

## Supplementary Materials

**Table S1-1.** Hematological values of male mice in the 28-day repeat-dose toxicity study.

Test items	Group								
	G1 (0)		G2 (7.45E+08)		G3 (2.98E+09)		G4 (1.19E+10)		
WBC <sup>1</sup> (K/μL)	2.29	±	1.18 (10)	3.78	±	3.39 (10)	2.29	±	1.16 (10)
NE <sup>2</sup> (K/μL)	0.27	±	0.10 (10)	0.36	±	0.26 (10)	0.23	±	0.06 (10)
EO <sup>3</sup> (K/μL)	0.07	±	0.09 (10)	0.26**	±	0.15 (10)	0.21**	±	0.14 (10)
BA <sup>4</sup> (K/μL)	0.00	±	0.00 (10)	0.00	±	0.00 (10)	0.00	±	0.00 (10)
LY <sup>5</sup> (K/μL)	1.89	±	1.05 (10)	3.07	±	2.96 (10)	1.80	±	1.03 (10)
MO <sup>6</sup> (K/μL)	0.04	±	0.02 (10)	0.06	±	0.04 (10)	0.04	±	0.03 (10)
LUC <sup>7</sup> (K/μL)	0.01	±	0.01 (10)	0.02	±	0.02 (10)	0.01	±	0.01 (10)
NEP <sup>8</sup> (%)	13.2	±	3.9 (10)	11.1	±	3.2 (10)	11.4	±	4.1 (10)
EOP <sup>9</sup> (%)	2.7	±	1.4 (10)	8.2**	±	3.7 (10)	9.2**	±	4.9 (10)
BAP <sup>10</sup> (%)	0.1	±	0.1 (10)	0.0	±	0.0 (10)	0.0	±	0.1 (10)
LYP <sup>11</sup> (%)	81.9	±	3.9 (10)	78.7	±	5.8 (10)	77.5	±	5.8 (10)
MOP <sup>12</sup> (%)	1.8	±	1.0 (10)	1.5	±	0.7 (10)	1.5	±	0.7 (10)
LUP <sup>13</sup> (%)	0.4	±	0.1 (10)	0.5	±	0.2 (10)	0.4	±	0.1 (10)
RBC <sup>14</sup> (M/μL)	8.12	±	0.38 (10)	8.19	±	0.40 (10)	7.59*	±	0.30 (10)
Hb <sup>15</sup> (g/dL)	13.2	±	0.5 (10)	13.1	±	0.9 (10)	12.4*	±	0.6 (10)
RDW <sup>16</sup> (%)	11.9	±	0.5 (10)	11.9	±	0.4 (10)	12.2	±	0.6 (10)
HCT <sup>17</sup> (%)	44.2	±	1.6 (10)	45.0	±	1.9 (10)	41.9*	±	1.4 (10)
MCV <sup>18</sup> (fL)	54.6	±	2.9 (10)	55.1	±	2.4 (10)	55.2	±	1.7 (10)
MCH <sup>19</sup> (pg)	16.3	±	0.6 (10)	16.0	±	0.9 (10)	16.3	±	0.7 (10)
MCHC <sup>20</sup> (g/dL)	29.8	±	0.7 (10)	29.1	±	1.5 (10)	29.6	±	1.1 (10)
Reti <sup>21</sup> (%)	3.80	±	0.50 (10)	3.34	±	0.36 (10)	3.43	±	0.40 (10)
PLT <sup>22</sup> (K/μL)	1349	±	98 (10)	1291	±	149 (10)	1171	±	140 (10)
MPV <sup>23</sup> (fL)	7.4	±	0.7 (10)	7.5	±	0.2 (10)	7.3	±	0.5 (10)

Mean ± S.D (number of animals). 1: white blood cell count, 2: neutrophil, 3: eosinophil, 4: basophil, 5: lymphocyte, 6: monocyte, 7: large unstained cell, 8: percent of neutrophil, 9: percent of eosinophil, 10: percent of basophil, 11: percent of lymphocyte, 12: percent of monocyte, 13: percent of the large unstained cell, 14: red blood cell count, 15: hemoglobin conc., 16: red cell distribution width, 17: hematocrit, 18: mean corpuscular volume, 19: mean corpuscular hemoglobin, 20: mean corpuscular hemoglobin concentration, 21: reticulocyte, 22: platelet, 23: mean platelet volume. \*: Significant difference compared to the control group value; p < 0.05. \*\*: Significant difference compared to the control group value; p < 0.01.

**Table S1-2.** Hematological values of female mice in the 28-day repeat-dose toxicity study.

Test items	Group								
	G1 (0)		G2 (7.45E+08)		G3 (2.98E+09)		G4 (1.19E+10)		
WBC <sup>1</sup> (K/μL)	2.70	±	1.12 (10)	3.11	±	1.34 (10)	3.25	±	0.96 (10)
NE <sup>2</sup> (K/μL)	0.34	±	0.16 (10)	0.31	±	0.13 (10)	0.42	±	0.11 (10)
EO <sup>3</sup> (K/μL)	0.12	±	0.10 (10)	0.29*	±	0.13 (10)	0.23*	±	0.09 (10)
BA <sup>4</sup> (K/μL)	0.00	±	0.00 (10)	0.00	±	0.00 (10)	0.00	±	0.00 (10)
LY <sup>5</sup> (K/μL)	2.17	±	1.01 (10)	2.42	±	1.14 (10)	2.51	±	0.80 (10)
MO <sup>6</sup> (K/μL)	0.06	±	0.03 (10)	0.07	±	0.04 (10)	0.07	±	0.03 (10)
LUC <sup>7</sup> (K/μL)	0.02	±	0.01 (10)	0.02	±	0.01 (10)	0.04*	±	0.02 (10)
NEP <sup>8</sup> (%)	12.7	±	4.4 (10)	10.2	±	1.6 (10)	13.2	±	2.9 (10)
EOP <sup>9</sup> (%)	5.5	±	6.8 (10)	10.0	±	4.0 (10)	7.0	±	1.9 (10)
BAP <sup>10</sup> (%)	0.1	±	0.1 (10)	0.1	±	0.1 (10)	0.1	±	0.1 (10)
LYP <sup>11</sup> (%)	79.0	±	5.4 (10)	77.0	±	4.9 (10)	76.5	±	4.1 (10)
MOP <sup>12</sup> (%)	2.2	±	1.3 (10)	2.0	±	1.3 (10)	2.1	±	0.8 (10)
LUP <sup>13</sup> (%)	0.6	±	0.3 (10)	0.6	±	0.3 (10)	1.1	±	0.7 (10)
RBC <sup>14</sup> (M/μL)	8.34	±	0.27 (10)	8.07	±	0.52 (10)	8.07	±	0.36 (10)

Hb <sup>15</sup> (g/dL)	13.8	±	0.4	(10)	13.6	±	0.8	(10)	13.3	±	0.4	(10)	13.7	±	0.5	(10)
RDW <sup>16</sup> (%)	12.2	±	0.7	(10)	12.4	±	0.5	(10)	12.6	±	0.4	(10)	12.6	±	0.6	(10)
HCT <sup>17</sup> (%)	45.1	±	1.6	(10)	44.4	±	2.1	(10)	44.6	±	1.7	(10)	45.9	±	2.3	(10)
MCV <sup>18</sup> (fL)	54.1	±	1.7	(10)	55.1	±	1.7	(10)	55.4	±	1.9	(10)	55.3	±	1.0	(10)
MCH <sup>19</sup> (pg)	16.6	±	0.4	(10)	16.9	±	0.4	(10)	16.6	±	0.4	(10)	16.6	±	0.3	(10)
MCHC <sup>20</sup> (g/dL)	30.7	±	1.0	(10)	30.6	±	0.8	(10)	30.0	±	0.6	(10)	29.9	±	0.7	(10)
Reti <sup>21</sup> (%)	3.08	±	1.42	(10)	3.01	±	1.23	(10)	3.86	±	0.89	(10)	4.05	±	0.98	(10)
PLT <sup>22</sup> (K/ $\mu$ L)	1103	±	213	(10)	1133	±	322	(10)	1120	±	126	(10)	1095	±	159	(10)
MPV <sup>23</sup> (fL)	7.0	±	0.4	(10)	7.2	±	0.5	(10)	7.5*	±	0.6	(10)	7.7*	±	0.4	(10)

Mean ± S.D (number of animals). 1: white blood cell count, 2: neutrophil, 3: eosinophil, 4: basophil, 5: lymphocyte, 6: monocyte, 7: large unstained cell, 8: percent of neutrophil, 9: percent of eosinophil, 10: percent of basophil, 11: percent of lymphocyte, 12: percent of monocyte, 13: percent of the large unstained cell, 14: red blood cell count, 15: hemoglobin conc., 16: red cell distribution width, 17: hematocrit, 18: mean corpuscular volume, 19: mean corpuscular hemoglobin, 20: mean corpuscular hemoglobin concentration, 21: reticulocyte, 22: platelet, 23: mean platelet volume. \*: Significant difference compared to the control group value; p < 0.05.

**Table S2-1.** Blood chemistry values for male mice in the 28-day repeat-dose toxicity study.

Test items	Group															
	G1 (0)			G2 (7.45E+08)			G3 (2.98E+09)			G4 (1.19E+10)						
AST <sup>1</sup> (IU/L)	53	±	9	(10)	57	±	6	(10)	61	±	23	(10)	51	±	7	(10)
ALT <sup>2</sup> (IU/L)	41	±	10	(10)	42	±	8	(10)	56	±	33	(10)	37	±	6	(10)
ALP <sup>3</sup> (IU/L)	222	±	35	(10)	227	±	45	(10)	231	±	33	(10)	230	±	74	(10)
BIL <sup>4</sup> (mg/dL)	0.15	±	0.04	(10)	0.16	±	0.03	(10)	0.18	±	0.0	(10)	0.18	±	0.1	(10)
BUN <sup>5</sup> (mg/dL)	26.8	±	4.0	(10)	28.6	±	4.4	(10)	24.9	±	3.9	(10)	25.0	±	2.9	(10)
CRE <sup>6</sup> (mg/dL)	0.3	±	0.0	(10)	0.3	±	0.0	(10)	0.3	±	0.0	(10)	0.3	±	0.1	(10)
UA <sup>7</sup> (mg/dL)	1.4	±	0.9	(10)	1.2	±	0.6	(10)	1.7	±	1.1	(10)	1.5	±	0.8	(10)
GLU <sup>8</sup> (mg/dL)	201	±	45	(10)	217	±	77	(10)	203	±	54	(10)	197	±	54	(10)
CHO <sup>9</sup> (mg/dL)	146	±	22	(10)	155	±	19	(10)	136	±	15	(10)	170	±	41	(10)
TG <sup>10</sup> (mg/dL)	89	±	35	(10)	129	±	53	(10)	108	±	75	(10)	113	±	90	(10)
PRO <sup>11</sup> (g/dL)	4.9	±	0.2	(10)	4.9	±	0.1	(10)	4.8*	±	0.1	(10)	5.1	±	0.2	(10)
ALB <sup>12</sup> (g/dL)	1.7	±	0.1	(10)	1.7	±	0.1	(10)	1.7	±	0.1	(10)	1.7	±	0.1	(10)
A/G ratio <sup>13</sup>	0.52	±	0.01	(10)	0.53	±	0.02	(10)	0.52	±	0.02	(10)	0.52	±	0.02	(10)
LDH <sup>14</sup> (IU/L)	662	±	354	(10)	621	±	312	(10)	554	±	232	(10)	572	±	289	(10)
CPK <sup>15</sup> (U/L)	132	±	87	(10)	164	±	63	(10)	109	±	30	(10)	107	±	39	(10)
Ca <sup>16</sup> (mg/dL)	9.1	±	0.3	(10)	9.0	±	0.4	(10)	9.0	±	0.4	(10)	9.2	±	0.6	(10)
IP <sup>17</sup> (mg/dL)	8.2	±	1.9	(10)	8.5	±	1.8	(10)	7.7	±	1.5	(10)	8.7	±	2.1	(10)
Mg <sup>18</sup> (mg/dL)	3.1	±	0.3	(10)	3.0	±	0.4	(10)	2.9	±	0.3	(10)	3.1	±	0.4	(10)
Na <sup>19</sup> (mmol/L)	161	±	4	(10)	161	±	3	(10)	159	±	2	(10)	160	±	4	(10)
K <sup>20</sup> (mmol/L)	5.4	±	0.7	(10)	5.3	±	0.5	(10)	5.0	±	0.5	(10)	5.2	±	0.7	(10)
Cl <sup>21</sup> (mmol/L)	113	±	1	(10)	113	±	2	(10)	115**	±	3	(10)	116**	±	1	(10)

Mean ± S.D (number of animals). 1: aspartate aminotransferase, 2: alanine aminotransferase, 3: alkaline phosphatase, 4: total bilirubin, 5: blood urea nitrogen, 6: creatinine, 7: uric acid, 8: glucose, 9: total cholesterol, 10: triglyceride, 11: total protein, 12: albumin, 13: albumin/globulin ratio, 14: lactate dehydrogenase, 15: creatine phosphokinase, 16: calcium, 17: inorganic phosphorus, 18: magnesium, 19: sodium, 20: potassium, 21: chloride. \*: Significant difference compared to the control group value; p < 0.05. \*\*: Significant difference compared to the control group value; p < 0.01.

**Table S2-2.** Blood chemistry values for female mice in the 28-day repeat-dose toxicity study.

Test items	Group															
	G1 (0)			G2 (7.45E+08)			G3 (2.98E+09)			G4 (1.19E+10)						
AST <sup>1</sup> (IU/L)	54	±	9	(10)	51	±	6	(10)	52	±	5	(10)	60	±	16	(10)
ALT <sup>2</sup> (IU/L)	33	±	9	(10)	29	±	5	(10)	33	±	7	(10)	38	±	19	(10)
ALP <sup>3</sup> (IU/L)	269	±	67	(10)	245	±	52	(10)	246	±	32	(10)	238	±	55	(10)
BIL <sup>4</sup> (mg/dL)	0.06	±	0.03	(10)	0.05	±	0.02	(10)	0.06	±	0.0	(10)	0.06	±	0.0	(10)
BUN <sup>5</sup> (mg/dL)	19.9	±	3.3	(10)	19.3	±	3.2	(10)	17.7	±	3.5	(10)	20.5	±	4.7	(10)

CRE <sup>6</sup> (mg/dl)	0.3	±	0.1	(10)	0.3	±	0.0	(10)	0.3	±	0.0	(10)	0.3	±	0.1	(10)
UA <sup>7</sup> (mg/dl)	1.0	±	0.6	(10)	0.9	±	0.4	(10)	0.9	±	0.2	(10)	0.9	±	0.2	(10)
GLU <sup>8</sup> (mg/dl)	190	±	66	(10)	178	±	54	(10)	185	±	41	(10)	217	±	53	(10)
CHO <sup>9</sup> (mg/dl)	101	±	16	(10)	102	±	16	(10)	112	±	14	(10)	111	±	18	(10)
TG <sup>10</sup> (mg/dl)	82	±	46	(10)	97	±	42	(10)	85	±	42	(10)	78	±	35	(10)
PRO <sup>11</sup> (g/dl)	4.8	±	0.2	(10)	4.8	±	0.3	(10)	4.8	±	0.2	(10)	5.0	±	0.2	(10)
ALB <sup>12</sup> (g/dl)	1.7	±	0.1	(10)	1.7	±	0.1	(10)	1.7	±	0.1	(10)	1.7	±	0.1	(10)
A/G ratio <sup>13</sup>	0.55	±	0.02	(10)	0.53	±	0.02	(10)	0.54	±	0.03	(10)	0.53	±	0.02	(10)
LDH <sup>14</sup> (IU/L)	306	±	193	(10)	291	±	118	(10)	263	±	155	(10)	271	±	142	(10)
CPK <sup>15</sup> (U/L)	71	±	34	(10)	83	±	44	(10)	69	±	20	(10)	62	±	22	(10)
Ca <sup>16</sup> (mg/dl)	9.7	±	0.6	(10)	9.8	±	0.4	(10)	9.7	±	0.4	(10)	9.7	±	0.6	(10)
IP <sup>17</sup> (mg/dl)	9.8	±	2.3	(10)	9.4	±	1.7	(10)	10.5	±	2.1	(10)	10.6	±	2.6	(10)
Mg <sup>18</sup> (mg/dl)	3.2	±	0.6	(10)	3.1	±	0.3	(10)	3.1	±	0.3	(10)	3.1	±	0.5	(10)
Na <sup>19</sup> (mmol/L)	154	±	3	(10)	153	±	2	(10)	153	±	3	(10)	151*	±	2	(10)
K <sup>20</sup> (mmol/L)	4.8	±	0.7	(10)	4.9	±	0.5	(10)	4.9	±	0.6	(10)	5.0	±	0.5	(10)
Cl <sup>21</sup> (mmol/L)	114	±	3	(10)	113	±	2	(10)	115	±	2	(10)	114	±	2	(10)

Mean ± S.D (number of animals). 1: aspartate aminotransferase, 2: alanine aminotransferase, 3: alkaline phosphatase, 4 total bilirubin, 5: blood urea nitrogen, 6: creatinine, 7: uric acid, 8: glucose, 9: total cholesterol, 10: triglyceride, 11: total protein, 12: albumin, 13: albumin/globulin ratio, 14: lactate dehydrogenase, 15: creatine phosphokinase, 16: calcium, 17: inorganic phosphorus, 18: magnesium, 19: sodium, 20: potassium, 21: chloride. \*: Significant difference compared to the control group value;  $p < 0.05$ .