

**Supplementary material**

**Preclinical safety profile of RC88-ADC: a novel mesothelin-targeted antibody conjugated with MMAE**

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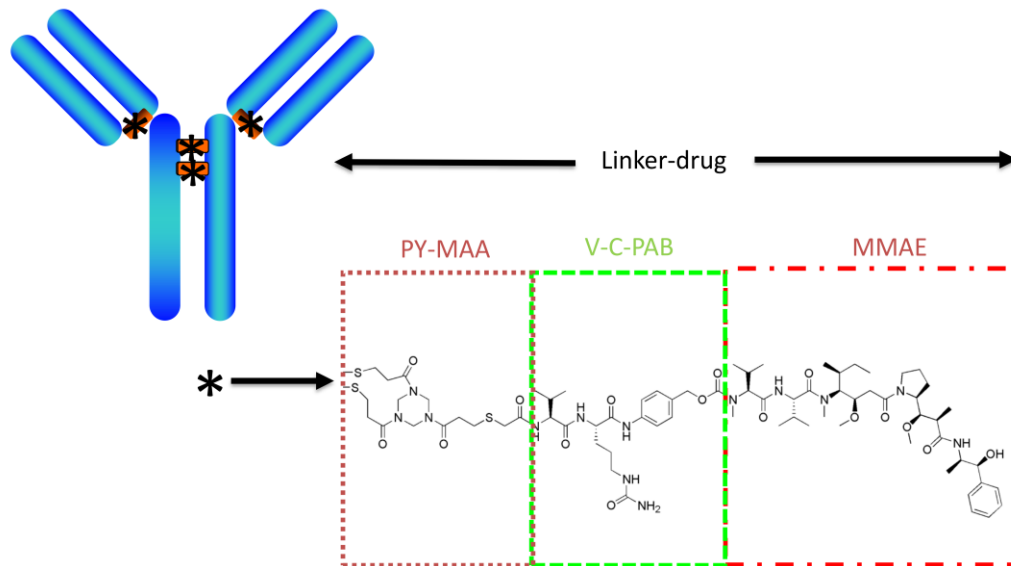
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PY-MAA:Triacryloylhexahydro triazine-mercaptoacetic acid  
 V-C-PAB:valine-citrulline-p-aminobenzyloxycarbonyl  
 MMAE:MonoMethyl Auristatin E

**Supplementary Fig. 1** Structure of RC88-ADC

**Supplementary Table 1** Organs/tissues for Histopathological Examination

Brain (cerebellum, cerebrum, brainstem)	Spinal cord (cervical, mid-thoracic, lumbar)
Pituitary	Thymus
Thyroid	Parathyroid
Esophagus	Salivary glands (submandibular glands)
Stomach	Small intestine (duodenum, jejunum, ileum)
Liver	Large intestine (cecum, colon, rectum)
Kidneys	Pancreas
Spleen	Adrenals
Trachea	Heart
Aorta	Lungs with main-stem bronchi, including pleura
Epididymides	Testes
Ovaries	Uterus (include cervix and oviduct)
Prostates	Mammary glands (females and males)+ local skin at mammary glands
Sciatic nerve	Urinary bladder
Optic nerve	Eyeballs
Lymph nodes (mesenteric and submandibular lymph node)	Bone marrow (sternum)
Skeletal muscle(biceps femoral muscle)	Femurs (include metaphysis)
Lacrimal Gland	Vagina
Peyer's patch	Urinary bladder
Peritoneum	Pericardium
Seminal vesicle	Dose site (See Section 4.2.3)
All gross lesions	Pleura

**Supplementary Table 2** Electrocardiograms (ECG) Examination (Lead II) of Female Monkeys

	<b>Vehicle Control (0 mg/kg)</b>	<b>ADC Low dose</b>	<b>ADC Mid dose</b>	<b>ADC High dose</b>	<b>Naked antibody Mid dose</b>	<b>Naked antibody High dose</b>	<b>Small molecule dose</b>
<b>Baseline</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
PR(ms)	68.00 ± 13.04	68.00 ± 4.47	72.00 ± 10.95	72.00 ± 17.89	74.00 ± 8.94	70.00 ± 14.14	66.00 ± 8.94
RR(ms)	272.80 ± 16.83	303.20 ± 24.19	281.20 ± 27.63	287.20 ± 37.67	312.40 ± 35.84	298.00 ± 48.74	295.20 ± 22.30
QRS(ms)	36.00 ± 5.48	40.00 ± 0.00	38.00 ± 4.47	38.00 ± 4.47	34.00 ± 5.48	40.00 ± 0.00	36.00 ± 5.48
QT(ms)	184.00 ± 11.40	186.00 ± 8.94	172.00 ± 21.68	184.00 ± 15.17	190.00 ± 12.25	182.00 ± 17.89	188.00 ± 8.37
QTcf(ms)	283.79 ± 16.43	277.40 ± 19.34	262.28 ± 26.27	279.01 ± 12.68	280.20 ± 11.34	272.74 ± 15.41	282.46 ± 9.13
HR(bpm)	220.60 ± 13.34	198.86 ± 15.20	215.10 ± 22.07	212.09 ± 30.34	194.03 ± 21.60	205.69 ± 33.65	204.19 ± 15.50
<b>4 h after D1 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
PR(ms)	76.00 ± 5.48	68.00 ± 4.47	72.00 ± 10.95	70.00 ± 10.00	66.00 ± 8.94	66.00 ± 13.42	66.00 ± 8.94
RR(ms)	287.60 ± 15.06	281.60 ± 32.39	278.40 ± 30.80	290.00 ± 25.96	300.80 ± 21.84	297.60 ± 58.68	316.00 ± 29.02
QRS(ms)	36.00 ± 5.48	38.00 ± 4.47	38.00 ± 4.47	40.00 ± 0.00	40.00 ± 0.00	38.00 ± 4.47	38.00 ± 4.47
QT(ms)	176.00 ± 15.17	178.00 ± 16.43	178.00 ± 14.83	174.00 ± 11.40	190.00 ± 10.00	182.00 ± 17.89	196.00 ± 11.40
QTcf(ms)	266.56 ± 20.33	272.04 ± 24.36	272.62 ± 14.80	263.13 ± 16.64	283.60 ± 10.30	273.25 ± 13.20	287.97 ± 14.37
HR(bpm)	209.10 ± 11.38	215.55 ± 27.11	217.60 ± 23.64	208.26 ± 19.03	200.31 ± 14.51	208.33 ± 43.38	191.07 ± 16.33
<b>24 h after D1 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
PR(ms)	68.00 ± 8.37	68.00 ± 4.47	70.00 ± 10.00	70.00 ± 17.32	72.00 ± 8.37	78.00 ± 10.95	68.00 ± 8.37
RR(ms)	277.20 ± 27.91	290.80 ± 9.12	279.20 ± 7.82	325.60 ± 29.17	296.40 ± 27.87	322.40 ± 51.19	320.00 ± 28.04
QRS(ms)	38.00 ± 4.47	36.00 ± 5.48	36.00 ± 5.48	40.00 ± 0.00	34.00 ± 5.48	36.00 ± 5.48	36.00 ± 5.48
QT(ms)	170.00 ± 14.14	184.00 ± 11.40	182.00 ± 13.04	200.00 ± 7.07	186.00 ± 8.94	190.00 ± 24.49	208.00 ± 13.04*
QTcf(ms)	260.76 ± 16.19	277.77 ± 17.15	278.44 ± 19.13	290.94 ± 6.74*	279.13 ± 8.09	277.10 ± 25.87	304.17 ± 13.60**
HR(bpm)	218.38 ± 23.98	206.49 ± 6.48	215.03 ± 5.89	185.44 ± 16.24	203.84 ± 18.76	189.84 ± 29.54	188.62 ± 16.04
<b>D70</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=2)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>
PR(ms)	64.00 ± 11.40	76.00 ± 5.48	70.00 ± 7.07	65.00 ± 7.07	70.00 ± 7.07	72.00 ± 13.04	72.50 ± 5.00
RR(ms)	268.00 ± 7.48	291.20 ± 23.86	272.00 ± 13.86	270.00 ± 25.46	305.60 ± 45.40	286.40 ± 42.95	286.00 ± 12.44
QRS(ms)	36.00 ± 5.48	38.00 ± 4.47	38.00 ± 4.47	40.00 ± 0.00	36.00 ± 5.48	36.00 ± 5.48	35.00 ± 5.77
QT(ms)	172.00 ± 13.04	182.00 ± 10.95	176.00 ± 5.48	185.00 ± 7.07	188.00 ± 16.43	180.00 ± 21.21	185.00 ± 5.77
QTcf(ms)	266.69 ± 18.19	274.60 ± 10.32	271.73 ± 8.42	286.34 ± 1.94	279.58 ± 18.82	272.91 ± 19.11	280.79 ± 5.21
HR(bpm)	224.02 ± 6.38	207.17 ± 17.18	221.06 ± 11.55	223.21 ± 21.04	199.87 ± 30.16	213.62 ± 34.63	210.09 ± 9.14
<b>4 h after D71 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=2)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>

	Vehicle Control (0 mg/kg)	ADC Low dose	ADC Mid dose	ADC High dose	Naked antibody Mid dose	Naked antibody High dose	Small molecule dose
PR(ms)	68.00 ± 10.95	74.00 ± 11.40	66.00 ± 5.48	65.00 ± 7.07	72.00 ± 8.37	62.00 ± 4.47	67.50 ± 15.00
RR(ms)	275.20 ± 14.53	272.00 ± 14.42	268.40 ± 9.21	272.00 ± 45.25	299.20 ± 29.58	285.20 ± 39.99	290.00 ± 21.79
QRS(ms)	40.00 ± 0.00	36.00 ± 5.48	36.00 ± 5.48	40.00 ± 0.00	36.00 ± 5.48	36.00 ± 5.48	40.00 ± 0.00
QT(ms)	174.00 ± 15.17	172.00 ± 8.37	174.00 ± 8.94	180.00 ± 14.14	188.00 ± 13.04	178.00 ± 17.89	187.50 ± 12.58
QTcf(ms)	267.40 ± 19.94	265.70 ± 15.88	269.75 ± 13.00	278.06 ± 6.38	281.24 ± 15.49	270.51 ± 18.38	283.20 ± 12.62
HR(bpm)	218.52 ± 11.76	221.08 ± 11.63	223.76 ± 7.61	223.68 ± 37.22	202.10 ± 19.88	213.83 ± 30.95	207.78 ± 15.69
<b>24 h after D71 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=2)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>
PR(ms)	66.00 ± 5.48	72.00 ± 8.37	66.00 ± 8.94	65.00 ± 7.07	68.00 ± 8.37	66.00 ± 11.40	67.50 ± 9.57
RR(ms)	258.80 ± 13.83	298.00 ± 21.17	274.40 ± 22.20	262.00 ± 19.80	300.80 ± 24.40	290.00 ± 36.00	290.00 ± 17.74
QRS(ms)	36.00 ± 5.48	38.00 ± 4.47	40.00 ± 0.00	35.00 ± 7.07	38.00 ± 4.47	38.00 ± 4.47	37.50 ± 5.00
QT(ms)	172.00 ± 8.37	184.00 ± 11.40	174.00 ± 8.94	180.00 ± 14.14	186.00 ± 8.94	180.00 ± 14.14	182.50 ± 12.58
QTcf(ms)	269.91 ± 10.51	275.53 ± 14.27	267.81 ± 7.96	281.20 ± 15.02	277.73 ± 9.52	272.11 ± 12.89	275.72 ± 16.38
HR(bpm)	232.40 ± 13.07	202.18 ± 14.70	219.82 ± 18.04	229.66 ± 17.36	200.55 ± 16.71	209.84 ± 29.75	207.51 ± 13.41
<b>R56</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=1)</b>
PR(ms)	65.00 ± 7.07	70.00 ± 0.00	65.00 ± 7.07	65.00 ± 7.07	65.00 ± 7.07	60.00 ± 0.00	60.00
RR(ms)	255.00 ± 12.73	297.00 ± 29.70	262.00 ± 0.00	266.00 ± 19.80	288.00 ± 0.00	304.00 ± 16.97	302.00
QRS(ms)	40.00 ± 0.00	35.00 ± 7.07	40.00 ± 0.00	35.00 ± 7.07	40.00 ± 0.00	40.00 ± 0.00	40.00
QT(ms)	165.00 ± 7.07	180.00 ± 0.00	165.00 ± 7.07	170.00 ± 14.14	180.00 ± 0.00	195.00 ± 7.07	190.00
QTcf(ms)	260.36 ± 15.49	270.09 ± 9.02	257.86 ± 11.05	264.23 ± 15.44	272.57 ± 0.00	290.21 ± 15.92	283.19
HR(bpm)	235.59 ± 11.76	203.04 ± 20.30	229.01 ± 0.00	226.19 ± 16.84	208.33 ± 0.00	197.68 ± 11.04	198.68

Note: D: Dosing period; R: Recovery; n: the number of animals in each group; Data were expressed as  $\bar{x} \pm SD$ ; <sup>§</sup>: ADC High dose was adjusted from 10 mg/kg to 7.5 mg/kg from the second dose, \* $P \leq 0.05$ , \*\* $P \leq 0.01$  as compared with Vehicle Control. No statistic was performed and inferred due to the animal number s was < 3.

**Supplementary Table 3** Electrocardiograms (ECG) Examination (Lead II) of Male Monkeys

	<b>Vehicle Control (0 mg/kg)</b>	<b>ADC Low dose (2.5 mg/kg)</b>	<b>ADC Middle dose (5 mg/kg)</b>	<b>ADC High dose (10 mg/kg)<sup>&amp;</sup></b>	<b>Naked antibody Middle dose (5 mg/kg)</b>	<b>Naked antibody High dose (10 mg/kg)</b>	<b>Small molecule dose (0.1 mg/kg)</b>
<b>Baseline</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
PR(ms)	74.00 ± 8.94	66.00 ± 5.48	70.00 ± 7.07	64.00 ± 5.48	82.00 ± 17.89	74.00 ± 5.48	72.00 ± 4.47
RR(ms)	366.80 ± 22.87	302.00 ± 22.89*	314.00 ± 40.05	301.20 ± 20.18*	354.40 ± 16.64	308.80 ± 8.67*	316.00 ± 53.59
QRS(ms)	40.00 ± 0.00	38.00 ± 4.47	36.00 ± 5.48	38.00 ± 4.47	40.00 ± 0.00	40.00 ± 0.00	38.00 ± 4.47
QT(ms)	204.00 ± 15.17	180.00 ± 12.25*	182.00 ± 14.83*	186.00 ± 5.48	202.00 ± 8.37	182.00 ± 4.47*	184.00 ± 18.17
QTcf(ms)	284.96 ± 17.76	268.38 ± 16.35	267.83 ± 12.07	277.63 ± 7.29	285.45 ± 9.04	269.30 ± 7.18	270.50 ± 16.11
HR(bpm)	164.08 ± 10.11	199.57 ± 14.72*	193.51 ± 23.98	199.93 ± 13.64*	169.60 ± 8.06	194.42 ± 5.51*	194.43 ± 33.76
<b>4 h after D1 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
PR(ms)	68.00 ± 8.37	66.00 ± 5.48	72.00 ± 10.95	68.00 ± 4.47	76.00 ± 11.40	66.00 ± 8.94	64.00 ± 8.94
RR(ms)	335.60 ± 34.88	284.00 ± 12.00	279.60 ± 19.72	286.40 ± 24.71	308.80 ± 18.42	291.20 ± 24.68	274.40 ± 38.84
QRS(ms)	40.00 ± 0.00	40.00 ± 0.00	40.00 ± 0.00	40.00 ± 0.00	40.00 ± 0.00	40.00 ± 0.00	38.00 ± 4.47
QT(ms)	190.00 ± 10.00	180.00 ± 12.25	172.00 ± 16.43	182.00 ± 16.43	190.00 ± 15.81	176.00 ± 5.48	170.00 ± 14.14
QTcf(ms)	273.54 ± 5.22	273.96 ± 19.42	262.89 ± 20.05	275.98 ± 18.26	280.99 ± 19.37	265.72 ± 5.60	261.75 ± 9.77
HR(bpm)	180.32 ± 18.46	211.58 ± 9.30	215.44 ± 15.06	210.78 ± 18.58	194.82 ± 11.00	207.19 ± 16.92	222.49 ± 33.94
<b>24 h after D1 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
PR(ms)	76.00 ± 8.94	62.00 ± 4.47	74.00 ± 8.94	62.00 ± 4.47	70.00 ± 14.14	72.00 ± 16.43	64.00 ± 11.40
RR(ms)	354.00 ± 45.39	272.00 ± 24.98**	286.40 ± 21.61**	296.40 ± 23.77*	301.20 ± 17.64*	304.80 ± 40.56	276.00 ± 23.79**
QRS(ms)	38.00 ± 4.47	38.00 ± 4.47	38.00 ± 4.47	40.00 ± 0.00	40.00 ± 0.00	40.00 ± 0.00	40.00 ± 0.00
QT(ms)	188.00 ± 13.04	174.00 ± 11.40	176.00 ± 11.40	190.00 ± 7.07	184.00 ± 16.73	188.00 ± 17.89	178.00 ± 16.43
QTcf(ms)	265.97 ± 10.32	268.64 ± 13.33	266.97 ± 11.82	285.17 ± 9.04	274.49 ± 23.16	279.48 ± 19.39	273.23 ± 18.29
HR(bpm)	171.65 ± 21.19	221.93 ± 18.32**	210.47 ± 16.14*	203.48 ± 16.42	199.72 ± 10.95	199.63 ± 26.21	218.69 ± 18.86**
<b>D70</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
PR(ms)	72.00 ± 4.47	68.00 ± 8.37	80.00 ± 12.25	65.00 ± 5.77	72.00 ± 13.04	66.00 ± 8.94	68.00 ± 8.37
RR(ms)	334.80 ± 27.19	286.80 ± 33.45*	302.80 ± 16.71	293.00 ± 12.38	332.80 ± 21.84	298.40 ± 27.03	274.80 ± 27.55**
QRS(ms)	36.00 ± 5.48	40.00 ± 0.00	40.00 ± 0.00	40.00 ± 0.00	40.00 ± 0.00	40.00 ± 0.00	38.00 ± 4.47
QT(ms)	190.00 ± 10.00	178.00 ± 13.04	178.00 ± 16.43	185.00 ± 12.91	192.00 ± 8.37	176.00 ± 16.73	168.00 ± 8.37
QTcf(ms)	273.73 ± 10.61	270.03 ± 11.46	264.97 ± 21.45	278.49 ± 17.24	277.15 ± 9.97	263.23 ± 18.33	258.59 ± 7.17
HR(bpm)	180.14 ± 14.38	211.65 ± 26.41*	198.64 ± 11.08	205.06 ± 8.89	180.94 ± 12.33	202.30 ± 16.99	220.22 ± 23.56**

	Vehicle Control (0 mg/kg)	ADC Low dose (2.5 mg/kg)	ADC Middle dose (5 mg/kg)	ADC High dose (10 mg/kg) <sup>&amp;</sup>	Naked antibody Middle dose (5 mg/kg)	Naked antibody High dose (10 mg/kg)	Small molecule dose (0.1 mg/kg)
<b>4 h after D71 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
PR(ms)	74.00 ± 8.94	66.00 ± 8.94	76.00 ± 8.94	70.00 ± 8.16	78.00 ± 17.89	78.00 ± 4.47	72.00 ± 8.37
RR(ms)	338.80 ± 43.53	292.40 ± 30.64	297.20 ± 25.04	287.00 ± 26.81	323.20 ± 36.49	315.20 ± 25.75	296.00 ± 26.38
QRS(ms)	38.00 ± 4.47	38.00 ± 4.47	38.00 ± 4.47	35.00 ± 5.77	40.00 ± 0.00	38.00 ± 4.47	36.00 ± 5.48
QT(ms)	188.00 ± 10.95	182.00 ± 8.37	180.00 ± 12.25	182.50 ± 9.57	186.00 ± 13.42	180.00 ± 12.25	184.00 ± 8.94
QTcf(ms)	270.06 ± 12.04	274.54 ± 9.40	269.71 ± 12.65	276.74 ± 5.85	271.09 ± 10.27	264.44 ± 12.07	276.21 ± 7.85
HR(bpm)	179.13 ± 19.81	207.26 ± 24.63	203.13 ± 18.54	210.50 ± 20.56	187.56 ± 21.28	191.38 ± 15.65	203.99 ± 18.14
<b>24 h after D71 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
PR(ms)	78.00 ± 10.95	70.00 ± 7.07	72.00 ± 8.37	70.00 ± 8.17	78.00 ± 13.04	72.00 ± 4.47	64.00 ± 5.48
RR(ms)	302.00 ± 36.93	289.60 ± 30.01	293.60 ± 28.75	302.50 ± 18.86	328.40 ± 28.19	336.80 ± 18.58	294.40 ± 26.92
QRS(ms)	36.00 ± 5.48	36.00 ± 5.48	38.00 ± 4.47	40.00 ± 0.00	40.00 ± 0.00	40.00 ± 0.00	38.00 ± 4.47
QT(ms)	170.00 ± 12.25	176.00 ± 15.17	174.00 ± 11.40	182.50 ± 5.00	190.00 ± 12.25	194.00 ± 19.49	190.00 ± 17.32
QTcf(ms)	253.96 ± 19.80	266.00 ± 16.19	261.84 ± 10.43	271.94 ± 3.46	275.40 ± 11.90	279.02 ± 28.91	285.48 ± 19.55
HR(bpm)	201.06 ± 24.47	208.95 ± 21.43	205.83 ± 18.78	198.91 ± 12.07	183.77 ± 15.62	178.57 ± 9.49	205.22 ± 19.37
<b>R56</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>
PR(ms)	70.00 ± 0.00	60.00 ± 0.00	80.00 ± 0.00	65.00 ± 7.07	85.00 ± 7.07	80.00 ± 0.00	85.00 ± 7.07
RR(ms)	284.00 ± 8.49	242.00 ± 14.14	278.00 ± 8.49	280.00 ± 28.28	302.00 ± 2.83	272.00 ± 11.31	288.00 ± 11.31
QRS(ms)	35.00 ± 7.07	30.00 ± 0.00	35.00 ± 7.07	35.00 ± 7.07	40.00 ± 0.00	40.00 ± 0.00	35.00 ± 7.07
QT(ms)	165.00 ± 7.07	160.00 ± 14.14	170.00 ± 14.14	175.00 ± 7.07	190.00 ± 0.00	185.00 ± 21.21	180.00 ± 0.00
QTcf(ms)	250.99 ± 8.26	256.63 ± 17.70	260.39 ± 19.02	267.62 ± 1.79	283.20 ± 0.88	285.36 ± 28.79	272.61 ± 3.57
HR(bpm)	211.36 ± 6.32	248.36 ± 14.51	215.93 ± 6.59	215.38 ± 21.76	198.68 ± 1.86	220.78 ± 9.18	208.49 ± 8.19

Note: D: Dosing period; R: Recovery; n: the number of animals in each group; Data were expressed as  $\bar{x} \pm SD$ ; <sup>&</sup>: ADC High dose was adjusted from 10 mg/kg to 7.5 mg/kg from the second dose, \* $P \leq 0.05$ , \*\*  $P \leq 0.01$  as compared with Vehicle Control. No statistic was performed and inferred due to the animal number  $s$  was  $< 3$ .



**Supplementary Table 4** Blood Pressure of Female Monkeys

	<b>Vehicle Control (0 mg/kg)</b>	<b>ADC Low dose (2.5 mg/kg)</b>	<b>ADC Middle dose (5 mg/kg)</b>	<b>ADC High dose (10 mg/kg)<sup>&amp;</sup></b>	<b>Naked antibody Middle dose (5 mg/kg)</b>	<b>Naked antibody High dose (10 mg/kg)</b>	<b>Small molecule dose (0.1 mg/kg)</b>
<b>Baseline</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
SBP(mmHg)	127.20 ± 29.71	135.80 ± 25.67	132.20 ± 11.05	127.60 ± 22.15	126.80 ± 28.00	146.60 ± 28.56	119.20 ± 17.05
DBP(mmHg)	85.20 ± 21.09	86.80 ± 13.55	80.00 ± 13.23	75.20 ± 16.45	75.80 ± 24.31	97.60 ± 16.99	68.80 ± 20.36
MABP (mmHg)	99.20 ± 23.92	103.13 ± 16.62	97.40 ± 10.91	92.67 ± 14.45	92.80 ± 23.25	113.93 ± 20.05	85.60 ± 12.77
<b>4 h after D1 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
SBP(mmHg)	146.60 ± 19.37	148.20 ± 29.20	123.80 ± 23.15	131.60 ± 28.66	132.80 ± 14.46	139.80 ± 23.56	115.80 ± 19.56
DBP(mmHg)	74.20 ± 27.53	79.20 ± 16.51	75.20 ± 12.19	78.60 ± 13.67	90.40 ± 10.60	82.20 ± 14.87	79.40 ± 20.18
MABP (mmHg)	98.33 ± 13.64	102.20 ± 7.93	91.40 ± 15.65	96.27 ± 11.32	104.53 ± 11.21	101.40 ± 13.74	91.53 ± 19.66
<b>24 h after D1 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
SBP(mmHg)	146.40 ± 19.72	137.20 ± 17.50	131.00 ± 4.47	122.00 ± 14.05	129.00 ± 18.07	139.40 ± 30.30	112.80 ± 9.50
DBP(mmHg)	75.00 ± 22.27	75.40 ± 12.70	75.00 ± 7.91	76.80 ± 3.27	76.60 ± 20.66	71.20 ± 10.23	72.80 ± 8.79
MABP (mmHg)	98.80 ± 10.14	96.00 ± 13.84	93.67 ± 5.25	91.87 ± 6.73	94.07 ± 17.81	93.93 ± 8.60	86.13 ± 7.00
<b>D70</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=2)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>
SBP(mmHg)	138.00 ± 18.04	131.00 ± 20.69	124.60 ± 16.98	131.50 ± 7.78	127.00 ± 15.56	131.60 ± 9.07	136.75 ± 22.16
DBP(mmHg)	90.60 ± 9.99	73.00 ± 21.59	77.40 ± 16.65	74.50 ± 13.44	75.80 ± 11.21	75.60 ± 18.23	71.50 ± 4.36
MABP (mmHg)	106.40 ± 10.76	92.33 ± 19.67	93.13 ± 16.34	93.50 ± 6.36	92.87 ± 12.47	94.27 ± 11.84	93.25 ± 10.21
<b>4 h after D71 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=2)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>
SBP(mmHg)	130.00 ± 9.90	142.60 ± 22.76	120.20 ± 5.07	133.50 ± 4.95	120.80 ± 11.90	124.60 ± 10.88	127.00 ± 12.52
DBP(mmHg)	82.20 ± 15.66	76.60 ± 7.06	76.00 ± 7.68	80.50 ± 0.71	72.00 ± 15.52	84.00 ± 11.94	82.75 ± 4.19
MABP (mmHg)	98.13 ± 13.59	98.60 ± 6.80	90.73 ± 5.95	98.17 ± 2.12	88.27 ± 12.42	97.53 ± 9.88	97.50 ± 5.95
<b>24 h after D71 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=2)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>

	<b>Vehicle Control (0 mg/kg)</b>	<b>ADC Low dose (2.5 mg/kg)</b>	<b>ADC Middle dose (5 mg/kg)</b>	<b>ADC High dose (10 mg/kg)<sup>&amp;</sup></b>	<b>Naked antibody Middle dose (5 mg/kg)</b>	<b>Naked antibody High dose (10 mg/kg)</b>	<b>Small molecule dose (0.1 mg/kg)</b>
SBP(mmHg)	135.60 ± 25.74	126.20 ± 13.14	128.80 ± 14.62	143.00 ± 15.56	114.40 ± 8.62	126.40 ± 13.39	108.50 ± 9.81
DBP(mmHg)	92.20 ± 16.04	79.60 ± 15.34	77.40 ± 8.44	92.50 ± 43.13	67.20 ± 20.87	86.20 ± 19.11	72.50 ± 20.37
MABP (mmHg)	106.67 ± 18.81	95.13 ± 14.29	94.53 ± 6.57	109.33 ± 33.94	82.93 ± 16.29	99.60 ± 16.97	84.50 ± 16.44
<b>R56</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=1)</b>
SBP(mmHg)	97.00 ± 2.83	109.00 ± 8.49	122.50 ± 14.85	120.50 ± 3.54	81.00 ± 8.49	114.00 ± 48.08	99.00 ± 0.00
DBP(mmHg)	58.00 ± 9.90	66.50 ± 4.95	82.00 ± 7.07	69.00 ± 4.24	49.00 ± 5.66	57.00 ± 26.87	45.00 ± 0.00
MABP (mmHg)	71.00 ± 7.54	80.67 ± 6.13	95.50 ± 9.66	86.17 ± 4.01	59.67 ± 6.60	76.00 ± 33.94	63.00 ± 0.00

Note: D: Dosing period; R: Recovery; n: the number of animals in each group; Data were expressed as  $\pm$  SD; &: ADC High dose was adjusted from 10 mg/kg to 7.5 mg/kg from the second dose, \*P $\leq$ 0.05, \*\* P $\leq$ 0.01 as compared with Vehicle Control. No statistic was performed and inferred due to the animal number s was < 3.

**Supplementary Table 5** Blood Pressure of Male Monkeys

	<b>Vehicle Control (0 mg/kg)</b>	<b>ADC Low dose (2.5 mg/kg)</b>	<b>ADC Mid dose (5 mg/kg)</b>	<b>ADC High dose (10 mg/kg)<sup>&amp;</sup></b>	<b>Naked antibody Mid dose (5 mg/kg)</b>	<b>Naked antibody High dose (10 mg/kg)</b>	<b>Small molecule dose (0.1 mg/kg)</b>
<b>Baseline</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
SBP(mmHg)	130.60 ± 15.63	131.20 ± 6.87	137.20 ± 26.66	155.40 ± 28.88	145.60 ± 24.17	149.40 ± 40.76	148.40 ± 19.55
DBP(mmHg)	71.00 ± 12.98	87.00 ± 3.54	90.80 ± 15.55	75.40 ± 10.90	90.40 ± 13.74	84.00 ± 13.40	88.60 ± 17.59
MABP (mmHg)	90.87 ± 12.57	101.73 ± 2.01	106.27 ± 19.10	102.07 ± 9.26	108.80 ± 16.31	105.80 ± 19.51	108.53 ± 16.11
<b>4 h after D1 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
SBP(mmHg)	131.00 ± 3.39	138.40 ± 7.96	130.60 ± 13.18	124.20 ± 18.46	136.40 ± 12.82	120.40 ± 17.24	147.00 ± 29.06
DBP(mmHg)	81.80 ± 6.50	83.20 ± 5.54	87.80 ± 6.26	75.60 ± 8.26	91.80 ± 9.20	73.80 ± 21.06	89.40 ± 13.56
MABP (mmHg)	98.20 ± 5.10	101.60 ± 5.91	102.07 ± 8.20	91.80 ± 9.38	106.67 ± 10.14	89.33 ± 19.67	108.60 ± 17.88
<b>24 h after D1 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
SBP(mmHg)	124.80 ± 20.39	112.60 ± 5.50	123.80 ± 14.64	132.80 ± 38.95	120.60 ± 14.43	128.80 ± 6.46	112.80 ± 18.09
DBP(mmHg)	71.40 ± 5.41	61.20 ± 17.28	67.00 ± 17.35	70.60 ± 24.64	67.80 ± 14.60	77.40 ± 6.66	72.80 ± 19.31
MABP (mmHg)	89.20 ± 8.96	78.33 ± 11.01	85.93 ± 14.47	91.33 ± 24.48	85.40 ± 14.42	94.53 ± 5.86	86.13 ± 18.47
<b>D70</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
SBP(mmHg)	142.80 ± 13.86	119.20 ± 17.30	129.40 ± 8.38	122.50 ± 6.45	129.20 ± 13.14	124.40 ± 16.29	130.80 ± 13.54
DBP(mmHg)	75.00 ± 8.25	69.00 ± 15.86	74.40 ± 10.88	71.50 ± 5.32	72.20 ± 7.89	80.60 ± 7.96	74.00 ± 12.12
MABP (mmHg)	97.60 ± 3.37	85.73 ± 16.12	92.73 ± 9.24	88.50 ± 5.47	91.20 ± 9.20	95.20 ± 10.51	92.93 ± 8.04
<b>4 h after D71 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
SBP(mmHg)	137.00 ± 9.25	132.80 ± 21.04	138.40 ± 35.70	133.75 ± 9.91	124.40 ± 6.19	133.20 ± 9.55	128.60 ± 6.77
DBP(mmHg)	85.20 ± 11.65	80.40 ± 13.09	80.80 ± 11.03	73.50 ± 5.26	82.80 ± 6.61	85.40 ± 13.58	74.80 ± 8.07
MABP (mmHg)	102.47 ± 9.55	97.87 ± 15.21	100.00 ± 17.33	93.58 ± 6.14	96.67 ± 4.18	101.33 ± 11.86	92.73 ± 5.60

	<b>Vehicle Control (0 mg/kg)</b>	<b>ADC Low dose (2.5 mg/kg)</b>	<b>ADC Mid dose (5 mg/kg)</b>	<b>ADC High dose (10 mg/kg)<sup>&amp;</sup></b>	<b>Naked antibody Mid dose (5 mg/kg)</b>	<b>Naked antibody High dose (10 mg/kg)</b>	<b>Small molecule dose (0.1 mg/kg)</b>
<b>24 h after D71 dosing</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>
SBP(mmHg)	139.60 ± 17.10	127.60 ± 19.22	135.00 ± 14.82	137.50 ± 21.44	122.80 ± 11.78	126.20 ± 17.75	127.20 ± 9.63
DBP(mmHg)	84.00 ± 8.46	84.00 ± 17.06	87.80 ± 15.64	84.00 ± 8.60	66.00 ± 5.79	70.40 ± 13.28	66.80 ± 8.90
MABP (mmHg)	102.53 ± 10.83	98.53 ± 16.31	103.53 ± 15.07	101.83 ± 3.50	84.93 ± 7.19	89.00 ± 12.62	86.93 ± 6.72
<b>R56</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>
SBP(mmHg)	126.50 ± 10.61	140.50 ± 12.02	174.00 ± 29.70	117.00 ± 14.14	115.50 ± 10.61	150.50 ± 24.75	128.50 ± 14.85
DBP(mmHg)	85.00 ± 1.41	90.00 ± 11.31	102.00 ± 16.97	51.00 ± 2.83	68.00 ± 22.63	73.50 ± 2.12	82.00 ± 19.80
MABP (mmHg)	98.83 ± 4.48	106.83 ± 11.55	126.00 ± 21.21	73.00 ± 2.83	83.83 ± 18.62	99.17 ± 9.66	97.50 ± 18.15

Note: D: Dosing period; R: Recovery; n: the number of animals in each group; Data were expressed as  $\bar{x} \pm SD$ ; &: ADC High dose was adjusted from 10 mg/kg to 7.5 mg/kg starting from the second dose, \*P≤0.05, \*\* P≤0.01 as compared with Vehicle Control. No statistic was performed and inferred due to the animal number s was < 3.

**Supplementary Table 6** Respiratory Rate of Female Monkeys

	<b>Vehicle Control (0 mg/kg) (n=5)</b>	<b>ADC Low dose (2.5 mg/kg) (n=5)</b>	<b>ADC Middle dose (5 mg/kg) (n=5)</b>	<b>ADC High dose (10/7.5 mg/kg)<sup>&amp;</sup> (n=5)</b>	<b>Naked antibody Middle dose (5 mg/kg) (n=5)</b>	<b>Naked antibody High dose (10 mg/kg) (n=5)</b>	<b>Small molecule dose (0.1 mg/kg) (n=5)</b>
<b>Baseline</b>	27.00 ± 7.35	31.00 ± 8.75	33.20 ± 1.92	30.40 ± 12.99	34.20 ± 9.91	25.20 ± 0.84	27.40 ± 6.35
<b>4 h after D1 dosing</b>	30.20 ± 9.04	32.60 ± 6.58	27.60 ± 7.30	25.60 ± 4.16	34.00 ± 9.95	28.00 ± 4.42	21.40 ± 4.72
<b>24 h after D1 dosing</b>	29.60 ± 8.79	27.20 ± 2.95	38.20 ± 13.33	23.80 ± 7.19	28.00 ± 4.06	24.60 ± 4.04	23.20 ± 6.50
	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=2)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>
<b>D70</b>	30.40 ± 7.64	28.00 ± 5.34	30.00 ± 5.96	19.00 ± 1.41	28.80 ± 4.82	28.40 ± 6.27	25.50 ± 6.86
	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=2)</b>	<b>(n=5)</b>	<b>(n=5)</b>	<b>(n=4)</b>
<b>4 h after D71 dosing</b>	28.40 ± 6.35	31.20 ± 9.44	30.60 ± 6.27	23.00 ± 2.83	22.20 ± 5.45	27.60 ± 4.98	26.00 ± 4.97
<b>24 h after D71 dosing</b>	29.60 ± 9.10	24.00 ± 7.14	24.20 ± 7.98	24.50 ± 0.71	28.20 ± 3.56	27.20 ± 5.12	27.00 ± 8.04
	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=2)</b>	<b>(n=1)</b>
<b>R56</b>	34.00 ± 0.00	30.00 ± 1.41	40.50 ± 20.51	31.00 ± 7.07	30.50 ± 2.12	28.00 ± 8.49	22.00 ± 0.00

Note: D: Dosing period; R: Recovery; n: the number of animals in each group; Data were expressed as  $\bar{x} \pm SD$ ; <sup>&</sup>: ADC High dose was adjusted from 10 mg/kg to 7.5 mg/kg from the second dose. \* $P \leq 0.05$ , \*\* $P \leq 0.01$  as compared with Vehicle Control. No statistic was performed and inferred due to the animal number s was < 3.

**Supplementary Table 7** Respiratory Rate of Male Monkeys

	<b>Vehicle Control (0 mg/kg) (n=5)</b>	<b>ADC Low dose (2.5 mg/kg) (n=5)</b>	<b>ADC Mid dose (5 mg/kg) (n=5)</b>	<b>ADC High dose (10 mg/kg)<sup>&amp;</sup> (n=5)</b>	<b>Naked antibody Mid dose (5 mg/kg) (n=5)</b>	<b>Naked antibody High dose (10 mg/kg) (n=5)</b>	<b>Small molecule dose (0.1 mg/kg) (n=5)</b>
<b>Baseline</b>	37.40 ± 6.91	32.00 ± 4.58	31.60 ± 6.84	28.00 ± 4.85	30.60 ± 6.88	35.80 ± 8.26	38.00 ± 15.49
<b>4 h after D1 dosing</b>	36.60 ± 8.73	38.60 ± 8.05	32.40 ± 5.13	31.60 ± 8.17	31.80 ± 1.64	39.40 ± 7.30	37.60 ± 15.31
<b>24 h after D1 dosing</b>	36.40 ± 10.78 <b>(n=5)</b>	29.20 ± 8.41 <b>(n=5)</b>	35.20 ± 10.55 <b>(n=5)</b>	32.60 ± 10.01 <b>(n=4)</b>	35.20 ± 11.17 <b>(n=5)</b>	35.00 ± 9.75 <b>(n=5)</b>	27.40 ± 4.04 <b>(n=5)</b>
<b>D70</b>	29.40 ± 2.30 <b>(n=5)</b>	30.40 ± 16.80 <b>(n=5)</b>	31.80 ± 6.94 <b>(n=5)</b>	24.50 ± 9.26 <b>(n=4)</b>	33.40 ± 6.35 <b>(n=5)</b>	31.80 ± 11.99 <b>(n=5)</b>	27.60 ± 4.34 <b>(n=5)</b>
<b>4 h after D71 dosing</b>	32.60 ± 5.22	30.40 ± 11.33	33.60 ± 6.50	24.50 ± 1.29	34.00 ± 5.24	25.60 ± 7.23	26.20 ± 5.07
<b>24 h after D71 dosing</b>	38.00 ± 3.81 <b>(n=2)</b>	23.00 ± 2.92** <b>(n=2)</b>	31.00 ± 6.04 <b>(n=2)</b>	22.50 ± 2.38** <b>(n=2)</b>	28.20 ± 6.10 <b>(n=2)</b>	28.80 ± 8.20 <b>(n=2)</b>	24.00 ± 0.00* <b>(n=2)</b>
<b>R56</b>	29.00 ± 4.24	28.50 ± 0.71	33.50 ± 2.12	27.00 ± 5.66	23.50 ± 2.12	44.00 ± 15.56	31.50 ± 9.19

Note: D: Dosing period; R: Recovery; n: the number of animals in each group; Data were expressed as  $\bar{x} \pm SD$ ; <sup>&</sup>: ADC High dose was adjusted from 10 mg/kg to 7.5 mg/kg from the second dose, \* $P \leq 0.05$ , \*\* $P \leq 0.01$  as compared with Vehicle Control. No statistic was performed and inferred due to the animal number s was < 3.

**Supplementary Table 8** Body Weights (kg), Absolute Organ Weights (g) and Ratios (%) - At the End of Dosing Period /Female

Group Number	1 n=3	2 n=3	3 n=3	4 n=0 <sup>^</sup>	5 n=3	6 n=3	7 n=3	
Body weight	2.97 ± 0.289	3.00 ± 0.265	3.07 ± 0.379	- - -	2.90 ± 0.173	3.03 ± 0.252	3.03 ± 0.503	
<b>Brain</b>	Weight	66.50 ± 2.427	62.40 ± 3.764	69.53 ± 4.932	- - -	62.37 ± 1.358	63.93 ± 2.967	67.73 ± 13.639
	Ratio <sup>[a]</sup>	2.25 ± 0.188	2.09 ± 0.200	2.29 ± 0.315	- - -	2.15 ± 0.112	2.11 ± 0.157	2.23 ± 0.135
<b>Heart</b>	Weight	10.03 ± 0.924	10.73 ± 1.361	12.63 ± 2.060	- - -	10.50 ± 1.905	10.17 ± 0.231	11.37 ± 3.444
	Ratio <sup>[a]</sup>	0.34 ± 0.002	0.36 ± 0.014	0.41 ± 0.025	- - -	0.36 ± 0.043	0.34 ± 0.034	0.37 ± 0.065
<b>Liver</b>	Weight	72.10 ± 4.660	62.63 ± 7.921	74.33 ± 8.511	- - -	61.50 ± 10.006	61.13 ± 6.439	65.40 ± 10.540
	Ratio <sup>[a]</sup>	2.45 ± 0.309	2.08 ± 0.096	2.45 ± 0.426	- - -	2.13 ± 0.382	2.02 ± 0.230	2.16 ± 0.026
<b>Spleen</b>	Weight	2.83 ± 0.709	2.87 ± 1.041	3.87 ± 1.501	- - -	3.30 ± 0.819	3.17 ± 1.097	2.70 ± 0.361
	Ratio <sup>[a]</sup>	0.10 ± 0.031	0.09 ± 0.029	0.13 ± 0.057	- - -	0.11 ± 0.021	0.10 ± 0.027	0.09 ± 0.003
<b>Kidney<sup>#</sup></b>	Weight	13.50 ± 1.127	12.87 ± 1.185	15.23 ± 2.318	- - -	12.27 ± 0.577	13.53 ± 1.514	13.87 ± 3.465
	Ratio <sup>[a]</sup>	0.46 ± 0.041	0.43 ± 0.065	0.50 ± 0.108	- - -	0.42 ± 0.023	0.45 ± 0.026	0.46 ± 0.094
<b>Thymus</b>	Weight	1.03 ± 0.208	1.47 ± 1.514	1.10 ± 0.200	- - -	1.57 ± 0.603	1.53 ± 0.757	0.77 ± 0.503
	Ratio <sup>[a]</sup>	0.03 ± 0.006	0.05 ± 0.046	0.04 ± 0.004	- - -	0.05 ± 0.018	0.05 ± 0.021	0.02 ± 0.015
<b>Uterus<sup>&amp;</sup></b>	Weight	7.77 ± 5.150	6.27 ± 2.101	4.53 ± 1.102	- - -	9.90 ± 3.724	6.27 ± 3.536	4.23 ± 2.021
	Ratio <sup>[a]</sup>	0.27 ± 0.189	0.21 ± 0.054	0.15 ± 0.044	- - -	0.34 ± 0.105	0.21 ± 0.135	0.13 ± 0.044
<b>Ovary<sup>#</sup></b>	Weight	0.26 ± 0.119	0.24 ± 0.052	0.22 ± 0.117	- - -	0.32 ± 0.097	0.41 ± 0.037	0.19 ± 0.083
	Ratio <sup>[a]</sup>	0.01 ± 0.004	0.01 ± 0.001	0.01 ± 0.005	- - -	0.01 ± 0.003	0.01 ± 0.002	0.01 ± 0.002
<b>Adrenals<sup>#</sup></b>	Weight	0.53 ± 0.110	0.49 ± 0.024	0.56 ± 0.109	- - -	0.50 ± 0.022	0.53 ± 0.089	0.67 ± 0.200
	Ratio <sup>[a]</sup>	0.02 ± 0.004	0.02 ± 0.002	0.02 ± 0.002	- - -	0.02 ± 0.001	0.02 ± 0.004	0.02 ± 0.007
<b>Thyroid and Parathyroid<sup>#</sup></b>	Weight	0.27 ± 0.101	0.28 ± 0.104	0.32 ± 0.120	- - -	0.23 ± 0.077	0.24 ± 0.054	0.28 ± 0.053
	Ratio <sup>[a]</sup>	0.01 ± 0.002	0.01 ± 0.003	0.01 ± 0.004	- - -	0.01 ± 0.002	0.01 ± 0.002	0.01 ± 0.002

Values expressed as mean ± standard deviation (  $\bar{X} \pm SD$ ); n: Number of animals; #: Paired organs were weighted together;&: Uterus and oviduct were weighted together;Ratio<sup>[a]</sup>: Organ Weight (g) / Body Weight (kg) ÷100; ^: All female animals in 4 group were dead or moribund and necropsied ahead of schedule, hence the number of animal was 0.

**Supplementary Table 9** Body Weights (kg), Organ Weights (g) and Ratios (%) - At the End of Dosing Period /Male

Group Number		1 n=3	2 n=3	3 n=3	4 n=2 <sup>^</sup>	5 n=3	6 n=3	7 n=3
Body weight		4.30 ± 0.361	3.87 ± 0.404	4.13 ± 0.208	3.70 ± 0.283	4.13 ± 0.451	3.93 ± 0.451	3.90 ± 0.200
<b>Brain</b>	Weight	71.07 ± 5.654	75.47 ± 1.172	72.90 ± 3.843	72.45 ± 1.344	67.00 ± 4.574	72.63 ± 1.801	73.83 ± 2.155
	Ratio <sup>[a]</sup>	1.65 ± 0.038	1.96 ± 0.178	1.77 ± 0.097	1.97 ± 0.187	1.63 ± 0.083	1.86 ± 0.237	1.89 ± 0.042
<b>Heart</b>	Weight	14.47 ± 2.548	13.03 ± 1.617	13.20 ± 1.389	13.05 ± 0.495	14.53 ± 1.903	14.23 ± 1.185	13.83 ± 0.896
	Ratio <sup>[a]</sup>	0.33 ± 0.033	0.34 ± 0.014	0.32 ± 0.051	0.35 ± 0.040	0.35 ± 0.008	0.37 ± 0.071	0.35 ± 0.013
<b>Liver</b>	Weight	74.93 ± 4.174	72.90 ± 6.722	71.13 ± 6.475	68.25 ± 0.495	69.73 ± 3.427	62.97 ± 5.701	69.37 ± 3.592
	Ratio <sup>[a]</sup>	1.75 ± 0.073	1.90 ± 0.276	1.72 ± 0.181	1.85 ± 0.128	1.70 ± 0.144	1.60 ± 0.072	1.78 ± 0.021
<b>Spleen</b>	Weight	3.97 ± 1.422	4.80 ± 0.954	4.43 ± 1.206	3.20 ± 1.131	3.87 ± 1.168	3.23 ± 0.252	3.23 ± 0.306
	Ratio <sup>[a]</sup>	0.09 ± 0.040	0.12 ± 0.018	0.11 ± 0.024	0.09 ± 0.024	0.09 ± 0.035	0.08 ± 0.015	0.08 ± 0.010
<b>Kidney<sup>#</sup></b>	Weight	15.93 ± 2.040	15.17 ± 0.929	17.07 ± 3.202	17.55 ± 3.465	16.57 ± 2.003	15.97 ± 0.737	15.83 ± 1.358
	Ratio <sup>[a]</sup>	0.37 ± 0.025	0.40 ± 0.049	0.41 ± 0.058	0.47 ± 0.058	0.40 ± 0.045	0.41 ± 0.065	0.41 ± 0.040
<b>Thymus</b>	Weight	2.23 ± 0.586	0.83 ± 0.513	0.73 ± 0.231	0.90 ± 0.283	2.10 ± 1.572	2.70 ± 0.819	1.30 ± 0.954
	Ratio <sup>[a]</sup>	0.05 ± 0.017	0.02 ± 0.011	0.02 ± 0.005	0.02 ± 0.006	0.05 ± 0.045	0.07 ± 0.023	0.03 ± 0.024
<b>Testis<sup>#</sup></b>	Weight	11.70 ± 8.506	8.90 ± 6.023	12.53 ± 8.687	9.05 ± 9.122	14.23 ± 16.579	9.57 ± 12.500	5.80 ± 5.110
	Ratio <sup>[a]</sup>	0.26 ± 0.184	0.24 ± 0.166	0.31 ± 0.221	0.24 ± 0.228	0.32 ± 0.350	0.22 ± 0.278	0.15 ± 0.121
<b>Epididymis<sup>#</sup></b>	Weight	2.35 ± 1.236	1.53 ± 0.483	2.26 ± 0.848	1.59 ± 1.218	2.50 ± 2.051	1.95 ± 1.236	1.46 ± 0.556
	Ratio <sup>[a]</sup>	0.05 ± 0.028	0.04 ± 0.014	0.05 ± 0.021	0.04 ± 0.030	0.06 ± 0.042	0.05 ± 0.025	0.04 ± 0.012
<b>Adrenals<sup>#</sup></b>	Weight	0.74 ± 0.243	0.57 ± 0.074	0.47 ± 0.020	0.71 ± 0.086	0.52 ± 0.147	0.57 ± 0.046	0.49 ± 0.089
	Ratio <sup>[a]</sup>	0.02 ± 0.005	0.01 ± 0.001	0.01 ± 0.001	0.02 ± 0.001	0.01 ± 0.003	0.01 ± 0.002	0.01 ± 0.003
<b>Thyroid and Parathyroid<sup>#</sup></b>	Weight	0.42 ± 0.358	0.32 ± 0.147	0.34 ± 0.023	0.28 ± 0.148	0.45 ± 0.070	0.30 ± 0.022	0.30 ± 0.083
	Ratio <sup>[a]</sup>	0.01 ± 0.009	0.01 ± 0.004	0.01 ± 0.001	0.01 ± 0.005	0.01 ± 0.003	0.01 ± 0.000	0.01 ± 0.002

Values expressed as mean ± standard deviation (X±SD);n: Number of animals; #: Paired organs were weighted together;Ratio[a]: Organ Weight (g) / Body Weight (kg) ÷100;  
\*: Compared with Vehicle Control Group, P≤0.05;^ 1 male animal of 4 group was dead and necropsied ahead of schedule, hence the number of animal was 2.



**Supplementary Table 10** Body Weights (kg), Organ Weights (g) and Ratios (%) - At the End of Recovery Period /Female

Group Number		1 n=2	2 n=2	3 n=2	4 n=2	5 n=2	6 n=2	7 n=1 <sup>^</sup>
	Body weight	3.70 ± 0.283	3.55 ± 0.071	3.65 ± 0.071	3.50 ± 0.283	3.70 ± 0.000	3.70 ± 0.000	3.60
<b>Brain</b>	Weight	62.80 ± 1.838	64.85 ± 0.778	67.05 ± 7.425	59.94 ± 1.492	64.50 ± 1.697	68.60 ± 0.283	59.50
	Ratio <sup>[a]</sup>	1.70 ± 0.180	1.83 ± 0.014	1.84 ± 0.239	1.72 ± 0.096	1.74 ± 0.046	1.85 ± 0.008	1.65
<b>Heart</b>	Weight	11.65 ± 2.051	11.10 ± 0.141	11.75 ± 1.909	12.15 ± 0.778	11.30 ± 0.707	13.55 ± 0.778	10.30
	Ratio <sup>[a]</sup>	0.31 ± 0.031	0.31 ± 0.002	0.32 ± 0.059	0.35 ± 0.050	0.31 ± 0.019	0.37 ± 0.021	0.29
<b>Liver</b>	Weight	61.35 ± 8.839	64.95 ± 0.212	71.20 ± 4.526	56.60 ± 0.141	56.00 ± 5.657	60.90 ± 3.253	66.30
	Ratio <sup>[a]</sup>	1.65 ± 0.112	1.83 ± 0.030	1.95 ± 0.086	1.62 ± 0.127	1.51 ± 0.153	1.65 ± 0.088	1.84
<b>Spleen</b>	Weight	2.35 ± 0.495	3.20 ± 0.566	3.00 ± 0.707	3.35 ± 0.354	3.45 ± 0.212	2.65 ± 0.495	3.60
	Ratio <sup>[a]</sup>	0.06 ± 0.009	0.09 ± 0.014	0.08 ± 0.021	0.10 ± 0.002	0.09 ± 0.006	0.07 ± 0.013	0.10
<b>Kidney<sup>#</sup></b>	Weight	14.60 ± 2.121	15.85 ± 1.626	14.10 ± 2.263	13.55 ± 0.919	13.65 ± 2.333	15.85 ± 0.778	15.10
	Ratio <sup>[a]</sup>	0.39 ± 0.027	0.45 ± 0.037	0.39 ± 0.055	0.39 ± 0.058	0.37 ± 0.063	0.43 ± 0.021	0.42
<b>Thymus</b>	Weight	2.25 ± 1.344	1.05 ± 0.071	2.05 ± 0.212	2.85 ± 1.768	2.95 ± 1.061	2.25 ± 0.354	2.10
	Ratio <sup>[a]</sup>	0.06 ± 0.032	0.03 ± 0.003	0.06 ± 0.007	0.08 ± 0.044	0.08 ± 0.029	0.06 ± 0.010	0.06
<b>Uterus<sup>&amp;</sup></b>	Weight	7.55 ± 0.778	7.25 ± 0.071	12.05 ± 0.354	5.90 ± 2.404	6.25 ± 0.919	8.40 ± 0.283	11.50
	Ratio <sup>[a]</sup>	0.21 ± 0.037	0.20 ± 0.006	0.33 ± 0.016	0.17 ± 0.083	0.17 ± 0.025	0.23 ± 0.008	0.32
<b>Ovary<sup>#</sup></b>	Weight	0.42 ± 0.062	0.54 ± 0.197	0.32 ± 0.046	0.23 ± 0.069	0.38 ± 0.014	0.41 ± 0.145	0.28
	Ratio <sup>[a]</sup>	0.01 ± 0.001	0.02 ± 0.005	0.01 ± 0.001	0.01 ± 0.003	0.01 ± 0.000	0.01 ± 0.004	0.01
<b>Adrenals<sup>#</sup></b>	Weight	0.51 ± 0.073	0.64 ± 0.190	0.50 ± 0.035	0.55 ± 0.074	0.42 ± 0.098	0.62 ± 0.194	0.63
	Ratio <sup>[a]</sup>	0.01 ± 0.003	0.02 ± 0.005	0.01 ± 0.001	0.02 ± 0.003	0.01 ± 0.003	0.02 ± 0.005	0.02
<b>Thyroid and Parathyroid<sup>#</sup></b>	Weight	0.38 ± 0.081	0.25 ± 0.112	0.45 ± 0.203	0.38 ± 0.049	0.29 ± 0.098	0.45 ± 0.163	0.45
	Ratio <sup>[a]</sup>	0.01 ± 0.001	0.01 ± 0.003	0.01 ± 0.006	0.01 ± 0.002	0.01 ± 0.003	0.01 ± 0.004	0.01

Values expressed as mean ± standard deviation (X±SD);n: Number of animals; #: Paired organs were weighted together;&: Uterus and oviduct were weighted together;Ratio<sup>[a]</sup>: Organ Weight (g) / Body Weight (kg) ÷100; ^: 1 female animal of 7 group was moribund and necropsied ahead of schedule, hence the number of animal was 1.

**Supplementary Table 11** Body Weights (kg), Organ Weights (g) and Ratios (%) - At the End of Recovery Period /Male

Group Number		1 n=2	2 n=2	3 n=2	4 n=2	5 n=2	6 n=2	7 n=2
	Body weight	5.05 ± 0.495	5.00 ± 0.000	4.85 ± 0.212	4.95 ± 0.212	5.00 ± 0.141	4.65 ± 0.212	5.05 ± 0.495
<b>Brain</b>	Weight	77.70 ± 5.798	77.65 ± 2.899	74.25 ± 5.586	75.25 ± 3.606	69.15 ± 4.455	71.10 ± 16.122	71.15 ± 3.465
	Ratio <sup>[a]</sup>	1.54 ± 0.036	1.55 ± 0.058	1.53 ± 0.048	1.52 ± 0.008	1.38 ± 0.050	1.52 ± 0.277	1.42 ± 0.208
<b>Heart</b>	Weight	15.00 ± 0.990	16.10 ± 0.141	16.05 ± 0.212	14.65 ± 0.212	17.75 ± 0.495	16.60 ± 2.263	17.05 ± 0.071
	Ratio <sup>[a]</sup>	0.30 ± 0.010	0.32 ± 0.003	0.33 ± 0.010	0.30 ± 0.017	0.35 ± 0.000	0.36 ± 0.032	0.34 ± 0.035
<b>Liver</b>	Weight	80.70 ± 13.294	86.80 ± 0.283	84.50 ± 1.273	94.15 ± 11.384	82.00 ± 9.475	68.00 ± 2.687	68.75 ± 4.738
	Ratio <sup>[a]</sup>	1.59 ± 0.107	1.74 ± 0.006	1.74 ± 0.103	1.90 ± 0.149	1.64 ± 0.236	1.46 ± 0.009	1.36 ± 0.040
<b>Spleen</b>	Weight	4.25 ± 0.071	4.00 ± 0.283	7.20 ± 4.101	5.10 ± 0.424	4.00 ± 0.141	2.95 ± 0.212	5.00 ± 1.838
	Ratio <sup>[a]</sup>	0.08 ± 0.010	0.08 ± 0.006	0.15 ± 0.078	0.10 ± 0.004	0.08 ± 0.001	0.06 ± 0.002	0.10 ± 0.027
<b>Kidney<sup>#</sup></b>	Weight	16.90 ± 1.697	20.80 ± 1.131	16.70 ± 1.131	15.60 ± 1.556	18.75 ± 1.485	15.95 ± 1.626	18.05 ± 0.919
	Ratio <sup>[a]</sup>	0.33 ± 0.001	0.42 ± 0.023	0.34 ± 0.008	0.31 ± 0.018	0.38 ± 0.040	0.34 ± 0.051	0.36 ± 0.053
<b>Thymus</b>	Weight	2.05 ± 0.212	1.50 ± 1.273	1.40 ± 0.566	3.70 ± 2.828	1.15 ± 0.636	0.65 ± 0.212	2.80 ± 0.424
	Ratio <sup>[a]</sup>	0.04 ± 0.008	0.03 ± 0.025	0.03 ± 0.013	0.07 ± 0.054	0.02 ± 0.013	0.01 ± 0.004	0.06 ± 0.003
<b>Testis<sup>#</sup></b>	Weight	13.90 ± 10.324	15.00 ± 16.829	27.85 ± 8.132	21.20 ± 6.930	45.80 ± 5.091	17.80 ± 0.707	49.15 ± 34.578
	Ratio <sup>[a]</sup>	0.29 ± 0.233	0.30 ± 0.337	0.57 ± 0.143	0.43 ± 0.158	0.92 ± 0.128	0.38 ± 0.002	1.01 ± 0.784
<b>Epididymis<sup>#</sup></b>	Weight	2.22 ± 0.918	2.97 ± 2.268	3.29 ± 0.123	2.68 ± 0.543	5.78 ± 0.062	3.69 ± 0.371	3.26 ± 0.453
	Ratio <sup>[a]</sup>	0.04 ± 0.023	0.06 ± 0.045	0.07 ± 0.000	0.05 ± 0.009	0.12 ± 0.004	0.08 ± 0.012	0.06 ± 0.003
<b>Adrenals<sup>#</sup></b>	Weight	0.57 ± 0.008	0.66 ± 0.119	0.67 ± 0.173	0.63 ± 0.026	0.60 ± 0.060	0.69 ± 0.097	0.77 ± 0.182
	Ratio <sup>[a]</sup>	0.01 ± 0.001	0.01 ± 0.002	0.01 ± 0.004	0.01 ± 0.000	0.01 ± 0.002	0.01 ± 0.003	0.02 ± 0.005
<b>Thyroid and Parathyroid<sup>#</sup></b>	Weight	0.30 ± 0.136	0.45 ± 0.062	0.23 ± 0.059	0.39 ± 0.245	0.28 ± 0.084	0.30 ± 0.061	0.41 ± 0.196
	Ratio <sup>[a]</sup>	0.01 ± 0.002	0.01 ± 0.001	0.00 ± 0.001	0.01 ± 0.005	0.01 ± 0.002	0.01 ± 0.002	0.01 ± 0.003

Values expressed as mean ± standard deviation ( $\bar{X} \pm SD$ ); n: Number of animals; #: Paired organs were weighted together; Ratio<sup>[a]</sup>: Organ Weight (g) / Body Weight (kg) ÷ 100;

