4%	↑ 16%	↑ 42%*	↑ 24%	↓ 10%	↑ 7%	↑ 25%

* - statistically significant

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

Microscopic Findings Following 39 Weeks of GW572016 in Dogs Including Unscheduled Death Males

	Control		LD 10 mg/kg		MD 40 mg/kg		HD 100 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
Adrenal glands								
Pigment deposits								
Grade 1	-	-	-	-	-	-	2/4	2/4
Grade 2	-	-	-	-	-	-	2/4	-
Cytoplasmic alterations, cortex								
Grade 1	-	-	-	-	1/4	-	1/4	1/4
Grade 2	-	-	-	-	-	-	3/4	2/4
Bile duct								
Hyperplasia, epithelium								
Grade 2	-	-	-	-	-	-	1/1	-
Dilatation								
Grade 2	-	-	-	-	-	-	1/1	-
Inflammation, chronic								
Grade 2	-	-	-	-	-	-	1/1	-
Cecum								
Pigment deposition								
Grade 1	-	-	-	2/4	4/4	2/4	-	1/4
Grade 2	-	-	-	-	-	1/4	2/4	2/4
Grade 3	-	-	-	-	-	-	2/4	1/4
Lymphoid depletion								
Grade 1	-	-	-	-	-	-	2/4	-
Grade 2	-	-	-	-	-	-	1/4	-
Colon								
Pigment deposition								
Grade 1	-	-	-	-	2/4	-	1/4	1/4
Grade 2	-	-	-	-	-	-	1/4	-
Lymphoid depletion								
Grade 1	-	-	-	-	-	-	-	2/4
Grade 2	-	-	-	-	-	-	2/4	1/4
Gut-associated lymphoid tissue not present in section	-	1/4	-	1/4	-	2/4	2/4	1/4
Duodenum								
Pigment deposition								
Grade 1	-	-	-	-	-	1/4	2/4	-
Ulceration								
Grade 2	-	-	-	-	-	-	1/4	-
Lymphoid depletion								
Grade 1	-	-	-	-	-	-	2/4	1/4

Gut-associated lymphoid tissue not present in section	1/4	1/4	2/4	-	1/4	1/4	2/4	3/4
Epididymis								
Vacuolation, tubular epithelium								
Grade 1	1/4		-		-		-	
Grade 3	-		-		-		1/4	
Spermatic debris, intratubular								
Grade 2	-		-		-		1/4	
Granuloma, spermatic								
Grade 2	1/4		-		-		-	
Esophagus								
Infiltration, mononuclear cell								
Grade 1	-	2/4	-	-	-	-	-	-
Gallbladder								
Pigment deposition								
Grade 1	-	-	1/4	-	2/4	2/4	-	1/4
Grade 2	-	-	-	-	1/4	1/4	4/4	2/4
Grade 3	-	-	-	-	-	-	-	1/4
Cholelithiasis								
Grade 2	-	-	-	-	-	-	-	1/4
Lymphoid depletion								
Grade 1	-	-	-	-	-	-	-	1/4
Cystic hyperplasia, mucosa								
Grade 1	-	-	-	1/4	-	-	-	-
Inflammation, acute								
Grade 2	-	-	-	-	-	-	1/4	-
Hemorrhage								
Grade 2	-	-	-	-	-	-	1/4	-
Heart								
Hemorrhage								
Grade 2	-	-	-	-	-	-	1/4	-
Hematocyst								
Grade 2	-	-	-	1/4	-	-	-	-
Ileum								
Pigment deposition								
Grade 1	-	-	-	-	-	-	3/4	2/4
Grade 2	-	-	-	-	-	-	1/4	1/4
Lymphoid depletion								
Grade 1	-	-	-	-	-	-	1/4	1/4
Grade 2	-	-	-	-	-	-	1/4	2/4
Grade 3	-	-	-	-	-	-	2/4	-
Jejunum								
Pigment deposition								
Grade 1	-	-	-	1/4	3/4	-	1/4	-
Grade 2	-	-	-	-	-	-	2/4	1/4

Lymphoid depletion								
Grade 1	-	-	-	-	-	-	1/4	2/4
Grade 2	-	-	-	-	-	-	2/4	-
Gut-associated lymphoid tissue not present in section	1/4	1/4	2/4	-	-	3/4	1/4	2/4
Kidney								
Pigment accumulations								
Grade 2	-	-	1/4	-	-	-	-	-
Necrosis, single cell								
Grade 2	-	-	-	-	-	-	1/4	-
Basophilia, tubular								
Grade 1	-	-	3/4	-	1/4	-	1/4	-
Grade 2	-	-	-	-	-	-	1/4	-
Grade 3	-	-	-	-	-	-	1/4	-
Inflammation, acute								
Grade 1	-	-	1/4	-	-	-	1/4	-
Pyelitis/pyelonephritis								
Grade 3	-	-	-	-	-	1/4	-	-
Lacrimal gland								
Infiltration, mononuclear cell								
Grade 1	1/2	-	-	-	-	-	-	-
Grade 2	-	-	1/3	-	-	-	-	-
Pigment deposition								
Grade 1	-	-	-	-	-	-	-	1/3
Grade 2	-	-	-	-	-	-	-	1/3
Liver								
Pigment deposition								
Grade 1	-	-	-	-	2/4	2/4	-	-
Grade 2	-	-	-	-	1/4	1/4	-	3/4
Grade 3	-	-	-	-	-	-	4/4	1/4
Reactive sinusoidal lining cells								
Grade 1	-	-	-	-	1/4	2/4	-	-
Grade 2	-	-	-	-	-	-	1/4	3/4
Grade 3	-	-	-	-	-	-	3/4	-
Inflammation, subacute								
Grade 1	-	-	-	-	2/4	1/4	3/4	3/4
Grade 2	-	-	-	-	-	2/4	1/4	-
Grade 3	-	-	-	-	-	-	-	1/4
Degeneration and/or necrosis								
Grade 1	-	-	-	-	-	-	-	1/4
Grade 2	-	-	-	-	-	-	2/4	1/4
Cholestasis								
Grade 1	-	-	-	-	-	-	-	1/4
Grade 2	-	-	-	-	-	-	1/4	-
Grade 3	-	-	-	-	-	-	1/4	-

Lung								
Pigment deposition								
Grade 1	-	-	-	-	2/4	1/4	-	1/4
Grade 2	-	-	-	-	-	2/4	3/4	1/4
Grade 3	-	-	-	-	-	-	1/4	2/4
Inflammation, granulomatous								
Grade 2	-	-	-	-	-	-	1/4	1/4
Inflammation								
Grade 1	1/4	2/4	-	-	-	-	-	1/4
Grade 2	1/4	1/4	-	1/4	3/4	1/4	1/4	1/4
Grade 3	-	-	-	1/4	-	-	-	1/4
Histiocytosis								
Grade 1	-	-	-	-	-	-	1/4	-
Osseous metaplasia								
Grade 2	-	-	-	-	1/4	-	-	-
Polyarteritis								
Grade 2	-	-	-	1/4	-	-	-	-
Lymph node								
Pigment deposition								
Grade 1	-	-	-	-	-	-	-	1/3
Grade 2	-	-	-	-	-	-	-	1/3
Grade 3	-	-	-	-	-	-	3/3	1/3
Hyperplasia, lymphoid								
Grade 1	-	-	-	-	-	1/3	-	-
Grade 2	-	-	-	-	-	-	-	3/3
Plasmocytosis								
Grade 2	-	-	-	-	-	1/3	-	1/3
Grade 3	-	-	-	-	-	-	-	2/3
Inflammation								
Grade 2	-	-	-	-	-	1/3	-	-
Lymphoid depletion								
Grade 3	-	-	-	-	-	-	1/3	-
Necrosis, single cell								
Grade 1	-	-	-	-	-	-	1/3	-
Grade 2	-	-	-	-	-	-	1/3	-
Erythrophagocytosis and/or hemosiderosis								
Grade 2	2/2	-	-	1/1	2/2	1/3	2/3	3/3
Erythrocytosis/hemorrhage, sinusal								
Grade 2	1/2	-	1/1	-	-	2/3	-	-
Lymph node, mandibular								
Pigment deposition								
Grade 1	-	-	-	-	1/4	2/4	-	-

Grade 2	-	-	-	-	-	-	4/4	1/4
Grade 3	-	-	-	-	-	-	-	3/4
Necrosis, single cell								
Grade 1	-	-	-	-	-	-	1/4	2/4
Grade 2	-	-	-	-	-	-	1/4	1/4
Grade 3	-	-	-	-	-	-	1/4	-
Hyperplasia, lymphoid								
Grade 2	-	-	-	-	-	-	-	2/4
Erythrocytosis/hemorrhage, sinusal								
Grade 1	-	1/4	-	-	-	-	-	-
Lymph node, mesenteric								
Pigment deposition								
Grade 1	-	-	-	-	1/4	2/4	-	1/4
Grade 2	-	-	-	-	-	-	3/4	2/4
Grade 3	-	-	-	-	-	-	1/4	1/4
Lymphoid depletion								
Grade 1	-	-	-	-	-	-	1/4	3/4
Grade 2	-	-	-	-	-	-	2/4	-
Grade 3	-	-	-	-	-	-	1/4	-
Necrosis, single cell								
Grade 1	-	1/4	-	-	-	-	1/4	2/4
Grade 2	-	-	-	-	-	-	2/4	-
Erythrophagocytosis and/or hemosiderosis								
Grade 1	1/4	1/4	2/4	2/4	1/4	2/4	3/4	3/4
Grade 2	1/4	-	-	-	2/4	1/4	1/4	1/4
Mammary gland								
Pigment deposition								
Grade 1	-	2/4	-	2/4	-	1/4	-	-
Grade 2	-	-	-	-	-	2/4	-	1/4
Grade 3	-	-	-	-	-	-	-	2/4
Ovary								
Pigment deposition								
Grade 1		2/4		3/4		2/4		1/4
Grade 2		-		-		-		3/4
Pancreas								
Inflammation, chronic								
Grade 1	-	1/4	-	-	-	-	-	-
Parathyroid gland								
Cyst								
Grade 1	-	1/4	-	-	-	-	-	-
Grade 2	-	-	-	-	-	-	1/4	1/4
Pituitary								
Cyst								
Grade 1	-	1/4	-	-	-	1/4	-	-
Grade 2	1/4	2/4	1/4	1/4	-	1/4	1/4	1/4
Grade 3	-	-	1/4	-	-	-	2/4	1/4
Prostate								
Infiltration, mononuclear cell								

Grade 1	-		1/4		-		-	
Rectum								
Pigment deposition								
Grade 1	-	-	-	-	3/4	-	1/4	-
Grade 2	-	-	-	-	-	3/4	2/4	-
Grade 3	-	-	-	-	-	-	1/4	3/4
Lymphoid depletion								
Grade 1	-	-	-	-	-	-	1/4	-
Grade 2	-	-	-	-	-	-	2/4	-
Salivary gland, mandibular								
Inflammation, chronic								
Grade 1	-	-	1/4	-	-	-	-	-
Infiltration, mononuclear cell								
Grade 1	2/4	-	1/4	1/4	-	1/4	-	1/4
Grade 2	-	1/4	-	-	-	-	-	-
Salivary gland, parotid								
Pigment deposition								
Grade 1	-	-	-	-	-	-	3/4	2/4
Grade 2	-	-	-	-	-	-	-	1/4
Inflammation, chronic								
Grade 1	1/4	-	-	-	-	-	-	1/4
Infiltration, mononuclear cell								
Grade 1	-	-	1/4	-	-	1/4	-	1/4
Grade 2	1/4	1/4	-	1/4	-	-	-	1/4
Skin								
Ulceration								
Grade 1	-	-	-	-	-	1/4	-	-
Atrophy, hair follicle								
Grade 1	-	-	-	-	-	-	2/4	1/4
Grade 2	-	-	-	-	-	1/4	1/4	-
Inflammation, follicular/perifollicular								
Grade 1	1/4	-	-	1/4	-	1/4	-	1/4
Grade 2	-	-	1/4	-	-	-	1/4	-
Infiltration, mixed cell								
Grade 1	-	-	-	-	-	1/4	1/4	-
Grade 2	-	1/4	1/4	-	-	-	1/4	-
Skin, miscellaneous								
Ulceration								
Grade 2	-	-	-	-	-	-	1/2	-
Grade 3	-	-	-	-	-	-	1/2	-
Hyperplasia, epidermis								
Grade 2	-	-	-	-	-	1/1	2/2	-
Atrophy, hair follicle								
Grade 1	-	-	-	-	-	-	1/2	-
Grade 2	-	-	-	-	-	-	1/2	-

Inflammation, follicular/perifollicular								
Grade 1	-	-	-	-	-	-	1/2	-
Grade 2	-	-	-	-	-	-	1/2	-
Inflammation, subacute								
Grade 2	-	-	-	-	-	1/1	-	-
Spleen								
Pigment deposition								
Grade 1	1/4	1/4	1/4	2/4	2/4	-	1/4	1/4
Grade 2	2/4	1/4	2/4	2/4	2/4	2/4	2/4	-
Grade 3	-	-	-	-	-	2/4	1/4	3/4
Siderotic plaque								
Grade 2	-	1/4	-	1/4	-	1/4	-	1/4
Stomach								
Pigment deposition								
Grade 1	-	-	-	-	-	2/4	-	-
Grade 2	-	-	-	-	-	-	4/4	2/2
Grade 3	-	-	-	-	-	-	-	2/2
Atrophy/degeneration, mucosal								
Grade 1	-	-	-	-	-	-	1/4	4/4
Grade 2	-	-	-	-	-	-	2/4	-
Infiltration, mixed cell								
Grade 1	-	-	-	-	1/4	-	2/4	-
Grade 2	-	-	-	-	-	-	2/4	4/4
Polyarteritis								
Grade 1	-	-	-	1/4	-	-	-	-
Testis								
Degeneration, seminiferous epithelium								
Grade 1	-		-		-		1/4	
Thymus								
Pigment deposition								
Grade 1	-	-	-	-	-	-	-	1/4
Grade 2	-	-	-	-	-	-	3/4	1/4
Lymphoid depletion								
Grade 1	1/4	1/4	1/4	1/4	2/4	1/4	-	-
Grade 2	2/4	-	1/4	1/4	1/4	-	-	1/4
Grade 3	-	-	-	-	-	-	4/4	1/4
Thyroid								
Infiltration, mononuclear cell								
Grade 1	-	-	1/4	-	-	-	-	-
Tongue								
Erosion								
Grade 1	-	-	1/4	-	-	-	1/4	-
Ulceration								
Grade 2	-	-	-	-	-	-	-	1/4
Urinary bladder								
Pigment deposition								
Grade 1	-	-	-	-	-	-	-	1/4
Uterus								

Pigment deposition								
Grade 1		3/4		2/4		2/4		2/4
Grade 2		-		-		2/4		2/4
Hyperplasia, endometrial cystic								
Grade 1		1/4		-		-		1/4
Grade 2		-		1/4		-		-

Microscopic Findings Following 39 Weeks of GW572016 Recovery Dogs

	Control		HD 100 mg/kg	
	♂	♀	♂	♀
Adrenal glands				
Pigment deposits				
Grade 1	-	-	1/2	1/2
Cecum				
Pigment deposition				
Grade 1	-	-	2/2	1/2
Grade 2	-	-	-	1/2
Lymphoid depletion				
Grade 1	-	-	-	1/2
Colon				
Pigment deposition				
Grade 1	-	-	-	1/2
Grade 2	-	-	-	1/2
Gut-associated lymphoid tissue not present in section	1/2	-	1/2	-
Duodenum				
Gut-associated lymphoid tissue not present in section	1/2	1/2	1/2	2/2
Gallbladder				
Pigment deposition				
Grade 1	1/2	-	-	-
Grade 2	-	-	2/2	2/2
Ileum				
Pigment deposition				
Grade 1	-	-	2/2	2/2
Jejunum				
Gut-associated lymphoid tissue not present in section	1/2	1/2	2/2	2/2
Lacrimal gland				
Pigment deposition				
Grade 1	-	-	-	1/2
Liver				
Pigment deposition				
Grade 1	-	-	1/2	1/2
Grade 2	-	-	1/2	1/2
Inflammation, subacute				
Grade 1	-	-	-	1/2
Lung				

Pigment deposition				
Grade 1	-	-	1/2	-
Grade 2	-	-	-	1/2
Grade 3	-	-	-	1/2
Inflammation, granulomatous				
Grade 3	-	-	-	1/2
Inflammation				
Grade 1	2/2	-	-	2/2
Hemorrhage				
Grade 1	1/2	-	-	-
Grade 2	1/2	-	-	-
Lymph node				
Pigment deposition				
Grade 1	-	-	1/2	-
Grade 3	-	-	-	1/2
Erythrophagocytosis and/or hemosiderosis				
Grade 1	1/2	-	1/2	-
Lymph node, mandibular				
Pigment deposition				
Grade 1	-	-	1/2	-
Grade 2	-	-	1/2	-
Grade 3	-	-	-	1/2
Erythrocytosis/hemorrhage, sinusal				
Grade 1	1/2	-	-	-
Lymph node, mesenteric				
Pigment deposition				
Grade 1	-	-	1/2	1/2
Grade 2	-	-	1/2	1/2
Erythrophagocytosis and/or hemosiderosis				
Grade 1	-	-	1/2	2/2
Grade 2	1/2	1/2	-	-
Mammary gland				
Pigment deposition				
Grade 1	-	2/2	-	-
Grade 2	-	-	-	1/2
Ovary				
Pigment deposition				
Grade 1		2/2		-
Grade 2		-		2/2
Rectum				
Pigment deposition				
Grade 1	1/2	-	1/2	1/2
Grade 2	-	-	1/2	-
Salivary gland, parotid				
Pigment deposition				
Grade 1	-	-	-	1/2
Grade 2	-	-	-	1/2

Infiltration, mononuclear cell				
Grade 1	-	1/2	-	1/2
Grade 2	-	-	1/2	-
Skin				
Inflammation, follicular/perifollicular				
Grade 2	-	-	-	1/2
Infiltration, mixed cell				
Grade 2	-	-	1/2	-
Skin, miscellaneous				
Inflammation, follicular/perifollicular				
Grade 1	-	-	-	1/1
Spleen				
Pigment deposition				
Grade 1	-	-	1/2	1/2
Grade 2	1/2	2/2	1/2	-
Grade 3	-	-	-	1/2
Stomach				
Pigment deposition				
Grade 1	-	-	1/2	-
Thymus				
Lymphoid depletion				
Grade 1	1/2	-	1/2	-
Grade 2	1/2	-	-	-
Hyperplasia, lymphoid				
Grade 1	1/2	-	-	-

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Toxicokinetics:

Toxicokinetic Parameters During 39-Week Administration of GW572016 in Dogs

Dose	Sample Point	AUC_{last} (ng*h/mL)		C_{max} (ng/mL)		Dose Normalized AUC[1]		AUC Ratio[2]	
		♂	♀	♂	♀	♂	♀	♂	♀
LD 10 mg/kg	Day 1	4278	4422	545	598	4278	4422	---	---
	Week 13	3882	6538	530	953	3882	6538	1.50	1.81
	Week 26	5593	7900	683	1002	5593	7900	1.99	2.31
	Week 39	5425	8155	652	1018	5425	8155	1.95	2.25
MD 40 mg/kg	Day 1	36112	28468	2843	2197	9028	7177	---	---
	Week 13	22452	28033	1885	2647	5613	7008	0.60	1.23
	Week 26	14117	42980	1110	2922	3529	10745	0.37	1.78
	Week 39	18700	54450	1467	3521	4675	13612	0.60	2.53
HD 100 mg/kg	Day 1	94448	101156	6105	6784	9445	10116	---	---
	Week 13	33063	64058	2372	3929	3306	6406	0.47	0.79
	Week 26	70468	93499	4305	5592	7047	9350	0.87	1.00
	Week 39	70797	77239	4466	4734	7080	7724	1.01	0.80

[1] – dose normalized to 10 mg/kg dose

[2] – AUC ratio is the AUC from the time point after repeated doses divided by the Day 1 AUC (single administration)

Several additional toxicology studies were conducted using two components of the final lapatinib product, the impurity — and — and has been found in the final drug product. — is genotoxic and present in the final product at a level that exceeds the current guideline Threshold for Toxicological Concern (TTC) for genotoxic impurities. The recommended threshold is 1.5 µg/person/day and at the proposed dose of lapatinib, 1250 mg/day, patients will be exposed to approximately — day. Because of this, additional studies have been conducted with both the impurity — and the genotoxic —

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Study title: Twenty-eight day repeated dose oral (gavage) toxicity study in the rat

Key study findings:

- Study conducted to examine the toxicology of —— —— that is genotoxic and still present in the final product
- Slight reductions in body weight and food consumption at MD and HD
- Hematology indicative of anemia and methemoglobinemia
- Increased bilirubin and cholesterol in HD
- Most microscopic effects seen in HD in the spleen, liver, lungs, thyroid, kidneys, bone marrow, stomach and urinary bladder

Study no:	RD2005/00355/00
Volume #, and page #:	4.2.3.7.6.2
Conducting laboratory and location:	/ /
Date of study initiation:	11 July 2002
GLP compliance:	Letter included and signed
QA report:	yes (X) no ( )
Drug, lot #, radiolabel, and % purity:	—— Lot 0203021-E, purity not given

Methods:

Doses:	0, 15, 150 and 500 mg/kg
Species/strain:	Rat/Sprague-Dawley
Number/sex/group or time point:	5/sex/dose
Route, formulation, volume, and infusion rate:	PO, in polyethylene glycol 400, 2 mL/kg volume
Satellite groups for toxicokinetics or recovery:	Not conducted
Age:	≈ 5-6 weeks
Weight:	♂ 125 – 159 g ♀ 121 – 160 g
Sampling times:	NA
Unique study design or methodology (if any):	None

Observation times and results:

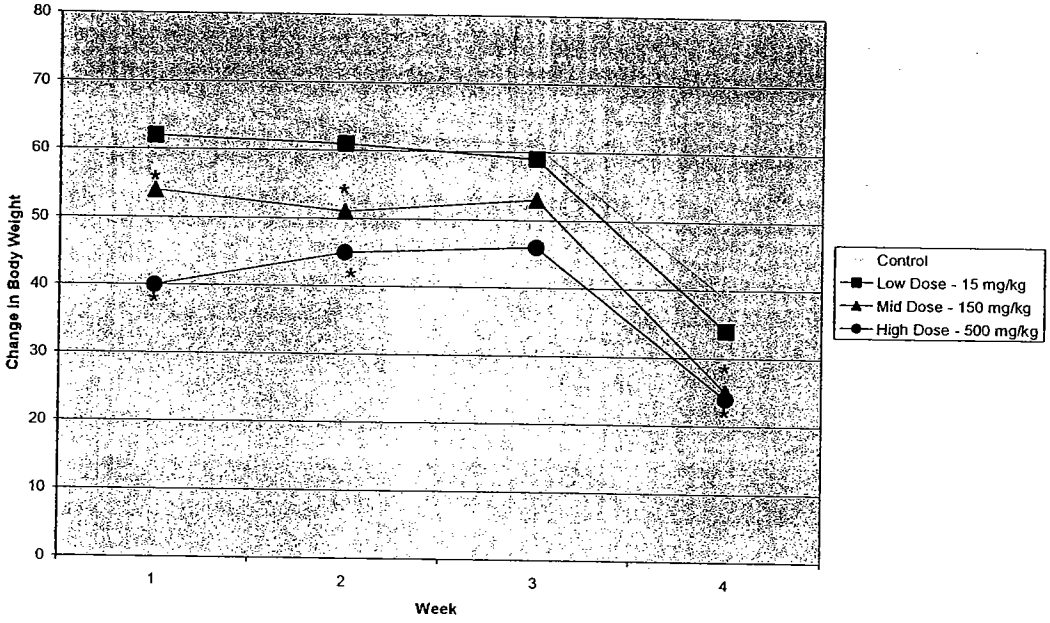
Mortality: monitored daily
No deaths occurred on study

Clinical signs: monitored twice daily after drug administration
Clinical signs were seen mostly in the HD female rats and included pallor of extremities, increased salivation, fur loss and staining, diuresis, tiptoe gait and hunched posture.

Functional observations: monitored weekly
Open field assessments indicated pallor, hunched posture and tiptoe gait in HD
Functional performance indicated no effect of treatment
Sensory reactivity assessment showed no treatment-related effect

Body weights: recorded weekly
Statistically significantly decreased body weight gains were seen in the HD male and female rats and MD male rats when compared to control. Female MD rats also had decreased body weight gains, though not with statistical significance. The graph below shows the data. Asterisks mark where the body weight changes were significant.

Male Rat Body Weight Changes



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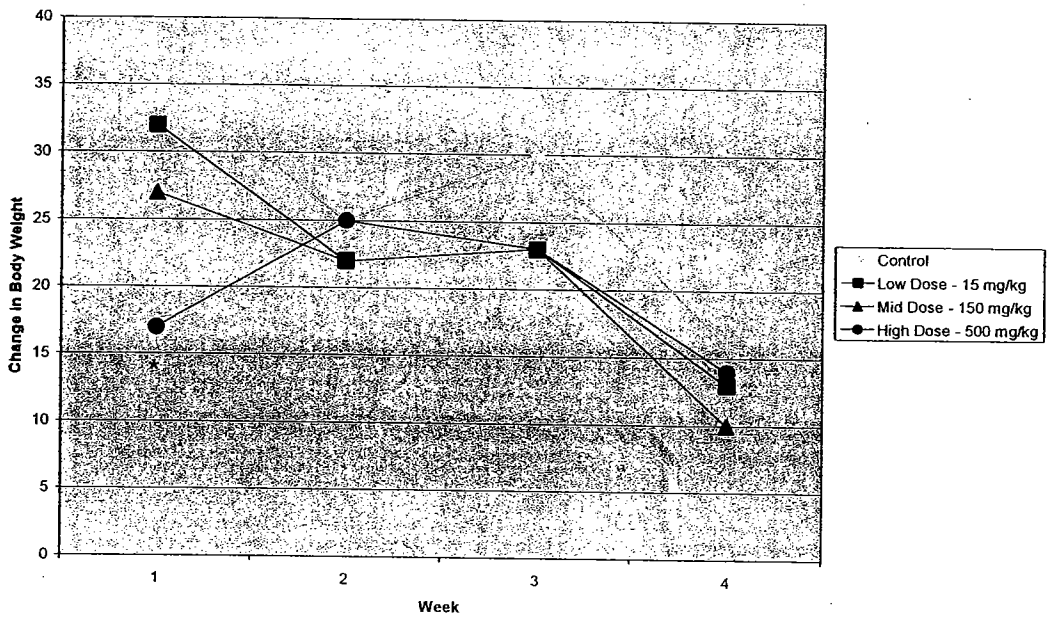
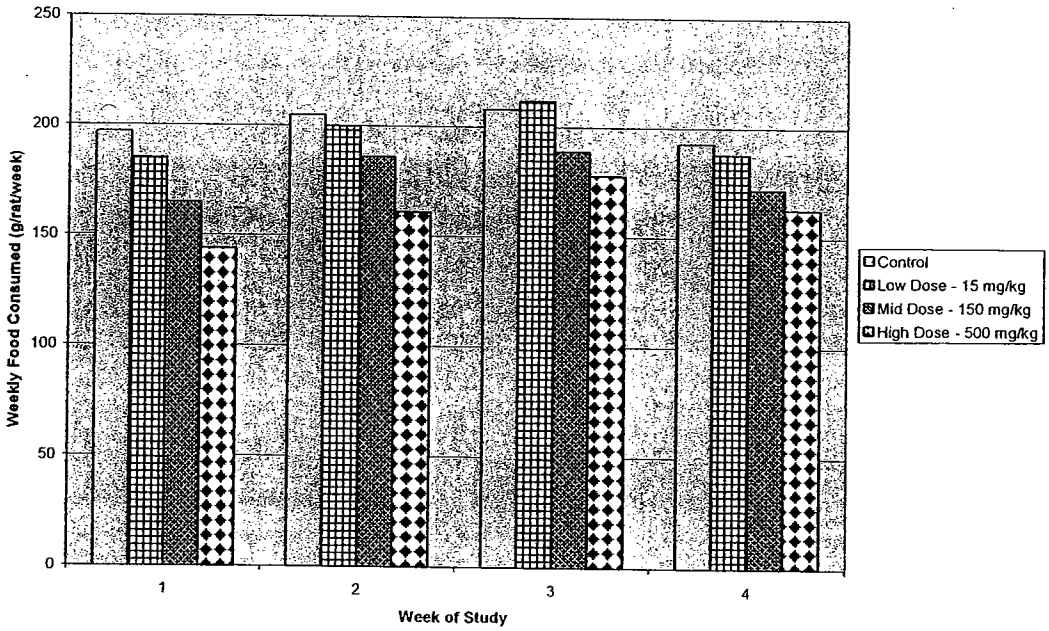
Female Rat Body Weight Changes

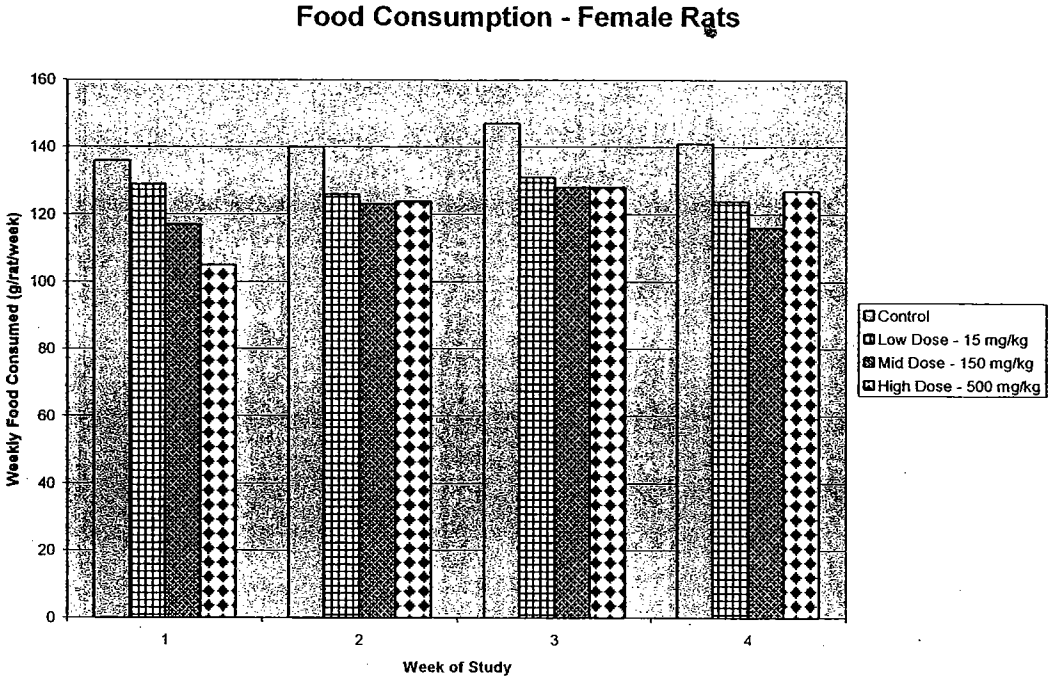


Food consumption: recorded weekly

Reduced food consumption was seen in the MD and HD males throughout the study and in the HD females in Week 1 only.

Food Consumption - Male Rats





Ophthalmoscopy: not conducted

EKG: not conducted

Hematology: conducted on Day 28
The table below shows the changes in hematology, with statistically significant effects presented as bolded numbers. Most numbers are indicative of an anemia response.

Changes in Hematology Percent Change From Control				
	Mid Dose 150 mg/kg		High Dose 500 mg/kg	
	Males	Females	Males	Females
Hemoglobin	**↓ 8%**	**↓ 19%**	**↓ 13%**	**↓ 30%**
RBCs	**↓ 8%**	**↓ 24%**	**↓ 27%**	**↓ 44%**
Hematocrit	**↓ 8%**	**↓ 18%**	**↓ 11%**	**↓ 25%**
MCH	↓ 0.5%	**↑ 7%**	**↓ 20%**	**↑ 28%**
MCV	↓ 0.3%	**↑ 8%**	**↑ 22%**	**↑ 35%**
MCHC	↓ 03%	↓ 1%	**↓ 3%**	**↓ 6%**
Methemoglobin	**↑ 182%**	**↑ 781%**	**↑ 1094%**	**↑ 1017%**
Reticulocytes (%)	**↑ 40%**	↑ 75%	**↑ 320%**	**↑ 850%**

Clinical chemistry: conducted on Day 28
Significant changes in clinical chemistry, presented in bold in the table below, show increases in bilirubin and an increase in cholesterol in the HD females only.

Changes in Clinical Chemistry Percent Change From Control				
	Mid Dose 150 mg/kg		High Dose 500 mg/kg	
	Males	Females	Males	Females
Bilirubin	↑ 38%	**↑ 63%**	**↑ 138%**	**↑ 250%**
Cholesterol	↓ 14%	↑ 13%	↑ 6%	**↑ 60%**

Urinalysis: not conducted

Gross pathology:
Gross pathology findings included
Spleen – dark and enlarged - 5/5 ♂ and 5/5 ♀ HD rats and 1/5 ♀ MD rat
Kidney – dark – 0/5 ♂ and 5/5 ♀ HD rats

Organ weights:
Significant organ weight changes were seen primarily in the HD group, with a few significant changes seen in the MD. All the bolded numbers in the table were statistically significantly different when compared to control. Major findings include increases in the spleen and liver weights.

Changes in Organ Weights (Absolute and Relative to Body Weight) Percent Change From Control				
	Mid Dose 150 mg/kg		High Dose 500 mg/kg	
	Males	Females	Males	Females
Spleen				
Absolute	↓ 11%	↑ 39%	**↑ 56%**	**↑ 241%**
Relative to BW	↑ 3%	**↑ 51%**	**↑ 100%**	**↑ 272%**
Liver				
Absolute	↑ 9%	↑ 19%	↑ 16%	**↑ 52%**
Relative to BW	**↑ 26%**	**↑ 30%**	↑ 47%	**↑ 67%**
Thymus				
Absolute	↓ 18%	↓ 30%	**↓ 42%**	↓ 25%
Relative to BW	↓ 4%	↓ 23%	**↓ 26%**	↓ 18%
Kidney				
Absolute	↓ 7%	↑ 0.8%	↓ 13%	↑ 8%
Relative to BW	↑ 7%	↑ 9%	↑ 11%	**↑ 18%**
Brain				
Absolute	↓ 5%	↓ 0.3%	↓ 4%	↓ 3%
Relative to BW	↑ 11%	↑ 10%	**↑ 23%**	↑ 7%

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

Microscopic Findings in Rats Exposed to the GW572016 Genotoxic Impurity						
	Control		Mid Dose 150 mg/kg		High Dose 500 mg/kg	
	♂	♀	♂	♀	♂	♀
Bone marrow						
Absence of adipose infiltration	1/5	1/5	1/5	0/5	5/5	5/5
Kidney						
Pigment deposition						
Minimal	--	--	--	1/5	5/5	--
Slight	--	--	--	--	--	1/5
Moderate	--	--	--	--	--	3/5
Marked	--	--	--	--	--	1/5
Groups of basophilic tubules						
Minimal	1/5	3/5	2/5	3/5	3/5	1/5
Slight	--	--	--	--	--	1/5
Hyperplasia pelvic/papillary epithelium						
Present	--	--	--	--	--	2/5
Pyelitis						
Present	--	--	--	--	--	1/5
Dilatation of inner cortex tubules						
Present	--	--	--	2/5	--	3/5
Liver						
Centrolobular enlargement						
Minimal	--	--	5/5	3/5	1/5	2/5
Slight	--	--	--	--	3/5	3/5
Moderate	--	--	--	--	1/5	--
Lungs						
Alveolar macrophages						
Minimal	1/5	--	2/5	1/5	2/5	2/5
Slight	--	--	--	--	1/5	2/5
Spleen						
Extramedullary hemopoiesis						
Minimal	4/5	--	--	1/5	--	--
Slight	1/5	--	5/5	3/5	2/5	1/5
Moderate	--	--	--	--	3/5	3/5
Marked	--	--	--	--	--	1/5
Pigment deposition						
Minimal	--	5/5	--	--	--	--

Slight	--	--	5/5	--	--	--
Moderate	--	--	--	4/5	5/5	4/5
Marked	--	--	--	--	--	1/5
Hyperemia						
Present	--	--	1/5	4/5	5/5	5/5
Stomach						
Acanthosis						
Minimal	--	--	2/5	--	4/5	--
Slight	--	--	--	2/5	1/5	3/5
Moderate	--	--	--	--	--	2/5
Hyperkeratosis						
Minimal	--	--	4/5	1/5	2/5	1/5
Slight	--	--	--	1/5	3/5	3/5
Moderate	--	--	--	1/5	--	1/5
Thyroid						
Follicular cell hypertrophy						
Minimal	1//5	--	4/5	2/5	2/5	2/5
Slight	--	--	--	--	1/5	2/5
Moderate	--	--	--	--	1/5	1/5
Urinary bladder						
Vacuolation/disruption of surface epithelium						
Minimal	--	--	--	--	2/5	4/5
Slight	--	--	--	--	1/5	--
Thickening of lamina propria						
Present	--	--	--	--	3/5	--
Epithelial hyperplasia						
Minimal	--	--	--	--	4/5	2/5
Slight	--	--	--	--	--	1/5
Epithelial/subepithelial inflammatory cells						
Minimal	--	--	--	--	--	2/5
Moderate	--	--	--	--	--	1/5

Toxicokinetics: Not conducted

Other: None

Histopathology inventory:

Study	13-wk	7-day	14-day	13-wk	26-wk	7-day	14-day	13-wk	39-wk	28-wk
Species	Mouse	Rat	Rat	Rat	Rat	Dog	Dog	Dog	Dog	Rat
Adrenals	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Aorta	X	X	X	X	X	X	X	X	X	
Bone Marrow smear	X		X	X	X					X
Bone (femur)	X		X	X	X	X	X	X	X	
Brain	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Cecum	X	X	X	X	X	X	X	X	X	X
Cervix	X*									
Colon	X	X	X	X	X	X	X	X	X	X
Duodenum	X	X	X	X	X	X	X	X	X	X
Epididymis	X*	X	X*	X*	X*	X	X	X	X	X*
Esophagus	X	X	X	X	X	X	X	X	X	
Eye	X	X	X	X	X	X	X	X	X	
Fallopian tube										
Gall bladder	X*					X	X	X	X	
Gross lesions										X
Harderian gland	X	X	X	X	X					
Heart	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Ileum	X	X	X	X	X	X	X	X	X	X
Injection site										
Jejunum	X	X	X	X	X	X	X	X	X	X
Kidneys	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Lachrymal gland						X	X	X	X	
Larynx	X		X	X	X					
Liver	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*
Lungs	X*	X*	X*	X*	X*	X*	X*	X*	X*	X
Lymph nodes, cervical										X
Lymph node, mandibular	X	X	X	X	X	X	X	X	X	
Lymph node, mesenteric	X	X	X	X	X	X	X	X	X	X
Mammary Gland	X	X	X	X	X					
Nasal cavity	X				X					
Optic nerves	X	X	X	X	X	X	X	X	X	
Ovaries	X*		X*	X*	X*		X*	X*	X*	X*
Pancreas	X	X	X	X	X	X	X	X	X	
Parathyroid	X*	X	X	X	X*	X*	X*	X*	X*	
Peripheral nerve		X	X	X		X	X	X	X	
Pharynx										
Pituitary	X*	X*	X*	X*	X*	X*	X*	X*	X*	
Prostate	X*	X*	X*	X*	X*	X*	X*	X*	X*	X
Rectum	X	X	X	X	X	X	X	X	X	X
Salivary gland	X	X	X	X	X	X	X	X	X	
Sciatic nerve	X	X	X	X	X	X	X	X	X	X
Seminal vesicles	X	X	X	X	X					X
Skeletal muscle	X	X	X	X	X	X	X	X	X	
Skin	X	X	X	X	X	X	X	X	X	
Spinal cord	X	X	X	X	X	X	X	X	X	X
Spleen	X*	X*	X*	X*	X*	X*	X*	X*	X*	X*