TRPM8 Antagonism with Elismetrep: A Novel Approach for Treating Migraine

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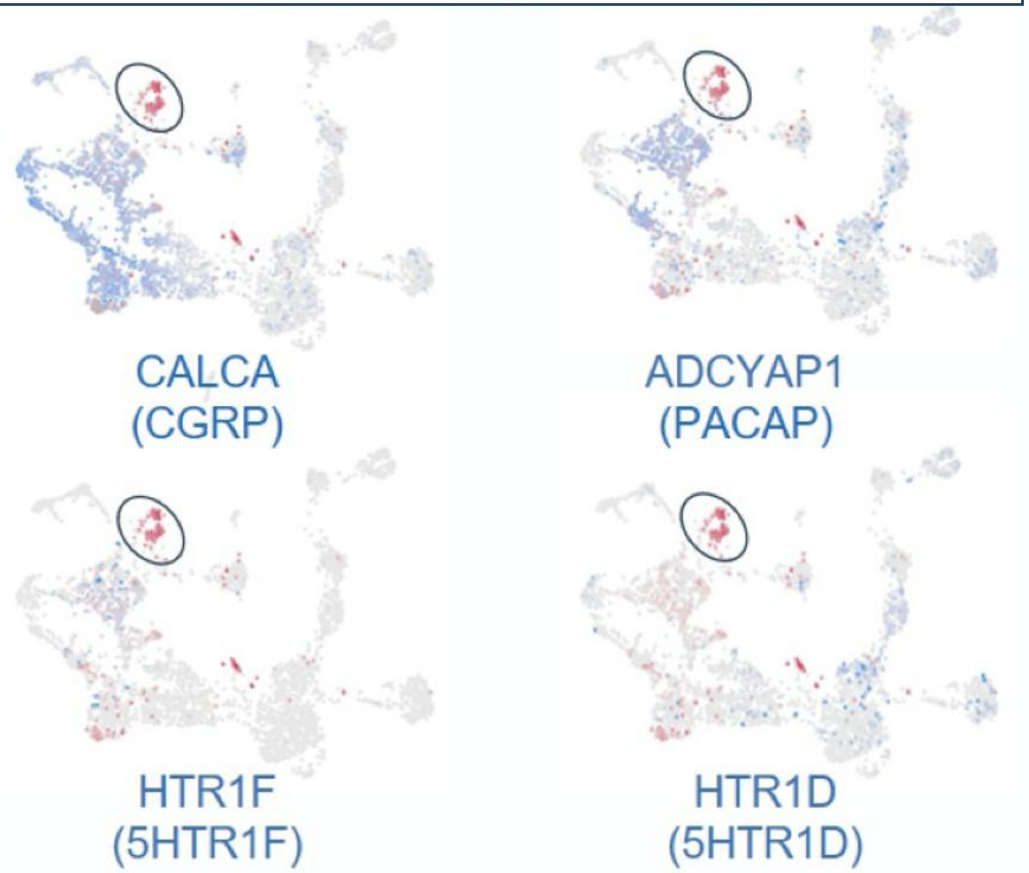
Disclosures: B.L. - Employee of Kallyope (Sponsor of trial) and may own stock

Transient Receptor Potential Melastatin 8 (TRPM8): A Novel and Mechanistically Distinct Target for Migraine

- TRPM8 encodes a non-selective cation channel[1,2] in a known migraine GWAS locus[3,4]
- Allele-specific expression observed in disease-relevant tissue (sensory neurons) suggesting therapeutic benefit with TRPM8 blockade[5]
- TRPM8 expression in human trigeminal neurons distinct from other migraine-relevant targets[6,7,8]
- No reported clinical studies to date of a TRPM8 blocker in migraine

TRPM8 expression in human trigeminal ganglion (Red)



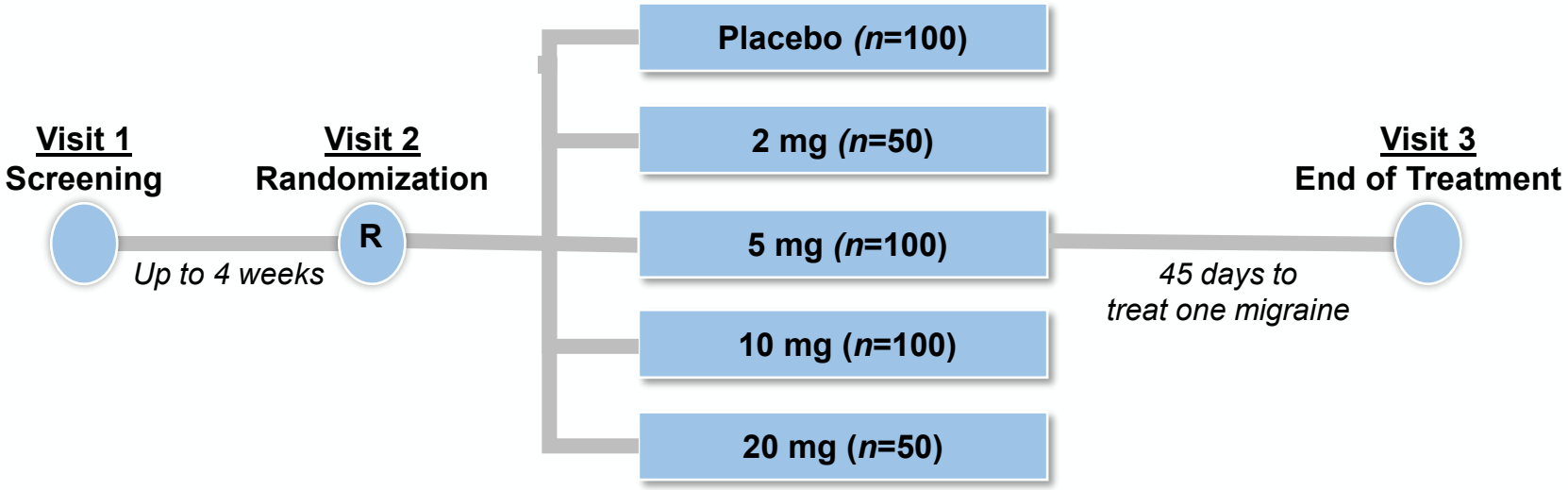
1. McKemy, D. et al., Nature 2002; 2. Peier, A. et al. Cell, 2002; 3. Chasman et al., Nat. Genetics, 2011; 4. Hautakangas, H. et al., Nat. Genetics, 2022; 5. Gavva et al., Sci Rep, 2019; 6. Kallyope data; 7. Bhuiyan, S. et al., Sci. Advances, 2024; 8. Yang, L., et al., Neuron, 2022

Elismetrep: A Novel Oral, Highly Selective TRPM8 Migraine-Associated Channel Blocker (MACB)

- Potent and selective blocker of the TRPM8 channel
  - IC_{50} of 4.49 ± 1.38 nM
  - No or minimal activity at other TRP channels (hTRPA1, hTRPC6, hTRPM2 and hTRPV1)
  - No off-target activity in screen of 81 receptors, ion channels, transporters, and enzymes
- Good pharmacokinetic profile for the treatment of migraine
  - T_{max}: 1.5-3.5 h
  - Terminal half-life: 11-18 h after single dose
  - No significant effect of food on pharmacokinetics
  - No significant DDI liabilities either as victim or perpetrator
- Prior human exposure: Good safety profile in 13 completed Phase 1 and Phase 2 studies
  - 1,055 people exposed to at least one dose
  - Single doses up to 900 mg and multiple doses up to 400 mg QD explored
  - Phase 2 studies in several populations up to 12 weeks
  - Longest exposure 64 weeks

Elismetrep: Phase 2b Study Design

- Double-blind, placebo-controlled, single-attack design
- Key Endpoints
  - Pain freedom at 2 hours postdose (primary)
  - Freedom from the most bothersome migraine-associated symptom (MBS) at 2 hours postdose (secondary)
  - Pain relief at 2 hours postdose (secondary)



Key Inclusion Criteria

- 18-70 years
- ≥1 yr history of migraine headache ± aura (by ICHD criteria[1]) lasting 4-72 h
- 2-10 moderate-severe migraine/month
- Stable prophylaxis allowed

Key Exclusion Criteria

- Difficulty distinguishing migraine attacks from tension-type headaches
- History of predominantly mild migraine attacks
- More than 15 headache-days per month
- Brainstem (basilar-type) or hemiplegic migraine headache, or retinal migraine
- >50 years old at age of first migraine onset
- Recent change in dose of migraine preventive medication

K-304 P001; NCT06848075

1. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd Edition. Cephalalgia. 2018;38:1-211.

Phase 2b Study for Elismetrep: Subject Accounting and Disposition

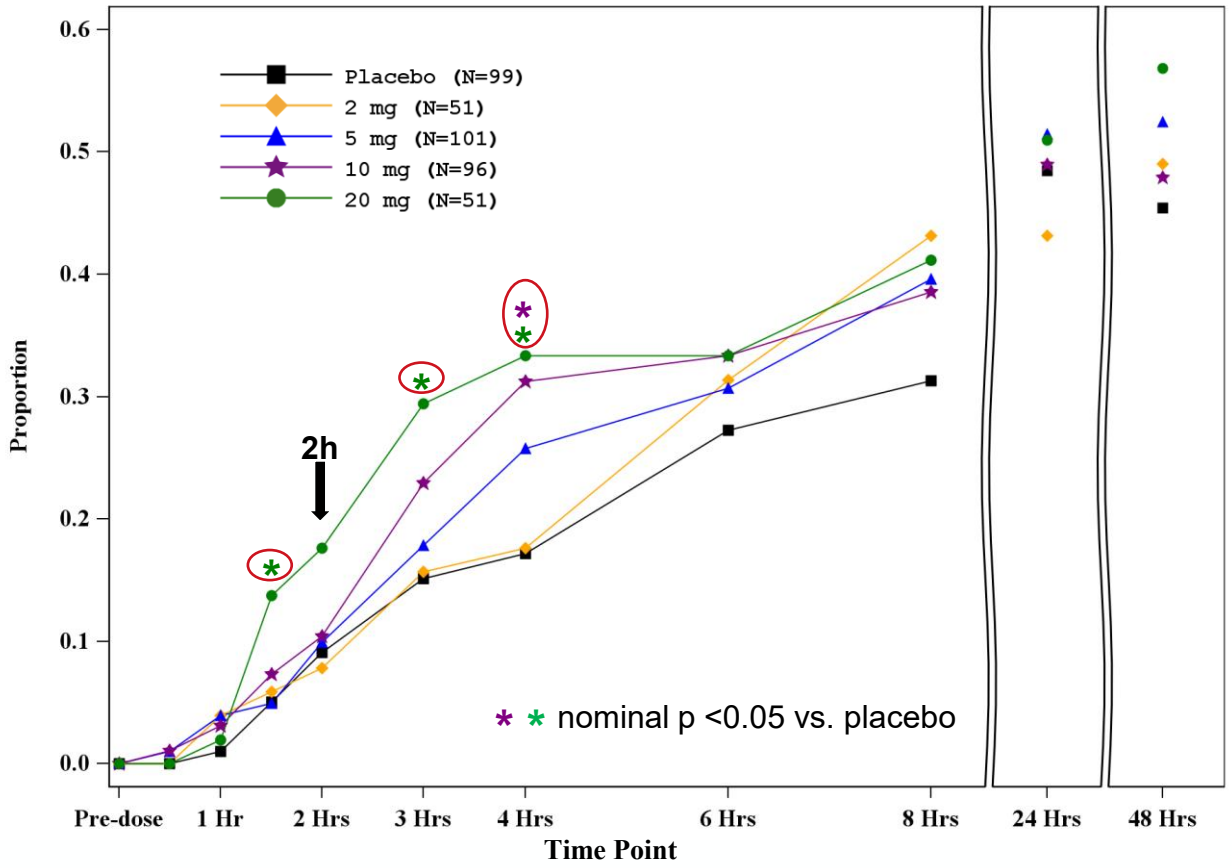
	Placebo *n* (%)	2 mg *n* (%)	5 mg *n* (%)	10 mg *n* (%)	20 mg *n* (%)	Overall *N* (%)	
Randomized	108 (100)	54 (100)	107 (100)	108 (100)	54 (100)	431 (100)	
• Took Study Drug	104 (96.3)	51 (94.4)	101 (94.4)	97 (89.8)	51 (94.4)	404 (93.7)	➡ ITT, safety population
• With Qualifying Migraine*	99 (91.7)	51 (94.4)	101 (94.4)	96 (88.9)	51 (94.4)	398 (92.3)	➡ mITT population**
• Completed Study	106 (98.1)	54 (100)	106 (99.1)	106 (98.1)	54 (100)	426 (98.8)	
Discontinued from Study	2 (1.9)	0	1 (0.9)	2 (1.9)	0	5 (1.2)	
• Lost to Follow up	2 (1.9)	0	1 (0.9)	2 (1.9)	0	5 (1.2)	

*Qualifying migraine (confirmed by ePRO) ** Six subjects dosed without qualifying migraine excluded from mITT population
ITT = intention-to-treat; mITT = modified intention-to-treat

Phase 2b Study for Elismetrep: Demographics and Baseline Characteristics

	Placebo *n* (%)	2 mg *n* (%)	5 mg *n* (%)	10 mg *n* (%)	20 mg *n* (%)	Overall *N* (%)
N	99	51	101	96	51	398
Mean age (y)	46.5	44.5	44.5	46.1	47.4	45.8
Female, n (%)	84 (84.8)	43 (84.3)	89 (88.1)	86 (89.6)	44 (86.3)	346 (86.9)
White, n (%)	74 (74.7)	40 (78.4)	71 (70.3)	81 (84.4)	43 (84.3)	309 (77.6)
Black, n (%)	17 (17.2)	9 (17.6)	24 (23.8)	10 (10.4)	7 (13.7)	67 (16.8)
Asian, n (%)	4 (4.0)	2 (3.9)	2 (2.0)	2 (2.1)	1 (2.0)	11 (2.8)
Mean BMI, kg/m^2	30.0	29.9	30.1	30.3	29.4	30.0
Migraine with aura, n (%)	40 (40.4)	25 (49.0)	44 (43.6)	40 (41.7)	23 (45.1)	172 (43.2)
Mean # attacks/month	5.1	5.5	5.6	5.5	5.7	5.4
Using prevention medication, n (%)	34 (34.3)	18 (35.3)	38 (37.6)	33 (34.4)	18 (35.3)	141 (35.4)
Triptan resistant, n (%)	28 (28.3)	13 (25.5)	33 (32.7)	35 (36.5)	15 (29.4)	124 (31.2)

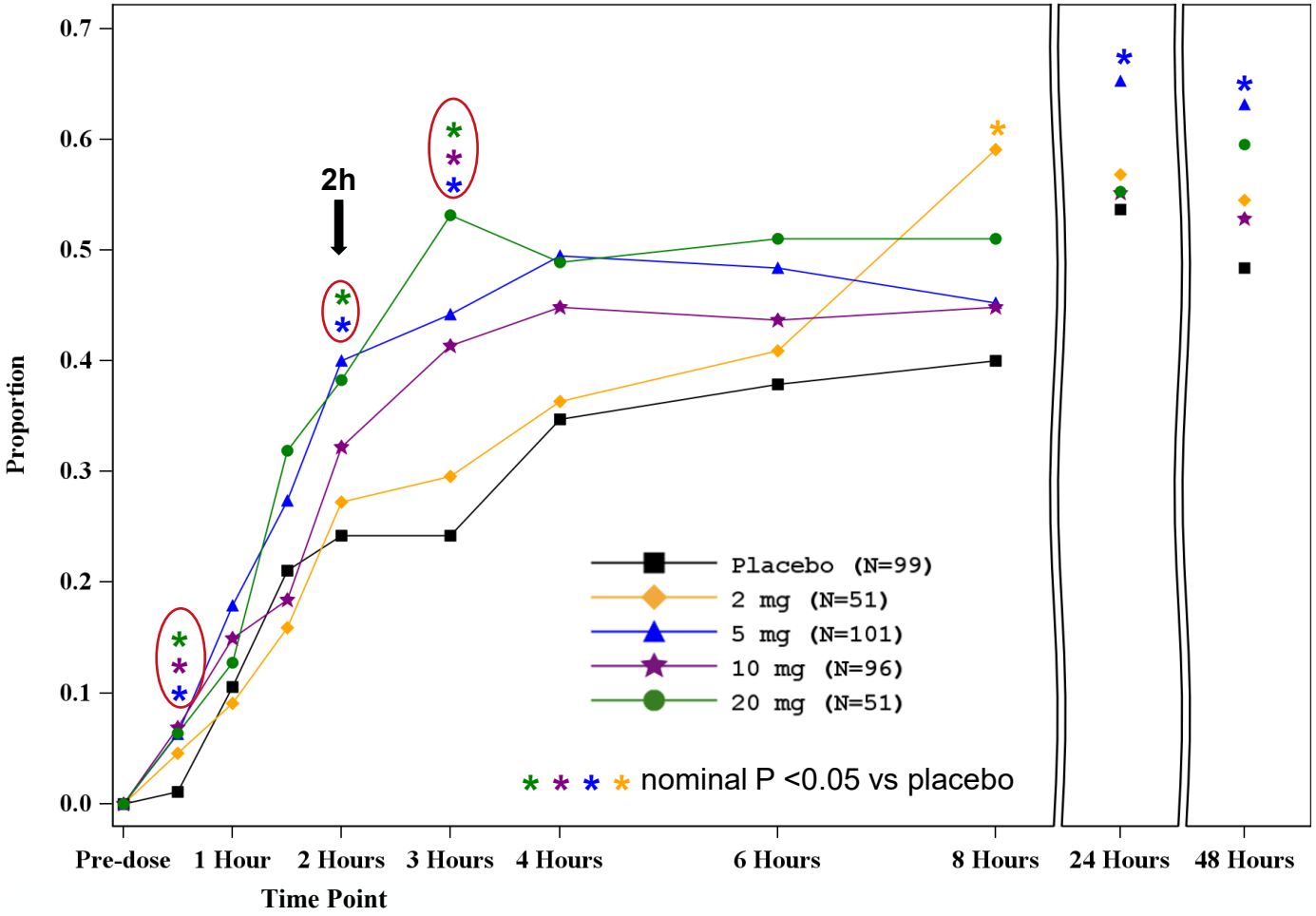
Primary Endpoint: Pain Freedom (PF) at 2 Hours



PF at 2 Hours	PBO (*n*=99)	2 mg (*n*=51)	5 mg (*n*=101)	10 mg (*n*=96)	20 mg (*n*=51)
mITT, e-diary data					
Pain Freedom, n/N (%)	9/99 (9.1)	4/51 (7.8)	10/101 (9.9)	10/96 (10.4)	9/51 (17.6)
Missing Data, n/N (%)	4/99 (4.0)	3/51 (5.9)	9/101 (8.9)	10/96 (10.4)	2/51 (3.9)
OR vs. PBO (90% CI)	--	0.9 (0.3, 2.4)	1.1 (0.5, 2.4)	1.2 (0.5, 2.6)	2.1 (0.9, 4.9)
Risk Difference vs. PBO (90% CI)	--	-1.2 (-9.0, 6.6)	0.8 (-6.0, 7.6)	1.3 (-5.7, 8.3)	8.5 (-1.4, 18.5)
P-value vs. PBO	--	0.4002	0.4240	0.3774	0.0650
mITT, e-diary + interview data					
Pain Freedom, n/N (%)	9/99 (9.1)	4/51 (7.8)	12/101 (11.9)	11/96 (11.5)	10/51 (19.6)
Missing Data, n/N (%)	1/99 (1.0)	2/51 (3.9)	1/101 (1.0)	2/96 (2.1)	0/51 (0.0)
OR vs. PBO (90% CI)	--	0.9 (0.3, 2.4)	1.3 (0.6, 2.9)	1.3 (0.6, 2.8)	2.4 (1.1, 5.5)
Risk Difference vs. PBO (90%CI)	--	-1.2 (-9.0, 6.6)	2.8 (-4.4, 9.9)	2.4 (-4.8, 9.5)	10.5 (0.2, 20.8)
Nominal p-value vs. PBO	--	0.4002	0.2632	0.2933	0.0344

Pain Freedom assessment: Four-point pain scale: 0 = Pain Free, 1 = mild, 2 = moderate, 3 = severe ; Qualifying migraines were moderate-severe (baseline pain score of 2 or 3) ; Subjects recorded pain level at each timepoint in e-diary; Pain Freedom = score of 0
mITT = modified intention-to-treat; LOCF (*ad hoc*) = last observation carried forward; OR = Odds Ratio; PBO = placebo
90% CI and one-sided P-value are derived from Cochran-Mantel-Haenszel (CMH) test stratified by background prophylactic medications for migraine (yes/no).

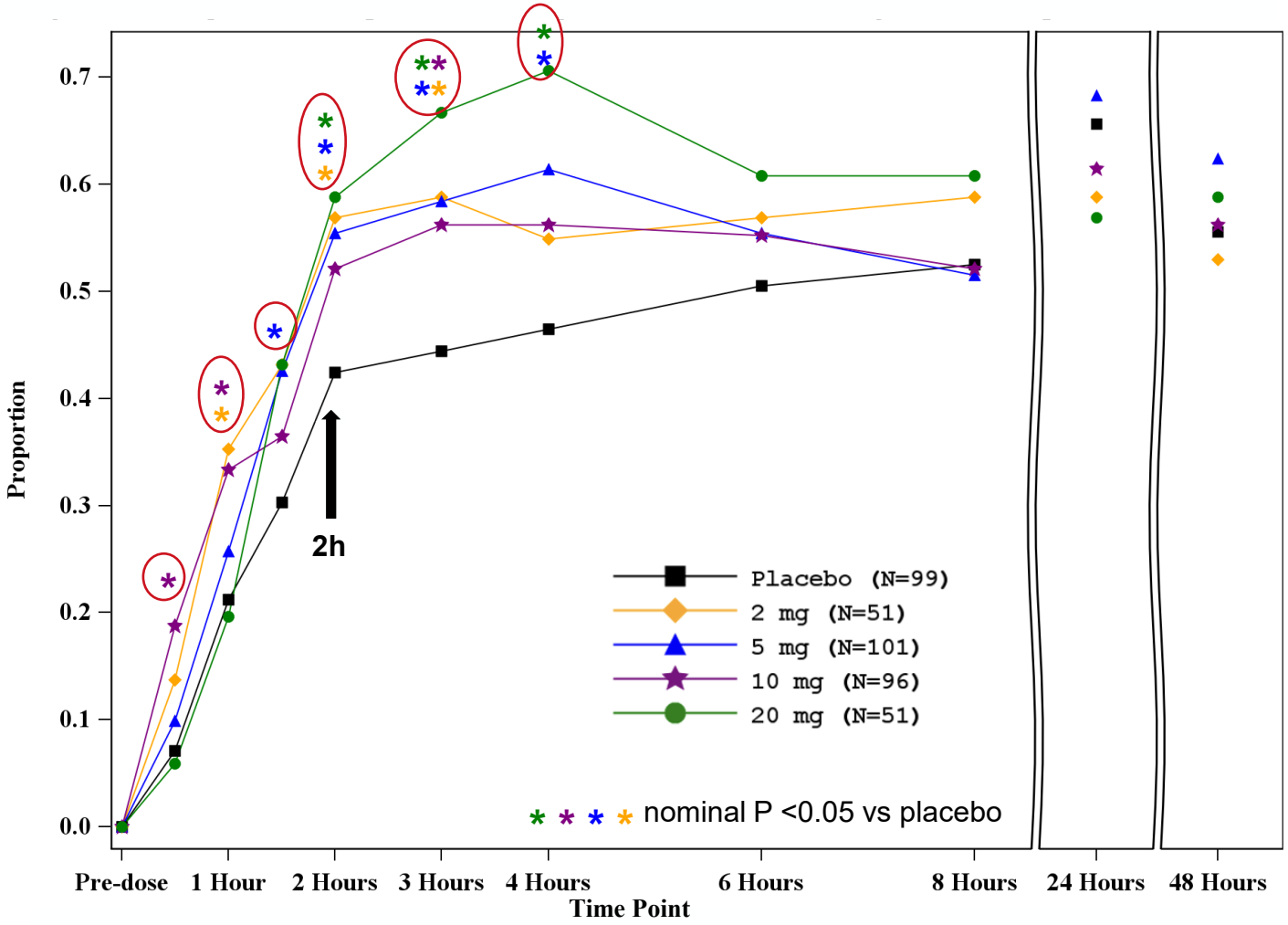
Secondary Endpoint: Freedom from Most Bothersome Symptom (MBS) at 2 Hrs



MBS at 2 Hours (mITT)	Placebo (*n*=99)	2 mg (*n*=51)	5 mg (*n*=101)	10 mg (*n*=96)	20 mg (*n*=51)
MBS Freedom, n/N (%)	23/95 (24.2)	12/44 (27.3)	38/95 (40.0)	28/87 (32.2)	18/47 (38.3)
OR vs. PBO (90% CI)	--	1.2 (0.6, 2.3)	2.1 (1.2, 3.5)	1.5 (0.9, 2.5)	1.9 (1.0, 3.6)
Risk Difference vs. PBO (90% CI)		3.0 (-10.2, 16.3)	15.3 (4.3, 26.2)	7.9 (-3.1, 18.8)	14.0 (0.1, 27.9)
Nominal p-value vs. PBO	--	0.3511	0.0122	0.1199	0.0425

Most Bothersome Symptom (MBS) assessment: At onset of a qualifying migraine, subjects recorded presence of migraine-associated symptoms (photophobia, phonophobia, nausea) and indicated which was the most bothersome ; at each subsequent timepoint, subjects indicated presence or absence of MBS
mITT = modified intention-to-treat; OR = Odds Ratio; PBO = placebo
90% CI and one-sided P-value are derived from Cochran-Mantel-Haenszel (CMH) test stratified by background prophylactic medications for migraine (yes/no).

Secondary Endpoint: Pain Relief (PR) at 2 Hours



PR at 2 Hours (mITT)	Placebo (*n*=99)	2 mg (*n*=51)	5 mg (*n*=101)	10 mg (*n*=96)	20 mg (*n*=51)
Pain Relief, n/N (%)	42/99 (42.4)	29/51 (56.9)	56/101 (55.4)	50/96 (52.1)	30/51 (58.8)
Missing Data, n/N (%)	4/99 (4.0)	3/51 (5.9)	9/101 (8.9)	10/96 (10.4)	2/51 (3.9)
OR vs. PBO (90% CI)	--	1.8 (1.0, 3.2)	1.7 (1.1, 2.7)	1.5 (0.9, 2.4)	1.9 (1.1, 3.4)
Risk Difference vs. PBO (90% CI)		14.4 (0.4, 28.5)	13.0 (1.4, 24.5)	9.7 (-2.0, 21.4)	16.4 (2.4, 30.4)
Nominal p-value vs. PBO	--	0.0479	0.0339	0.0891	0.0293

Pain Relief assessment: Four-point pain scale: 0 = Pain Free, 1 = mild, 2 = moderate, 3 = severe ; Qualifying migraines were moderate-severe (baseline pain score of 2 or 3) ; Subjects recorded pain level at each timepoint in e-diary; Pain Relief = score of 0 or 1
mITT = modified intention-to-treat; OR = Odds Ratio; PBO = placebo
90% CI and one-sided P-value are derived from Cochran-Mantel-Haenszel (CMH) test stratified by background prophylactic medications for migraine (yes/no).

Phase 2b Study for Elismetrep: Treatment-Emergent Adverse Events ≥5% in any Group

MedDRA Preferred Term	Placebo (*n*=104) *n* (%)	2 mg (*n*=51) *n* (%)	5 mg (*n*=101) *n* (%)	10 mg (*n*=97) *n* (%)	20 mg (*n*=51) *n* (%)
Paresthesia oral	0	0	0	2 (2.1)	5 (9.8)
Feeling hot	0	0	0	4 (4.1)	5 (9.8)
Paresthesia	0	0	0	5 (5.2)	4 (7.8)
Flushing	0	2 (3.9)	1 (1.0)	4 (4.1)	3 (5.9)
Hot flush	0	0	0	1 (1.0)	4 (7.8)

- No serious adverse events
- At 20 mg, all AEs were mild (70%) or moderate

Conclusions and Next Steps

- Elismetrep, an oral TRPM8 migraine-associated channel blocker, when compared to placebo, achieved superior:
  - Pain freedom (interview data included) at 2 hours
  - Freedom from most bothersome symptom at 2 hours
  - Pain relief at 2 hours
  - Good tolerability with no safety signals
- TRPM8 channel blockade represents a new, mechanistically distinct approach for the treatment of migraine
- Registration trials expected to initiate in mid-2026 with a novel drug formulation that in a recent human study results in more rapid absorption which is anticipated to result in earlier onset of efficacy and greater 2-h efficacy vs Phase 2b formulation
  - Formulation results to be presented at a medical meeting in the coming months