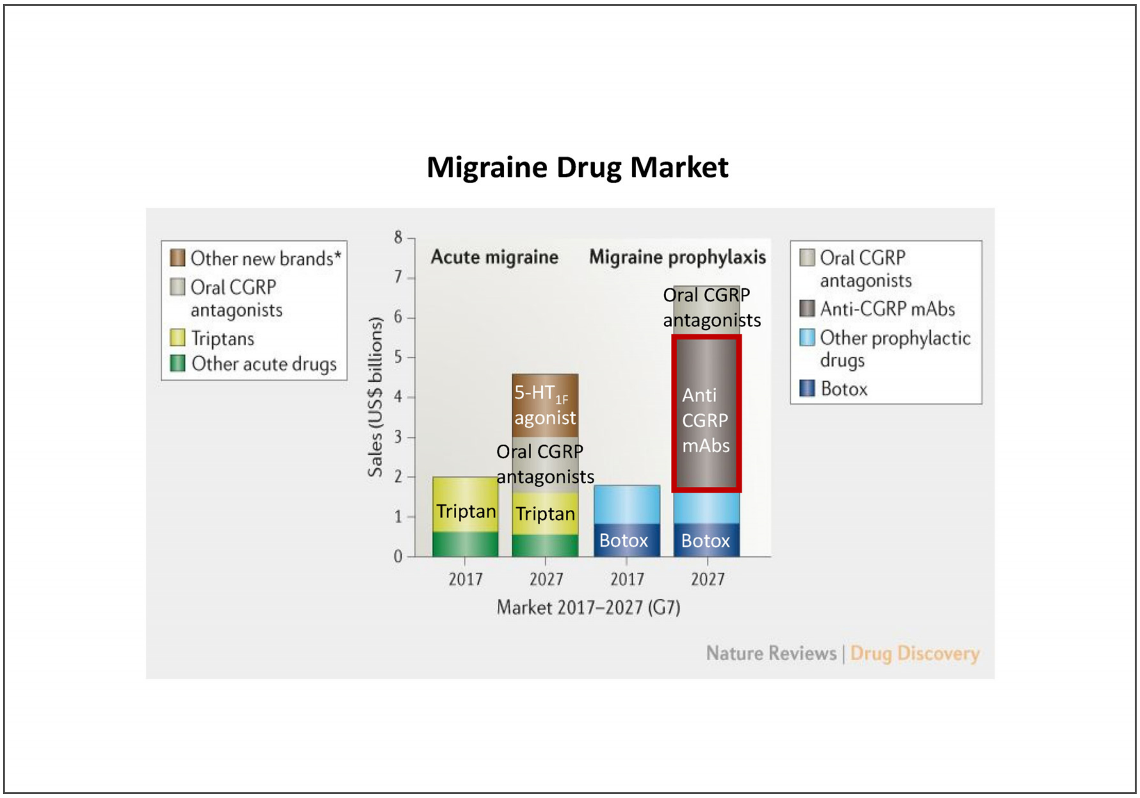
CGRP 항체주사

문 희 수
강북삼성병원



Migraine Drug Market

기존 편두통 치료의 문제점

Underuse of treatment → Delay in diagnosis → Delayed/ poor treatment efficacy

TRIPTANS

- Not effective in 30%
- Headache recurrence: 40% of patients
- Frequent use (≥10 d/M): MOH
- Vasoconstrictive 5-HT_{1B} mediated effect
  Contraindications
  - High blood pressure
  - Ischemic heart disease
  - Incidence of Heart attack or stroke in 1:1000000
- Side effects: nausea, GI, 'triptan chest'

ORAL PREVENTIVES

- Titration Schedule
  Gradual dose escalation
  The late emerging onset of action
- Limited efficacy
- Many Side effects
- Contraindications
- Lack of target specificity
- Drug interaction
- Daily multiple dosing schedule
- Low drug adherence

새로운 약에 대한 갈망

1. **Speed!**
2. **Effectiveness!**
3. **Tolerability!**
4. **Safety!**
5. **Convenience!**

New and emerging treatments

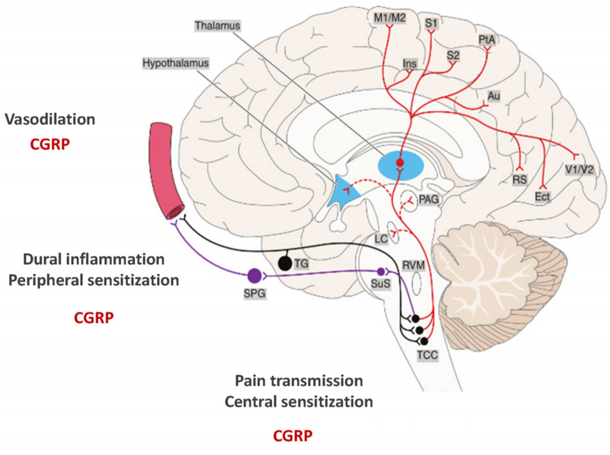
- New routes of administration
- **Novel mechanisms of action**
- Neurostimulation

New Action drug :
Neuronal Action↑
Vasoconstriction Effect↓
BBB Penetration ↑

Novel mechanisms of action

- **CGRP antagonists/antibody**
- **5-HT_{1F} Receptor agonist**
- Nitric oxide synthetase inhibitor
- Transient Receptor Potential Vanilloid (TRPV1)Receptor agonists
- Orexin Receptor Antagonists

New Migraine Targets


Thalamus
Hypothalamus
M1/M2
S1
PtA
Ins
S2
Au
RS
Ect
V1/V2
PAG
LC
RVM
TG
SPG
SuS
TCC
Vasodilation
CGRP
Dural inflammation
Peripheral sensitization
CGRP
Pain transmission
Central sensitization
CGRP

CGRP Role in Migraine

- Inflammatory protein thought to play a role in headache
- Initiating headache
- Propagate headache

Increased CGRP levels correlate with onset and pain intensity in migraine attacks[1,2]

Infusion of CGRP has been shown to induce migraine-like attacks in susceptible patients[1,3,4]

CGRP levels may return to normal following cessation of migraine headache[2]

CGRP is associated with photophobia[5-7]

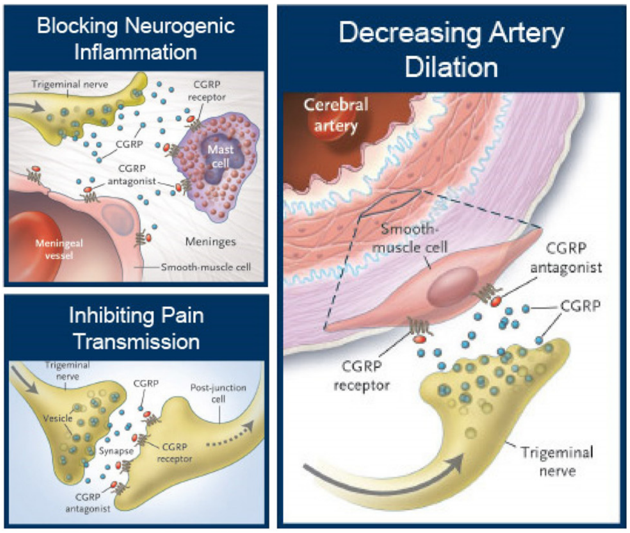
1. Arulmani U, et al. *Eur J Pharmacol.* 2004;500(1-3):315-330.
2. Juhasz G, et al. *Pain.* 2003;106(3):461-470.
3. Hansen JM, et al. *Cephalalgia.* 2010;30(10):1179-1186.
4. Lassen LH, et al. *Cephalalgia.* 2002;22(1):54-61.
5. Russo AF. *Annu Rev Pharmacol Toxicol.* 2015;55:533-552.
6. Recober A, et al. *J Neurosci.* 2009;29(27):8798-8804.
7. Recober A, et al. *Neuropharmacology.* 2010;58(1):156-165.

(galcanezumab) injection

CGRP Inhibition in Migraine

Triptans, medications commonly used for the acute treatment of migraine, may reduce CGRP levels[1,2]

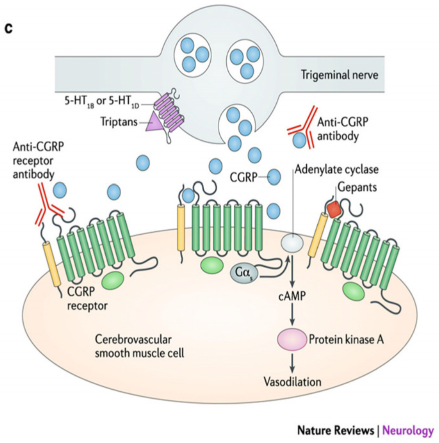
Blocking the CGRP ligand or receptor reduces migraine symptoms[3,4]


Blocking Neurogenic Inflammation
Trigeminal nerve
CGRP receptor
CGRP
CGRP antagonist
Mast cell
Meningeal vessel
Meninges
Smooth-muscle cell
Inhibiting Pain Transmission
Trigeminal nerve
Vesicle
CGRP
Post-junction cell
Synapse
CGRP receptor
CGRP antagonist
Decreasing Artery Dilation
Cerebral artery
Smooth-muscle cell
CGRP antagonist
CGRP
CGRP receptor
Trigeminal nerve

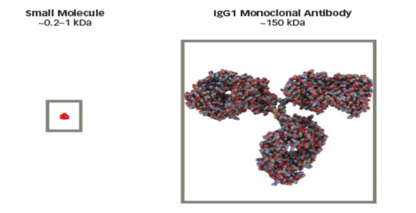
1. Arulmani U, et al. *Eur J Pharmacol.* 2004;500(1-3):315-330.
2. Goadsby PJ, Edvinsson L. *Brain.* 1994;117(Pt 3):427-434.
3. Edvinsson L. *Br J Clin Pharmacol.* 2015:80(2):193-199 (v1.0).
4. Peroutka SJ. *BioDrugs.* 2014;28(3):237-244.

(galcanezumab) injection

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

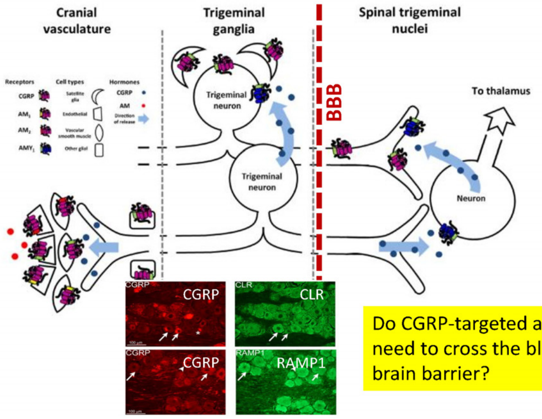

c
Trigeminal nerve
5-HT$_{1B}$ or 5-HT$_{1D}$
Triptans
Anti-CGRP antibody
Anti-CGRP receptor antibody
CGRP
Adenylate cyclase
Gepants
$G\alpha_s$
CGRP receptor
cAMP
Cerebrovascular smooth muscle cell
Protein kinase A
Vasodilation

Nature Reviews | Neurology


Small Molecule
~0.2–1 kDa
IgG1 Monoclonal Antibody
~150 kDa

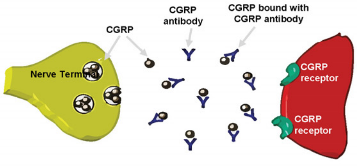
Small molecules	Monoclonal antibodies
Target specificity lower	Target specificity high
Clearance (liver, kidney)	Clearance RES
Size <1 kDa	Size ~150 kDa
Oral	Parenteral
Many enter cells and cross BBB	Do not enter cells or cross BBB
Half-life minutes to hours	Half-life 3–6 weeks
Immunogenicity (No)	Immunogenicity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

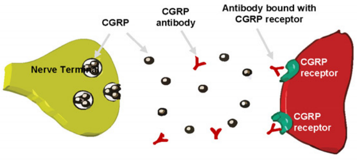

Cranial vasculature
Trigeminal ganglia
Spinal trigeminal nuclei
BBB
Receptors
Cell types
Hormones
CGRP
AM$_1$
AM$_2$
AMY$_1$
Satellite glia
Endothelial
Vascular smooth muscle
Other glial
CGRP
AM
Direction of release
Trigeminal neuron
Trigeminal neuron
To thalamus
Neuron
CGRP
CLR
CGRP
RAMP1

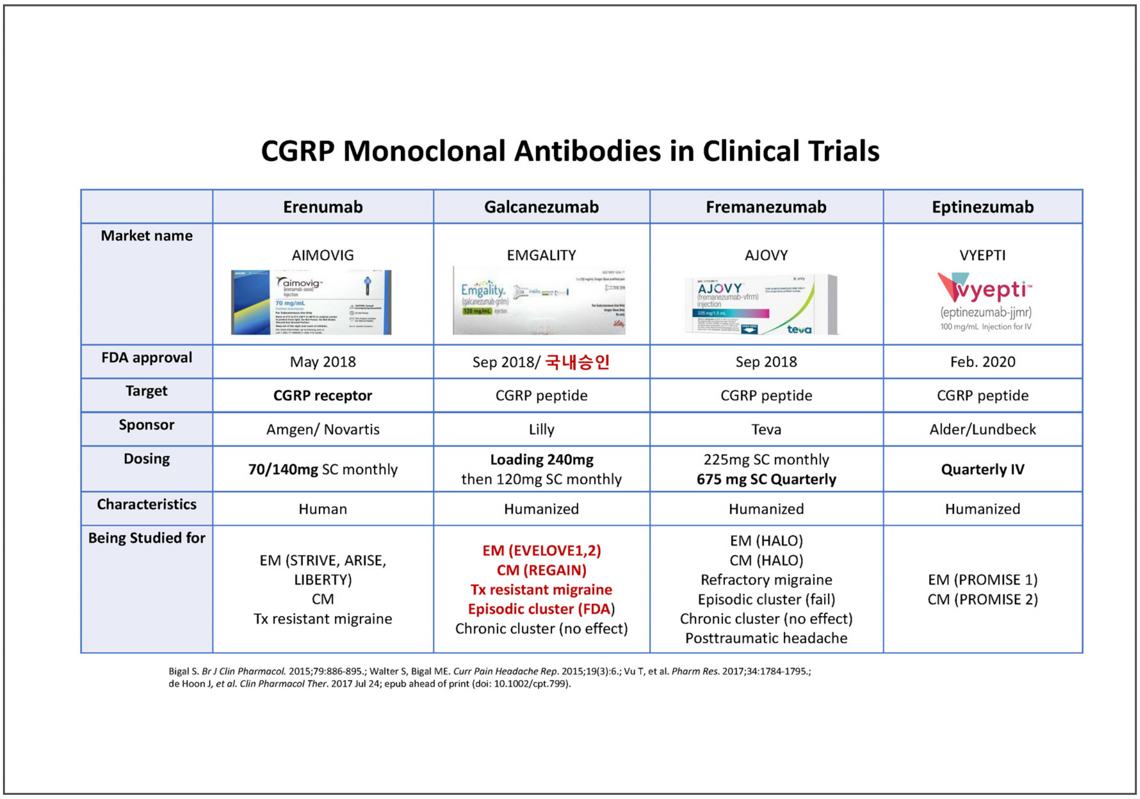
Do CGRP-targeted agents need to cross the blood-brain barrier?

1. CGRP Ligand antibodies (3) : Galcanezumab
Fremanezumab
Eptinezumab


CGRP
CGRP antibody
CGRP bound with CGRP antibody
Nerve Terminal
CGRP receptor
CGRP receptor

2. CGRP receptor antibody (1): Erenumab

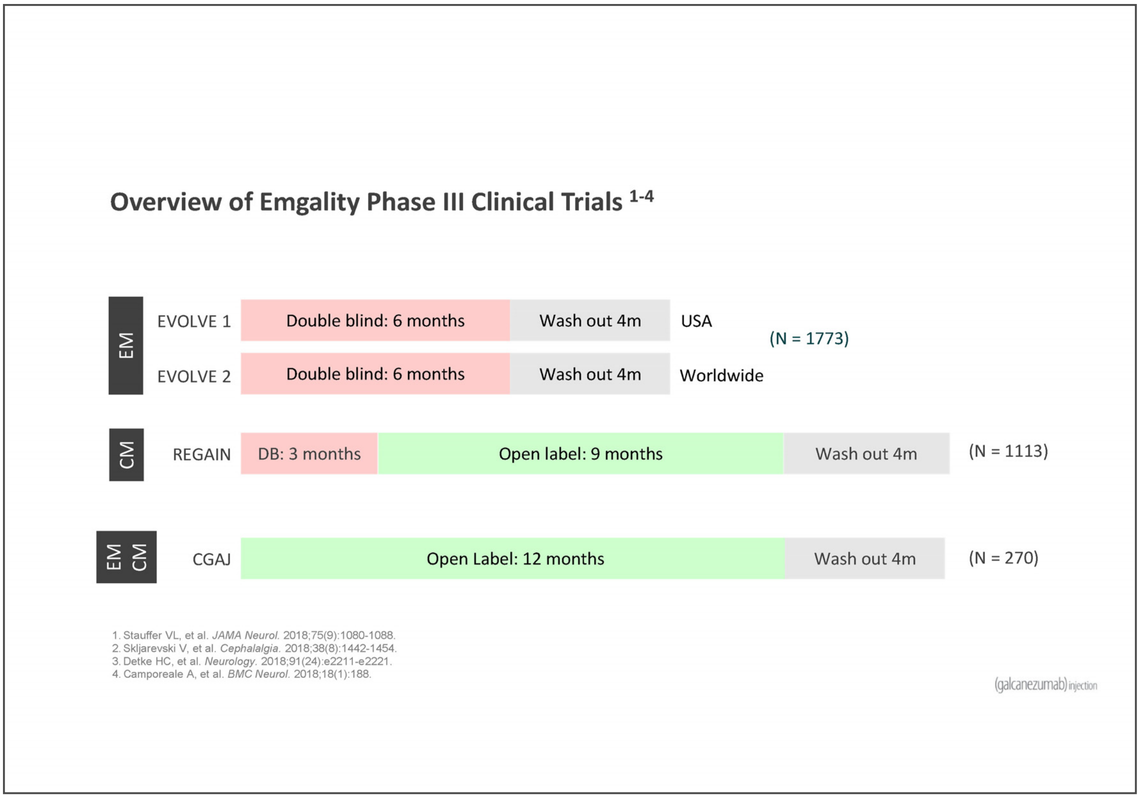

CGRP
CGRP antibody
Antibody bound with CGRP receptor
Nerve Terminal
CGRP receptor
CGRP receptor



CGRP Monoclonal Antibodies in Clinical Trials

	Erenumab	**Galcanezumab**	**Fremanezumab**	**Eptinezumab**
Market name	AIMOVIG	EMGALITY	AJOVY	VYEPTI (eptinezumab-jjmr) 100 mg/mL Injection for IV
FDA approval	May 2018	Sep 2018/ **국내승인**	Sep 2018	Feb. 2020
Target	**CGRP receptor**	CGRP peptide	CGRP peptide	CGRP peptide
Sponsor	Amgen/ Novartis	Lilly	Teva	Alder/Lundbeck
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)

Bigal S. *Br J Clin Pharmacol.* 2015;79:886-895.; Walter S, Bigal ME. *Curr Pain Headache Rep.* 2015;19(3):6.; Vu T, et al. *Pharm Res.* 2017;34:1784-1795.; de Hoon J, *et al. Clin Pharmacol Ther.* 2017 Jul 24; epub ahead of print (doi: 10.1002/cpt.799).



Overview of Emgality Phase III Clinical Trials [1-4]

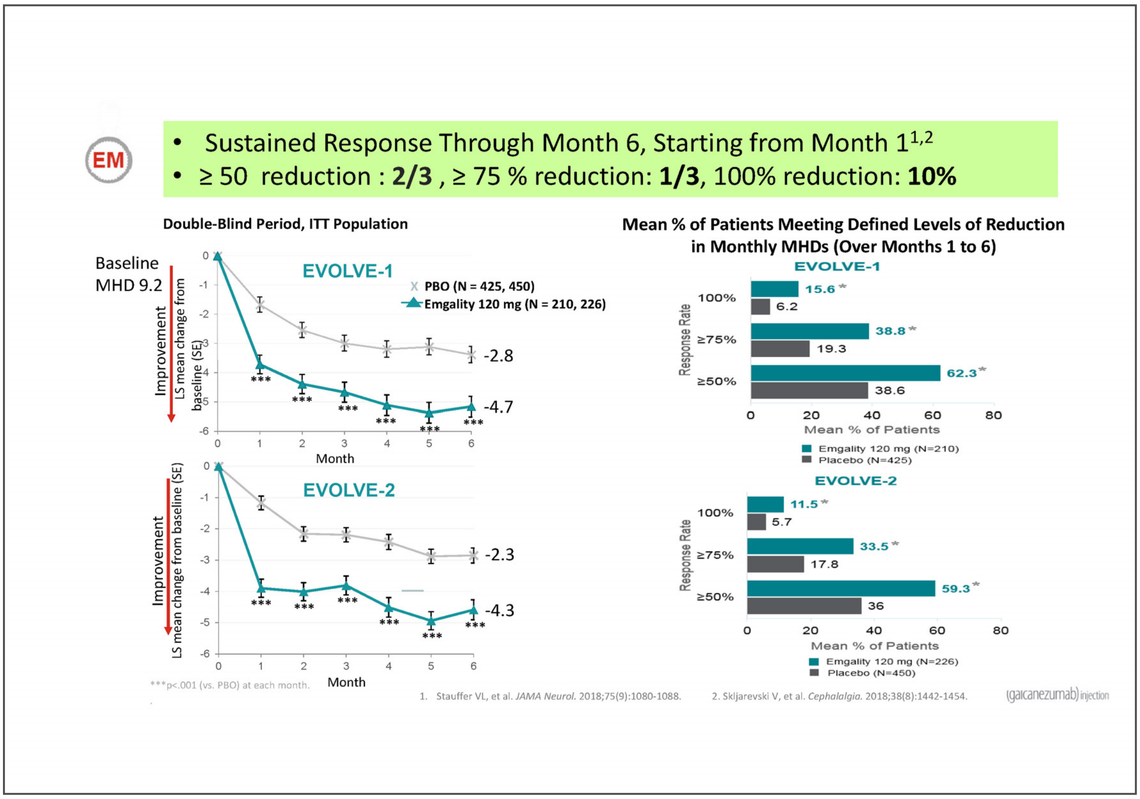
EM
EVOLVE 1 | Double blind: 6 months | Wash out 4m | USA
EVOLVE 2 | Double blind: 6 months | Wash out 4m | Worldwide
(N = 1773)

CM
REGAIN | DB: 3 months | Open label: 9 months | Wash out 4m | (N = 1113)

EM CM
CGAJ | Open Label: 12 months | Wash out 4m | (N = 270)

1. Stauffer VL, et al. *JAMA Neurol.* 2018;75(9):1080-1088.
2. Skljarevski V, et al. *Cephalalgia.* 2018;38(8):1442-1454.
3. Detke HC, et al. *Neurology.* 2018;91(24):e2211-e2221.
4. Camporeale A, et al. *BMC Neurol.* 2018;18(1):188.

(galcanezumab) injection



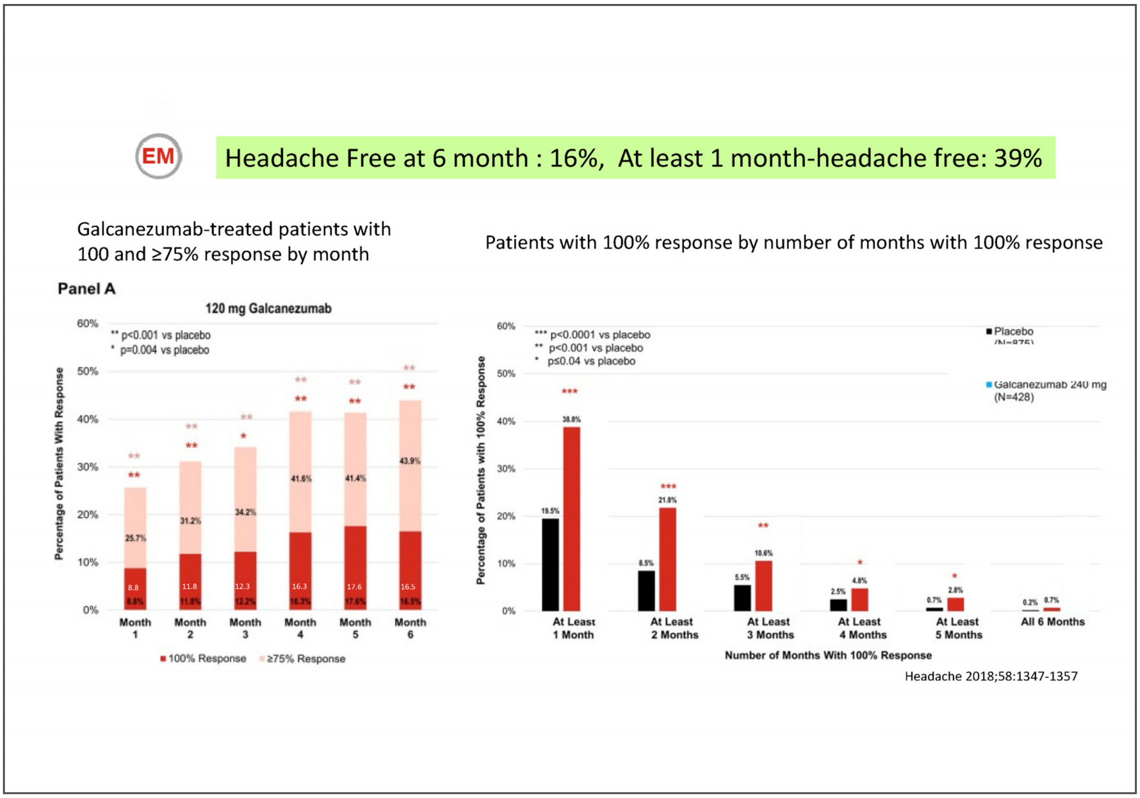
EM

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

Double-Blind Period, ITT Population

Mean % of Patients Meeting Defined Levels of Reduction in Monthly MHDs (Over Months 1 to 6)

1. Stauffer VL, et al. *JAMA Neurol.* 2018;75(9):1080-1088.
2. Skljarevski V, et al. *Cephalalgia.* 2018;38(8):1442-1454.



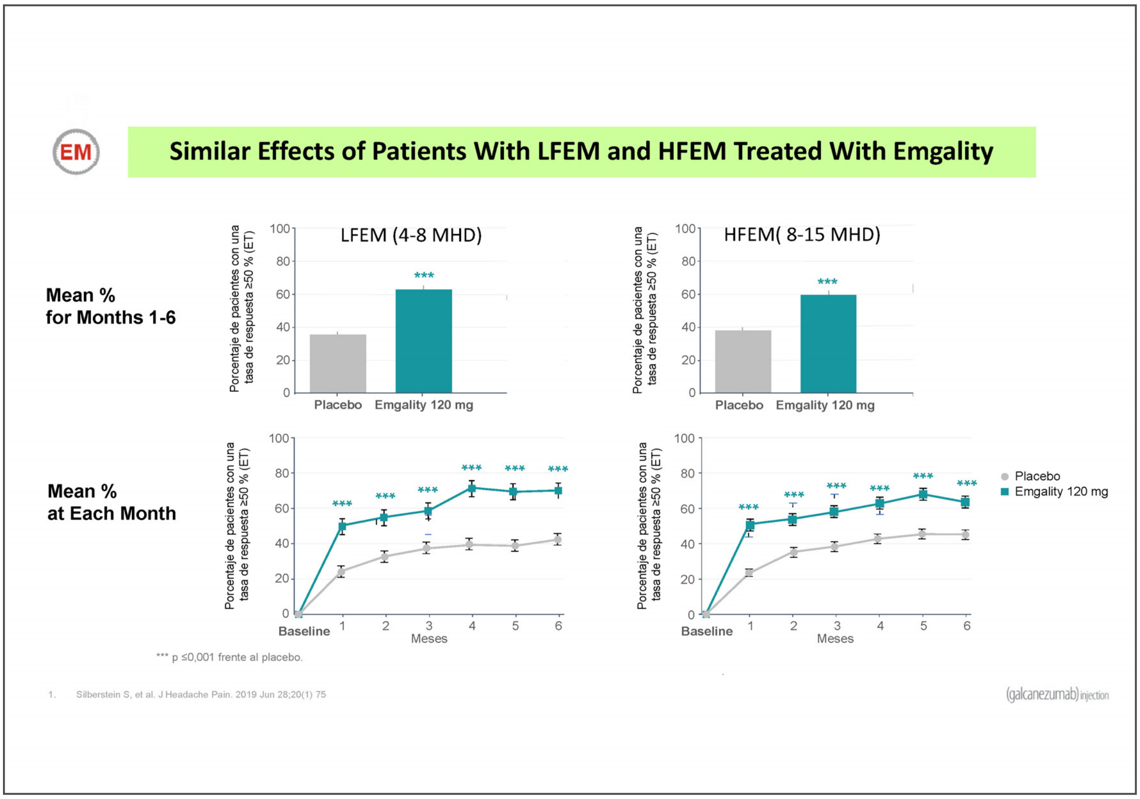
EM

Headache Free at 6 month : 16%, At least 1 month-headache free: 39%

Galcanezumab-treated patients with 100 and ≥75% response by month

Patients with 100% response by number of months with 100% response

Headache 2018;58:1347-1357



EM

Similar Effects of Patients With LFEM and HFEM Treated With Emgality

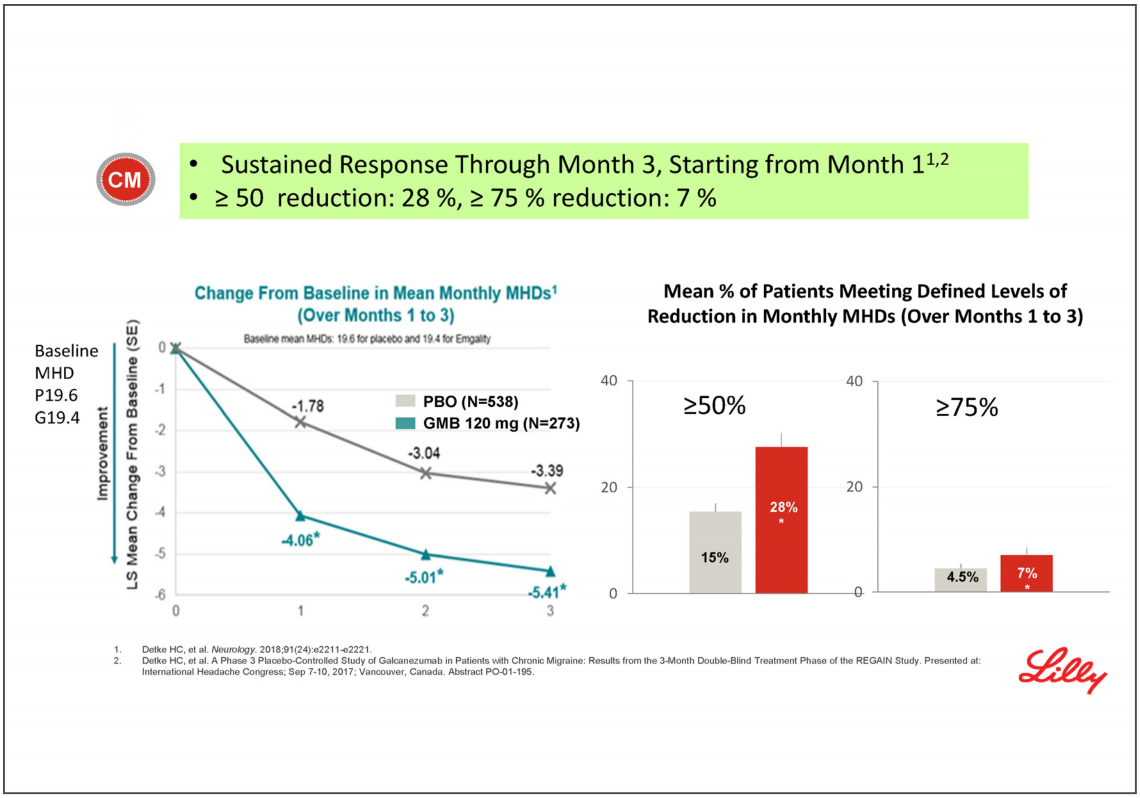
**Mean %
for Months 1-6**

**Mean %
at Each Month**

*** p ≤0,001 frente al placebo.

1. Silberstein S, et al. J Headache Pain. 2019 Jun 28;20(1) 75

(galcanezumab) injection



CM

- Sustained Response Through Month 3, Starting from Month 1[1,2]
- ≥ 50 reduction: 28 %, ≥ 75 % reduction: 7 %

Baseline
MHD
P19.6
G19.4

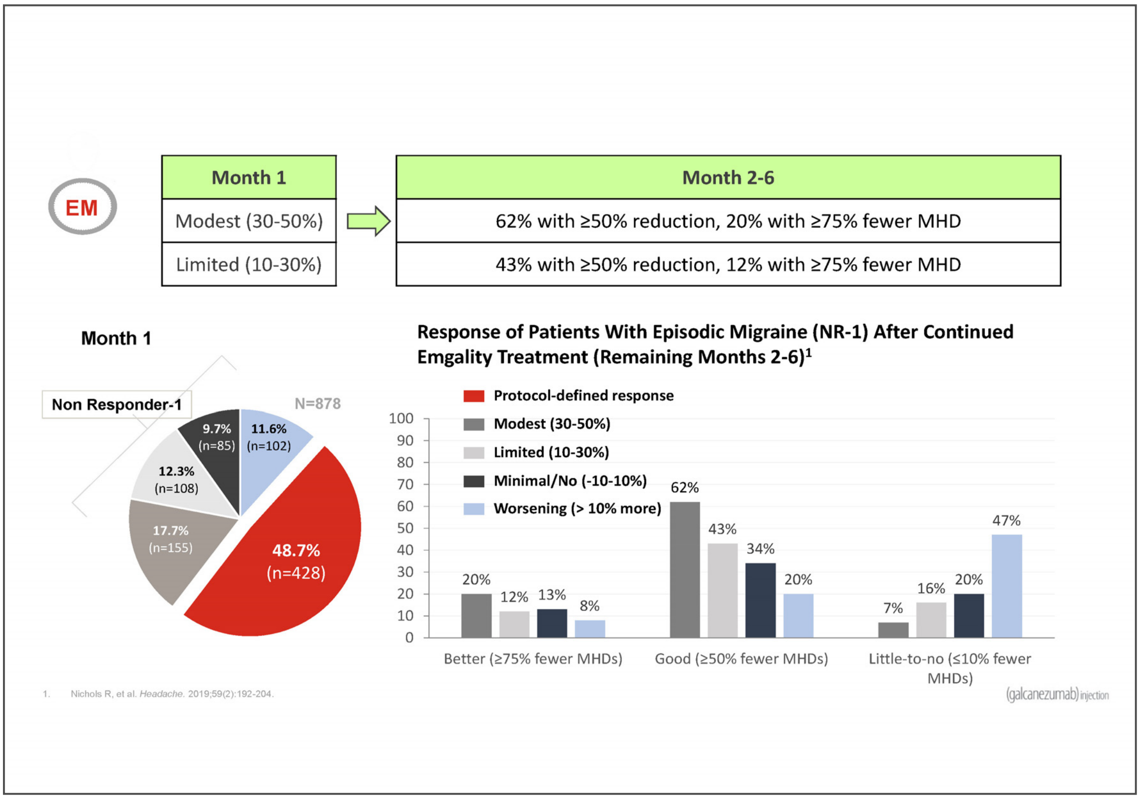
**Change From Baseline in Mean Monthly MHDs[1]
(Over Months 1 to 3)**

Baseline mean MHDs: 19.6 for placebo and 19.4 for Emgality

Mean % of Patients Meeting Defined Levels of Reduction in Monthly MHDs (Over Months 1 to 3)

1. Detke HC, et al. *Neurology*. 2018;91(24):e2211-e2221.
2. Detke HC, et al. A Phase 3 Placebo-Controlled Study of Galcanezumab in Patients with Chronic Migraine: Results from the 3-Month Double-Blind Treatment Phase of the REGAIN Study. Presented at: International Headache Congress; Sep 7-10, 2017; Vancouver, Canada. Abstract PO-01-195.

Lilly



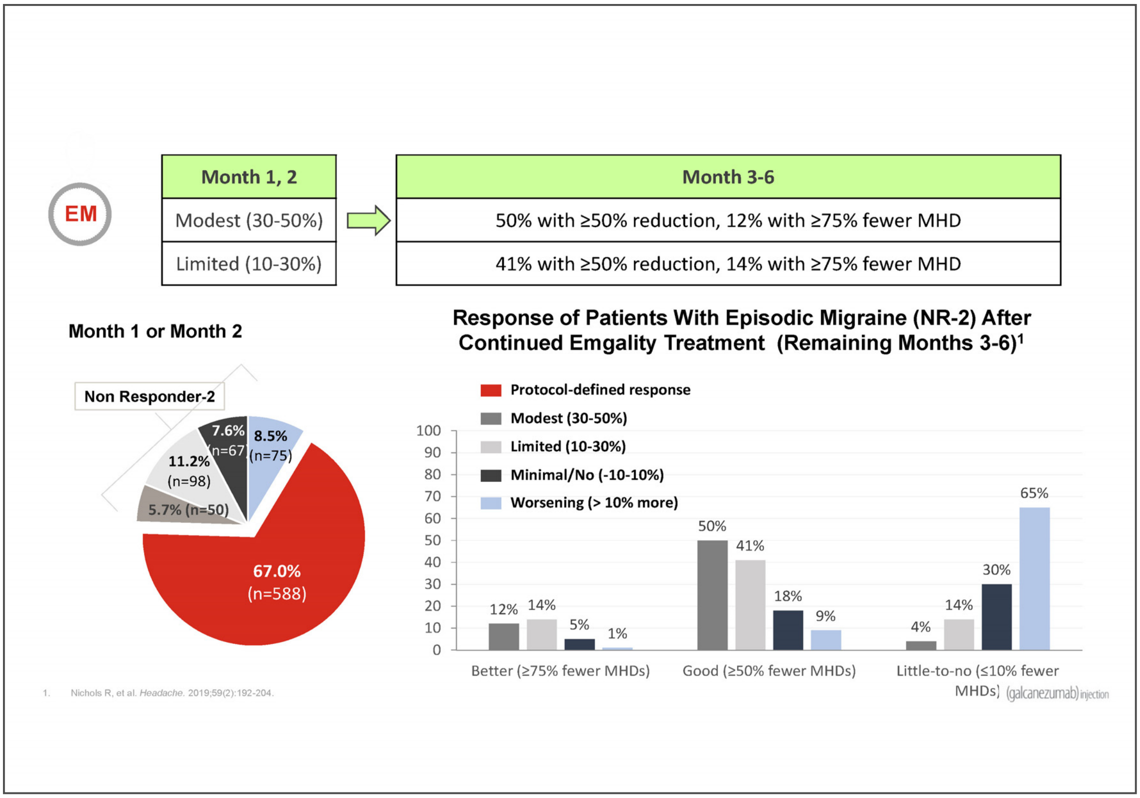
EM

Month 1	Month 2-6
Modest (30-50%)	62% with ≥50% reduction, 20% with ≥75% fewer MHD
Limited (10-30%)	43% with ≥50% reduction, 12% with ≥75% fewer MHD

Month 1

Response of Patients With Episodic Migraine (NR-1) After Continued Emgality Treatment (Remaining Months 2-6)[1]

1. Nichols R, et al. *Headache*. 2019;59(2):192-204.



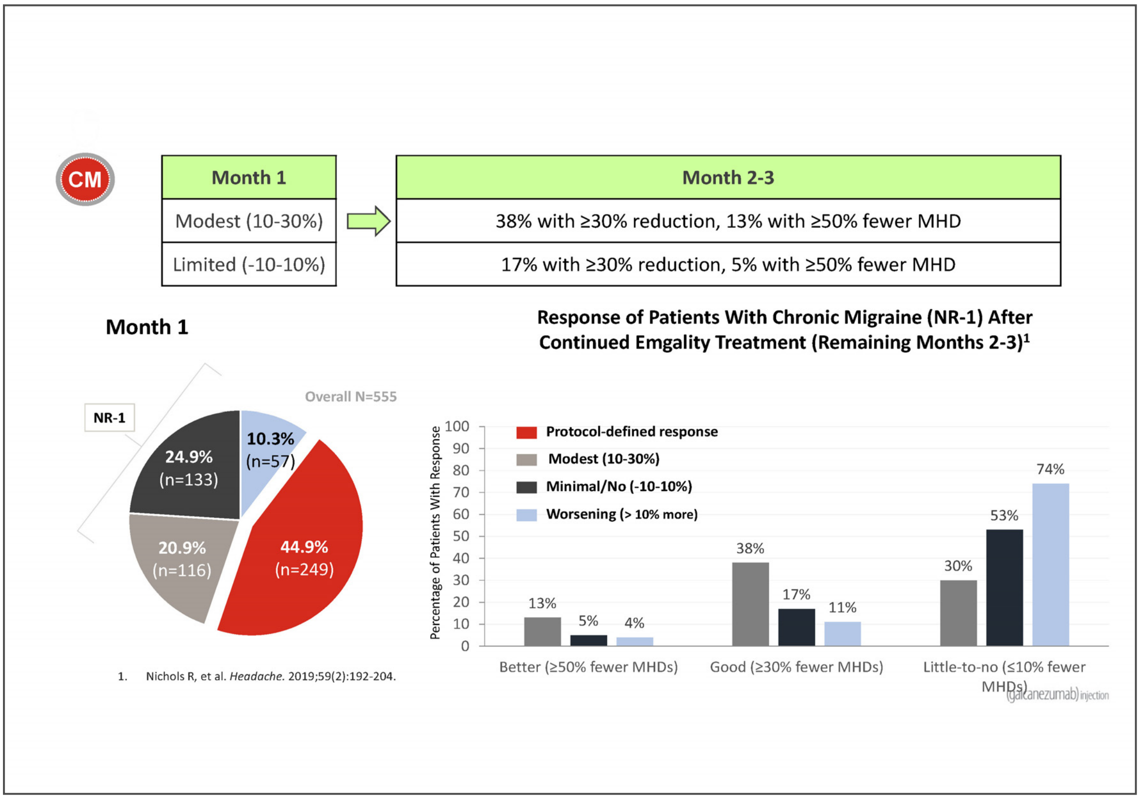
EM

Month 1, 2	Month 3-6
Modest (30-50%)	50% with ≥50% reduction, 12% with ≥75% fewer MHD
Limited (10-30%)	41% with ≥50% reduction, 14% with ≥75% fewer MHD

Month 1 or Month 2

Response of Patients With Episodic Migraine (NR-2) After Continued Emgality Treatment (Remaining Months 3-6)[1]

1. Nichols R, et al. *Headache*. 2019;59(2):192-204.



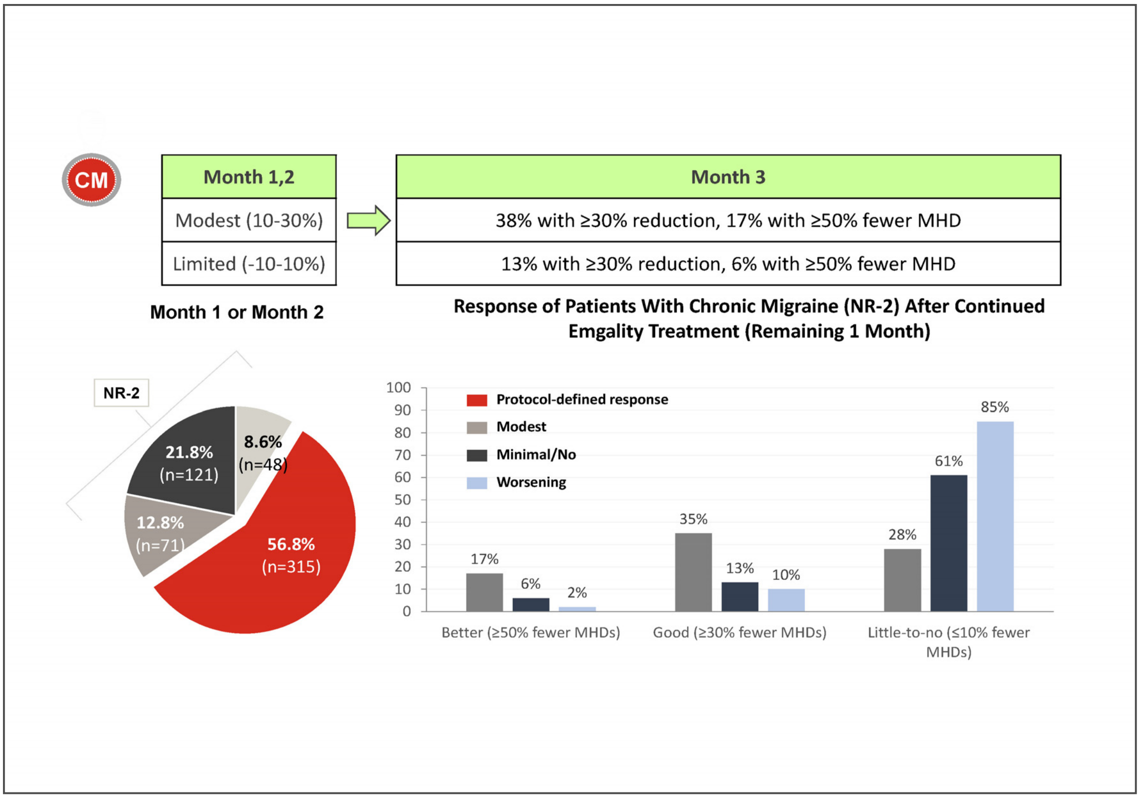
CM

Month 1		Month 2-3
Modest (10-30%)	⇨	38% with ≥30% reduction, 13% with ≥50% fewer MHD
Limited (-10-10%)		17% with ≥30% reduction, 5% with ≥50% fewer MHD

Month 1

Response of Patients With Chronic Migraine (NR-1) After Continued Emgality Treatment (Remaining Months 2-3)[1]

1. Nichols R, et al. *Headache.* 2019;59(2):192-204.

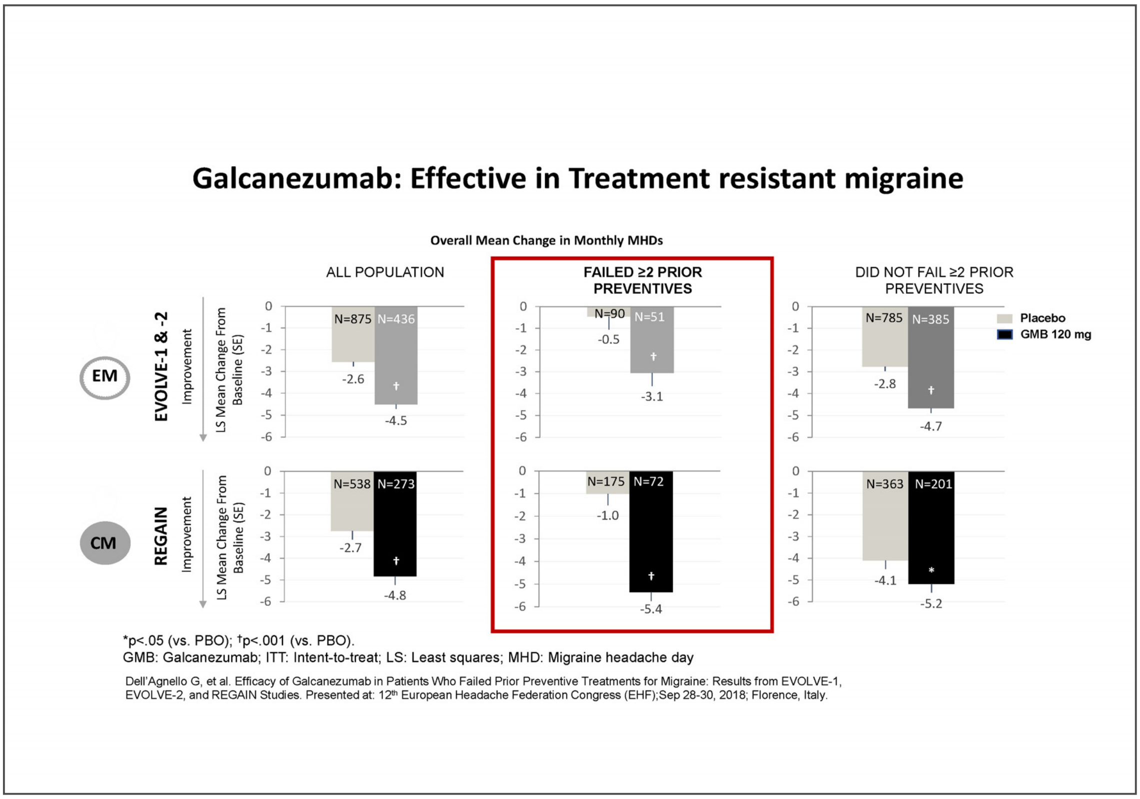


CM

Month 1,2		Month 3
Modest (10-30%)	⇨	38% with ≥30% reduction, 17% with ≥50% fewer MHD
Limited (-10-10%)		13% with ≥30% reduction, 6% with ≥50% fewer MHD

Month 1 or Month 2

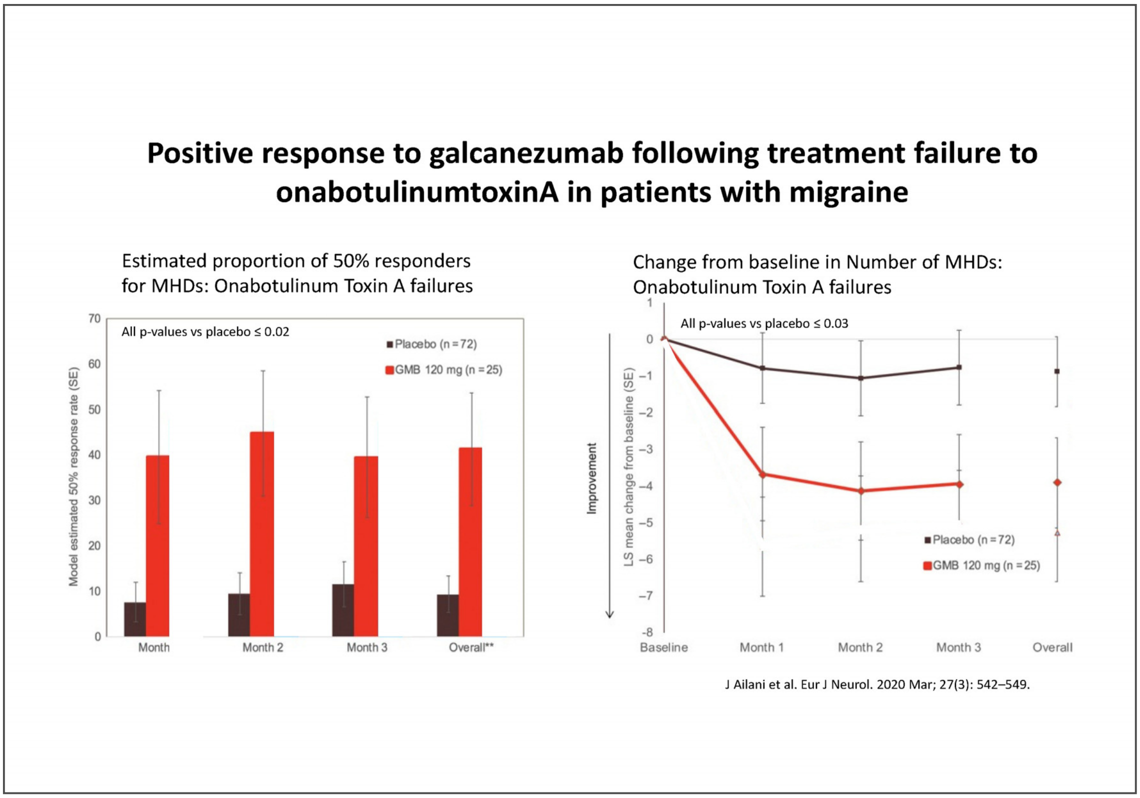
Response of Patients With Chronic Migraine (NR-2) After Continued Emgality Treatment (Remaining 1 Month)



Galcanezumab: Effective in Treatment resistant migraine

*p<.05 (vs. PBO); †p<.001 (vs. PBO).
GMB: Galcanezumab; ITT: Intent-to-treat; LS: Least squares; MHD: Migraine headache day

Dell'Agnello G, et al. Efficacy of Galcanezumab in Patients Who Failed Prior Preventive Treatments for Migraine: Results from EVOLVE-1, EVOLVE-2, and REGAIN Studies. Presented at: 12th European Headache Federation Congress (EHF);Sep 28-30, 2018; Florence, Italy.

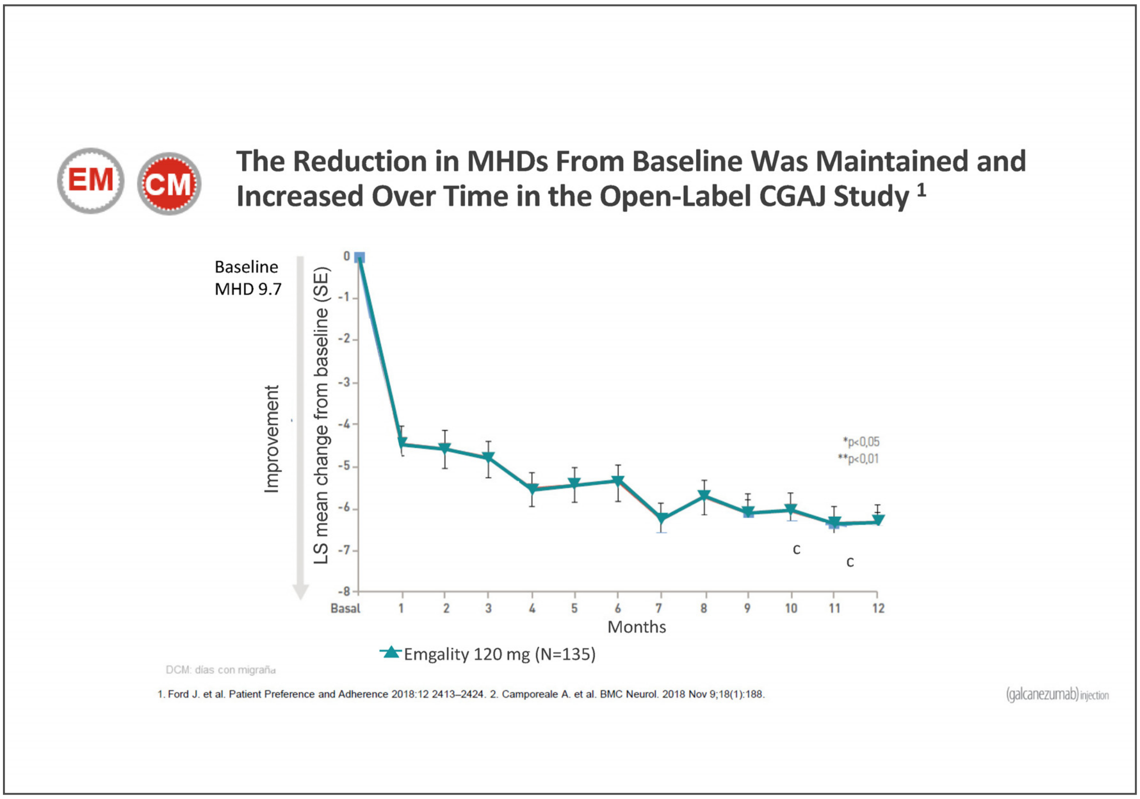


Positive response to galcanezumab following treatment failure to onabotulinumtoxinA in patients with migraine

Estimated proportion of 50% responders for MHDs: Onabotulinum Toxin A failures

Change from baseline in Number of MHDs: Onabotulinum Toxin A failures

J Ailani et al. Eur J Neurol. 2020 Mar; 27(3): 542–549.



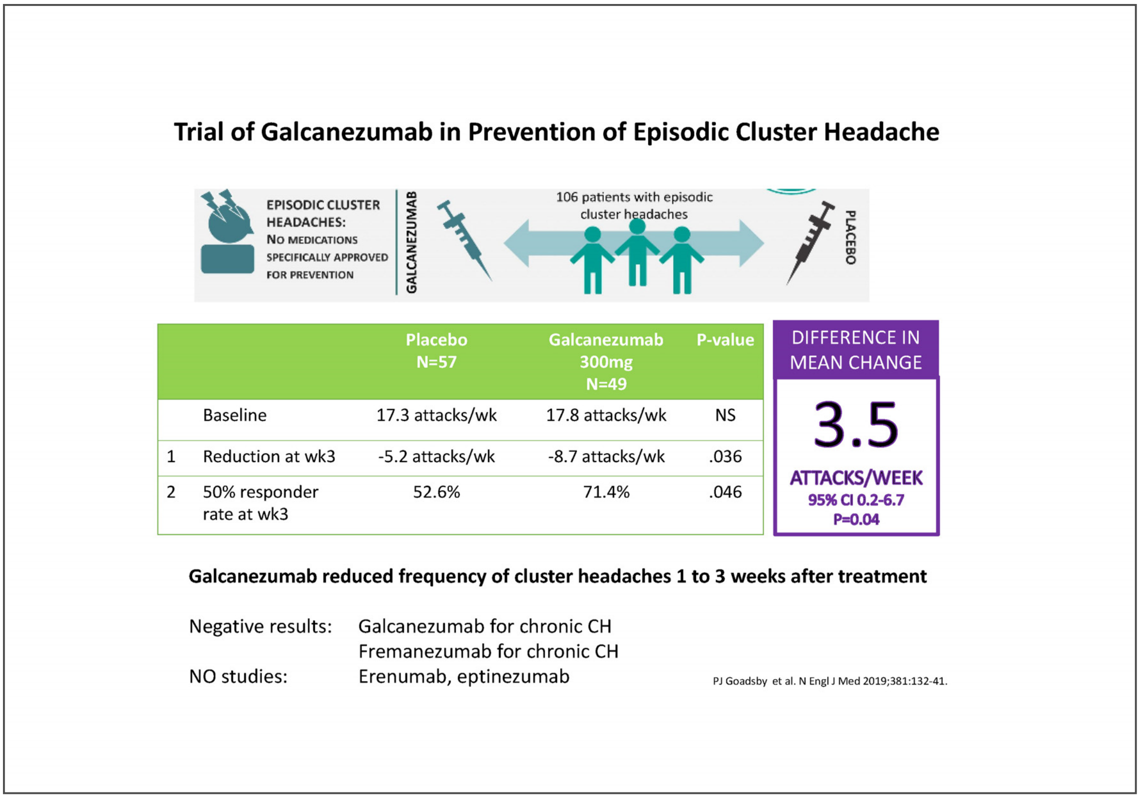
EM CM

The Reduction in MHDs From Baseline Was Maintained and Increased Over Time in the Open-Label CGAJ Study [1]

DCM: días con migraña

1. Ford J. et al. Patient Preference and Adherence 2018:12 2413–2424. 2. Camporeale A. et al. BMC Neurol. 2018 Nov 9;18(1):188.

(galcanezumab) injection



Trial of Galcanezumab in Prevention of Episodic Cluster Headache

EPISODIC CLUSTER
HEADACHES:
NO MEDICATIONS
SPECIFICALLY APPROVED
FOR PREVENTION
GALCANEZUMAB
106 patients with episodic
cluster headaches
PLACEBO

		Placebo N=57	Galcanezumab 300mg N=49	P-value
	Baseline	17.3 attacks/wk	17.8 attacks/wk	NS
1	Reduction at wk3	-5.2 attacks/wk	-8.7 attacks/wk	.036
2	50% responder rate at wk3	52.6%	71.4%	.046

DIFFERENCE IN MEAN CHANGE

3.5

ATTACKS/WEEK
95% CI 0.2-6.7
P=0.04

Galcanezumab reduced frequency of cluster headaches 1 to 3 weeks after treatment

Negative results:	Galcanezumab for chronic CH Fremanezumab for chronic CH
NO studies:	Erenumab, eptinezumab

PJ Goadsby et al. N Engl J Med 2019;381:132-41.

Event, n (%)	Placebo N=1451	Galcanezumab 120 mg N=705
Injection site pain	**138 (9.5)**	**71 (10.1)**
Nasopharyngitis[a]	**94 (6.5)**	**52 (7.4)**
Upper respiratory tract infection	60 (4.1)	31 (4.4)
Injection site reaction	14 (1.0)	22 (3.1)†
Dizziness	41 (2.8)	20 (2.8)
Injection site erythema	20 (1.4)	20 (2.8)*
Sinusitis	31 (2.1)	20 (2.8)
Urinary tract infection	33 (2.3)	19 (2.7)
Fatigue	34 (2.3)	17 (2.4)
Injection site pruritus	2 (0.1)	15 (2.1)†
Neck pain	21 (1.5)	15 (2.1)
Abdominal pain	24 (1.7)	13 (1.8)
Cough	19 (1.3)	12 (1.7)
Oropharyngeal pain	13 (0.9)	10 (1.4)
Bronchitis	17 (1.2)	9 (1.3)
Influenza	34 (2.3)	8 (1.1)
Constipation	8 (0.6)	7 (1.0)
Migraine	14 (1.0)	7 (1.0)
Rash	17 (1.2)	8 (1.1)
Weight increased	12 (0.8)	9 (1.3)
Influenza-like illness	8 (0.6)	6 (0.9)
Injection site bruising	9 (0.6)	4 (0.6)
Pruritus	4 (0.3)	5 (0.7)
Vertigo	3 (0.2)	5 (0.7)
Dyspepsia	9 (0.6)	5 (0.7)
Hypertension	15 (1.0)	8 (1.1)
Anxiety	13 (0.9)	9 (1.3)
Injection site swelling	1 (0.1)	8 (1.1)†
Viral infection	11 (0.8)	8 (1.1)
Nasal congestion	8 (0.6)	3 (0.4)

Good Safety Profiles in Clinical Trials

- The most common AE(5%)
  - Nasopharyngitis/URI
  - Injection site reaction
- Constipation
  esp. Erenumab (1-3%)
  esp. long term use
  -- Direct inhibition or down-regulation of CGRP receptors on gut smooth muscle

Low Adverse Events, Even Compared to Placebo

Good Safety Profiles in Clinical Trials

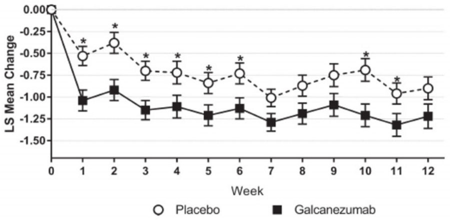
Oral	Propranolol	Valproate	Topiramate	Amitriptyline
Dropout rate due to AEs	20%	8%	22%	12%

mAb	Erenumab 70mg, 140mg	Galcanezumab 120mg, 240mg	Fremanezumab 225mg, 625mg	Eptinezumab 100mg, 300mg
Dropout rate due to AEs	2.2% in each group	4.2%, 2.3%	1.7% in each group	2% in each group

ONSET of EFFICACY

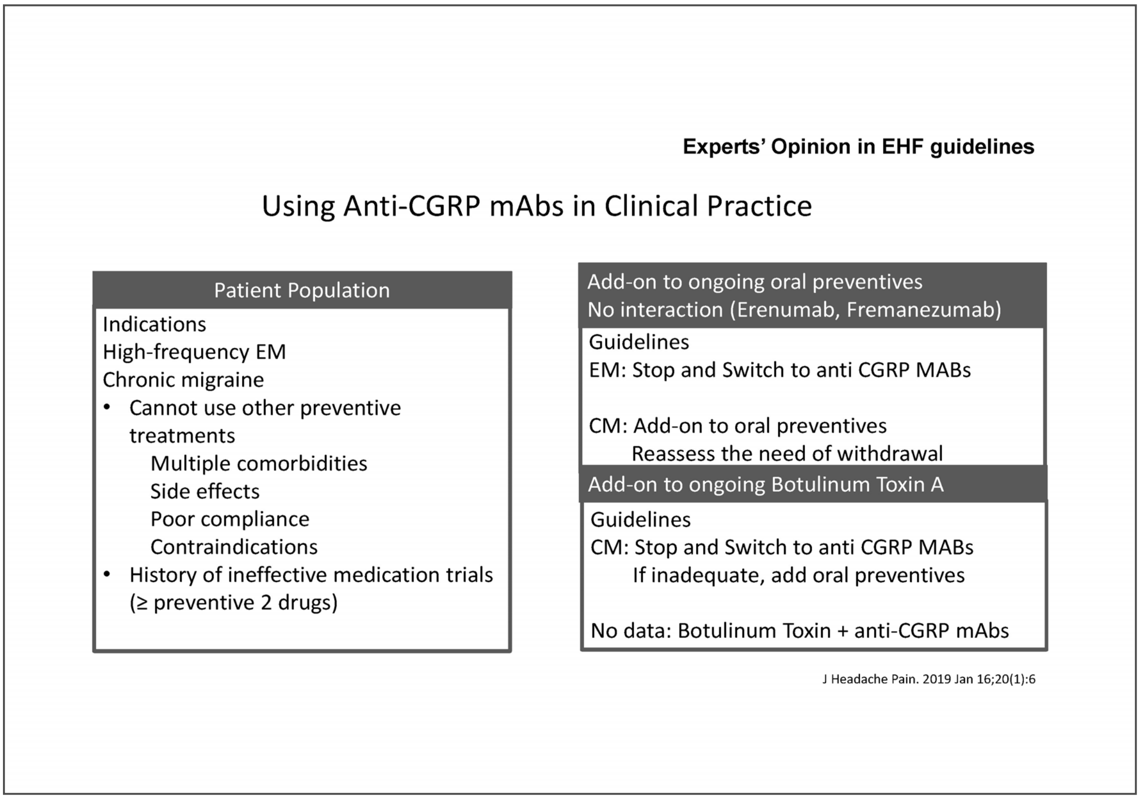
24 hour -1week

Demonstrated clinical benefit often within 1 month



a. Diener H-C, et al. *J Neurol.* 2004;251:943-950 ; b. Freitag FG, et al. *Neurology*. 2002;58:1652-1659; c. Brandes JL, et al. *JAMA.* 2004;291:965-973; d. Couch JR, et al. *Headache* 2011;51:33-51; e. Stauffer VL, et al. *JAMA Neurol.* 2018;75:1080-1088; f. Goadsby PJ, et al. *N Engl J Med.* 2017;377:2123-2132; g. Silberstein S, et al. AAN 2018. Abstract P4.091; h. Dodick DW, et al. *JAMA.* 2018;319:1999-2008.

Goadsby PJ, et al. J Neurol Neurosurg Psychiatry 2019;90:939–944



Experts' Opinion in EHF guidelines

Using Anti-CGRP mAbs in Clinical Practice

Patient Population

Indications
High-frequency EM
Chronic migraine

- Cannot use other preventive treatments
    - Multiple comorbidities
    - Side effects
    - Poor compliance
    - Contraindications
- History of ineffective medication trials (≥ preventive 2 drugs)

Add-on to ongoing oral preventives
No interaction (Erenumab, Fremanezumab)

Guidelines
EM: Stop and Switch to anti CGRP MABs

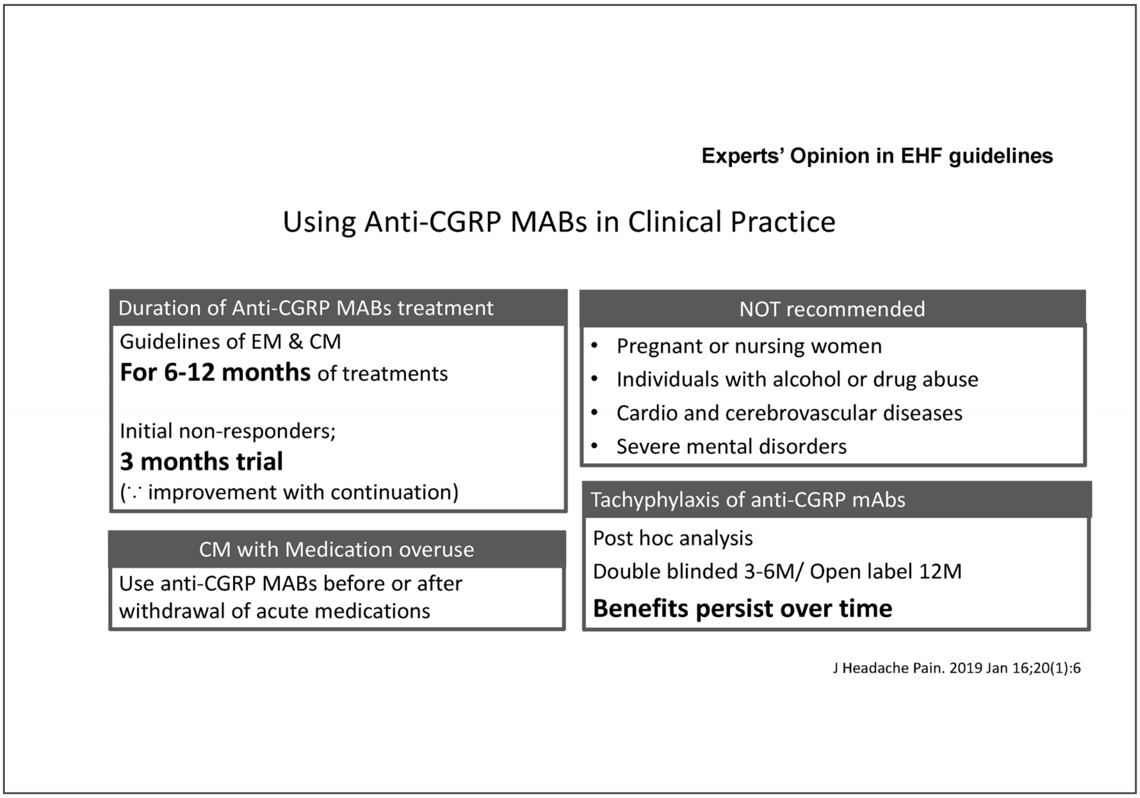
CM: Add-on to oral preventives
Reassess the need of withdrawal

Add-on to ongoing Botulinum Toxin A

Guidelines
CM: Stop and Switch to anti CGRP MABs
If inadequate, add oral preventives

No data: Botulinum Toxin + anti-CGRP mAbs

J Headache Pain. 2019 Jan 16;20(1):6



Experts' Opinion in EHF guidelines

Using Anti-CGRP MABs in Clinical Practice

Duration of Anti-CGRP MABs treatment

Guidelines of EM & CM
For 6-12 months of treatments

Initial non-responders;
3 months trial
(∵ improvement with continuation)

CM with Medication overuse

Use anti-CGRP MABs before or after withdrawal of acute medications

NOT recommended

- Pregnant or nursing women
- Individuals with alcohol or drug abuse
- Cardio and cerebrovascular diseases
- Severe mental disorders

Tachyphylaxis of anti-CGRP mAbs

Post hoc analysis
Double blinded 3-6M/ Open label 12M
Benefits persist over time

J Headache Pain. 2019 Jan 16;20(1):6

Experts' Opinion in AHS guidelines

Using Anti-CGRP MABs in Clinical Practice

The striking benefits of anti-CGRP mAb

- High safety profile
- High target specificity
- No drug interaction
- Monthly dosing schedule
- Drug adherence
- Lack of titration
- The quick onset of action
- Ease to use

Add-on to ongoing other preventives
No / Minimal interaction

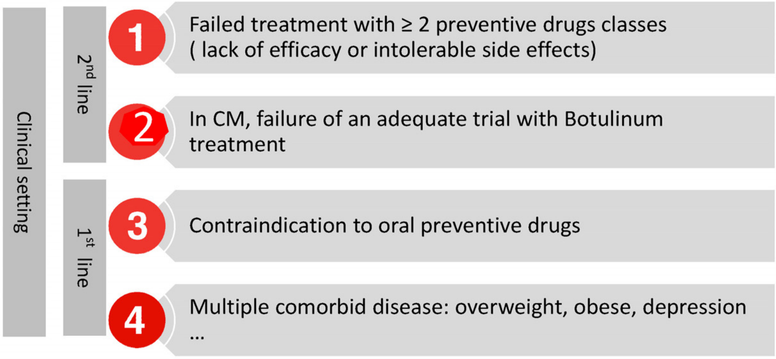
EM and CM

- Add-on to the existing regimen
- Make no other changes until the effectiveness of the mAb is determined.
- Reassess the need of withdrawal

American Headache Society. *Headache* 2019;59:1-18

Patient eligible for CGRP mAb (UK National Institute for health and care excellence, NICE)

- ≥ 4 MMD(monthly migraine days), ≥ 10 MMDs (High frequency EM)
- CM (≥ 15 Headache days & ≥ 8 MMDs)
- 18-70 YO

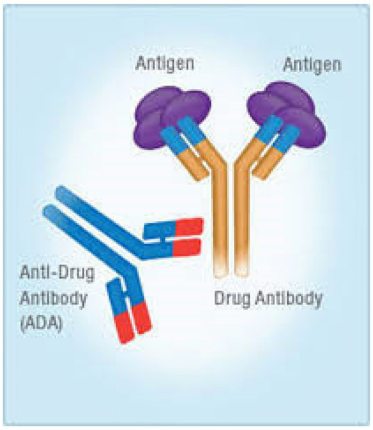


1. Failed treatment with ≥ 2 preventive drugs classes (lack of efficacy or intolerable side effects)
2. In CM, failure of an adequate trial with Botulinum treatment
3. Contraindication to oral preventive drugs
4. Multiple comorbid disease: overweight, obese, depression …

Unanswered questions

- ? Is it better to target the CGRP ligand or the receptor?
- ? Will antidrug antibodies have a neutralizing efficacy over time?
- ? What is the long-term impact of CGRP antagonism?

Anti-drug Antibody of anti CGRP mAbs



ADA in Galcanezumab

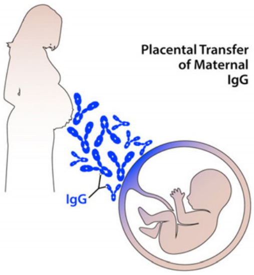
- Neutralizing antibodies
- For 6 months: 4.8% (33/688) in patients in the treated group
- For 12 months: 12.5% (16/128) in the treated group

The presence of anti-drug antibodies did not affect the pharmacokinetics, efficacy, or safety of galcanezumab

? Still uncertain if CGRP mAbs sustain their efficacy after many more years

1. European Medicines Agency. Emgality, INN: galcanezumab - Summary of Product Characteristics (SmPC). 2019.
2. Martinez JM, et al. Immunogenicity findings from phase 3 galcanezumab trials in patients with episodic or chronic migraine. Poster presented at: 12th European Headache Federation (EHF) Congress; Sep 28-30, 2018; Florence, Italy.

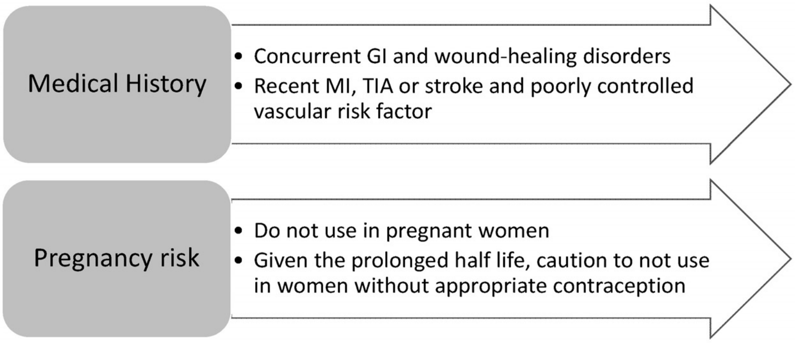
Anti CGRP mAbs and Pregnancy


Placental Transfer of Maternal IgG
IgG

- IgG can be actively transported through placenta and breast alveoli
- In animal studies, a CGRP antagonist increases fetal mortality in a dose-dependent fashion

- Potential risk of fetal or infant exposure to CGRP mAbs is unknown.
- **An extended washout time prior to conception** and after breastfeeding may be recommended

Which patients should proceed with caution?



Medical History

- Concurrent GI and wound-healing disorders
- Recent MI, TIA or stroke and poorly controlled vascular risk factor

Pregnancy risk

- Do not use in pregnant women
- Given the prolonged half life, caution to not use in women without appropriate contraception

Summary : Galcanezumab

1. **Speed!**
   They work in **<1 week**, and have clinically significant benefit in 1 month
2. **Effectiveness!**
   They work in episodic and chronic migraine and treatment resistant patients, cluster headache.
3. **Tolerability!**
   Side effects similar to placebo
4. **Safety!**
   No signal of any problem requiring monitoring of any sort
5. **Convenience, Wide Indication (MHD ≥ 4/M)**
6. **No drug interaction (combination Tx)**
7. **Remaining questions**
   Long-term safety / Cost and access

Galcanezumab
EMGALITY
Sep 2018/ **국내승인**
CGRP peptide
Lilly
Loading 240mg then 120mg SC monthly
Humanized
EM (EVELOVE1,2) CM (REGAIN) Tx resistant migraine Episodic cluster Chronic cluster (no effect)

THANKS FOR LISTENING! Q?