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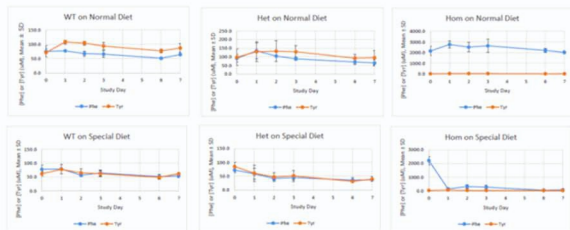
## **Supplemental information**

### **Development of an mRNA**

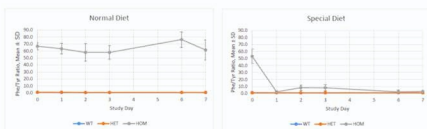
#### **replacement therapy for phenylketonuria**

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A



B



C

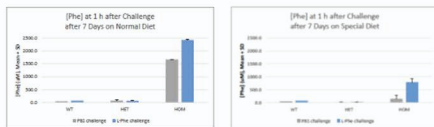
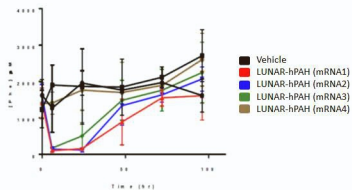


Figure S1. Phenylalanine metabolic characterization in WT, and heterozygous (Het) and homozygous (Hom) BTBR- Pahenu2 mice under normal or special Phe-restricted diet. A: Phe (blue) and Tyr (orange) plasma levels were measured for a week at 24 hours intervals under normal (top graphs) or special Phe-free diet (bottom graphs) in WT (left), Het Pahenu2 (middle) and Hom Pahenu2 (right) mice. B: Calculated Phe:Tyr ratios in WT (blue), Het (Orange) and Hom (gray) mice under normal (left graph) or special Phe-free diet (right graph). C: Plasma Phe levels in WT, Het and Hom Pahenu2 mice 1 hour after being challenge with an IV injection of either PBS or 100 mg/kg of Phe. Prior to the Phe challenge mice were for a week either under normal diet (left graph) or a special Phe-free diet (right graph). (N=10 mice per control group; n=14 mice per group in special diet group; n=6-7 mice per group in C)

A



B

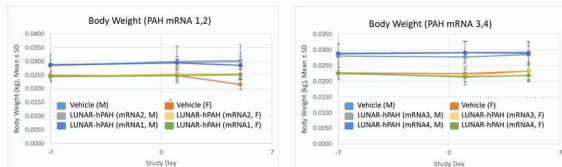


Figure S2. In vivo screening of hPAH using LUNAR<sup>®</sup>-hPAH mRNA (LUNAR 1) formulation in homozygous BTBR- Pahenu2 mice. A: Phe plasma levels and body weight (B) in mice at different time points before and after a 10 mg/kg single dose of LUNAR<sup>®</sup> formulation containing different hPAH mRNA.

A

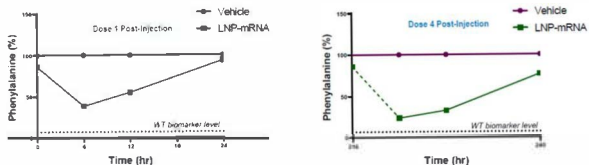


Figure S3. Efficacy of a dose of LUNAR®-hPAH mRNA (LUNAR 1) after repeated dosing. Phe plasma levels were measure at time 0-, 6-, 12- and 24-hours on the first (left graph) and last day of dosing (right graph). Dotted line indicates Phe WT levels. Vehicle indicate mice treated with PBS. (n=4 control, n=12 treated mice per groups)

	11	12	13	14	15
ALP (U/L)	58	43	87	35	54
AST (U/L)	59	70	32	55	58
ALT (U/L)	34	30	43	36	39
Creatine kinase (U/L)	208	308	49	155	168
Albumin (g/dL)	2.5	2.1	2.5	2.6	2.7
Total Bilirubin (mg/dL)	0.2	0.2	0.2	0.3	0.2
Total Protein (g/dL)	4.5	4.0	4.3	4.8	4.5
Globulin (g/dL)	2.0	1.9	1.8	2.2	1.8
Bilirubin - Conjugated (mg/dL)	0.0	0.0	0.0	0.0	0.0
BUN (mg/dL)	18	15	12	18	15
Creatinine (mg/dL)	0.1	0.0 <sup>1</sup>	0.1	0.0 <sup>1</sup>	0.1
Cholesterol (mg/dL)	116	89	105	105	105
Glucose (mg/dL)	280	336	298	334	254
Calcium (mg/dL)	8.7	7.7	9.2	9.3	8.8
Phosphorus (mg/dL)	7.4	7.8	9.6	10.1	7.6
Bicarbonate TCO2 (mmol/L)	20	17	19	21	21
Chloride (mmol/L)	116	see below <sup>3</sup>	115	see below <sup>3</sup>	116
Potassium (mmol/L)	4.7	see below <sup>3</sup>	4.8	see below <sup>3</sup>	6.2
ALB/GLOB ratio	1.3	1.1	1.4	1.2	1.5
Sodium (mmol/L)	153	see below <sup>3</sup>	150	see below <sup>3</sup>	148
BUN/Creatinine Ratio	180.0	0.0	120.0	0.0	150.0
Bilirubin - Unconjugated (mg/dL)	0.2	0.2	0.2	0.3	0.2
NAK Ratio	33	see below <sup>3</sup>	31	see below <sup>3</sup>	24
Hemolysis Index	+	Normal	Normal	+	++
Lipemia Index	Normal	Normal	Normal	Normal	Normal

	26	27	28	29	41
ALP (U/L)	40	38	36	60	93
AST (U/L)	117	72	40	49	49
ALT (U/L)	46	70	37	44	33
Creatine kinase (U/L)	126	126	126	179	147

	26	27	28	29	41
Albumin (g/dL)	2.4	2.4	2.4	2.4	2.5
Total Bilirubin (mg/dL)	0.2	0.2	0.2	0.2	0.1
Total Protein (g/dL)	4.4	4.4	4.2	4.2	4.0
Globulin (g/dL)	2.0	2.0	1.8	1.8	1.5
Bilirubin - Conjugated (mg/dL)	0.0	0.0	0.0	0.0	0.0
BUN (mg/dL)	16	19	15	18	12
Creatinine (mg/dL)	0.1	0.1	0.1 <sup>1</sup>	0.1	0.1
Cholesterol (mg/dL)	136	134	132	127	84
Glucose (mg/dL)	345	251	337	307	322
Calcium (mg/dL)	9.5	9.2	8.8	8.8	8.9
Phosphorus (mg/dL)	10.4	11.5	9.0	9.4	7.3
Bicarbonate TCO2 (mmol/L)	18	19	21	21	19
Chloride (mmol/L)	119	115	114	115	114
Potassium (mmol/L)	6.1	5.8	5.5	6.1	4.9
ALB/GLOB ratio	1.2	1.2	1.3	1.3	1.7
Sodium (mmol/L)	157	153	148	149	145
BUN/Creatinine Ratio	160.0	190.0	150.0	180.0	120.0
Bilirubin - Unconjugated (mg/dL)	0.2	0.2	0.2	0.2	0.1
NAK Ratio	26	26	27	24	30
Hemolysis Index	+	Normal	+	Normal	Normal
Lipemia Index	Normal	Normal	Normal	Normal	Normal

	42	43	44	45	56
ALP (U/L)	65	85	74	79	61
AST (U/L)	205	85	431	88	128
ALT (U/L)	86	32	136	41	54
Creatine kinase (U/L)	551	216	667	321	264
Albumin (g/dL)	3.0	2.8	2.5	2.7	2.8
Total Bilirubin (mg/dL)	0.3	0.1	0.5	0.1	0.3
Total Protein (g/dL)	5.2	4.4	4.4	4.4	4.6
Globulin (g/dL)	2.2	1.6	1.9	1.7	1.8
Bilirubin - Conjugated (mg/dL)	0.0	0.0	0.2	0.0	0.1
BUN (mg/dL)	16	15	15	16	14
Creatinine (mg/dL)	0.0 <sup>1</sup>	0.2 <sup>1</sup>	0.0 <sup>1</sup>	0.1	0.1

	42	43	44	45	56
Cholesterol (mg/dL)	102	92	85	97	110
Glucose (mg/dL)	289	329	243	251	252
Calcium (mg/dL)	10.0	9.4	8.8	9.1	8.9
Phosphorus (mg/dL)	13.2	9.4	10.3	12.9	6.1
Bicarbonate TCO2 (mmol/L)	20	19	20	17	22
Chloride (mmol/L)	see below <sup>3</sup>	114	see below <sup>3</sup>	116	113
Potassium (mmol/L)	see below <sup>3</sup>	5.4	see below <sup>3</sup>	4.6	5.3
ALB/GLOB ratio	1.4	1.8	1.3	1.6	1.6
Sodium (mmol/L)	see below <sup>3</sup>	149	see below <sup>3</sup>	151	148
BUN/Creatinine Ratio	0.0	75.0	0.0	160.0	140.0
Bilirubin - Unconjugated (mg/dL)	0.3	0.1	0.3	0.1	0.2
NAK Ratio	see below <sup>3</sup>	25	see below <sup>3</sup>	31	28
Hemolysis Index	+	Normal	+	+	+
Lipemia Index	Normal	Normal	Normal	Normal	Normal

	57	58	59	60	1
ALP (U/L)	97	106	43	53	39
AST (U/L)	77	95	216	50	678
ALT (U/L)	47	42	85	36	220
Creatine kinase (U/L)	146	291	700	99	8872 <sup>1</sup>
Albumin (g/dL)	2.9	2.8	2.8	2.4	2.5
Total Bilirubin (mg/dL)	0.1	0.2	0.4	0.1	0.3
Total Protein (g/dL)	4.7	4.5	5.0	4.2	4.5
Globulin (g/dL)	1.8	1.7	2.2	1.8	2.0
Bilirubin - Conjugated (mg/dL)	0.0	0.0	0.0	0.0	0.0
BUN (mg/dL)	18	17	18	14	27
Creatinine (mg/dL)	0.1 <sup>1</sup>	0.1	0.0 <sup>1</sup>	0.1 <sup>1</sup>	0.1 <sup>1</sup>
Cholesterol (mg/dL)	110	106	110	98	112
Glucose (mg/dL)	278	290	316	263	252
Calcium (mg/dL)	8.9	9.2	8.9	8.4	8.6
Phosphorus (mg/dL)	7.0	8.7	9.1	11.0	8.2
Bicarbonate TCO2 (mmol/L)	22	20	17	24	16
Chloride (mmol/L)	117	116	see below <sup>3</sup>	116	110
Potassium (mmol/L)	4.9	6.1	see below <sup>3</sup>	5.3	8.0 <sup>1</sup>
ALB/GLOB ratio	1.6	1.6	1.3	1.3	1.3

	57	58	59	60	1
Sodium (mmd/L)	150	150	see below <sup>3</sup>	147	144
BUN/Creatinine Ratio	180.0	170.0	0.0	140.0	270.0
Bilirubin - Unconjugated (mg/dL)	0.1	0.2	0.4	0.1	0.3
NAK Ratio	31	25	see below <sup>3</sup>	28	18
Hemolysis Index	Normal	+	++	Normal	+++
Lipemia Index	Normal	Normal	Normal	Normal	Normal

	2	4	5	16	17
ALP (U/L)	37	42	27	66	21
AST (U/L)	38	47	47	171	901
ALT (U/L)	38	36	41	141	180
Creatine kinase (U/L)	97	96	102	159	see below <sup>2</sup>
Albumin (g/dL)	2.4	2.2	2.4	2.5	2.4
Total Bilirubin (mg/dL)	0.2	0.2	0.3	0.3	0.5
Total Protein (g/dL)	4.6	4.3	4.7	4.6	4.5
Globulin (g/dL)	2.2	2.1	2.3	2.1	2.1
Bilirubin - Conjugated (mg/dL)	0.0	0.0	0.0	0.0	0.1
BUN (mg/dL)	34	22	30	28	16
Creatinine (mg/dL)	0.1 <sup>1</sup>	0.0 <sup>1</sup>	0.1 <sup>1</sup>	0.1	0.1
Cholesterol (mg/dL)	136	103	125	146	125
Glucose (mg/dL)	238	220	273	267	232
Calcium (mg/dL)	9.1	9.1	8.9	9.4	8.2
Phosphorus (mg/dL)	8.6	10.7	11.2	9.4	10.7
Bicarbonate TCO2 (mmol/L)	22	22	19	13	15
Chloride (mmol/L)	112	see below <sup>3</sup>	112	111	110
Potassium (mmol/L)	5.8	see below <sup>3</sup>	6.7	6.5	8.3
ALB/GLOB ratio	1.1	1.0	1.0	1.2	1.1
Sodium (mmd/L)	151	see below <sup>3</sup>	149	150	150
BUN/Creatinine Ratio	340.0	0.0	300.0	280.0	160.0
Bilirubin - Unconjugated (mg/dL)	0.2	0.2	0.3	0.3	0.4
NAK Ratio	26	see below <sup>3</sup>	22	23	18
Hemolysis Index	++	+	+++	+++	++++
Lipemia Index	Normal	Normal	Normal	Normal	Normal

	18	20	31	32	33
ALP (U/L)	29	54	67	60	68
AST (U/L)	105	90	191	70	288
ALT (U/L)	70	88	50	37	120
Creatine kinase (U/L)	235	95	639	165	610
Albumin (g/dL)	2.3	2.6	3.0	2.4	2.9
Total Bilirubin (mg/dL)	0.4	0.3	0.4	0.2	0.3
Total Protein (g/dL)	4.9	5.1	5.2	4.2	4.9
Globulin (g/dL)	2.6	2.5	2.2	1.8	2.0
Bilirubin - Conjugated (mg/dL)	0.0	0.0	0.1	0.0	0.0
BUN (mg/dL)	26	23	22	15	19
Creatinine (mg/dL)	0.0 <sup>1</sup>	0.0 <sup>1</sup>	0.0 <sup>1</sup>	0.0 <sup>1</sup>	0.0 <sup>1</sup>
Cholesterol (mg/dL)	124	130	109	93	96
Glucose (mg/dL)	225	178	272	224	229
Calcium (mg/dL)	8.2	10.2	10.3	7.1	9.9
Phosphorus (mg/dL)	11.6	13.7	11.6	8.2	12.3
Bicarbonate TCO2 (mmol/L)	19	17	19	13	17
Chloride (mmol/L)	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
Potassium (mmol/L)	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
ALB/GLOB ratio	0.9	1.0	1.4	1.3	1.5
Sodium (mmol/L)	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
BUN/Creatinine Ratio	0.0	0.0	0.0	0.0	0.0
Bilirubin - Unconjugated (mg/dL)	0.4	0.3	0.3	0.2	0.3
NAK Ratio	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
Hemolysis Index	**	+	**	Normal	+
Lipemia Index	Normal	Normal	Normal	Normal	Normal

	34	35	46	47	48
ALP (U/L)	68	68	72	54	85
AST (U/L)	74	114	116	100	93
ALT (U/L)	35	81	75	48	59
Creatine kinase (U/L)	199	254	123	239	163
Albumin (g/dL)	3.0	3.0	2.6	2.6	2.9
Total Bilirubin (mg/dL)	0.3	0.2	0.2	0.1	0.3

	34	35	46	47	48
Total Protein (g/dL)	4.9	5.1	4.8	4.6	5.1
Globulin (g/dL)	1.9	2.1	2.2	2.0	2.2
Bilirubin - Conjugated (mg/dL)	0.0	0.0	0.0	0.0	0.0
BUN (mg/dL)	18	84	12	15	15
Creatinine (mg/dL)	0.1 <sup>1</sup>	0.0 <sup>1</sup>	0.0 <sup>1</sup>	0.1	0.0 <sup>1</sup>
Cholesterol (mg/dL)	109	110	106	117	105
Glucose (mg/dL)	325	238	273	261	240
Calcium (mg/dL)	8.3	9.9	9.2	9.9	10.1
Phosphorus (mg/dL)	9.7	13.2	6.1	8.0	12.7
Bicarbonate TCO2 (mmol/L)	21	18	16	16	23
Chloride (mmol/L)	113	see below <sup>3</sup>	see below <sup>3</sup>	114	see below <sup>3</sup>
Potassium (mmol/L)	6.3	see below <sup>3</sup>	see below <sup>3</sup>	6.6	see below <sup>3</sup>
ALB/GLOB ratio	1.6	1.4	1.2	1.3	1.3
Sodium (mmol/L)	147	see below <sup>3</sup>	see below <sup>3</sup>	147	see below <sup>3</sup>
BUN/Creatinine Ratio	180.0	0.0	0.0	150.0	0.0
Bilirubin - Unconjugated (mg/dL)	0.3	0.2	0.2	0.1	0.3
NAK Ratio	23	see below <sup>3</sup>	see below <sup>3</sup>	31	see below <sup>3</sup>
Hemolysis Index	++++	+	+	Normal	+
Lipemia Index	Normal	Normal	Normal	Normal	Normal

	6	7	8	9	10
ALP (U/L)	30	31	31	47	42
AST (U/L)	136	90	147	340	110
ALT (U/L)	92	44	73	111	47
Creatine kinase (U/L)	326	241	354	1782	439
Albumin (g/dL)	2.3	2.8	2.3	2.8	2.4
Total Bilirubin (mg/dL)	0.2	0.2	0.3	0.3	0.3
Total Protein (g/dL)	4.5	4.8	4.3	5.1	4.6
Globulin (g/dL)	2.2	2.0	2.0	2.3	2.2
Bilirubin - Conjugated (mg/dL)	0.0	0.1	0.1	0.0	0.0
BUN (mg/dL)	21	18	18	21	29
Creatinine (mg/dL)	0.1 <sup>1</sup>	0.1 <sup>1</sup>	0.0 <sup>1</sup>	0.0 <sup>1</sup>	0.0 <sup>1</sup>
Cholesterol (mg/dL)	124	132	106	110	110
Glucose (mg/dL)	265	269	223	292	205
Calcium (mg/dL)	8.8	9.0	7.7	9.3	8.6

	6	7	8	9	10
Phosphorus (mg/dL)	7.8	7.6	6.0	7.3	8.8
Bicarbonate TCO2 (mmol/L)	20	23	18	26	22
Chloride (mmol/L)	112	111	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
Potassium (mmol/L)	6.5	6.4	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
ALBGLOB ratio	1.0	1.4	1.2	1.2	1.1
Sodium (mmol/L)	149	149	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
BUN/Creatinine Ratio	210.0	180.0	0.0	0.0	0.0
Bilirubin - Unconjugated (mg/dL)	0.2	0.1	0.2	0.3	0.3
NAK Ratio	23	23	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
Hemolysis Index	+	++	+	+	+
Lipemia Index	Normal	Normal	Normal	Normal	Normal

	21	22	23	24	25
ALP (U/L)	44	37	42	42	78
AST (U/L)	45	55	115	77	74
ALT (U/L)	31	42	47	31	35
Creatine kinase (U/L)	226	261	346	299	341
Albumin (g/dL)	2.4	2.4	2.4	2.3	2.6
Total Bilirubin (mg/dL)	0.2	0.3	0.3	0.2	0.2
Total Protein (g/dL)	4.7	4.6	4.5	4.4	4.9
Globulin (g/dL)	2.3	2.2	2.1	2.1	2.3
Bilirubin - Conjugated (mg/dL)	0.1	0.0	0.0	0.0	0.0
BUN (mg/dL)	15	21	23	15	17
Creatinine (mg/dL)	0.1 <sup>1</sup>	0.1 <sup>1</sup>	0.0 <sup>1</sup>	0.1 <sup>1</sup>	0.0 <sup>1</sup>
Cholesterol (mg/dL)	114	147	115	117	152
Glucose (mg/dL)	222	257	275	241	291
Calcium (mg/dL)	8.1	8.9	8.3	8.4	9.9
Phosphorus (mg/dL)	6.9	7.5	7.8	8.7	9.0
Bicarbonate TCO2 (mmol/L)	20	22	18	17	24
Chloride (mmol/L)	111	113	see below <sup>3</sup>	114	see below <sup>3</sup>
Potassium (mmol/L)	5.2	5.6	see below <sup>3</sup>	4.7	see below <sup>3</sup>
ALBGLOB ratio	1.0	1.1	1.1	1.1	1.1
Sodium (mmol/L)	148	149	see below <sup>3</sup>	149	see below <sup>3</sup>
BUN/Creatinine Ratio	150.0	210.0	0.0	150.0	0.0

	21	22	23	24	25
Bilirubin - Unconjugated (mg/dL)	0.1	0.3	0.3	0.2	0.2
NAK Ratio	29	27	see below <sup>3</sup>	32	see below <sup>3</sup>
Hemolysis Index	Normal	++	+	Normal	Normal
Lipemia Index	Normal	Normal	Normal	Normal	Normal

	36	37	38	39	40
ALP (U/L)	78	81	56	71	67
AST (U/L)	123	78	65	47	253
ALT (U/L)	44	44	43	34	73
Creatine kinase (U/L)	458	306	124	135	1475
Albumin (g/dL)	2.8	3.0	2.8	3.0	2.6
Total Bilirubin (mg/dL)	0.2	0.2	0.1	0.1	0.2
Total Protein (g/dL)	4.7	5.1	5.0	5.3	4.6
Globulin (g/dL)	1.9	2.1	2.2	2.3	2.0
Bilirubin - Conjugated (mg/dL)	0.0	0.1	0.0	0.0	0.0
BUN (mg/dL)	16	13	20	14	15
Creatinine (mg/dL)	0.0 <sup>1</sup>	0.0 <sup>1</sup>	0.0 <sup>1</sup>	0.0 <sup>1</sup>	0.0 <sup>1</sup>
Cholesterol (mg/dL)	100	113	109	118	87
Glucose (mg/dL)	297	292	328	347	243
Calcium (mg/dL)	8.4	10.2	9.6	9.9	8.3
Phosphorus (mg/dL)	6.4	7.2	6.1	6.8	6.9
Bicarbonate TCO2 (mmol/L)	18	22	25	26	19
Chloride (mmol/L)	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
Potassium (mmol/L)	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
ALBGLOB ratio	1.5	1.4	1.3	1.3	1.3
Sodium (mmol/L)	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
BUN/Creatinine Ratio	0.0	0.0	0.0	0.0	0.0
Bilirubin - Unconjugated (mg/dL)	0.2	0.1	0.1	0.1	0.2
NAK Ratio	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>	see below <sup>3</sup>
Hemolysis Index	Normal	Normal	Normal	Normal	+
Lipemia Index	Normal	Normal	Normal	Normal	Normal

	51	52	53	54	55
ALP (U/L)	63	50	55	44	67



	51	52	53	54	55
AST (U/L)	39	167	37	152	47
ALT (U/L)	34	55	32	48	32
Creatine kinase (U/L)	76	639	68	571	139
Albumin (g/dL)	2.7	2.5	2.7	2.7	2.7
Total Bilirubin (mg/dL)	0.1	0.2	0.2	0.2	0.1
Total Protein (g/dL)	5.0	4.6	4.9	4.9	4.5
Globulin (g/dL)	2.3	2.1	2.2	2.2	1.8
Bilirubin - Conjugated (mg/dL)	0.0	0.0	0.1	0.0	0.0
BUN (mg/dL)	19	17	13	16	18
Creatinine (mg/dL)	0.0 <sup>1</sup>	0.0 <sup>1</sup>	0.1 <sup>1</sup>	0.0 <sup>1</sup>	0.1 <sup>1</sup>
Cholesterol (mg/dL)	109	105	105	104	108
Glucose (mg/dL)	323	331	275	269	240
Calcium (mg/dL)	10.1	9.0	9.8	9.4	9.4
Phosphorus (mg/dL)	5.8	6.3	7.2	7.7	9.5
Bicarbonate TCO2 (mmol/L)	26	25	20	21	20
Chloride (mmol/L)	see below <sup>3</sup>	see below <sup>3</sup>	113	see below <sup>3</sup>	111
Potassium (mmol/L)	see below <sup>3</sup>	see below <sup>3</sup>	4.5	see below <sup>3</sup>	4.5
ALB/GLOB ratio	1.2	1.2	1.2	1.2	1.5
Sodium (mmol/L)	see below <sup>3</sup>	see below <sup>3</sup>	151	see below <sup>3</sup>	146
BUN/Creatinine Ratio	0.0	0.0	130.0	0.0	180.0
Bilirubin - Unconjugated (mg/dL)	0.1	0.2	0.1	0.2	0.1
NA/K Ratio	see below <sup>3</sup>	see below <sup>3</sup>	34	see below <sup>3</sup>	32
Hemolysis Index	Normal	Normal	Normal	+	Normal
Lipemia Index	Normal	Normal	Normal	Normal	Normal

Figure S4. Full panel of clinical chemistry analytes analyzed to evaluate effect of LUNAR®-hPAH mRNA (LUNAR 1) delivery in liver and kidney markers (n=15 mice per group).