Title: A randomized phase 1 study of safety, tolerability, and pharmacokinetics of MK-1088, a novel dual adenosine receptor antagonist, in healthy adult participants

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Online Resource 1 MK-1088 dosing schedule

Panel	**Period 1**		**Period 2[c]**			**Period 3[c]**			**Period 4**		**Period 5**	
Panel A[a] (n = 8)	1 mg		10 mg			50 mg			150 mg		50 mg[b]	
Panel B[a] (n = 8)		3 mg		25 mg			100 mg			224 mg		cancelled

[a]In each period, 6 participants received MK-1088 and 2 participants received placebo

[b]Dose given with a high-fat meal. The assigned treatment of periods 3 and 5 (fasted/fed) in panel A were the same for each participant such that the same participants received active drug of matching placebo in both treatment periods

[c]A pharmacokinetic break for all participants occurred after completion of the 25-mg dose in panel B (period 2) and the 100-mg dose in panel B (period 3)

Online Resource 2 Baseline characteristics

Baseline characteristic	Panel A	Panel B	Total
Male[a]	8 (100)	8 (100)	16 (100)
Age, median (range), years	33.0 (20–43)	33.0 (21–38)	33.0 (20–43)
Race[a]			
White	8 (100)	8 (100)	16 (100)
Ethnicity[a]			
Not Hispanic or Latino	8 (100)	7 (88)[b]	15 (94)

[a]Data are presented as *n* (%)

[b]Ethnicity was unknown for one participant in panel B

Online Resource 3 Model-based geometric mean C_{12h}

Fasted dose	**n**	**GM, µM (95% CI)[a]**	**Posterior probability (GM > 0.3 µM), %**
1 mg	6	0.008 (0.005–0.011)	0
3 mg	6	0.021 (0.015–0.030)	0
10 mg	6	0.072 (0.050–0.104)	0
25 mg	6	0.180 (0.125–0.260)	0.04
50 mg	6	0.348 (0.241–0.503)	94.8
100 mg	6	0.769 (0.532–1.110)	100
150 mg	6	1.204 (0.834–1.740)	100
224 mg	6	1.834 (1.270–2.650)	100

C_{12h} concentration at 12 hours; *CI* confidence interval; *GM* geometric mean

[a]Least-squares means and CIs were obtained by a linear mixed-effects model containing dose level and participants as fixed effects and a random effect, respectively

Online Resource 4 Assessment of dose proportionality of plasma MK-1088

	Slope estimate[a] (95% CI)	**Predicted fold-change[b] (95% CI)**
AUC_{0-inf},[c] hr*µmol/L	1.01 (0.98–1.05)	239.4 (199.43–286.86)
AUC_{0-24h},[c] hr*µmol/L	0.99 (0.94–1.03)	209.72 (161.89–263.48)
C_{max},[c] µmol/L	0.93 (0.88–0.99)	157.26 (118.54–209.21)

AUC_{0-24h} area under the curve from 0 to 24 hours; *AUC_{0-inf}* area under the concentration-time curve extrapolated to infinity; *CI* confidence interval; *C_{max}* maximum concentration

[a]Least squares estimates and CIs were obtained by a linear mixed model containing natural log of the dose as a fixed effect and participants within the panel as a random effect

[b]Expected fold-change with perfect dose proportionality, defined as a slope of 1.0, was 224. The predicted fold-change was calculated as the parameter at highest dose level over the lowest dose level

[c]Dose range from 1 mg to 224 mg (*n* = 6, each dose) administered in the fasted state was analyzed