Faculty of Health and Medical Sciences



## PACAP in Migraine and Cluster Headache

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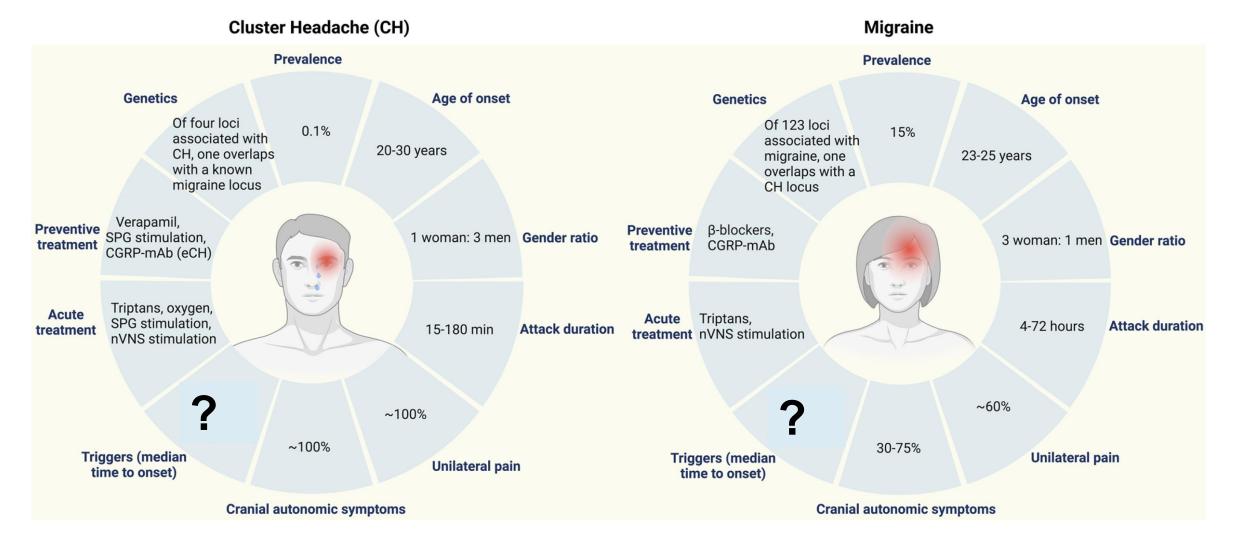






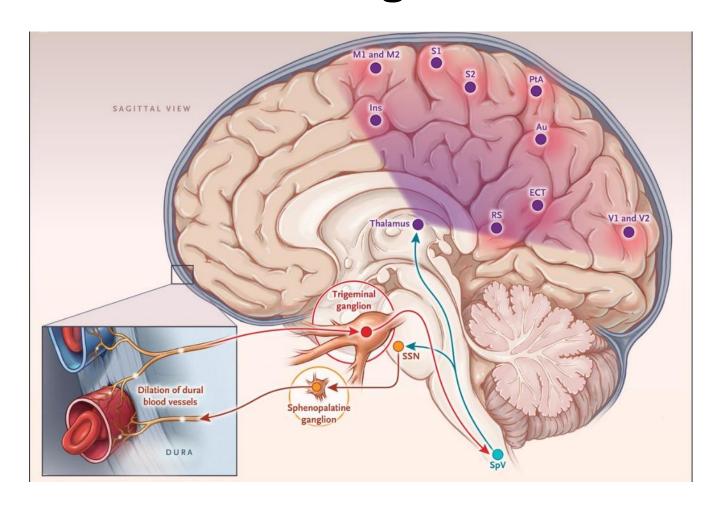
Potential COI	Organisation
Advisory Boards	AbbVie, Amgen, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Novartis and Teva.
Speaker / Speakers Boards	AbbVie, Amgen, Astra Zeneca, Eli Lilly, GlaxoSmithKline, Lundbeck, Novartis and Teva.
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Editorial Board	Associate editor of the Journal of Headache and Pain Associate editor of Brain
Other	None

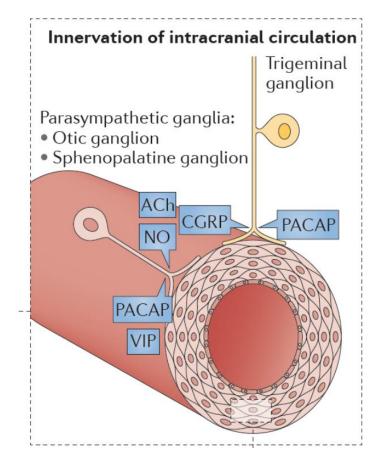






### The trigeminovascular system

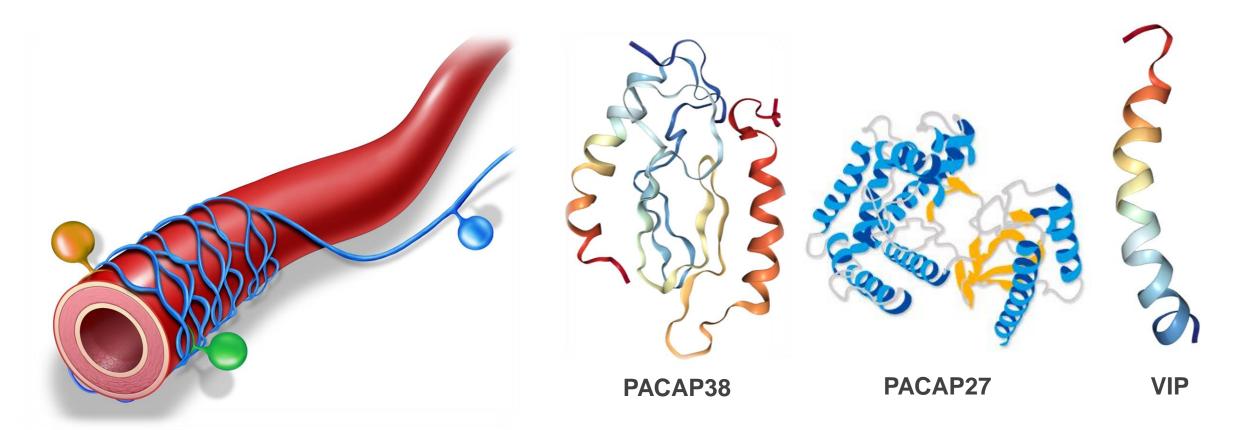




ACh, acetylcholine; CGRP, calcitonin gene-related peptide; NO, nitric oxide; PACAP, pituitary adenylate cyclase-activating polypeptide; VIP, vasoactive intestinal peptide.

Ashina M, et al. *Nat Rev Neurol* 2017; Ashina M, et al. *Lancet Neurol* 2019; Ashina M. *N Engl J Med* 2020.

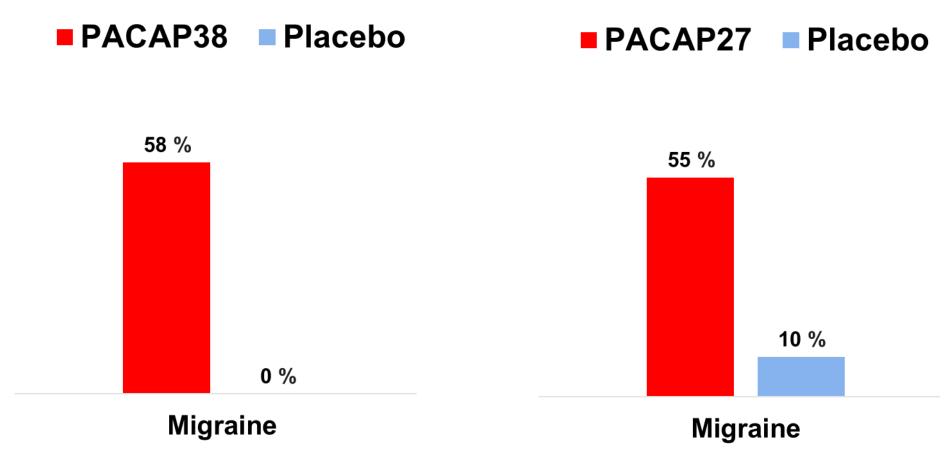




Pituitary adenylate cyclase-activating polypeptide (PACAP)
Vasoactive intestinal peptide (VIP)



### **PACAP** induces migraine

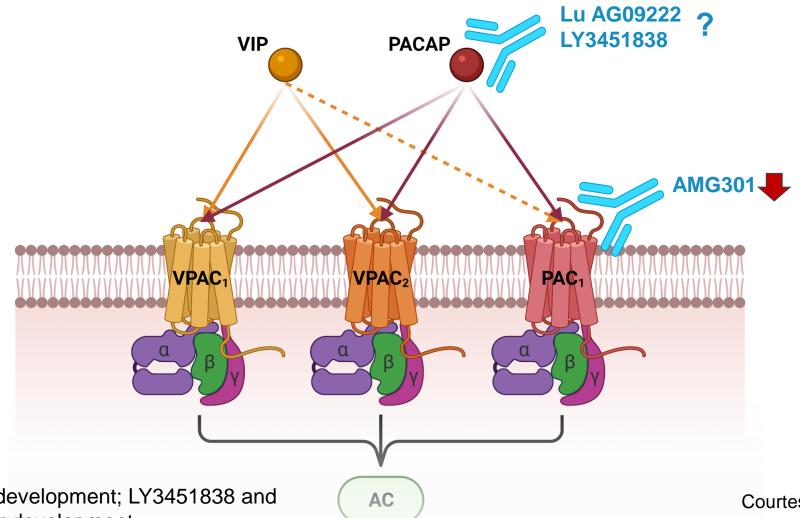


Schytz et al, Brain 2009

Ghanizada et al, Cephalalgia 2019



### Can we block PACAP in migraine?



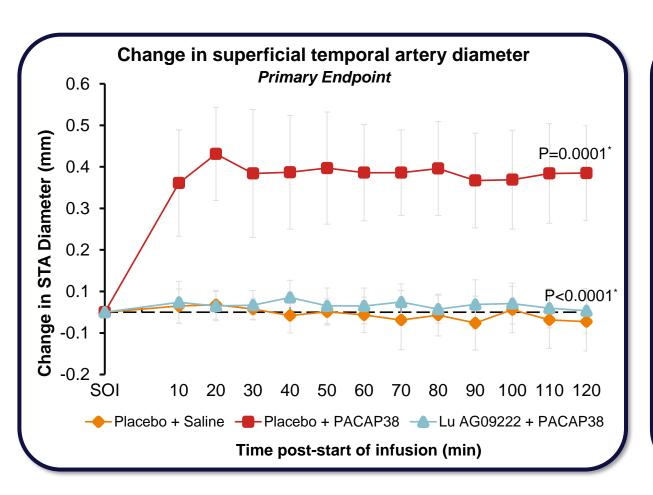


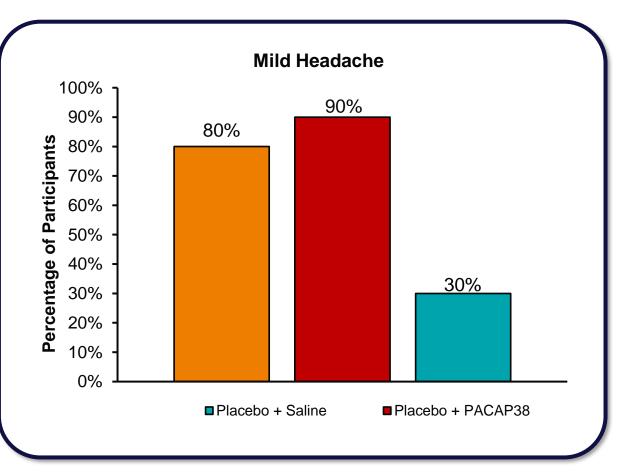


Pre-treatment with Lu AG09222 binds and neutralizes exogenously administered PACAP38 and prevents PACAP38-induced vasodilatory responses and headache



# Results: Lu AG09222 prevented PACAP38-induced physiological responses





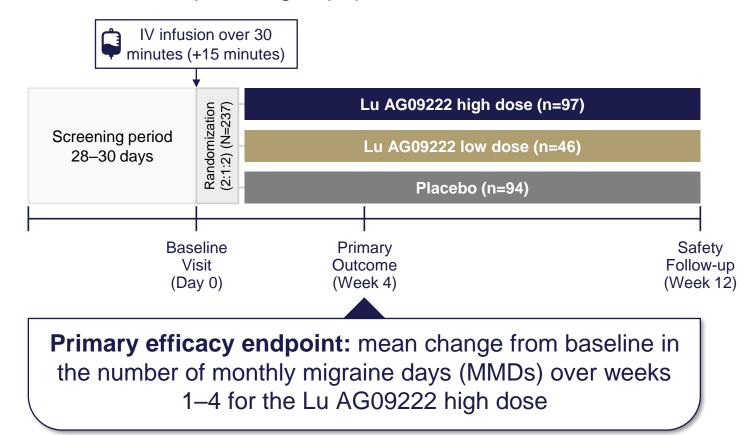
This proof-of-concept trial of Lu AG09222 (HOPE) was designed to assess the **efficacy, safety, and tolerability** of a single intravenous infusion of **Lu AG09222 for migraine prevention** in adults with migraine who had 2–4 unsuccessful prior preventive treatments.

Multi-national, multi-site, randomized, double-blind, parallel-group, placebo-controlled Phase 2 trial



#### **Eligible participants:**

- Aged 18–65 years (inclusive)
- Diagnosed with migraine (episodic or chronic)
- Had documented failure of 2–4 previous preventive migraine treatments



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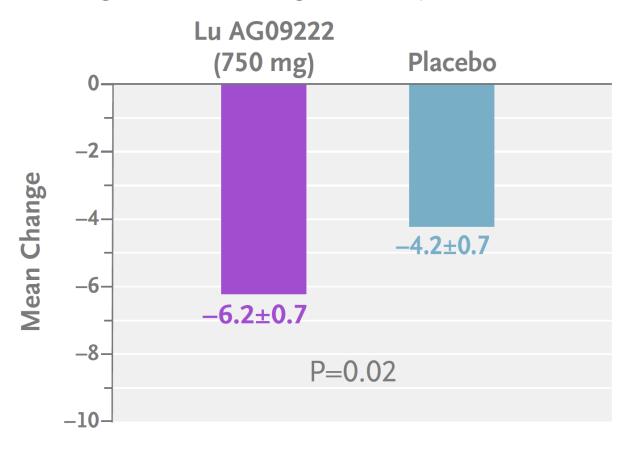
#### ORIGINAL ARTICLE

# A Monoclonal Antibody to PACAP for Migraine Prevention

Messoud Ashina, M.D., Ravinder Phul, Ph.D., Melanie Khodaie, Ph.D., Elin Löf, Ph.D., and Ioana Florea, M.D.



### Change in No. of Migraine Days over 4 Wk





# Can cluster headache attacks be triggered?



#### **POPULATION**

Adults with cluster headache (CH)

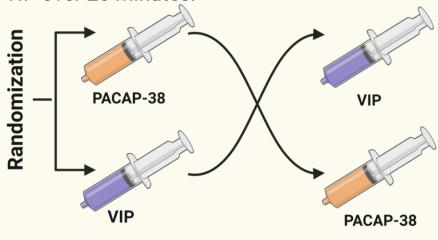


#### The study included:

- 14 participants with active episodic CH.
- 15 participants with remission CH.
- **15** participants with chronic CH.

#### INTERVENTION

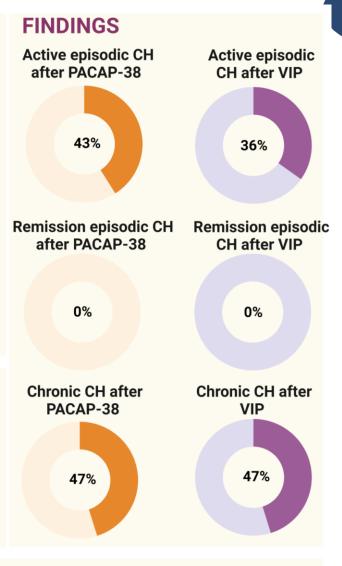
**41** participants with CH were randomized to receive intravenous infusion of PACAP-38 or VIP over 20 minutes.



#### **PRIMARY OUTCOME**

#### Incidence of CH attacks

The primary endpoint is the difference in the incidence of CH attacks between PACAP-38 and VIP infusion.



#### CONCLUSION

PACAP-38 and VIP induces cluster attacks in participants with active episodic CH and chronic CH. Participants with remission episodic CH did not experience CH attacks following PACAP-38 or VIP infusion.



### **Key points**

- PACAP is involved in the genesis of both migraine and cluster headache attacks.
- The Phase 2 trial provides proof-of-concept for Lu AG09222 (mAbs targeting PACAP) in migraine prevention.
- Insights from human models of migraine and cluster headache, along with supporting preclinical data, have established a foundation for developing targeted therapies.



### Acknowledgements

### **Funding**

Lundbeck Foundation (R155-2014-171 and R310-2018-3711)

### **Participants**

Migraine patients and healthy volunteers



Colleagues