Supplementary Information

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Methods

Radiolabeling [^{177}Lu]Lu-NeoB and [^{175}Lu]Lu-NeoB

For lutetium-177 labeling, three solutions were prepared prior to radiolabeling:
Solution 1: 0.250 mL gentisic acid (20 mg/mL) + 1.75 mL acetate buffer (0.5 M, pH 4.5-5.0).
Solution 2: ~1 mg NeoB + 5 mL kolliphor HS 15 (2 mg/mL).
Solution 3: 3 mL ascorbic acid (22.5 mg/mL) + 1 mL acetate buffer (1 M, pH 5).
First, 0.5 mL of lutetium-177 (50 GBq/mL) was added to 1 mL of solution 1. Subsequently ~66 µL of solution 2 was added, and the mixture was left in a 95°C heating block for 7 minutes. After cooling, 500 µL of solution 3 and 420 µL MilliQ and 50 µL of DTPA (4 mM) were added. The radiochemical yield and the radiochemical purity of [^{177}Lu]Lu-NeoB were measured to determine the quality of the labeling. The radiochemical yield was measured by instant thin-layer chromatography on silica gel (Varian) using a 1.0 M aqueous solution of ammonium acetate:methanol (40:60 V/V) as the mobile phase. The radiochemical purity of [^{177}Lu]Lu-NeoB was measured by high-pressure liquid chromatography (HPLC) using an Alliance HPLC system (Waters) containing the W2998 PDA Detector. UV absorbance was measured at 278 nm and a peptide XB-C18 column (3.6 µm, 150 x 4.6 mm) was used with a gradient profile of 0.1% formic acid (A) and acetonitrile (B) (Table S2). Radioactivity was monitored with a system holding a NaI detector, digital multichannel analyzer and dedicated software (MetorX BV) connected to the HPLC system.
For the lutetium-175 labeling , a 1:1 molar ratio of lutetium-175 (ICP-standard 1g/L, Merck) was added to a labeling mixture containing NeoB and sodium-acetate as buffer, final pH 4.0. The mixture was left in a 95°C heating block for 20 minutes. To determine the chemical yield, UHPLC (Acquity H-Class, waters) with a W2998 PDA detector including a HSS-C18 (1.8 µm, 2.1 x 50 mm) column with a gradient profile of 20 mM ammonium acetate (A) acid and methanol (B) (Table S1) was used.

Table S1. UHPLC-method

Time (min)	A (%)	B (%)
0.0-0.14	100	0
0.14-0.2	35	65
0.2-3.5	5	95
3.5-3.51	0	100
3.51-4.0	0	100
4.0-4.01	100	0
4.01-4.5	100	0

Table S2. HPLC-method

Time (min)	A (%)	B (%)
0-2	85	15
2-9	60	40
9-11	60	40
11-11.5	0	100
11.5-13.0	0	100
13.0-13.1	85	15
13.1-15.5	85	15

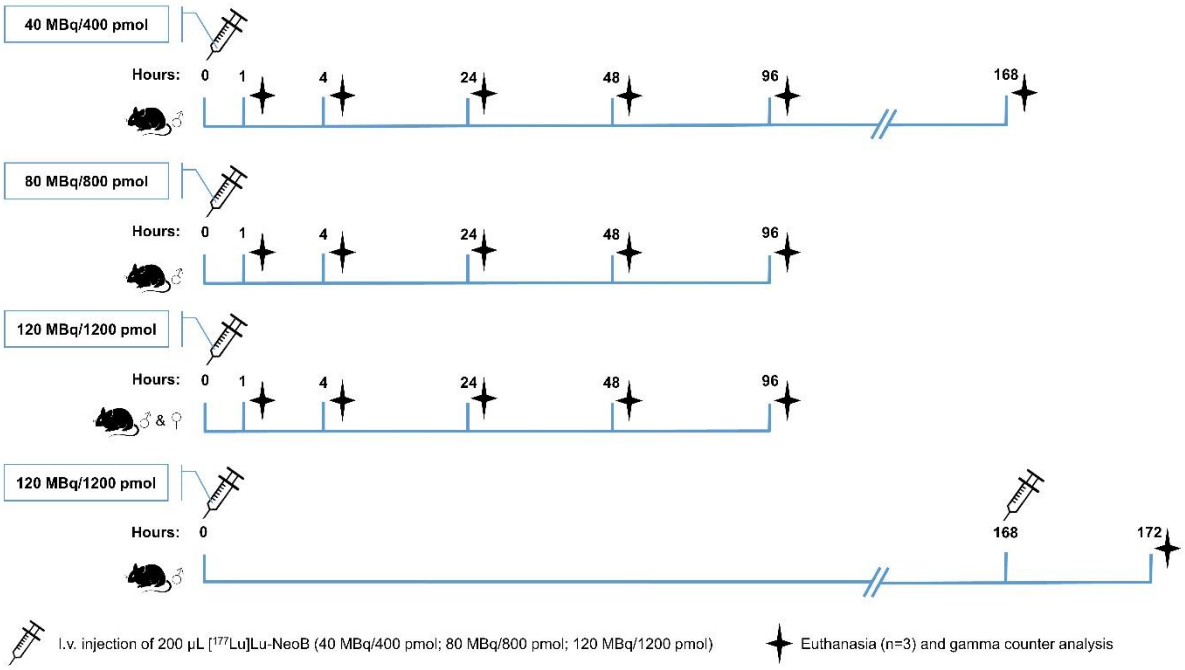

Figure S1: Schematic overview of the biodistribution study

Timelines of the biodistribution study per injected [^{177}Lu]Lu-NeoB dosage.

Table S3. Biodistribution uptake values (%IA/g) of all male animals injected with 40 MBq/400 pmol [^{177}Lu]Lu-NeoB.

	1h*	**4h**	**24h**	**48h**	**96h**	**168h**
Adrenal glands	2.77±0.63	1.38±0.09	0.31±0.17	0.29±0.08	0.16±0.01	0.18±0.12
Blood	2.50±0.77	0.08±0.02	0.01±0.002	0.002±0.0004	0.001±0.0001	0.0005±0.0001
Brain	0.11±0.04	0.02±0.02	0.004±0.001	0.003±0.0003	0.001±0.0002	0.0015±0.001
Heart	0.85±0.19	0.09±0.01	0.07±0.07	0.02±0.003	0.008±0.003	0.01±0.0002
Intestine	1.45±0.29	0.68±0.24	0.35±0.21	0.12±0.05	0.03±0.01	0.01±0.004
Kidneys	6.01±1.24	1.62±0.11	0.57±0.05	0.30±0.03	0.06±0.01	0.11±0.02
Liver	7.25±1.14	0.71±0.07	0.34±0.05	0.27±0.02	0.19±0.01	0.14±0.01
Lungs	1.16±0.16	0.18±0.08	0.07±0.01	0.06±0.03	0.02±0.01	0.02±0.01
Mammary fat pad	0.74±0.39	0.08±0.02	0.03±0.01	0.02±0.001	0.01±0.002	0.06±0.0003
Muscle	0.23±0.05	0.05±0.02	0.01±0.003	0.005±0.001	0.002±0.001	0.002±0.0004
Pancreas	8.27±0.80	4.39±0.50	0.58±0.04	0.12±0.01	0.02±0.0004	0.01±0.001
Prostate gland	1.34±0.07	0.14±0.03	0.03±0.01	0.02±0.01	0.04±0.05	0.03±0.02
Spleen	0.76±0.07	0.20±0.03	0.09±0.004	0.07±0.01	0.02±0.003	0.05±0.01
Stomach	2.36±0.66	0.93±0.15	0.44±0.05	0.18±0.15	0.10±0.03	0.04±0.01
Testes	0.38±0.06	0.05±0.004	0.02±0.004	0.01±0.005	0.006±0.0003	0.01±0.0001^
Urinary bladder	3.19±0.81	2.43±1.79	0.17±0.14	0.08±0.04	0.04±0.03	0.02±0.004

***** Outlier excluded from dataset based on body weight (N = 2 for the 1h time point)

^ Testes could not be located for one mouse due to a shrunken reproductive system (N=2 at the 168 h time point)

Table S4. Biodistribution uptake values (%IA/g) of male animals injected with 80 MBq/800 pmol [^{177}Lu]Lu-NeoB.

	1h	**4h**	**24h**	**48h**	**96h**
Adrenal glands	1.70±0.17	0.81±0.09	0.21±0.17	0.20±0.001	0.10±0.01
Blood	2.19±0.26	0.16±0.08	0.005±0.001	0.002±0.0001	0.001±0.00001
Brain	0.11±0.01	0.07±0.10	0.004±0.001	0.003±0.001	0.002±0.0002
Heart	0.88±0.03	0.14±0.05	0.04±0.004	0.03±0.002	0.02±0.01
Intestine	1.39±0.43	0.71±0.24	0.16±0.06	0.12±0.04	0.04±0.01
Kidneys	5.83±0.35	1.93±0.34	0.51±0.10	0.25±0.02	0.14±0.02
Liver	5.70±0.24	0.91±0.19	0.34±0.01	0.28±0.02	0.19±0.02
Lungs	1.14±0.14	0.29±0.14	0.11±0.06	0.10±0.04	0.05±0.03
Mammary fat pad	0.48±0.15	0.20±0.18	0.02±0.01	0.02±0.004	0.01±0.002
Muscle	0.25±0.04	0.05±0.01	0.01±0.002	0.01±0.001	0.004±0.002
Pancreas	4.05±0.40	2.33±0.37	0.29±0.04	0.08±0.05	0.02±0.001
Prostate gland	0.66±0.30	0.76±0.31	0.05±0.04	0.02±0.01	0.02±0.02
Spleen	0.62±0.10	0.21±0.02	0.10±0.001	0.06±0.01	0.05±0.01
Stomach	1.05±0.05	0.55±0.07	0.25±0.02	0.13±0.02	0.06±0.01
Testes	0.34±0.03	0.08±0.01	0.02±0.004	0.01±0.001	0.01±0.002
Urinary bladder	16.25±23.63	6.97±5.71	0.12±0.03	0.09±0.05	0.03±0.004

Table S5. Biodistribution uptake values (%IA/g) of male animals injected with 120 MBq/1200 pmol [^{177}Lu]Lu-NeoB.

	1h	4h	4h (168h after 1st injection)	24h	48h	96h
Adrenal glands	0.82±0.21	0.34±0.05	0.34±0.11	0.16±0.06	0.15±0.02	0.10±0.003
Blood	1.24±0.21	0.02±0.001	0.04±0.02	0.004±0.0004	0.002±0.001	0.001±0.0002
Brain	0.08±0.04	0.01±0.003	0.01±0.001	0.004±0.002	0.004±0.003	0.003±0.001
Heart	0.40±0.03	0.05±0.005	0.06±0.01	0.03±0.004	0.02±0.01	0.02±0.004
Intestine	0.73±0.12	0.18±0.04	0.13±0.07	0.09±0.03	0.05±0.01	0.03±0.01
Kidneys	2.86±0.24	0.77±0.03	0.89±0.07	0.30±0.06	0.13±0.03	0.17±0.04
Liver	3.44±0.44	0.29±0.02	0.43±0.08	0.28±0.01	0.22±0.01	0.23±0.02
Lungs	0.61±0.11	0.11±0.03	0.10±0.01	0.11±0.05	0.10±0.01	0.17±0.05
Mammary fat pad	0.47±0.27	0.03±0.01	0.08±0.004	0.03±0.01	0.01±0.001	0.02±0.01
Muscle	0.24±0.20	0.02±0.003	0.03±0.02	0.01±0.001	0.004±0.001	0.004±0.001
Pancreas	1.79±0.20	0.76±0.06	0.88±0.13	0.20±0.02	0.04±0.002	0.02±0.004
Prostate gland	0.67±0.23	0.05±0.01	0.20±0.03	0.03±0.003	0.02±0.01	0.01±0.004
Spleen	0.39±0.06	0.09±0.002	0.10±0.01	0.05±0.004	0.04±0.002	0.07±0.002
Stomach	0.62±0.13	0.18±0.02	0.18±0.004	0.13±0.02	0.07±0.01	0.05±0.004
Testes	0.20±0.03	0.03±0.001	0.03±0.01	0.01±0.003	0.01±0.002	0.01±0.001
Urinary bladder	5.93±7.80	2.40±3.52	0.54±0.58	0.11±0.022	0.07±0.03	0.06±0.02

Table S6. Biodistribution uptake values (%IA/g) of female animals injected with 120 MBq/1200 pmol [^{177}Lu]Lu-NeoB.

	1h	4h	24h	48h	96h
Adrenal glands	2.00±0.38	0.77±0.19	0.41±0.14	0.25±0.04	0.14±0.02
Blood	1.96±0.36	0.04±0.01	0.01±0.002	0.003±0.001	0.001±0.0002
Brain	0.27±0.22	0.01±0.001	0.003±0.001	0.002±0.001	0.001±0.001
Heart	0.61±0.09	0.06±0.004	0.03±0.01	0.01±0.002	0.01±0.001
Intestine	0.81±0.07	0.26±0.03	0.14±0.01	0.08±0.03	0.10±0.12^
Kidneys	3.84±0.56	1.21±0.13	0.74±0.04	0.40±0.12	0.11±0.04
Liver	3.71±0.51	0.48±0.05	0.38±0.08	0.25±0.05	0.21±0.03
Lungs	0.88±0.09	0.07±0.02	0.03±0.01	0.02±0.01	0.01±0.005
Mammary fat pad	0.81±0.03	0.09±0.03	0.05±0.01	0.05±0.04	0.02±0.003
Muscle	0.24±0.02	0.02±0.002	0.01±0.001	0.004±0.002	0.002±0.001
ovaries	0.90±0.36	0.09±0.02	0.04±0.01	0.02±0.01	0.02±0.01
Pancreas	1.82±0.23	0.92±0.18	0.26±0.09	0.05±0.02	0.01±0.001
Spleen	0.47±0.09	0.10±0.01	0.06±0.004	0.04±0.004	0.03±0.01
Stomach	0.80±0.14	0.18±0.01	0.14±0.02	0.06±0.01	0.02±0.003
Urinary bladder	2.67±1.96	0.18±0.02	0.13±0.08	0.11±0.04	0.06±0.03

^ Large SD caused by deviating organ weight of one mouse

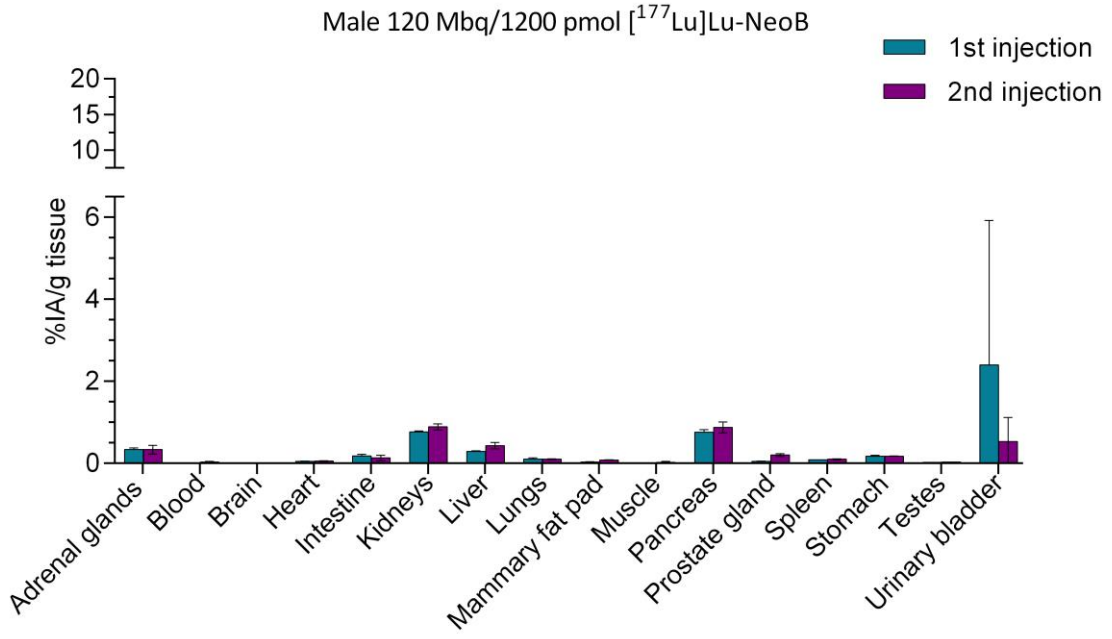

Figure S2: Biodistribution uptake values

Uptake expressed in percentage of injected activity per grams of tissue (%IA/g). Comparison in uptake between animals receiving one versus 2 injections with a 7-day interval.

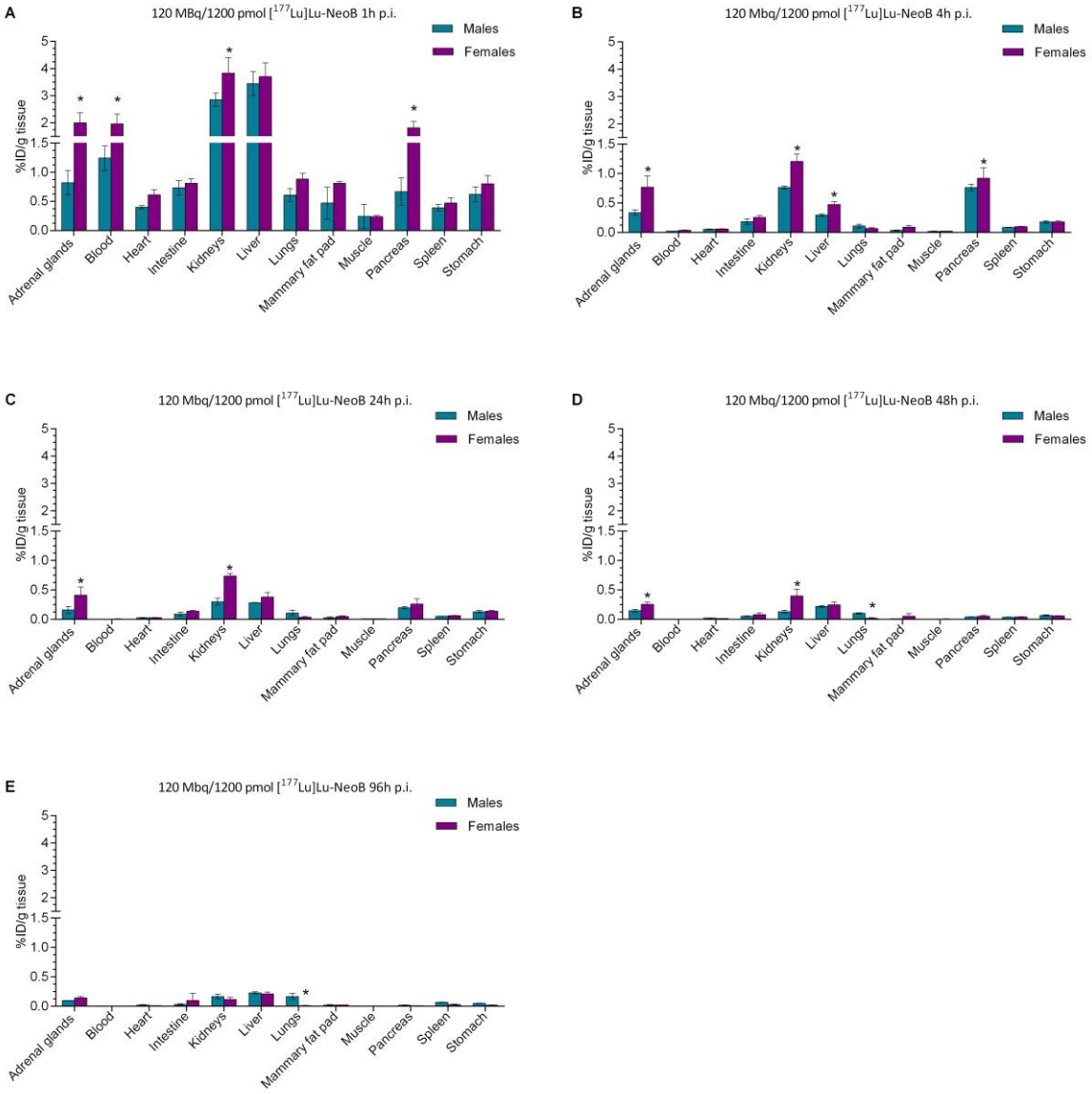

Figure S3: Biodistribution uptake values

Uptake expressed in percentage of injected activity per grams of tissue (%IA/g). Comparison in uptake between male and female animals receiving 120 MBq/1200 pmol [^{177}Lu]Lu-NeoB at (A) 1h, (B) 4h, (C) 24h, (D) 48h and (E) 96h after injection. Error bars represent the standard deviation.

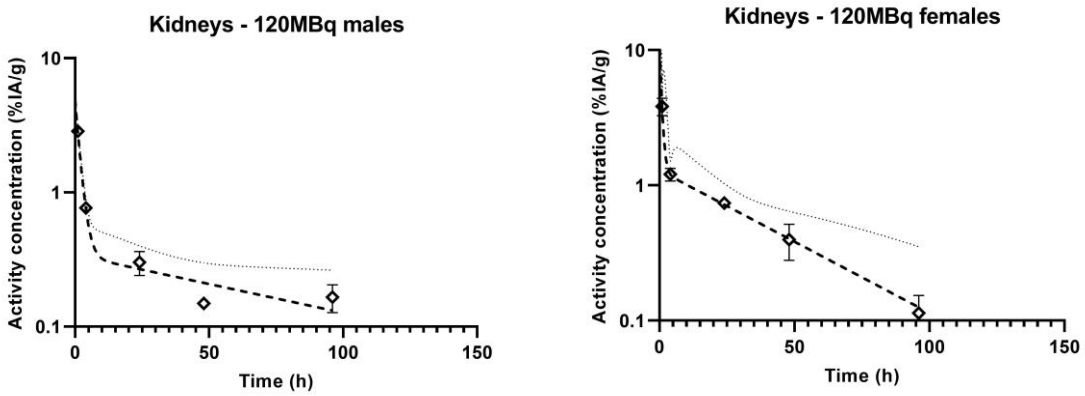

Figure S4: Pharmacokinetic modeling of [^{177}Lu]Lu-NeoB kidney clearance
Comparison in kidney clearance between male (left) and female (right) animals receiving 120 MBq/1200 pmol [^{177}Lu]Lu-NeoB. The exponential fit was performed using a two-phase decay model with an R^2 of 0.95 for males and 0.97 for females.

Table S7. Microscopic observations during histopathological evaluation of organs/tissues of male mice sacrificed 5 weeks after the first injection. A 5-point grading scale was used: 1. Minimal change, 2. Mild change, 3. Moderate change, 4. Marked change, 5. Severe change.

Sex	**Males**																								
Group	Control group 1					Control group 2					Treatment group 1					Treatment group 2					Treatment group 3				
N	3					3					3					3					3				
Score	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Adrenal glands – Subcapsular cell hyperplasia		1/3				1/3	1/3				1/3														
Adrenal glands – accessory cortical tissue						1/3																			
Urinary bladder – inflammatory cell foci																					3/3				
Urinary bladder – urothelium vacuolation																					2/3	1/3			
Urinary bladder – mineralization																						1/3			
Testes – germ cell depletion												1/3				1/3					1/3				
Thyroid gland – ectopic thymus											1/3					1/3									
Spleen – extramedullary haematopoiesis							1/3					2/3													
Pancreas – acinar cell degeneration											1/3														
Pancreas – mineralization																						1/3			
Prostate gland – inflammatory cell foci																					2/3				
Heart – inflammatory cell foci																						1/3			

Table S8. Microscopic observations during histopathological evaluation of organs/tissues of female mice sacrificed 5 weeks after the first injection. A 5-point grading scale was used: 1. Minimal change, 2. Mild change, 3. Moderate change, 4. Marked change, 5. Severe change.

Sex	**Females**																								
Group	Control group 1					Control group 2					Treatment group 1					Treatment group 2					Treatment group 3				
N	3					3					3					3					3				
Score	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Adrenal glands – Subcapsular cell hyperplasia	1/3					2/3					1/3	1/3				3/3					1/3				
Urinary bladder – inflammatory cell foci											1/3					1/3	2/3				1/3	2/3			
Urinary bladder – urothelium vacuolation																2/3	1/3				1/3	2/3			
Spleen – extramedullary haematopoiesis												2/3										1/3			
Thyroid gland – follicular cyst/s																					1/3				
Liver – inflammatory cell foci	1/3															1/3					1/3				
Brain - artifacts						1/3															1/3				

Table S9. Microscopic observations during histopathological evaluation of organs/tissues of male mice sacrificed 19 weeks after the first injection. A 5-point grading scale was used: 1. Minimal change, 2. Mild change, 3. Moderate change, 4. Marked change, 5. Severe change.

Sex	**Males**																								
Group	Control group 1					Control group 2					Treatment group 1					Treatment group 2					Treatment group 3				
N	3					3					3					3					3				
Score	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Adrenal glands – Subcapsular cell hyperplasia	2/3					2/3					1/3	1/3				1/3	1/3				2/3	1/3			
Adrenal glands – accessory cortical tissue	1/3																								
Urinary bladder – inflammatory cell foci																2/3									
Urinary bladder – urothelium vacuolation																3/3					1/3				
Urinary bladder – proteinaceous plug		1/3					1/3																		
Testes – germ cell depletion											2/3														
Thyroid gland – ectopic thymus											1/3										1/3				
Spleen – extramedullary haematopoiesis												1/3										1/3			
Pancreas – inflammatory cell foci		3/3				1/3											2/3								
Kidneys – hydronephrosis																		1/3	2/3					2/3	
Kidneys – nephropathy																		1/3					1/3		

Table S10. Microscopic observations during histopathological evaluation of organs/tissues of female mice sacrificed 19 weeks after the first injection. A 5-point grading scale was used: 1. Minimal change, 2. Mild change, 3. Moderate change, 4. Marked change, 5. Severe change.

Sex	**Females**																								
Group	Control group 1					Control group 2					Treatment group 1					Treatment group 2					Treatment group 3				
N	3					3					3					3					3				
Score	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Adrenal glands – Subcapsular cell hyperplasia	2/3	1/3				1/3	2/3				1/3	2/3				2/3	1/3				1/3	2/3			
Urinary bladder – inflammatory cell foci											2/3	1/3				2/3					1/3	1/3	1/3		
Urinary bladder – urothelium vacuolation											2/3					2/3	1/3				1/3	1/3			
Spleen – extramedullary haematopoiesis																	1/3								
Pancreas – inflammatory cell foci	1/3										2/3					1/3					1/3	1/3			
Kidneys – hydronephrosis														1/3										3/3	
Kidneys – nephropathy																						1/3			
Liver – inflammatory cell foci	1/3										1/3	1/3				2/3									
Ureter(s) - dilatation																						1/3			

Table S11. Microscopic observations during histopathological evaluation of organs/tissues of male mice sacrificed 43 weeks after the first injection. A 5-point grading scale was used: 1. Minimal change, 2. Mild change, 3. Moderate change, 4. Marked change, 5. Severe change.

Sex	**Males**																								
Group	Control group 1					Control group 2					Treatment group 1					Treatment group 2					Treatment group 3				
N	4					4					3					4					4				
Score	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Adrenal glands – Subcapsular cell hyperplasia	1/4	3/4				3/4	1/4				2/3	1/3				2/4	1/4	1/4			3/4	1/4			
Urinary bladder – inflammatory cell foci											1/3					2/4	1/4								
Urinary bladder – urothelium vacuolation																1/4									
Testes – germ cell depletion	1/4					1/4															1/4				
Pancreas – inflammatory cell foci	1/4						1/4				1/3	2/3					2/4				2/4				
Pancreas – acinar cell degeneration											1/3														
Kidneys – hydronephrosis				1/4															2/4					3/4	
Kidneys – nephropathy											2/3					1/4	1/4				1/4				
Kidneys – inflammatory cell foci						1/4					1/3														
Kidneys – Cyst/s								1/4														1/4			
Lungs – B-adenoma	1/4																								
Skin – inflammatory cell foci											1/3										1/4				
Skin – scab formulation											1/3														
Liver – inflammatory cell foci																					2/4				
Ureter(s) - dilation																							1/4		
Epididymides – spermatic granuloma																							1/4		

Table S12. Microscopic observations during histopathological evaluation of organs/tissues of female mice sacrificed 43 weeks after the first injection. A 5-point grading scale was used: 1. Minimal change, 2. Mild change, 3. Moderate change, 4. Marked change, 5. Severe change.

Sex	**Females**																								
Group	Control group 1					Control group 2					Treatment group 1					Treatment group 2					Treatment group 3				
N	4					4					3					4					4				
Score	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5
Adrenal glands – Subcapsular cell hyperplasia		4/4				1/4	2/4					2/3	1/3				3/4	1/4				4/4			
Urinary bladder – inflammatory cell foci											1/3					1/4									
Urinary bladder – urothelium vacuolation											1/3					1/4									
Urinary bladder – mineralization																						1/4			
Spleen – extramedullary haematopoiesis		1/4																							
Pancreas – inflammatory cell foci							1/4															1/4			
Kidneys – hydronephrosis																				1/4				1/4	1/4
Kidneys – nephropathy																			1/4						
Lungs – alveolar epithelialization																	1/4								
Lungs – B-adenoma																					1/4				
Liver – inflammatory cell foci						1/4										3/4									
Ureter(s) - dilation																							1/4		
Ovaries – atrophy														3/3					3/4					4/4	
Uterus – endometrial hyperplasia									1/4					3/3											

Table S13. Hematologic parameters in male mice. Values represent the mean ± SD. The reference values are based on the baseline (-1 wk) measurements. Asterisks show the significance level with *: $p \leq 0.05$.
$^{C1/C2/T1/T2/T3}$ Significant difference as compared with e.g. control group 1 (C1) at the same time point.
^ Outlier excluded from dataset (N = N-1)

Males	N	WBC (10^3/mm^3)	RBC (10^6/mm^3)	HGB (g/dl)	HCT (%)
Reference value	50	7.68 ± 1.85	9.21 ± 0.66	16.41 ± 0.84	44.49 ± 3.06
Control group 1: 5 wk	10	8.63 ± 1.77^{T3*}	8.92 ± 0.29^	16.52 ± 0.80	42.52 ± 1.44^
11 wk	7	8.38 ± 1.06^	9.40 ± 0.25	17.21 ± 0.41	44.11 ± 1.11
19 wk	7	11.17 ± 5.92	9.42 ± 0.30	16.80 ± 0.65	44.81 ± 1.69
30 wk	4	10.18 ± 3.47	9.21 ± 0.37	17.13 ± 0.85	44.30 ± 1.59
43 wk	4	5.98 ± 1.18	8.66 ± 0.19	15.63 ± 0.59	41.05 ± 0.74
Control group 2: 5 wk	10	7.67 ± 1.50	9.03 ± 0.65	16.45 ± 0.49	43.00 ± 3.33
11 wk	7	8.37 ± 2.67	9.13 ± 1.47	17.11 ± 0.85	44.96 ± 3.10
19 wk	7	9.53 ± 2.84	8.64 ± 0.42 $^{T1*/T2*}$	15.59 ± 0.31^{T2*}	40.80 ± 1.97$^{T1*/T2*}$
30 wk	4	9.80 ± 2.25	9.35 ± 0.34	17.20 ± 0.43	44.90 ± 1.44
43 wk	4	6.70 ± 2.71	8.79 ± 0.34	15.38 ± 0.75	41.88 ± 1.83
Treatment group 1: 5 wk	10	8.08 ± 2.38	8.96 ± 0.30	16.78 ± 0.48^	42.96 ± 1.20
11 wk	7	8.53 ± 1.17	9.56 ± 0.79	17.49 ± 1.16	45.46 ± 3.66
19 wk	6	8.12 ± 1.98	9.58 ± 0.55^{C2*}	16.88 ± 0.38	45.67 ± 2.97 ^{C2*}
30 wk	3	9.77 ± 2.82	9.58 ± 0.27	16.93 ± 0.32	45.97 ± 2.38
43 wk	3	7.53 ± 0.83	8.90 ± 1.54	16.03 ± 2.27	42.70 ± 6.76
Treatment group 2: 5 wk	10	6.65 ± 2.80	8.75 ± 0.44	16.35 ± 0.65	42.99 ± 2.34
11 wk	7	9.61 ± 1.52	10.50 ± 1.43	18.46 ± 2.23	49.27 ± 7.70
19 wk	7	8.68 ± 0.34^	9.69 ± 0.91^{C2*}	17.44 ± 1.54^{C2*}	46.13 ± 4.88 ^{C2*}
30 wk	4	11.13 ± 3.50	9.14 ± 0.52	16.60 ± 0.10^	42.07 ± 0.45^
43 wk	4	7.30 ± 2.24	8.77 ± 0.41	15.63 ± 0.74	41.48 ± 2.44
Treatment group 3: 5 wk	10	5.48 ± 1.82^{C1*}	8.70 ± 0.35	16.02 ± 0.63	42.81 ± 2.14
11 wk	7	7.29 ± 1.54	9.26 ± 0.28	16.81 ± 0.43	43.09 ± 1.65
19 wk	7	8.40 ± 1.33	9.24 ± 0.34	16.63 ± 0.78	43.34 ± 2.21
30 wk	4	12.63 ± 3.38	9.31 ± 0.70	17.08 ± 0.94	44.23 ± 3.32
43 wk	4	7.68 ± 3.01	9.03 ± 0.35	16.10 ± 0.00^	42.80 ± 1.56

HCT: hematocrit; HGB: hemoglobin;; RBC: red blood cell count; WBC: white blood cell count.

Table S14. Hematologic parameters in male mice. Values represent the mean ± SD. The reference values are based on the baseline (-1 wk) measurements. Asterisks show the significance level with *: $p \leq 0.05$.
$^{C1/C2/T1/T2/T3}$ Significant difference as compared with e.g. control group 1 (C1) at the same time point.
^ Outlier excluded from dataset (N = N-1)

Males	N	MCV (µm³)	MCH (pg)	MCHC (g/dl)	PLT (10^3/mm³)
Reference value	50	48.31 ± 0.68^	17.85 ± 0.55	36.93 ± 1.12	718.02 ± 175.49
Control group 1: 5 wk	10	47.70 ± 0.67^{T2*}	18.27 ± 0.47	38.29 ± 1.36	825.60 ± 121.58
11 wk	7	47.14 ± 0.69	18.33 ± 0.39	39.04 ± 0.82	744.71 ± 130.80
19 wk	7	47.43 ± 0.53	18.17 ± 0.35^	38.22 ± 0.81^	935.14 ± 164.96
30 wk	4	48.25 ± 0.50	18.58 ± 0.68	38.60 ± 1.29	1163.75 ± 168.54
43 wk	4	47.50 ± 0.58	18.17 ± 0.06$^{\wedge/C2*/T3*}$	38.00 ± 0.85	1183.75 ± 141.96
Control group 2: 5 wk	10	47.50 ± 0.71$^{T2*/T3*}$	18.29 ± 1.12	38.44 ± 2.56	863.90 ± 120.87
11 wk	7	46.86 ± 0.90	18.20 ± 0.26^	38.60 ± 0.35^	738.14 ± 174.38
19 wk	7	47.43 ± 0.98	18.09 ± 0.79	38.11 ± 1.44	947.29 ± 198.53
30 wk	4	48.00 ± 0.82	18.43 ± 0.43	38.33 ± 1.04	1157.25 ± 52.10
43 wk	4	47.50 ± 0.58	17.48 ± 0.38$^{C1*/T1*}$	36.70 ± 0.89	1005.25 ± 118.46
Treatment group 1: 5 wk	10	48.10 ± 0.74	18.50 ± 0.58	38.54 ± 1.27	839.00 ± 102.63
11 wk	7	47.57 ± 0.98	18.31 ± 0.74	38.51 ± 1.74	719.00 ± 153.62
19 wk	6	47.20 ± 0.45^	17.67 ± 0.90	37.08 ± 2.28	929.50 ± 162.70
30 wk	3	47.67 ± 1.15	17.70 ± 0.70	37.00 ± 2.23	1110.33 ± 130.11
43 wk	3	48.00 ± 1.00	18.50 ± 0.00^$^{/C2*}$	37.70 ± 1.15	1133.67 ± 46.61
Treatment group 2: 5 wk	10	49.20 ± 1.23$^{C1*/C2*}$	18.68 ± 0.52	38.03 ± 1.64	870.44 ± 38.83^
11 wk	7	47.00 ± 1.00	17.63 ± 0.60	37.69 ± 1.71	693.57 ± 226.99
19 wk	7	47.57 ± 1.40	18.01 ± 0.46	38.47 ± 1.34^	873.17 ± 90.74^
30 wk	4	47.00 ± 0.00^	18.50 ± 0.57	39.13 ± 0.83	1086.25 ± 76.59
43 wk	4	47.50 ± 1.29	17.90 ± 0.00^	37.75 ± 1.19	1278.50 ± 89.12
Treatment group 3: 5 wk	10	48.67 ± 0.87$^{\wedge/C2*}$	18.42 ± 0.83	37.48 ± 2.49	798.40 ± 121.37
11 wk	7	46.43 ± 0.79	18.14 ± 0.29	39.03 ± 0.67	830.00 ± 73.06^
19 wk	7	46.86 ± 1.21	17.99 ± 0.58	38.41 ± 1.24	917.86 ± 118.00
30 wk	4	48.00 ± 0.00^	18.38 ± 0.40	38.65 ± 0.85	955.50 ± 188.55
43 wk	4	48.00 ± 0.00^	17.60 ± 0.22$^{C1*/T1*}$	37.08 ± 0.53	1062.75 ± 90.16

MCH: mean cell hemoglobin; MCHC: mean cell hemoglobin concentration; MCV: mean cell volume; PLT: platelet count.

Table S15. Hematologic parameters in female mice. Values represent the mean ± SD. The reference values are based on the baseline (-1 wk) measurements. Asterisks show the significance level with *: $p \leq 0.05$.
$^{C1/C2/T1/T2/T3}$ Significant difference as compared with e.g. control group 1 (C1) at the same time point.
^ Outlier excluded from dataset (N = N-1)

Females	N	WBC (10^3/mm^3)	RBC (10^6/mm^3)	HGB (g/dl)	HCT (%)
Reference value	50	7.63 ± 2.25	8.53 ± 0.57^	15.75 ± 0.75	41.69 ± 2.64
Control group 1: 5 wk	10	7.15 ± 0.94^{T3*}	8.36 ± 0.57^	15.76 ± 0.96	40.88 ± 2.65^
11 wk	7	7.71 ± 2.53	9.19 ± 0.38	17.00 ± 0.19^	43.61 ± 1.51
19 wk	7	7.63 ± 0.51^	9.07 ± 0.50	17.00 ± 0.81	42.86 ± 2.27
30 wk	4	9.03 ± 1.48	9.34 ± 0.19	17.00 ± 0.00$^{\wedge/T3}$	44.90 ± 1.64
43 wk	4	8.30 ± 3.68	8.94 ± 0.47	16.00 ± 0.50	42.65 ± 1.82
Control group 2: 5 wk	10	7.27 ± 1.51^{T3*}	8.42 ± 0.39	15.61 ± 0.74^	40.85 ± 3.14
11 wk	7	8.51 ± 2.34	9.01 ± 0.34	16.27 ± 0.49	42.01 ± 1.60
19 wk	7	6.74 ± 3.19	8.57 ± 0.55	15.97 ± 1.00	40.57 ± 2.81
30 wk	4	10.38 ± 2.86	9.30 ± 0.44	16.53 ± 0.51	44.18 ± 2.83
43 wk	4	7.40 ± 0.72^	8.92 ± 0.63	16.38 ± 1.01	42.08 ± 3.01
Treatment group 1: 5 wk	10	6.20 ± 2.24	8.51 ± 0.45	16.19 ± 0.58	41.51 ± 2.18
11 wk	7	7.60 ± 3.77	8.59 ± 0.31^	15.88 ± 0.43^	40.26 ± 1.41
19 wk	7	6.80 ± 1.64	9.37 ± 1.10	16.90 ± 1.83	43.89 ± 5.14
30 wk	4	9.70 ± 2.96	8.71 ± 0.27	16.30 ± 0.52	41.33 ± 0.79
43 wk	3	7.20 ± 3.97	8.91 ± 0.89	16.50 ± 0.66	43.27 ± 3.17
Treatment group 2: 5 wk	10	5.89 ± 2.56	8.70 ± 0.63	16.27 ± 0.78	41.91 ± 3.22
11 wk	7	7.97 ± 2.09	9.05 ± 0.72	16.59 ± 0.85	41.64 ± 3.22
19 wk	7	6.74 ± 1.77	8.61 ± 0.98	15.59 ± 1.56	39.66 ± 4.17
30 wk	4	8.98 ± 1.67	9.07 ± 0.27	16.65 ± 0.31	43.50 ± 1.68
43 wk	4	9.10 ± 3.17	8.96 ± 0.18	15.53 ± 0.85	41.90 ± 1.79
Treatment group 3: 5 wk	10	4.36 ± 1.67$^{C1*/C2*}$	8.75 ± 0.47	16.04 ± 0.44	42.16 ± 2.40
11 wk	7	7.57 ± 1.58	9.04 ± 0.32^	16.56 ± 0.81	43.04 ± 2.97
19 wk	7	7.69 ± 2.31	9.62 ± 1.71	16.44 ± 1.77	44.93 ± 7.28
30 wk	4	7.93 ± 2.49	9.22 ± 0.66	15.83 ± 0.06$^{\wedge/C1*}$	41.13 ± 0.23^
43 wk	4	8.90 ± 3.34	9.72 ± 0.26	15.30 ± 0.29	44.95 ± 1.05

HCT: hematocrit; HGB: hemoglobin;; RBC: red blood cell count; WBC: white blood cell count.

Table S16. Hematologic parameters in female mice. Values represent the mean ± SD. The reference values are based on the baseline (-1 wk) measurements. Asterisks show the significance level with *: $p \leq 0.05$.
$^{C1/C2/T1/T2/T3}$ Significant difference as compared with e.g. control group 1 (C1) at the same time point.
^ Outlier excluded from dataset (N = N-1)

Females	N	MCV (µm³)	MCH (pg)	MCHC (g/dl)	PLT (10^3/mm³)
Reference value	50	48.78 ± 0.65	18.46 ± 0.63	37.77 ± 1.09	665.68 ± 177.78
Control group 1: 5 wk	10	49.10 ± 0.99$^{C2*/T3*}$	18.80 ± 0.44	38.80 ± 0.77^	828.80 ± 209.20
11 wk	7	47.43 ± 0.79^{T2*}	18.34 ± 0.36	38.60 ± 0.55	872.71 ± 104.41
19 wk	7	47.29 ± 0.76	18.76 ± 0.41^{T3*}	39.71 ± 0.84^{T3*}	910.14 ± 153.55
30 wk	4	48.00 ± 0.82	17.98 ± 0.68	37.50 ± 2.07	966.25 ± 201.80
43 wk	4	48.00 ± 0.82	17.95 ± 1.12	37.55 ± 1.74^{T3*}	1041.25 ± 87.21
Control group 2: 5 wk	10	47.50 ± 0.71^{C1*}	18.55 ± 0.34	39.02 ± 0.47	949.60 ± 59.20^{T2*}
11 wk	7	46.57 ± 0.53	18.07 ± 0.29	38.77 ± 0.49	839.00 ± 244.75
19 wk	7	47.14 ± 0.69	18.67 ± 0.50^{T3*}	39.43 ± 1.37	910.29 ± 143.31
30 wk	4	47.75 ± 0.96	17.80 ± 0.91	37.55 ± 2.64	982.75 ± 135.76
43 wk	4	47.00 ± 0.00^	18.35 ± 0.19^{T3*}	38.88 ± 0.59^{T3*}	854.75 ± 343.71
Treatment group 1: 5 wk	10	48.33 ± 0.71^	19.04 ± 0.44^{T3*}	39.05 ± 1.35	774.80 ± 109.24
11 wk	7	46.71 ± 0.95	18.50 ± 0.71	39.76 ± 1.01	722.14 ± 162.36
19 wk	7	46.86 ± 0.69	18.37 ± 0.28^	38.43 ± 1.45	792.14 ± 187.73
30 wk	4	47.00 ± 0.00^	18.75 ± 0.99	39.45 ± 1.74	1011.67 ± 28.22^
43 wk	3	49.00 ± 0.00^	18.60 ± 1.08^{T3*}	38.30 ± 1.30^{T3*}	675.33 ± 129.51
Treatment group 2: 5 wk	10	48.10 ± 0.74	18.74 ± 0.80	38.91 ± 1.70	698.60 ± 200.39^{C2*}
11 wk	7	45.86 ± 0.69^{C1*}	18.37 ± 0.74	39.93 ± 1.51	798.71 ± 116.74
19 wk	7	46.00 ± 1.15	18.16 ± 0.81	39.31 ± 1.26	806.14 ± 175.91
30 wk	4	48.00 ± 0.00^	17.93 ± 0.06^	37.27 ± 0.23^	1028.00 ± 41.41
43 wk	4	46.75 ± 2.06	17.33 ± 1.17	37.05 ± 1.17^{T3*}	952.00 ± 199.80
Treatment group 3: 5 wk	10	48.00 ± 0.82^{C1*}	18.25 ± 0.66^{T1*}	38.14 ± 1.64	764.67 ± 72.21^
11 wk	7	46.43 ± 0.98	17.90 ± 0.63	38.56 ± 1.23	731.29 ± 144.20
19 wk	7	46.86 ± 1.77	17.29 ± 1.56$^{C1*/C2*}$	36.94 ± 2.97^{C1*}	742.14 ± 181.84
30 wk	4	46.50 ± 1.29	17.75 ± 0.42	38.50 ± 0.10^	996.50 ± 96.63
43 wk	4	46.25 ± 0.96	15.90 ± 0.00$^{^/C2*/T1*}$	34.08 ± 0.28$^{C1*/C2*/T1*/T2*}$	763.00 ± 260.79

MCH: mean cell hemoglobin; MCHC: mean cell hemoglobin concentration; MCV: mean cell volume; PLT: platelet count.

Table S17. Clinical chemistry parameters in male mice. Values represent the mean ± SD. The reference values are based on the baseline (-1 wk) measurements. Asterisks show the significance level with *: $p \leq 0.05$.
$^{C1/C2/T1/T2/T3}$ Significant difference as compared with e.g. control group 1 (C1) at the same time point.
^ Outlier excluded from dataset (N = N-1)

		Electrolytes			*Ions*	*Small molecules (nutrition)*	*Small molecules (waste products)*	
Males	**N**	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Calcium (mmol/L)	Glucose (mmol/L)	Creatinine (µmol/L)	Urea (mmol/L)
Reference value	50	166.92 ± 3.52	8.59 ± 0.89	111.34 ± 4.66	2.75 ± 0.10	8.27 ± 1.33	45.30 ± 11.08	6.95 ± 0.85
Control group 1: 5 wk	10	149.30 ± 4.22	6.38 ± 0.84	98.90 ± 6.17	2.36 ± 0.06	5.74 ± 1.24	32.00 ± 12.90	7.05 ± 1.00
11 wk	7	158.57 ± 2.07	7.24 ± 0.32	100.29 ± 1.60	2.37 ± 0.04	5.91 ± 0.64	51.00 ± 19.67	6.39 ± 0.73
19 wk	4	142.50 ± 2.89	6.63 ± 0.48	100.00 ± 4.08	1.99 ± 0.09	5.50 ± 0.58	ND	5.75 ± 0.65
30 wk	4	168.75 ± 4.79	7.00 ± 0.41	111.25 ± 4.79	2.31 ± 0.07	6.50 ± 0.41	21.25 ± 11.81	6.38 ± 0.85
43 wk	4	150.00 ± 0.00	5.50 ± 0.41	100.00 ± 0.00	1.98 ± 0.14	6.38 ± 0.85	ND	8.50 ± 2.12
Control group 2: 5 wk	10	149.10 ± 3.70	6.71 ± 1.10	99.90 ± 7.28	2.38 ± 0.10	6.69 ± 1.54	32.90 ± 16.20	7.17 ± 0.64^
11 wk	7	158.14 ± 1.46	7.33 ± 0.29	100.71 ± 2.93	2.36 ± 0.02^	7.41 ± 2.00	50.14 ± 21.47	5.61 ± 0.86^{T2*}
19 wk	4	140.00 ± 0.00^{T2*}	6.63 ± 0.48	100.00 ± 0.00^	1.96 ± 0.09	5.50 ± 0.00^	ND	5.75 ± 0.65
30 wk	4	165.00 ± 0.00	7.00 ± 0.41	110.00 ± 0.00	2.38 ± 0.12	7.63 ± 0.48	36.25 ± 16.52	6.75 ± 1.55
43 wk	4	151.25 ± 6.29	5.38 ± 0.63	100.00 ± 0.00^	1.98 ± 0.03	6.50 ± 1.47	ND	8.00 ± 2.12
Treatment group 1: 5 wk	10	148.22 ± 3.56^	6.70 ± 1.10	100.00 ± 6.83	2.33 ± 0.05	5.77 ± 1.70	32.80 ± 14.64	7.44 ± 0.85
11 wk	7	158.50 ± 2.95^	7.50 ± 0.55	101.00 ± 1.55^	2.35 ± 0.11	6.56 ± 0.84	70.00 ± 5.25^	6.60 ± 0.60
19 wk	3	145.00 ± 0.00^	6.50 ± 0.00^	100.00 ± 0.00	2.05 ± 0.00^	5.17 ± 0.76	ND	7.00 ± 0.00^
30 wk	3	170.00 ± 0.00	7.00 ± 0.00^	110.00 ± 0.00^	2.37 ± 0.08	6.83 ± 1.04	35.00 ± 13.23	7.50 ± 0.00
43 wk	3	150.00 ± 0.00^	6.00 ± 0.00^	100.00 ± 0.00^	2.02 ± 0.10	6.17 ± 1.89	ND	7.50 ± 0.00^
Treatment group 2: 5 wk	10	150.11 ± 2.32^	6.26 ± 0.79	100.30 ± 5.87	2.38 ± 0.10	5.13 ± 1.11	35.70 ± 11.01	7.46 ± 1.14
11 wk	7	160.71 ± 2.36	7.25 ± 0.23^	103.71 ± 2.36	2.37 ± 0.03^	5.31 ± 1.34	ND	7.24 ± 1.41^{C2*}
19 wk	4	147.50 ± 2.89^{C2*}	6.50 ± 0.00^	105.00 ± 0.00^	2.06 ± 0.09	5.75 ± 0.65	ND	7.13 ± 0.85
30 wk	4	165.00 ± 0.00^	7.25 ± 0.29	110.00 ± 0.00^	2.25 ± 0.00^	6.63 ± 2.10	42.50 ± 25.98	8.00 ± 1.35
43 wk	4	150.00 ± 4.08	6.75 ± 2.06	100.00 ± 0.00^	1.98 ± 0.13	5.25 ± 0.87	ND	7.33 ± 1.26^
Treatment group 3: 5 wk	10	150.20 ± 4.44	6.27 ± 0.75	99.80 ± 8.98	2.36 ± 0.07	5.60 ± 2.45	31.50 ± 16.08	7.59 ± 1.51
11 wk	7	159.00 ± 2.45	7.24 ± 0.50	102.00 ± 2.45	2.42 ± 0.08	6.09 ± 1.80	ND	6.77 ± 0.71
19 wk	4	143.75 ± 4.79	6.25 ± 0.29	100.00 ± 0.00^	2.05 ± 0.14	4.75 ± 0.87	ND	7.25 ± 0.87
30 wk	4	166.25 ± 6.29	7.00 ± 0.00^	110.00 ± 4.08	2.30 ± 0.11	6.88 ± 1.89	30.00 ± 15.81	6.50 ± 0.00^
43 wk	4	150.00 ± 4.08	5.13 ± 0.63	100.00 ± 0.00^	2.00 ± 0.00	6.13 ± 1.65	ND	6.75 ± 1.04

ND: Not determined. (Value was below detection limit.)

Table S18. Clinical chemistry parameters in male mice. Values represent the mean ± SD. The reference values are based on the baseline (-1 wk) measurements. Asterisks show the significance level with *: $p \leq 0.05$.
$^{C1/C2/T1/T2/T3}$ Significant difference as compared with e.g. control group 1 (C1) at the same time point.
^ Outlier excluded from dataset (N = N-1)

		Proteins (general)	*Proteins (enzymes)*					*Lipids*
Males	**N**	Total Protein (g/L)	ALT (U/L)	AST (U/L)	Alk. Phosphatase (U/L)	Amylase (U/L)	Lipase (U/L)	Cholesterol (mmol/L)
Reference value	50	62.70 ± 3.11	37.84 ± 10.74^	221.33 ± 152.18^	202.78 ± 21.39^	3821.14 ± 922.61^	34.80 ± 4.16	3.60 ± 0.32
Control group 1: 5 wk	10	48.50 ± 3.21	38.22 ± 6.14^	86.90 ± 21.42^{T1*}	120.44 ± 8.59$^{\wedge/T3*}$	2537.80 ± 263.31	27.20 ± 2.82	3.00 ± 0.22
11 wk	7	54.00 ± 0.00^	42.00 ± 6.00	136.29 ± 55.96	98.14 ± 8.25	2586.00 ± 69.30^	29.57 ± 2.70	3.00 ± 0.00^
19 wk	4	42.50 ± 6.45	ND	88.75 ± 11.09	70.00 ± 0.00$^{\wedge/T2*/T3*}$	2075.00 ± 37.75^	12.50 ± 6.45	2.50 ± 0.00^
30 wk	4	50.00 ± 4.08^{C2*}	23.83 ± 0.29^	110.00 ± 25.50	72.50 ± 6.45	2667.50 ± 251.35	33.75 ± 6.29	2.50 ± 0.00^
43 wk	4	45.00 ± 4.08	58.75 ± 17.97	81.25 ± 30.92	72.50 ± 6.45	2458.75 ± 46.08 ^{T1*}	25.00 ± 0.00^	2.50 ± 0.41
Control group 2: 5 wk	10	48.60 ± 1.78	50.20 ± 16.17	119.56 ± 53.82^	117.70 ± 8.30	2488.67 ± 189.94^	29.20 ± 3.68^{T3*}	2.84 ± 0.15^
11 wk	7	54.86 ± 1.46	40.71 ± 7.32	111.50 ± 30.02^	100.29 ± 7.72	2499.00 ± 138.83^	25.29 ± 2.93	2.87 ± 0.24
19 wk	4	46.25 ± 4.79	ND	158.75 ± 58.65	62.50 ± 6.45$^{T2*/T3**}$	2016.25 ± 219.79	20.00 ± 7.07	2.38 ± 0.48
30 wk	4	55.00 ± 0.00^{C1*}	31.25 ± 6.29	136.25 ± 53.44	80.00 ± 7.07	2700.00 ± 135.83	32.50 ± 6.45	2.75 ± 0.29
43 wk	4	45.00 ± 0.00^	50.00 ± 16.83	65.00 ± 19.58	67.50 ± 2.89	2427.50 ± 167.21^{T1*}	25.00 ± 0.00^	2.50 ± 0.00^
Treatment group 1: 5 wk	10	49.40 ± 2.41	48.44 ± 11.20^	158.70 ± 85.00 ^{C1*}	114.00 ± 8.28^	2539.56 ± 142.08^	27.07 ± 4.24^	3.02 ± 0.23
11 wk	7	53.57 ± 3.64^{T3*}	42.00 ± 4.58	149.57 ± 51.97	98.57 ± 4.04	2644.00 ± 166.86$^{\wedge/T2*}$	30.50 ± 2.26^	2.87 ± 0.24
19 wk	3	40.00 ± 0.00^	ND	93.33 ± 23.63	70.00 ± 0.00^	2098.33 ± 102.63	25.00 ± 13.23	2.50 ± 0.00^
30 wk	3	55.00 ± 0.00^	25.00 ± 0.00^	80.00 ± 22.91	85.00 ± 10.00	3003.33 ± 122.51	35.00 ± 5.00	2.50 ± 0.00^
43 wk	3	45.00 ± 0.00^	40.00 ± 0.00^	113.33 ± 27.57	68.33 ± 20.82	2970.00 ± 0.00$^{\wedge/C1*/C2*/T3*}$	36.67 ± 12.58	2.50 ± 0.00
Treatment group 2: 5 wk	10	51.20 ± 3.26	43.67 ± 9.67^	146.40 ± 38.81	112.40 ± 16.22	2535.80 ± 223.82	24.98 ± 4.66	3.13 ± 0.41
11 wk	7	56.14 ± 2.27	36.86 ± 2.85	117.00 ± 41.82	96.86 ± 9.44	2424.43 ± 133.11^{T1*}	25.71 ± 2.93	3.04 ± 0.21
19 wk	4	45.00 ± 0.00^	ND	106.25 ± 56.77	85.00 ± 0.00$^{\wedge/C1*/C2*}$	2172.50 ± 97.77	18.75 ± 8.54	2.50 ± 0.00
30 wk	4	50.00 ± 0.00^	32.63 ± 8.42	152.50 ± 72.63	80.00 ± 0.00	2852.50 ± 169.53	35.00 ± 13.54	2.50 ± 0.00
43 wk	4	47.50 ± 2.89	53.75 ± 20.56	93.75 ± 8.54	75.00 ± 15.81	2566.25 ± 206.74	33.75 ± 11.81	2.50 ± 0.00^
Treatment group 3: 5 wk	10	49.50 ± 2.42	46.70 ± 13.01	116.80 ± 47.99	103.20 ± 13.73^{C1*}	2547.22 ± 278.84^	22.50 ± 3.27^{C2*}	3.15 ± 0.34
11 wk	7	57.43 ± 2.07^{T1*}	44.14 ± 4.14	102.86 ± 34.63	99.43 ± 5.59	2533.50 ± 45.96^	27.00 ± 4.90	3.04 ± 0.27
19 wk	4	48.75 ± 6.29	ND	88.75 ± 40.29	83.75 ± 7.50$^{C1*/C2**}$	2346.67 ± 32.53^	23.75 ± 7.50	2.50 ± 0.41
30 wk	4	50.00 ± 0.00^	30.00 ± 0.00^	117.50 ± 32.02	87.50 ± 8.66	2842.50 ± 114.20	30.00 ± 7.07	2.75 ± 0.29
43 wk	4	45.00 ± 0.00^	63.75 ± 24.96	97.50 ± 49.41	80.00 ± 17.80	2453.75 ± 188.74^{T1*}	30.00 ± 7.07	2.50 ± 0.00^

ND: Not determined. (Value was below detection limit.)

Table S19. Clinical chemistry parameters in female mice. Values represent the mean ± SD. The reference values are based on the baseline (-1 wk) measurements. Asterisks show the significance level with *: $p \leq 0.05$.
$^{C1/C2/T1/T2/T3}$ Significant difference as compared with e.g. control group 1 (C1) at the same time point.
^ Outlier excluded from dataset (N = N-1)

		Electrolytes			*Ions*	*Small molecules (nutrition)*	*Small molecules (waste products)*	
Females	**N**	Sodium (mmol/L)	Potassium (mmol/L)	Chloride (mmol/L)	Calcium (mmol/L)	Glucose (mmol/L)	Creatinine (µmol/L)	Urea (mmol/L)
Reference value	25	172.32 ± 4.25	8.18 ± 0.80	106.68 ± 2.75	2.61 ± 0.12	7.24 ± 0.76	51.64 ± 10.42	7.41 ± 1.11
Control group 1: 5 wk	10	142.20 ± 3.22$^{T2**/T3**}$	9.75 ± 1.76	102.30 ± 2.63$^{T2*/T3*}$	2.24 ± 0.07	5.10 ± 1.16	39.30 ± 3.59	7.71 ± 1.32^{T2*}
11 wk	7	150.00 ± 0.00	7.11 ± 0.79	99.00 ± 0.00	2.29 ± 0.07	4.76 ± 0.59	69.86 ± 13.93	6.20 ± 0.73^
19 wk	7	142.86 ± 4.88	5.71 ± 0.76	100.71 ± 3.45	2.13 ± 0.11	5.50 ± 1.12	ND	6.29 ± 0.95^{T3**}
30 wk	4	167.50 ± 2.89	6.75 ± 0.29	110.00 ± 0.00	2.34 ± 0.06	6.38 ± 0.48	40.00 ± 14.72	6.38 ± 0.85
43 wk	4	150.00 ± 0.00	5.00 ± 0.41	105.00 ± 0.00^$^{/T1*/T2*}$	2.01 ± 0.07	5.88 ± 1.31	37.00 ± 1.73^	6.50 ± 0.00^
Control group 2: 5 wk	10	144.60 ± 3.10	8.52 ± 1.83	104.10 ± 2.47^{T2*}	2.22 ± 0.06	4.95 ± 1.06	38.70 ± 4.79	7.83 ± 0.88^{T2*}
11 wk	7	145.29 ± 7.52$^{T2*/T3*}$	7.07 ± 0.62	97.29 ± 6.21	2.24 ± 0.13^{T2*}	5.40 ± 1.04	69.86 ± 25.96	7.07 ± 1.19
19 wk	7	147.14 ± 2.67	5.71 ± 1.15	103.57 ± 2.44	2.11 ± 0.13	5.79 ± 0.39	ND	6.14 ± 0.38^{T3**}
30 wk	4	165.00 ± 4.08	6.75 ± 0.29	112.50 ± 2.89	2.35 ± 0.06	6.50 ± 1.08	23.75 ± 7.50	7.00 ± 0.00^
43 wk	4	145.00 ± 5.00^	4.38 ± 1.03	101.67 ± 2.89^	2.02 ± 0.06^	5.00 ± 2.08	28.00 ± 4.24	6.17 ± 0.76^
Treatment group 1: 5 wk	10	142.50 ± 2.92$^{T2**/T3*}$	9.09 ± 1.84	102.60 ± 3.10$^{T2*/T3*}$	2.22 ± 0.07	4.50 ± 1.49	37.20 ± 9.61	6.84 ± 1.27$^{T2***/T3**}$
11 wk	7	150.00 ± 0.00	7.37 ± 0.45	100.71 ± 1.60	2.27 ± 0.08	5.96 ± 0.74^{T2*}	56.14 ± 22.30	7.24 ± 1.10
19 wk	7	142.86 ± 2.67	5.64 ± 0.94	102.86 ± 2.67	2.14 ± 0.12	5.93 ± 1.06	ND	7.29 ± 1.04
30 wk	4	165.00 ± 0.00^	7.50 ± 0.00^	111.25 ± 4.79	2.33 ± 0.03	6.50 ± 1.22	37.50 ± 24.66	7.00 ± 1.78
43 wk	3	145.00 ± 0.00^	5.00 ± 0.00^	100.00 ± 0.00^$^{/C1*/T3*}$	2.05 ± 0.00^	6.83 ± 1.04	33.00 ± 0.00^	6.00 ± 0.00^
Treatment group 2: 5 wk	10	147.90 ± 2.47$^{C1**/T1**}$	8.04 ± 1.38	108.30 ± 2.63$^{C1*/C2*/T1*}$	2.28 ± 0.07	5.91 ± 1.17	36.30 ± 3.59	9.48 ± 0.83$^{C1*/C2*/T1***}$
11 wk	7	152.57 ± 4.72^{C2*}	7.33 ± 0.62	100.71 ± 3.82	2.40 ± 0.10^{C2*}	4.60 ± 0.41^$^{/T1*}$	73.29 ± 19.12	7.41 ± 0.62
19 wk	7	143.57 ± 3.78	5.71 ± 1.04	102.14 ± 2.67	2.10 ± 0.16	6.00 ± 0.82	ND	6.64 ± 1.07^{T3*}
30 wk	4	165.00 ± 0.00^	7.38 ± 0.48	110.00 ± 0.00^	2.41 ± 0.05	7.13 ± 0.48	61.25 ± 18.87	7.50 ± 0.71
43 wk	4	150.00 ± 7.07	5.25 ± 0.65	100.00 ± 0.00^$^{/C1*/T3*}$	2.15 ± 0.20	5.88 ± 0.95	34.00 ± 9.59	8.13 ± 2.95
Treatment group 3: 5 wk	10	147.30 ± 4.11$^{C1**/T1*}$	8.19 ± 1.94	107.10 ± 3.75$^{C1*/T1*}$	2.25 ± 0.08	5.28 ± 1.42	35.40 ± 4.86	8.94 ± 1.32^{T1**}
11 wk	7	153.00 ± 3.46^{C2*}	7.67 ± 0.52	101.14 ± 2.27	2.37 ± 0.08	5.57 ± 1.02	72.00 ± 25.40	7.97 ± 1.26
19 wk	7	143.57 ± 2.44	5.86 ± 0.90	102.86 ± 2.67	2.08 ± 0.08	6.43 ± 1.17	ND	8.50 ± 1.80$^{C1**/C2**/T2*}$
30 wk	4	167.50 ± 2.89	7.13 ± 0.48	112.50 ± 2.89	2.39 ± 0.05	7.00 ± 0.41	37.50 ± 22.17	9.25 ± 2.40
43 wk	4	150.00 ± 0.00^	5.75 ± 1.19	105.00 ± 0.00^$^{/T1*/T2*}$	2.10 ± 0.05^	9.50 ± 4.38	36.75 ± 7.09	8.63 ± 2.56

ND: Not determined. (Value was below detection limit.)

Table S20. Clinical chemistry parameters in female mice. Values represent the mean ± SD. The reference values are based on the baseline (-1 wk) measurements. Asterisks show the significance level with *: $p \leq 0.05$.
$^{C1/C2/T1/T2/T3}$ Significant difference as compared with e.g. control group 1 (C1) at the same time point.
^ Outlier excluded from dataset (N = N-1)

		Proteins (general)	*Proteins (enzymes)*					*Lipids*
Females	**N**	Total Protein (g/L)	ALT (U/L)	AST (U/L)	Alk. Phosphatase (U/L)	Amylase (U/L)	Lipase (U/L)	Cholesterol (mmol/L)
Reference value	25	56.72 ± 3.12	36.36 ± 10.22	236.08 ± 104.44^	187.17 ± 21.50^	3043.58 ± 362.10^	33.32 ± 3.29	2.94 ± 0.28
Control group 1: 5 wk	10	48.30 ± 3.30	34.00 ± 15.66^	137.40 ± 57.25	103.67 ± 4.27^	2264.10 ± 320.44	25.50 ± 3.54$^{T2*/T3*}$	2.43 ± 0.22
11 wk	7	51.86 ± 1.46	33.00 ± 9.64	142.50 ± 56.63^	94.71 ± 9.93	2343.50 ± 56.65^	24.00 ± 2.45	2.19 ± 0.23
19 wk	7	47.14 ± 5.67	ND	100.00 ± 39.48	73.57 ± 5.56	2177.14 ± 88.59	22.86 ± 15.24	1.79 ± 0.27
30 wk	4	55.00 ± 0.00^	25.38 ± 3.50	115.00 ± 12.91	80.00 ± 12.25	2872.50 ± 241.95	35.00 ± 4.08	2.00 ± 0.00^
43 wk	4	45.00 ± 0.00^	52.50 ± 16.58	105.00 ± 30.28	77.50 ± 9.57	2368.75 ± 192.67	35.00 ± 5.77	1.75 ± 0.29
Control group 2: 5 wk	10	48.00 ± 2.00	35.33 ± 15.06^	159.90 ± 75.14	100.20 ± 6.96	2394.00 ± 456.64	23.70 ± 1.70	2.46 ± 0.13
11 wk	7	49.29 ± 2.93^{T2*}	33.00 ± 4.58	156.43 ± 55.17	84.43 ± 7.63	2479.00 ± 508.35^	22.71 ± 2.36	2.23 ± 0.24
19 wk	7	45.71 ± 6.07	ND	113.57 ± 40.28	73.57 ± 9.88	2310.00 ± 387.62	17.14 ± 8.09	1.86 ± 0.38
30 wk	4	52.50 ± 2.89	23.00 ± 0.87^	97.50 ± 17.56	86.25 ± 8.54	2881.25 ± 244.76	30.00 ± 0.00^	2.00 ± 0.00
43 wk	4	41.25 ± 11.09	38.75 ± 8.54	87.50 ± 22.55	71.25 ± 14.93^{T3*}	2196.25 ± 660.32	32.50 ± 8.66	2.00 ± 0.00^
Treatment group 1: 5 wk	10	47.70 ± 3.86	30.67 ± 7.76^	146.33 ± 50.91^	104.70 ± 11.61	2207.00 ± 90.54^	24.60 ± 2.76^{T2*}	2.52 ± 0.15
11 wk	7	50.14 ± 1.46^{T2*}	31.71 ± 8.64	168.43 ± 97.85	85.71 ± 8.98	2291.50 ± 234.84^	22.71 ± 5.44	2.23 ± 0.24
19 wk	7	45.00 ± 5.00	ND	93.57 ± 26.41	68.75 ± 4.76	2194.29 ± 115.59	18.57 ± 10.69	1.79 ± 0.27
30 wk	4	50.00 ± 0.00^	26.75 ± 10.37	177.50 ± 166.76	75.00 ± 0.00^	2801.25 ± 269.86	32.50 ± 2.89	2.00 ± 0.00^
43 wk	3	45.00 ± 5.00	80.00 ± 27.84	98.33 ± 10.41	86.67 ± 16.07	2558.33 ± 396.78	30.00 ± 0.00^	1.50 ± 0.00^
Treatment group 2: 5 wk	10	48.60 ± 3.95	39.67 ± 16.14^	166.00 ± 42.43^	96.60 ± 11.73	2298.30 ± 208.47	20.10 ± 4.01$^{C1*/T1*}$	2.67 ± 0.26
11 wk	7	54.00 ± 3.00$^{C2*/T1*}$	32.57 ± 8.90	168.00 ± 92.01	92.57 ± 8.90	2444.50 ± 166.64^	22.71 ± 2.93	2.49 ± 0.29
19 wk	7	43.57 ± 6.27	ND	121.43 ± 62.70	75.00 ± 8.16	2123.57 ± 314.48	16.43 ± 9.88	1.86 ± 0.24
30 wk	4	52.50 ± 2.89	31.88 ± 9.44	203.75 ± 113.31	87.50 ± 8.66	2660.00 ± 124.30	43.75 ± 4.79	2.50 ± 0.00^
43 wk	4	46.25 ± 6.29	65.00 ± 30.00	96.25 ± 34.73	88.75 ± 7.50	2225.00 ± 21.79^	33.75 ± 4.79	2.00 ± 0.00^
Treatment group 3: 5 wk	10	48.30 ± 4.11	38.33 ± 12.53	192.00 ± 67.84	96.00 ± 15.81	2403.60 ± 343.28	21.00 ± 4.69^{C1*}	2.47 ± 0.13^
11 wk	7	51.00 ± 3.00	38.57 ± 10.88	179.14 ± 76.54	93.00 ± 4.65^	2658.00 ± 343.28	25.29 ± 5.15	2.49 ± 0.33
19 wk	7	41.43 ± 2.44	ND	124.29 ± 33.59	81.43 ± 10.69	2228.57 ± 261.88	16.43 ± 10.69	2.00 ± 0.29
30 wk	4	52.50 ± 2.89	28.75 ± 8.33	156.25 ± 76.63	90.00 ± 9.13	2912.50 ± 427.40	36.25 ± 10.31	2.38 ± 0.48
43 wk	4	45.00 ± 0.00^	80.00 ± 27.99	135.00 ± 64.16	110.00 ± 26.46^{C2*}	2690.00 ± 667.66	45.00 ± 0.00^	2.00 ± 0.71

ND: Not determined. (Value was below detection limit.)