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Data Article

Data set on Separase Inhibitor—Sepin-1 toxicity on organ weights, hematology and clinical parameters in Sprague-Dawley rats

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ABSTRACT

Separase Inhibitor—Sepin-1 has shown great promise as a developmental chemotherapeutic agent to treat Separase-overexpressing tumors, however, very little is known about its toxicity profile. Here we present the data set of organ weights, hematology, and clinical chemistry parameters in Sepin-1-treated Sprague-Dawley rats. The data set was generated from two study groups—Main Study and Recovery Study, with in-life duration of 29 and 57 days, respectively. Rats in both groups were dosed with 0, 5, 10 and 20 mg/kg of Sepin-1 once daily for 28 consecutive days. Blood samples from rats in Main Study were collected and their organs were weighed on day 29. The animals in Recovery Study were on a dose-off period of 28 days after dosed with Sepin-1 for 28 days, and their blood samples and organ weight data were collected on day 57. Body weights of rats in both Main and Recovery Study were collected twice a week. Hematology parameters of whole blood samples, such as hemoglobin concentration, counts of platelet and blood cells etc., were determined. Clinical chemistry parameters of serum, such as concentrations of albumin, glucose, cholesterol, triglyceride, alanine/aspartate aminotransferase, ect., were measured. Further analysis may yield useful information regarding the toxicity of Sepin-1 in Sprague-Dawley Rats. Data presented here are related to a research article entitled "Toxicity

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study of separase inhibitor—Sepin-1 in Sprague-Dowley rats", available in Pathology — Research and Practice Journal [1].

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Specifications Table

Subject	Toxicology
Specific subject area	Toxicity profiling of Sepin-1 in Sprague-Dawley Rats
Type of data	Tables
How data were acquired	Body and organ weights were collected by using a standard measuring scale. Hematology data were obtained using Siemens Advia 120 Hematology System (Siemens Healthineers, Erlangen, Germany). Clinical chemistry data were collected using Randox Imola Clinical Chemistry Analyzer (Randox Laboratories-US, Ltd, Kearneysville, WV).
Data format	Raw, Analysed
Experimental factors	Body and organ weights were collected. Hematology and clinical chemistry parameters were obtained from blood samples.
Experimental Features	Body and organ were weighed. Blood samples collected with K_2EDTA were analyzed for the hematology parameters using Siemens Advia 120 Hematology System. Clotted blood samples were centrifuged, and the serum was used for the clinical chemistry analyses using Randox Imola Clinical Chemistry Analyzer.
Data source location	Baylor College of Medicine Houston, Texas 77030 USA
Data accessibility	With the article

Value of the Data

- Sepin-1 is a novel inhibitor of Separase and its toxicity is unknown in animals. These data are collected in a GLP setting and useful for Sepin-1 to be further developed in pre-clinical and clinical studies.
- Researchers in cancer research, pharmacology, toxicology and pharmaceutics will benefit from these data.
- These data can be used to further study Sepin-1 in haematopoiesis, mechanisms of toxicity, and metabolism.

1. Data

The dataset in this article contains body and organ weights, hematology, and clinical chemistry parameters in Sprague-Dawley rats that were dosed with Separase inhibitor—Sepin-1 in Good Laboratory Practice (GLP) setting. The animals randomly assigned in two study groups—Main Study and Recovery Study. Both study groups were dosed with Sepin-1 once daily for 28 consecutive days. Animals in Main Study group were terminated on day 29. Animals in Recovery Study were allowed to recover for 28 days and terminated on day 57. On the termination day organ weights were collected and blood samples were obtained for hematology and clinical chemistry analyses. Tables 1 and 2 show group mean body weights data in Main Study and Recovery Study, respectively, which were collected twice a week. Tables 3—5 are group mean organ weights, organ weights relative to brain weight, and organ weights relative to body weight in rats of Main Study, respectively. Tables 6—8 describe group mean organ weights, organ weights relative to brain weight, and organ weights relative to body weight in rats of Recovery Study, respectively. Tables 9 and 10 show group mean hematology parameters in male and female rats of Main Study, respectively. Tables 11 and 12 display group mean hematology parameters in male and female rats of Recovery Study, respectively. Tables 13 and 14 show group mean clinical chemistry parameters in male and female rats of Main Study, respectively. Tables 15 and 16 show group mean clinical chemistry parameters in male and female rats of Recovery Study, respectively. These data are complementary to the toxicity study of Sepin-1 in Sprague-Dowley rats published previously [1].

Table 1
Group mean body weights (g) of rats in Main Study.

	Group 1 (0 mg/kg)		Group 2 (5 mg/kg)		Group 3 (10 mg/kg)		Group 4 (20 mg/kg)	
	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N
Body weight (g) of male rats in Main Study								
Predose	256.71 ± 9.05	10	256.36 ± 10.13	9	258.88 ± 12.19	10	259.35 ± 11.47	8
Day 1	265.73 ± 12.65	10	264.14 ± 12.42	9	274.45 ± 11.54	10	274.64 ± 11.03	8
Day 4	280.32 ± 11.8	10	268.73 ± 15.23	9	280.12 ± 8.65	10	277.21 ± 11.24	8
Day 9	303.22 ± 14.63	10	293.07 ± 10.84	9	297.00 ± 10.33	10	292.07 ± 13.13	8
Day 11	311.12 ± 16.67	10	302.96 ± 12.9	9	304.31 ± 12.8	10	293.7 ± 21.9	8
Day 15	325.66 ± 19.04	10	318.34 ± 13.53	9	315.55 ± 14.88	10	306.44[a]±17.58	8
Day 18	333.95 ± 17.37	10	324.56 ± 12.51	9	318.41 ± 13.82	10	311.03[a]±20.85	8
Day 22	347.71 ± 22.17	9	339.88 ± 14.21	9	330.40 ± 19.4	10	326.2 ± 16.62	7
Day 25	353.8 ± 25.49	9	346.72 ± 12.85	9	339.50 ± 14.34	10	327.64[a]±15.91	7
Day 28	364.99 ± 24.92	9	353.14 ± 14.39	8	348.46 ± 14.74	10	344.47 ± 20.11	7
Body weight (g) of female rats in Main Study								
Predose	206.04 ± 9.09	10	207.15 ± 8.19	9	208.71 ± 8.02	8	208.98 ± 8.05	8
Day 1	207.47 ± 10.15	10	204.79 ± 14.99	9	214.34 ± 7.49	8	213.5 ± 7.17	8
Day 4	219.16 ± 7.77	10	211.37 ± 6.01	9	220.09 ± 8.89	8	215.41 ± 6.7	8
Day 9	229.33 ± 8.61	10	224.73 ± 7.07	9	227.94 ± 9.92	8	225.78 ± 6.67	8
Day 11	230.97 ± 12.19	10	228.97 ± 7.23	9	232.73 ± 10.36	8	230.24 ± 10.18	8
Day 15	241.01 ± 11.33	10	239.78 ± 7.9	9	242.99 ± 12.89	8	236.67 ± 10.99	8
Day 18	243.97 ± 8.99	10	239.29 ± 8.22	9	244.17 ± 9.06	8	242.05 ± 15.82	8
Day 22	249.09 ± 12.7	10	252.86 ± 10.52	9	250.57 ± 6	8	247.31 ± 8.57	8
Day 25	253.32 ± 16.35	10	248.6 ± 10.63	9	248.81 ± 11.7	8	243.42 ± 12.07	8
Day 28	260.57 ± 19.65	10	254.24 ± 11.36	9	253.74 ± 13.09	8	250.47 ± 10.47	8

[a] Marked statistically significant by Minitab Version 16.2.4.

2. Experimental design, materials, and methods

2.1. Animals

Male and female Sprague-Dawley rats with femoral vein catheters (FVC) (Envigo, Surgical Facility 237, Livermore, CA) were used. The studies were conducted in AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care International) accredited BTS Research (San Diego, CA), the contract research organization (CRO). Animals were acclimated to the laboratory environment for a period of 7–8 days. Animals were individually housed in polycarbonate cages containing animal bedding and provided Certified Teklad Rodent Chow 2918 C feed and water at *ad libitum*. The animals were maintained in environmentally controlled room conditions (18–23 °C, 30–70% relative humidity). At the initiation of dosing, rats were 7–9 weeks old with body weights ranging from 180 to 260 g for males and 160–240 g for females. The in-life procedures were performed at BTS Research in accordance with "U.S. Food and Drug Administration (FDA) Good Laboratory Practice (GLP) Regulations; Final Rule. 21 CFR Part 58, October 5, 1987" and BTS Standard Operating Procedures (SOPs).

2.2. Dose formulation

Sepin-1 was synthesized by ChemBridge (San Diego, CA). A 40 mg/ml stock solution was prepared by dissolving Sepin-1 in DMSO. Dosing solution for the group receiving 20 mg/kg was prepared by diluting 40 mg/ml stock to 4 mg/ml in 0.01 M citrate-buffed saline (CBS) (0.8%), pH 4.0. The subsequent dosing solutions of 1 and 2 mg/ml were prepared by diluting 4 mg/ml in vehicle control buffer consisting of CBS with 10% dimethyl sulfoxide (CBSD). Dose formulations were prepared daily, and formulations from days 1 and 28 were assessed for drug concentration, homogeneity, and stability by Keystone Bioanalytical (North Wales, PA) using a validated method. All dose solutions were within ±10% of intended concentrations.

Table 2
Group mean body weights (g) of rats in Recovery Study.

	Group 1 (0 mg/kg)		Group 2 (5 mg/kg)		Group 3 (10 mg/kg)		Group 4 (20 mg/kg)	
	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	N
Body weight (g) of male rats in Recovery Study								
Predose	252.54 ± 30.1	5	240.82 ± 24.66	5	234.74 ± 21.46	5	249.77 ± 22.34	5
Day 1	275.01 ± 32.23	5	261.21 ± 18.85	5	275.35 ± 20.64	5	271.32 ± 20.47	5
Day 4	278.26 ± 28.85	5	262.18 ± 28.48	5	262.12 ± 16.66	5	274.55 ± 17.97	5
Day 8	296.74 ± 26.31	5	285.56 ± 28.37	5	275.35 ± 20.64	5	292.16 ± 18.09	5
Day 11	309.2 ± 28.07	5	294.65 ± 38.3	5	288.58 ± 22.11	5	301.75 ± 18.39	5
Day 16	327.72 ± 26.07	5	318.74 ± 27.35	5	300.36 ± 25.96	5	312.27 ± 18.27	5
Day 18	332.39 ± 25.37	5	325.79 ± 30.4	5	305.13 ± 31.92	5	317.44 ± 17.42	5
Day 22	351.14 ± 25	5	338.12 ± 33.88	5	318.17 ± 31.83	5	331.59 ± 17.06	5
Day 25	356.89 ± 22.6	5	345.8 ± 34.32	5	323.93 ± 28.48	5	337.24 ± 15.44	5
Day 29	372.95 ± 25.03	5	360.19 ± 34.88	5	335.05 ± 31.32	5	350.0614.52	5
Day 32	380.17 ± 25.2	5	367.23 ± 34.87	5	336.18 ± 33.55	5	350.97 ± 11.5	5
Day 36	393.44 ± 24.22	5	380.25 ± 34.14	5	351.32 ± 31.6	5	371.86 ± 7.1	5
Day 39	397.91 ± 25.19	5	372.15 ± 28.52	4	356.67 ± 32.02	5	364.64 ± 17.55	3
Day 43	406.92 ± 24.84	5	394.28 ± 38.18	5	370.74 ± 29.11	5	370.72 ± 39.12	5
Day 50	424.56 ± 24.11	5	412.35 ± 37.79	5	386.79 ± 27.28	5	398.55 ± 15.64	5
Day 53	424.44 ± 28.45	4	405.23 ± 33.13	4	391.6 ± 26.76	5	404.7 ± 14.67	3
Day 56	431.85 ± 29.76	4	426.76 ± 36.62	5	402.34 ± 27.96	5	416.53 ± 12.23	5
Body weight (g) of female rats in Recovery Study								
Predose	209.63 ± 19.78	5	211.49 ± 18.33	5	208.96 ± 15.03	5	208.26 ± 13.03	5
Day 1	221.69 ± 29.32	5	221.32 ± 15.36	5	217.71 ± 12.76	5	218.35 ± 11.86	5
Day 4	222.38 ± 26.43	5	226.56 ± 12.06	5	222.16 ± 11.29	5	219.14 ± 12.71	5
Day 8	234.04 ± 22.05	5	237.02 ± 10.88	5	230.3 ± 9.02	5	229.06 ± 12.57	5
Day 11	243.3 ± 18.74	5	238.84 ± 10.76	5	236.28 ± 11.34	5	235.91 ± 11.79	5
Day 16	246.66 ± 19.34	5	247.71 ± 13.15	5	243.11 ± 10.22	5	244.36 ± 15.14	5
Day 18	244.33 ± 25.27	5	248.8 ± 13.71	5	247.91 ± 9.88	5	245.04 ± 13.33	5
Day 22	263.52 ± 16.86	5	257.63 ± 12.16	5	257.6 ± 12.7	5	252.69 ± 15.07	5
Day 25	265.83 ± 16.66	5	261.37 ± 14.1	5	251.78 ± 8.31	5	253.14 ± 13.46	5
Day 29	270.11 ± 19.79	5	269.31 ± 15.85	5	259.36 ± 7.98	5	264.45 ± 16.72	5
Day 32	270.06 ± 18.51	5	267.37 ± 17.98	5	258.48 ± 7.66	5	262.77 ± 15.69	5
Day 36	277.11 ± 15.6	5	264.72 ± 24.87	5	258.39 ± 8.75	5	265.21 ± 15.55	5
Day 39	278.55 ± 15.16	5	272.68 ± 21.48	3	259.94 ± 9.88	3	273.91 ± 16.31	3
Day 43	272.53 ± 20.54	5	281.46 ± 22.07	4	262.54 ± 8.73	5	272.18 ± 19.66	5
Day 50	285.32 ± 20.39	5	287.65 ± 23.94	4	271.1 ± 11.23	5	278.29 ± 18.99	5
Day 53	285.16 ± 17.3	5	279.8 ± 21.5	3	268.97 ± 11.94	3	288.93 ± 18.67	3
Day 56	292.3 ± 14.86	5	291.36 ± 18.18	4	275.58 ± 11.47	5	289.22 ± 25.34	5

Mean ± SD, N = number of animals.

2.3. Dosing and Catheter Maintenance

The patency of the FVC was restored every time for dosing. First, exteriorized septum port of FVC was wiped with alcohol wipe or gauze sprayed with 70% alcohol. Then, an appropriate sterile adapter was attached to a 1 ml syringe to access the septum port and withdraw the lock solution until blood is observed. Next, a preloaded syringe was attached, and the preloaded formulated test article was injected at a rate of approximately 2 ml/min. In addition, a preloaded third syringe was attached to inject sterile saline to the flush the line via the adapter (up to 0.4 ml). Finally, a preloaded fourth syringe was attached to inject required amount of lock solution as determined by surgical vendor documentation for FVC indwelling dead volume.

2.4. Experimental design

2.4.1. Toxicity Study

A total of 120 Sprague-Dawley rats with indwelling FVCs were randomly assigned to four dose groups (0, 5, 10, or 20 mg/kg/day corresponding to Group 1, 2, 3 and 4, respectively) in the Main Study

Table 3
Group mean organ weights (g) of rats in Main Study (Day 29).

Organ weight (g) of male rats in Main Study										
Group (Dose)	N	Brain	Kidneys	Adrenals	Testes	Prostate	Heart	Lungs	Thymus	Liver	Spleen
1 (0 mg/kg)	10	1.858± 0.100	2.429± 0.184	0.0675± 0.0187	3.537± 0.378	0.629± 0.085	1.188± 0.161	2.086± 0.263	0.487± 0.103	10.829± 1.441	0.856± 0.154
2 (5 mg/kg)	9	1.957[a]± 0.108	2.658± 0.239	0.0747± 0.0167	3.902[a]± 0.298	0.547± 0.110	1.205± 0.158	2.164± 0.376	0.455± 0.069	11.215± 0.793	0.898± 0.147
3 (10 mg/kg)	10	1.852± 0.045	2.597± 0.241	0.0673± 0.0113	3.680± 0.211	0.585± 0.113	1.187± 0.199	2.443± 0.779	0.357[a]± 0.061	10.964± 0.794	1.058± 0.191
4 (20 mg/kg)	8	1.903± 0.071	2.760[a]± 0.259	0.1431± 0.2157	3.747± 0.098	0.522± 0.196	1.413[a]± 0.187	2.557± 0.418	0.364[a]± 0.119	11.353± 1.507	1.695[a]± 0.361
Organ weight (g) of female rats in Main Study										
Group (Dose)	N	Brain	Kidneys	Adrenals	Ovaries	Heart	Lungs	Thymus	Liver	Spleen	
1 (0 mg/kg)	10	1.841± 0.074	1.710± 0.156	0.0889± 0.0217	0.170± 0.029	0.922± 0.125	1.924± 0.219	0.339± 0.066	7.745± 0.927	0.722± 0.185	
2 (5 mg/kg)	9	1.760± 0.108	1.697± 0.156	0.0839± 0.0149	0.170± 0.046	0.911± 0.058	1.864± 0.235	0.315± 0.083	7.967± 0.802	0.690± 0.307	
3 (10 mg/kg)	8	1.775± 0.097	1.713± 0.124	0.0810± 0.0080	0.195± 0.023	0.962± 0.093	2.197± 0.536	0.279± 0.049	8.107± 0.699	0.836± 0.119	
4 (20 mg/kg)	8	1.816± 0.087	1.824± 0.196	0.0865± 0.0108	0.177± 0.024	1.080[a]± 0.132	1.975± 0.316	0.262[a]± 0.038	8.639± 0.514	1.214[a]± 0.289	

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

(40 males and 40 females) and Recovery Study (20 males and 20 females). The animals were dosed via bolus intravenous injection once daily for 28 consecutive days. Animals assigned to the Main Study were euthanized on Day 29 and subjected to histopathological evaluations. The animals in the Recovery Study remained on study for a 28-day off-dose observation period followed by euthanasia and necropsy on Day 29 of the recovery period for histopathological evaluations. Toxicological parameters evaluated were mortality, clinical observations, body weights, food consumption, ophthalmoscopy,

Table 4
Group mean organ weights relative to brain weight (%) of rats in Main Study (Day 29).

Relative organ to brain weight (%) of males in Main Study										
Group (Dose)	N	Kidneys	Adrenals	Testes	Prostate	Heart	Lungs	Thymus	Liver	Spleen
1 (0 mg/kg)	10	131.02± 12.19	3.67± 1.16	190.77± 22.28	34.06± 6.03	64.01± 8.76	112.57± 15.61	26.26± 5.54	584.66± 87.07	46.11± 8.20
2 (5 mg/kg)	9	135.98± 11.48	3.82± 0.87	199.85± 17.99	27.74± 4.56	61.65± 7.95	110.38± 15.54	23.22± 3.27	573.94± 41.73	45.67± 5.00
3 (10 mg/kg)	10	140.20± 11.36	3.64± 0.61	198.85± 12.38	31.72± 6.12	64.06± 10.10	131.74± 41.00	19.30± 3.29	592.49± 45.23	57.12± 10.02
4 (20 mg/kg)	8	145.26± 15.39	7.33± 10.70	197.11± 8.71	29.83± 12.03	74.52± 11.55	134.67± 23.77	19.21± 6.65	597.66± 86.54	88.92[a]± 17.33	
Relative organ to brain weight (%) of females in Main Study										
Group (Dose)	N	Kidneys	Adrenals	Ovaries	Heart	Lungs	Thymus	Liver	Spleen	
1 (0 mg/kg)	10	92.91± 8.38	4.83± 1.16	9.22± 1.54	50.09± 6.56	104.68± 13.02	18.37± 3.35	420.54± 46.57	39.34± 10.30	
2 (5 mg/kg)	9	96.40± 5.46	4.79± 0.96	9.65± 2.57	51.81± 2.53	105.97± 12.59	17.88± 4.72	453.17± 41.74	39.29± 17.32	
3 (10 mg/kg)	8	96.62± 7.06	4.60± 0.67	10.98± 1.05	54.18± 3.73	123.31± 26.58	15.78± 3.05	457.75± 43.96	46.96± 4.48	
4 (20 mg/kg)	8	100.26± 7.96	4.78± 0.70	9.83± 1.74	59.40[a]± 6.03	109.12± 19.00	14.40± 1.86	475.85[a]± 21.01	66.80[a]± 15.37	

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

Table 5
Group mean organ weights relative to body weight (%) of rats in Main Study (Day 29).

Relative organ to body weight (%) of male rats in Main Study											
Group (Dose)	N	Brain	Kidneys	Adrenals	Testes	Prostate	Heart	Lungs	Thymus	Liver	Spleen
1 (0 mg/kg)	10	0.51± 0.04	0.67± 0.02	0.02± 0.00	0.98± 0.09	0.17± 0.03	0.33± 0.03	0.58± 0.05	0.13± 0.02	2.98± 0.25	0.24± 0.05
2 (5 mg/kg)	9	0.55[a]± 0.02	0.75[a]± 0.06	0.02± 0.00	1.10[a]± 0.07	0.18± 0.10	0.34± 0.04	0.61± 0.10	0.13± 0.02	3.16± 0.19	0.25± 0.04
3 (10 mg/kg)	10	0.53± 0.02	0.75[a]± 0.06	0.02± 0.00	1.06± 0.08	0.19± 0.09	0.34± 0.06	0.70± 0.20	0.10[a]± 0.02	3.15± 0.26	0.30[a]± 0.05
4 (20 mg/kg)	8	0.55[a]± 0.03	0.80[a]± 0.07	0.04± 0.06	1.09[a]± 0.05	0.16± 0.06	0.41[a]± 0.07	0.74[a]± 0.13	0.11[a]± 0.03	3.29± 0.37	0.49[a]± 0.09
Relative organ to body weight (%) of female rats in Main Study											
Group (Dose)	N	Brain	Kidneys	Adrenals	Ovaries	Heart	Lungs	Thymus	Liver	Spleen	
1 (0 mg/kg)	10	0.71± 0.05	0.66± 0.05	0.03± 0.01	0.07± 0.01	0.35± 0.04	0.74± 0.07	0.13± 0.02	2.97± 0.21	0.28± 0.06	
2 (5 mg/kg)	8	0.69± 0.03	0.67± 0.04	0.03± 0.01	0.07± 0.02	0.36± 0.02	0.73± 0.08	0.12± 0.03	3.13± 0.25	0.30± 0.08	
3 (10 mg/kg)	8	0.70± 0.05	0.68± 0.04	0.03± 0.00	0.08± 0.01	0.38± 0.03	0.86± 0.20	0.11± 0.02	3.19± 0.21	0.33± 0.05	
4 (20 mg/kg)	8	0.73± 0.03	0.73[a]± 0.07	0.03± 0.00	0.07± 0.01	0.43[a]± 0.05	0.79± 0.13	0.10± 0.01	3.45[a]± 0.20	0.48[a]± 0.11	

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

Table 6
Group mean organ weights (g) of rats in Recovery Study (Day 57).

Organ weight (g) of male rats in Recovery Study											
Group (Dose)	N	Brain	Kidneys	Adrenals	Testes	Prostate	Heart	Lungs	Thymus	Liver	Spleen
1 (0 mg/kg)	5	2.029± 0.119	2.741± 0.318	0.0684± 0.0116	3.891± 0.366	0.800± 0.138	1.456± 0.167	2.781± 0.721	0.379± 0.057	11.551± 1.389	0.887± 0.135
2 (5 mg/kg)	5	1.936± 0.087	2.909± 0.309	0.0700± 0.0330	3.692± 0.227	0.792± 0.163	1.428± 0.046	2.383± 0.146	0.413± 0.098	12.135± 1.140	0.893± 0.120
3 (10 mg/kg)	5	1.998± 0.074	2.772± 0.281	0.0684± 0.0147	3.819± 0.184	0.691± 0.141	1.263± 0.107	2.582± 0.484	0.352± 0.056	10.674± 1.363	1.026± 0.093
4 (20 mg/kg)	5	1.799[a]± 0.144	2.806± 0.565	0.0608± 0.0208	3.679±± 0.441	1.162± 0.406	1.424± 0.155	2.344± 0.280	0.334± 0.041	12.747± 1.084	1.086± 0.182
Organ weight (g) female rats in Recovery Study											
Group (Dose)	N	Brain	Kidneys	Adrenals	Ovaries	Heart	Lungs	Thymus	Liver	Spleen	
1 (0 mg/kg)	5	1.862± 0.103	1.823± 0.099	0.0855± 0.0175	0.194± 0.030	1.071± 0.245	2.272± 0.210	0.300± 0.120	7.898± 0.733	0.709± 0.121	
2 (5 mg/kg)	5	1.785± 0.120	1.927± 0.278	0.2501± 0.3411	0.196± 0.033	1.076± 0.168	2.424± 0.468	0.273± 0.055	8.654± 2.151	0.889± 0.387	
3 (10 mg/kg)	5	1.956± 0.117	1.876± 0.243	0.0812± 0.0113	0.189± 0.037	1.033± 0.086	2.078± 0.292	0.346± 0.129	7.633± 0.848	0.832± 0.199	
4 (20 mg/kg)	5	1.848± 0.045	1.942± 0.326	0.0869± 0.0189	0.193± 0.042	1.026± 0.161	2.062± 0.208	0.283± 0.045	8.258± 1.024	0.940± 0.168	

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

clinical pathology (hematology, coagulation, clinical chemistry, and urinalysis), necropsy, organ weights, and histopathology. Unscheduled dead animals were also subjected to necropsy evaluations.

2.4.2. In-life Observations

All animals were observed daily for clinical signs; detailed clinical observations were done once daily during dosing days and once weekly during recovery and prior to necropsy at 4 hours. Individual food consumption was recorded weekly; individual body weights were recorded once during

Table 7
Group mean organ weights relative to brain weight (%) of rats in Recovery Study (Day 57).

Relative organ to brain weight (%) of male rats in Recovery Study										
Group (Dose)	N	Kidneys	Adrenals	Testes	Prostate	Heart	Lungs	Thymus	Liver	Spleen
1 (0 mg/kg)	5	135.10± 14.39	3.36± 0.48	191.52± 9.37	39.73± 8.34	72.04± 9.99	136.07± 28.36	18.68± 2.82	569.89± 67.81	43.72± 6.46
2 (5 mg/kg)	5	150.06± 10.16	3.64± 1.75	194.94± 12.36	41.23± 9.95	73.90± 4.26	123.21± 7.82	21.26± 4.83	626.32± 42.15	46.07± 5.47
3 (10 mg/kg)	5	138.98± 15.47	3.43± 0.76	191.13± 5.73	34.70± 7.33	63.22± 4.60	129.25± 23.38	17.72± 3.37	535.89± 81.24	51.33± 3.74
4 (20 mg/kg)	5	155.16± 24.92	3.38± 1.20	204.57± 19.84	65.08[a]± 23.26	79.71± 12.08	130.95± 17.38	18.67± 2.50	715.81[a]± 115.47	60.23[a]± 7.39
Relative organ to brain weight (%) of female rats in Recovery Study										
Group (Dose)	N	Kidneys	Adrenals	Ovaries	Heart	Lungs	Thymus	Liver	Spleen	
1 (0 mg/kg)	5	98.00± 4.23	4.57± 0.73	10.47± 1.81	57.52± 12.54	122.04± 10.01	16.06± 6.07	425.66± 50.16	38.24± 7.63	
2 (5 mg/kg)	5	108.92± 22.21	14.23± 19.31	10.94± 1.38	60.85± 13.26	136.73± 31.71	15.29± 3.06	491.57± 155.32	50.79± 25.59	
3 (10 mg/kg)	5	95.76± 8.65	4.16± 0.62	9.65± 1.71	52.87± 4.19	105.95± 9.77	17.64± 6.23	391.47± 50.53	42.38± 8.95	
4 (20 mg/kg)	5	105.16± 18.22	4.70± 1.00	10.43± 2.20	55.51± 8.56	111.57± 11.17	15.31± 2.29	446.85± 55.37	50.83± 8.89	

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

acclimation and at least twice per week during dosing and recovery periods. Ophthalmic evaluations (Direct and Slit-Lamp) of animals in both the Main and Recovery Studies were conducted prior to initiation of treatment and towards the end of the 4th week of the dosing period.

2.4.3. Clinical Pathology

Animals were fasted for at least 8 hours prior to collection of blood for clinical pathology (hematology and clinical chemistry) evaluations at scheduled necropsy on Day 29 (Main Study) and 57

Table 8
Group mean organ weights relative to body weight (%) of rats in Recovery Study (Day 57).

Relative organ to body weight (%) of male rats in Recovery Study											
Group (Dose)	N	Brain	Kidneys	Adrenals	Testes	Prostate	Heart	Lungs	Thymus	Liver	Spleen
1 (0 mg/kg)	5	0.47± 0.02	0.63± 0.06	0.02± 0.00	0.90± 0.07	0.19± 0.03	0.34± 0.04	0.64± 0.16	0.09± 0.01	2.67± 0.21	0.21± 0.03
2 (5 mg/kg)	5	0.46± 0.03	0.68± 0.05	0.02± 0.01	0.87± 0.11	0.19± 0.05	0.34± 0.04	0.56± 0.04	0.10± 0.02	2.84± 0.13	0.21± 0.02
3 (10 mg/kg)	5	0.50± 0.03	0.69± 0.06	0.02± 0.00	0.95± 0.02	0.17± 0.03	0.32± 0.03	0.64± 0.11	0.09± 0.02	2.66± 0.35	0.26± 0.03
4 (20 mg/kg)	5	0.43± 0.05	0.68± 0.15	0.01± 0.00	0.89± 0.12	0.28± 0.10	0.34± 0.04	0.56± 0.07	0.08± 0.01	3.06± 0.21	0.26[a]± 0.05
Relative organ to body weight (%) of female rats in Recovery Study											
Group (Dose)	N	Brain	Kidneys	Adrenals	Ovaries	Heart	Lungs	Thymus	Liver	Spleen	
1 (0 mg/kg)	5	0.64± 0.04	0.62± 0.03	0.03± 0.01	0.07± 0.01	0.36± 0.07	0.78± 0.05	0.10± 0.04	2.70± 0.22	0.24± 0.03	
2 (5 mg/kg)	5	0.64± 0.05	0.71± 0.19	0.09± 0.13	0.07± 0.01	0.40± 0.12	0.89± 0.26	0.10± 0.03	3.21± 1.27	0.33± 0.20	
3 (10 mg/kg)	5	0.71± 0.06	0.68± 0.08	0.03± 0.00	0.07± 0.01	0.37± 0.02	0.75± 0.10	0.12± 0.04	2.77± 0.22	0.30± 0.07	
4 (20 mg/kg)	5	0.64± 0.06	0.67± 0.08	0.03± 0.01	0.07± 0.01	0.35± 0.04	0.72± 0.10	0.10± 0.01	2.85± 0.12	0.32± 0.04	

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

Table 9
Group mean hematology parameters in male rats of Main Study (Day 29).

Group (Dose)	N	WBC 10^3 cells/μL	RBC 10^6 cells/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %
1 (0 mg/kg)	10	9.93± 4.23	7.16± 0.29	13.8± 0.6	41.1± 1.7	57.4± 1.2	19.2± 1.0	33.5± 1.4	11.4± 0.6
2 (5 mg/kg)	9	7.60± 2.82	7.70[a]± 0.39	13.3± 0.8	44.5[a]± 1.4	57.8± 2.2	17.3[a]± 0.8	29.9[a]± 0.9	11.5± 0.9
3 (10 mg/kg)	10	9.20± 4.09	6.86± 0.26	12.8[a]± 0.7	41.2± 1.8	60.0[a]± 1.0	18.7± 0.4	31.1[a]± 0.6	11.5± 0.6
4 (20 mg/kg)	8	9.65± 2.96	6.36[a]± 0.33	12.6[a]± 0.6	44.8[a]± 2.0	70.6[a]± 2.3	19.8± 0.7	28.0[a]± 0.8	12.8[a]± 1.4

Group (Dose)	N	PLT 10^3 cells/μL	Retic 10^3 cells/μL	Neut 10^3 cells/μL	Lymph 10^3 cells/μL	Mono 10^3 cells/μL	Eos 10^3 cells/μL	Baso 10^3 cells/μL	LUC 10^3 cells/μL
1 (0 mg/kg)	10	741± 195	251.1± 51.5	1.81± 1.43	7.57± 2.63	0.32± 0.23	0.13± 0.04	0.04± 0.03	0.05± 0.04
2 (5 mg/kg)	9	915± 145	311.9± 53.4	1.41± 1.13	5.73± 1.83	0.32± 0.21	0.08[a]± 0.03	0.03± 0.02	0.03± 0.01
3 (10 mg/kg)	10	916± 78	430.5[a]± 70.7	1.73± 1.19	6.96± 2.68	0.32± 0.35	0.11± 0.04	0.03± 0.02	0.05± 0.02
4 (20 mg/kg)	8	1175[a]± 221	1190.3[a]± 151.6	1.96± 0.99	7.16± 2.05	0.34± 0.18	0.09± 0.04	0.04± 0.02	0.06± 0.03

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

Table 10
Group mean hematology parameters in female rats of Main Study (Day 29).

Group (Dose)	N	WBC 10^3 cells/μL	RBC 10^6 cells/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %
1 (0 mg/kg)	10	7.15± 2.32	7.11± 0.42	13.5± 0.4	41.2± 2.1	57.9± 1.1	19.0± 1.1	32.9± 1.8	10.4± 0.5
2 (5 mg/kg)	9	6.36± 2.99	6.66± 1.14	12.1[a]± 2.0	39.2± 6.0	59.1± 2.0	18.2± 0.5	30.8[a]± 0.7	10.5± 1.4
3 (10 mg/kg)	7	7.03± 2.26	6.36± 0.39	12.6± 0.7	39.1± 2.2	61.5[a]± 0.7	19.7± 0.5	32.1± 0.5	10.6± 0.2
4 (20 mg/kg)	8	5.07± 1.83	5.61[a]± 0.25	11.2[a]± 0.5	38.9± 1.8	69.5[a]± 2.5	19.9± 0.3	28.7[a]± 0.7	12.0[a]± 1.1

Group (Dose)	N	PLT 10^3 cells/μL	Retic 10^3 cells/μL	Neut 10^3 cells/μL	Lymph 10^3 cells/μL	Mono 10^3 cells/μL	Eos 10^3 cells/μL	Baso 10^3 cells/μL	LUC 10^3 cells/μL
1 (0 mg/kg)	10	835± 138	237.0± 43.7	1.15± 0.72	5.54± 1.45	0.25± 0.14	0.12± 0.04	0.03± 0.02	0.05± 0.04
2 (5 mg/kg)	9	985± 143	294.0± 72.8	1.21± 1.22	4.74± 1.82	0.22± 0.11	0.13± 0.04	0.02± 0.01	0.05± 0.03
3 (10 mg/kg)	7	912± 100	397.5[a]± 65.6	0.86± 0.37	5.80± 1.96	0.17± 0.06	0.13± 0.07	0.02± 0.01	0.05± 0.03
4 (20 mg/kg)	8	1154[a]± 136	1034.5[a]± 220.1	0.89± 0.40	3.89± 1.54	0.16± 0.09	0.08± 0.04	0.01[a]± 0.00	0.03± 0.02

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

(Recovery Study). Clotted blood samples were centrifuged, and the serum was used for the following clinical chemistry analyses using Randox Imola Clinical Chemistry Analyzer (Randox Laboratories-US, Ltd, Kearneysville, WV): alanine aminotransferase (ALT), albumin, alkaline phosphatase, aspartate aminotransferase, calcium, chloride, creatinine kinase, creatinine, gamma glutamyl transferase, globulin, glucose, phosphorus, potassium, and sodium. Blood samples collected with K_2EDTA were analyzed for the following hematology parameters using Siemens Advia 120 Hematology System

Table 11
Group mean hematology parameters in male rats of Recovery Study (Day 57).

Group (Dose)	N	WBC 10^3 cells/μL	RBC 10^6 cells/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %
1 (0 mg/kg)	4	7.03± 2.93	8.87± 0.42	13.9± 0.8	48.5± 2.5	54.6± 0.9	15.7± 0.2	28.7± 0.3	11.5± 0.3
2 (5 mg/kg)	5	8.65± 5.52	9.00± 0.47	14.5± 0.5	50.0± 2.4	55.5± 1.0	16.1± 0.5	29.0± 0.8	10.4± 0.4
3 (10 mg/kg)	5	8.36± 2.86	8.53± 0.22	14.3± 0.5	48.3± 1.8	56.5± 1.4	16.7± 0.6	29.5± 0.6	10.1[a]± 0.8
4 (20 mg/kg)	5	6.69± 2.65	8.54± 0.55	14.9± 1.1	49.3± 3.8	57.8[a]± 1.5	17.5[a]± 1.0	30.2[a]± 1.4	10.2[a]± 0.8

Group (Dose)	N	PLT 10^3 cells/μL	Retic 10^3 cells/μL	Neut 10^3 cells/μL	Lymph 10^3 cells/μL	Mono 10^3 cells/μL	Eos 10^3 cells/μL	Baso 10^3 cells/μL	LUC 10^3 cells/μL
1 (0 mg/kg)	4	1032± 141	208.3± 34.4	1.21± 0.50	5.52± 2.57	0.16± 0.07	0.09± 0.03	0.03± 0.02	0.03± 0.01
2 (5 mg/kg)	5	1015± 160	210.4± 29.5	2.11± 2.24	6.09± 3.34	0.26± 0.21	0.09± 0.03	0.04± 0.03	0.06± 0.05
3 (10 mg/kg)	5	1047± 151	234.3± 51.7	2.07± 1.42	5.86± 1.34	0.26± 0.15	0.11± 0.06	0.03± 0.02	0.04± 0.02
4 (20 mg/kg)	5	795± 119	205.2± 36.0	1.15± 0.58	5.24± 2.03	0.16± 0.08	0.09± 0.03	0.03± 0.02	0.03± 0.02

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

Table 12
Group mean hematology parameters in female rats of Recovery Study (Day 57).

Group (Dose)	N	WBC 10^3 cells/μL	RBC 10^6 cells/μL	HGB g/dL	HCT %	MCV fL	MCH pg	MCHC g/dL	RDW %
1 (0 mg/kg)	5	4.82± 1.56	8.58± 0.38	14.4± 0.4	48.6± 1.2	56.7± 1.8	16.8± 0.4	29.6± 0.2	10.0± 0.2
2 (5 mg/kg)	4	7.54± 1.86	8.28± 0.66	14.4± 0.7	47.1± 2.4	56.9± 1.7	17.5± 0.8	30.7± 0.8	9.4± 0.2
3 (10 mg/kg)	4	5.37± 0.88	8.03± 0.62	14.1± 0.7	46.5± 3.5	57.9± 0.6	17.6± 0.5	30.4± 0.7	8.9± 0.4
4 (20 mg/kg)	5	6.20± 2.16	7.30± 1.50	13.4± 1.9	44.8± 6.0	62.4± 6.3	18.7± 2.2	30.0± 1.3	10.7± 2.7

Group (Dose)	N	PLT 10^3 cells/μL	Retic 10^3 cells/μL	Neut 10^3 cells/μL	Lymph 10^3 cells/μL	Mono 10^3 cells/μL	Eos 10^3 cells/μL	Baso 10^3 cells/μL	LUC 10^3 cells/μL
1 (0 mg/kg)	5	994± 133	206.1± 32.3	0.82± 0.44	3.72± 1.11	0.12± 0.05	0.11± 0.06	0.02± 0.01	0.02± 0.01
2 (5 mg/kg)	4	911± 172	186.0± 13.2	1.43± 0.47	5.65± 1.38	0.24± 0.10	0.16± 0.08	0.03± 0.01	0.04± 0.02
3 (10 mg/kg)	4	998± 220	171.1± 68.4	0.92± 0.32	4.19± 0.94	0.14± 0.05	0.07± 0.03	0.02± 0.01	0.03± 0.01
4 (20 mg/kg)	5	948± 227	307.1± 296.2	1.45± 1.32	4.30± 1.33	0.20± 0.09	0.19± 0.10	0.02± 0.01	0.04± 0.03

Mean ± SD, N = number of animals.

(Siemens Healthineers, Erlangen, Germany): hemoglobin, hematocrit, platelet counts, leukocyte cell types, and red cell indices (MCV, MCH, and MCHC).

2.4.4. Body and organ weight

Individual body weights were collected from all animals once during acclimation, and at least twice per week for dosing and recovery phase animals. Body weights were collected prior to the withdrawal of food for overnight fasting when fasting and body weights fell on the same day.

Table 13
Group mean clinical chemistry parameters in male rats of Main Study (Day 29).

Group (Dose)	N	Glob g/dL	Alb g/dL	A/G ratio	AST U/L	ALP U/L	ALT U/L	Ca mg/dL	Chol mg/dL	Creat mg/dL	GGT U/L
1 (0 mg/kg)	10	2.35± 0.21	3.09± 0.17	1.32± 0.13	152.2± 26.8	136.2± 21.9	60.6± 8.8	9.72± 0.28	93.8± 10.7	0.62± 0.06	<4.0
2 (5 mg/kg)	9	2.27± 0.20	3.06± 0.19	1.36± 0.15	143.9± 35.6	132.3± 40.2	56.0± 10.9	9.60± 0.31	89.0± 5.7	0.59± 0.04	<4.0
3 (10 mg/kg)	10	2.55± 0.18	3.27[a]± 0.16	1.29± 0.13	157.9± 21.1	166.9± 24.9	73.8[a]± 11.3	9.85± 0.23	100.1± 8.1	0.62± 0.05	<4.0
4 (20 mg/kg)	8	2.48± 0.15	3.24± 0.11	1.31± 0.10	127.0± 13.3	143.6± 42.0	61.4± 9.8	10.13[a]± 0.16	95.2± 7.6	0.60± 0.02	<4.0

Group (Dose)	N	Gluc mg/dL	Phos mg/dL	TBil mg/dL	Trig mg/dL	BUN mg/dL	TPro g/dL	Na mmol/L	K mmol/L	Cl mmol/L	CK U/L
1 (0 mg/kg)	10	180.18± 60.70	7.85± 0.42	0.06± 0.03	23.93± 7.10	18.66± 2.97	5.45± 0.28	138.7± 1.4	5.37± 0.52	96.8± 0.8	1342.1± 467.6
2 (5 mg/kg)	9	200.86± 40.37	9.18[a]± 0.88	0.05± 0.05	28.52± 11.14	19.22± 3.21	5.33± 0.24	144.1± 16.5	6.10± 1.89	101.5± 15.2	1083.6± 365.4
3 (10 mg/kg)	10	120.16[a]± 39.23	8.21± 0.83	0.16[a]± 0.02	39.52± 17.15	17.95± 3.49	5.82[a]± 0.18	141.3± 1.9	5.14± 0.28	96.7± 1.0	1260.5± 330.4
4 (20 mg/kg)	8	112.09[a]± 32.13	8.48± 0.48	0.17[a]± 0.07	52.72[a]± 20.15	16.42± 2.47	5.73[a]± 0.16	140.3± 1.2	5.35± 0.31	96.3± 1.5	851.8[a]± 285.9

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

Table 14
Group mean clinical chemistry parameters in female rats of Main Study (Day 29).

Group (Dose)	N	Glob g/dL	Alb g/dL	A/G ratio	AST U/L	ALP U/L	ALT U/L	Ca mg/dL	Chol mg/dL	Creat mg/dL	GGT U/L
1 (0 mg/kg)	10	2.41± 0.26	3.26± 0.15	1.36± 0.15	138.0± 34.0	87.1± 14.6	47.4± 6.9	9.99± 0.25	103.5± 8.2	0.69± 0.04	<4.0
2 (5 mg/kg)	9	2.39± 0.18	3.11± 0.20	1.31± 0.11	126.2± 26.6	126.5[a]± 42.3	45.1± 7.4	9.95± 0.24	106.0± 9.7	0.65± 0.04	<4.0
3 (10 mg/kg)	7	2.46± 0.12	3.38± 0.10	1.37± 0.07	147.5± 18.0	107.3± 25.6	58.8[a]± 6.6	10.11± 0.23	128.2[a]± 18.9	0.64[a]± 0.02	<4.0
4 (20 mg/kg)	8	2.21± 0.18	3.23± 0.15	1.46± 0.08	104.7[a]± 9.2	102.6± 24.5	44.7± 10.9	9.94± 0.29	113.0± 11.5	0.63[a]± 0.05	<4.0

Group (Dose)	N	Gluc mg/dL	Phos mg/dL	TBil mg/dL	Trig mg/dL	BUN mg/dL	TPro g/dL	Na mmol/L	K mmol/L	Cl mmol/L	CK U/L
1 (0 mg/kg)	10	132.15± 19.94	8.12± 1.30	0.06± 0.05	37.18± 20.02	19.70± 3.22	5.68± 0.28	138.4± 1.9	5.66± 1.48	97.6± 1.5	1087.7± 437.8
2 (5 mg/kg)	9	159.58± 28.11	8.53± 1.08	0.10± 0.06	46.52± 25.37	22.44± 1.57	5.50± 0.30	137.8± 1.0	5.71± 1.18	97.4± 1.2	481.5[a]± 223.8
3 (10 mg/kg)	7	120.18± 29.18	7.82± 0.76	0.13± 0.12	53.24± 35.82	17.03± 2.78	5.84± 0.17	139.9± 1.7	5.26± 0.72	98.0± 1.5	1063.7± 169.8
4 (20 mg/kg)	8	161.45± 26.89	7.45± 0.78	0.19[a]± 0.05	39.50± 14.75	18.24± 4.66	5.44± 0.30	138.2± 1.5	5.04± 0.32	97.6± 2.4	638.7[a]± 303.0

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

At the end of study, animals were euthanized via inhalation of isoflurane at 5% followed by exsanguination. Complete necropsy examinations were done for all animals. The organs weighted were brain, adrenal gland, prostate gland, heart, kidney, liver, lung, ovary, spleen, testis, and thymus. Organ weight as a percent of body weight (using the terminal body weight) and organ weight as a percent of brain weight were calculated.

Table 15
Group mean clinical chemistry parameters in male rats of Recovery Study (Day 57).

Group (Dose)	N	Glob g/dL	Alb g/dL	A/G ratio	AST U/L	ALP U/L	ALT U/L	Ca mg/dL	Chol mg/dL	Creat mg/dL	GGT U/L
1 (0 mg/kg)	5	2.50± 0.20	3.07± 0.19	1.24± 0.14	171.9± 71.6	93.5± 13.4	58.0± 4.5	9.56± 0.33	99.7± 11.1	0.63± 0.02	<4.0
2 (5 mg/kg)	5	2.46± 0.30	3.12± 0.24	1.28± 0.11	120.0± 19.3	81.5± 17.1	54.4± 7.5	9.46± 0.87	94.2± 8.0	0.63± 0.06	<4.0
3 (10 mg/kg)	5	2.54± 0.18	3.05± 0.14	1.20± 0.10	149.0± 18.9	84.7± 22.2	38.9[a]± 3.6	9.40± 0.35	100.6± 4.4	0.57± 0.01	<4.0
4 (20 mg/kg)	5	2.60± 0.15	3.06± 0.13	1.18± 0.03	109.0± 23.6	85.4± 9.9	44.1[a]± 7.4	9.67± 0.24	85.8± 15.0	0.57± 0.05	<4.0

Group (Dose)	N	Gluc mg/dL	Phos mg/dL	TBil mg/dL	Trig mg/dL	BUN mg/dL	TPro g/dL	Na mmol/L	K mmol/L	Cl mmol/L	CK U/L
1 (0 mg/kg)	5	125.59± 18.37	7.34± 0.52	0.07± 0.05	25.79± 6.50	17.81± 2.88	5.57± 0.24	139.7± 2.0	5.58± 0.36	97.4± 0.8	1297.5± 441.8
2 (5 mg/kg)	5	134.91± 25.46	8.47± 1.04	0.07± 0.05	20.03± 3.86	19.25± 2.29	5.59± 0.50	138.4± 1.7	7.24± 3.84	96.9± 1.6	881.8± 328.1
3 (10 mg/kg)	5	105.16± 43.47	8.24± 0.48	0.12± 0.03	22.28± 9.50	17.29± 2.52	5.59± 0.25	139.3± 1.2	6.51± 1.56	97.5± 1.0	1303.2± 122.6
4 (20 mg/kg)	5	146.98± 40.71	7.92± 0.81	0.06± 0.01	24.81± 10.37	17.49± 0.94	5.67± 0.27	140.9± 2.2	5.63± 0.16	97.6± 2.3	740.0[a]± 336.1

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

2.5. Statistical evaluation

Data for male and female rats were analyzed separately. All statistics were calculated in Minitab version 16.2.4 by performing an Equal Variance Test with a confidence interval of 95% followed by a One-Way ANOVA with a confidence interval of 95% and a Dunnett comparison test with a family error rate of 5%. Any data that were found to be statistically significant by the Levene's Test P-Value in the Equal Variance Test were normalized by taking the square root of the data and adapting the confidence interval and family error rate for the One-Way ANOVA and Dunnett's comparison test, respectively.

Table 16
Group mean clinical chemistry parameters in female rats of Recovery Study (Day 57).

Group (Dose)	N	Glob g/dL	Alb g/dL	A/G ratio	AST U/L	ALP U/L	ALT U/L	Ca mg/dL	Chol mg/dL	Creat mg/dL	GGT U/L
1 (0 mg/kg)	5	2.46± 0.28	3.31± 0.09	1.36± 0.16	162.1± 29.2	59.6± 10.1	44.8± 7.8	9.76± 0.19	103.7± 7.4	0.65± 0.04	<4.0
2 (5 mg/kg)	4	2.38± 0.35	3.15± 0.17	1.34± 0.17	165.8± 30.6	101.1± 69.0	40.1± 5.0	9.52± 0.25	88.8± 9.7	0.69± 0.06	<4.0
3 (10 mg/kg)	5	2.81± 0.24	3.12± 0.15	1.12± 0.12	137.3± 12.7	122.4± 115.0	39.1± 4.4	9.78± 0.20	107.6± 15.1	0.67± 0.07	<4.0
4 (20 mg/kg)	4	2.63± 0.28	3.04[a]± 0.09	1.17± 0.13	114.6[a]± 12.3	90.4± 33.1	34.3[a]± 2.2	9.64± 0.42	112.1± 23.5	0.58± 0.03	<4.0

Group (Dose)	N	Gluc mg/dL	Phos mg/dL	TBil mg/dL	Trig mg/dL	BUN mg/dL	TPro g/dL	Na mmol/L	K mmol/L	Cl mmol/L	CK U/L
1 (0 mg/kg)	5	111.28± 25.47	7.93± 0.98	0.11± 0.03	30.22± 4.80	20.28± 2.90	5.77± 0.26	139.1± 1.2	5.77± 1.18	97.9± 1.9	1231.1± 367.6
2 (5 mg/kg)	4	100.18± 15.11	7.66± 0.38	0.11± 0.05	28.04± 6.50	20.52± 2.00	5.54± 0.50	140.5± 2.3	5.14± 0.74	98.9± 1.0	1402.3± 454.9
3 (10 mg/kg)	5	95.88± 17.32	7.48± 1.38	0.11± 0.05	27.80± 5.81	20.97± 2.60	5.93± 0.21	141.7± 2.4	5.36± 0.13	99.7± 1.8	1141.8± 342.4
4 (20 mg/kg)	4	117.28± 13.42	7.17± 0.81	0.09± 0.03	25.92± 12.90	20.17± 4.97	5.67± 0.27	141.0± 1.8	4.84± 0.76	98.9± 0.6	760.2[a]± 376.4

[a] Marked statistically significant by Minitab Version 16.2.4; Mean ± SD, N = number of animals.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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