In vitro Profile of Elismetrep: A Potent and Highly Selective Blocker of the Migraine-Associated Channel TRPM8

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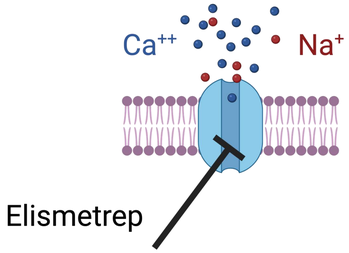
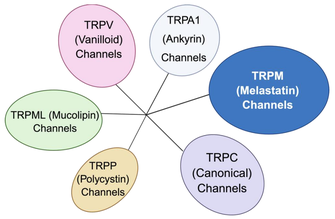
Key Takeaways

- Elismetrep is a potent blocker of the migraine-associated channel (MACB), TRPM8
- Elismetrep is highly selective for TRPM8 over other tested TRP channels & has no meaningful off-target activity
- Elismetrep has a low risk for drug-drug interactions either as perpetrator or victim



TRP Family of Channels



Background and Methods

- TRPM8 (Transient Receptor Potential Melastatin 8) is a polymodal gated non-selective cation channel that has a genetic association with migraine
- Elismetrep is a novel, oral, TRPM8 MACB
- 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
- hTRPM8 antagonism was determined by assessing the inhibition of menthol-induced changes in intracellular calcium in HEK293 cells overexpressing hTRPM8
- Selectivity was assessed by evaluating inhibition of agonist-induced calcium elevation in HEK293 cells overexpressing hTRPA1, hTRPC6, hTRPM2, or hTRPV1 channels

Elismetrep is Potent and Selective

- Elismetrep blocks TRPM8 with sub-nanomolar potency (IC_{50}=0.61 nM).
- Elismetrep is >1,800-fold selective over other TRP channels

	Antagonistic effect		Agonistic effect
	IC_{50} (95% CI)	IC_{50} ratio vs. hTRPM8	% Activation vs reference agonist at 10 µmol/L[b]
hTRPM8	0.61 nmol/L (0.41-0.90 nmol/L)	1	1.6 ± 0.2%
hTRPA1	> 3 µmol/L [a]	>4910	13.0 ± 0.3%
hTRPC6	> 3 µmol/L [a]	>4910	28.5 ± 2.2%
hTRPM2	1.14 µmol/L (0.0806-16.2 µmol/L)	1870	-4.7 ± 0.4%
hTRPV1	> 3 µmol/L [a]	>4910	12.9 ± 1.8%

[a] % inhibition did not exceed 50% up to 3 µmol/L.
[b] % activation compared to the estimated maximum effect of the reference agonist are shown. Menthol, 4-hydroxy-2-nonenal, 1-oleoyl-2-acetoyl-*sn*-glycerol, hydrogen peroxide or capsaicin was used as the reference agonists for hTRPM8, hTRPA1, hTRPC6, hTRPM2 and hTRPV1 channels. Data represents mean ± SEM.

- The interaction of elismetrep with 81 targets (receptors, ion channels, transporters, and enzymes) was evaluated using well-established standard assays
- Only six targets were inhibited ≥ 50% by 10 µmol/L of elismetrep
- Inhibition of agonist binding to all six targets was at least 4650-fold weaker compared to the IC_{50} value for hTRPM8 channels

Assay name	Species	IC_{50} (µmol/L)	Ki (µmol/L)	Fold-weaker vs hTRPM8
Adrenergic α_{2A}	human	2.84	1.06	4657
Dopamine D_3	human	9.75	3.31	15,984
Leukotriene, Cysteinyl $CysLT_1$	human	8.86	3.65	14525
Purinergic P_{2Y}	rat	5.71	5.67	9361
Thyroid Hormone	rat	6.45	3.42	1886
Transporter, Norepinephrine	human	5.29	5.24	8672

Elismetrep Has Low Risk of Drug Interactions as Perpetrator or Victim

CYP Enzyme	Without Pre-Incubation IC_{50} (µmol/L)	With Pre-Incubation IC_{50} (µmol/L)
1A2	24.1	19.5
2A6	30.0	17.9
2B6	13.0	10.7
2C8	0.0805	0.0997
2C9	15.4	15.5
2C19	40.1	30.1
2D6	–	–
2E1	>50.0	>50.0
3A (testosterone)	27.7	11.5
3A (midazolam)	20.2	10.9

– IC_{50} value was not calculated due to a lack of inhibition at ≤30 µmol/L

- Minimal direct or time-dependent inhibition of CYP isoforms with the exception of CYP2C8 (Ki = 0.04 µmol/L) and weak time-dependent inhibition of CYP3A
- Simcyp modeling suggests that elismetrep is unlikely to affect the pharmacokinetics of repaglinide (substrate of CYP2C8)
- In humans, multiple doses of elismetrep (150 mg QD) had no clinically meaningful effect the single dose pharmacokinetics of rosuvastatin and simvastatin (CYP3A4 and OATP1B1 substrates) [see Poster T 34]
- No induction of mRNA or enzyme activity of CYP1A2, 2B6, 2Cs, and 3A
- Metabolized by multiple pathways including both glucuronidation (UGT1A1, 1A3, 1A8, and 2B7) and oxidation (CYP2C9, 2C19, 3A4, and 3A5) suggesting low risk for being a victim of DDIs due to concomitant use of CYP or UGT inhibitors