

Exposure–Response Modeling Predicts Improved Anti-Migraine Efficacy of Elismetrep with an Optimized Formulation Enabling Faster Drug Absorption

William S. Denney¹, Devon Bartlett¹, Michael Crutchlow², Daniel Boisvert², Jiajun Liu², Brett Lauring²

¹Human Predictions , ²Kallyope, Inc

KALLYOPE

Background

- Elismetrep is a novel, oral, highly selective blocker of the TRPM8 channel
- In a recently completed Phase 2b study (see poster T03) elismetrep demonstrated promising efficacy in the acute treatment of migraine validating a new approach for treating migraine
- We developed a novel liquid-filled softgel capsule (LSGC) formulation of elismetrep that exhibited faster and earlier absorption compared to the dry-filled capsule (DFC) formulation containing crystalline elismetrep used in Phase 2b
- Exposure-response modeling predict earlier onset of action and improved 2-h efficacy with the LGSC to compared to the DFC formulation

Methods

- PK was simulated using a prior PK model (no covariates causing differences within treatment groups) and applied to the Phase 2b participants
- Last observation carried forward was used to impute values any post-rescue medication observations.
- The best model was selected based on Akaike information criterion(AIC), goodness of fit plots, and biological plausibility
- The final estimated exposure by pain freedom response (left) and exposure by most bothersome symptom response (right) models are Binomial models with fixed effects for mean concentration by continuous time to allow for concentration effects to vary over time since the migraine onset and each time by baseline to allow for varying placebo effects by baseline severity over time
- We conducted a Phase 1 crossover study in 30 male and female volunteers that evaluated the PK of the LSGC 20 mg, LSGC 10 mg, and DFC 20 mg; these PK data were used for clinical trial simulations to estimate the impact of reformulation on efficacy

$$DV \sim Cc \times TIME + fTIME \times AVALBLN$$

Where:

- DV is the observed pain freedom response (1) or non-response (0),
- Cc is the simulated plasma K304 concentration (ng/mL),
- TIME is continuous time in hours,
- fTIME is categorical time in hours, and
- AVALBLN is the baseline pain score (2 = moderate, 3 = severe).

Term	Estimate	Standard error
(Intercept)	18.84	508.3
Cc	0.001074	0.00118
TIME	-0.3893	10.59
fTIME1	-19.24	497.7
fTIME1.5	-15.94	492.4
fTIME2	-18.63	487.1
fTIME3	-18.25	476.5
fTIME4	-17.4	465.9
fTIME6	-16.8	444.7
fTIME8	-16.05	423.6
fTIME24	-10.01	254.1
fTIME48	NA	NA
AVALBLN	-11.75	251.5
Cc:TIME	0.0005443	0.0003958
fTIME1:AVALBLN	10.42	251.5
fTIME1.5:AVALBLN	9.375	251.5
fTIME2:AVALBLN	10.94	251.5
fTIME3:AVALBLN	11.31	251.5
fTIME4:AVALBLN	11.28	251.5
fTIME6:AVALBLN	11.55	251.5
fTIME8:AVALBLN	11.74	251.5
fTIME24:AVALBLN	11.98	251.5
fTIME48:AVALBLN	11.72	251.5

$$DV \sim Cc + fTIME + AVALBLN$$

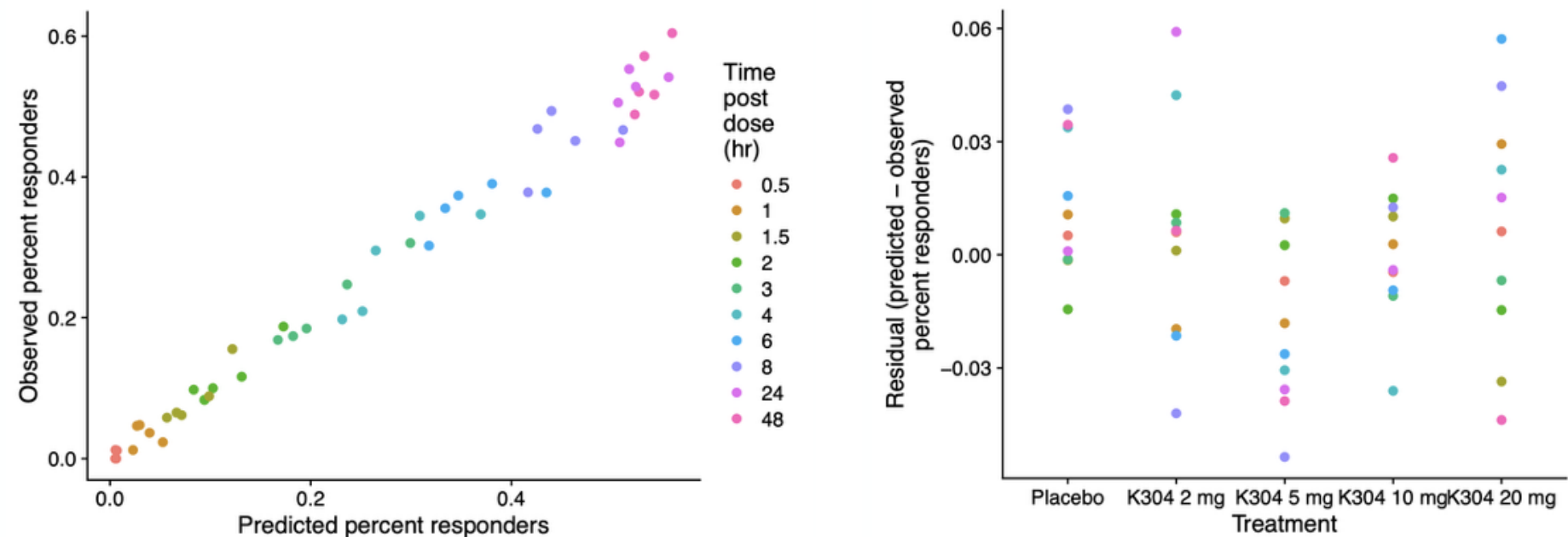
Where parameters are as defined in the pain freedom model.

Table 4: Model parameters for the final general linear binomial model for migraine most bothersome symptom

Term	Estimate	Standard error
(Intercept)	-2.915	0.3069
Cc	0.00161	0.0005249
fTIME1	0.8498	0.2995
fTIME1.5	1.53	0.2816
fTIME2	2.052	0.2729
fTIME3	2.333	0.2682
fTIME4	2.608	0.2657
fTIME6	2.669	0.2645
fTIME8	2.789	0.264
fTIME24	3.259	0.2643
fTIME48	3.162	0.264
AVALBLN	-0.01404	0.08331

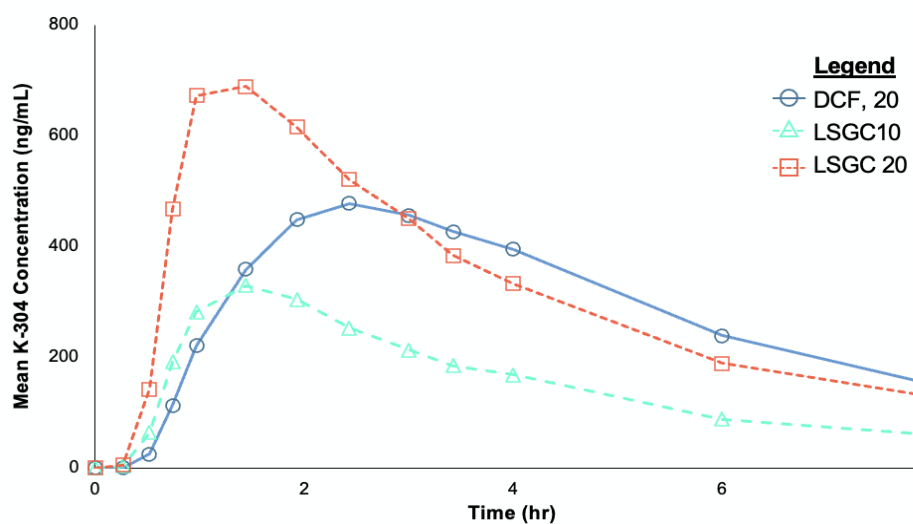
Clinical Data are Well-Described by the Model

	2-h Pain Freedom		2-h Freedom from MBS	
	Observed responders (%)	Predicted responders (%)	Observed responders (%)	Predicted responders (%)
Placebo	9.783	8.337	25	29
2 mg	8.333	9.412	27.27	30.09
5 mg	10	10.25	40.86	31.75
10 mg	11.63	13.12	32.56	34.67
20 mg	18.75	17.28	36.96	40.74



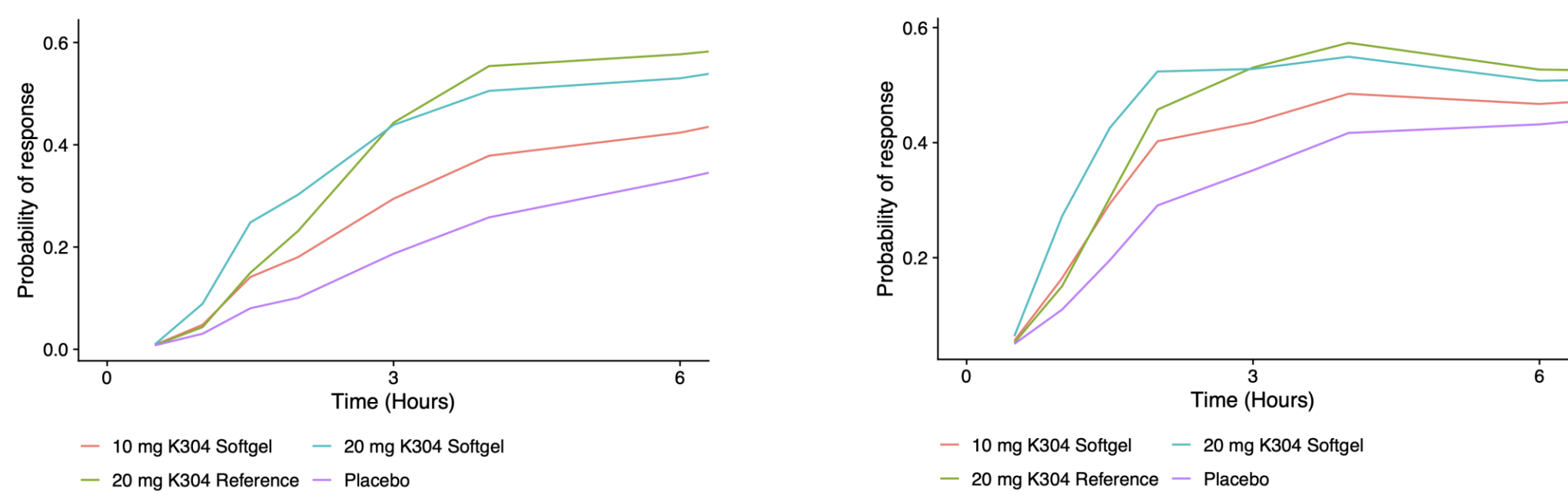
Earlier Absorption with the LSGC Formulation

- LSGC formulation results in significantly earlier absorption than DFC formulation used in Ph 2b trial without meaningful effects on overall extent of absorption**
 - LFC 20 mg achieved T_{max} of 1 h versus 2.5 h for DFC 20 mg
 - AUC_{0-2h} following LFC 20 mg is ~2.3x that following DCF 20 mg (AUC_{0-inf} 7% higher with LFC vs DFC)
- LFC 10 mg demonstrated similar PK profile as dry-filled capsule 20 mg up to ~1.5-2 hours**



Key Pharmacokinetic Parameters (Geometric Mean)				
Form/ Dose mg	T _{max} (hr) Median (min, max)	C _{max} (ng/mL) (%GCV)	AUC _{0-2h} (ng/mL·hr) (%GCV)	AUC _{0-inf} (ng/mL·hr) (%GCV)
DFC/20	2.50 (1.50, 6.00)	517 (27.9)	377 (44.5)	3379 (29.7)
LSGC/20	1.00 (0.75, 3.00)	744 (26.1)	864 (31.9)	3603 (27.7)
LSGC/10	1.50 (0.75, 2.00)	339 (27.2)	399 (31.8)	1735 (29.1)

Simulations Comparing Efficacy of LSGC to DFC



	2-h Pain Freedom (% responders)	
Treatment	Mean	Placebo-adjusted Mean
20 mg LSGC	30.25	20.2
20 mg DFC	23.14	13.1
10 mg LSGC	18.03	8.0
Placebo	10.07	--

	2-h MBS (% responders)	
Treatment	Mean	Placebo-adjusted Mean
20 mg LSGC	52.37	23.3
20 mg DFC	45.75	16.7
10 mg LSGC	40.24	11.2
Placebo	29.09	--

Conclusions

- An optimized LGSC formulation provides earlier absorption compared to the DFC formulation used in Phase 2b
- At 20 mg, LSGC is predicted to result in ~54% and ~40% improvements in placebo-corrected response rates for 2-hr pain freedom and 2-hr freedom from the most bothersome symptom, vs DFC, respectively
- Onset of action is predicted to occur earlier with LSGC vs DFC
- Clinically meaningful effects expected at 10 mg and 20 mg with the LSGC
- These analyses support the evaluation of elismetrep 20 mg LSGC and elismetrep 10 mg LSGC in upcoming Phase 3 trials