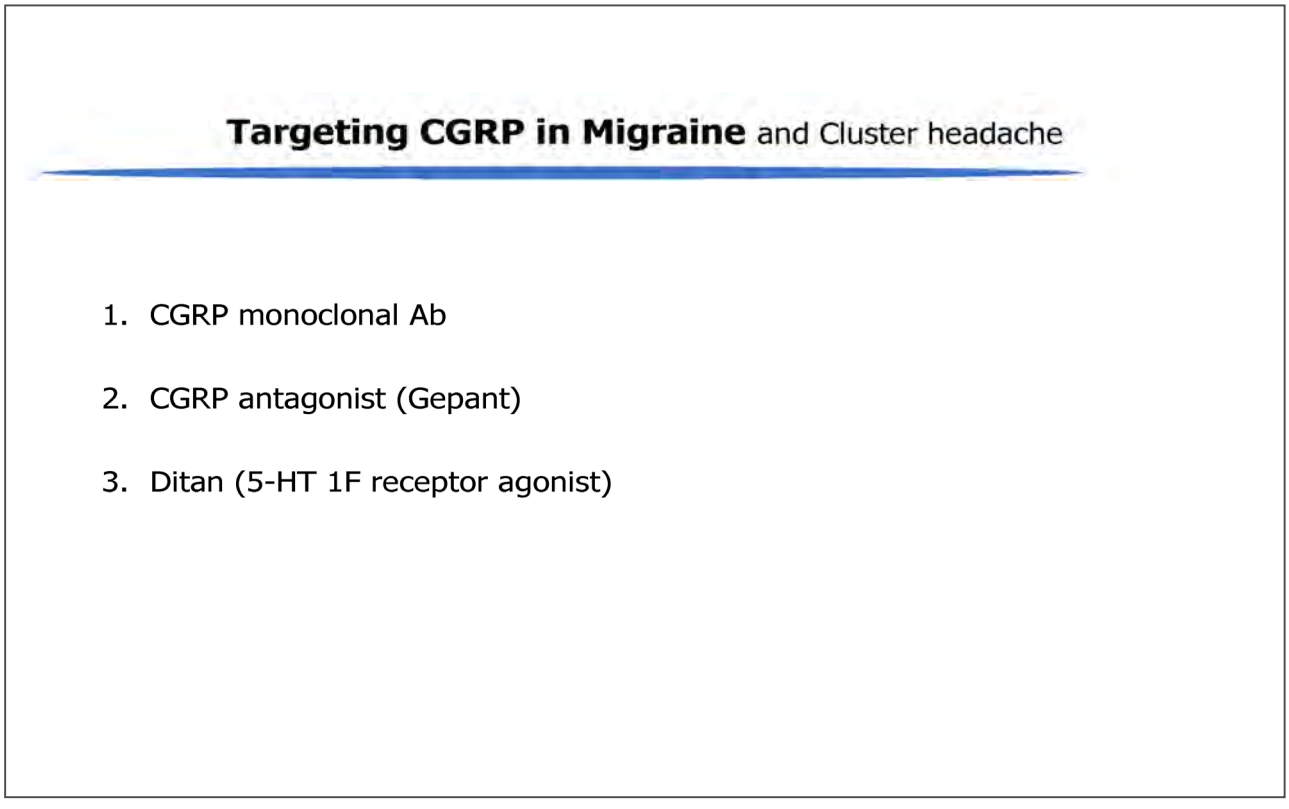
Headache

정 필 욱
성균관의대 강북삼성병원 신경과



FDA approval status : Migraine medication

- Erene**mab** *for prevention 2018 May (Norvatis/Amgen)*
- Galcanezu**mab** *for prevention 2018 Sep (Lilly)*
- Fremanezu**mab** *for prevention 2018 Sep (Teva)*
- Lasmi**ditan** *for acute 2019 Oct (Lilly)*
- Ubro**gepant** *for acute 2019 Dec (Allergan)*
- Rime**gepant** *for acute 2020 Feb (Biohaven)*
- Eptinezu**mab** *for prevention 2020 Feb (Lundbeck)*
- Ato**gepant** *for prevention pending (Allergan/Abbivie)*
- Rime**gepant** *for prevention*

Migraine until yesterday : Acute medication

- Triptans /Ergotamine only migraine-specific treatments available
- Vasoconstrictor properties

--Contraindicated in coronary artery disease, uncontrolled hypertension, cerebrovascular disease

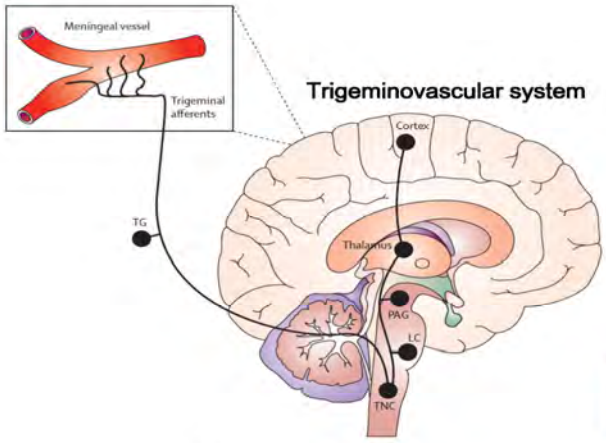
- Tolerability
- Insufficient efficacy
- Potential development of MOH

Migraine until yesterday : Prevention

- B-blockers, calcium channel blockers, TCA, AED, ARB ...
  --Not initially developed to treat migraine
- Poor tolerability, contraindications, drug–drug interactions
- Poor adherence
- Modest efficacy

Development of CGRP-targeted therapies

- Successful translation from bench to clinic
- Discovery of CGRP
  &
- Concept of Trigeminovascular system



Ferrari et al. Lancet neurol 2015

Hyperexcitable brain

Cortical spreading depression / Other triggers

Activation of Trigeminal ganglion/Nerve

자극된 삼차신경의 **신경펩티드 분비**

말초성 자극:혈관확장, 혈장 단백질 삼출: neurogenic inflammation

중추성자극 :TNC을 통한 구심성통증신호

시상/대뇌 경로를 통한 통증

CGRP (Calcitonin gene-related peptide)

- 37 amino acid long peptide, potent vasodilatory peptide
- Widely expressed through both in PNS and CNS
- Most abundant Neuropeptide in the trigeminal system
- In Trigeminal ganglion, CGRP is expressed in C-fiber and CGRP receptor is expressed in Aδ-fiber
- CGRP interacts with receptors on trigeminal Aδ fibers/neurons, satellite glial cells, endothelial cells, immune cells, and blood vessel smooth muscle cells

Clinical data showing causative role of CGRP in Migraine

- Release of CGRP following stimulation of trigeminal ganglion
- Elevated CGRP in jugular vein during migraine attack
- Lowering of CGRP level after sumatriptan treatment
- Infusion of CGRP evoked headache attack in patients with migraine

CGRP Blocking

CGRP antagonist (small molecules, Gepants) vs. Monoclonal Antibody

Small molecules	Monoclonal antibodies
Target specificity lower	Target specificity high
Clearance (liver, kidney)	Clearance RES
Size <1 kDa	Size ~150 kDa
Oral	Parenteral
Many enter cells and cross BBB	Do not enter cells or cross BBB
Half-life minutes to hours	Half-life 3–6 weeks
Immunogenicity (No)	Immunogenicity (yes)

Mainly by CYP and phase II enzymes; metabolized to nonactive and active metabolites

Catabolism; degraded to peptides or amino acids Mostly recycled as peptide fragments by the body

CGRP Monoclonal antibody therapy

- Potential advantages

--Target specific: less likely to have off-target effects

--Long half-lives: monthly or quarterly dosing

--Metabolized by the reticuloendothelial system : low potential for hepatic or renal toxicity

--Large molecules, do not cross BBB : reducing the possibility of CNS adverse events

- Disadvantages

--Subcutaneous injection or intravenous infusion

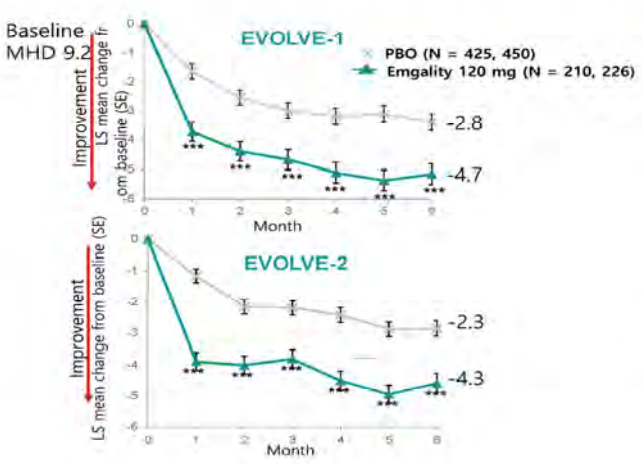
--Potential to evoke antibody response

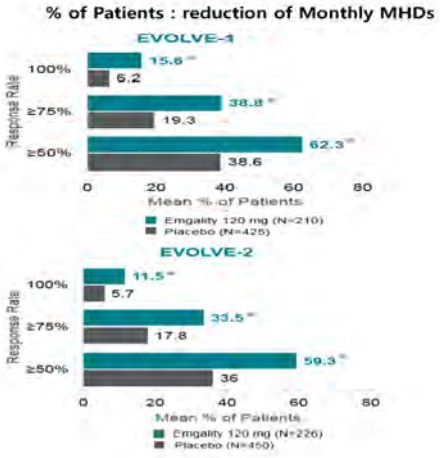
CGRP Monoclonal Antibodies

	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
Market name	AIMOVIG	EMGALITY	AJOVY	VYEPTI
FDA approval	May 2018	Sep 2018/ **국내승인**	Sep 2018	Feb. 2020
Target	**CGRP receptor**	CGRP peptide	CGRP peptide	CGRP peptide
Dosing	**70/140mg** SC monthly	**Loading 240mg** then 120mg SC monthly	225mg SC monthly **675 mg SC Quarterly**	**Quarterly IV**
Characteristics	Human	Humanized	Humanized	Humanized
Being Studied for	EM (STRIVE, ARISE, LIBERTY) CM Tx resistant migraine	EM (EVELOVE1,2) CM (REGAIN) Tx resistant migraine Episodic cluster (FDA) Chronic cluster (no effect)	EM (HALO) CM (HALO) Refractory migraine Episodic cluster (fail) Chronic cluster (no effect) Posttraumatic headache	EM (PROMISE 1) CM (PROMISE 2)

EM

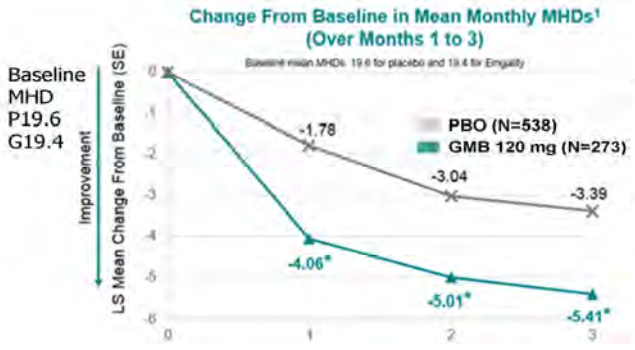
- Sustained Response Through Month 6, starting from Month 1
- ≥ 50% reduction : **2/3** , ≥ 75 % reduction: **1/3**, 100% reduction: **10%**

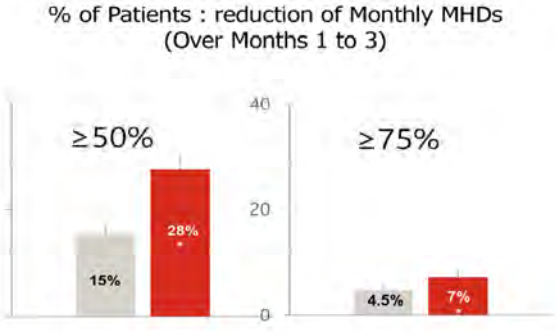




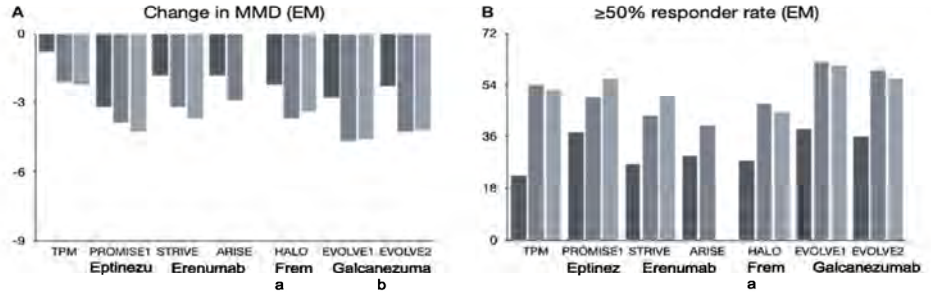
CM

- Sustained Response Through Month 3, starting from Month 1
- ≥ 50% reduction: 28 %, ≥ 75 % reduction: 7 %



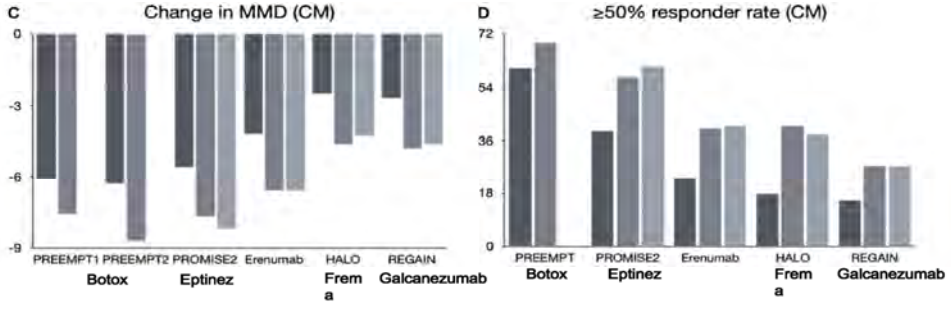


CGRP mAb in Episodic Migraine Prevention trials



Yuan et al. Headache 2019

CGRP mAb in Chronic Migraine Prevention trials



Yuan et al. Headache 2019

Efficacy in patients who have previously failed preventive therapy

- Subgroup analysis of the pivotal trials / RCT showed efficacy in pts who failed 2 -4 drugs
- In a subgroup analysis from EVOLVE-1, EVOLVE-2, and REGAIN studies on subjects who failed onabotulinumtoxinA, galcanezumab showed significant reduction of headache

Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial

Wim M Mulleners, Byung-Kun Kim, Miguel J A Láinez, Michel Lanteri-Minet, Patricia Pozo-Rosich, Shufang Wang, Antje Tockhorn-Heidenreich, Sheena K Aurora, Russell M Nichols, Laura Yunes-Medina, Holland C Detke

Lancet Neurol 2020; 19: 814–25

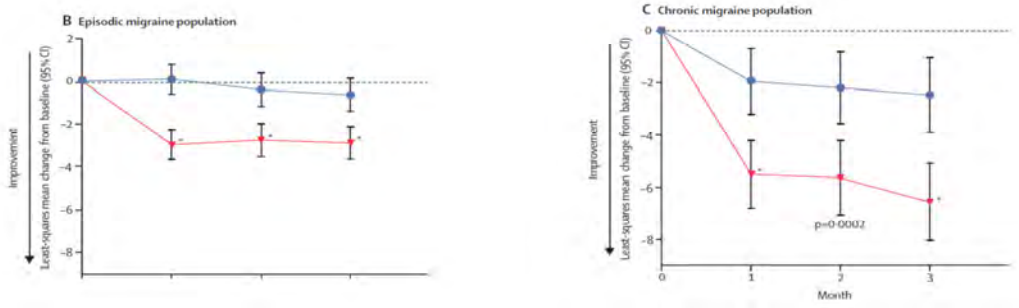
See Comment page 798

Neurology Department, Canisius Wilhelmina Ziekenhuis, Nijmegen, Netherlands (Prof W M Mulleners MD); Neurology Department, Nowon Eulji Medical Center, Seoul, South Korea (Prof B-K Kim MD); Hospital Clínico Universitario, Universidad Católica de Valencia, Valencia, Spain (Prof M J A Láinez MD); Pain Department CHU Nice and FHU InovPain Côte Azur University, Nice, France (Prof M Lanteri-Minet MD); INSERM/UdA, U1107, Neuro-Dol, Auvergne University, Clermont-Ferrand, France (Prof M Lanteri-Minet); Headache Unit, Neurology

Summary

Background Many patients who require migraine preventive treatment have not been able to tolerate or have not responded to multiple previous preventive medications. We aimed to assess the safety and efficacy of galcanezumab, an antibody to calcitonin gene-related peptide, in patients with migraine who had not benefited from preventive medications from two to four categories.

Methods CONQUER was a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial done at 64 sites (hospitals, clinics, or research centres) in 12 countries (Belgium, Canada, Czech Republic, France, Germany, Hungary, Japan, the Netherlands, South Korea, Spain, the UK, and the USA). Patients were 18–75 years of age, with episodic or chronic migraine, with migraine onset before the age of 50 years, who had a documented failure of preventive medications from two to four drug categories in the past 10 years owing to lack of efficacy or tolerability, or both. Patients were randomised 1:1 to receive subcutaneous placebo or galcanezumab 120 mg per month (with a 240 mg loading dose administered as two 120 mg injections) for 3 months. For masking purposes, patients receiving placebo also received two injections during the first dosing visit. Randomisation was done by a computer-generated random sequence by means of an interactive web-response system stratified by country and migraine frequency (low frequency episodic migraine, four to fewer than eight migraine headache days per month; high frequency episodic migraine, eight to 14 migraine headache days per month and fewer than 15 headache days per month; chronic migraine, at least eight migraine headache days per month and at least 15 headache days per month). The primary endpoint was the overall mean change from baseline in number of monthly migraine headache days during the 3-month treatment period in all patients who were randomly assigned and received at least one dose of study drug. This trial is registered with ClinicalTrials.gov, NCT03559257, and is now completed.



Onset of response : CGRP mAb

- 24 hour -1week
  Often within 1 month
- Rapid, within days or even sooner after administration

- Possible use in an emergency or urgent care department, or inpatient setting, by providing both rapid and sustained relief
- Useful as a new approach for patients with status migrainosus

Duration of response

- Post-hoc analysis and open-label extension studies suggest that responses to erenumab, fremanezumab, and galcanezumab are sustained, and typically increase over 3–6 month period
- Results from a 64-week interim analysis of the open-label phase 2 study on erenumab in EM and from 1-year analysis of galcanezumab in both EM and CM show long-term efficacy

Tolerability and Safety

- No serious treatment-emergent adverse events attributable to mAbs have been reported
- Concern about potential vascular consequences of inhibiting CGRP signalling

  -- No major cardiovascular AEs were observed in all trial populations (even in patients with stable angina)
- Constipation : inhibition of CGRP receptors on gut smooth muscle?

Issues of CGRP mAb use in guidelines

	EHF guideline[85]	AHS position statement[85]
Which patients with migraine are eligible for treatment with CGRP MAbs?	Patients with episodic or chronic migraine who have been unsuccessfully treated with two or more preventive treatments and those who cannot use other preventive treatments because of comorbidities, side-effects, or poor compliance	Patients older than 18 years of age who fulfil diagnostic criteria for migraine with or without aura or chronic migraine,[3] and patients who are unable to tolerate, or have inadequate response to, two oral preventive treatments
How should other preventive treatments be managed when using CGRP MAbs in patients with migraine?	Patients with episodic migraine should discontinue oral preventives before initiating CGRP MAb; patients with chronic migraine can add CGRP MAbs to oral preventives; the need for subsequent withdrawal can be assessed; onabotulinumtoxinA regimens should be discontinued before CGRP MAb administration	The risk of drug–MAb interactions is minimal; addition of a CGRP MAb to the existing regimen is appropriate, but efficacy should be assessed before making further changes
When should treatment with CGRP MAbs be stopped in patients with migraine?	In patients with either episodic or chronic migraine CGRP MAb discontinuation should be considered after 6–12 months	The benefits of CGRP MAb should be assessed after 3 months and treatment should only be continued if reduction in monthly migraine days is ≥50% compared with baseline or a clinically meaningful improvement is achieved in the MIDAS, MPFID, or HIT-6 scores
What should we do with partial responders?	Consider adding a preventive treatment	No recommendation
In which patients should CGRP MAbs not be used?	CGRP MAbs are not recommended for use in patients who are pregnant or nursing, are alcohol or drug abusers, have cerebrovascular or cardiovascular disease, or have severe mental disorders	No recommendation

Charles et al. Lancet 2019

Targeting CGRP in Migraine

1. CGRP monoclonal Ab
2. **CGRP antagonist (Gepant)**
3. Ditan (5-HT 1F receptor agonist)

First-generation CGRP receptor antagonists

- Olcegepant

--First CGRP-targeted therapy to show efficacy 2004

--Acute treatment of migraine : IV administration

- Telcagepant

--First oral gepant

--Efficacy as acute and preventive treatment / No cardiovascular adverse event

--Hepatotoxicity

Second generation Gepants show efficacy and safety

Acute medication

ORIGINAL ARTICLE

Rimegepant, an Oral Calcitonin Gene–Related Peptide Receptor Antagonist, for Migraine

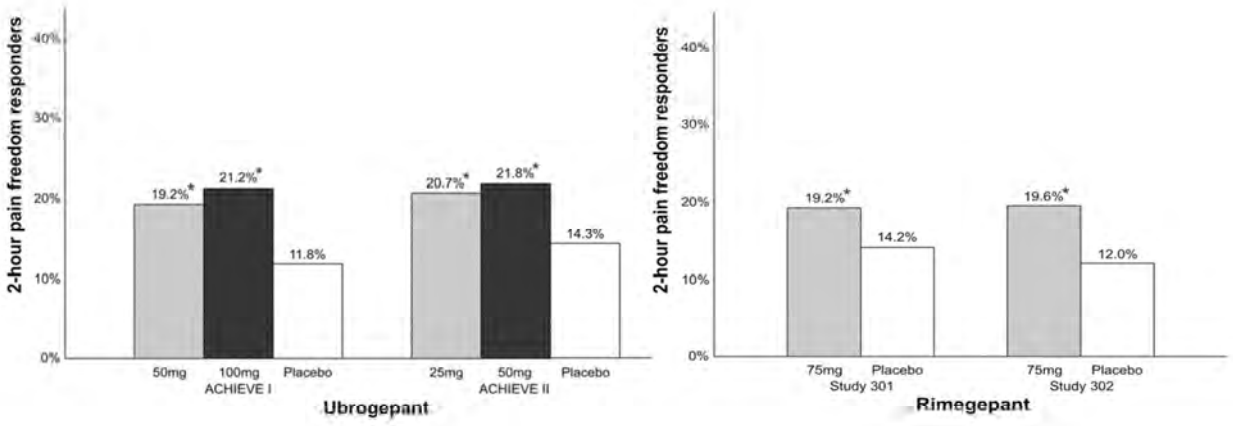
Richard B. Lipton, M.D., Robert Croop, M.D., Elyse G. Stock, M.D., David A. Stock, Ph.D., Beth A. Morris, B.A., Marianne Frost, M.A., Gene M. Dubowchik, Ph.D., Charles M. Conway, Ph.D., Vladimir Coric, M.D., and Peter J. Goadsby, M.D., Ph.D.

ORIGINAL ARTICLE

Ubrogepant for the Treatment of Migraine

David W. Dodick, M.D., Richard B. Lipton, M.D., Jessica Ailani, M.D., Kaifeng Lu, Ph.D., Michelle Finnegan, M.P.H., Joel M. Trugman, M.D., and Armin Szegedi, M.D.

2Hr pain free rate of CGRP antagonist



CGRP antagonists (Gepants) : Acute medication

Therapeutic gain for gepants (5-10%)
-- Seems to be low, compared to sumatriptan (16-21%) and lasmiditan (7-17.5%)

Previous trials of gepants caused concerns of hepatic toxicity
-- No hepatotoxicity with treatments of rimegepants and ubrogepants

Not constrict cranial arteries

Clinical implication
-- First line anti-migraine treatment in patient with CV risk
-- Second line treatment for the patient who failed with triptans/ not tolerated
-- The first gepant approved by FDA in 2019

Gepant for migraine Prevention

- **Atogepant**

--Developed exclusively for the prevention of migraine

- **Rimegepant**

--Studied for acute and preventive medication

Atogepant for prevention

Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial

Peter J Goadsby, David W Dodick, Jessica Ailani, Joel M Trugman, Michelle Finnegan, Kaifeng Lu, Armin Szegedi

Summary

Background Atogepant is an orally administered, small-molecule, calcitonin gene-related peptide (CGRP) receptor antagonist under investigation for treatment of migraine. We aimed to examine a range of oral doses for safety, tolerability, and efficacy for the preventive treatment of migraine.

Methods In this double-blind, phase 2b/3 trial, adults (aged 18–75 years), with a history (≥1 year) of migraine and 4–14 migraine days per month, were randomly assigned 2:1:2:2:1:1 (by means of a sequence generated by the statistical programming department of the sponsor, and operationalised through an automated interactive web-based response system) to receive placebo or atogepant 10 mg once daily, 30 mg once daily, 60 mg once daily, 30 mg twice daily, or 60 mg twice daily, in matching capsules. Participants, site personnel, and all study sponsor personnel were masked to treatment allocations. The study was done in 78 academic and private practice settings in the USA. The primary outcome was change from baseline in monthly migraine days across 12 weeks of treatment using a modified intention-to-treat approach. The overall type I error rate for multiple comparisons across active treatment doses was controlled at the 0·05 level by means of a graphic approach. The main outcomes to assess safety and tolerability were adverse event recordings. The trial is registered with ClinicalTrials.gov, NCT02848326 and is completed.

Lancet Neurol 2020; 19: 727–37

This online publication has been corrected. The corrected version first appeared at thelancet.com/neurology on October 21, 2020

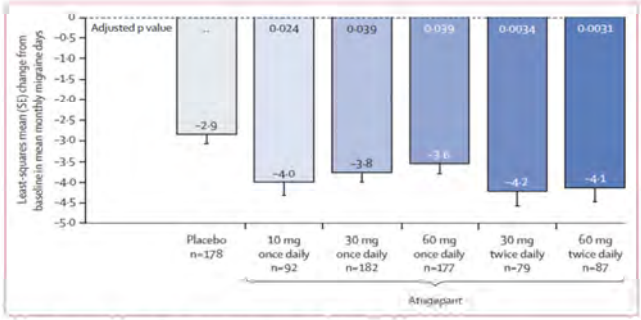
See Comment page 712

NIHR-Wellcome Trust King's Clinical Research Facility, SLaM Biomedical Research Centre, King's College London, London, UK (Prof P J Goadsby MD); Mayo Clinic, Phoenix, AZ, USA (Prof D W Dodick MD); Medstar Georgetown University Hospital, Washington DC, USA (J Ailani MD); and AbbVie,

Goadsby et al. Lancet Neurol 2020

Atogepant for Prevention

Change from baseline in mean monthly migraine days across the 12-week



No hepatic safety issues / No CV issues
Nausea 5%

Goadsby et al. Lancet Neurol 2020

Rimegepant for Prevention

Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial

Robert Croop, Richard B Lipton, David Kudrow, David A Stock, Lisa Kamen, Charles M Conway, Elyse G Stock, Vladimir Coric, Peter J Goadsby

Summary

Background Rimegepant is a calcitonin gene-related peptide receptor antagonist that has shown efficacy and safety in the acute treatment of migraine. We aimed to compare the efficacy of rimegepant with placebo for preventive treatment of migraine.

Lancet 2021; 397: 51–60
Published Online December 15, 2020 https://doi.org/10.1016/

	Rimegepant (n=348)		Placebo (n=347)		Least squares mean difference between groups (95% CI)	p value
	n	Point estimate (95% CI)	n	Point estimate (95% CI)		
Change in mean number of migraine days per month during weeks 9–12, days (primary efficacy outcome)†	348	−4·3 (−4·8 to −3·9)	347	−3·5 (−4·0 to −3·0)	−0·8 (−1·5 to −0·2)	0·0099
≥50% reduction in mean number of moderate or severe migraine days per month during weeks 9–12	171	49% (44 to 54)	144	41% (36 to 47)	8% (0 to 15)	0·044

(Prof P J Goadsby MD);

Croop et al. Lancet 2021

Gepants for migraine

- Ubrogepant : Acute (Approved 2019)
- Rimegepant : Acute (Approved 2020), Prevention
- Atogepant : Prevention

Gepants : Efficacy and Perspective

- Acute

--10% over than placebo in 2hr pain free rate

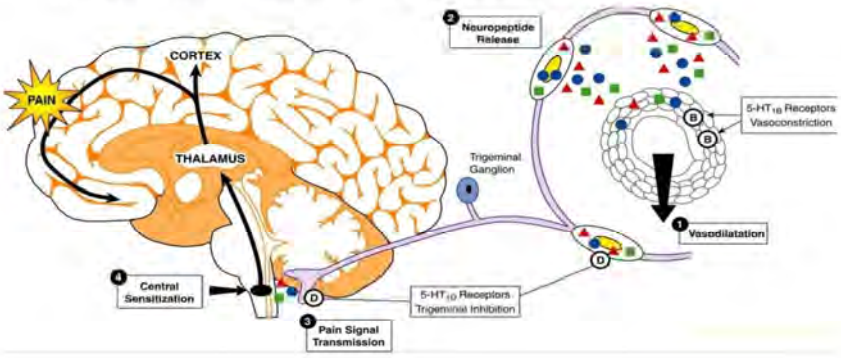
- Prevention

--1 day reduction than placebo in MMD (monthly migraine day)

- Continuum between acute and prophylactic treatment
- Departure from the concept of distinction between acute and prophylactic treatment of migraine

Lasmiditan : Selective 5-HT1F receptor agonist

Triptan : 5-HT1B/1D receptor agonist



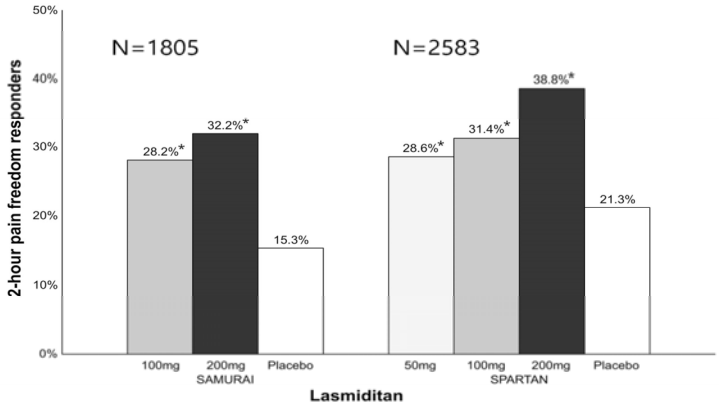
Vasoconstriction by binding to 5-HT$_{1B}$ receptor on smooth muscle cells in the coronary and cerebral arteries

Triptans /ergots contraindicated in patients with CVD, hemiplegic migraine or migraine with complicated aura

Lasmiditan

- Highly selective 5-HT1F receptor agonist
- 5-HT1F receptor is expressed on the presynaptic surface of central and peripheral trigeminal sensory neurons
- Activation do not lead to vasoconstriction
- Ideal target for new migraine acute treatments

Lasmiditan : Phase 3 study results



Most frequent AEs:

Dizziness(10-15%),
Paresthesia(5%),
Somnolence, fatigue,
nausea

No reports of chest pain or serious cardiovascular side effects

Response to lasmiditan differed according to prior triptan response?

- In a post-hoc analysis of both pivotal studies
- Patients taking lasmiditan experienced higher rates of headache pain freedom at 2 h versus placebo regardless of prior response to Triptans
- Possible alternative migraine therapy option regardless of prior response to triptans

Lasmiditan vs Gepants for acute medication

- Pain-free rates of lasmiditan seem to be above gepant pain-free rates
- CNS adverse events are more common than gepant CNS side effects
- Differential medication overuse headache risk? Gepant

CGRP targeted therapy in Cluster headache

	Erenumab	Galcanezumab	Fremanezumab	Eptinezumab
FDA approval	May 2018	Sep 2018/ 국내승인	Sep 2018	Feb. 2020
Target	**CGRP receptor**	CGRP peptide	CGRP peptide	CGRP peptide
Dosing	**70/140mg** SC monthly	**Loading 240mg** then 120mg SC monthly	225mg SC monthly **675 mg SC Quarterly**	**Quarterly IV**
Trials done	EM (STRIVE, ARISE, LIBERTY) CM Tx resistant migraine	EM (EVELOVE1,2) CM (REGAIN) Tx resistant migraine Episodic cluster (FDA) Chronic cluster (fail)	EM (HALO) CM (HALO) Refractory migraine Episodic cluster (fail) Chronic cluster (no effect)	EM (PROMISE 1) CM (PROMISE 2)

ORIGINAL ARTICLE

Trial of Galcanezumab in Prevention of Episodic Cluster Headache

Peter J. Goadsby, M.D., Ph.D., David W. Dodick, M.D., Massimo Leone, M.D., Jennifer N. Bardos, Pharm.D., Tina M. Oakes, Ph.D., Brian A. Millen, Ph.D., Chunmei Zhou, M.S., Sherie A. Dowsett, Ph.D., Sheena K. Aurora, M.D., Andrew H. Ahn, M.D., Ph.D., Jyun-Yan Yang, M.D., Robert R. Conley, M.D., and James M. Martinez, M.D.

Table 2. Primary and Key Secondary End Points.*

End Point	Placebo (N=57)	Galcanezumab (N=49)	P Value
Least-squares mean change from baseline in weekly frequency of cluster headache attacks across wk 1–3	−5.2±1.3	−8.7±1.4	0.04
Percentage of patients with a response at wk 3†	53	71	0.046

Galcanezumab (300 mg/month × 2 months) significantly reduced weekly CH attack frequency and showed higher responder rate

NEJM 2019

Other trials on Cluster headache : Failed

- Episodic CH prevention study for fremanezumab was terminated early after a prespecified futility analysis
- Chronic CH : Galcanezumab and Fremanezumab both failed

맺음말

- CGRP target therapy 는 efficacy와 safety가 모두 입증되었음
- CGRP target therapy는 편두통와 군발두통의 치료에 획기적 변화를 가져올 것임
- CGRP target therapy 의 등장으로 원발두통의 정확한 진단, 치료반응평가가 매우 중요해질 것이므로 신경과 의사의 두통 치료에서의 역할이 더 중요해질 것임