The Human Pharmacokinetics of Elismetrep, a TRPM8 Migraine-Associated Channel Blocker (MACB), are Well-Suited for a Migraine Therapeutic

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Background

- Elismetrep is an oral, highly selective blocker of TRPM8, a polymodal gated cation channel associated with migraine in genome-wide association studies, that is being developed for the acute treatment of migraine
- Elismetrep has a good safety profile in 13 completed clinical trials (4 Phase 2 and 9 Phase 1) with 1,055 people exposed.
- A Phase 2b study evaluating doses of 2-20 mg in the acute treatment of migraine established proof of concept for TRMP8 blockade as a novel approach to treating migraine
- Here we present the pharmacokinetic profile of elismetrep with PK data from:
  - Single and multiple ascending dose studies using a dry-filled capsule reference formulation containing crystalline elismetrep
  - PK data with an optimized liquid-filled softgel capsule (LSGC) formulation that affords more rapid absorption and that will be used in Phase 3 studies
  - A statin drug-drug interaction study evaluating the potential of elismetrep to inhibit CYP3A4 and OATP1B1

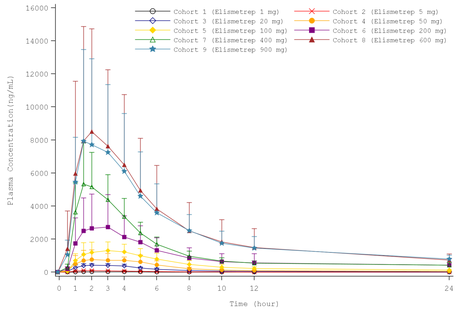
Methods

- A single ascending dose evaluated doses from 1-900 mg in serial cohorts of young healthy male volunteers (N=72 dosed in cohorts of 8 per dose cohort with 6 allocated to elismetrep and 2 to placebo). Dosing was in the morning in the fasted state. The study also evaluated the impact of food, gender, age on PK.
- A multiple ascending dose study evaluated doses of 20 to 400 mg QD x 8 days in serial cohorts of young male healthy volunteers (N=48 dosed in cohorts of 12 per dose cohort (9 allocated to elismetrep and 3 to placebo in each cohort). Dosing was in the morning in the fasted state.
- A formulation bio-comparison study was conducted in (N=30, 17 men, 13 women) to compare the PK of an optimized liquid filled soft gel capsule (LSGC) formulation to the dry-filled reference capsules used in the other studies including Phase 2b. Dosing was in the morning in the fasted state. The study used a crossover design with a 1-week washout between dosing periods.
- A drug-drug interaction study evaluated the impact of multiple 150 mg doses of elismetrep on the PK of a single dose of rosuvastatin 10 mg and of simvastatin 40 mg in healthy male and female volunteers (N=28) 1. Dosing was in the morning in the fasted state.

Single and Multiple Dose PK

- Absorption was rapid with the dry-filled capsule formulation containing crystalline elisimetrep
- Single and multiple dose PK are dose proportional
- The terminal elimination half-life of elismetrep was independent of dose, with geometric mean values ranging from ~11 to 21 h
- Modest accumulation of ~20-30% at steady state
- Food resulted in 13% and 47% higher in AUC and C_{max} with no impact on T_{max}
- Age had no effect on the PK of elismetrep
- The fraction of dose excreted in the urine as unchanged drug is <1%

Mean Plasma Concentrations Following Single Doses

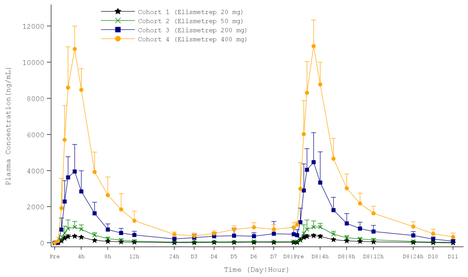


Plasma PK Parameter Values Following Single Doses

Parameter	1 mg (n=6)	5 mg (n=6)	20 mg (n=6)	50 mg (n=6)	100 mg (n=6)	200 mg (n=6)	400 mg (n=6)	600 mg (n=6)	900 mg (n=6)
$AUC_{0\text{-}inf}$ (ng*h/mL)	117.9 (24.0)	630.6 (23.0)	3260.2 (33.8)	6532.0 (26.7)	12743.8 (43.7)	27789.4 (63.5)	41368.8 (30.4)	77590.8 (57.9)	71740.8 (39.4)
C_{max} (ng/mL)	18.11 (23.3)	101.75 (18.2)	454.71 (26.3)	929.04 (53.9)	1292.33 (42.3)	2417.73 (69.6)	5241.58 (43.7)	7653.27 (76.2)	7715.69 (54.1)
T_{max} (h)	3.50	2.00	2.50	3.00	3.00	3.00	1.50	2.50	1.53
$t_{1/2}$ (h)	11.17 (34.1)	16.85 (60.1)	16.01 (27.2)	12.48 (39.6)	18.04 (32.5)	17.60 (11.6)	16.72 (35.4)	20.72 (93.4)	12.69 (34.4)

Values are LS Means (% CV) except for Tmax where medians are shown

Mean Plasma Concentrations Following Multiple Doses



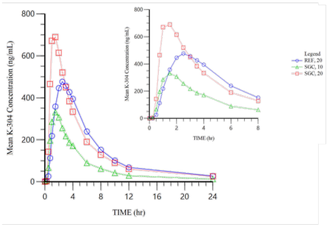
Plasma PK Parameter Values Following Multiple Doses

Parameter	20 mg QD		50 mg QD		200 mg QD		400 mg QD	
	Day 1 (n=9)	Day 8 (n=9)	Day 1 (n=9)	Day 8 (n=9)	Day 1 (n=9)	Day 8 (n=9)	Day 1 (n=9)	Day 8 (n=8)
$AUC_{0\text{-}24h}$ (ng*h/mL)	2229.9 (17.3)	2772.1 (20.2)	5282.7 (30.8)	6637.0 (25.2)	21857.0 (24.0)	27470.2 (32.5)	60553.7 (18.1)	71486.3 (12.9)
$AUC_{0\text{-}inf}$ (ng*h/mL)	2511.2 (19.3)	3771.0 (22.3)	5802.0 (30.3)	10287.4 (24.0)	25295.4 (21.6)	40921.8 (34.3)	65336.9 (17.5)	107943.9 (25.9)
C_{max} (ng/mL)	396.43 (10.7)	444.86 (13.2)	925.26 (37.4)	1073.78 (24.7)	4101.20 (37.7)	4539.41 (43.8)	10686.35 (12.4)	10825.24 (12.8)
T_{max} (h)	3.00	3.00	3.00	4.00	3.00	2.00	3.00	3.00
$t_{½}$ (h)	8.88 (38.7)	18.99 (23.7)	8.13 (21.8)	25.41 (35.6)	9.60 (46.4)	21.33 (39.4)	7.16 (20.7)	22.69 (31.2)

Values are LS Means (% CV) except for Tmax where medians are shown

Earlier Absorption with Optimized LSGC Formulation

- T_{max} notably earlier with LSGC C (1 h) vs. DFC (2.5 h)
- C_{max} ~43% higher with LSGC, not considered clinically meaningful
- $AUC_{0\text{-}2h}$: ~2x higher with LSGC vs DFC ($AUC_{0\text{-}inf}$ 7% higher)
- $AUC_{0\text{-}2h}$: LSGC 10 mg ≈ DFC 20 mg
- C_{max} and AUC trended higher in women compared to men.
  - C_{max} and $AUC_{0\text{-}inf}$ were ~20% and ~29% higher in women vs men with the DFC 20 mg.
  - C_{max} and AUC were ~34% and~40% higher with the LSGC



Key Pharmacokinetic Parameters (Geometric Mean)					
Form/ Dose mg	T_{max} (hr) Median (min, max)	$AUC_{0\text{-}2}$ (ng/mL•hr) (%GCV)	C_{max} (ng/mL) (%GCV)	$AUC_{0\text{-}\infty}$ (ng/mL•hr) (%GCV)	$AUC_{0\text{-}24}$ (ng/mL•hr) (%GCV)
DFC/20	2.50 (1.50, 6.00)	377 (44.5)	517 (27.9)	3379 (29.7)	3116 (29.4)
LSGC/20	1.00 (0.75, 3.00)	864 (31.9)	744 (26.1)	3603 (27.7)	3364 (27.4)
LSGC/10	1.50 (0.75, 2.00)	399 (31.8)	339 (27.2)	1735 (29.1)	1597 (31.0)

No Clinically Meaningful Impact of Elismetrep on the PK of Rosuvastatin or Simvastatin

	Statin+elismetrep (N=27) LS Mean	Statin alone (N=27) LS Mean	Statin+elismetrep/ statin alone GMR (90%CI)
Rosuvastatin			
$AUC_{0\text{-}inf}$ (ng*h/mL)	31.51	27.58	1.14 (1.02, 1.28)
C_{max} (ng/mL)	3.93	3.23	1.21 (1.07, 1.38)
Simvastatin			
$AUC_{0\text{-}inf}$ (ng*h/mL)	58.63	43.19	1.36 (1.19, 1.55)
C_{max} (ng/mL)	11.08	8.05	1.38 (1.17, 1.61)
Simvastatin acid			
$AUC_{0\text{-}inf}$ (ng*h/mL)	25.10	18.23	1.38 (1.20, 1.58)
C_{max} (ng/mL)	2.15	1.57	1.37 (1.18, 1.58)

Conclusions

The PK properties of elismetrep are well-suited for a drug for the treatment of migraine:

- **Rapid absorption (particularly with LSGC formulation)**
- **Long half-life**
- **Can be taken without regard to food**
- **Low risk for perpetrating drug-drug interactions via effects on CYP3A4 and OATP1B1**