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Supplementary Materials for

A Peptidomimetic Targeting White Fat Causes Weight Loss and Improved Insulin Resistance in Obese Monkeys

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The PDF file includes:

Supplementary Materials and Methods

Body weight and anthropomorphic measurements

Crown-rump length, abdominal circumference, and chest circumference were measured with the monkey in right lateral recumbency. Crown-rump length was calculated as the distance from the crown to the junction of the spine and tail. Abdominal and chest circumference were determined at the level of the umbilicus and the mammary glands, respectively. Upper and lower abdominal skin fold thickness was measured in dorsal recumbency with callipers above and below the umbilicus. Additional anthropomorphic measurements that included thigh circumference, upper arm circumference, triceps skin fold and scapular skin fold thickness were carried out as described (*S1*). The BMI of rhesus monkeys was calculated by division of the body weight, measured in kg by the crown-rump length, measured in m^2 (*S2*).

Clinical pathology

Blood samples for hematology, serum chemistry, and coagulation analysis, as well as urine samples for urinalysis, were collected from each monkey immediately prior to the onset of dosing and weekly throughout the dosing and recovery intervals for all studies. Blood samples were obtained from the femoral vein after a 12-hour fast. During the collection procedure, the monkeys were anesthetized with ketamine hydrochloride or tiletamine plus zolazepam (Telazol®). Complete blood counts were performed on an Advia 120 Hematology Analyzyer. All serum chemistry analytes were analyzed on an Olympus AU400^e instrument with the exception of lipid analytes (cholesterol, triglyceride, high density lipoprotein, and low density lipoprotein), which were measured on a Dade Behring Vista instrument. A coagulation panel that included fibrinogen, antithrombin III, prothrombin time, and activated partial thromboplastin time was performed on a Beckman Coulter ACL 7000 instrument.

Measurement of serum free fatty acids

Total lipid free fatty acids in serum were analyzed by using a gas chromatographer equipped with a flame ionization detector (Kronos Science Laboratory, Phoenix, AZ). Serum free fatty acids (n=28; table S3) were quantitatively analyzed and reported as both a concentration and a percentage of total free fatty acids.

Intravenous glucose tolerance test

To assess the initial metabolic status of each monkey, we obtained fasting blood glucose and insulin levels, and an IVGTT within one week of initial dose administration and within 72 hours of the final dose. Insulin was measured with a chemiluminescent assay. Following a 12-16 hour fast, an IVGTT was performed by intravenous administration of glucose as a 25 g/dl solution (at a concentration of 0.5 g/kg) over 3 min. Insulin and glucose were determined at baseline and 5, 10, 20, 30, 40, 50, and 60 min after the midpoint of the glucose infusion. Glucose was analyzed on an Olympus AU400^{e} instrument, and insulin was measured on a Beckman Coulter DXI instrument. The AUC for insulin was determined with the trapezoidal rule (*S3*).

Statistical methods

Mann-Whitney-Wilcoxon test was used to assess the difference of a numerical variable between treatment groups and a paired t-test was used to assess the difference of a numerical variable between treatment groups at different time points. For numerical variables, a mixed-effects model was fitted with a group-by-time interaction to assess the changes over time between treatment groups (*S4*).

Supplementary Figures

Fig. S1

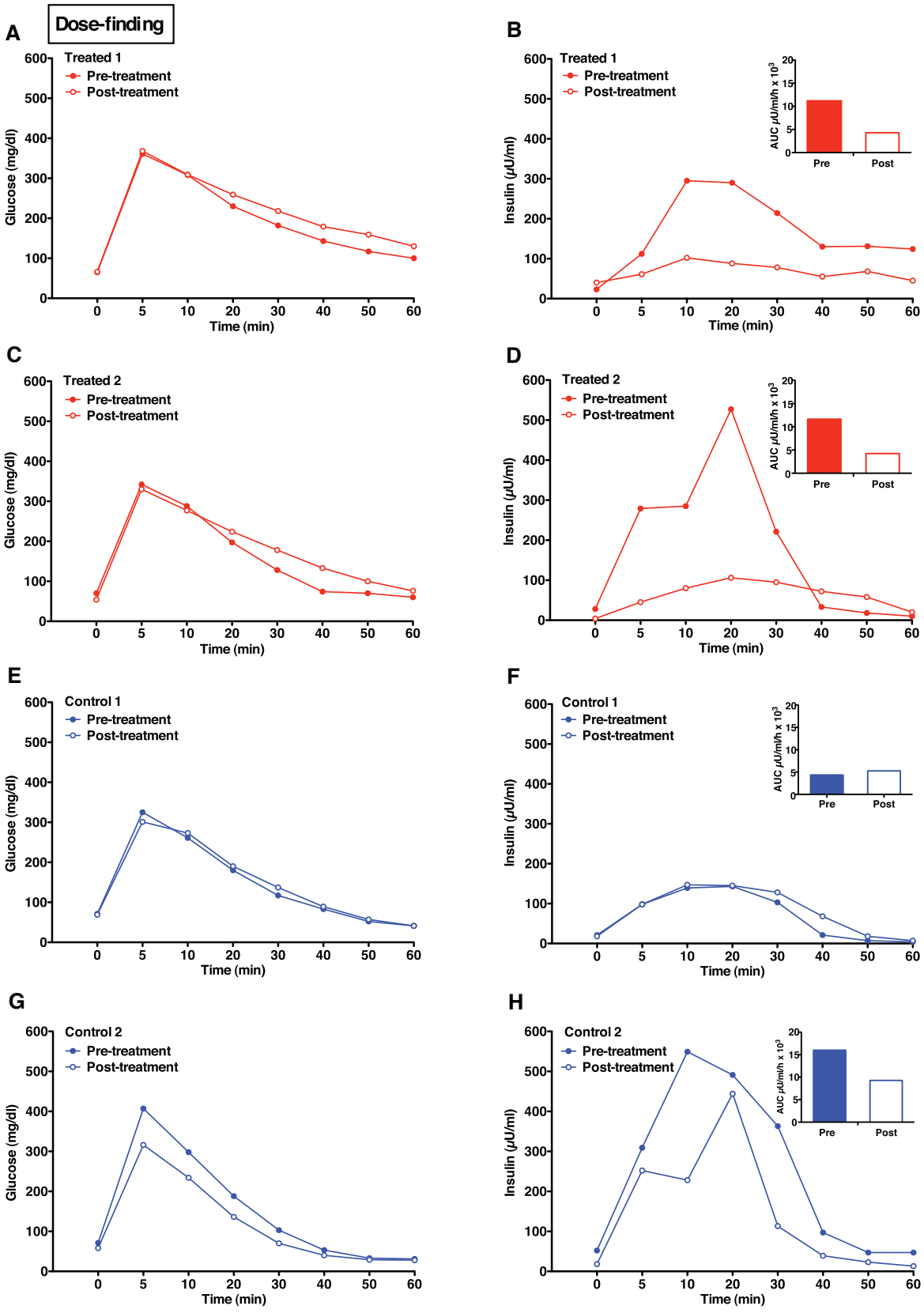


Fig. S1. Intravenous glucose tolerance test for the dose-finding study. An intravenous glucose tolerance test (IVGTT) was performed within seven days of the initial dose and three days following the final dose of adipotide. (**A**) In a single morbidly obese monkey, blood glucose levels failed to return to baseline 60 min after glucose administration. (**B**) After nine weeks of daily treatment with adipotide, blood glucose remained elevated at 60 min, but the area under the curve (AUC) for insulin markedly dropped (>60% decrease from baseline). (**C** and **D**) The AUC for insulin in a second adipotide-treated obese monkey also markedly decreased (> 60%) while glucose levels remained normal before and after treatment. (**E** to **H**) Obese monkeys that received saline as a negative control exhibited no detectable alterations between the pre- and post-treatment measurements.

Fig. S2

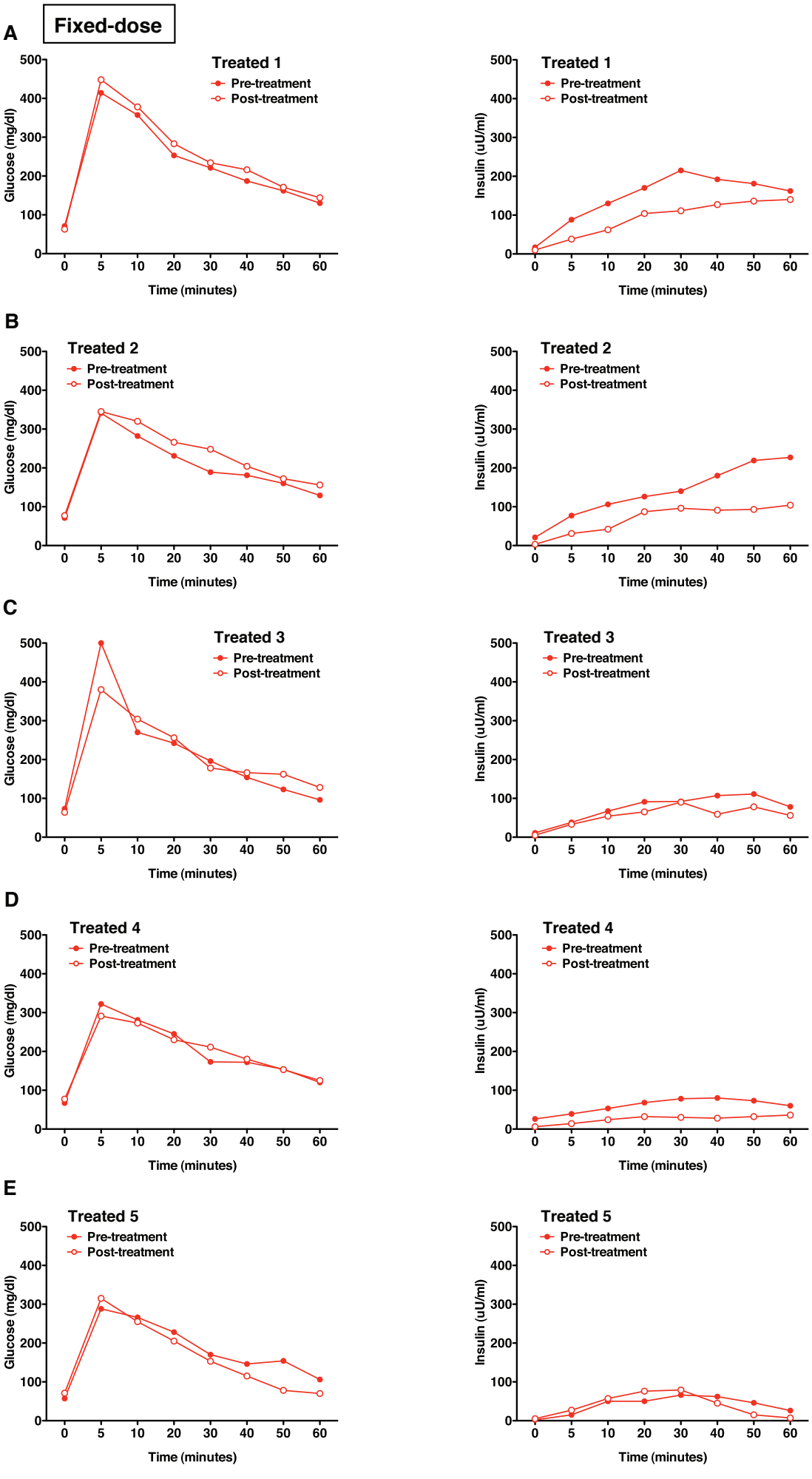

A
Fixed-dose
Treated 1
Pre-treatment
Post-treatment
Glucose (mg/dl)
Insulin (uU/ml)
Time (minutes)
B
Treated 2
C
Treated 3
D
Treated 4
E
Treated 5

Fig. S2cont.

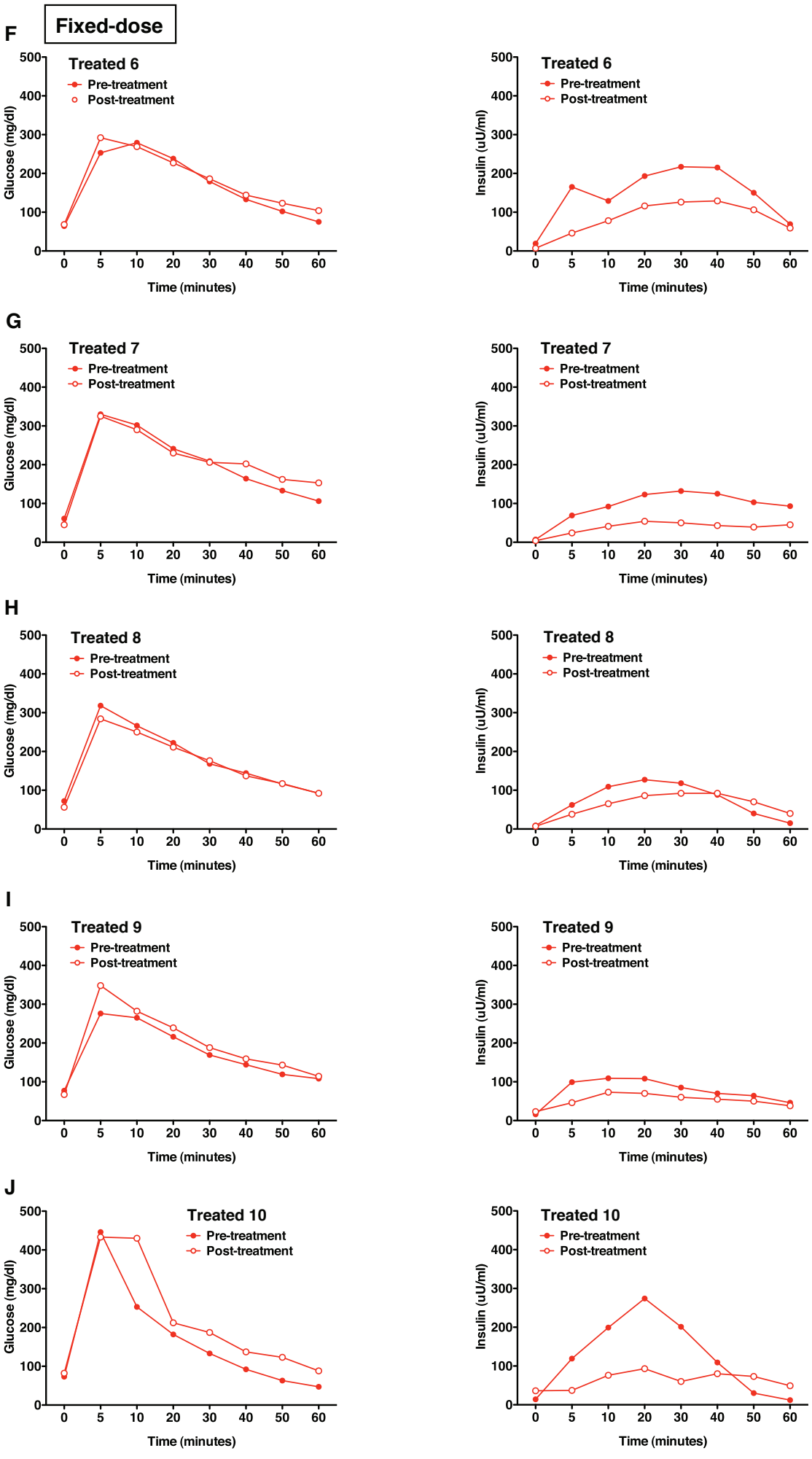

F
Fixed-dose
Treated 6
Pre-treatment
Post-treatment
Glucose (mg/dl)
Insulin (uU/ml)
Time (minutes)
G
Treated 7
H
Treated 8
I
Treated 9
J
Treated 10

Fig. S2cont.

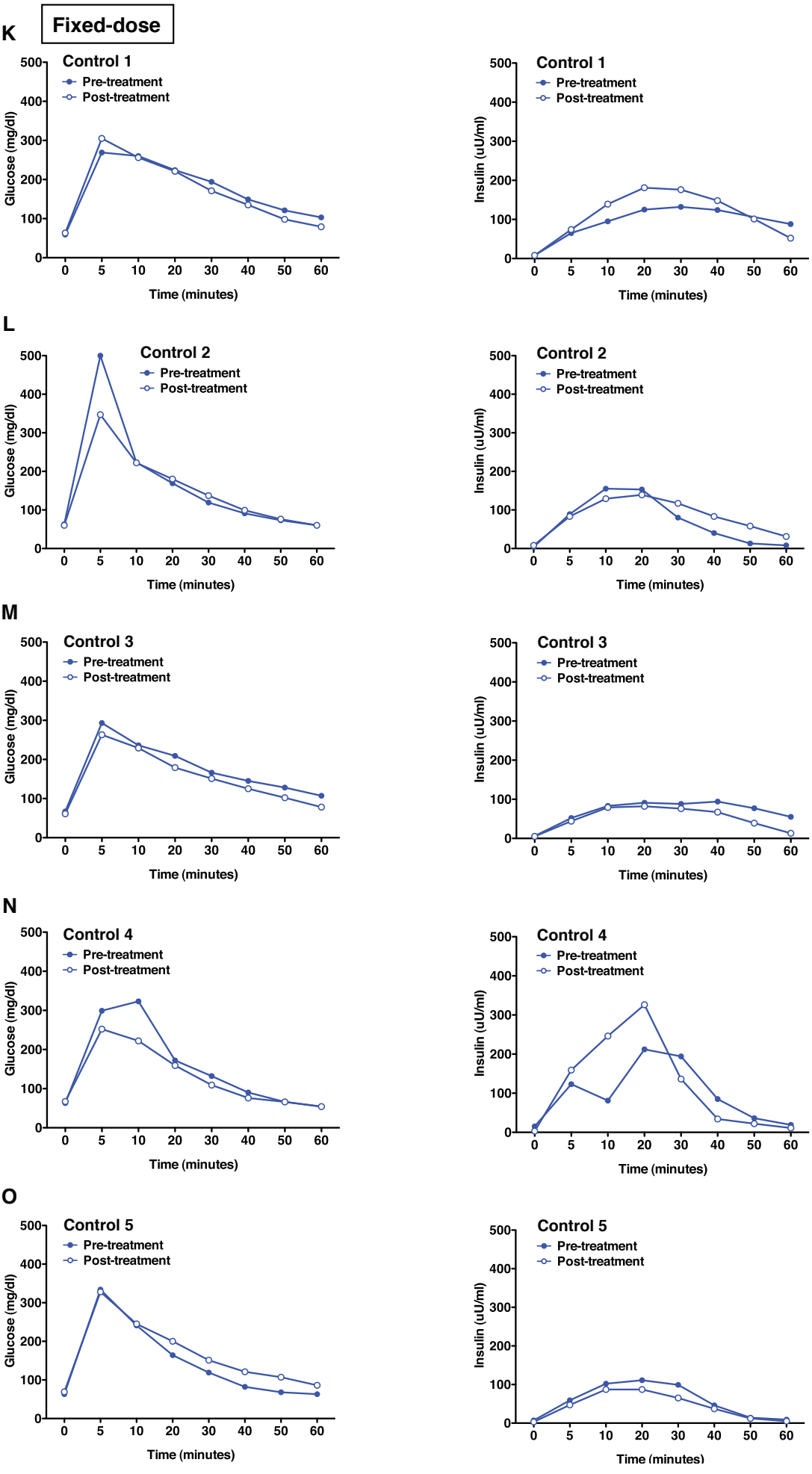

K
Fixed-dose
Control 1
Pre-treatment
Post-treatment
Glucose (mg/dl)
Insulin (uU/ml)
Time (minutes)
L
Control 2
M
Control 3
N
Control 4
O
Control 5

Fig. S2. Intravenous glucose tolerance test for the fixed-dose study. An intravenous glucose tolerance test (IVGTT) was performed within seven days of the initial dose and within three days following the final dose of adipotide. (**A** to **O**) Glucose levels for the treated (A to J) and control (K to O) monkeys were normal and relatively unchanged from pre- to post-treatment. The insulin response was reduced in treated monkeys (A to J) and unchanged in control monkeys (K to O).

Fig. S3

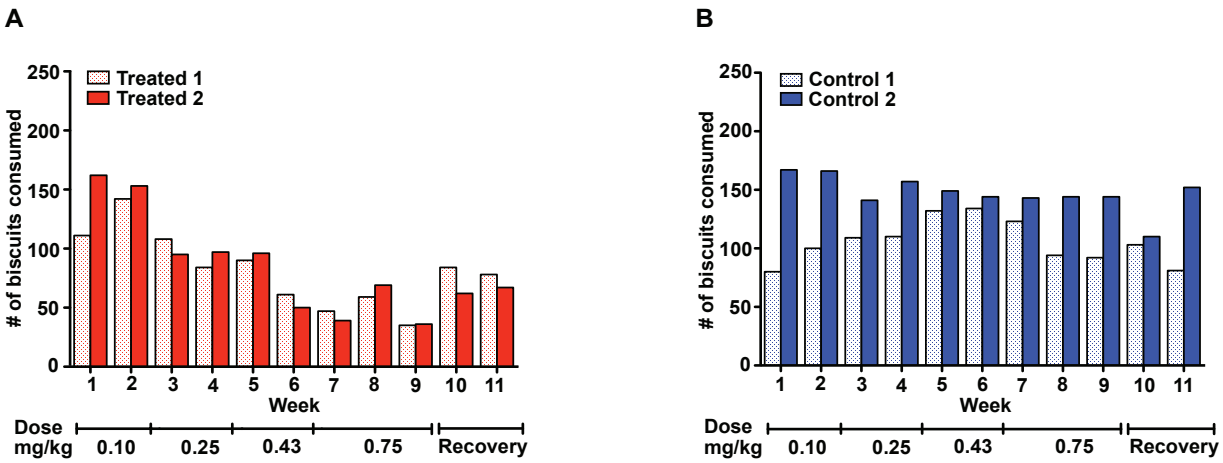


Fig. S3. Biscuit consumption during dose-finding study of adipotide. (**A**) An inverse relationship between biscuit consumption and the dose of adipotide was observed. Consumption appeared to increase following cessation of drug administration in the treated groups; (**B**) consumption remained relatively constant throughout the studies in control groups.

Fig. S4

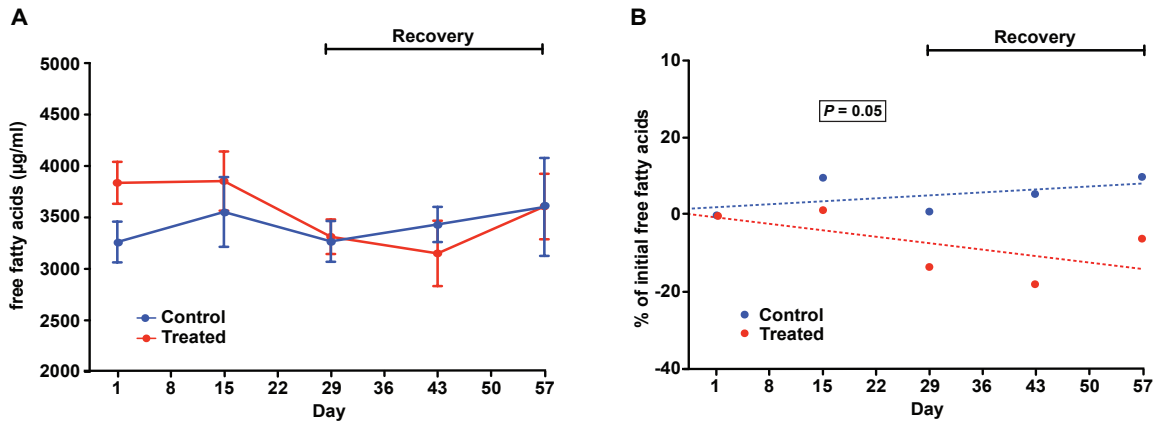


Fig. S4. Total serum-free fatty acid change during treatment with adipotide. (**A**) The microgram per milliliter plasma of twenty-four different fatty acids decreased during adipotide treatment. (**B**) There is a marginal significant difference between the slopes of the treated and control groups for percent change in fatty acids over time (control, n=3; treated, n=6).

Fig. S5

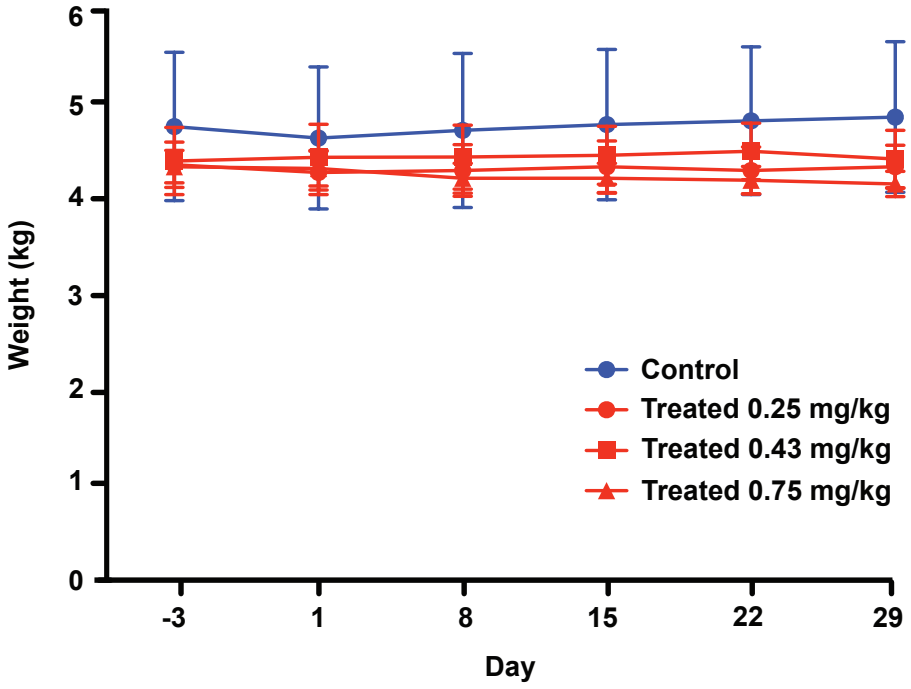


Fig. S5. Body weights of lean rhesus monkeys receiving daily subcutaneous injections of adipotide. Monkeys received three dose levels of adipotide (from 0.25 to 0.75 mg/kg) daily for 28 days (n=5 per group). Monkeys receiving 0.25 mg/kg and 0.43 mg/kg of adipotide did not lose weight while monkeys receiving 0.75 mg/kg of adipotide either maintained their pre-study weight or displayed mild weight loss. This trend was not statistically significant.

Fig. S6

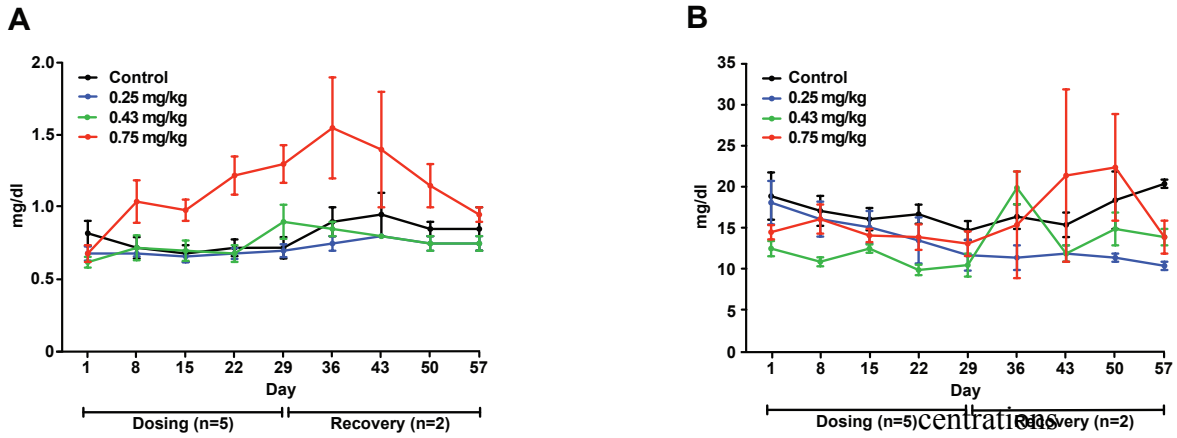


Fig. S6. BUN and creatine levels in lean rhesus monkeys receiving daily subcutaneous injections of adipotide. Monkeys received three dose levels of adipotide (from 0.25 to 0.75 mg/kg) daily for 28 days (n=5 per group). (A) Creatinine was elevated primarily in the high dose group (0.75 mg/kg) throughout the dosing period. This change was nearly resolved at the end of the recovery period. (B) Concurrent elevations in BUN from baseline where not observed at any dose level.

Fig. S7

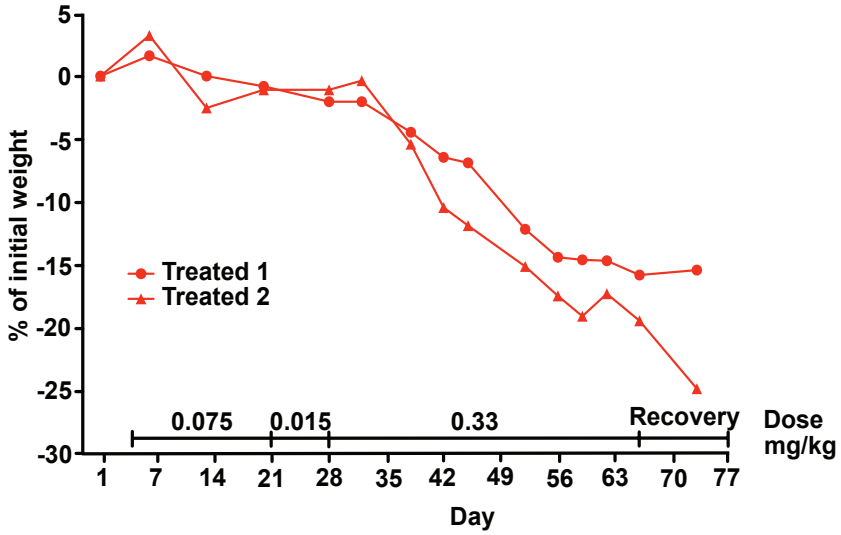
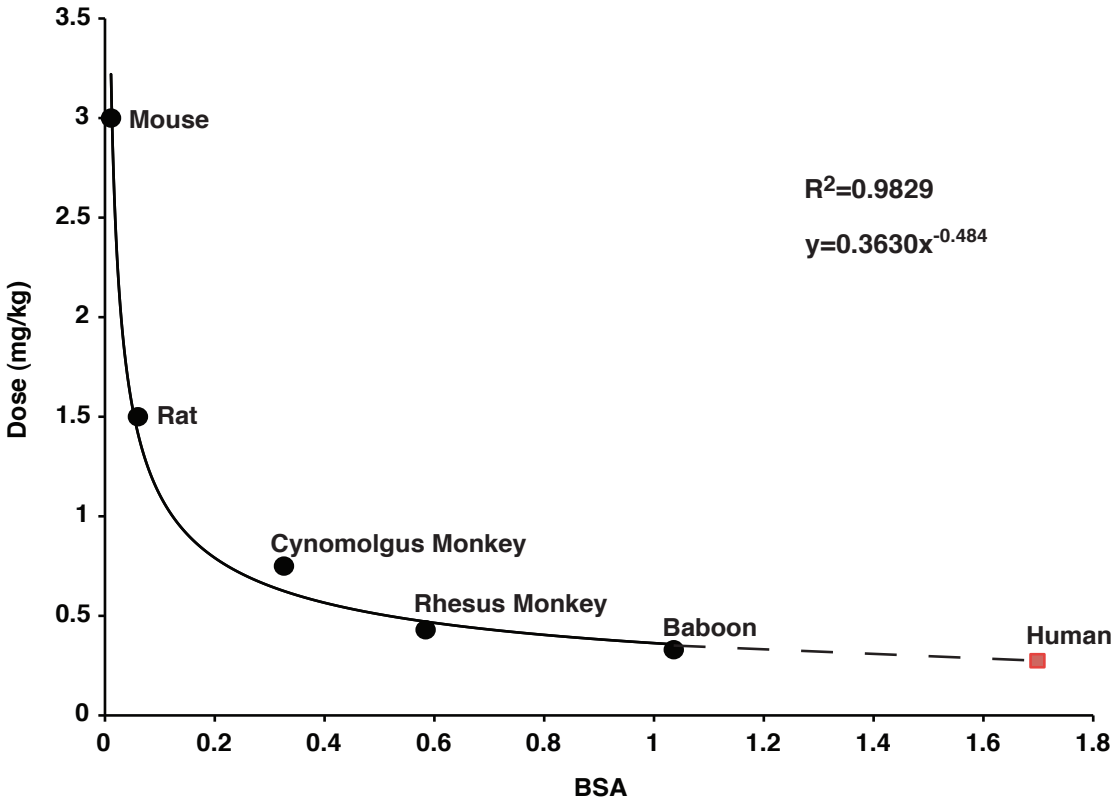


Fig. S7. Dose-finding study in adipotide-treated obese baboons. We determined the optimal dose of adipotide to be 0.33 mg/kg.

Fig. S8

A



B

Species	Body Weight (kg)	BSA (m^2)	Dose (mg/kg)
Mouse	0.04	0.011	3
Rat	0.55	0.06	1.5
Cynomolgus Monkey	4.6	0.326	0.75
Rhesus Monkey	11	0.584	0.43
Baboon	26	1.036	0.33
Human	65	1.7	0.28

Fig. S8. Relative therapeutic dose of adipotide in mammalian species. (**A**) A non-linear regression was used to fit an empiric correlation between the optimal therapeutic dose of adipotide (experimentally determined) and the body surface area (BSA). (**B**) Based on these five rodent and non-human primate species, we extrapolated a predicted dose of adipotide for human application (indicated in red).

Table S1. Glucoregulatory measurements for the dose-finding study

	Treated 1		Treated 2		Control 1		Control 2	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Fasting glucose (mg/dl)	65	65	70	54	71	69	71	58
60 min glucose (mg/dl)	100	130	60	76	41	41	31	33
Fasting insulin (μU/ml)	23	40	28	4	21	18	52	18
Peak insulin (μU/ml)	295	102	527	106	143	147	549	444
Time of insulin peak (min)	10	10	20	20	20	10	10	20
AUC of insulin (μU/ml/h)	11,100	4,285	11,643	4,245	4,345	5,263	16,008	9,270

Table S2. Glucoregulatory measurements for the fixed-dose study

	Treated 1		Treated 2		Treated 3		Treated 4		Treated 5		Treated 6		Treated 7		Treated 8		Treated 9		Treated 10	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Fasting glucose (mg/dl)	71	63	73	64	64	45	73	82	67	77	57	71	64	68	72	56	77	67	71	77
60 min glucose (mg/dl)	130	144	96	128	106	153	47	88	120	125	106	70	75	104	92	92	108	114	129	156
Fasting insulin (μU/ml)	17	10	11	5	7	4	14	36	26	6	2	5	19	7	9	7	16	23	21	3
Peak insulin (μU/ml)	215	140	111	90	132	54	274	93	80	36	66	79	217	129	127	92	109	73	227	104
Time of insulin peak (min)	30	60	50	30	30	20	20	20	40	60	30	30	30	40	20	30	10	10	60	60
AUC of insulin (μU/ml/h)	9,848	6,160	5,120	3,783	6,348	2,523	8,323	4,150	3,948	1,665	2,760	2,825	9,935	5,898	4,955	4,295	4,853	3,375	9,018	4,668

	Control 1		Control 2		Control 3		Control 4		Control 5	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Fasting glucose (mg/dl)	63	60	63	69	63	67	67	61	59	63
60 min glucose (mg/dl)	60	60	63	86	54	54	107	78	103	79
Fasting insulin (μU/ml)	4	8	7	3	15	3	6	5	8	8
Peak insulin (μU/ml)	155	87	111	139	212	326	94	82	132	176
Time of insulin peak (min)	10	10	20	20	20	20	40	20	30	30
AUC of insulin (μU/ml/h)	4,518	2,943	3,823	5,515	6,625	7,883	4,673	3,530	6,368	7,753

Table S3. Summary of lipid profile for the fixed-dose efficacy study: Control animals C1-C5

Animal ID#	Day	Chol mg/dl	Trig mg/dl	HDL mg/dl	LDL mg/dl
C1	1	119	59	69	38
C1	8	119	59	69	38
C1	15	116	38	64	44
C1	22	122	40	73	41
C1	29	141	46	81	51
C1	36	132	47	71	52
C1	43	143	54	80	52
C1	50	144	59	90	42
C1	57	145	49	77	58
C2	1	95	91	44	33
C2	8	95	91	44	33
C2	15	87	103	42	24
C2	22	96	99	44	33
C2	29	92	98	45	27
C2	36	96	104	44	31
C2	43	94	104	44	29
C2	50	89	137	45	17
C2	57	100	92	49	33
C3	1	123	48	76	37
C3	8	123	48	76	37
C3	15	124	27	80	39
C3	22	122	30	80	36
C3	29	120	67	72	35
C3	36	118	41	71	39
C3	43	121	31	76	39
C3	50	117	37	76	34
C3	57	127	67	67	47
C4	1	149	101	79	50
C4	8	127	39	84	35
C4	15	145	48	85	50
C4	22	154	46	93	52
C4	29	161	56	87	63
C4	36	149	47	89	51
C4	43	155	60	95	48
C4	50	168	46	102	57
C4	57	155	45	101	45
C5	1	102	38	60	34
C5	8	102	21	59	39
C5	15	105	31	62	37
C5	22	111	24	69	37
C5	29	100	23	57	38
C5	36	94	20	58	32
C5	43	113	39	61	44
C5	50	112	27	68	39
C5	57	97	28	62	29

Table S3 (cont.). Summary of lipid profile for the fixed-dose efficacy study: Treated animals T1-T10

Animal ID#	Day	Chol mg/dl	Trig mg/dl	HDL mg/dl	LDL mg/dl
T1	1	153	116	70	60
T1	8	153	116	70	60
T1	15	155	93	77	59
T1	22	158	41	86	64
T1	29	148	59	82	54
T1	36	133	63	71	49
T1	43	133	88	74	41
T1	50	127	79	71	40
T1	57	152	99	71	61
T2	1	144	48	73	61
T2	8	144	48	73	61
T2	15	144	32	76	62
T2	22	137	37	76	54
T2	29	133	29	70	57
T2	36	132	29	73	53
T2	43	120	29	68	46
T2	50	114	43	64	41
T2	57	134	42	68	58
T3	1	114	80	52	46
T3	8	114	80	52	46
T3	15	125	47	69	47
T3	22	112	50	62	40
T3	29	115	54	59	45
T3	36	102	49	57	35
T3	43	112	36	63	42
T3	50	106	48	65	31
T3	57	109	114	46	40
T4	1	221	56	114	96
T4	8	221	56	114	96
T4	15	210	39	118	84
T4	22	203	26	123	74
T4	29	202	29	116	80
T4	36	174	31	103	65
T4	43	169	33	100	62
T4	50	164	40	107	49
T4	57	170	43	90	71
T5	1	205	75	98	93
T5	8	206	75	98	93
T5	15	162	51	94	58
T5	22	169	78	81	72
T5	29	147	77	68	64
T5	36	114	67	59	42
T5	43	82	37	57	18
T5	50	129	47	69	51
T5	57	148	41	92	48

Animal ID#	Day	Chol mg/dl	Trig mg/dl	HDL mg/dl	LDL mg/dl
T6	1	123	82	71	36
T6	8	123	82	71	36
T6	15	105	64	59	33
T6	22	95	53	60	24
T6	29	82	55	51	20
T6	36	76	62	47	17
T6	43	78	59	46	20
T6	50	68	101	38	10
T6	57	77	98	44	13
T7	1	100	143	47	24
T7	8	89	87	45	27
T7	15	106	159	39	35
T7	22	90	55	61	18
T7	29	92	44	58	25
T7	36	101	79	40	45
T7	43	89	106	38	30
T7	50	96	68	47	35
T7	57	89	140	40	21
T8	1	122	70	59	49
T8	8	138	49	67	61
T8	15	127	67	59	55
T8	22	124	54	59	54
T8	29	119	41	56	55
T8	36	114	40	57	49
T8	43	106	49	51	45
T8	50	100	41	53	39
T8	57	109	99	47	42
T9	1	141	62	73	56
T9	8	155	53	83	61
T9	15	150	66	76	61
T9	22	142	59	73	57
T9	29	155	44	83	63
T9	36	145	33	74	64
T9	43	127	38	73	46
T9	50	107	67	60	34
T9	57	NA	NA	NA	NA
T10	1	94	103	59	14
T10	8	112	54	79	22
T10	15	98	72	58	26
T10	22	101	97	46	36
T10	29	78	54	56	11
T10	36	67	53	46	10
T10	43	61	40	43	10
T10	50	67	46	45	13
T10	57	64	49	42	12

Table S4. Serum-free fatty acids measured

ALPHA-LINOLENIC	ERUCIC
ARACHIDIC	GAMMA-LINOLENIC
ARACHIDONIC	HENEICOSANOIC
BEHENIC	HEPTADECANOIC
cis-10-HEPTADECANOIC	LIGNOCERIC
DIHOMO-GAMMA-LINOLENIC	LINOLEIC
DOCOSADIENOIC	LINOLELAIDIC
DOCOSAHEXAENOIC	NERVONIC
DOCOSAPENTAENOIC	OLEIC
EICOSADIENOIC	PALMITIC
EICOSAPENTAENOIC	PALMITOLEIC
EICOSATRIENOIC	PENTADECENOIC
EICOSENOIC	STEARIC
ELAIDIC	TRICOSANOIC

Table S5. Summary of physical exam findings for the dose-finding study

TREATED ANIMALS			
LARGE BOWEL	**INTEGUMENT**	**HANDS, ARMS AND EARS**	**COMMENTS**
Very firm feces in the large colon.	Small fleshy lipoma in right inguinal. Lipoma at right axillary.	Missing tops of digit 2, 4, and 5 on right hand. Missing most of left pinna and right pinna	Approximately 5% dehydrated.
Mildly dehydrated with firm feces in large colon	Mild inguinal bruising - on left side predominantly	Missing digit 1 on left hand. Missing tip on digit 3 on right hand. Missing parts of pinna bilaterally	Mensing
Firm stool palpated in abdomen	Left upper quadrant - scarring - slightly raised areas - no erythema (two areas)		A 2 cm incision was made lateral to umbilicus on left side
Pelleted stool felt in large colon on palpation	Bruising to left lower and upper quadrants - stable from previous exam (raised scars; no erythema). Bruising - ventral midline above pubic symphasis		Small umbilical hernia
Pelleted stool felt in large colon	Left upper and lower quadrants - bruising is resolving.		5% dehydrated
Pelleted stool palpated in abdomen.	Lower left quadrant. Area of skin discoloration and depression - approximately (1.5 cm x 1.5 cm). There is a 2cm streak of erythema on the dorsal edge of the discoloration. This could represent an area of ulceration in its infancy. Small pinpoint areas of erythema localized to upper thoracic wall extending to ventral neck.		Approximately 5% dehydrated
Pelleted stool in abdomen but less firm than previous exam	Left lower quadrant - ulcer is still evident (1.5cm x 1cm) - no additional erythema around edges - area of ulcer is discolored to a black color. Small 1.5 cm x 0.25 cm streak of hemorrhage in upper left quadrant.		Mildly dehydrated (5%)
	There are streaks of erythema with bruising (approx 7 cm in length) in the upper left quadrant. In addition, there is a small ulceration in upper left quadrant. In lower quadrant, there is erythema and bruising on the ventral portion of the quadrant (approx 5.5 cm in length). The ulcer is black and necrotic in middle (1.5 cm x 1 cm) with erythema around edge. There are additional scratches to posterior region of quadrant as well.		Approximately 5% dehydrated. A 2 cm incision was made lateral to umbilicus on left side.
	Left lower quadrant - sutures removed and the scab over the ulcer has been removed. There is a purulent material within the wound, which will be cleaned and left to heal by second intention. The other biopsy site has mild bruising. There is bruising in the inguinal area.		
	Bruising around biopsy site on ventral abdomen. Ulcer - lower left quadrant - erythema around edges. Biopsy site in upper right quadrant - crusted no bruising. Inguinal bruising bilateral. Bruising of forearms bilateral (catheter sites)		

Table S5 (cont.). Summary of physical exam findings for the dose-finding study

LARGE BOWEL	INTEGUMENT	HANDS, ARMS AND EARS	COMMENTS
	Lower left quadrant - ulcer is healing well - slight erythema on edges (1 cm x 0.5 cm). No discharge noted. SQ fat biopsy healing well - dark center with slight erythema on edges. Upper right quadrant - very small crust left at biopsy site.		
	Bruising erythema along both arms		
	Erythema on wrists - stable		
	Erythema at wrists bilateral - improving		
	Erythema stable from previous examination. Right upper quadrant - below axillary, 3 cm x 1.5 cm - area of erythema with clearing in middle. Appears like an ulcer that has crusted and healed.		
	Erythema stable from previous examination. Right upper quadrant - below axillary - are of crusting - much less erythema than previous. (1.3 cm x 1.7 cm)		
	Erythema on wrists stable. Right upper quadrant ulcer is resolved to scar.		
	Bruising to inguinal region. Very mild bruising around biopsy sites. Right upper quadrant healed.		
	Crusting at skin biopsy sites - no discharge seen. Very minimal bruising at subcutaneous fat biopsy location.		
	All biopsy sites (upper quadrants and SQ fat biopsy) are healing well with very small crusts and no discharge.		
	Erythema stable from previous examination. Right upper quadrant - below axillary region (1.6 cm x 1.7 cm) - crust almost completely resolved - erythema has lessened and healing appears good.		
	Erythema stable on wrists. Right upper quadrant - ulceration completely crusted over - healing very well.		
	Erythema on wrists stable. Right upper quadrant ulcer - healed to a single line (0.5 cm in length)		

Table S5 (cont.). Summary of physical exam findings for the dose-finding study

CONTROL ANIMALS			
HAIR COAT	**INTEGUMENT**	**FEET, LEGS, EARS, ORAL MUCOSA**	**COMMENTS**
Alopecia on right arm at level of elbow	Mild inguinal bruising	Missing end of digit 5 on left foot. Missing part of pinna on left ear	Sex swelling prominent along back (normal).
Alopecia along arms bilaterally	Right side inguinal bruising due to previous venipuncture	Missing part of right pinna	Mensing
Mild alopecia along arms	Bruising to upper right quadrant - injection site	Extracted two premolars on the lower left side; gum recession at the site of extracted teeth	
Alopecia to left dorsal arm and at area of elbow - appears to be barbered. Area of alopecia at right elbow smaller than left arm - appears to be plucked. Area of alopecia on lateral surface of right and left thighs	Bruising in both inguinal areas. There is bruising around lower left quadrant biopsy site. Very minor bruising to biopsy site in upper right quadrant.	Area of tooth extraction appears healthy with some signs of the gum recession. Gum is pink with no signs of infection	
Alopecia to left dorsal arm from elbow down the antebrachium. Alopecia at right elbow stable since last time. Alopecia on lateral surface left/right is stable.	Small bruise to upper left quadrant at injection site	Tooth extraction area appears healthy	
Alopecia stable	Resolving bruise on upper right quadrant. Bruise completely resolved in upper left quadrant from previous exam	First premolar on bottom right gum line is discolored. The tooth is not loose but gum is friable.	
Alopecia is the same as previous exams	Bruising to inguinal areas - very mild bruising to biopsy sites (right and left upper quadrants). Some bruising to catheter site on right arm.		
	Bruising to SQ fat biopsy site. Crusting to skin biopsy sites - upper right and left quadrants. No discharge noted.		
	Bruising around SQ fat biopsy site on ventral abdomen. Crusting of skin biopsies in upper right and upper left quadrants.		
	Upper quadrant biopsy sites crusted over completely, almost healed. SQ fat biopsy site erythema on edges - healing nicely with no additional swelling and/or discharge		

Table S6. Summary of serum chemistry profile for the fixed-dose efficacy study: Control animals C1-C5

Animal	Day	T.Bili	GGT	ALT	AST	LDH	ALK	CK	BUN	Crea	Glu	TP	Alb	Glob	Ca	P	Na	K	Cl	CO2	AG	Osm	Iron	TIBC	% Sat
ID#		mg/dl	U/L	U/L	U/L	U/L	U/L	U/L	mg/dl	mg/dl	mg/dl	g/dl	g/dl	g/dl	mg/dl	mg/dl	mEq/l	mEq/l	mEq/l	mEq/l	mEq/l	mOsmol/kg	ug/dl	ug/dl	%
C1	1	0.22	37	63	22	209	115	328	11	0.7	64	7.2	4.8	2.4	9.6	4.4	144	3.7	109	24	14.7	295.5	119	300	39.67
C1	8	0.15	36	45	22	238	121	88	13	0.7	67	7.2	4.6	2.6	9.7	3.6	146	3.7	112	22	15.7	300.4	109	316	34.49
C1	15	0.26	35	19	23	318	121	150	10	0.7	97	7.6	4.7	2.9	9.8	3.8	146	3.7	111	22	16.7	299.3	152	325	46.77
C1	22	0.17	34	21	18	170	104	117	11	0.7	69	7.4	4.7	2.7	9.7	4.5	146	3.7	110	24	15.7	299.8	109	323	33.75
C1	29	0.17	35	49	19	133	109	77	10	0.7	71	7.5	4.8	2.7	9.7	4.4	147	3.5	112	25	13.5	301.5	110	325	33.85
C1	36	0.18	34	39	16	138	93	96	9	0.6	67	7.0	4.4	2.6	9.6	4.1	146	3.6	111	25	13.6	298.9	91	321	28.35
C1	43	0.19	37	71	22	171	91	81	11	0.6	61	8.0	4.7	3.3	10.0	4.8	147	3.7	110	23	17.7	301.3	94	347	27.09
C1	50	0.19	34	62	26	258	99	83	10	0.6	61	7.6	4.6	3.0	9.9	5.1	146	4.0	111	22	17.0	299.0	108	313	34.50
C1	57	0.20	36	41	20	139	96	175	13	0.7	61	7.3	4.7	2.6	9.7	4.6	145	3.5	109	23	16.5	298.0	64	335	19.10
C2	1	0.30	46	38	25	332	87	222	14	0.9	89	6.4	4.0	2.4	9.0	4.7	147	3.9	108	26	16.9	303.9	160	317	50.47
C2	8	0.27	44	31	30	481	92	102	15	0.8	59	6.2	4.0	2.2	9.1	3.3	146	4.1	107	26	17.1	300.6	132	321	41.12
C2	15	0.22	46	28	26	452	100	51	13	0.8	62	6.4	3.8	2.6	8.9	4.2	147	3.9	110	25	15.9	302.1	147	332	44.28
C2	22	0.25	43	33	30	189	100	75	14	0.8	66	6.6	4.0	2.6	8.8	4.8	147	4.4	110	26	15.4	302.7	112	336	33.33
C2	29	0.17	46	39	25	216	121	129	11	0.8	76	6.5	4.0	2.5	9.0	3.7	147	3.8	107	32	11.8	302.2	132	348	37.93
C2	36	0.21	45	35	29	472	111	78	14	0.8	62	6.4	3.9	2.5	9.1	4.6	148	4.0	109	28	15.0	304.4	70	358	19.55
C2	43	0.22	46	39	25	305	89	81	13	0.8	69	6.5	4.1	2.4	9.0	5.0	148	4.0	108	27	17.0	304.5	108	355	30.42
C2	50	0.23	46	36	29	456	96	83	13	0.8	71	6.8	4.1	2.7	9.1	5.1	147	4.0	107	28	16.0	302.6	111	352	31.53
C2	57	0.18	48	38	24	247	110	79	16	0.8	71	6.8	4.1	2.7	9.2	4.1	147	4.1	107	30	14.1	303.7	116	368	31.52
C3	1	0.24	57	25	19	166	58	45	14	0.8	58	7.0	4.7	2.3	9.7	3.6	148	4.3	113	21	18.3	304.2	84	332	25.30
C3	8	0.19	54	30	21	189	73	185	14	1.0	61	6.8	4.6	2.2	10.0	3.6	149	3.9	111	24	17.9	306.4	109	342	31.87
C3	15	0.20	53	26	22	224	64	187	12	1.0	55	6.9	4.5	2.4	9.6	3.2	148	4.0	111	22	19.0	303.3	107	342	31.29
C3	22	0.15	57	28	18	109	63	177	12	0.9	55	6.8	4.4	2.4	9.4	3.8	148	3.9	113	25	13.9	303.3	108	348	31.03
C3	29	0.15	56	30	18	128	60	80	12	0.8	75	6.8	4.4	2.4	9.7	3.0	147	3.9	113	26	11.9	302.5	126	367	34.33
C3	36	0.13	54	36	22	217	70	743	14	0.8	62	6.8	4.2	2.6	9.6	4.1	149	3.9	110	28	14.9	306.4	96	381	25.20
C3	43	0.15	56	27	21	164	63	62	15	0.8	60	7.5	4.6	2.9	10.0	5.9	148	4.1	109	23	20.1	304.7	80	401	19.95
C3	50	0.39	51	23	15	145	68	61	14	0.8	62	6.8	4.2	2.6	9.5	4.3	145	3.9	109	26	13.9	298.4	91	366	24.86
C3	57	0.17	56	36	20	117	65	64	15	0.8	66	6.8	4.3	2.5	9.9	4.5	148	4.0	110	25	17.0	305.0	61	395	15.44
C4	1	0.11	46	37	30	493	110	260	15	0.8	63	7.1	4.2	2.9	9.3	2.6	144	3.6	109	23	15.6	296.9	99	337	29.4
C4	8	0.16	44	40	36	634	112	393	12	0.7	55	7.1	4.2	2.9	9.3	3.1	146	3.6	112	22	15.6	299.3	90	358	25.1
C4	15	0.14	41	31	34	626	106	621	12	0.8	51	6.5	4.0	2.5	9.1	3.9	145	3.6	107	27	14.6	297.1	148	348	42.5
C4	22	0.14	42	31	35	716	124	271	11	0.8	49	7.0	4.2	2.8	9.2	3.8	145	3.5	110	25	13.5	296.7	123	347	35.4
C4	29	0.11	44	28	21	275	94	556	13	0.8	52	7.1	4.2	2.9	9.3	3.6	146	3.9	110	28	11.9	299.5	137	357	38.4
C4	36	0.14	40	41	38	730	100	605	13	0.8	50	7.0	4.2	2.8	9.2	3.6	146	3.6	109	26	14.6	299.4	134	357	37.5
C4	43	0.14	41	61	38	670	89	464	11	0.8	49	6.8	4.2	2.6	9.3	3.5	146	3.4	109	27	13.4	298.7	123	353	34.8
C4	50	0.15	42	36	29	435	92	235	14	0.9	57	7.2	4.4	2.8	9.3	4.6	143	3.7	107	23	16.7	294.2	110	366	30.1
C4	57	0.12	42	51	29	304	86	428	12	0.8	61	7.2	4.2	3.0	9.4	4.3	145	3.6	108	25	15.6	297.7	127	367	34.6
C5	1	0.16	62	46	28	185	90	238	15	0.8	67	6.3	3.9	2.4	9.0	3.1	145	3.9	111	26	11.9	299.1	100	299	33.4
C5	8	0.20	61	66	25	206	83	385	14	0.9	53	6.2	4.1	2.1	9.0	3.0	145	3.8	112	24	12.8	297.9	100	306	32.7
C5	15	0.15	58	42	28	246	77	465	14	0.9	57	6.4	4.1	2.3	9.2	3.6	145	3.6	110	26	12.6	298.2	125	325	38.5
C5	22	0.14	59	91	42	318	89	312	13	0.8	61	6.5	4.2	2.3	9.2	4.2	144	3.3	109	26	12.3	296.0	103	322	32.0
C5	29	0.15	57	74	29	123	73	342	15	0.9	63	6.0	3.9	2.1	9.1	4.2	146	3.6	111	28	10.6	300.9	111	297	37.4
C5	36	0.17	56	40	25	215	72	482	17	0.8	70	6.5	4.1	2.4	8.9	4.0	146	3.5	111	24	14.5	302.0	140	322	43.5
C5	43	0.14	70	108	40	233	78	212	14	0.8	60	6.8	4.2	2.6	9.5	3.2	146	3.4	111	26	12.4	300.3	105	333	31.5
C5	50	0.19	67	84	31	180	74	502	17	0.8	70	6.9	4.2	2.7	9.3	4.5	144	3.5	110	24	13.5	298.0	122	331	36.9
C5	57	0.14	63	44	26	147	71	262	14	0.9	65	6.6	4.1	2.5	9.4	4.3	144	3.6	109	22	16.6	296.6	90	325	27.7

Table S6 (cont.). Summary of serum chemistry profile for the fixed-dose efficacy study: Treated animals T1-T5

Animal	Day	T.Bili	GGT	ALT	AST	LDH	ALK	CK	BUN	Crea	Glu	TP	Alb	Glob	Ca	P	Na	K	Cl	CO2	AG	Osm	Iron	TIBC	% Sat
ID#		mg/dl	U/L	U/L	U/L	U/L	U/L	U/L	mg/dl	mg/dl	mg/dl	g/dl	g/dl	g/dl	mg/dl	mg/dl	mEq/l	mEq/l	mEq/l	mEq/l	mEq/l	mOsmol/kg	ug/dl	ug/dl	%
T1	1	0.15	40	39	19	148	133	226	11	0.7	71	7.6	4.5	3.1	9.4	5.2	145	4.2	111	21	17.2	297.9	126	410	30.73
T1	8	0.13	37	34	26	345	164	245	14	1.1	67	7.4	4.0	3.4	9.3	3.4	147	4.0	113	22	16.0	302.7	106	381	27.82
T1	15	0.16	36	27	24	293	144	489	18	1.1	68	7.2	3.9	3.3	9.3	4.0	149	3.8	113	23	16.8	308.2	77	367	20.98
T1	22	0.17	34	17	18	209	137	319	15	1.1	70	7.4	4.1	3.3	9.3	3.3	148	3.9	116	22	13.9	305.2	65	382	17.02
T1	29	0.17	36	22	19	205	141	365	19	1.2	78	7.5	4.3	3.2	9.4	2.9	144	4.2	113	22	13.2	299.1	84	378	22.22
T1	36	0.14	33	20	18	184	138	119	17	1.0	75	7.2	4.2	3.0	9.2	1.8	147	3.6	114	21	15.6	304.2	55	358	15.36
T1	43	0.19	37	20	21	211	128	190	15	1.0	71	7.7	4.5	3.2	9.8	2.4	148	3.7	113	22	16.7	305.3	58	387	14.99
T1	50	0.19	36	24	21	243	124	115	13	0.9	63	7.3	4.4	2.7	9.5	3.7	146	3.6	109	24	16.6	300.1	77	366	21.04
T1	57	0.21	39	40	22	138	126	117	14	0.9	64	7.9	4.6	3.3	10.0	4.0	146	3.8	112	22	15.8	300.6	52	427	12.18
T2	1	0.16	45	21	27	187	72	400	17	0.7	62	7.1	4.3	2.8	9.2	5.1	148	3.6	110	24	17.6	305.5	52	336	15.48
T2	8	0.16	45	32	36	386	85	275	19	1.1	60	7.2	4.0	3.2	9.4	3.6	148	3.4	111	24	16.4	306.1	77	351	21.94
T2	15	0.15	44	23	26	311	77	151	17	1.3	62	7.3	3.9	3.4	9.3	2.2	149	3.4	114	22	16.4	307.5	48	322	14.91
T2	22	0.16	42	21	25	297	89	147	16	1.4	66	7.1	4.0	3.1	9.4	2.0	149	3.3	114	24	14.3	307.4	47	331	14.20
T2	29	0.17	45	22	23	225	95	220	16	2.0	71	7.3	4.3	3.0	9.8	1.8	148	3.2	113	25	13.2	305.7	78	350	22.29
T2	36	0.16	46	15	20	180	93	54	16	1.8	68	7.2	4.3	2.9	9.9	1.3	149	3.3	113	24	15.3	307.5	53	351	15.10
T2	43	0.20	47	14	22	175	87	58	17	1.3	60	7.6	4.3	3.3	9.3	<1.0	149	3.1	113	24	15.1	307.4	39	355	10.99
T2	50	0.15	48	17	22	170	95	102	16	1.1	67	7.3	4.2	3.1	9.4	1.9	145	3.1	106	26	16.1	299.4	62	350	17.71
T2	57	0.18	51	19	24	156	82	90	17	0.9	64	7.4	4.3	3.1	9.5	3.5	148	3.4	111	26	14.4	305.6	44	370	11.89
T3	1	0.16	35	44	21	168	144	123	13	0.7	69	7.2	4.1	3.1	9.6	4.6	146	3.5	108	24	17.5	300.5	90	376	23.94
T3	8	0.17	31	38	24	375	268	149	18	1.3	64	6.6	3.7	2.9	9.1	2.4	145	3.5	113	19	16.5	300.0	57	329	17.33
T3	15	0.15	34	33	19	240	254	204	18	1.3	63	7.0	3.9	3.1	9.7	2.8	147	3.2	114	19	17.2	303.9	49	342	14.33
T3	22	0.15	29	24	19	251	213	193	15	1.2	63	6.8	3.8	3.0	9.3	1.7	147	3.4	115	20	15.4	302.9	53	317	16.72
T3	29	0.16	32	27	18	186	263	251	8	1.5	76	7.1	4.1	3.0	9.8	1.4	147	3.2	117	20	13.2	301.1	45	338	13.31
T3	36	0.16	29	17	16	173	226	134	11	1.4	73	6.4	3.8	2.6	9.4	1.4	144	3.3	111	22	14.3	296.0	34	309	11.00
T3	43	0.16	31	17	18	241	183	86	11	1.2	59	7.1	4.1	3.0	9.6	1.7	147	3.3	113	21	16.3	301.2	46	328	14.02
T3	50	0.15	29	23	18	140	167	377	10	1.1	72	6.7	3.8	2.9	9.3	1.9	145	3.2	111	24	13.2	297.6	63	288	21.88
T3	57	0.13	32	19	17	171	131	140	12	0.9	68	6.8	4.1	2.7	9.9	1.9	146	3.4	111	24	14.4	300.1	49	338	14.50
T4	1	0.18	41	41	23	149	89	239	14	0.6	71	7.1	4.2	2.9	9.5	6.0	145	4.1	110	22	17.1	298.9	67	360	18.61
T4	8	0.15	38	42	24	304	115	51	13	1.4	67	6.9	3.7	3.2	9.5	3.4	145	3.4	114	17	17.4	298.4	61	345	17.68
T4	15	0.16	36	28	21	188	107	49	14	1.1	62	7.2	3.8	3.4	9.7	3.7	148	3.5	114	21	16.5	304.4	55	349	15.76
T4	22	0.18	33	18	23	310	110	191	10	1.0	69	7.3	3.9	3.4	9.7	2.3	147	4.0	114	22	15.0	301.4	44	345	12.75
T4	29	0.19	34	21	20	164	127	97	8	1.3	70	7.0	4.0	3.0	9.6	2.0	146	3.4	116	21	12.4	298.7	45	329	13.68
T4	36	0.13	32	21	20	163	120	64	13	1.0	77	6.9	3.9	3.0	9.4	1.5	144	3.4	113	20	14.4	296.9	40	350	11.43
T4	43	0.15	35	16	18	133	112	63	7	0.9	72	6.9	4.0	2.9	9.5	1.5	146	3.6	113	24	12..6	298.5	39	355	10.99
T4	50	0.16	35	20	20	138	118	49	11	1.0	74	7.0	4.0	3.0	9.8	2.4	146	3.5	111	24	14.5	300.0	54	343	15.74
T4	57	0.15	36	20	20	138	103	46	11	0.8	71	7.0	4.1	2.9	9.6	3.8	146	3.3	110	25	14.3	299.9	41	363	11.29
T5	1	0.17	36	28	20	182	179	162	11	0.5	67	6.7	3.9	2.8	9.4	5.8	146	4.2	109	24	17.2	299.7	107	336	31.85
T5	8	0.15	35	40	20	439	302	182	12	1.1	70	6.9	3.6	3.3	9.5	3.6	143	3.8	112	18	16.8	294.2	58	293	19.80
T5	15	0.21	32	20	17	280	444	181	6	1.0	67	7.2	3.6	3.6	9.4	2.6	149	3.1	110	22	20.1	303.9	25	277	9.03
T5	22	0.19	30	19	15	198	539	87	5	1.1	87	7.1	3.5	3.6	9.8	1.7	146	3.0	107	27	15.0	298.6	40	283	14.13
T5	29	0.24	31	17	16	243	779	45	5	1.1	59	7.3	3.5	3.8	9.7	3.3	144	3.0	106	21	20.0	293.1	26	279	9.32
T5	36	0.20	27	12	15	236	590	47	10	0.9	79	6.6	3.3	3.3	9.3	1.2	146	2.8	105	27	16.8	300.0	60	305	19.67
T5	43	0.30	27	14	26	449	868	35	6	0.7	78	6.2	2.9	3.3	8.9	1.7	147	4.2	116	22	15.2	304.5	28	192	14.58
T5	50	0.27	34	16	20	2	907	79	7	0.8	70	6.0	2.8	3.2	9.1	2.5	146	3.8	112	23	14.8	298.4	31	183	16.94
T5	57	0.18	39	17	17	175	645	37	8	0.7	73	6.2	3.2	3.0	9.3	4.0	147	3.9	112	22	16.9	300.9	29	224	12.95

Table S6 (cont.). Summary of serum chemistry profile for the fixed-dose efficacy study: Treated animals T6-T10

Animal	Day	T.Bili	GGT	ALT	AST	LDH	ALK	CK	BUN	Crea	Glu	TP	Alb	Glob	Ca	P	Na	K	Cl	CO2	AG	Osm	Iron	TIBC	% Sat
ID#		mg/dl	U/L	U/L	U/L	U/L	U/L	U/L	mg/dl	mg/dl	mg/dl	g/dl	g/dl	g/dl	mg/dl	mg/dl	mEq/l	mEq/l	mEq/l	mEq/l	mEq/l	mOsmol/kg	ug/dl	ug/dl	%
T6	1	0.18	61	56	27	245	61	303	18	1.1	74	6.8	3.8	3.0	9.1	6.2	149	3.9	106	27	19.9	308.5	167	320	52.19
T6	8	0.20	71	54	23	398	97	117	21	2.2	78	7.3	3.9	3.4	9.4	3.7	148	3.2	112	21	18.2	307.8	96	324	29.63
T6	15	0.20	76	32	28	514	91	627	11	2.2	75	7.4	3.9	3.5	10.2	3.4	152	3.5	113	26	16.5	312.1	96	313	30.67
T6	22	0.16	66	23	16	250	97	245	10	1.9	77	7.3	3.9	3.4	9.6	2.1	151	3.4	114	26	14.4	309.8	119	296	40.20
T6	29	0.17	68	20	16	188	139	175	8	2.2	83	7.1	3.7	3.4	9.3	1.9	151	3.3	115	26	13.3	309.5	63	283	22.26
T6	36	0.15	69	25	24	410	164	138	8	2.0	70	7.4	3.8	3.6	9.4	1.7	148	3.4	110	26	15.4	302.7	82	295	27.80
T6	43	0.18	74	17	25	405	154	71	11	1.6	75	7.8	3.8	4.0	9.3	1.7	147	3.6	110	24	16.6	302.1	78	290	26.90
T6	50	0.17	68	22	19	180	122	153	9	1.3	78	7.2	3.6	3.6	9.0	4.8	148	3.4	107	28	16.4	303.5	99	269	36.80
T6	57	0.13	70	17	21	228	85	60	13	1.1	80	7.3	3.8	3.5	9.3	4.5	146	3.4	105	26	18.4	301.1	83	301	27.57
T7	1	0.17	47	35	31	521	124	846	16	0.8	70	6.7	3.8	2.9	8.9	2.7	145	3.7	107	27	14.7	299.6	97	357	27.2
T7	8	0.27	44	40	42	960	140	353	23	1.5	51	6.4	3.8	2.6	8.9	3.6	146	3.4	112	21	16.4	303.0	108	328	32.9
T7	15	0.23	41	29	36	810	121	521	23	1.4	60	6.3	3.9	2.4	9.0	2.2	147	3.5	109	25	16.5	305.5	137	348	39.4
T7	22	0.17	60	23	34	856	118	109	10	2.2	74	7.6	3.9	3.7	9.4	2.5	148	3.2	110	25	16.2	303.7	34	353	9.6
T7	29	0.29	43	25	25	402	140	375	16	2.1	49	6.7	3.8	2.9	9.4	3.2	144	3.1	111	21	15.1	296.4	39	313	12.5
T7	36	0.31	44	23	31	635	143	306	17	1.5	55	6.5	3.8	2.7	9.1	1.8	147	3.5	112	23	15.5	303.1	141	334	42.2
T7	43	0.25	45	18	25	360	118	330	14	1.2	64	6.3	3.8	2.5	9.1	1.2	146	3.4	111	26	12.4	300.6	108	332	32.5
T7	50	0.31	49	19	21	278	119	167	14	1.0	68	6.7	3.9	2.8	9.2	3.9	146	3.6	108	24	17.6	300.8	120	350	34.3
T7	57	0.24	48	22	26	385	117	295	12	0.9	70	6.7	4.0	2.7	9.3	4.5	146	3.7	108	24	17.7	300.2	117	375	31.2
T8	1	0.13	33	33	27	326	61	575	15	0.7	78	6.2	3.5	2.7	8.5	4.4	143	3.3	108	26	12.3	295.7	80	300	26.7
T8	8	0.20	34	55	41	680	92	684	22	1.5	58	6.4	3.6	2.8	9.1	3.4	147	3.4	116	19	15.4	305.1	85	306	27.8
T8	15	0.18	31	28	34	651	98	739	17	1.4	59	6.5	3.7	2.8	9.1	3.6	147	3.5	112	23	15.5	303.3	127	321	39.6
T8	22	0.27	33	23	33	641	186	528	14	1.6	63	6.9	3.7	3.2	9.2	3.2	145	3.1	112	22	14.1	298.5	100	320	31.3
T8	29	0.23	33	21	26	258	129	448	14	1.7	64	6.8	3.9	2.9	9.2	2.8	147	3.2	115	21	14.2	302.6	102	318	32.1
T8	36	0.17	33	19	28	459	152	162	16	1.7	70	6.7	3.8	2.9	9.3	2.7	145	3.3	111	22	15.3	299.6	75	294	25.5
T8	43	0.16	33	14	27	395	113	161	12	1.3	70	6.6	3.8	2.8	9.1	1.8	144	3.1	111	24	12.1	296.2	60	291	20.6
T8	50	0.25	34	16	24	345	83	198	15	1.2	69	6.6	3.9	2.7	9.2	3.2	145	3.1	110	22	16.1	299.2	102	296	34.5
T8	57	0.18	35	25	28	346	78	172	14	1.0	64	6.9	3.9	3.0	9.4	4.2	145	3.2	109	21	18.2	298.6	158	339	46.6
T9	1	0.19	35	23	29	339	81	168	16	0.6	63	6.8	3.9	2.9	9.0	3.4	144	3.9	108	26	13.9	297.2	100	380	26.3
T9	8	0.23	35	30	30	502	132	416	21	1.3	61	6.8	3.8	3.0	9.0	3.6	143	3.6	113	18	15.6	296.9	74	355	20.8
T9	15	0.20	34	23	35	684	116	233	15	1.1	66	7.1	4.1	3.0	9.4	3.8	145	3.8	109	25	14.8	299.0	72	370	19.5
T9	22	0.22	34	19	38	733	117	413	18	1.4	59	7.2	4.1	3.1	9.6	2.1	143	3.4	109	23	14.4	295.7	104	356	29.2
T9	29	0.25	33	20	28	346	114	102	13	1.5	82	7.3	4.4	2.9	9.7	2.0	143	3.3	108	22	16.3	295.2	94	355	26.5
T9	36	0.19	31	14	35	604	114	228	13	1.4	65	7.0	4.2	2.8	9.6	2.4	144	3.2	109	22	16.2	296.3	83	346	24.0
T9	43	0.21	31	13	25	286	95	93	12	1.0	73	6.7	4.2	2.5	9.2	1.2	144	3.4	109	25	13.4	296.3	94	322	29.2
T9	50	0.18	33	15	26	305	98	155	15	1.0	77	7.1	4.3	2.8	9.3	1.3	144	3.4	111	23	13.4	297.6	118	347	34.0
T9	57	0.17	34	15	27	378	85	289	15	0.8	64	7.0	4.2	2.8	9.7	2.7	145	3.4	108	25	15.4	298.9	96	354	27.1
T10	1	0.11	53	30	25	417	69	473	21	1.1	81	7.3	3.7	3.6	9.1	3.3	146	3.8	104	32	13.8	304.0	41	370	11.1
T10	8	0.18	54	41	48	1469	104	1057	30	3.5	60	7.5	3.7	3.8	10.2	3.4	147	3.6	113	20	17.6	308.0	182	333	54.7
T10	15	0.15	57	27	34	776	94	1476	17	2.1	65	7.3	3.8	3.5	9.7	2.9	150	3.6	109	26	18.6	309.7	35	361	9.7
T10	22	0.32	45	29	40	903	157	286	13	1.8	52	6.9	3.9	3.0	9.4	2.4	146	3.7	110	23	16.7	299.5	115	334	34.4
T10	29	0.23	62	25	26	394	143	753	8	2.2	61	7.4	3.8	3.6	9.1	1.9	150	3.2	113	24	16.2	306.2	34	342	9.9
T10	36	0.17	56	20	30	635	211	716	7	1.9	78	7.1	3.4	3.7	9.1	2.0	149	3.2	111	25	16.2	304.8	24	329	7.3
T10	43	0.15	52	15	24	342	227	676	8	1.7	75	6.9	3.3	3.6	9.1	1.6	147	3.6	111	25	14.6	301.0	24	327	7.3
T10	50	0.16	64	17	22	229	198	446	12	1.5	74	7.4	3.4	4.0	9.0	2.2	146	3.4	109	25	15.4	300.4	24	352	6.8
T10	57	0.12	62	14	20	243	128	216	13	1.2	83	7.6	3.4	4.2	9.2	4.5	146	3.6	107	24	18.6	301.3	32	354	9.0

Table S7. Summary of urine analysis for the fixed-dose efficacy study: Control animals C1-C5

Animal ID#	Day	Color	Appear	Glu mg/dl	Ket mg/dl	Bili mg/dl	Sp Grav NA	Blood mg/dl	pH NA	Prot mg/dl	SSA mg/dl	Leuk cells/ul	Casts per hpf	Epi cells per hpf	WBC per hpf	RBC per hpf	Bacteria per hpf	Crystals per hpf
C1	1	Straw	Cloudy	Neg	Neg	Neg	1.014	Neg	8.5	Trace	Neg	Small	None	0-1sq	None	None	Neg	3+ AmP
C1	8	Straw	Clear	Neg	Neg	Neg	1.007	Neg	8.5	Neg	N/A	Neg	None	0-1sq	None	None	Neg	Neg
C1	15	Yellow	Clear	Neg	Neg	Neg	1.006	Neg	8.5	Neg	N/A	Neg	None	0-1sq	None	None	Neg	Neg
C1	22	Straw	Hazy	Neg	Neg	Neg	1.005	Large	8.5	Neg	N/A	Mod	None	0-1sq	0-1	0-1	Tr mixed	Neg
C1	29	Straw	Hazy	Neg	Neg	Neg	1.002	Neg	8.5	Neg	N/A	Neg	None	0-1sq	None	None	Tr mixed	Neg
C1	36	Straw	Hazy	Neg	Neg	Neg	1.003	Neg	8.5	Neg	N/A	Neg	Trace	None	2-5sq	0-1	None	2+
C1	43	Yellow	Hazy	Neg	Neg	Neg	1.010	Neg	8.5	Trace	Neg	Neg	None	2-5sq	0-1	None	1+ cocci	Neg
C1	50	Straw	Hazy	Neg	Neg	Neg	1.005	Neg	8.5	Neg	N/A	Neg	None	2-5sq	None	None	Tr mixed	Neg
C1	57	Yellow	Hazy	Neg	Neg	Neg	1.010	Neg	8.5	Trace	Neg	Neg	None	0-1sq	0-1	None	2+	Neg
C2	1	Yellow	Hazy	Neg	Neg	Neg	1.017	Neg	8.5	Neg	N/A	Norm	2-5 hyal	None	None	None	Neg	1+ CaOx
C2	8	Yellow	Hazy	Neg	Neg	Neg	1.008	Neg	8.5	Neg	N/A	Norm	None	0-1sq	None	None	Neg	Neg
C2	15	Yellow	Clear	Neg	Neg	Neg	1.009	Tr-NH	8.5	Neg	N/A	Norm	None	None	None	None	Neg	Neg
C2	22	Yellow	Clear	Neg	Neg	Neg	1.010	Neg	8.5	Trace	Neg	Norm	None	None	None	None	Neg	Neg
C2	29	Yellow	Hazy	Neg	Neg	Neg	1.007	Neg	8.5	Trace	Neg	Norm	None	None	None	None	Neg	1+ CaCarb
C2	36	Yellow	Cloudy	Neg	Neg	Neg	1.011	Small	8.5	Trace	Neg	Norm	None	6-10sq	None	None	None	2+
C2	43	Yellow	Clear	Neg	Neg	Neg	1.004	Neg	8.0	Neg	N/A	Norm	None	None	None	None	Neg	Neg
C2	50	Straw	Clear	Neg	Neg	Neg	1.003	Neg	8.0	Neg	N/A	Norm	None	None	None	0-1	Neg	Neg
C2	57	Yellow	Hazy	Neg	Neg	Neg	1.006	Neg	8.5	Neg	N/A	Norm	None	2-5sq	0-1	None	2+	Neg
C3	1	Straw	Hazy	Neg	Neg	Neg	1.008	Neg	8.5	Neg	N/A	Neg	0-1 hyal	0-1sq	0-1	0-1	Tr mixed	Neg
C3	8	Pink	Hazy	Neg	Neg	Neg	1.011	Large	8.5	30	1+	Neg	None	0-1sq	0-1	21-50	Neg	Neg
C3	15	Straw	Hazy	Neg	Neg	Neg	1.010	Tr-H	8.5	Trace	Trace	Small	None	6-10sq	2-5	None	Neg	2+ CaOx
C3	22	Straw	Hazy	Neg	Neg	Neg	1.005	Tr-H	8.5	Neg	N/A	Mod	None	2-5sq	None	None	Tr mixed	Neg
C3	29	Yellow	Hazy	Neg	Neg	Neg	1.004	Tr-H	8.5	Neg	N/A	Neg	None	2-5sq	0-1	2-5	Tr mixed	2+ AmP
C3	36	Amber	Cloudy	Neg	Neg	Neg	1.013	Large	8.5	30	1+	Trace	None	6-10sq	0-1	TNTC	1+	2+ CaOx
C3	43	Yellow	Hazy	Neg	Neg	Neg	1.009	Neg	8.5	Trace	Neg	Neg	None	6-10sq	None	None	Neg	1+ AmP
C3	50	Straw	Hazy	Neg	Neg	Neg	1.003	Neg	8.5	Neg	N/A	Large	None	2-5sq	2-5	None	Tr, some motile rods	Neg
C3	57	Yellow	Hazy	Neg	Neg	Neg	1.014	Neg	8.5	Trace	Neg	Neg	None	6-10sq	None	None	Trace	2+ CaOx
C4	1	Straw	Hazy	Neg	Neg	Neg	1.001	Tr-NH	8.0	Neg	N/A	Neg	None	0-1sq	2-5	0-1	3+ mixed	Neg
C4	8	Yellow	Hazy	Neg	Neg	Neg	1.010	Neg	8.5	Neg	N/A	Mod	None	0-3sq	2-5	None	Trace	Neg
C4	15	Pink	Hazy	Neg	Neg	Neg	1.004	Large	8.5	30	Neg	Small	None	0-1sq	0-1	2-5	Neg	Neg
C4	22	Straw	Clear	Neg	Neg	Neg	1.005	Neg	8.5	Neg	N/A	Trace	None	2-5sq	0-1	0-1	Neg	1+ CaOx
C4	29	Straw	Hazy	Neg	Neg	Neg	1.005	Neg	7.0	Neg	N/A	Mod	None	0-1sq	None	None	Tr mixed	Neg
C4	36	Yellow	Clear	Neg	Neg	Neg	1.006	Neg	8.5	Trace	N/A	Neg	None	0-1sq	None	None	Neg	Neg
C4	43	Yellow	Clear	Neg	Neg	Neg	1.010	Neg	8.5	Trace	N/A	Neg	None	2-5sq	0-1	None	Trace	Neg
C4	50	Straw	Hazy	Neg	Neg	Neg	1.009	Mod	8.5	Neg	N/A	Trace	None	0-1sq	0-1	None	Neg	1+ CaOx
C4	57	Straw	Hazy	Neg	Neg	Neg	1.007	Tr-H	8.5	Neg	N/A	Neg	None	0-2sq	None	0-1	1+ mixed	Neg
C5	1	Straw	Hazy	Neg	Neg	Neg	1.001	Large	8.5	Neg	N/A	Mod	None	2-5sq	2-5	0-1	Tr mixed	Neg
C5	8	Colorless	Hazy	Neg	Neg	Neg	1.002	Neg	8.0	Neg	N/A	Neg	None	0-1sq	0-1	0-1	Tr mixed	Neg
C5	15	Colorless	Hazy	Neg	Neg	Neg	1.003	Neg	8.5	Neg	N/A	Mod	None	0-1sq	None	None	Neg	Neg
C5	22	Straw	Hazy	Neg	Neg	Neg	1.004	Neg	8.5	Neg	N/A	Large	None	2-5sq	2-5	0-1	Tr mixed	Neg
C5	29	Straw	Hazy	Neg	Neg	Neg	1.004	Tr-H	8.0	Neg	N/A	Mod	None	6-10sq	2-5	0-1	Tr mixed	Neg
C5	36	Yellow	Clear	Neg	Neg	Neg	1.010	Neg	8.5	Neg	N/A	Neg	None	2-5sq	None	None	Neg	Neg
C5	43	Yellow	Clear	Neg	Neg	Neg	1.005	Neg	8.0	Neg	N/A	Trace	None	2-5sq	0-1	None	1+	Neg
C5	50	Yellow	Clear	Neg	Neg	Neg	1.016	Mod	6.5	Trace	N/A	Neg	None	2-5sq	0-1	11-20	Trace	Neg
C5	57	Yellow	Hazy	Neg	Neg	Neg	1.017	Neg	8.5	Neg	N/A	Trace	None	0-3sq	0-1	None	Neg	1+ CaOx

Table S7 (cont.). Summary of urinalysis for the fixed-dose efficacy study: Treated animals T1-T5

Anim ID#	Day	Color	Appear	Glu mg/dl	Ket mg/dl	Bili mg/dl	Sp Grav NA	Blood mg/dl	pH NA	Prot mg/dl	SSA mg/dl	Leuk cells/ul	Casts per hpf	Epi cells per hpf	WBC per hpf	RBC per hpf	Bacteria per hpf	Crystals per hpf
T1	1	Yellow	Cloudy	Neg	Neg	Neg	1.013	Neg	8.5	Neg	N/A	Neg	None	None	None	None	Neg	2+ AmP
T1	8	Straw	Cloudy	Neg	Neg	Neg	1.011	Tr-NH	8.5	300	2+	Neg	None	2-5sq	0-1	2-5	Neg	2+ AmP
T1	15	Straw	Hazy	1000	Neg	Neg	1.010	Neg	8.5	30	Trace	Neg	None	2-5sq	0-1	None	Neg	Neg
T1	22	Straw	Clear	1000	Neg	Neg	1.011	Neg	8.5	30	2+	Neg	None	0-1sq,0-1tr	None	0-1	Tr mixed	Neg
T1	29	Straw	Clear	500	Neg	Neg	1.006	Large	8.0	Trace	Trace	Neg	None	0-1sq	0-1	2-5	Neg	Neg
T1	36	Lt amber	Hazy	>2000	Neg	Neg	1.016	Large	8.5	30	Trace	Neg	None	11-20sq	None	TNTC	1+	Neg
T1	43	Yellow	Hazy	250	Neg	Neg	1.010	Neg	8.5	Trace	N/A	Neg	None	6-10sq,2-5tr	2-5	None	1+ mixed	Neg
T1	50	Straw	Hazy	Neg	Neg	Neg	1.005	Tr-NH	8.0	Neg	N/A	Neg	None	2-5sq	11-20	2-5	Tr mixed rods	Neg
T1	57	Yellow	Hazy	Neg	Neg	Neg	1.007	Neg	8.5	Neg	N/A	Neg	None	6-10sq	None	None	Trace	Neg
T2	1	Yellow	Hazy	Neg	Neg	Neg	1.015	Large	8.5	Trace	Tr	Mod	None	2-5sq	2-5	2-5	Neg	1+ CaOx
T2	8	Yellow	Hazy	Neg	Neg	Neg	1.024	Small	8.5	>2000	3+	Trace	Hyaline0-1	2-5sq,0-1tr	2-5	0-1	1+ mixed	1+ AmP
T2	15	Yellow	Hazy	250	Neg	Neg	1.018	Large	8.5	30	Trace	Trace	None	0-1sq	0-1	6-10	Neg	Neg
T2	22	Yellow	Clear	1000	Neg	Neg	1.015	Tr-H	7.5	100	Trace	Neg	None	0-1tr	None	0-1	Tr mixed	Neg
T2	29	Yellow	Hazy	500	Neg	Neg	1.014	Tr-H	8.5	100	1+	Neg	None	0-1sq	0-1	None	Tr mixed	Neg
T2	36	Yellow	Hazy	500	Neg	Neg	1.008	Neg	6.0	Trace	Trace	Neg	None	2-5sq	None	None	Trace	Neg
T2	43	Straw	Hazy	250	Neg	Neg	1.010	Neg	8.0	Trace	Neg	Neg	None	6-10sq,2-5tr	2-5	None	Tr mixed	Neg
T2	50	Yellow	Hazy	Neg	Neg	Neg	1.011	Neg	8.5	Neg	N/A	Neg	None	2-5sq	0-1	None	Neg	Neg
T2	57	Yellow	Hazy	Neg	Neg	Neg	1.014	Neg	8.5	Trace	Neg	Trace	None	6-10sq	2-5	None	1+	Neg
T3	1	Yellow	Hazy	Neg	Neg	Neg	1.011	Neg	8.5	Neg	N/A	Neg	None	2-5sq	0-1	0-1	Tr mixed	1+ AmP
T3	8	Yellow	Hazy	>2000	5	Neg	1.036	Large	7.5	>2000	3+	Trace	None	2-5sq	6-10	TNTC	1+ mixed	Neg
T3	15	Straw	Hazy	>2000	Neg	Neg	1.032	Small	6.0	100	1+	Neg	0-1 cellular	2-5tr	6-10	0-1	Neg	Neg
T3	22	Yellow	Hazy	1000	15	Neg	1.028	Small	6.0	100	1+	Neg	None	0-1sq	0-1	0-1	2+ mixed	Neg
T3	29	Yellow	Hazy	>2000	Neg	Neg	1.021	Small	6.0	100	1+	Neg	0-2 coarse gran	6-10sq	0-1	0-1	Neg	Neg
T3	36	Lt amber	Cloudy	>2000	Neg	Neg	1.024	Neg	6.0	100	2+	Trace	None	6-10sq	11-20	TNTC	1+	Neg
T3	43	Straw	Hazy	500	5	Neg	1.009	Neg	6.0	Trace	Neg	Trace	0-1hyaline	11-20sq	0-1	None	Tr mixed	Neg
T3	50	Straw	Hazy	250	Neg	Neg	1.007	Neg	6.5	Trace	Trace	Mod	None	0-1tr, 2-5sq	2-5	0-1	1+mixed motile rods	Neg
T3	57	Yellow	Hazy	100	Neg	Neg	1.009	Neg	6.0	Neg	N/A	Trace	None	2-5sq	0-1	None	Trace	Neg
T4	1	Yellow	Hazy	Neg	Neg	Neg	1.017	Neg	8.5	Neg	N/A	Neg	2-5 hyal	None	None	None	Neg	1+ CaOx
T4	8	Yellow	Hazy	Neg	Neg	Neg	1.008	Neg	8.5	Neg	N/A	Neg	None	0-1sq	None	None	Neg	Neg
T4	15	Yellow	Clear	Neg	Neg	Neg	1.009	Tr-NH	8.5	Neg	N/A	Neg	None	None	None	None	Neg	Neg
T4	22	Yellow	Clear	Neg	Neg	Neg	1.010	Neg	8.5	Trace	Neg	Neg	None	None	None	None	Neg	Neg
T4	29	Yellow	Hazy	Neg	Neg	Neg	1.007	Neg	8.5	Trace	Neg	Neg	None	None	None	None	Neg	1+ CaCarb
T4	36	Yellow	Cloudy	Neg	Neg	Neg	1.011	Small	8.5	Trace	Neg	Neg	None	6-10sq	None	None	None	2+
T4	43	Yellow	Clear	Neg	Neg	Neg	1.004	Neg	8.0	Neg	N/A	Neg	None	None	None	None	Neg	Neg
T4	50	Straw	Clear	Neg	Neg	Neg	1.003	Neg	8.0	Neg	N/A	Neg	None	None	None	0-1	Neg	Neg
T4	57	Yellow	Hazy	Neg	Neg	Neg	1.006	Neg	8.5	Neg	N/A	Neg	None	2-5sq	0-1	None	2+	Neg
T5	1	Yellow	Cloudy	Neg	Neg	Neg	1.012	Neg	8.5	Neg	N/A	Mod	None	0-1sq	0-1	0-1	Neg	2+ AmP
T5	8	Straw	Hazy	>2000	15	Neg	1.013	Mod	7.5	300	2+	Trace	None	2-5sq	2-5	2-5	Tr mixed	Neg
T5	15	Pink	Hazy	>2000	40	Neg	1.009	Large	6.0	30	1+	Neg	None	2-5sq	2-5	11-20	1+ mixed	Neg
T5	22	Straw	Clear	>2000	Neg	Neg	1.009	Large	7.0	30	Trace	Small	None	0-1sq,0-1tr	0-1	2-5	Tr mixed	Neg
T5	29	Yellow	Hazy	250	40	Neg	1.006	Small	6.0	100	1+	Small	0-1 coarse gran	2-5sq	6-10	2-5	1+ mixed	Neg
T5	36	Yellow	Hazy	100	5	Neg	1.004	Small	7.0	Neg	N/A	Neg	None	6-10sq	6-10	2-5	1+	Neg
T5	43	Yellow	Hazy	100	Neg	Neg	1.005	Neg	8.0	Neg	N/A	Neg	None	None	Neg	None	Neg	Neg
T5	50	Yellow	Hazy	Neg	80	Neg	1.006	Neg	6.0	Neg	N/A	Trace	None	0-1tr, 0-1sq	2-5	None	Neg	Neg
T5	57	Yellow	Clear	Neg	Neg	Neg	1.004	Neg	8.5	Neg	N/A	Trace	None	2-5sq	0-1	None	1+	Neg

Table S7 (cont.). Summary of urine analysis for the fixed-dose efficacy study: Treated animals T6-T10

Animal ID#	Day	Color	Appear	Glu mg/dl	Ket mg/dl	Bili mg/dl	Sp Grav NA	Blood mg/dl	pH NA	Prot mg/dl	SSA mg/dl	Leuk cells/ul	Casts per hpf	Epi cells per hpf	WBC per hpf	RBC per hpf	Bacteria per hpf	Crystals per hpf
T6	1	Yellow	Hazy	Neg	Neg	Neg	1.033	Neg	8.5	30	Tr	Neg	0-1 hyal	0-1sq	0-1	None	Neg	Neg
T6	8	Straw	Clear	Neg	Neg	Neg	1.010	Mod	6.0	100	1+	Neg	None	0-1sq,0-1tr	None	None	Neg	Neg
T6	15	Straw	Hazy	1000	Neg	Neg	1.012	Small	6.0	300	1+	Neg	None	2-5sq	0-1	None	Tr mixed	Neg
T6	22	Straw	Clear	>2000	Neg	Neg	1.012	Tr-NH	5.0	30	1+	Neg	None	None	0-1	None	Tr mixed	Neg
T6	29	Yellow	Hazy	1000	Neg	Neg	1.016	Small	6.5	100	1+	Neg	None	0-1sq	0-1	0-1	Tr mixed	Neg
T6	36	Straw	Hazy	500	Neg	Neg	1.010	Neg	6.5	Trace	Trace	Neg	None	0-1sq	None	None	Trace	Neg
T6	43	Yellow	Hazy	100	Neg	Neg	1.010	Neg	7.0	Neg	N/A	Neg	None	2-5sq	None	None	Tr mixed	Neg
T6	50	Yellow	Clear	Neg	Neg	Neg	1.011	Neg	8.0	Neg	N/A	Neg	None	None	0-1	None	Neg	Neg
T6	57	Yellow	Hazy	Neg	Neg	Neg	1.023	Neg	8.5	Trace	Trace	Neg	None	2-5sq	None	Trace	Neg	Neg
T7	1	Yellow	Clear	Neg	Neg	Neg	1.008	Neg	8.5	Neg	N/A	Neg	None	None	None	None	Neg	Neg
T7	8	Yellow	Cloudy	1000	Neg	Neg	1.014	Small	8.5	300	2+	Trace	None	0-2sq	0-1	None	Neg	Neg
T7	15	Yellow	Hazy	500	15	Neg	1.015	Small	8.5	30	1+	Neg	None	0-3sq	0-1	None	Neg	Neg
T7	22	Yellow	Hazy	500	Neg	Neg	1.010	Mod	7.5	100	2+	Neg	None	6-10sq	0-1	2-5	1+	Neg
T7	29	Yellow	Cloudy	500	15	Neg	1.011	Small	6.0	100	1+	Neg	None	6-10sq	0-1	0-1	1+	Neg
T7	36	Straw	Clear	1000	5	Neg	1.008	Neg	8.5	Trace	Neg	Neg	None	0-1sq	None	None	Neg	Neg
T7	43	Yellow	Clear	250	Neg	Neg	1.011	Neg	8.5	Trace	Neg	Neg	None	0-1sq	None	None	Trace	Neg
T7	50	Yellow	Hazy	Neg	Neg	Neg	1.010	Neg	8.5	Trace	Neg	Neg	None	0-1sq	0-1	None	Neg	Neg
T7	57	Yellow	Hazy	Neg	Neg	Neg	1.009	Neg	8.5	Neg	N/A	Neg	Nop	0-1sq	None	None	Neg	Tr CaOx
T8	1	Yellow	Hazy	Neg	Neg	Neg	1.013	Neg	8.5	Trace	Neg	Small	None	2-5sq	2-5	0-1	1+ mixed	Neg
T8	8	Yellow	Cloudy	500	Neg	Neg	1.012	Small	8.5	300	2+	Trace	None	5-8sq	0-1	None	Neg	Neg
T8	15	Yellow	Hazy	>2000	Neg	Neg	1.015	Neg	8.5	30	Neg	Neg	None	0-1sq	0-1	0-1	Neg	Neg
T8	22	Straw	Hazy	1000	Neg	Neg	1.010	Tr-NH	8.5	100	1+	Trace	None	2-5sq	0-1	0-1	Tr mixed	Neg
T8	29	Yellow	Hazy	500	Neg	Neg	1.010	Tr-H	8.0	30	Trace	Neg	None	0-3sq	None	None	Neg	Neg
T8	36	Straw	Clear	>2000	Neg	Neg	1.012	Neg	7.5	30	Trace	Neg	None	2-4sq	None	None	Neg	Neg
T8	43	Yellow	Clear	1000	Neg	Neg	1.017	Neg	8.0	Trace	Neg	Neg	None	2-5sq	0-1	None	Trace	Neg
T8	50	Yellow	Hazy	250	Neg	Neg	1.020	Neg	8.5	30	Trace	Trace	None	0-1sq	11-20	0-1	1+ mixed	Neg
T8	57	Yellow	Hazy	100	Neg	Neg	1.019	Neg	8.5	Trace	Neg	Neg	None	0-2sq	None	None	Neg	1+ CaOx
T9	1	Colorless	Clear	Neg	Neg	Neg	1.002	Neg	8.5	Neg	N/A	Small	None	0-1sq	0-1	0-1	1+ mixed	Neg
T9	8	Straw	Cloudy	1000	Neg	Neg	1.011	Small	8.5	300	2+	Neg	None	6-8sq	None	None	1+	Neg
T9	15	Colorless	Hazy	500	Neg	Neg	1.005	Neg	8.5	Trace	Neg	Small	None	0-1sq	0-1	None	Tr mixed	Neg
T9	22	Yellow	Hazy	1000	Neg	Neg	1.015	Tr-H	8.5	100	1+	Neg	None	2-5sq	0-1	None	Tr mixed	Neg
T9	29	Yellow	Hazy	1000	5	Neg	1.011	Tr-H	8.5	30	Trace	Neg	None	0-1sq	None	None	Neg	Neg
T9	36	Yellow	Clear	>2000	15	Neg	1.010	Small	6.0	30	Trace	Neg	None	0-3sq	None	None	Neg	Neg
T9	43	Yellow	Hazy	500	Neg	Neg	1.012	Neg	8.5	Trace	Neg	Neg	None	6-10sq	0-1	None	1+	Neg
T9	50	Straw	Hazy	Neg	Neg	Neg	1.005	Tr-H	8.5	Neg	N/A	Trace	None	0-1sq	0-1	0-1	Tr mixed	Neg
T9	57	Yellow	Hazy	Neg	Neg	Neg	1.015	Neg	8.5	Neg	N/A	Neg	None	0-1sq	None	None	Neg	Tr CaOx
T10	1	Yellow	Hazy	Neg	Neg	Neg	1.006	Neg	8.5	Neg	N/A	Neg	None	None	None	None	Neg	Tr AmP
T10	8	Straw	Hazy	>2000	Neg	Neg	1.009	Mod	6.0	300	1+	Neg	None	0-1tr	0-1	0-1	Neg	Neg
T10	15	Yellow	Hazy	1000	Neg	Neg	1.014	Large	6.0	100	2+	Neg	0-1fine gr	2-4sq	0-1	None	Neg	Neg
T10	22	Straw	Hazy	>2000	5	Neg	1.010	Small	6.0	100	1+	Neg	None	0-1sq,0-1tr	0-1	None	Neg	Neg
T10	29	Yellow	Hazy	500	5	Neg	1.007	Small	6.0	30	Trace	Neg	None	0-1sq	None	None	Neg	Neg
T10	36	Straw	Clear	>2000	5	Neg	1.015	Tr-H	6.0	100	1+	Neg	None	0-1sq	None	None	Neg	Neg
T10	43	Yellow	Clear	100	Neg	Neg	1.009	Neg	6.0	Trace	Neg	Neg	None	0-1sq	None	None	Trace	Neg
T10	50	Yellow	Hazy	Neg	Neg	Neg	1.014	Neg	8.5	Trace	Neg	Neg	None	0-1sq	None	None	Neg	Neg
T10	57	Yellow	Clear	Neg	Neg	Neg	1.017	Neg	8.5	Trace	Neg	Neg	None	0-1sq	None	None	Neg	Neg

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