

# Eemicrania: trattamento con i nuovi farmaci: sono utili?

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# Outline

✓ *CGRP Monoclonal Antibodies*

✓ *Efficacy*

✓ *Manageability*

✓ *Safety*

✓ *Cost*

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✓ *CGRP Monoclonal Antibodies*

✓ *Efficacy*

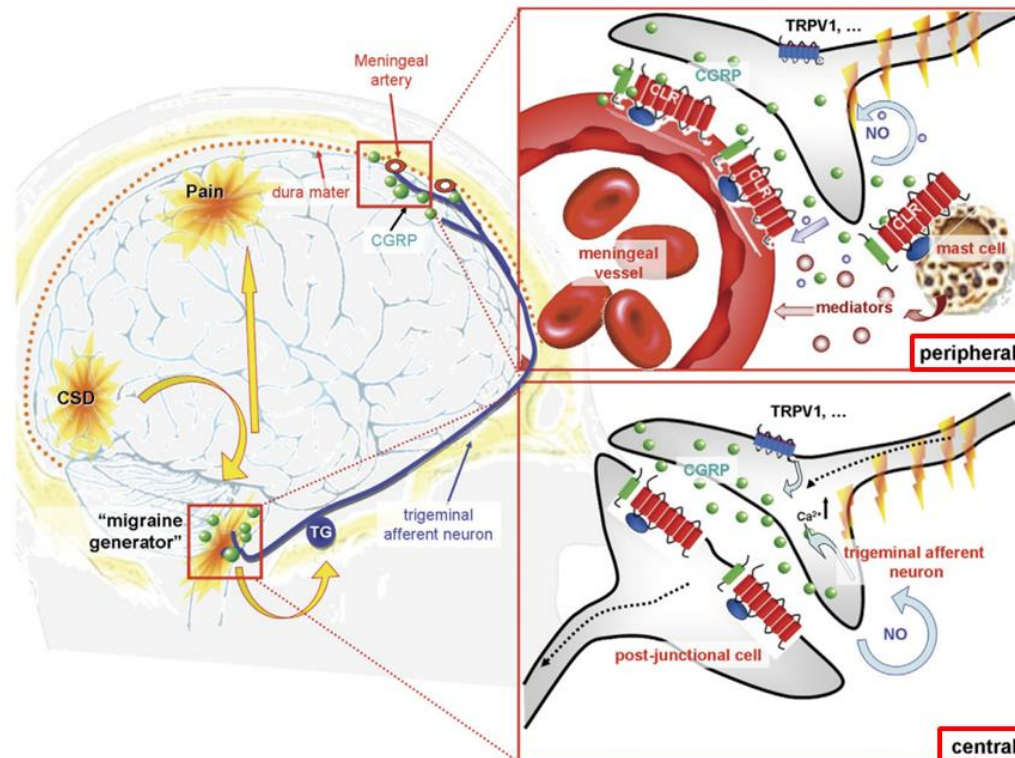
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# Calcitonin-Gen-Related-Peptide (CGRP)

CGRP is a 37-amino acid neuropeptide belonging to a family of peptides which encompasses calcitonin, adrenomedullin and amylin.



## Vasodilatation

activation of vascular CGRP

## Neurogenic inflammation

CGRP-dependent mediators from mast cells

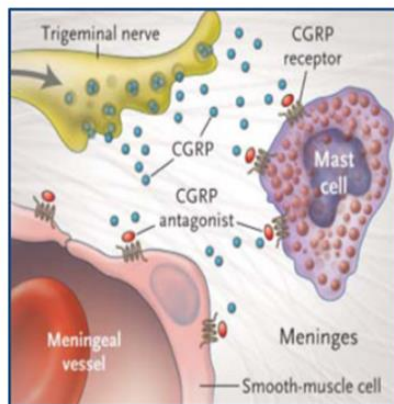
## Pain transmission

CGRP-release

# CGRP and Migraine

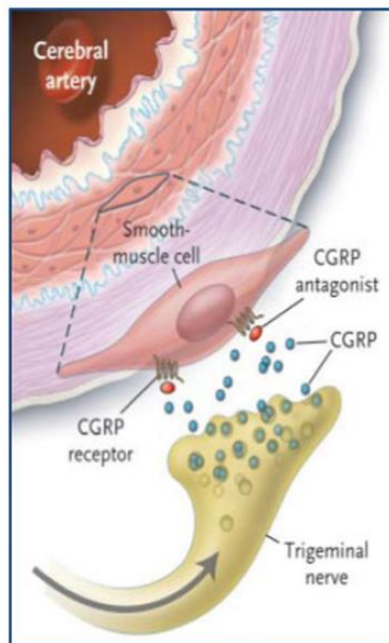
- ✓ During spontaneous migraine attacks, the level of CGRP is increased in blood from the external jugular vein, which drains the extracranial compartment.
- ✓ The intravenous infusion of CGRP elicited migraine-like headaches in 8 of 10 patients with a history of migraine (3/8 patients fulfilled the IHS criteria for migraine without aura)
- ✓ Sumatriptan normalizes elevated CGRP levels as it terminates a migraine attack

# CGRP antibodies (CGRP-Ab) mechanisms of action



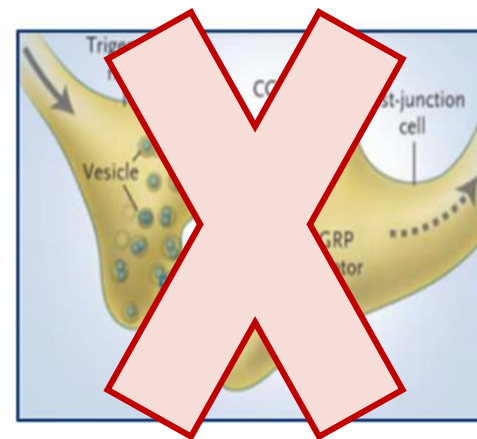
## Blocking neurogenic inflammation

Binding of CGRP receptor antagonists to CGRP receptors located on mast cells inhibits inflammation caused by release of CGRP onto mast cells within outer covering of the brain (meninges)



## Decreasing artery dilation

CGRP receptor antagonists inhibit pathologic dilation of arteries, without the unwanted effect of active vasoconstriction, by blocking CGRP receptors located in smooth muscle cells within vessel walls



## Inhibiting pain transmission

Binding of CGRP receptor antagonists to CGRP receptors suppresses transmission of pain by inhibiting central relay of pain signals from trigeminal nerve to caudal trigeminal nucleus

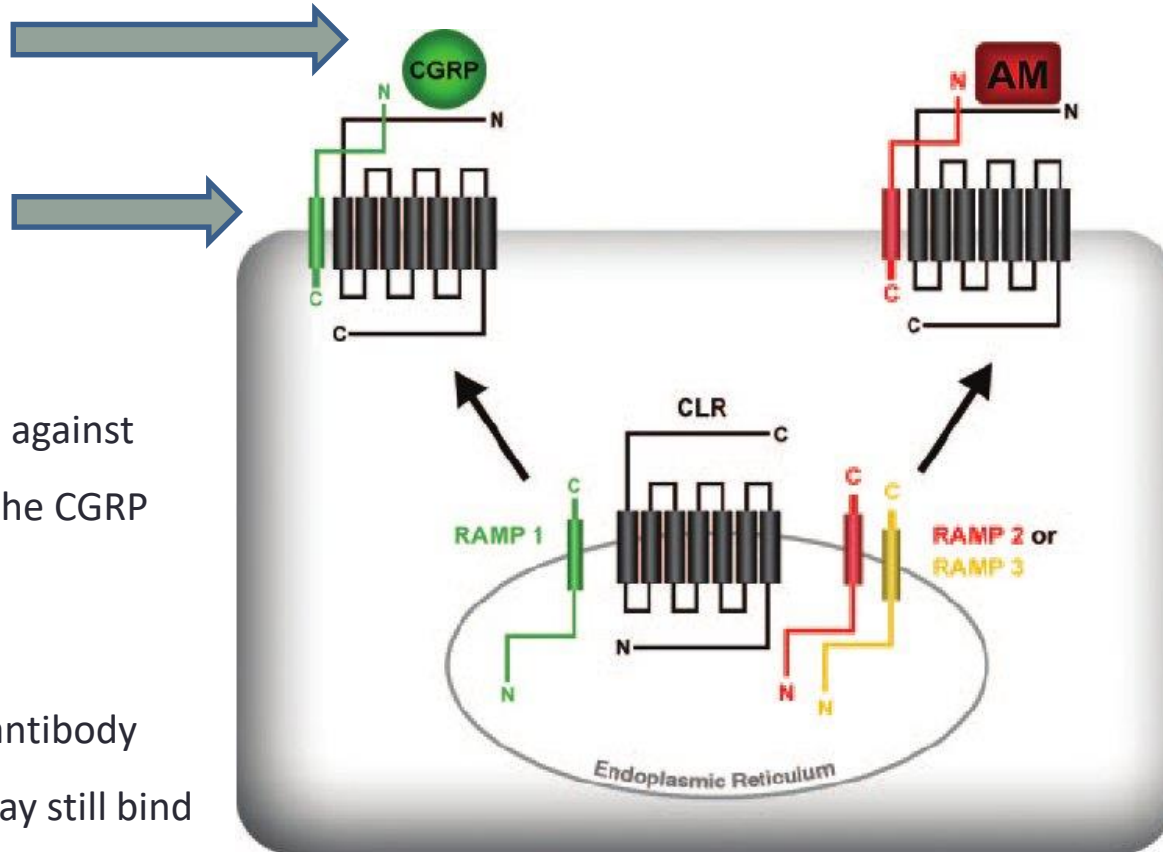
# CGRP-Ab and CGRP(r)-Ab

## Ab anti CGRP

Fremanezumab  
Galcanezumab  
Eptinezumab

## Ab anti CGRP(r)

Erenumab



- If CGRP is scavenged by an Ab directed against CGRP, other peptides with affinity for the CGRP receptor may bind to this receptor
- If the CGRP receptor is blocked by an antibody directed against this receptor, CGRP may still bind to other receptors for which it has affinity (e.g. in the human coronary artery)

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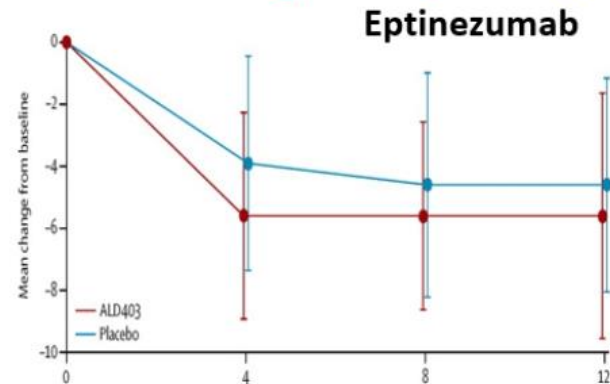
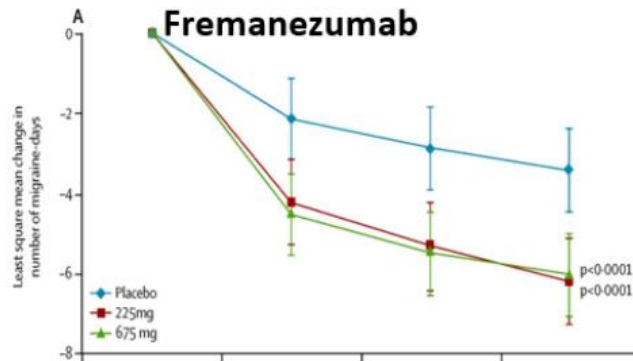
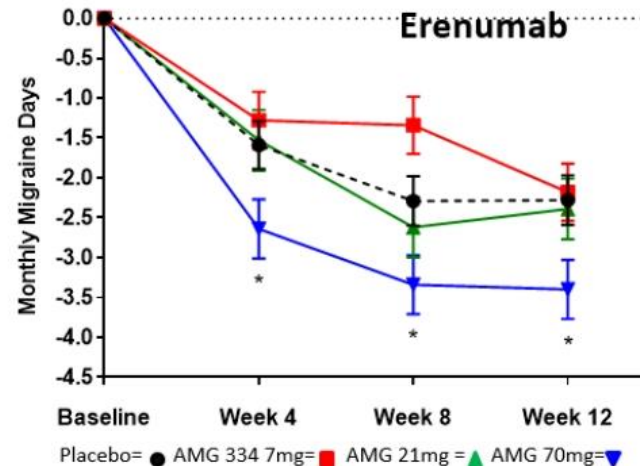
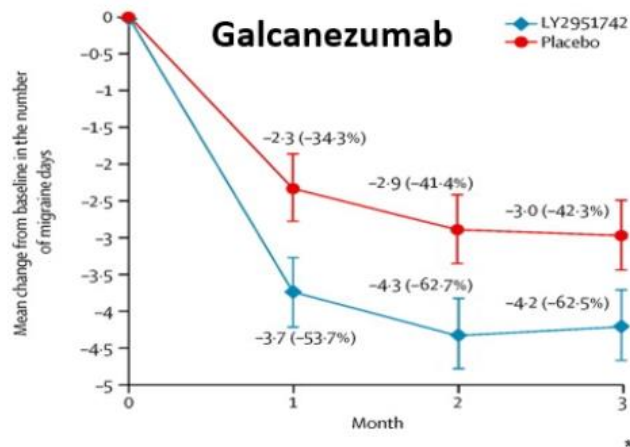
✓ *Safety*

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# CGRP-Ab: efficacy-1

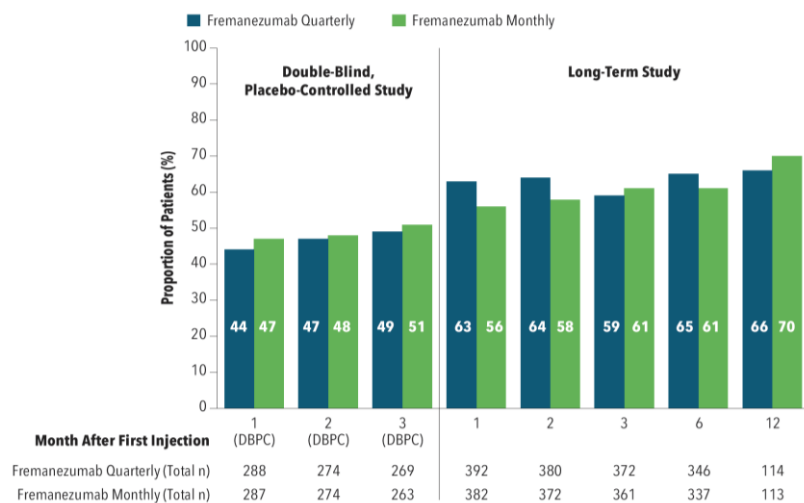
Significant reduction of migraine days/month (from 2 to 4)



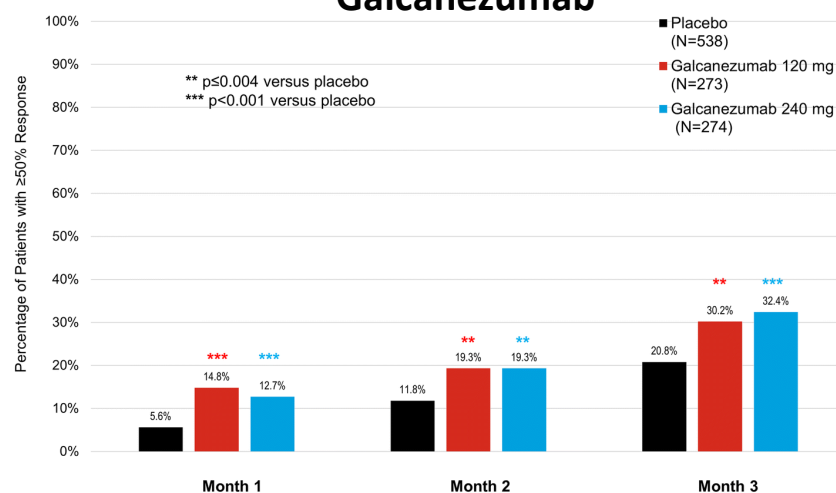
# CGRP-Ab: efficacy-2

≥50% responders from 56.3% to 62.3%

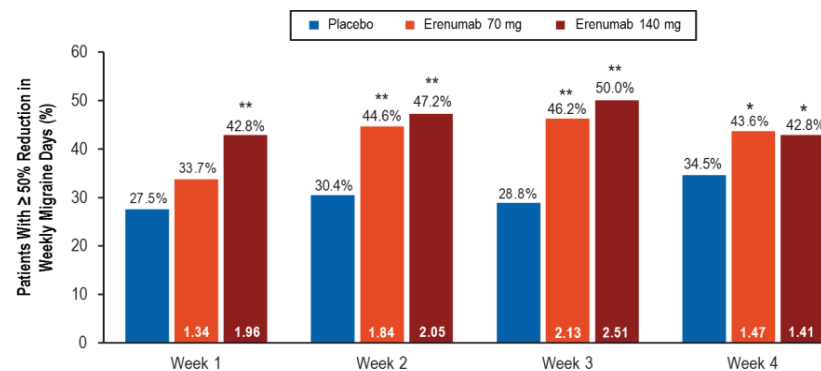
## Fremanezumab



## Galcanezumab



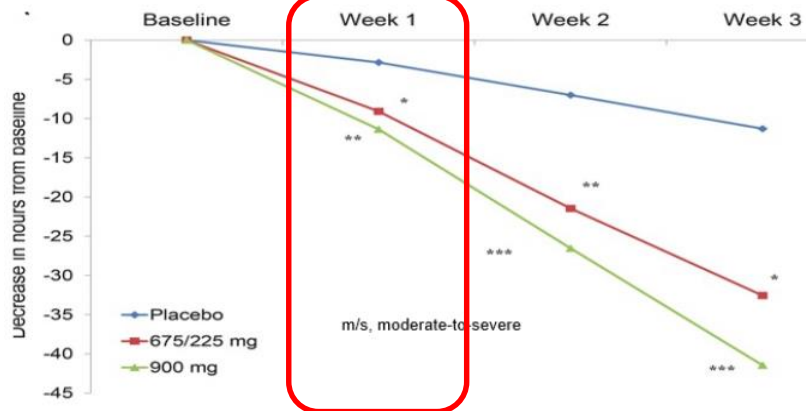
## Erenumab



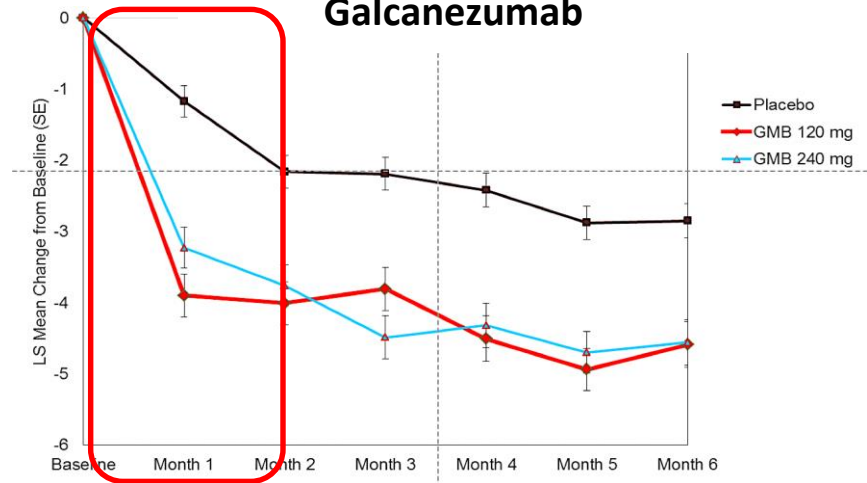
# CGRP-Ab: efficacy-3

## Early onset of activity

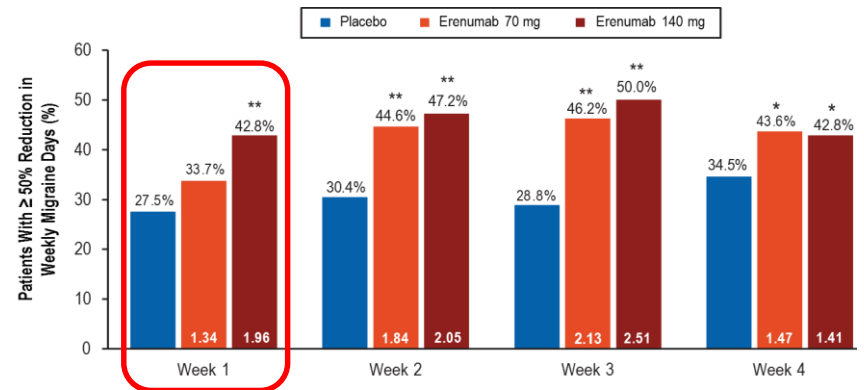
### Fremanezumab



### Galcanezumab



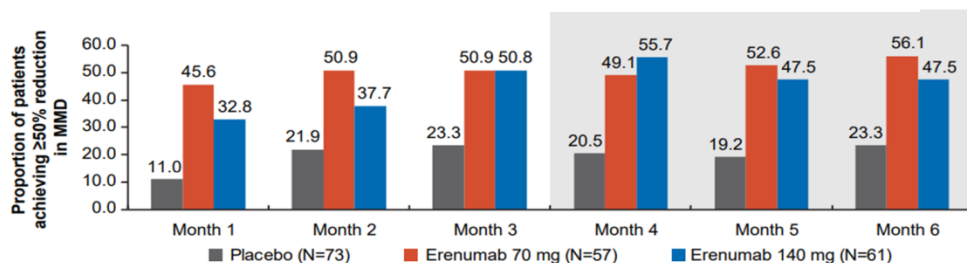
### Erenumab



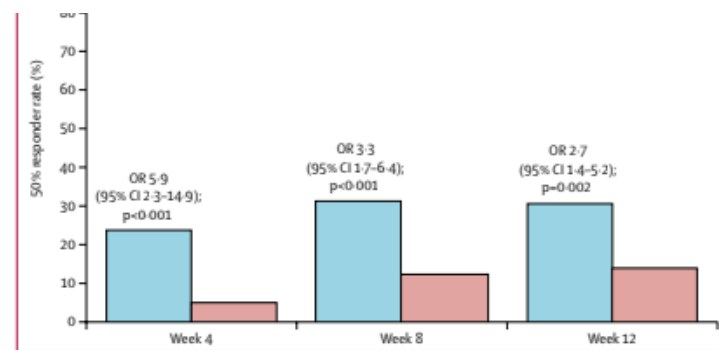
# CGRP-Ab: efficacy-4

## Effective also in complex migraine endo-phenotypes

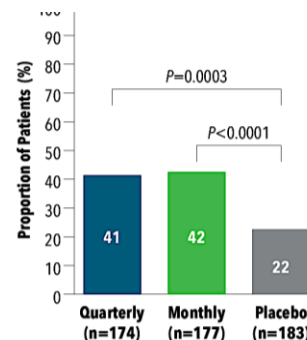
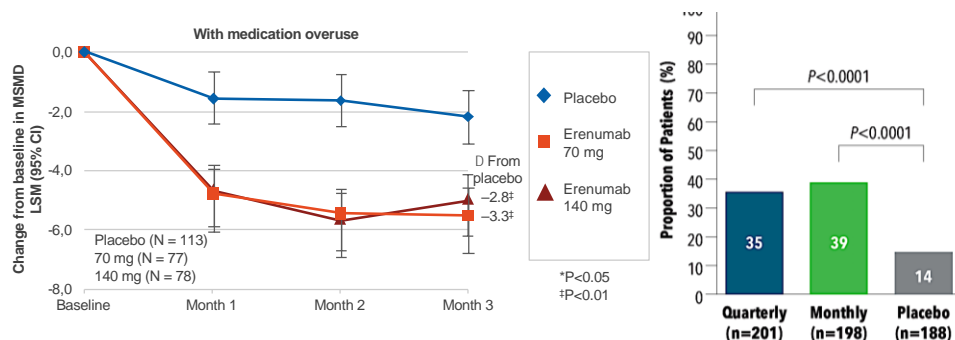
### History of depression and anxiety



### Episodic migraine non-responsive to two-to-four previous preventive treatments



### Patients with medication overuse headache



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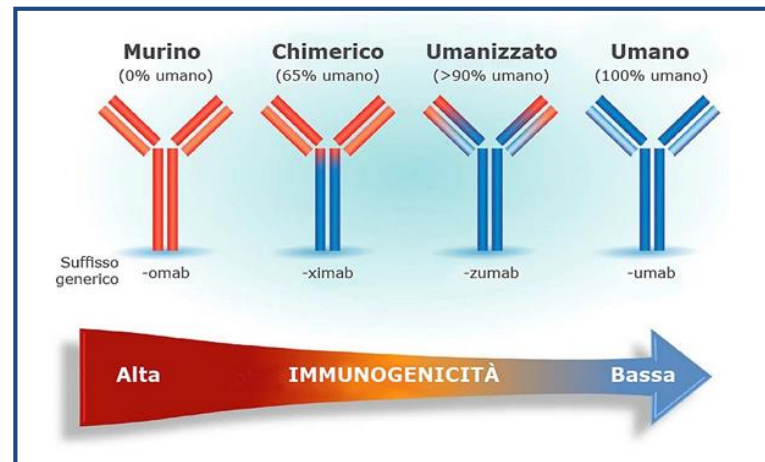
✓ *Manageability*

✓ *Safety*

✓ *Cost*

# CGRP-Ab: manageability

- ✓ Subcutaneous monthly administration (with the exception of Eptinezumab administered intravenously)
- ✓ Drug titration not needed
- ✓ The large size of these molecules prevents efficient filtration through the kidney glomerulus; therefore, PK is not influenced by renal or hepatic impairment
- ✓ Low immunogenicity



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# CGRP-Ab: safety

Event, n <sup>a</sup> (r)	Double-blind treatment phase, placebo (n = 153)	Double-blind treatment phase, erenumab 70 mg (n = 106)	OLE phase, erenumab 70 mg (n = 383)
All AEs	82 (350.1)	57 (326.2)	300 (140.6)
Common AEs			
Nasopharyngitis	12 (33.9)	6 (23.3)	66 (13.4)
Upper respiratory tract infection	3 (8.0)	3 (11.4)	42 (8.0)
Back pain	4 (10.8)	1 (3.8)	27 (5.0)
Influenza	5 (13.5)	1 (3.5)	27 (5.0)
Grade ≥2	37 (117.1)	23 (98.0)	216 (65.1)
Grade ≥3	2 (5.3)	3 (11.5)	47 (9.0)
Serious AEs	0	1 (3.8)	21 (3.8)
AEs leading to discontinuation of IP	2 (5.3)	3 (11.5)	14 (2.5)
Ischemic heart disease/cerebrovascular AEs of interest			
Arteriosclerosis	0	0	1 (0.2)
Myocardial ischemia	0	0	1 (0.2)
ECG T-wave inversion	1 (2.7)	0	1 (0.2)

Abbreviations: IP = investigational product; OLE = open-label extension; r = exposure-adjusted rate per 100 patient-years (n/e\*100).

<sup>a</sup> Number of patients reporting at least 1 occurrence of event.



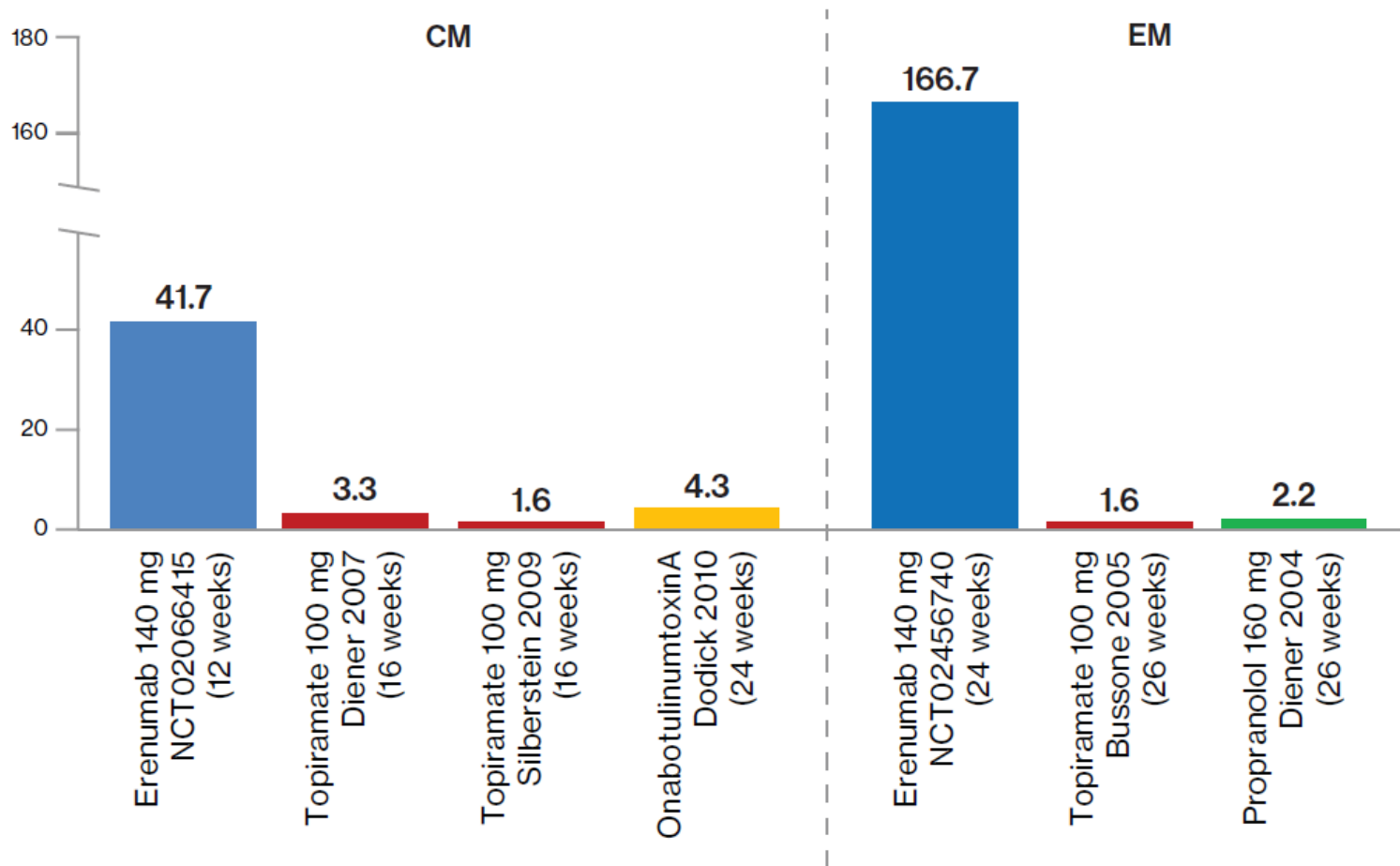
# CGRP-Ab: safety

	Chronic migraine				Episodic migraine		
	Erenumab 140 mg	Topiramate 100 mg	Onabotulinum- toxin A		Erenumab 140 mg	Topiramate 100 mg	Propranolol 160 mg
Data source :	Study 20120295	Silberstein et al 2007 & 2009	Diener et al 2007	Dodick et al 2010	Study 20120296	Bussone et al 2005	Diener et al 2004
<b>NNT -</b> 50% RR (95% CI)	6 (4,12)	13 (NE, NE)	4 (3, 10)	9 (6, 15)	6 (4, 9)	5 (4, 6)	5 (4, 10)
<b>NNH - % d/c</b> due to AEs (95% CI)	250 (NE, NE)	21 (NE, NE)	13 (NE, NE)	39 (23, 100)	1000* (NE, NE)	8 (6, 13)	11 (6, 72)

**NNT = Number Needed to Treat**  
**NNH = Number Needed to Harm**

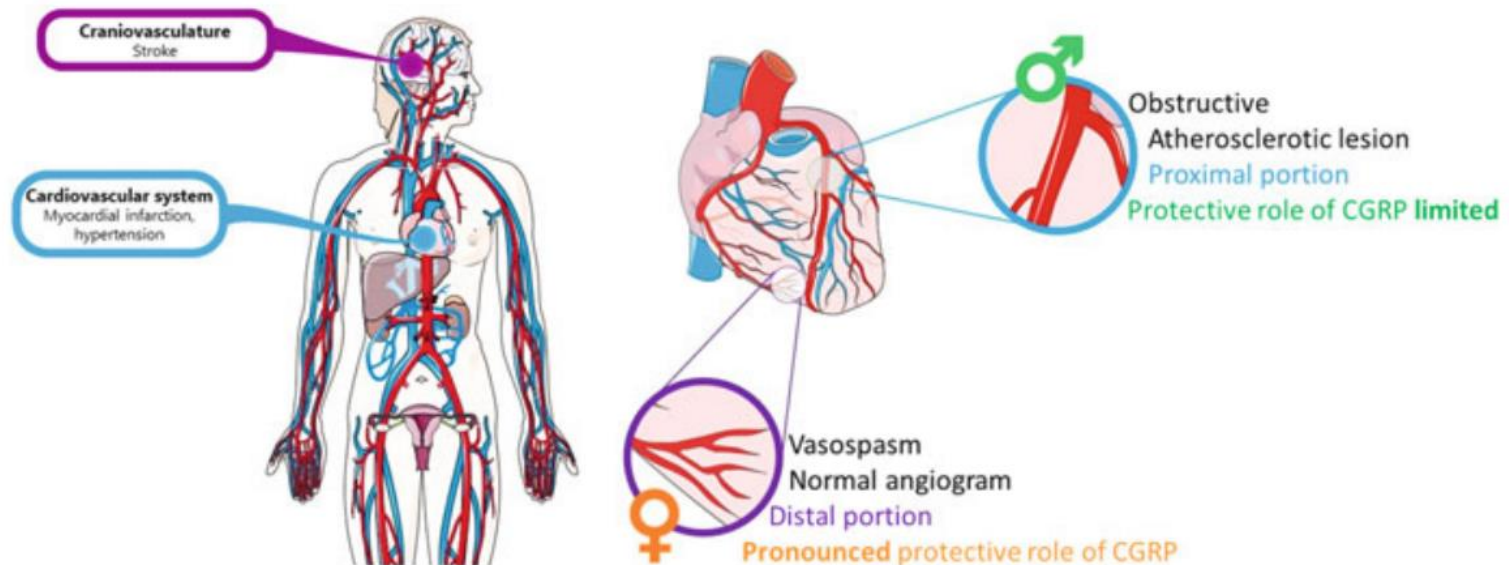
# CGRP-Ab: Likelihood of Being Helped or Harmed

$$LLH = NNH / NNT$$



# CGRP-Ab: safety

- CGRP is a vasodilatory mediator released during ischemia
- Other vasodilatory mediators: substance P, neurokinins and nitric oxide
- Theoretical risk in patients with cardiovascular conditions

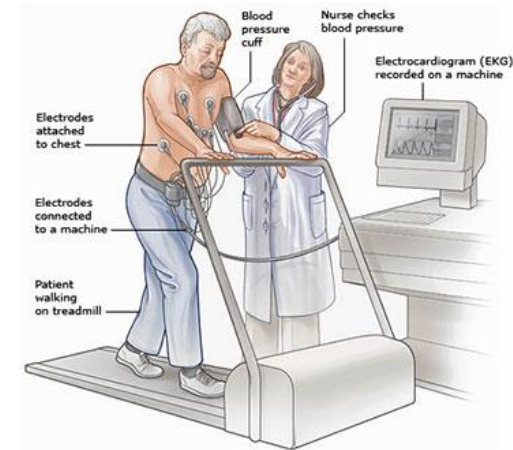


# CGRP-Ab: safety

## Research Submission

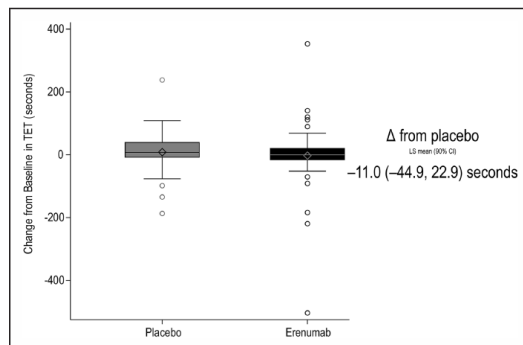
### A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Effect of Erenumab on Exercise Time During a Treadmill Test in Patients With Stable Angina

Christophe Depre, MD, PhD; Lubomir Antalík, MUDr; Amaal Starling, MD; Michael Koren, MD; Osaro Eisele, MD, MPH; Robert A. Lenz, MD, PhD; Daniel D. Mikol, MD, PhD

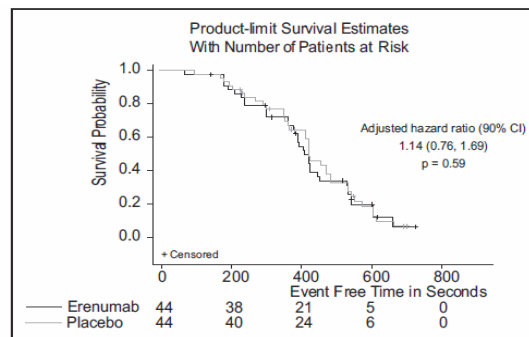


## No significant differences in:

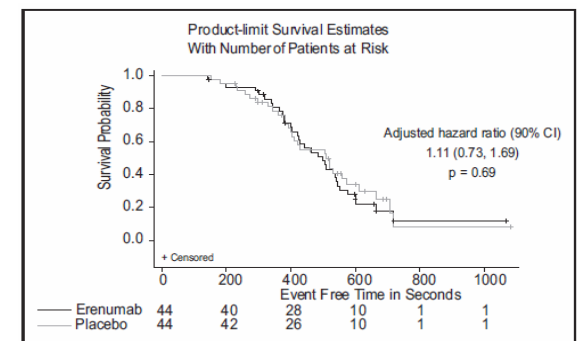
### Total exercise time (TET)



### Time to exercise-induced angina



### ST depression



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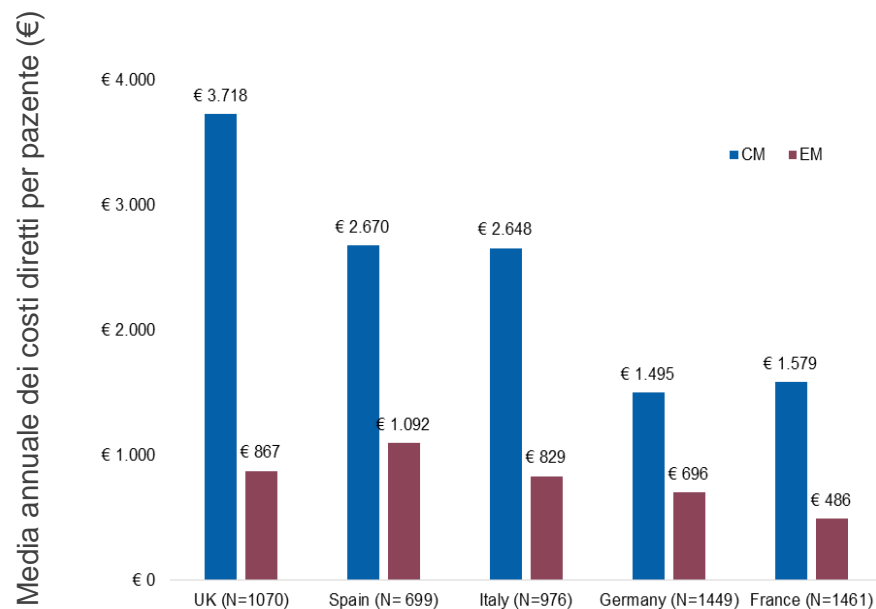
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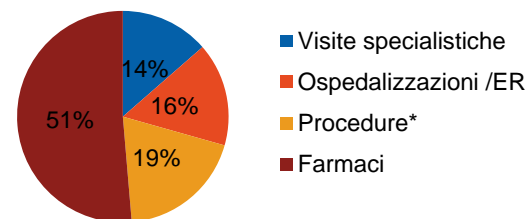
✓ *Cost*

# CGRP-Ab: cost

## Costo medio diretto annuo per paziente (€): IBMS-I study

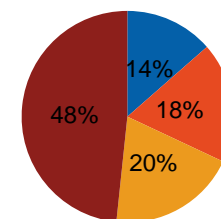


## Voci di costo diretto - EM



829 €

## Voci di costo diretto - CM



2648 €

Le perdite di produttività possono essere dovute all' **assenteismo**, assenza da lavoro e/o al **presenteismo**, ovvero presenza a lavoro con produttività ridotta



Studio Italiano su 92 pazienti con emicrania: 51 con emicrania cronica 21,3 giorni in media di emicrania/mese; 41 pazienti con emicrania episodica 4, giorni in media di emicrania mese; indice MIDAS medio 61,5

## CGRP-Ab: cost

- Compared with use of supportive care, erenumab treatment will reduce the direct and indirect costs associated with migraine and increase QALYs for patients who have previously experienced treatment failure with at least 1 preventive migraine treatment.

		Erenumab	SC	Incremental
Base Case Analysis (over 10 years)	Mean treatment duration (years)	2.01	—	—
	Mean migraine days	1805	1949	−144
	Mean discounted QALYs	5.1437	4.9588	0.1849
	Mean discounted migraine day-related costs	\$121,407	\$129,889	−\$8482
Medical Resource Use Costs	Hospitalizations	\$24,779	\$26,684	−\$1904
	Emergency room visits	\$12,061	\$12,988	−\$927
	Physician visits	\$2443	\$2631	−\$188
Indirect Costs	Presenteeism	\$45,025	\$48,382	−\$3357
	Absenteeism	\$31,339	\$32,997	−\$1658

SC indicates supportive care; QALY, quality-adjusted life-year.

# Grazie per l'attenzione

