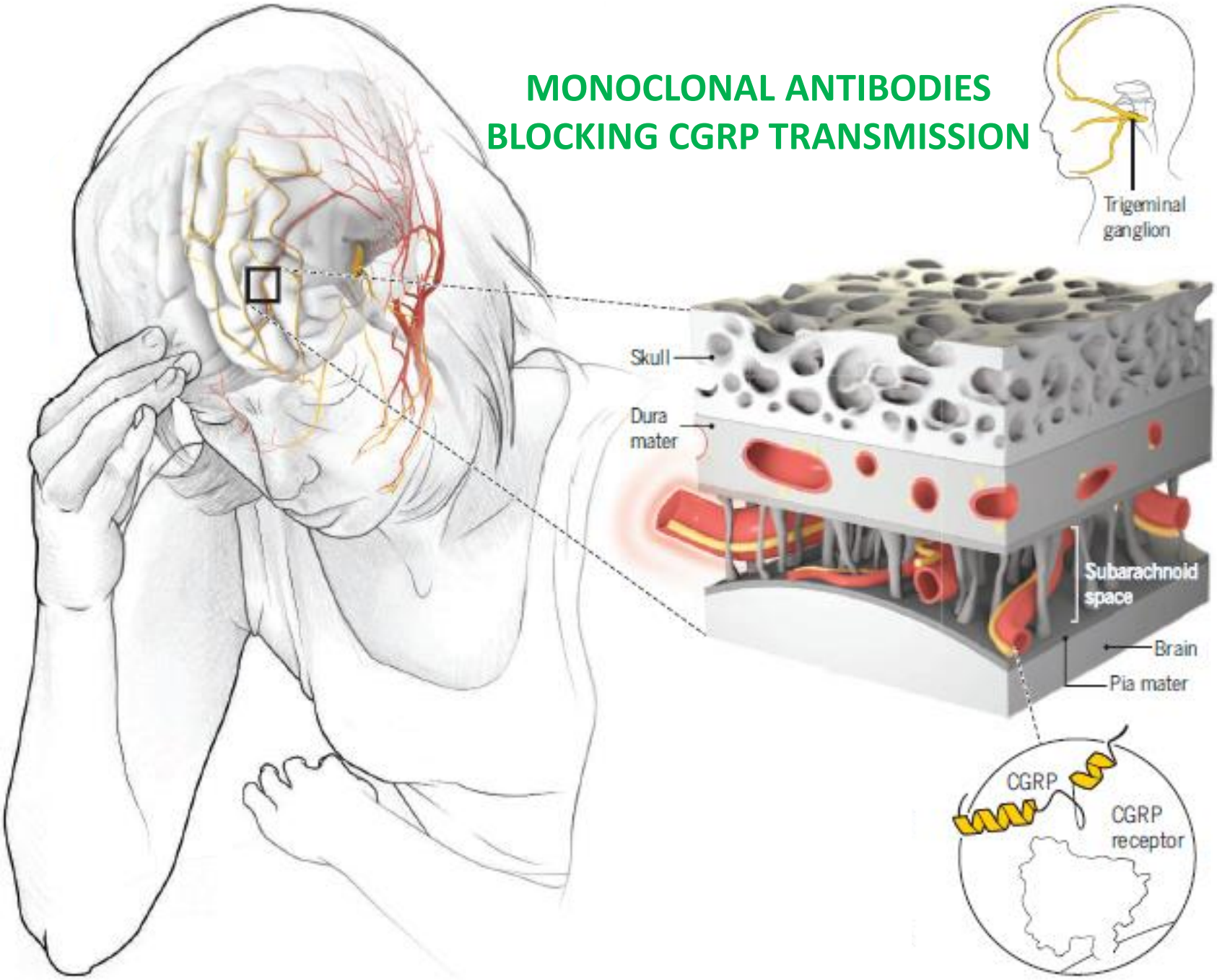
MIGRAINE, A NEW ERA

Prof Jan Versijpt, MD PhD
Neurologie@UZ Brussel
Board member of the EHF

MONOCLONAL ANTIBODIES BLOCKING CGRP TRANSMISSION



Lancet Neurol 2014; 13: 885–92

Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: a phase 2, randomised, double-blind, placebo-controlled study

David W Dodick, Peter J Goadsby, Egilius L H Spierings, Joel C Scherer, Steven P Sweeney, David S Grayzel

THE LANCET, JUNE 11, 1988

Preliminary Communication

POSSIBLE BENEFIT OF GR43175, A NOVEL 5-HT$_1$-LIKE RECEPTOR AGONIST, FOR THE ACUTE TREATMENT OF SEVERE MIGRAINE

ALFRED DOENICKE[1] JOCHEN BRAND[2]
VAL L. PERRIN[3]

Department of Anaesthetics, Ludwig-Maximilians University, Munich;[1] Migraine clinic, Koenigstein, West Germany;[2] and Medical Division, Glaxo Group Research Ltd, Greenford[3]

Nature **304**, 129 - 135 (14 July 1983); doi:10.1038/304129a0

Production of a novel neuropeptide encoded by the calcitonin gene via tissue-specific RNA processing

MICHAEL G. ROSENFELD[*], JEAN-JACQUES MERMOD[*], SUSAN G. AMARA[*], LARRY W. SWANSON[†], PAUL E. SAWCHENKO[†], JEAN RIVIER[‡], WYLIE W. VALE[‡] & RONALD M. EVANS[§]

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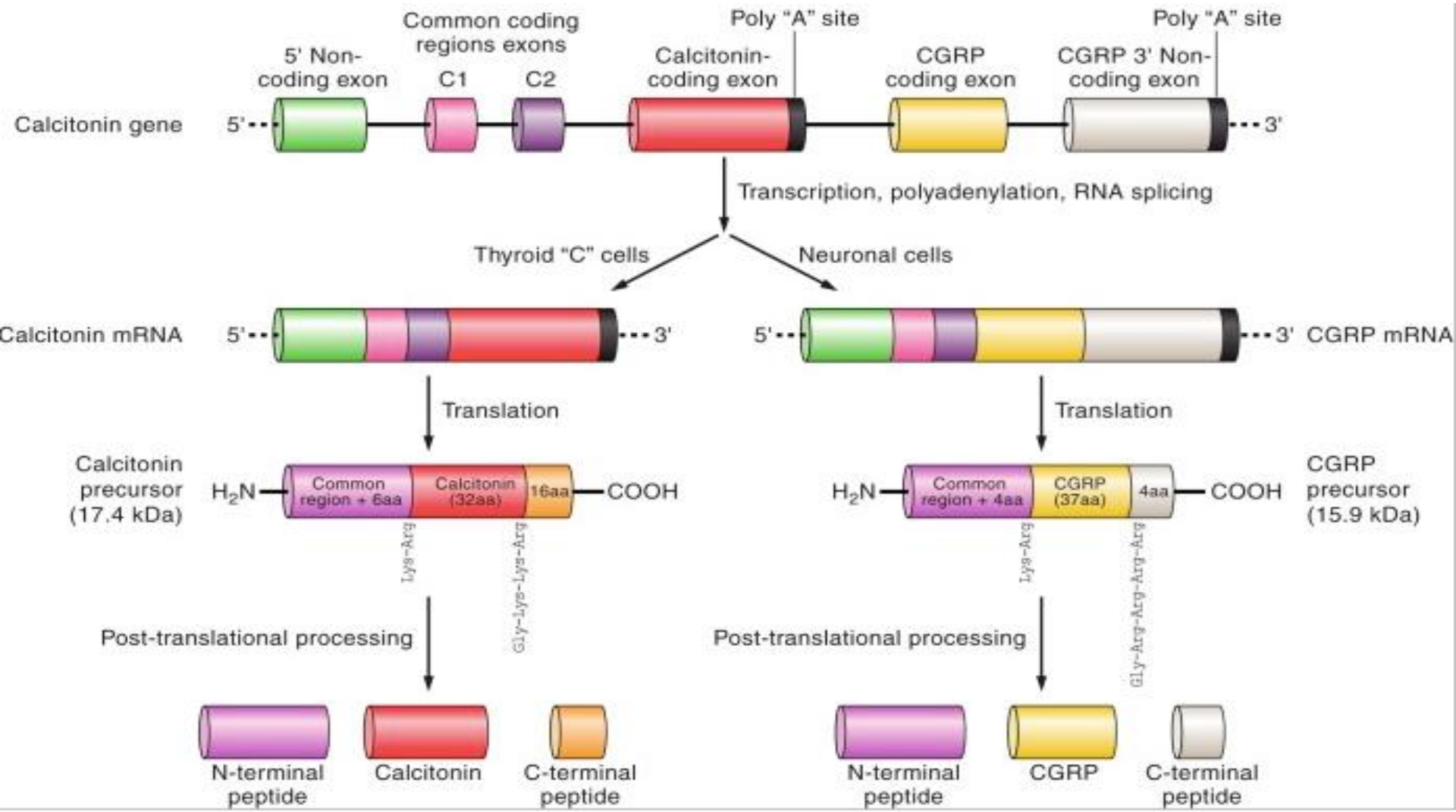
Alternative processing of the RNA transcribed from the calcitonin gene appears to result in the production of a messenger RNA in neural tissue distinct from that in thyroidal 'C' cells. The thyroid mRNA encodes a precursor to the hormone calcitonin whereas that in neural tissues generates a novel neuropeptide, referred to as calcitonin gene-related peptide (CGRP). The distribution of CGRP-producing cells and pathways in the brain and other tissues suggests functions for the peptide in nociception, ingestive behaviour and modulation of the autonomic and endocrine systems. The approach described here permits the application of recombinant DNA technology to analyses of complex neurobiological systems in the absence of prior structural or biological information.


Common coding regions exons
Poly "A" site
Poly "A" site
5' Non-coding exon
C1
C2
Calcitonin-coding exon
CGRP coding exon
CGRP 3' Non-coding exon
Calcitonin gene
5'
3'
Transcription, polyadenylation, RNA splicing
Thyroid "C" cells
Neuronal cells
Calcitonin mRNA
5'
3'
5'
3'
CGRP mRNA
Translation
Translation
Calcitonin precursor (17.4 kDa)
H2N
Common region + 6aa
Calcitonin (32aa)
16aa
COOH
Lys-Arg
Gly-Lys-Lys-Arg
H2N
Common region + 4aa
CGRP (37aa)
4aa
COOH
CGRP precursor (15.9 kDa)
Lys-Arg
Gly-Arg-Arg-Arg-Arg
Post-translational processing
Post-translational processing
N-terminal peptide
Calcitonin
C-terminal peptide
N-terminal peptide
CGRP
C-terminal peptide

Vasoactive Peptide Release in the Extracerebral Circulation of Humans During Migraine Headache

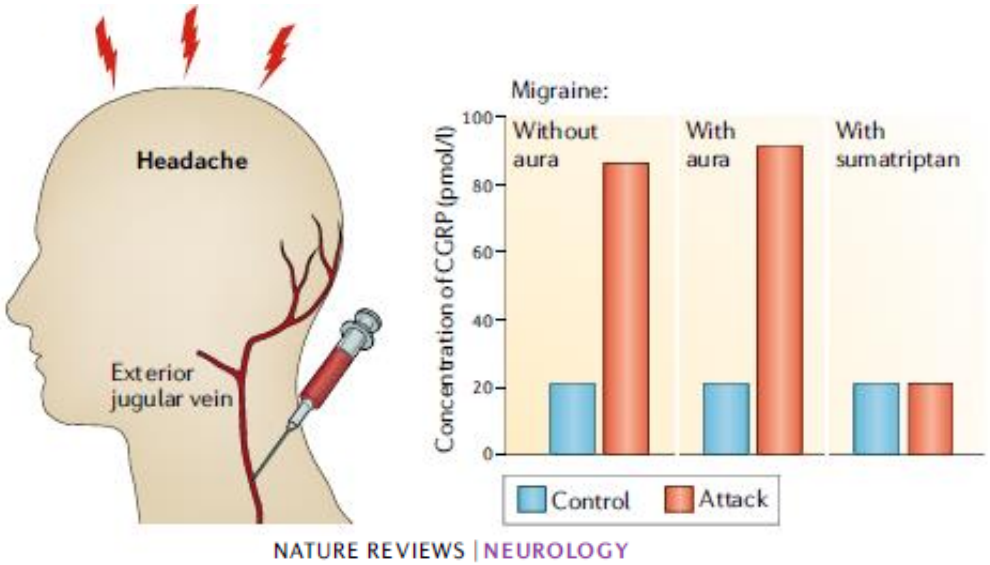
P. J. Goadsby, MD, PhD,* L. Edvinsson, MD, PhD,† and R. Ekman, MD‡

Table 1. Changes in Neuropeptides during Classic Migraine (with Aura) Headache[a]

	VIP	CGRP	SP	NPY
Site				
External jugular	9 ± 3[b]	92 ± 11[c]	5 ± 2	146 ± 15
Cubital fossa	< 6	40 ± 6	5 ± 3	140 ± 13
Control values	< 6	< 40	< 4	< 130

[a] All values are pmol/liter.
[b] Two patients were outliers and had higher levels; see text.
[c] CGRP level is significantly elevated in the external jugular blood of classic migraineurs ($t_{39} = 6.9$, $p < 0.001$).

VIP = vasoactive intestinal polypeptide; CGRP = calcitonin gene-related peptide; SP = substance P; NPY = neuropeptide Y.



NATURE REVIEWS | NEUROLOGY

Ann Neurol 1990;28(2):183-7
Brain 1994;117(Pt 3):427-34
Headache 2009;49:1258-66

Table 1 Number of patients who developed headache or migraine fulfilling the IHS criteria for migraine without aura after CGRP and placebo during the infusion and the following 40 min (immediate headache) or in the period from 1 to 12 h after the infusion (delayed headache/migraine)

	Immediate headache	Delayed headache	Delayed migraine
CGRP	8(9)	9(9)	3(9)
Placebo	1(9)	1(9)	0(9)
$P < 0.05$	*	*	

"Increased CGRP in external jugular venous blood is probably not an epiphenomenon but reflects direct participation of CGRP in migraine"

Cephalalgia 2002;22(1):54-61
Cephalalgia 2010;30(10):1179-86

Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial

Tony W Ho, Michel D Ferrari, David W Dodick, Vince Galet, James Kost, Xiaoyin Fan, Heather Leibensperger, Samar Froman, Christopher Assaid, Christopher Lines, Hille Koppen, Paul K Winner

Summary

Background Calcitonin gene-related peptide (CGRP) probably has a role in migraine pathophysiology, and antagonism of its receptors might provide treatment without the vasoconstrictor effects of triptans. We aimed to assess the clinical profile of MK-0974 (telcagepant), an orally bioavailable antagonist of CGRP receptor.

Methods In a randomised, parallel-treatment, placebo-controlled, double-blind, trial at 81 sites in the Europe and the USA, adults with migraine diagnosed by International Headache Society criteria treated moderate or severe attacks with either oral telcagepant 150 mg or 300 mg, zolmitriptan 5 mg, or placebo. The five co-primary endpoints were pain freedom, pain relief, or absence of photophobia, phonophobia, or nausea at 2 h after treatment. Analysis was by the full analysis set and multiplicity was controlled for with a step-down closed-testing procedure. This trial is registered with ClinicalTrials.gov, number NCT00442936.

Findings 1380 patients were randomly assigned to receive telcagepant 150 mg (n=333) or 300 mg (354), zolmitriptan (345), or placebo (348). Telcagepant 300 mg was more effective than placebo for pain freedom (95 [27%] of 353 patients *vs* 33 [10%] of 343 [p<0·0001]), pain relief (194 [55%] of 353 *vs* 95 [28%] of 343 [p<0·0001]), and absences of phonophobia (204 [58%] of 353 *vs* 126 [37%] of 342 [p<0·0001]), photophobia (180 [51%] of 353 *vs* 99 [29%] of 342 [p<0·0001]), and nausea (229 [65%] of 352 *vs* 189 [55%] of 342 [p=0·0061]). Efficacy of telcagepant 300 mg and zolmitriptan 5 mg were much the same, and both were more effective than telcagepant 150 mg. Adverse events were recorded for 31% taking telcagepant 150 mg, 37% taking telcagepant 300 mg, 51% taking zolmitriptan 5 mg, and 32% taking placebo.

Interpretation Telcagepant 300 mg is effective as an acute treatment for migraine with efficacy comparable to that of zolmitriptan 5 mg, but with fewer associated adverse effects.

Funding Merck Research Laboratories.

Lancet 2008; 372: 2115–23

Published Online November 25, 2008 DOI:10.1016/S0140-6736(08)61626-8

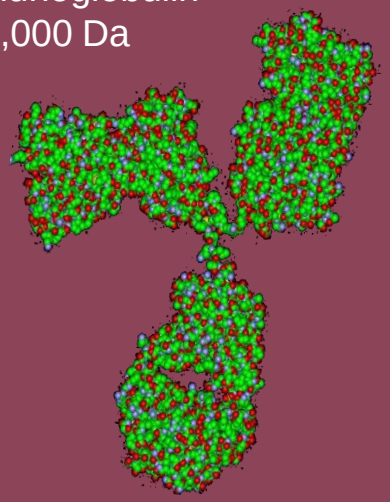
See Comment page 2089

Merck Research Laboratories, North Wales, PA, USA (TW Ho MD, V Galet PhD, J Kost PhD, X Fan PhD, H Leibensperger BS, S Froman BS, C Assaid PhD, C Lines PhD); **Leiden University Medical Center, Leiden, Netherlands** (Prof M D Ferrari MD, H Koppen MD); **Mayo Clinic, Scottsdale, AZ, USA** (Prof D W Dodick MD); **Palm Beach Headache Center, West Palm Beach, FL, USA** (P K Winner DO)

Correspondence to: Dr Tony Ho, Merck Research Laboratories, UG 4C-18, PO Box 1000, North Wales, PA 19454-1099, USA **tony_ho@merck.com**

Small molecule
chemical entity
500 Da

IgG1 antibody
immunoglobulin
150,000 Da

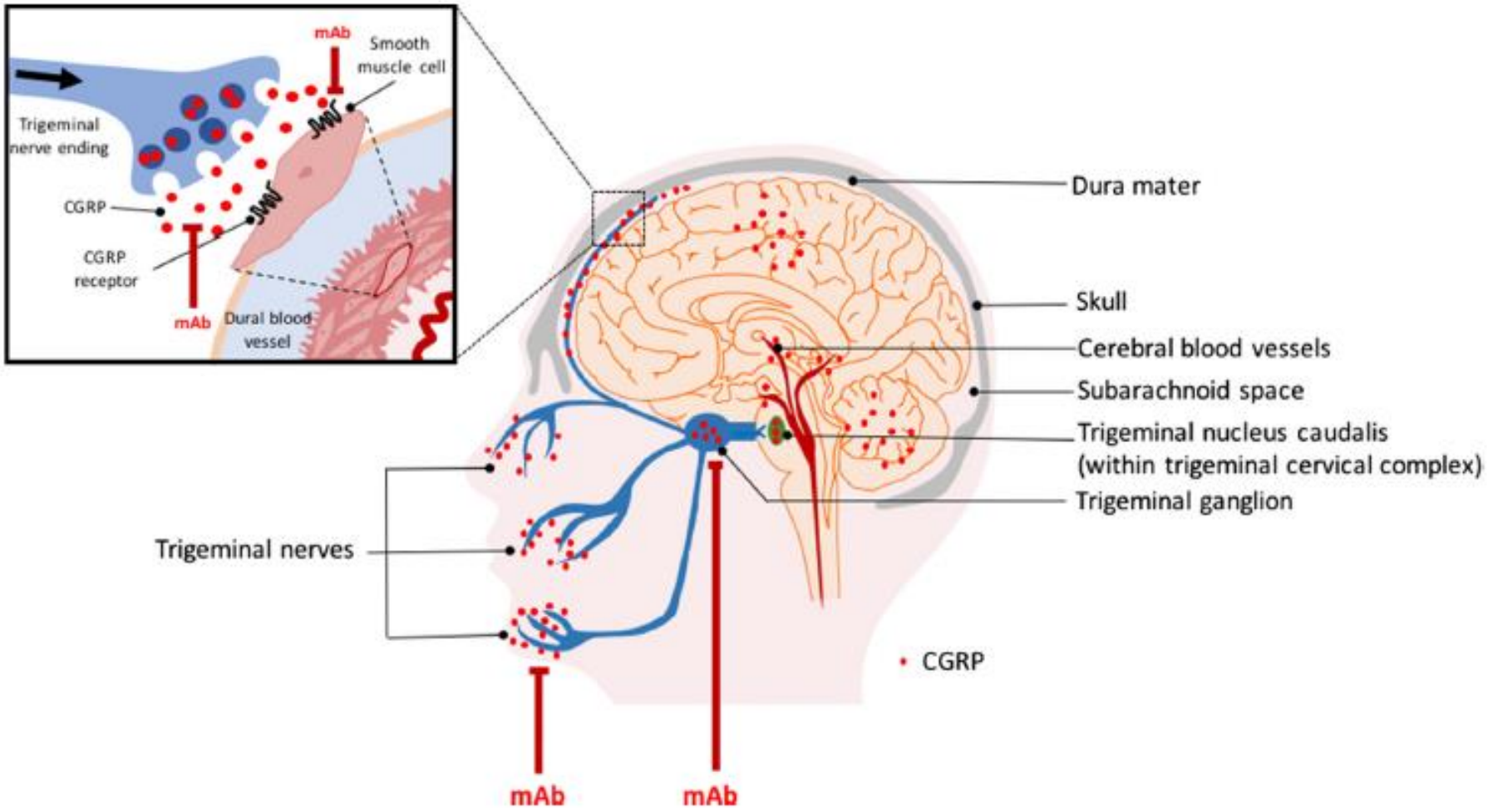


Property	Small molecule	mAb
Target[1]	Intracellular or extracellular	Extracellular
Specificity[1]	Low(er); more likely to have off-target activity	High; less likely to have off-target activity
Metabolism[1]	Hepatic/renal	RES, target-mediated disposition
Drug–drug Interactions[1]	More likely	Less likely
Crossing the BBB[1]	Possible*	Minimal
Administration[1]	Usually oral	IM, SC, or IV
Half-life[2]	~ Hours	Days to weeks
Dosing[1]	Usually daily	Typically less frequent
Production[1,3]	Chemical synthesis; relatively straightforward to make and reproduce reliably	Produced inside unique lines of modified living cells; difficult to make and reproduce precisely

Adapted from Foltz I, et al. Circulation. 2013;127:2222–2230 and Zhao L, et al. Acta Pharmacologica Sinica. 2012;33:1339–1347

*Dependent on the degree of lipid solubility.

1. Foltz I, et al. Circulation. 2013;127:2222–2230
2. Silberstein S, et al. Headache. 2015;1171–1182
3. Kleinberg M, et al. Am J Health Syst Pharm. 2004;61:695–708
4. Zhao L, et al. Acta Pharmacologica Sinica. 2012;33:1339–1347


mAb
Smooth muscle cell
Trigeminal nerve ending
CGRP
CGRP receptor
mAb
Dural blood vessel
Dura mater
Skull
Cerebral blood vessels
Subarachnoid space
Trigeminal nucleus caudalis (within trigeminal cervical complex)
Trigeminal ganglion
Trigeminal nerves
CGRP
mAb
mAb

	Eptinezumab[a] [98]	Erenumab [27, 28, 97]	Fremanezumab [99, 100]	Galcanezumab [29, 30]
Antibody type	Humanised IgG_1	Human IgG_2	Humanised IgG_2	Humanised IgG_4
Antibody target	CGRP	CLR/RAMP1 receptor	CGRP	CGRP
IC_{50}	No data	2.3 nM	No data	0.35 nM
Route of administration	Intravenous	Subcutaneous	Subcutaneous	Subcutaneous
Frequency of administration	3-Monthly	Monthly	Monthly or 3-monthly	Monthly
Production cell line	Yeast	Chinese hamster ovary	Chinese hamster ovary	Chinese hamster ovary
Bioavailability	Administered IV	Up to 74%	No data	No data
T_{max}	2.5–2.8 h	4–11 days	5–11 days	7–14 days
Clearance	0.146–0.1536 L/day	0.214 L/day	0.055–0.0625 L/day	0.452 L/day
$t_{½}$	23–33 days	~ 21 days	31–39 days	25–32 days

CNS Drugs
https://doi.org/10.1007/s40263-019-00665-9

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Erenumab for Episodic Migraine

Peter J. Goadsby, M.D., Ph.D., Uwe Reuter, M.D., Yngve Hallström, M.D., Gregor Broessner, M.D., Jo H. Bonner, M.D., Feng Zhang, M.S., Sandhya Sapra, Ph.D., Hernan Picard, M.D., Ph.D., Daniel D. Mikol, M.D., Ph.D., and Robert A. Lenz, M.D., Ph.D.

N Engl J Med 2017;377:2123-32.

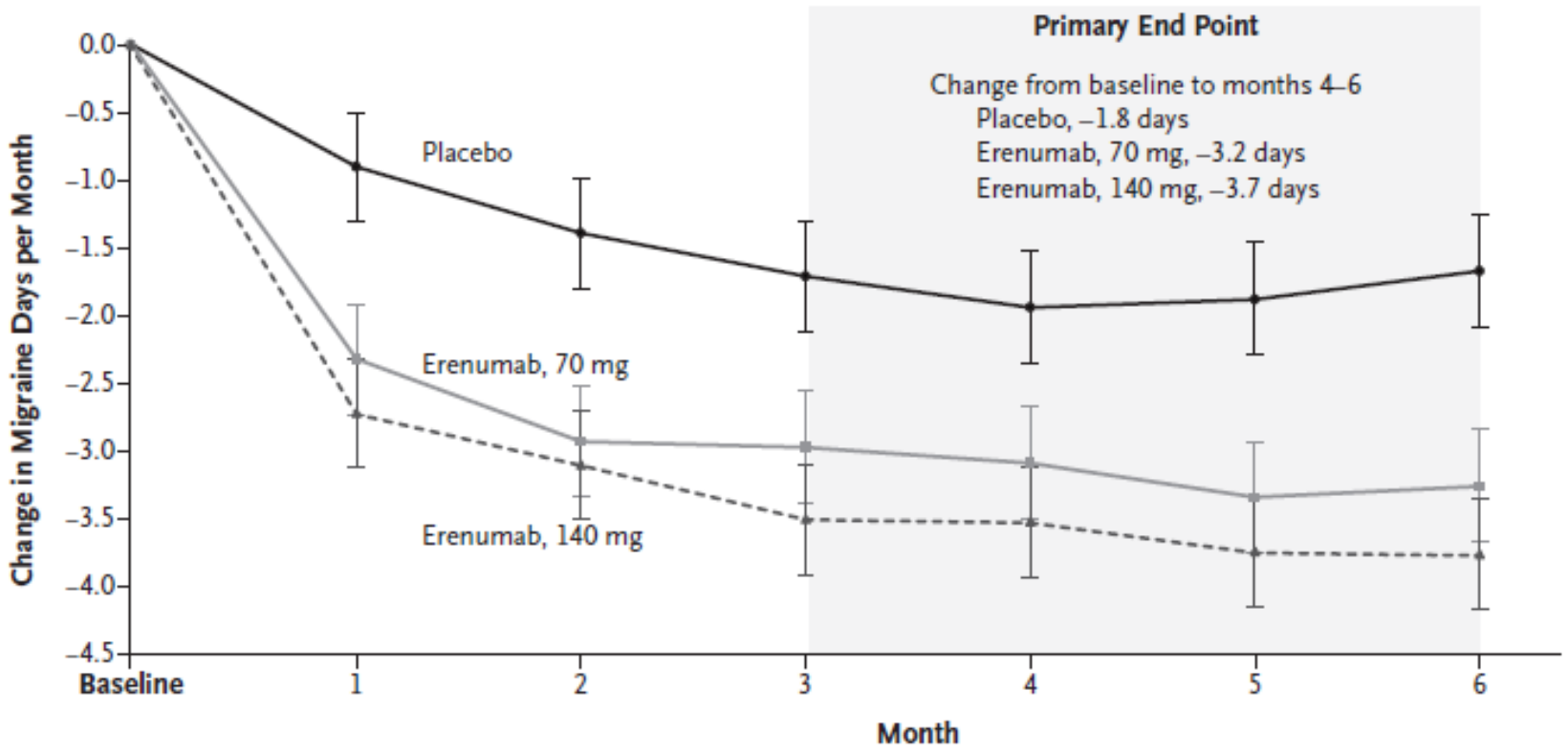
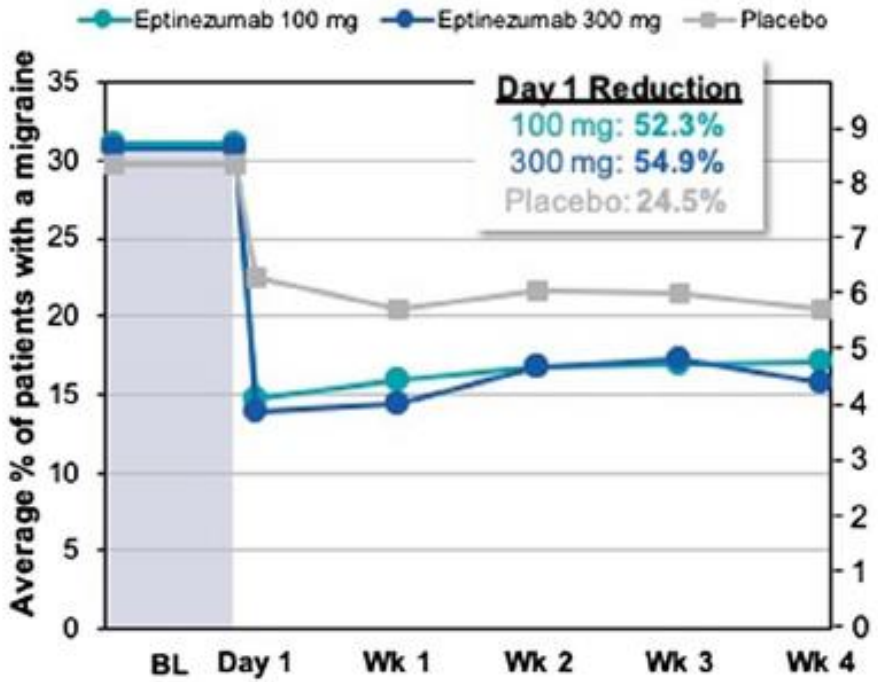


Figure 1. Primary End Point.



(*Headache* 2020;0:1-12)

Vandervorst *et al. The Journal of Headache and Pain* (2021) 22:128
https://doi.org/10.1186/s10194-021-01335-2

The Journal of Headache and Pain

RESEARCH ARTICLE Open Access

CGRP monoclonal antibodies in migraine: an efficacy and tolerability comparison with standard prophylactic drugs

Fenne Vandervorst[1], Laura Van Deun[1], Annelies Van Dycke[2], Koen Paemeleire[3], Uwe Reuter[4], Jean Schoenen[5] and Jan Versijpt[1*]

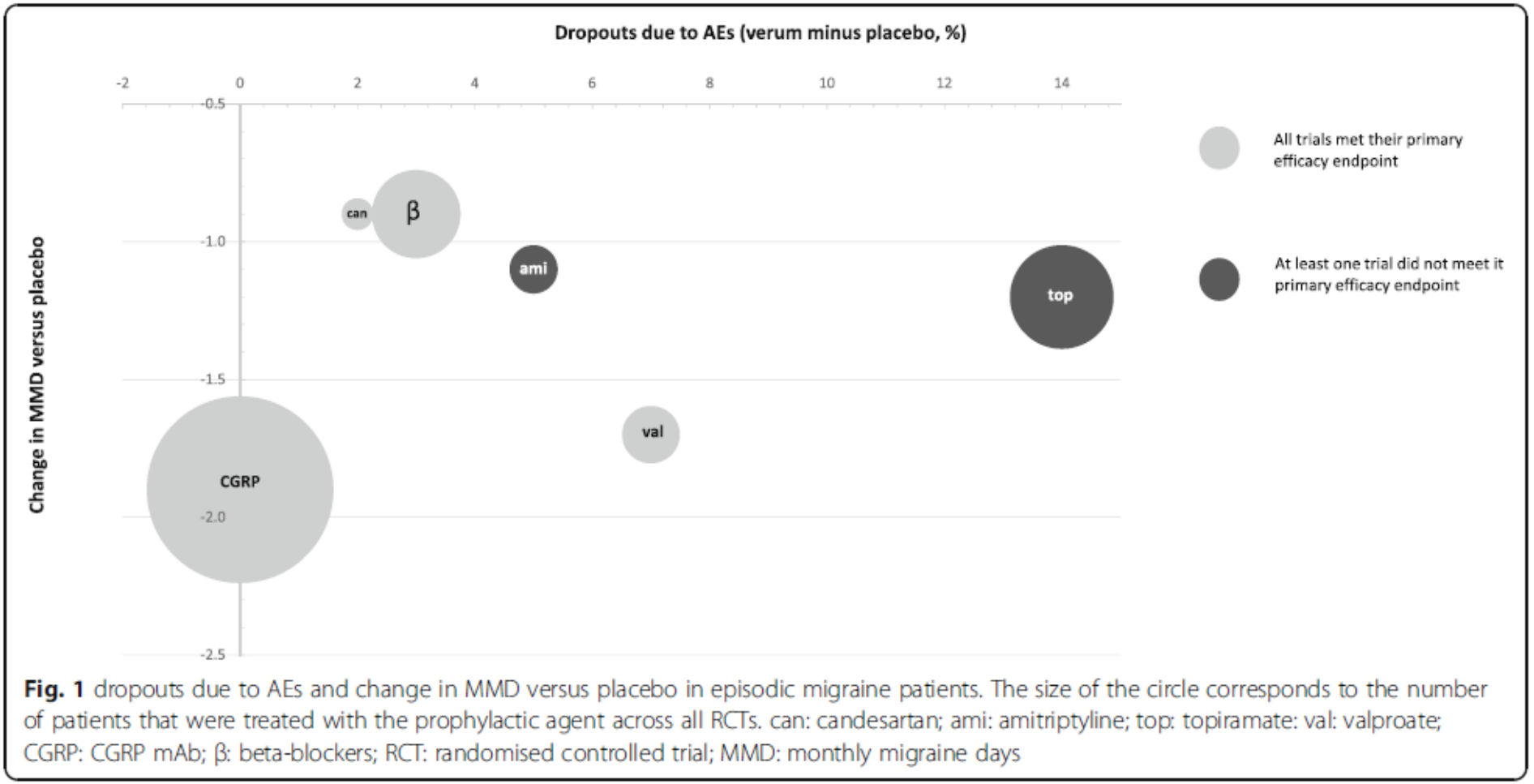


Fig. 1 dropouts due to AEs and change in MMD versus placebo in episodic migraine patients. The size of the circle corresponds to the number of patients that were treated with the prophylactic agent across all RCTs. can: candesartan; ami: amitriptyline; top: topiramate: val: valproate; CGRP: CGRP mAb; β: beta-blockers; RCT: randomised controlled trial; MMD: monthly migraine days

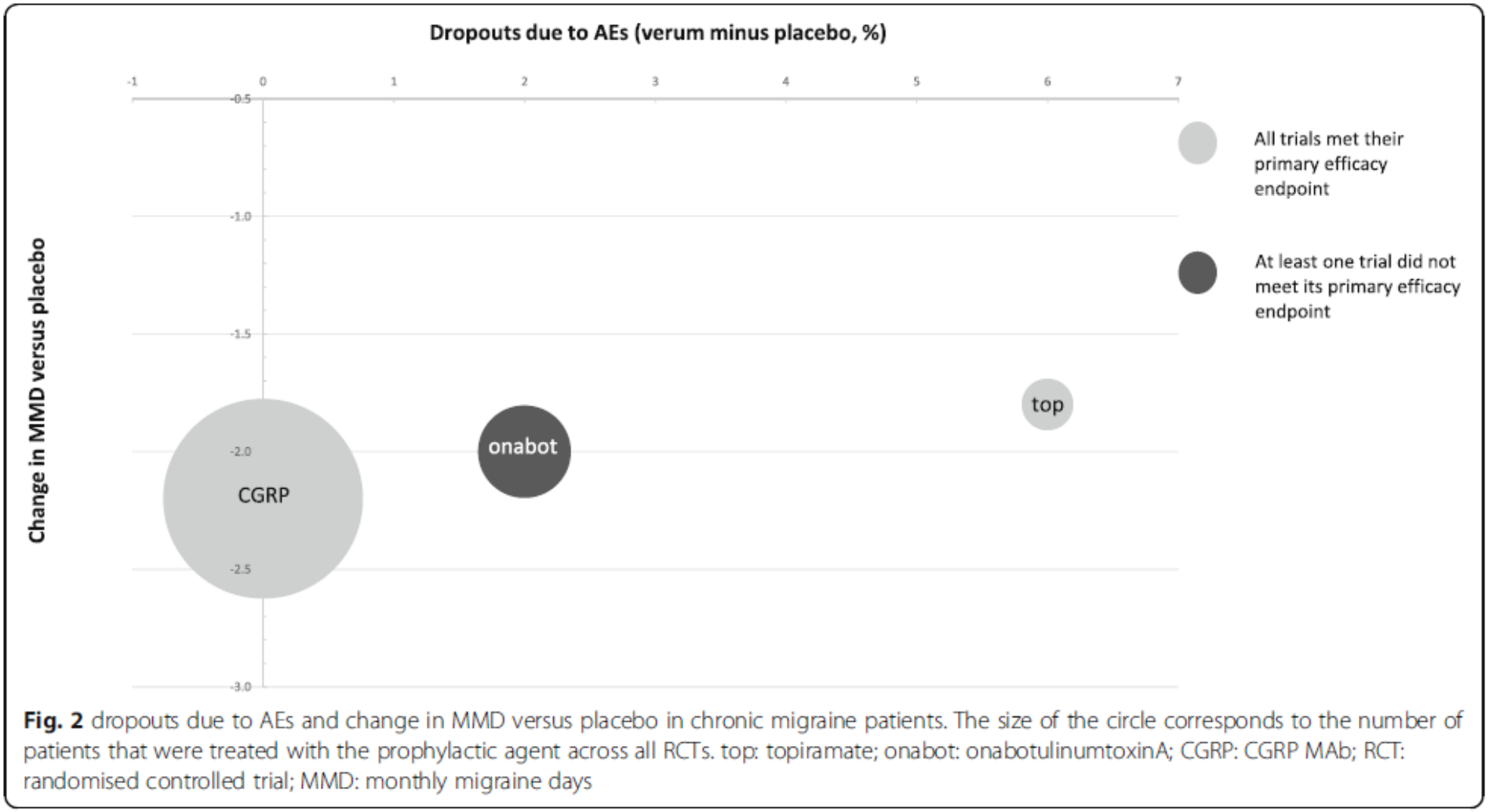


Fig. 2 dropouts due to AEs and change in MMD versus placebo in chronic migraine patients. The size of the circle corresponds to the number of patients that were treated with the prophylactic agent across all RCTs. top: topiramate; onabot: onabotulinumtoxinA; CGRP: CGRP MAb; RCT: randomised controlled trial; MMD: monthly migraine days

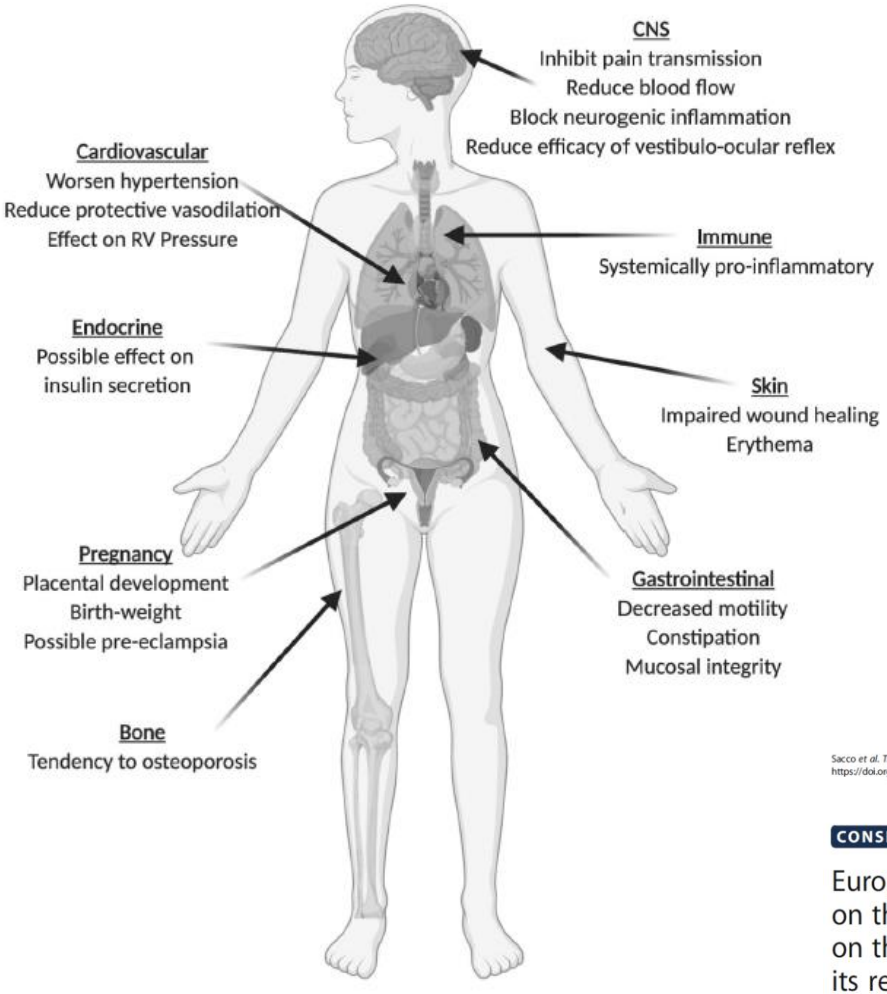


Figure 1 Possible systemic effects of calcitonin gene-related peptide inhibition.

Sacco *et al. The Journal of Headache and Pain* (2019) 20:6
https://doi.org/10.1186/s10194-018-0955-y

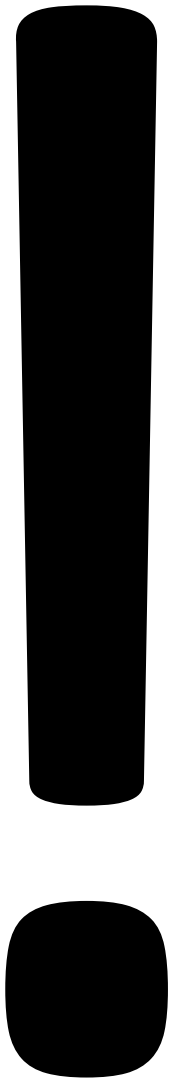
The Journal of Headache and Pain

CONSENSUS ARTICLE Open Access

European headache federation guideline on the use of monoclonal antibodies acting on the calcitonin gene related peptide or its receptor for migraine prevention

Simona Sacco[1*], Lars Bendtsen[2], Messoud Ashina[3], Uwe Reuter[3], Gisela Terwindt[4], Dimos-Dimitrios Mitsikostas[5†] and Paolo Martelletti[6†]

We suggest avoiding monoclonal antibodies targeting the CGRP pathway in pregnant or nursing women. We suggest caution and decision on a case-by-case basis in the presence of vascular disease or risk factors and Raynaud phenomenon. We suggest caution in erenumab use in individuals with migraine and history of severe constipation.



Superiority
Long-term safety

Efficacy
Efficacy in treatment-refractory patients
Short-term safety / tolerance

A Treatment for Migraines

Aimovig

Millions of Americans suffer debilitating migraines, affecting their performance at work or school and contributing to anxiety and other mental-health issues. But few treatment options exist. Pharmaceutical firms Amgen and Novartis are seeking to change that with Aimovig, which in May became the first Food and Drug Administration–approved drug designed to prevent migraines. Administered by monthly injection, the drug works by blocking a protein receptor in the brain, preventing a peptide that may trigger migraines from attaching to its target. During trials, it halved the number of recipients' migraine days. Cen Xu, Amgen's scientific director for neuroscience, says she has been overwhelmed by positive feedback from the more than 52,000 people using Aimovig so far. "Seeing the handwritten letters, I get very emotional," she says. Aimovig costs $575 per dose before insurance, but Amgen helps some patients, whose private health plans don't cover the drug, get it at no cost for up to a year. *—Jamie Ducharme*

BIJLAGE A

Aanvraagformulier voor de vergoeding van de **initiatiebehandeling** met de betrokken specialiteit (§ 10740100 van hoofdstuk IV van de lijst gevoegd bij het K.B. van 01 februari 2018)

☐ Bij de rechthebbende faalden ten minste de volgende profylactische behandelingen wegens een tolerantieprobleem of wegens onvoldoende respons (zijnde een reductie kleiner dan 50% van het aantal migrainedagen per maand tijdens de behandeling in vergelijking met de 4 weken voor de start van de behandeling) ondanks toediening van een volledige en adequate behandelingskuur.

Profylactische behandelingen:

☐ ten minste een bètablokker (propranolol, metoprolol, atenolol, bisoprolol of timolol)

☐ niet van toepassing wegens contra-indicatie

en

☐ ten minste topiramaat,

☐ niet van toepassing wegens contra-indicatie

en

☐ en ten minste één van volgende behandelingen: (alle voorgaande preventieve migraine-behandelingen aankruisen):

- ☐ valproïnezuur/valproaat
- ☐ amitriptyline
- ☐ venlafaxine
- ☐ flunarizine
- ☐ candesartan
- ☐ onabotulinetoxine A voor chronische migraine

☐ De rechthebbende vertoonde een minimaal aantal van gemiddeld 8 migrainedagen per maand voorafgaand aan de start van de behandeling met de betrokken specialiteit, gemeten gedurende een minimale periode van 4 weken op basis van een door de patiënt zorgvuldig bijgehouden migrainedagboek.

Hiermee bevestig ik dat deze rechthebbende de vergoeding van de specialiteit de betrokken specialiteit voor een periode van 3 maanden dient te krijgen aan een maximale dosis van 675 mg per 3 maanden [225 mg eenmaal per maand (maandelijkse dosering) of 675 mg eenmaal per drie maanden (driemaandelijkse dosering)].

Ik verbind mij ertoe de behandeling met de betrokken specialiteit stop te zetten indien onvoldoende respons wordt waargenomen na 3 toedieningen, gedefinieerd als een afname die kleiner is dan 50%, in het gemiddeld aantal migrainedagen per maand, gemeten gedurende een minimale periode van 4 weken op basis van een door de rechthebbende zorgvuldig bijgehouden migrainedagboek, in vergelijking met het gemiddeld aantal migrainedagen per maand, gemeten in de periode voorafgaand aan de start van de behandeling met de betrokken specialiteit en gedocumenteerd in het medisch dossier van de rechthebbende.

Ik verbind mij ertoe de bewijsstukken die aantonen dat de rechthebbende zich in de geattesteerde situatie bevindt ter beschikking te houden van de adviserend arts.

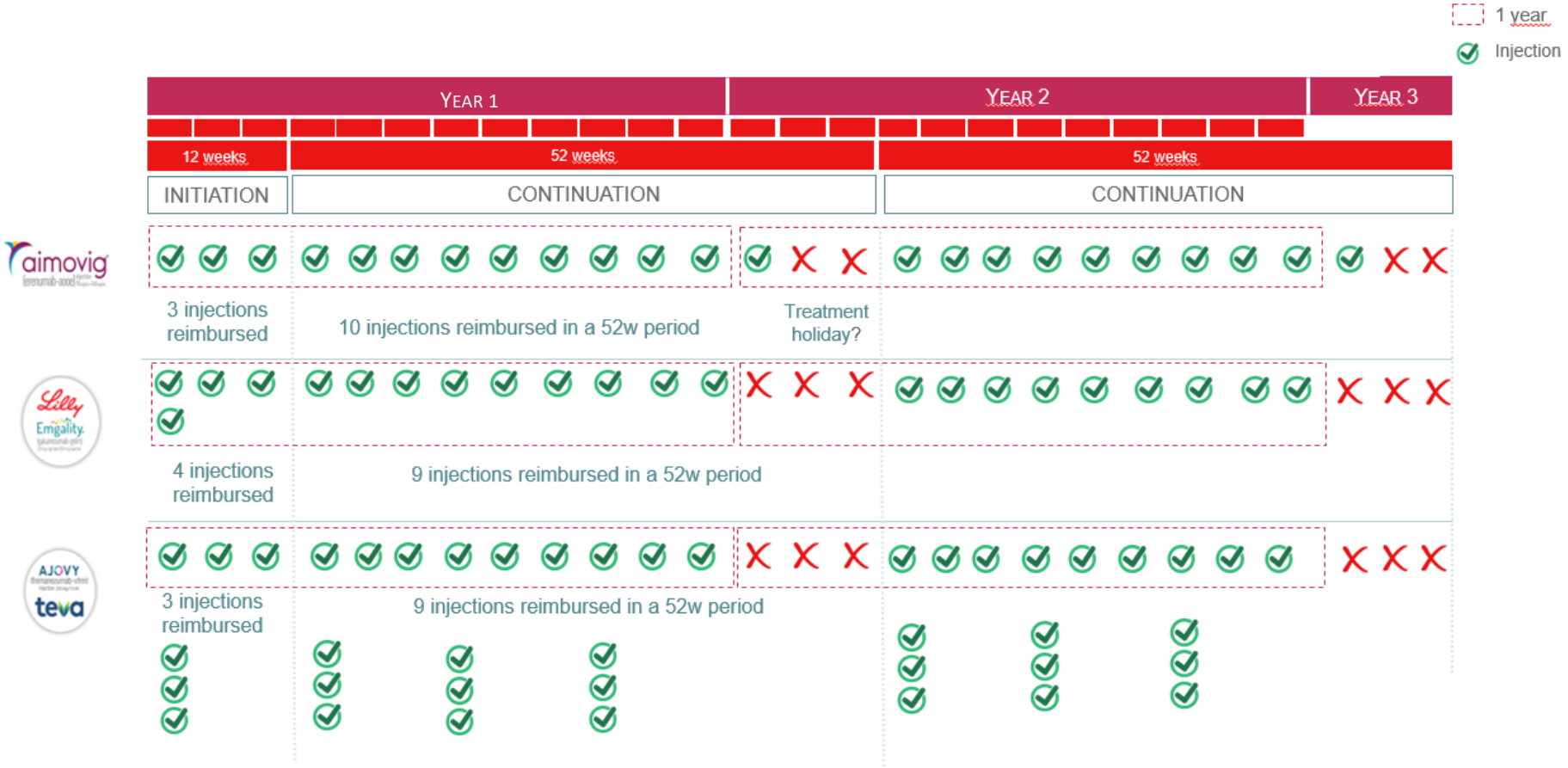
BIJLAGE A

Aanvraagformulier voor de vergoeding van de **verlenging van de behandeling** met de betrokken specialiteit (§ 10740200 van hoofdstuk IV van de lijst bijgevoegd bij het K.B. van 01 februari 2018)

Ik attesteer de medische noodzaak tot voortzetten van de behandeling met de betrokken specialiteit.

☐ aangetoond door het opnieuw toenemen van het gemiddeld aantal migrainedagen per maand tot een minimum van 8 migrainedagen per maand, gemeten tijdens een toegepaste "treatment holiday" op basis van een door de rechthebbende zorgvuldig bijgehouden migrainedagboek en gedocumenteerd in het medisch dossier van de rechthebbende.

☐ niet van toepassing wegens de eerste aanvraag tot verlenging


1 year
Injection
YEAR 1
YEAR 2
YEAR 3
12 weeks
52 weeks
52 weeks
INITIATION
CONTINUATION
CONTINUATION
aimovig
3 injections reimbursed
10 injections reimbursed in a 52w period
Treatment holiday?
Lilly Emgality
4 injections reimbursed
9 injections reimbursed in a 52w period
AJOVY teva
3 injections reimbursed
9 injections reimbursed in a 52w period

jan.versijpt@uzbrussel.be