Supplemental Material -- Supplemental Tables

Table S1. Trial Diagram

Panel	Period 1[g]			PK Break[e]	Period 2 [g]			Period 3 [g]		
A[a,b]	10 mg				200 mg			200 mg no PE[f]		
B[a,b]		35 mg				300 mg			120 mg with 720 mg Labrasol®[h]	
C[a,b]			100 mg[c]				100 mg with 1800 mg Na caprate[c]			40 mg with 720 mg Na caprate[c,d]
D[a,i]	20 mg with 360 mg Na caprate[i,j]				40 mg with 720 mg Na caprate[i,j]			40 mg with 360 mg Na caprate + food[i,j]		
F[a,i]	40 mg Na caprate EC[i, j]				40 mg Na caprate HG[i,j]			40 mg either Na caprate HG + food[i,j]		

EC=enteric coated, HG=hard gelatin immediate release, PE=permeation enhancer; PK=Pharmacokinetics, Na caprate (sodium caprate)

a. The suggested doses (with the exception of the starting dose) may have been adjusted downward based on evaluation of safety, tolerability, PK and/or pharmacodynamic data observed in previous intervention periods..
b. Within each Panel, 9 participants were randomized to receive MK-0616 + 1,800 mg Labrasol® (unless otherwise indicated above) and 3 participants received matching placebo according to a computer-generated allocation schedule. Dose escalation Panels were further sub-divided into 2 dosing cohorts (main cohort and an expansion cohort) with each cohort consisting of 6 subjects. Expansion cohorts initiated after at least 24 hours after the first cohort based upon acceptable safety and tolerability.
c. The assigned intervention for Panel C, Periods 1, 2 and 3 were the same, such that the same participants received active drug or matching placebo in all intervention periods.
d. The PE (sodium caprate) evaluated in Panel C, Period 3 was determined after a review of the available PK data from previous periods.
e. PK data up to 35 mg and safety data up to 100 mg was reviewed before continuing the dose escalation.
f. Panel A Period 3 (200 mg no PE) was administered as an oral suspension.
g. There was an interval of at least 4 days between dose escalations across panels and at least a 7-day (Panel A, B and C), 14-Day (Panel D) or 21-Day (Panel F) washout between consecutive dosing for any given subject. Participants were monitored for safety by reviewing adverse events, laboratory safety tests, vital signs, 12-lead ECGs, and physical examinations.
h. The decision to initiate Panel B Period 3 and the dose was based upon preliminary PK from previous dose escalation periods.
i. In Panel D and F, 9 participants were randomized to receive MK-0616 + Na caprate and 3 participants received matching placebo according to a computer-generated allocation schedule.
j. The assigned intervention for Panel D, Periods 1, 2 and 3 and Panel F, Periods 1, 2 and 3 were the same, such that the same participants will receive active drug or matching placebo in all intervention periods. The decision on the capsule type (EC or HG) administered for Panel F, Period 3 was based upon preliminary PK from Panel F, Periods 1 and 2.

Table S2. Specific adverse events reported during Study-001 with an incidence ³0% in ³1 treatment group by system organ class

Participants, *n* (%)	MK-0616 *n* = 51	Placebo *n* = 23
Gastrointestinal disorders		
Abdominal discomfort	1 (2.0)	1 (4.3)
Diarrhea	4 (7.8)	0 (0.0)
Dyspepsia	2 (3.9)	0 (0.0)
Nausea	1 (2.0)	1 (4.3)
Regurgitation	0 (0.0)	1 (4.3)
Toothache	1 (2.0)	0 (0.0)
Vomiting	1 (2.0)	0 (0.0)
General disorders and administration site conditions		
Asthenia	1 (2.0)	1 (4.3)
Fatigue	1 (2.0)	0 (0.0)
Medical device site reaction	0 (0.0)	1 (4.3)
Pyrexia	1 (2.0)	0 (0.0)
Vessel puncture site pain	2 (3.9)	0 (0.0)
Infections and infestations		
Gastroenteritis	2 (3.9)	0 (0.0)
Nasopharyngitis	7 (13.7)	4 (17.4)
Oral herpes	1 (2.0)	0 (0.0)
Pharyngitis	0 (0.0)	1 (4.3)
Rhinitis	1 (2.0)	0 (0.0)
Tooth Abscess	1(2.0)	0 (0.0)
Injury, poisoning and procedural complications		
Ligament sprain	1 (2.0)	1 (4.3)
Wound	1 (2.0)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Back Pain	1 (2.0)	0 (0.0)
Nervous system disorders		
Dizziness	1 (2.0)	0 (0.0)
Dizziness postural	0 (0.0)	1 (4.30
Headache	14 (27.5)	5 (21.7)
Paraesthesia	0 (0.0)	0 (0.0)
Renal and urinary disorders		
Hematuria	0 (0.0)	1 (4.3)
Respiratory, thoracic and mediastinal disorders		
Respiratory tract irritation	1 (2.0)	0 (0.0)
Throat irritation	1 (2.0)	0 (0.0)
Skin and subcutaneous tissue disorders		
Rash maculo-papular	1 (2.0)	0 (0.0)

Every participant was counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 21.1.

Table S3. Comparison of plasma pharmacokinetics following administration of MK-0616 without or with 1800 mg Labrasol®, or with 1800 mg Labrasol® or 1800 mg sodium caprate, to healthy male participants.

	MK-0616, single dose (mg)		
Parameter	**200 mg MK-0616 without Labrasol® (*n* = 8)**	**200 mg MK-0616 with Labrasol® (*n* = 8)**	**GMR without/with Labrasol® (90% CI)**
$AUC_{0-\infty}$[a] (h•nmol/L)	556 (448, 690)	1250 (946, 1650)	0.45 (0.35, 0.57)
AUC_{last}[a] (h•nmol/L)	481 (394, 588)	1160 (880, 1520)	0.42 (0.33, 0.52)
C_{max}[a] (nmol/L)	7.84 (6.32, 9.72)	45.3 (24.6, 83.2)	0.17 (0.11, 0.28)
T_{max}[b] (h)	14.53 (0.50, 36.00)	2.02 (1.07, 5.00)	----
$t_{1/2}$[c] (h)	56.41 (12.0)	95.47 (27.7)	----
	100 mg MK-0616 with Sodium Caprate (*n* = 9)	**100 mg MK-0616 with Labrasol® (*n* = 9)**	**GMR Caprate/Labrasol® (90% CI)**
$AUC_{0-\infty}$[a] (h•nmol/L)	979 (781, 1230)	1080 (860, 1350)	0.91 (0.70, 1.17)
AUC_{last}[a] (h•nmol/L)	855 (688, 1060)	1020 (821, 1270)	0.84 (0.65, 1.08)
C_{max}[a] (nmol/L)	41.3 (26.6, 64.0)	46.2 (25.4, 84.0)	0.89 (0.46, 1.73)
T_{max}[b] (h)	1.50 (1.00, 3.00)	1.50 (1.00, 3.00)	----
$t_{1/2}$[c] (h)	56.80 (10.2)	81.52 (16.9)	----

Values shown are geometric mean (95% confidence interval) unless otherwise indicated.

GMR = geometric mean ratio; CI = confidence interval; $AUC_{0-\infty}$ = area under the concentration versus time curve from pre-dose to infinity; AUC_{last} = AUC from pre-dose to last measurement taken; C_{max} = maximum observed plasma concentration; C_{24} = plasma concentration observed 24 hours post-dose; T_{max} = time when C_{max} was first observed; $t_{1/2}$ = apparent terminal half-life.

[a]Back-transformed least squares mean and 95% confidence interval from linear mixed effects model performed on natural log-transformed values.

[b]Median (min, max) reported for C_{24} and T_{max}.

[c]Geometric mean and percent geometric CV reported for $t_{1/2}$.

Table S4. Food effect comparison of plasma MK-0616 pharmacokinetics following administration of 40 mg MK-0616 with 720 mg sodium caprate to healthy male participants in the fasted state or 30 min after a high-fat breakfast, and in the fasted state or in the fasted state with a lower-fat meal 30 min after dose.

	MK-0616, single dose (mg)		
Parameter	**40 mg MK-0616 fasted (*n* = 9)**	**40 mg MK-0616 fed (30 min pre-dose) (*n* = 9)**	**GMR fed/fasted (90% CI)**
$AUC_{0-\infty}$[a] (h•nmol/L)	758 (594, 968)	251 (196, 320)	0.33 (0.28, 0.39)
AUC_{0-24}[a] (h•nmol/L)	171 (138, 211)	65.7 (53.2, 81.3)	0.39 (0.32, 0.46)
AUC_{last}[a] (h•nmol/L)	694 (546, 883)	209 (164, 266)	0.30 (0.25, 0.0.37)
C_{max}[a] (nmol/L)	14.3 (11.0, 18.7)	3.50 (2.68, 4.57)	0.25 (0.18, 0.33)
C_{24}[a] (nmol/L)	7.80 (6.30, 9.65)	2.92 (2.36, 3.61)	0.37 (0.32, 0.44)
T_{max}[b] (h)	1.50 (1.00, 2.00)	8.08 (4.87, 24.00)	----
$t_{1/2}$[c] (h)	97.20 (31.8)	58.88 (26.8)	----
	40 mg MK-0616 fasted (*n* = 8)	**40 mg MK-0616 fed (30 min post-dose) (*n* = 7[d])**	**GMR fed/fasted (90% CI)**
$AUC_{0-\infty}$[a] (h•nmol/L)	505 (398, 642)	452 (353, 577)	0.89 (0.78, 1/03)
AUC_{0-24}[a] (h•nmol/L)	138 (117, 164)	132 (111, 158)	0.96 (0.82, 1.11)
AUC_{last}[a] (h•nmol/L)	454 (364, 566)	409 (327, 513)	0.90 (0.79, 1.03)
C_{max}[a] (nmol/L)	9.21 (7.37, 11.5)	7.29 (5.75, 9.25)	0.79 (0.64, 0.98)
C_{24}[a] (nmol/L)	6.03 (5.16, 7.05)	5.83 (4.93, 6.91)	0.97 (0.81, 1.16)
T_{max}[b] (h)	0.75 (0.50, 2.00)	1.00 (0.42, 36.03)	----
$t_{1/2}$[c] (h)	46.37 (23.7)	51.07 (9.4)	----

Values shown are geometric mean (95% confidence interval) unless otherwise indicated.
GMR = geometric mean ratio; CI = confidence interval; $AUC_{0-\infty}$ = area under the concentration versus time curve from pre-dose to infinity; AUC_{last} = AUC from pre-dose to last measurement taken; C_{max} = maximum observed plasma concentration; C_{24} = plasma concentration observed 24 hours post-dose; T_{max} = time when C_{max} was first observed; $t_{1/2}$ = apparent terminal half-life.
[a]Back-transformed least squares mean and 95% confidence interval from linear mixed effects model performed on natural log-transformed values.
[b]Median (min, max) reported for C_{24} and T_{max}.
[c]Geometric mean and percent geometric CV reported for $t_{1/2}$.
[d]*n* = 6 for $AUC_{0-\infty}$ and $t_{1/2}$.

Table S5. Specific adverse events reported during Study-003 with an incidence ³0% in ³1 treatment group by system organ class

Participants, *n* (%)	MK-0616 *n* = 31	Placebo *n* = 23
Eye disorders		
Vision blurred	1 (3.2)	0 (0.0)
Gastrointestinal disorders		
Constipation	1 (3.2)	1 (11.1)
Diarrhea	3 (9.7)	0 (0.0)
Dry mouth	2 (6.5)	0 (0.0)
Dyspepsia	1 (3.2)	0 (0.0)
Gastroesophageal reflux disease	3 (9.7)	0 (0.0)
Nausea	1 (3.2)	0 (0.0)
Regurgitation	1 (3.2)	0 (0.0)
General disorders and administration site conditions		
Asthenia	1 (3.2)	0 (0.0)
Hunger	1 (3.2)	0 (0.0)
Infections and infestations		.
Conjunctivitis	0 (0.0)	1(11.1)
Oral herpes	1 (3.2)	0 (0.0)
Injury, poisoning and procedural complications		
Bone contusion	1 (3.2)	0 (0.0)
Post lumbar puncture syndrome	0 (0.0)	1 (11.1)
Metabolism and nutrition disorders		
Decreased appetite	0 (0.0)	1 (11.1)
Impaired fasting glucose	2 (6.5)	0 (0.0)
Musculoskeletal and connective tissue disorders		
Arthralgia	1 (3.2)	0 (0.0)
Back Pain	4 (12.9)	1 (11.1)
Limb discomfort	1 (3.2)	0 (0.0)
Neck Pain	1 (3.2)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Breast fibroma	0 (0.0)	1 (11.1)
Nervous system disorders		
Dizziness	2 (6.5)	2 (22.2)
Dizziness postural	0 (0.0)	1 (11.1)
Headache	5 (16.1)	1 (11.1)
Somnolence	0 (0.0)	1 (11.1)
Psychiatric disorders		
Abnormal dreams	1 (3.2)	0 (0.0)
Insomnia	1 (3.2)	0 (0.0)
Restlessness	0 (0.0)	1 (11.1)
Respiratory, thoracic and mediastinal disorders		
Nasal congestion	2 (6.5)	0 (0.0)
Skin and subcutaneous tissue disorders		
Dermatitis contact	0 (0.0)	1 (11.1)
Erythema	0 (0.0)	1 (11.1)
Hyperhidrosis	1 (3.2)	0 (0.0)
Skin irritation	2 (6.5)	0 (0.0)
Vascular disorders		
Flushing	1 (3.2)	0 (0.0)

Every participant was counted a single time for each applicable row and column.
Adverse event terms are from MedDRA Version 23.1.