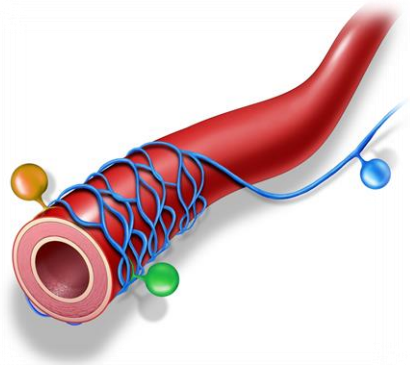
What we know about CGRP in headache?



Sait Ashina, MD, FAHS

Director of BIDMC Comprehensive Headache Center

Assistant Professor of Neurology and Anesthesia

Department of Neurology and Anesthesia, Critical Care and Pain Medicine

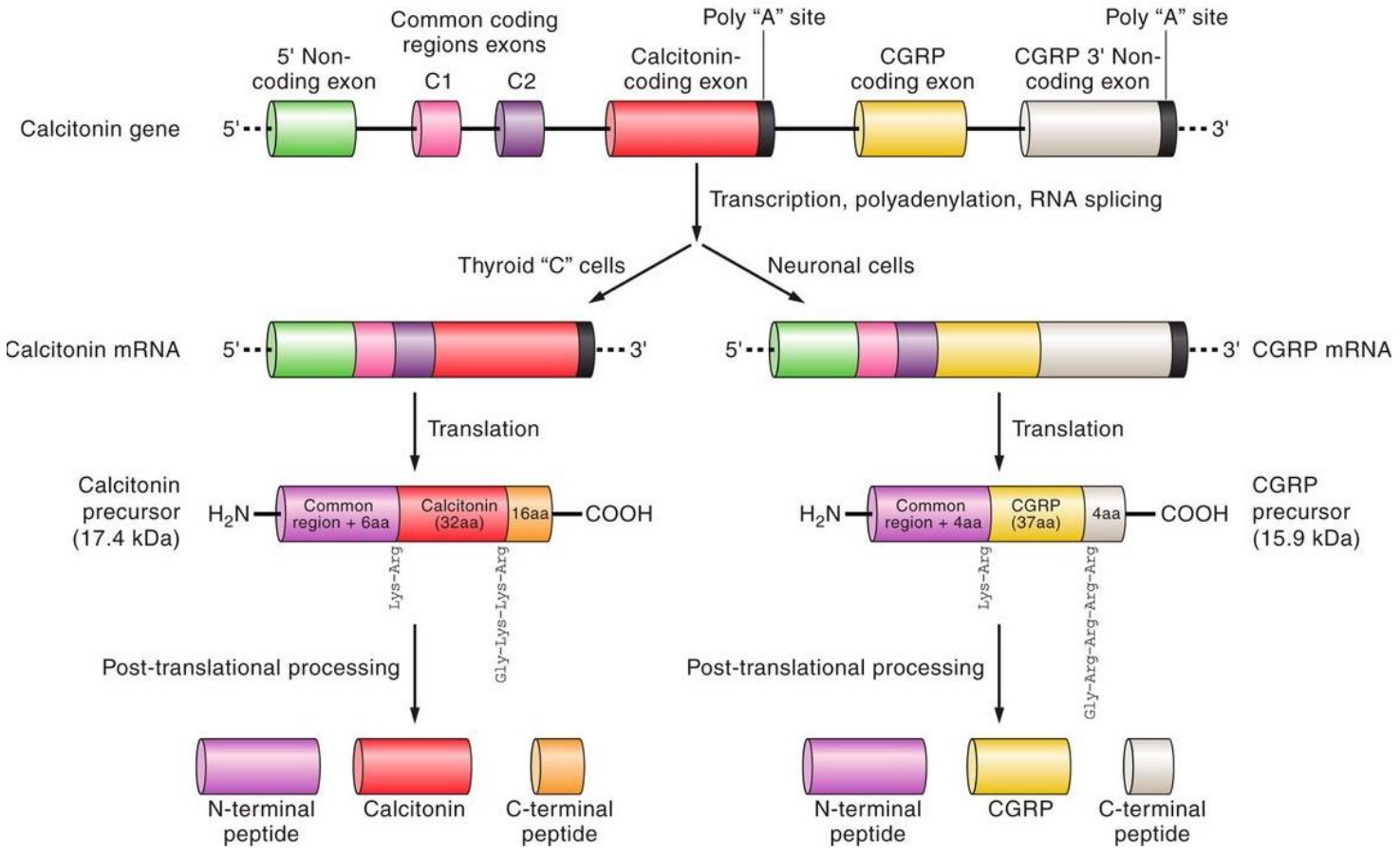
Harvard Medical School, Boston, MA, USA

Disclosures

- Consultant for Allergan, Amgen, Eli Lilly, Novartis, Promius , Satsuma, Supernus, Theranica

Calcitonin gene-related peptide (CGRP)

- discovered by Amara et al. *(Nature, 1982)*



From Russell FA et al. Physiol Rev 2014

Calcitonin gene-related peptide (CGRP)

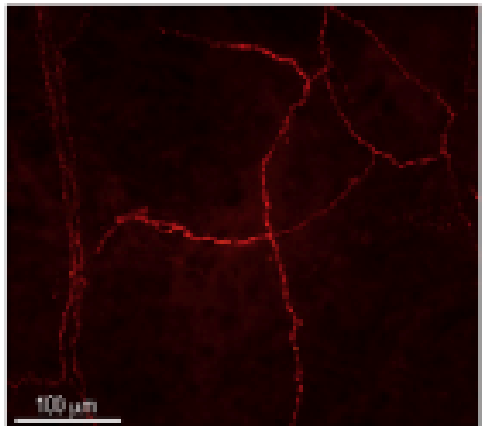
- Chromosome 11
- 37-amino-acid neuropeptide
- 2 isoforms
  - α-CGRP (central and peripheral nervous system)
  - β-CGRP (enteric nervous system)
- Coexists and interacts with neurotransmitters (SP, NKA, NPY, VIP etc.)
- In mammalian plasma, the half-life (T1/2) of CGRP is ~ 10 min

CGRP distribution in PNS and CNS

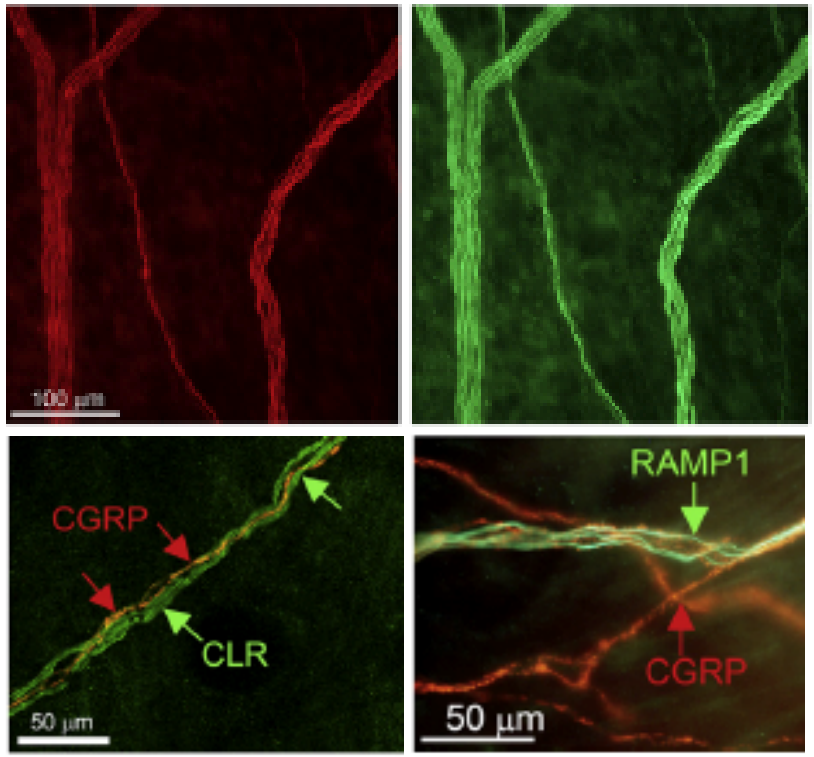
- Immunohistochemistry: mainly produced in cell bodies of both ventral and dorsal root neurons
- In C fibers and Aδ fibers
- Radioimmunology: especially common in trigeminal system (up to 50% of neurons produce CGRP)
- In perivascular fibers → major source of plasma CGRP
- In cortex, brain stem (locus coerulens, etc.), thalamus, cerebellum
- In glia cells

Presence of CGRP in C-fibers and CGRP receptors in Ad-fibers may explain the selective inhibition of Ad-fibers by the CGRP-mAb

C-fibers contain CGRP



Aδ-fibers contain CLR and RAMP1



~50% of trigeminal neurons contain CGRP
~35% of trigeminal neurons contain receptors
Little overlap between the ligand and receptor

C-fiber neurons:
Contain CGRP, unmyelinated, polymodal nociceptors that signal slow and dull pain

Aδ neurons:
Contain CGRP receptor, thinly myelinated, signal acute and sharp pain

Eftekhari et al. The Journal of Pain 2013

Trigeminal ganglion stimulation and CGRP

- In humans

	Flushers (n = 6)		Normal Subjects (n = 15)	
	Sub P	CGRP	Sub P	CGRP
Control	32 ± 6	30 ± 2	40 ± 4	21 ± 3
Stimulation	100 ± 5[b]	60 ± 11[c]	. . .	. . .
Poststimulation	62 ± 8	41 ± 9	. . .	. . .

[a]Values represent pmol/l of substance P or CGRP.

- In cats

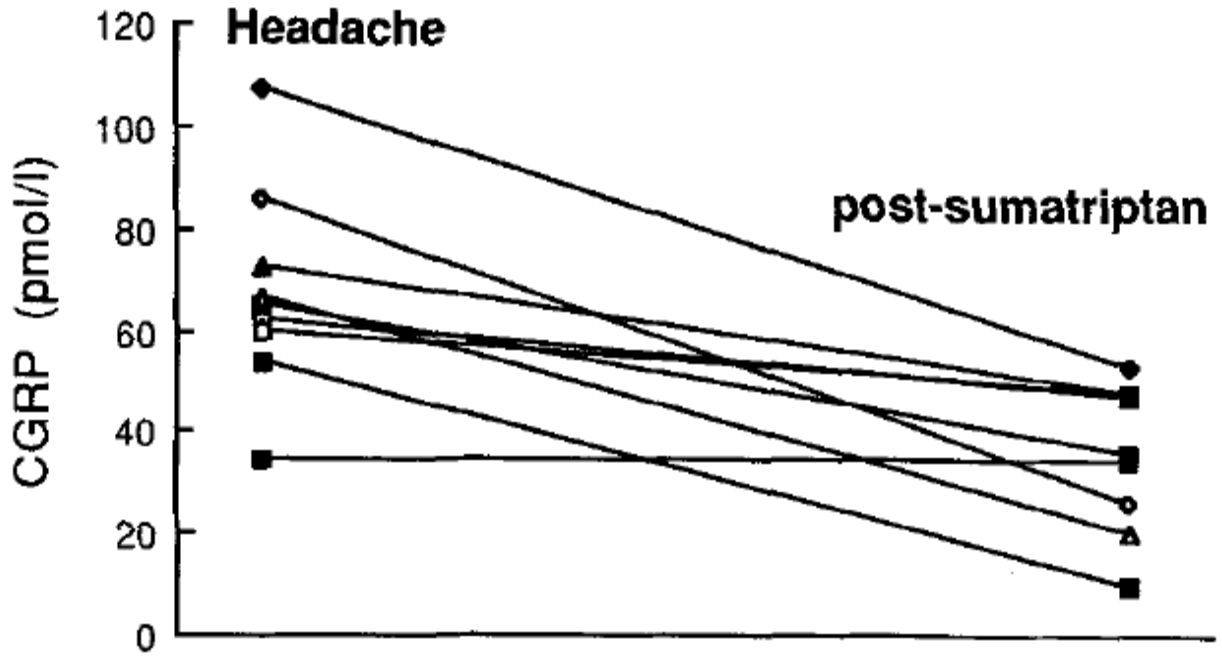
	Sub P (n = 5)	CGRP (n = 5)
Control	41 ± 5	68 ± 2
Stimulation	69 ± 5[b]	86 ± 3[c]

[a]Values represent pmol/l of substance P or CGRP.

Goadsby el al. Ann Neurol 1988

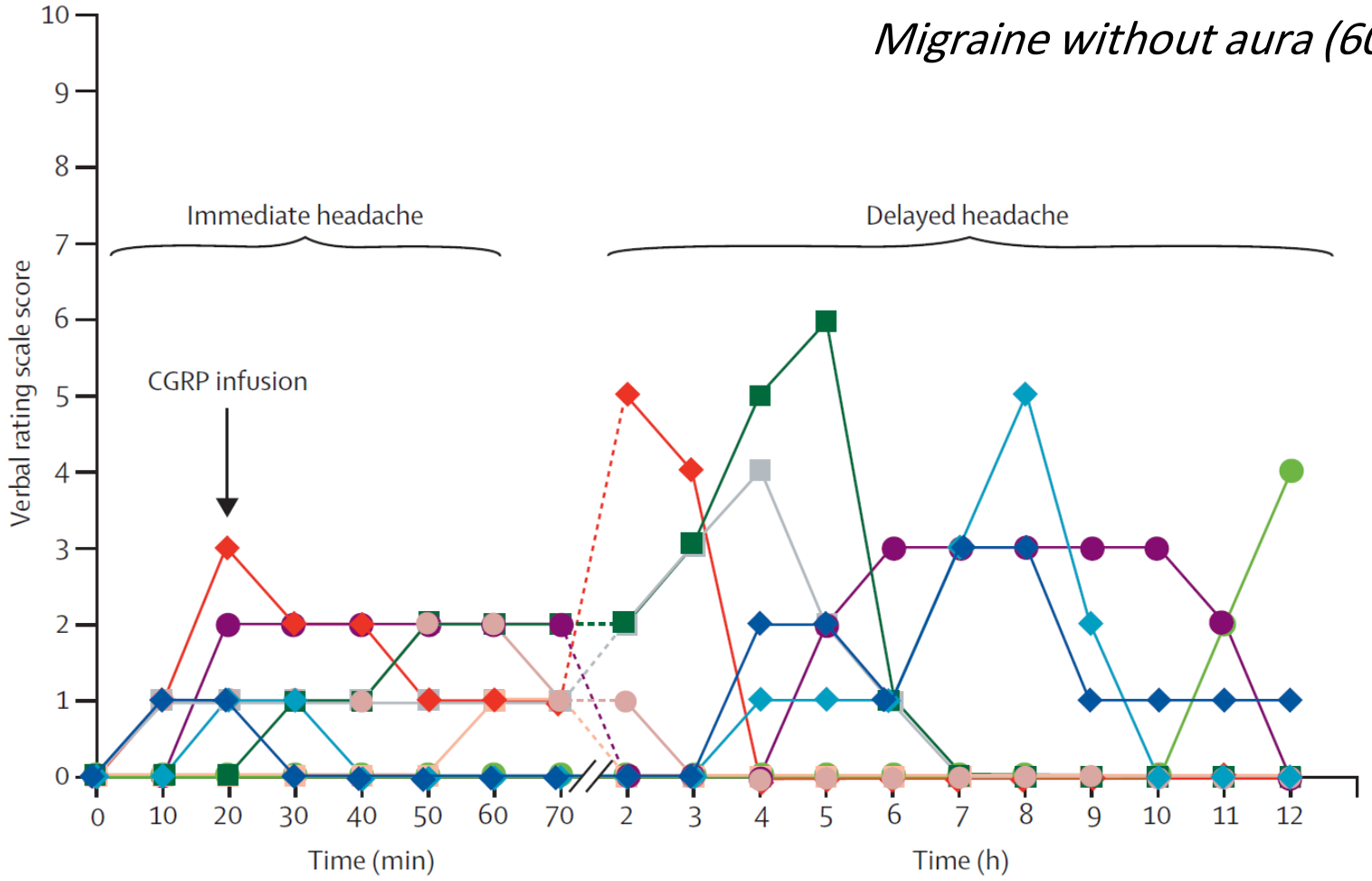
Plasma CGRP levels in migraine

- 60±8 pmol/L (reference < 40 pmol/L)
- After sumatriptan 3-6 mg SQ → 40±8 pmol/L



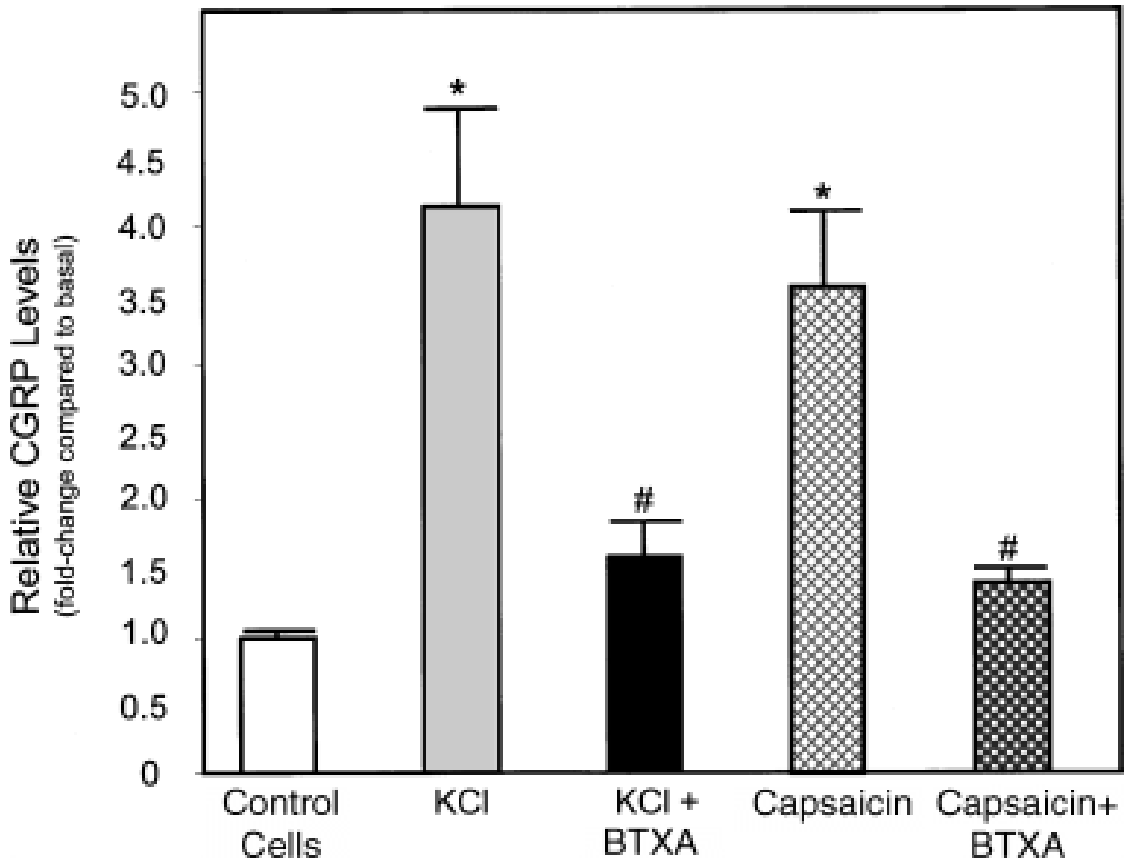
Goadsby and Edvinsson. Ann Neurol 1993

CGRP model of migraine: migraine *without* aura



Lassen et al. Cephalalgia 2002

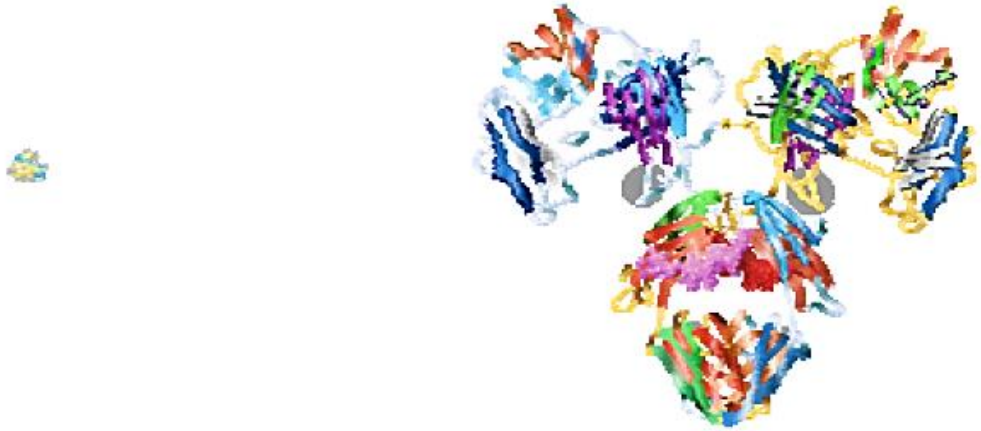
Regulation of CGRP secretion from trigeminal nerve cells by botulinum toxin type A: implications for migraine therapy



Durham et al. Headache 2006

CGRP-targeted therapy

Small molecule vs. monoclonal antibodies



Small molecule	Monoclonal antibodies
Target specificity lower	Target specificity high
Clearance (liver, kidney)	Clearance RES
Size < 1 kD	Size ~150 kD
Oral	Parenteral
Half-life minutes to hours	Half-life 1–4 weeks
Immunogenicity (no)	Immunogenicity (yes)

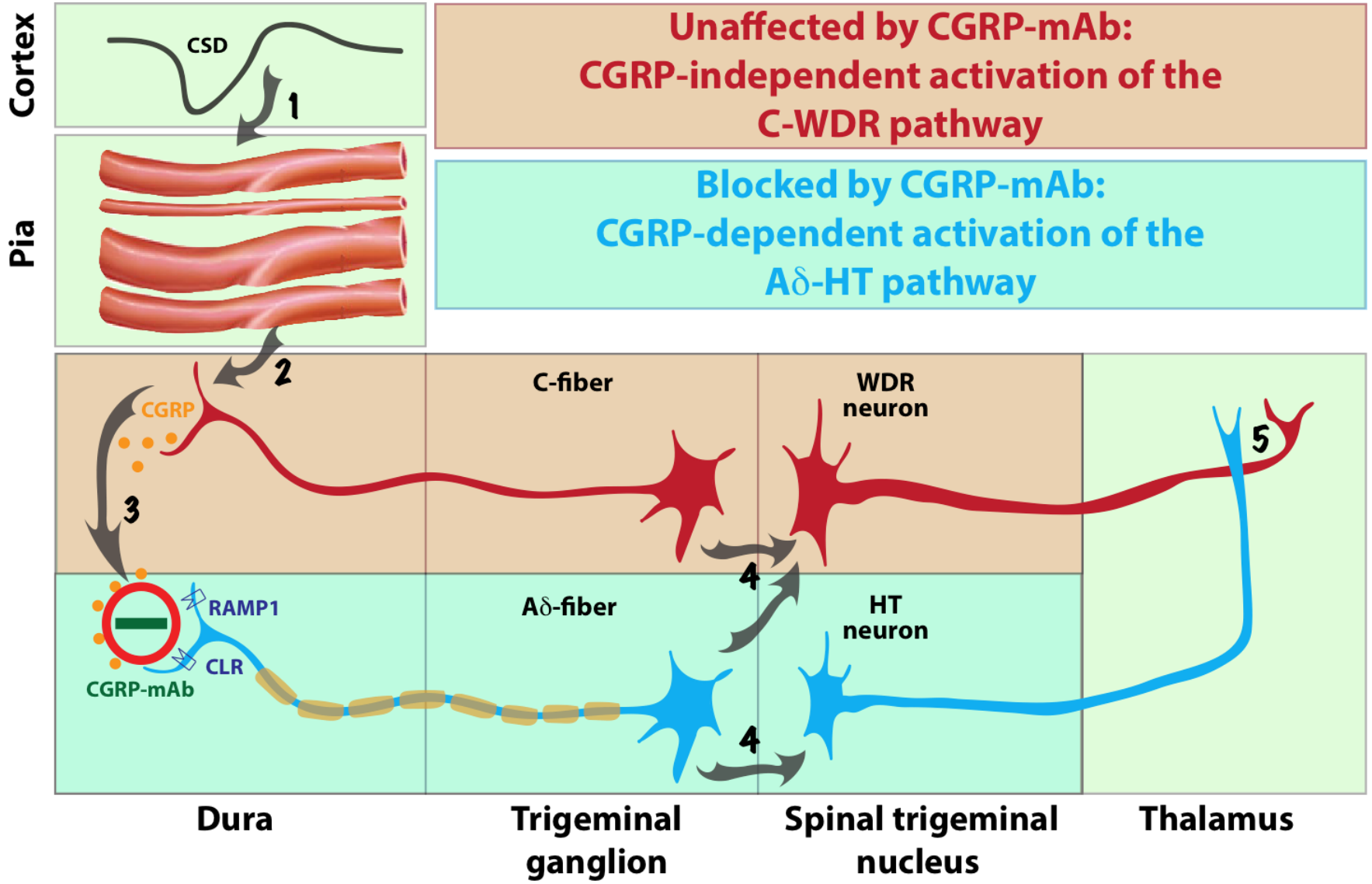
RES, reticuloendothelial system.

Monoclonal antibodies targeting CGRP pathway

	Erenumab	Fremanezumab	Galcanezumab	Eptinezumab
Compound	AMG 334	LBR-101	LY2951742	ALD403
Target	Receptor	Ligand	Ligand	Ligand
Type	Human (100% human)	Fully humanized (>95% human)	Humanized (>90% human)	Humanized (>90% human)
Route of administration	Subcutaneous	Subcutaneous	Subcutaneous	Intravenous
Dosing	Monthly	Monthly or quarterly	Monthly	Quarterly
Half life	21 days	32 days	~25–30 days	~32 days

Bigal and Walter, CNS Drugs 2014; Bigal ME et al. Br J Clin Pharmacol 2015; Harding FA et al. MAbs 2010

Proposed mechanisms for prevention of migraine aura by a CGRP-mAb



Melo-Carrillo A, et al. J. Neurosci. 2017

Phase 3 studies

EPISODIC MIGRAINE	Study name	Primary Endpoint	Study duration
Erenumab	ARISE	Monthly Migraine Days	Weeks 9–12
	STRIVE	Monthly Migraine Days	Months 4–6
Fremanezumab	HALO	Monthly Migraine Days	Months 1–3
Galcanezumab	EVOLVE-1	Monthly Migraine Days	Months 1–6
	EVOLVE-2	Monthly Migraine Days	Months 1–6
Eptinezumab	PROMISE-1	Monthly Migraine Days	Months 1–6

CHRONIC MIGRAINE	Study name	Primary Endpoint	Study duration
Fremanezumab	HALO	Headache Days	Months 1–3
Galcanezumab	REGAIN	Monthly Migraine Days	Months 1–3
Eptinezumab	PROMISE-2	Monthly Migraine Days	Months 1–3

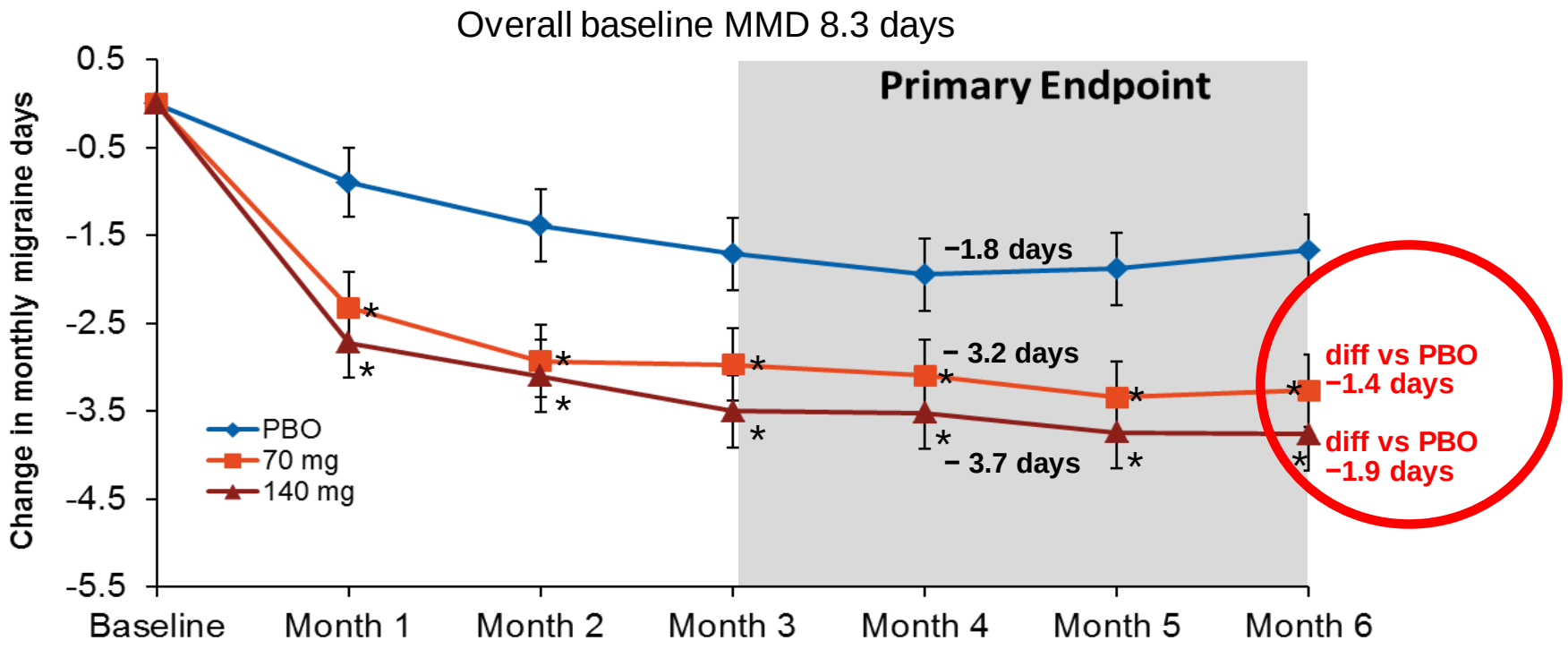
Primary endpoint:

total reduction in migraine/headache days per month:

- up to 2 days (difference vs. placebo)

in episodic and chronic migraine

STRIVE: Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel group study of **erenumab** for **episodic migraine**



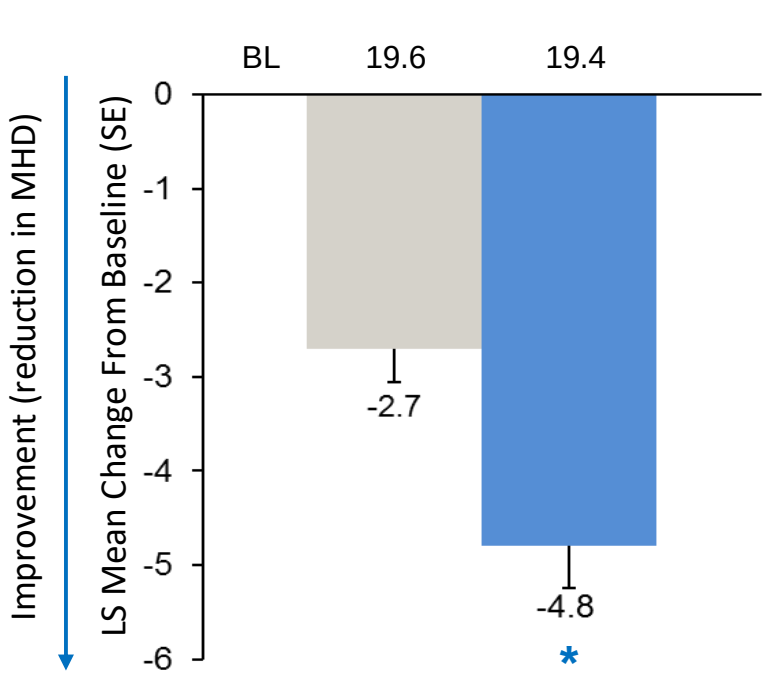
Data presented are least squares mean and 95% CI; *p<0.001 for each group vs placebo, not adjusted for multiplicity; Endpoint averaged over months 4, 5, and 6

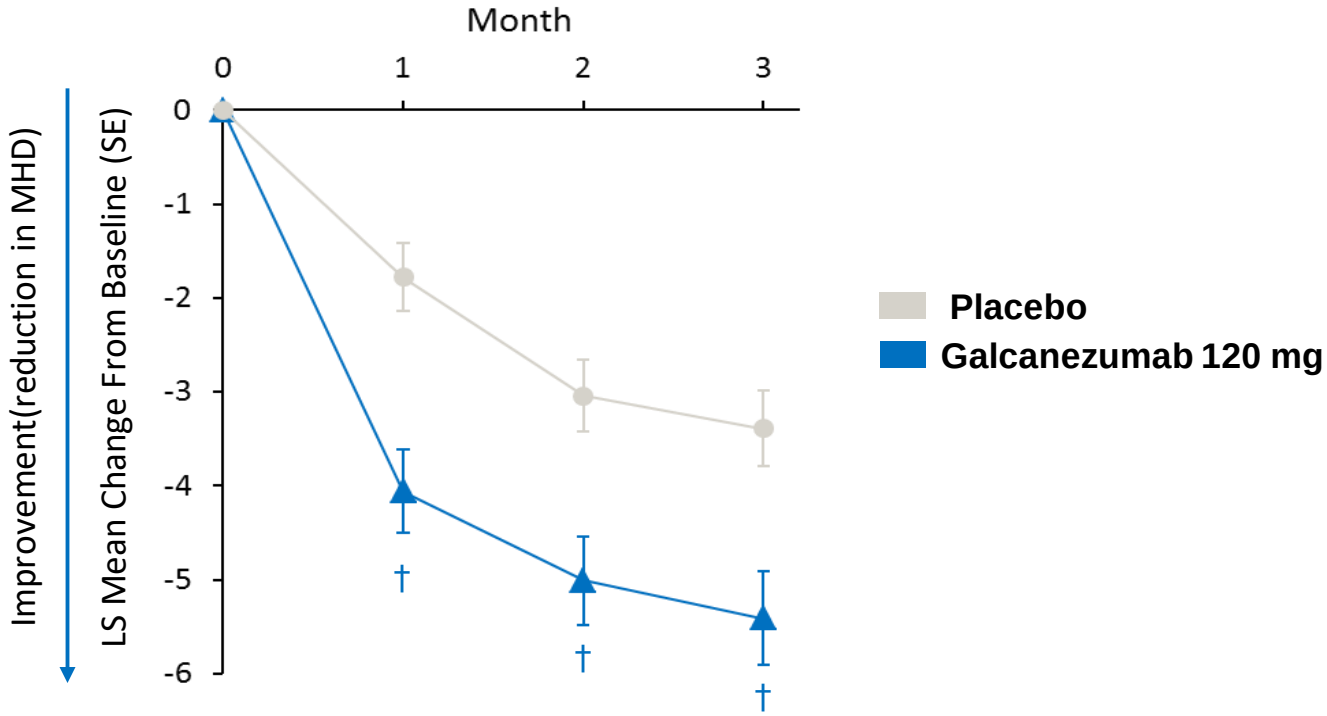
- Statistically significant reductions in monthly migraine days for both doses vs. placebo
- Mean number of migraine days per month at baseline: 8.3 days

MMD, monthly migraine days; PBO, placebo

Goadsby et al. N Engl J Med. 2017

REGAIN : Phase 3, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of **galcanezumab** for **chronic migraine**





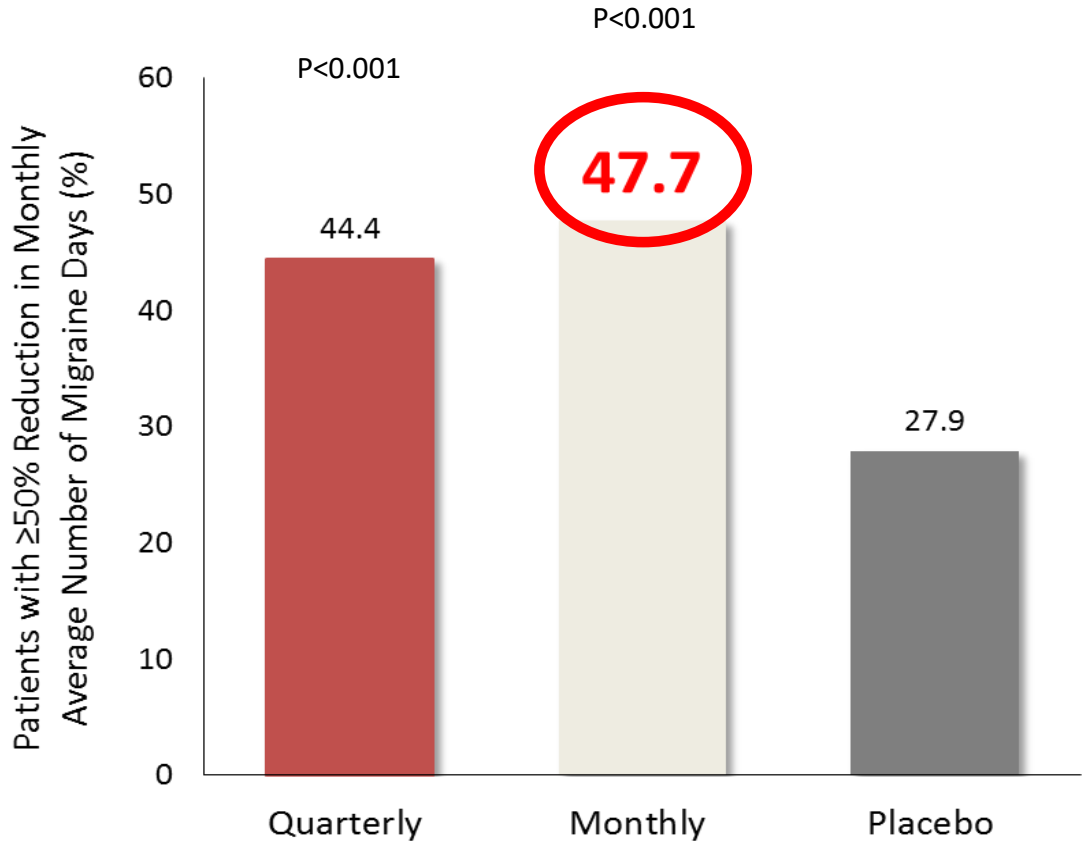
*p<.001 (vs. placebo) statistically significant after multiplicity adjustment (MMRM); †p<.001 (vs. placebo) at each month.
ITT: Intent-to-Treat; LS: Least Squares; MHD: Migraine headache day; MMRM: Mixed-Effect Model Repeated Measure;; SE: Standard error.

Detke HC et al. Neurology 2018

Secondary endpoints:
≥50% reduction from baseline in monthly migraine/headache days

Difference between active treatment and placebo was **20%** in Phase 3 trials

HALO: Effect of **Fremanezumab** Compared With Placebo for Prevention of **Episodic Migraine** — A Randomized Clinical Trial



Patients were randomized 1:1:1 to subcutaneous *monthly* dosing of fremanezumab (n = 290; 225 mg at baseline, week 4, and week 8); a single higher dose of fremanezumab, for *quarterly* dosing (n = 291; 675 mg of fremanezumab at baseline; placebo at weeks 4 and 8); or placebo (n = 294; at baseline, week 4, and week 8)

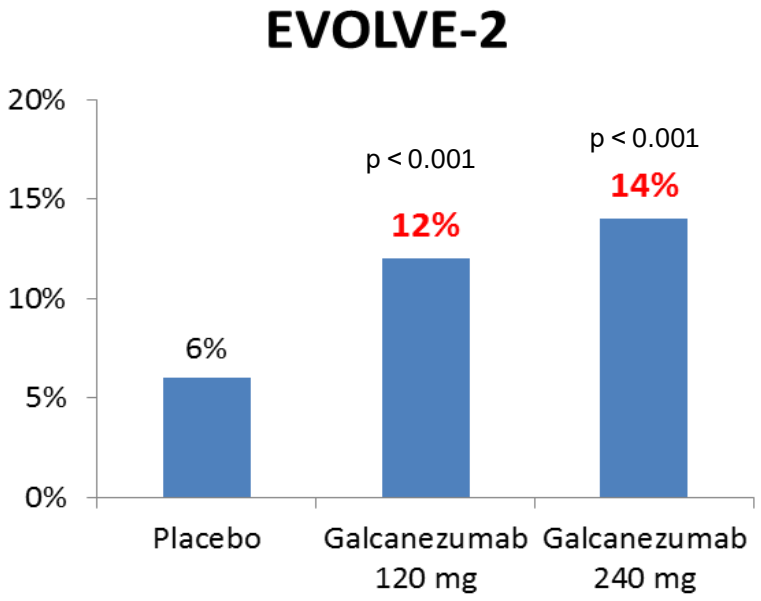
Mean migraine days per month at baseline: 8.9 days in fremanezumab *monthly* dosing group, 9.2 days in the fremanezumab *quarterly* dosing group, and 9.1 days in the placebo group

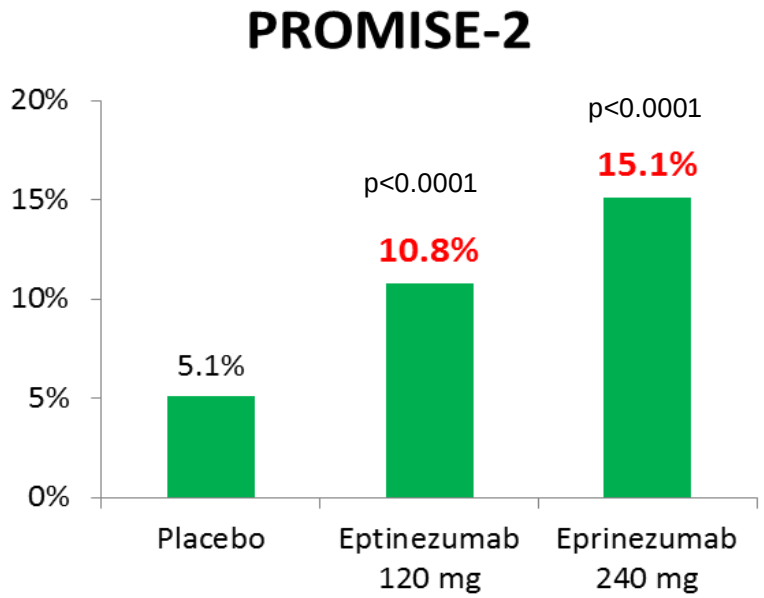
Dodick et al. JAMA 2018

Secondary endpoint:

100% reduction from baseline in monthly migraine/headache days

- Up to **15%** of patients experienced 100% reduction (complete elimination) in monthly migraine/headache days while on the active treatment
- Surprisingly, up to **6%** of the patients experienced 100% reduction (complete elimination) in monthly migraine/headache days while treated with placebo



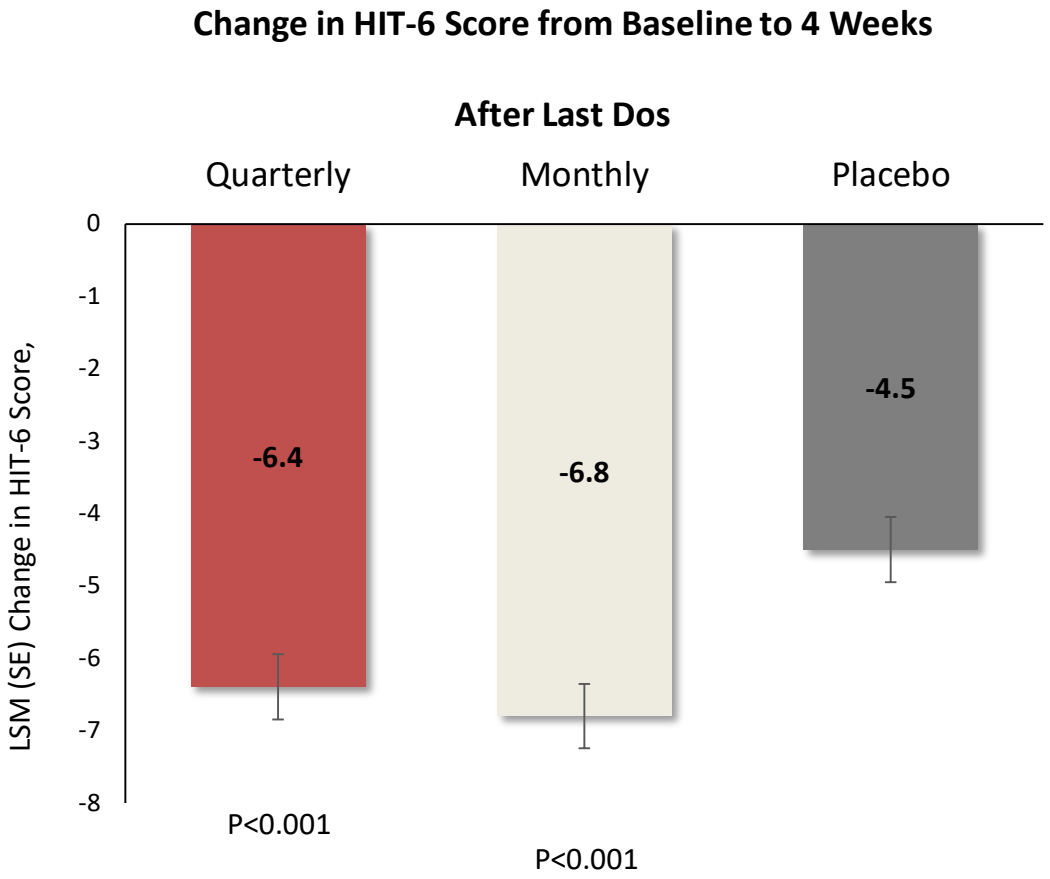


Skljarevski et al. Cephalalgia 2018 Jul; 38, 1442-1454

American Headache Society 2018 Annual Scientific Meeting

Secondary endpoints:
Improvement in
Patient-Reported Outcomes (PROs)

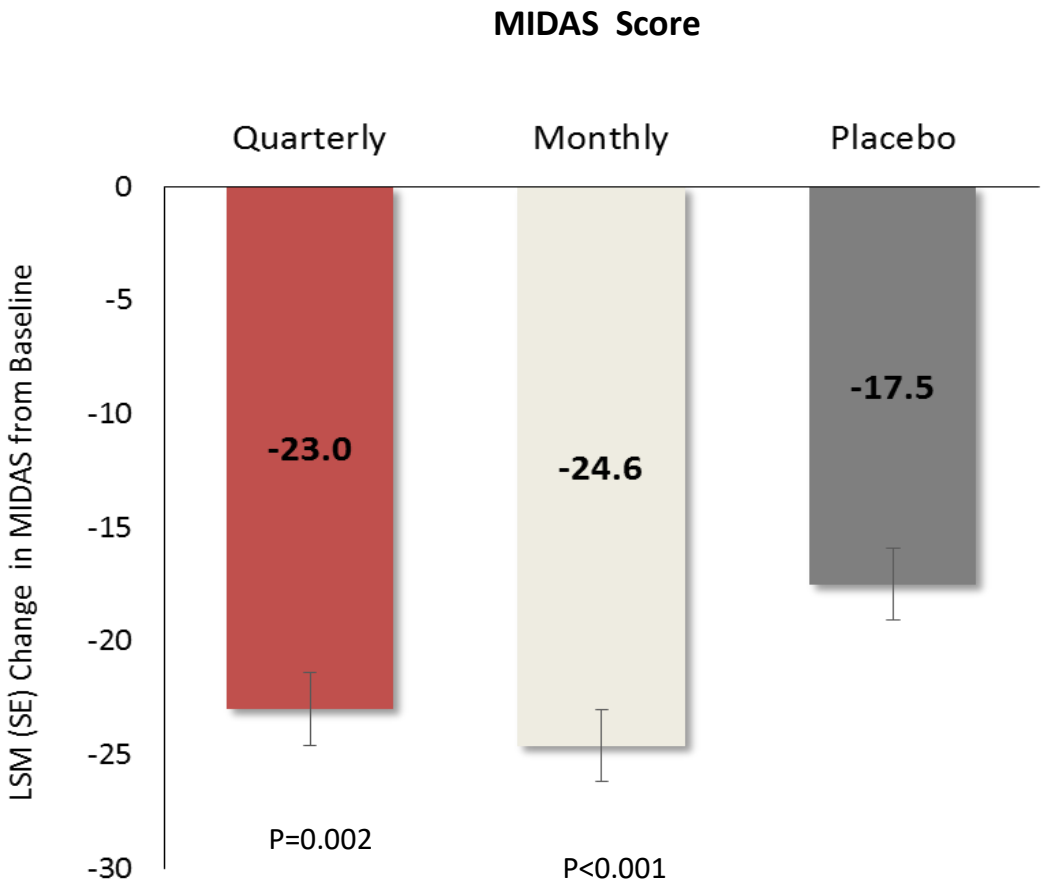
HALO: Chronic Migraine Trial



LSM, least-squares mean; HIT-6, Headache Impact Test; SE, standard error

6-item Headache Impact Test (HIT-6) questionnaire assesses headache-related disability over the preceding4 weeks, with scores ranging from 36 to 78 and with higher scores reflecting greater disability.

HALO: Episodic Migraine Trial



LSM, least-squares mean; MIDAS, Migraine Disability Assessment; SE, standard error

For the Migraine Disability Assessment (MIDAS), the score ranges from 0 to 270, with 0 to 5 indicating little or no disability; 6 to 10, mild disability; 11 to 20, moderate disability; and 21 or higher, severe disability.

Dodick et al. JAMA 2018; Silberstein SD et al. N Engl J Med 2017

Small-molecule CGRP receptor antagonists

First-generation CGRP small molecules

Telcagepant showed promise and efficacy but research stopped due to liver toxicity : 11 patients in a P2a exploratory chronic dosing, prophylaxis study (BID for 3 months) showed liver enzyme elevations more than 3 x the upper limit of normal

New generation of oral formulations

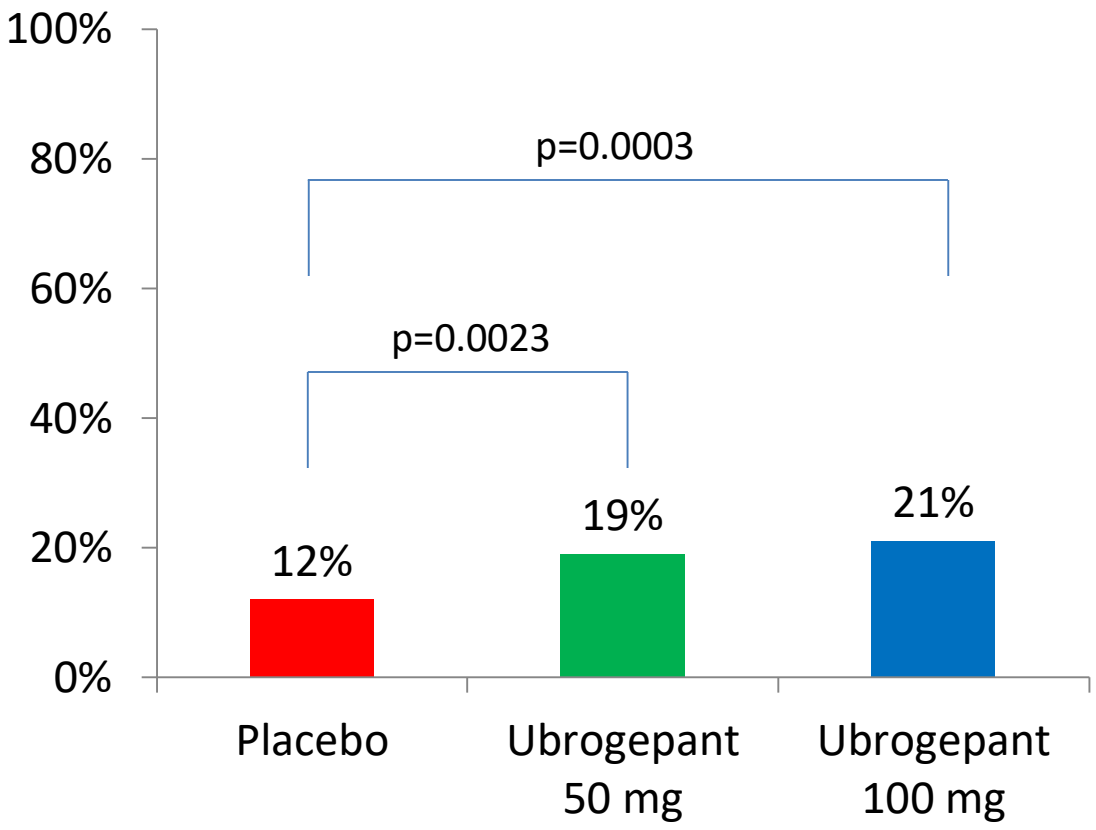
Ubrogepant-MK-1602, an oral small molecule CGRP receptor antagonist for the acute treatment of migraine. Phase II study supported ubrogepant's efficacy for acute treatment of migraine *(Voss et al., Cephalalgia. 2016)*

Atogepant-MK-8031, an oral small-molecule CGRP receptor antagonist for the prevention of episodic migraine. Phase 2b/3 Clinical Trial results announced by Allergan on June 11, 2018

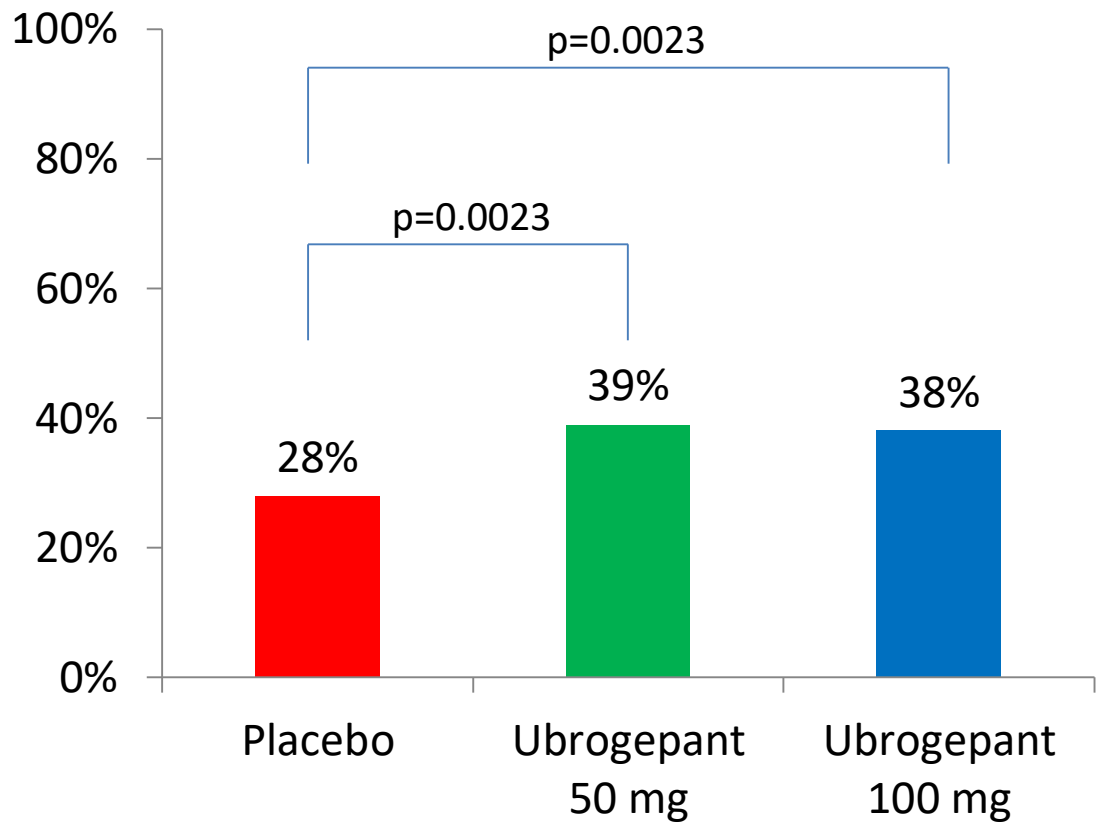
Rimegepant-BMS-927711, an oral small-molecule CGRP receptor antagonist for the acute treatment of migraine. Phase II study: Rimegepant is superior to placebo at several different doses (75 mg, 150 mg, and 300 mg) *(Marcus et al. Cephalalgia 2014).* Phase 3 trial results were last presented at AHS 2018 scientific meeting.

Ubrogepant for the Acute Treatment of Migraine: Efficacy, Safety, Tolerability, and Functional Impact Outcomes from a Single Attack Phase III Study, ACHIEVE I

Pain freedom at 2 hrs



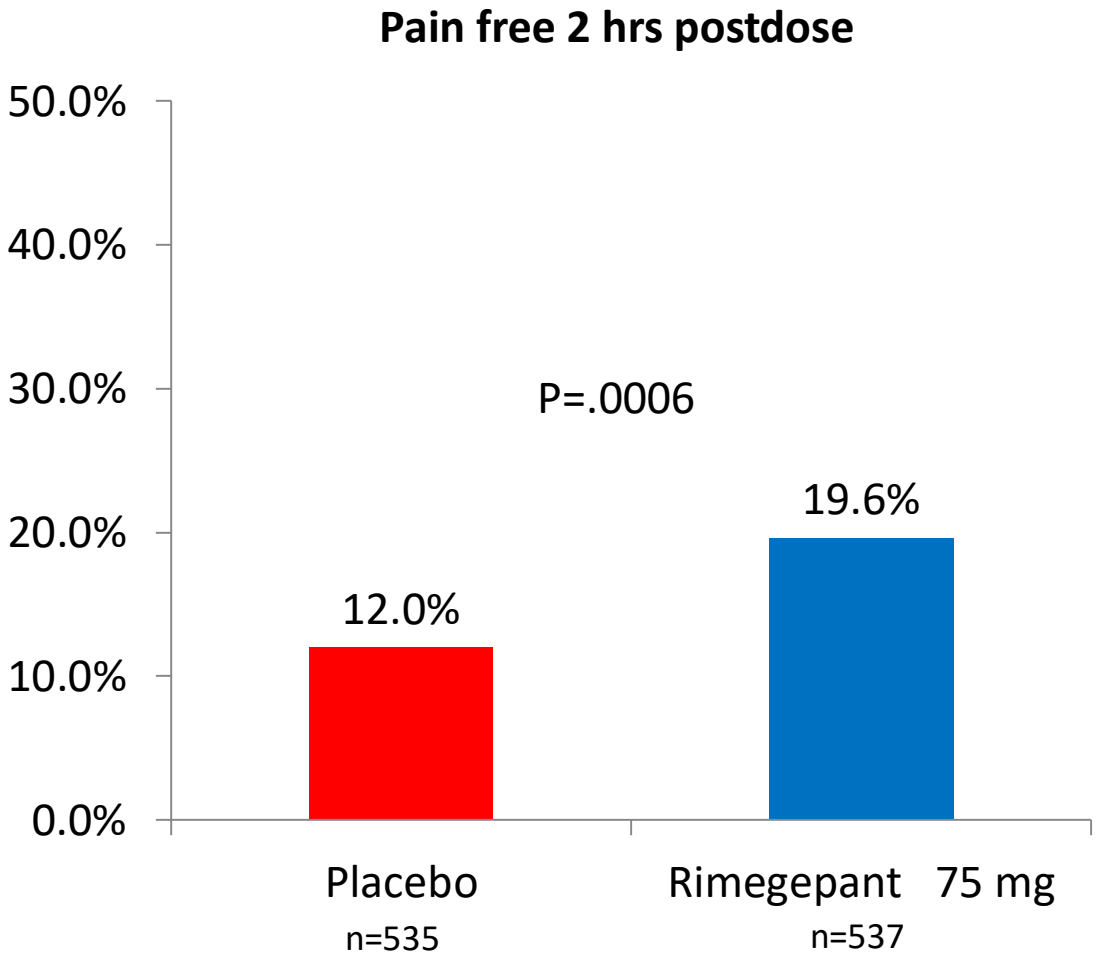
Absence of MBS

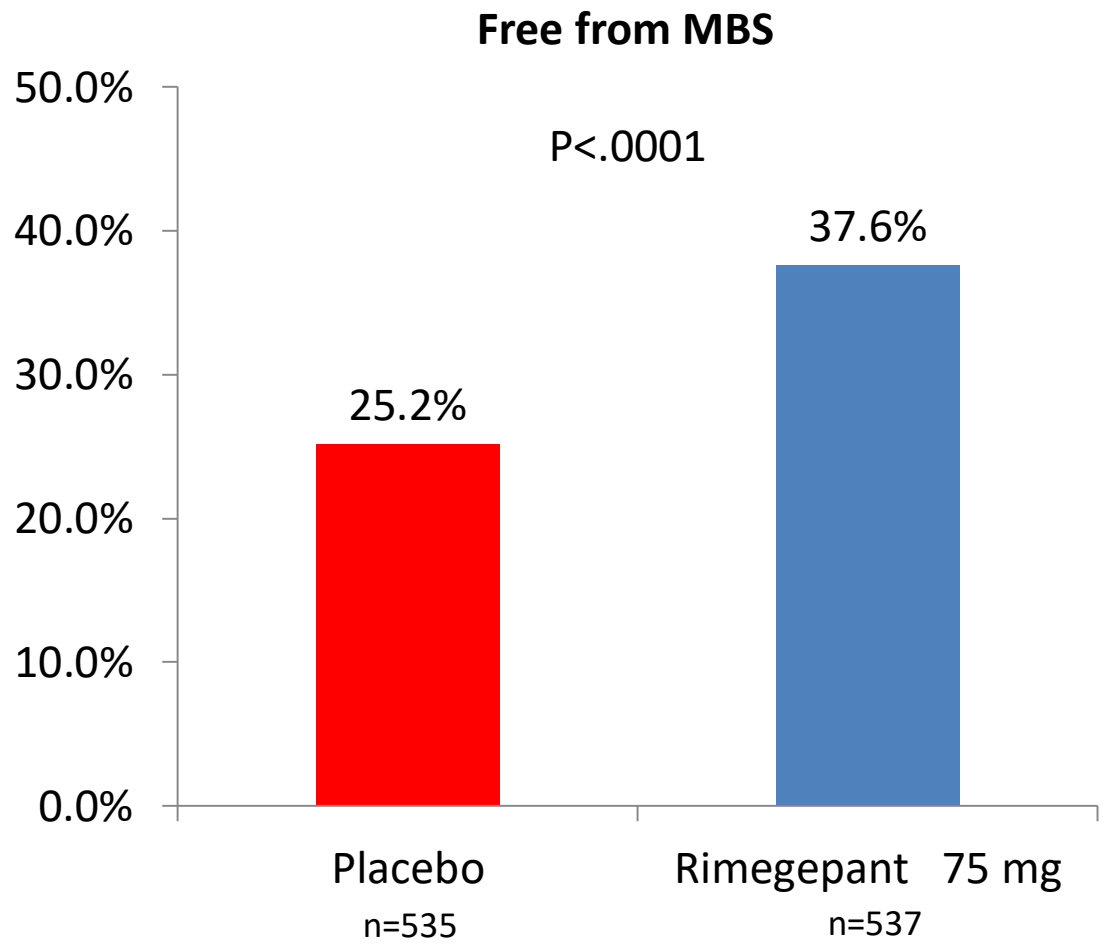


- Efficacy continued to increase beyond 2 hrs
- Pain relief at 2 hrs was significantly higher in ubrogepant-treated patients (61% both doses) vs. placebo

Allergan data; Presented at AAN Annual Meeting and American Headache Society 60th Annual Scientific Meeting, 2018

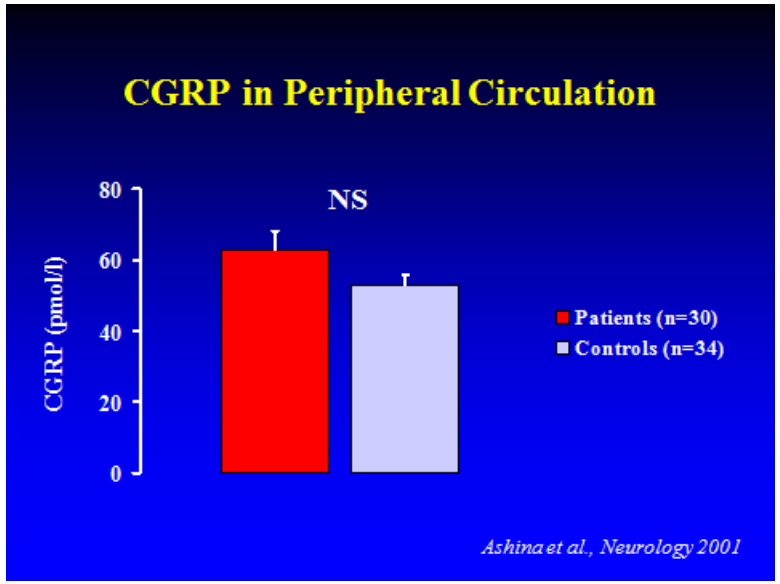
Efficacy, Safety, and Tolerability of **Rimegepant 75 mg**, an Oral CGRP Receptor Antagonist, for the Acute Treatment of Migraine: Results from a Double-Blind, Randomized, Placebo-Controlled Trial (Study 302, NCT03237845)

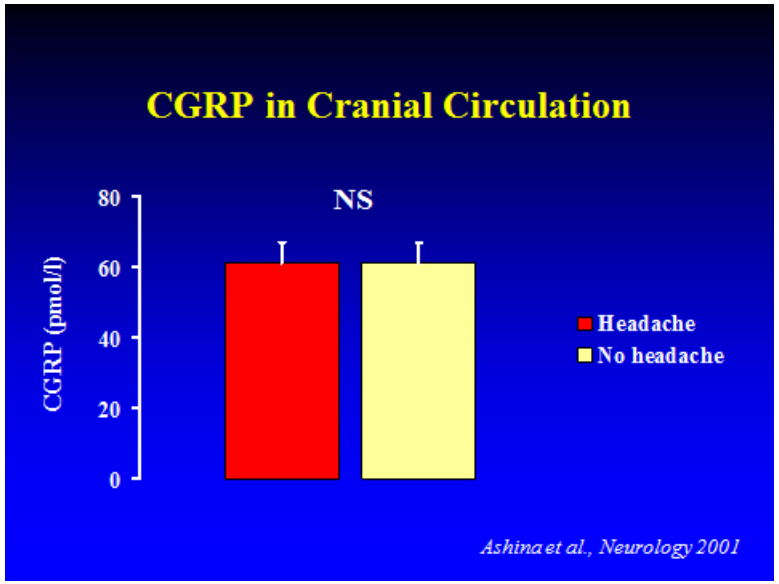




Subjects: mean age of 40.6±12.0 years, 88.7% were female, and had 4.6±1.8 headache attacks per month ; MBS: most bothersome symptom

CGRP and chronic tension-type headache

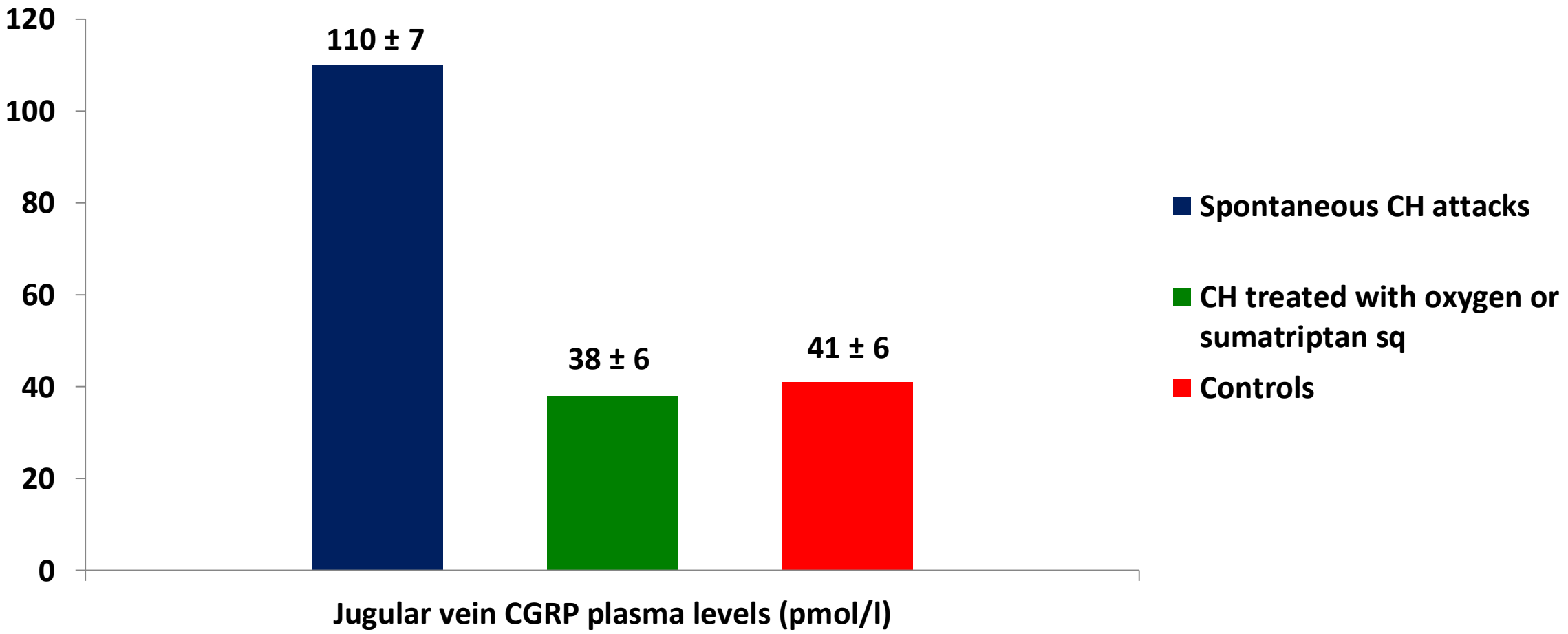




- CGRP levels are normal in chronic tension-type headache
- CGRP levels are unrelated to headache state
- No difference between cranial and peripheral circulation
- Nitric oxide induced immediate headache is not associated with release of CGRP

Ashina et al., Neurology 2001; Ashina et al. Eur J Neurol 2001

Cluster headache (CH) and CGRP



13 patients (10 male and 3 female)

Goadsby and Edvinsson , Brain.1994

Galcanezumab 300 mg in Prevention of Episodic Cluster Headache

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

* Plus–minus values are means ±SE.
† Response was defined as a reduction of at least 50% in the weekly frequency of cluster headache attacks. Patients with missing data at week 3 were considered not to have had a response.

Of 106 enrolled patients, 49 were randomly assigned to receive galcanezumab and 57 to receive placebo. The mean (±SD) number of cluster headache attacks per week in the baseline period was 17.8±10.1 in the galcanezumab group and 17.3±10.1 in the placebo group.

The NEW ENGLAND JOURNAL of MEDICINE

PJ Goadsby et al. N Engl J Med 2019;381:132-141.

Summary

- CGRP is a well-studied, ubiquitous neuropeptide
- CGRP is found both centrally and peripherally in nervous system
- Calcitonin gene-related peptide (CGRP) is relevant to migraine and cluster headache pathophysiology
- CGRP receptor antagonists have demonstrated proof of efficacy for acute treatment of migraine

Summary

- CGRP monoclonal antibodies demonstrated efficacy and tolerability across both episodic and chronic migraine (and galcanezumab for episodic cluster headache)

- CGRP monoclonal antibodies reduced the acute headache medication use days

- CGRP monoclonal antibodies have demonstrated improvement in Patient-Reported Outcomes (PROs) including migraine-related disability, quality of life and impact of headache on everyday life versus placebo