Pharmacokinetics and Pharmacodynamics of MK-5046, a Bombesin Receptor Subtype-3 (BRS-3) Agonist, in Healthy Subjects

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SUPPLEMENTARY INFORMATION

Safety and Tolerability

There was one serious adverse experience (ventricular tachycardia) and the subject was discontinued. He experienced four consecutive wide-complex beats on cardiac telemetry at 2 hours and 48 minutes following administration of 20 mg of MK-5046. The subject was asymptomatic with normal vital signs. An electrocardiogram performed within 10 minutes showed normal sinus rhythm with early repolarization. Electrolytes, calcium, magnesium, phosphorus, and glucose were within normal limits. Plasma MK-5046 concentrations were 106 nM at 2 hours and 46 nM at 3 hours postdose. There were no further events on telemetry except a single episode of 2 premature ventricular beats at 43 hours post dose; the subject was monitored for a total of 46 hours. This event was assessed by the investigator as possibly drug related. Follow up studies (including cardiologist consultation, echocardiography, Holter monitoring, physical examination, safety laboratory values, and electrocardiography) were unremarkable.

A second subject (AN21) was discontinued due to increased body temperature following a single 120 mg MK-5046 dose. The subject reported flushing/feeling warm at 140 minutes postdose, which was mild and lasted 24 minutes. Body temperatures at 2 and 3 hours were 37.3°C and 36.9°C, respectively. His temperature increased starting 6 hours postdose ranging from 37.8°C to 39.0°C and resolved spontaneously (Figure S5). There were no other signs or symptoms and the subject had no clinical or laboratory signs of infection at 24 and 48 hours. This event was assessed by the investigator as definitely drug related. On post-study evaluation, the subject noted no complaints and had a normal physical examination, safety laboratory values, and electrocardiogram. The subject exhibited no temperature increase on the previous dose of 80 mg (Figure S5).

Statistical Methods

For vital sign data in Tables S2 and S3, the mean and standard error summary statistics were computed for change from baseline by dose. In addition, model-based least squares means and standard errors (SE) were provided for difference from placebo by dose. A mixed model with treatment as fixed effect and subject as a random effect was used to calculate difference from placebo.

Table S1. Trial Demographics

Panel	Site	Age (y)	Weight (kg)	BMI (kg/m^2)	African American	Caucasian	Hispanic	Native American	Multiracial
A	TJU	36 (31-39)	86.3 (70-101)	26.5 (20-31)	8			1	
B	TJU	33 (20-40)	84.2 (65-95)	26.3 (23-28)	5	2			1
C	TJU, Prism	36 (25-45)	103.4 (91-123)	33.0 (31-36)	4	4	1		

Age, weight, and BMI are given as the mean (range). TJU, Thomas Jefferson University.

Table S2. Vital Signs, change from baseline at 1 hour after dosing

Dose (mg)	Panel	Systolic BP (mmHg)			Diastolic BP (mmHg)			Heart Rate (BPM)			Temperature (C)		
		N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
Placebo	A,B,C	27	1.30	1.97	27	-0.07	1.18	27	0.13	1.22	27	-0.03	0.06
Placebo (7 hours)*	A,B,C	27	2.97	1.91	27	-2.48	1.27	27	7.39	1.44	27	0.31	0.06
10	A	6	-6.78	3.81	6	-0.78	2.76	6	-2.44	2.48	6	0.32	0.11
20	A	6	1.72	3.69	6	3.61	3.97	6	-0.39	1.77	6	0.07	0.08
40	A,B	12	1.86	2.38	12	4.28	1.47	12	-1.61	1.67	12	0.06	0.09
40, fed	B	6	1.17	2.76	6	-1.72	5.03	6	6.17	2.76	5	-0.10	0.15
80	A,C	14	5.24	2.79	14	4.19	2.20	14	0.81	2.45	14	0.24	0.05
120, first dose[†]	B,C	23	6.79	2.02	23	7.57	1.42	23	-5.46	1.15	23	0.16	0.06
120, second dose[‡]	B,C	11	2.32	1.52	11	-0.55	1.37	11	2.11	1.58	11	0.31	0.09
160	A,B	12	12.53	2.16	12	9.50	3.20	12	6.22	5.81	12	0.09	0.08

*7 hours after the first dose; control for second dose of 120 mg given 6 hours apart

[†]Includes both 120 mg single dose and first dose of 120 mg given 6 hours apart

[‡]1 hour after the second dose of 120 mg given 6 hours apart

Table S3. Vital Signs, placebo-subtracted change from baseline at 1 hour after dosing

Dose (mg)	Panel	Systolic BP (mmHg)			Diastolic BP (mmHg)			Heart Rate (BPM)			Temperature (C)		
		N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
10	A	6	-8.06	4.23	6	-0.70	3.37	6	-2.51	3.89	6	0.35	0.13
20	A	6	0.43	4.24	6	3.68	3.37	6	-0.45	3.90	6	0.08	0.13
40	A,B	12	0.55	3.25	12	4.36	2.59	12	-1.69	2.99	12	0.08	0.10
40, fed	B	6	-0.16	4.26	6	-1.72	3.38	6	6.10	3.91	5	-0.08	0.14
80	A,C	14	3.93	3.08	14	4.24	2.46	14	0.81	2.83	14	0.27	0.09
120, first dose[†]	B,C	23	5.48	2.66	23	7.60	2.12	23	-5.55	2.44	23	0.19	0.08
120, second dose[‡]	B,C	11	-0.65	3.35	11	1.90	2.67	11	-5.23	3.08	11	-0.01	0.10
160	A,B	12	11.22	3.26	12	9.56	2.59	12	6.05	2.99	12	0.11	0.10

[†]Includes both 120 mg single dose and first dose of 120 mg given 6 hours apart

[‡]1 hour after the second dose of 120 mg given 6 hours apart (placebo for subtraction uses all data from 7 hours after the first dose; see Table S1)

Table S4. Time Course of Clinical Adverse Experiences (AE) Following Oral Doses of MK-5046.

	Cold		Jittery		Hot		Erection	
	onset (min)	**duration (min)**	**onset (min)**	**duration (min)**	**onset (min)**	**duration (min)**	**onset (min)**	**duration (min)**
mean	58.8	60.7	49.4	80.9	72.4	81.0	52.0	55.4
SD	36.0	39.0	18.9	42.5	49.0	76.7	41.2	64.9
n	15	15	14	14	36	36	10	10
min	25	5	19	21	15	1	25	5
max	165	140	93	160	230	391	165	215

AE groups are defined in Figure 5. Analysis set includes only AE on MK-5046; AE during placebo treatment are excluded.

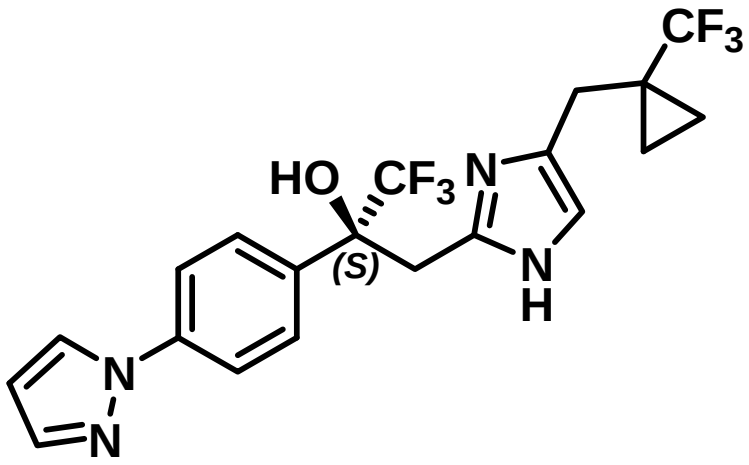

Figure S1. Structure of MK-5046, (2*S*)-1,1,1-Trifluoro-2-[4-(1*H*-pyrazol-1-yl)phenyl]-3-(4-{[1-(trifluoromethyl)cyclopropyl]methyl}-1*H*-imidazol-2-yl)propan-2-ol, from ref 24.

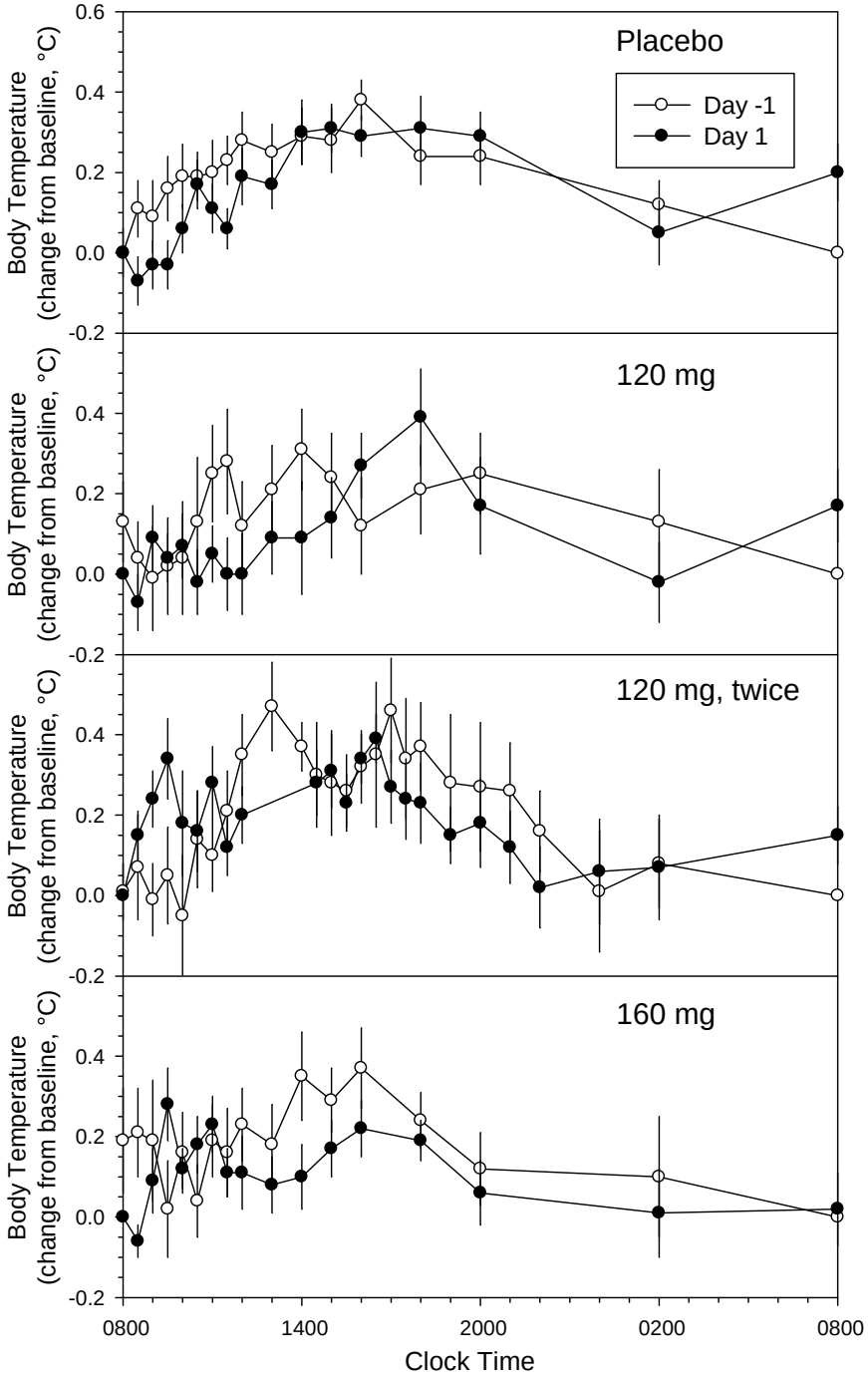

Figure S2. Effect of MK-5046 on body temperature. Data are change from the baseline (0 hours, 0800). Open circles are the 24 hours preceding dosing and the black circles are the 24 hours after dosing. Data are arithmetic mean ±SE in the 120 mg (N=12/group), 120mg dose twice (N=11/group, with N=8 for some of the predosing points due to missing data), 160 mg (N=12/group), and placebo-dosed groups (N=27 except N=22 at the 5- and 6-hour points). Placebo time points sampled only with the twice dosing cohort had an N=5 and were omitted.

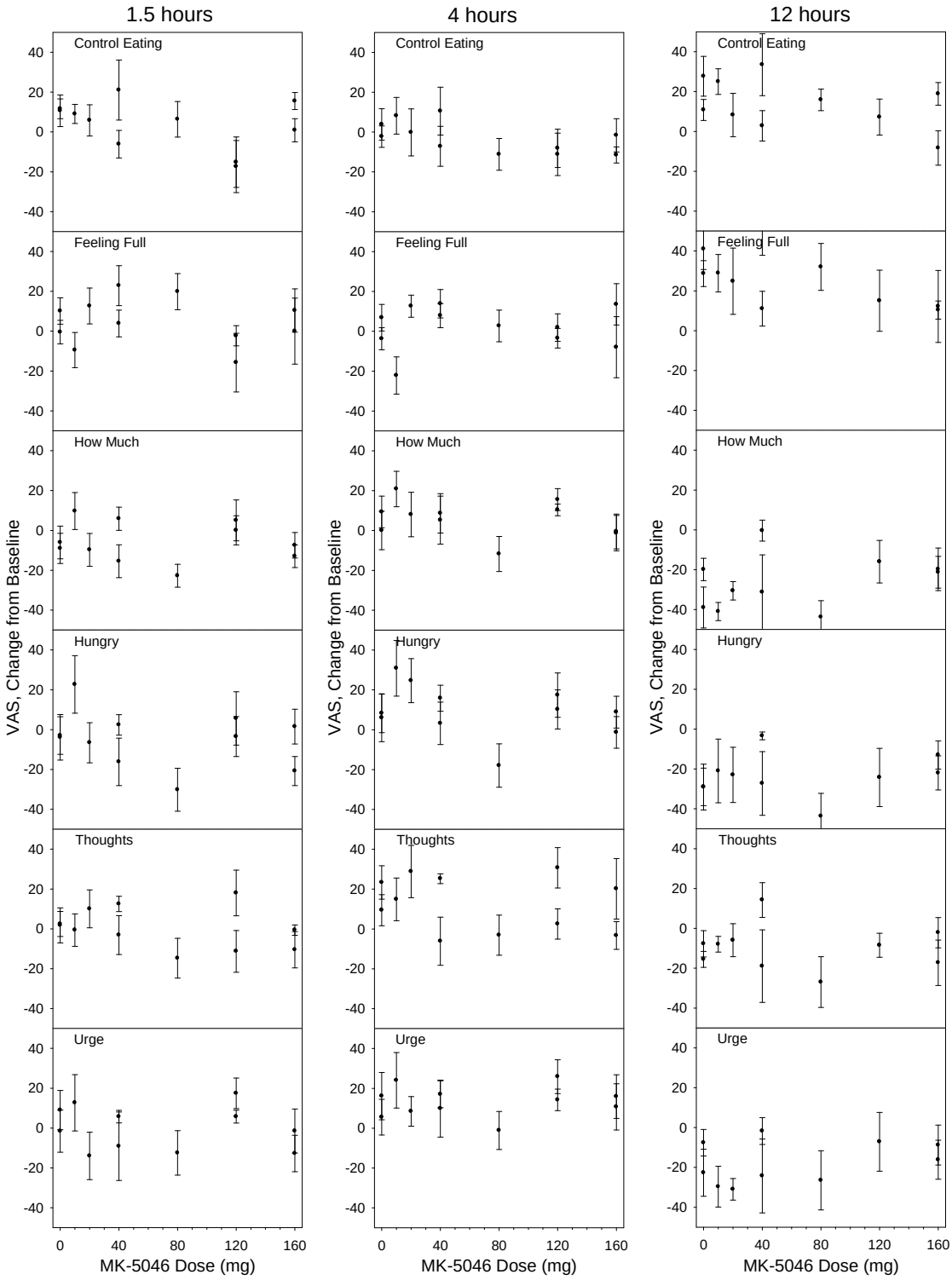

Figure S3. Visual Analog Scales for Hunger/Satiety. Data are mean ±SE of change from predose (0800) baseline for placebo (N=10) and the indicated doses of MK-5046 (N=6) at the indicated times (1.5, 4, and 12 hours) after dosing. The verbatim questions (in the order in which they were presented) are: How hungry do you feel? How much are you bothered or distracted by thoughts of food? How full do you feel? How much do you think you can eat? How easy do you find it to control your eating? How strong is your urge to eat?

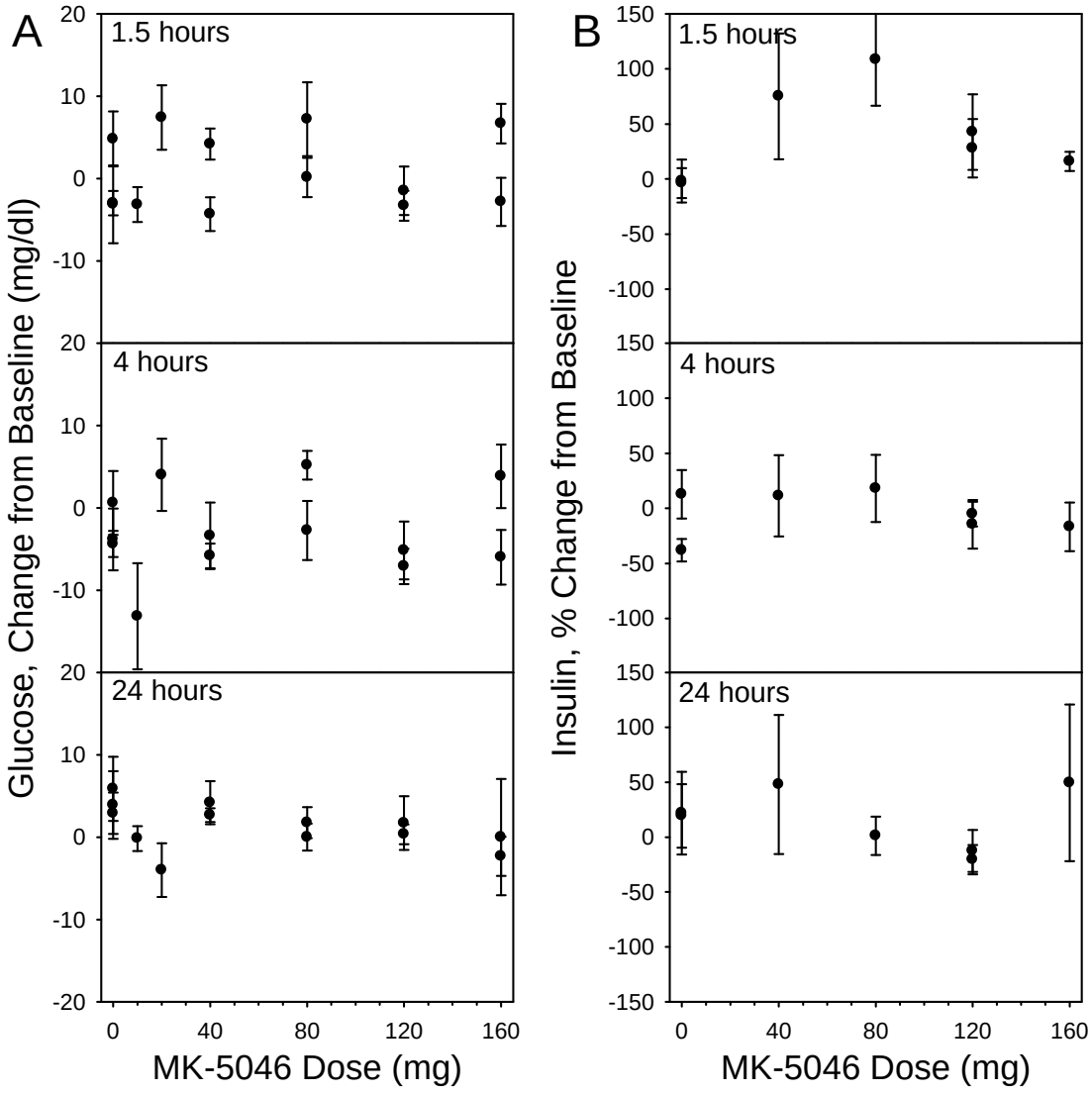

Figure S4. Effect of MK-5046 on glucose and insulin levels. Glucose and insulin were measured in the fasting state at predose and 1.5, 4, and 24 hours after dosing. Glucose was measured in Panels A, B, and C; insulin was measured only in panels B and C. The mean and SE for each dose and panel are reported separately. Arithmetic mean predose glucose levels were 86 to 94 mg/dl. Geometric mean predose insulin levels were 4.5 to 10.9 µIU/ml.

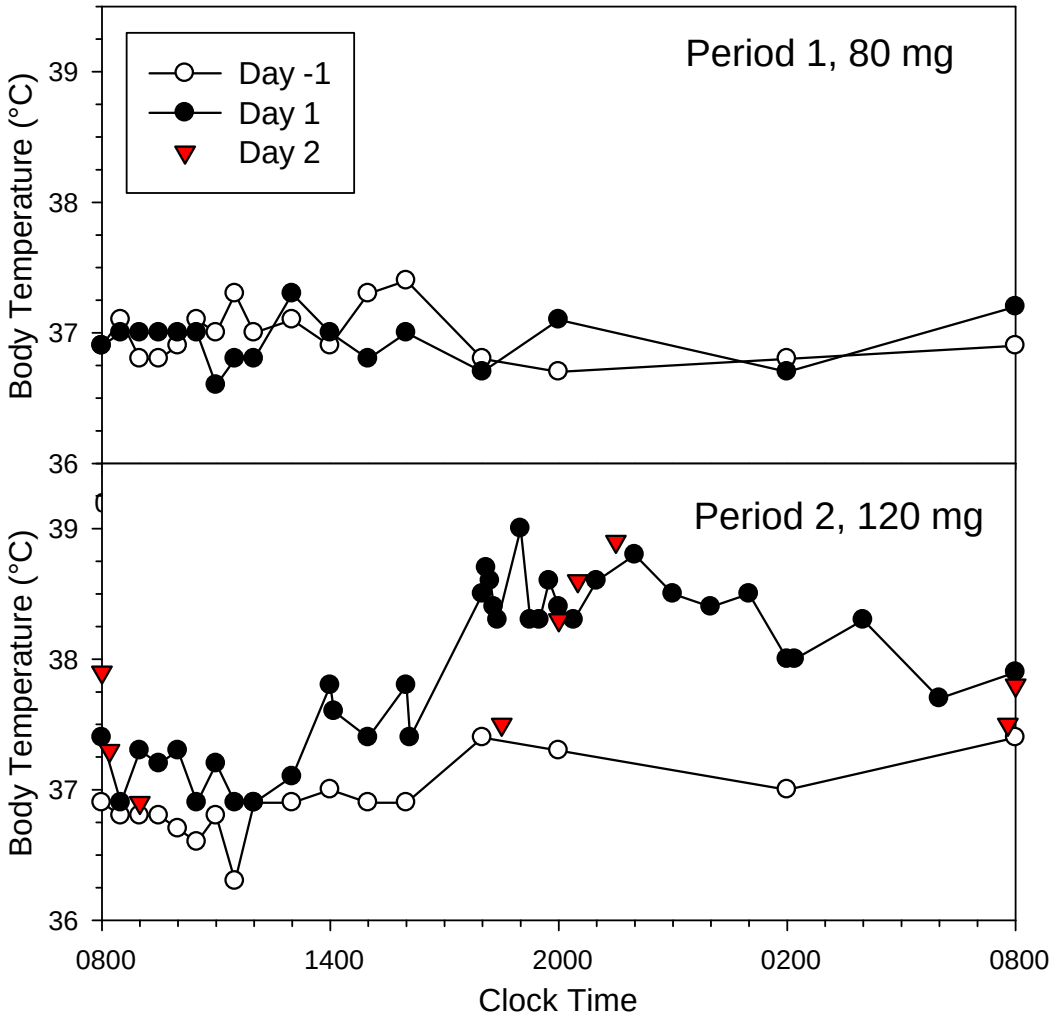

Figure S5. Body temperature in Subject AN21. Dosing was at 0800. Open circles are the day preceding dosing, black circles the day of dosing, and red triangles the day following the day of dosing. The top graph depicts results of dosing 80 mg MK-5046 and the bottom graph depicts results of dosing 120 mg.