Associazione Neurologia Emergenza Urgenza

VII CONGRESSO NAZIONALE ANEU

CONTROVERSIE IN NEUROLOGIA D'EMERGENZA E URGENZA

TERAPIE AVANZATE DELL'EMICRANIA: COSA È UTILE SAPERE NELL'AMBITO DELL'EMERGENZA

F. Vernieri, Roma

Unità Cefalee e Neurosonologia, Neurologia, Fondazione Policlinico Campus Bio-Medico di Roma
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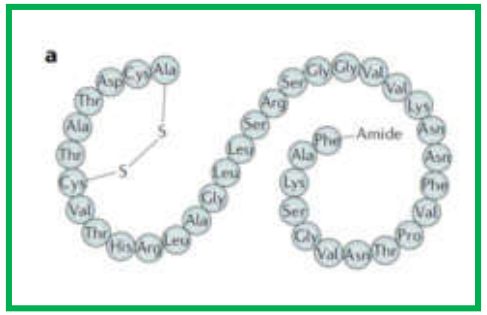
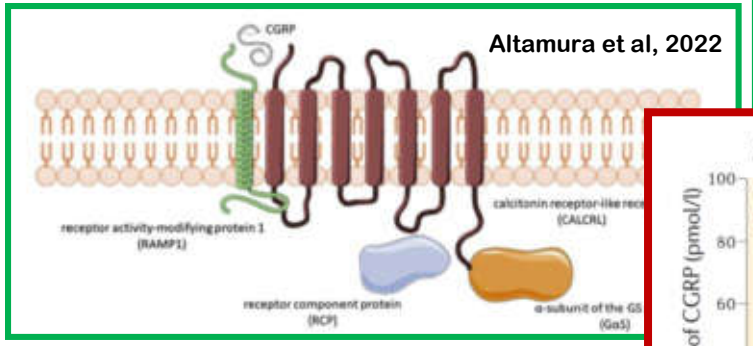
Fabrizio Vernieri - disclosures

- **Allergan/Abbvie** (consulenze scientifiche, Advisory Board, partecipazione a trial)
- **Angelini** (consulenze scientifiche, relazioni a convegni/corsi)
- **Lilly** (consulenze scientifiche, Advisory Board, relazioni a convegni/corsi, costruzione e partecipazione a trial)
- **Lundbeck** (Advisory Board, partecipazione a trial)
- **Novartis** (consulenze scientifiche, Advisory Board, relazioni a convegni/corsi, partecipazione a trial)
- **Teva** (consulenze scientifiche, Advisory Board, relazioni a convegni/corsi, partecipazione a trial)

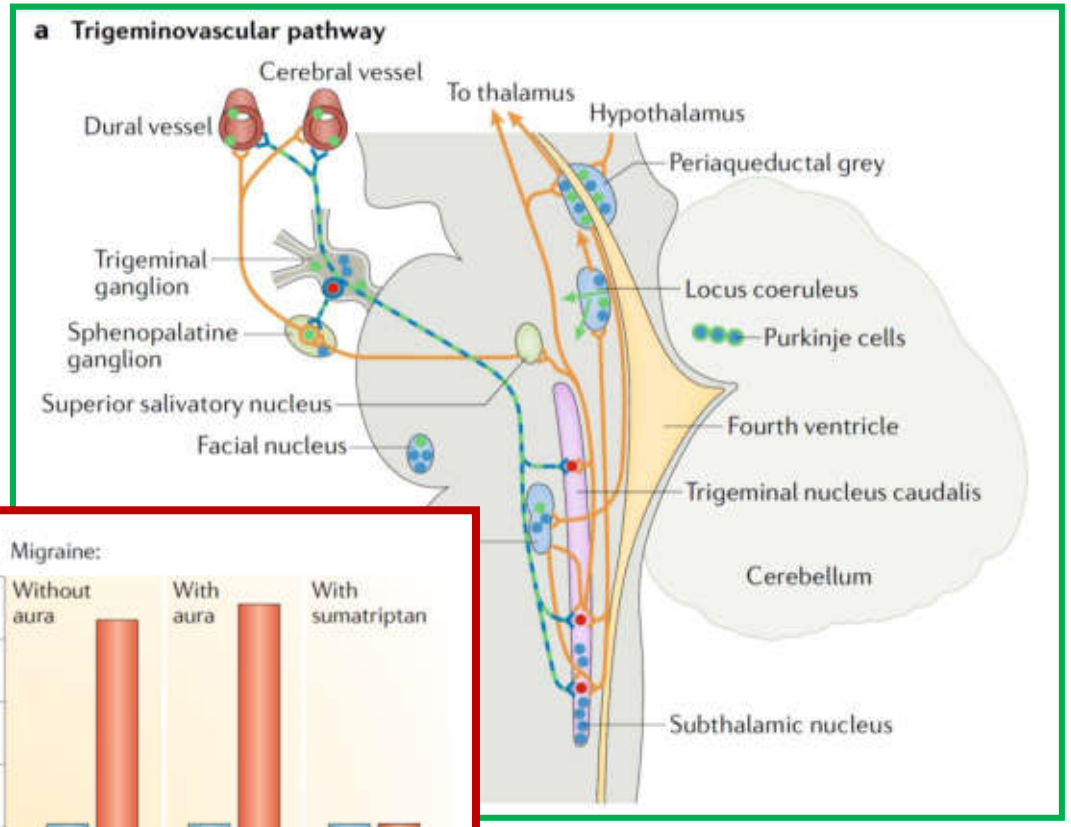
Il CGRP (calcitonin gene-related peptide) e l'attacco emicranico

Edvinsson et al, 2018

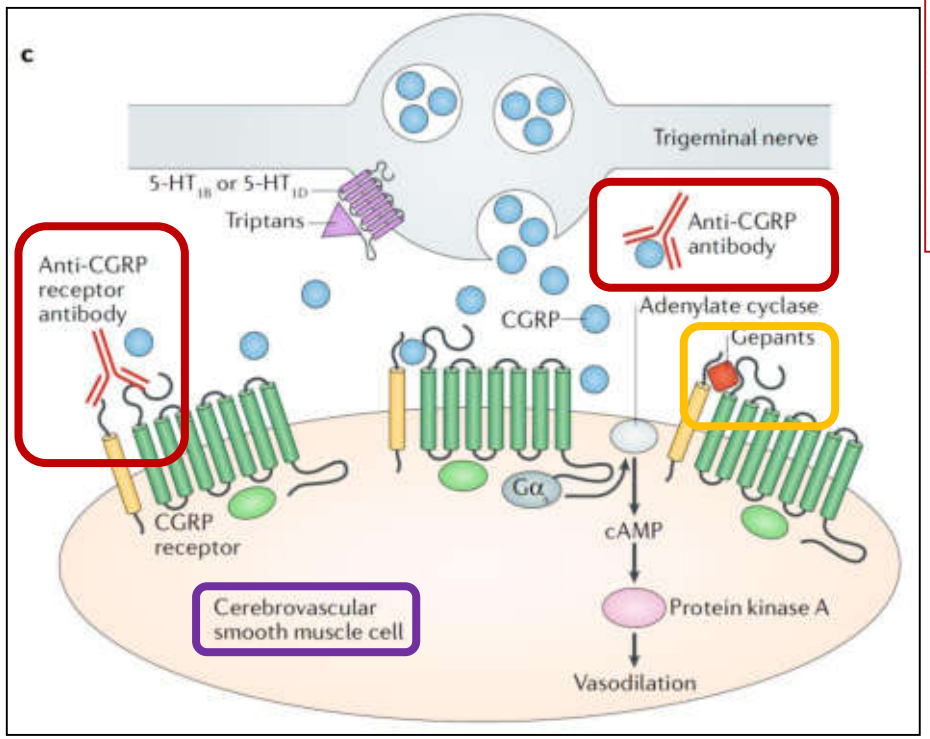


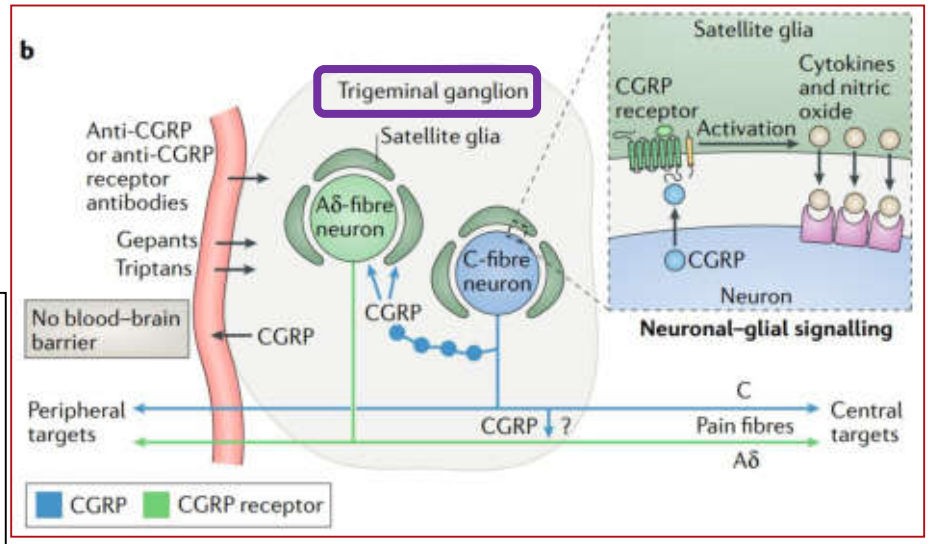


Altamura et al, 2022



CGRP e anti-CGRP (ligando e recettore)

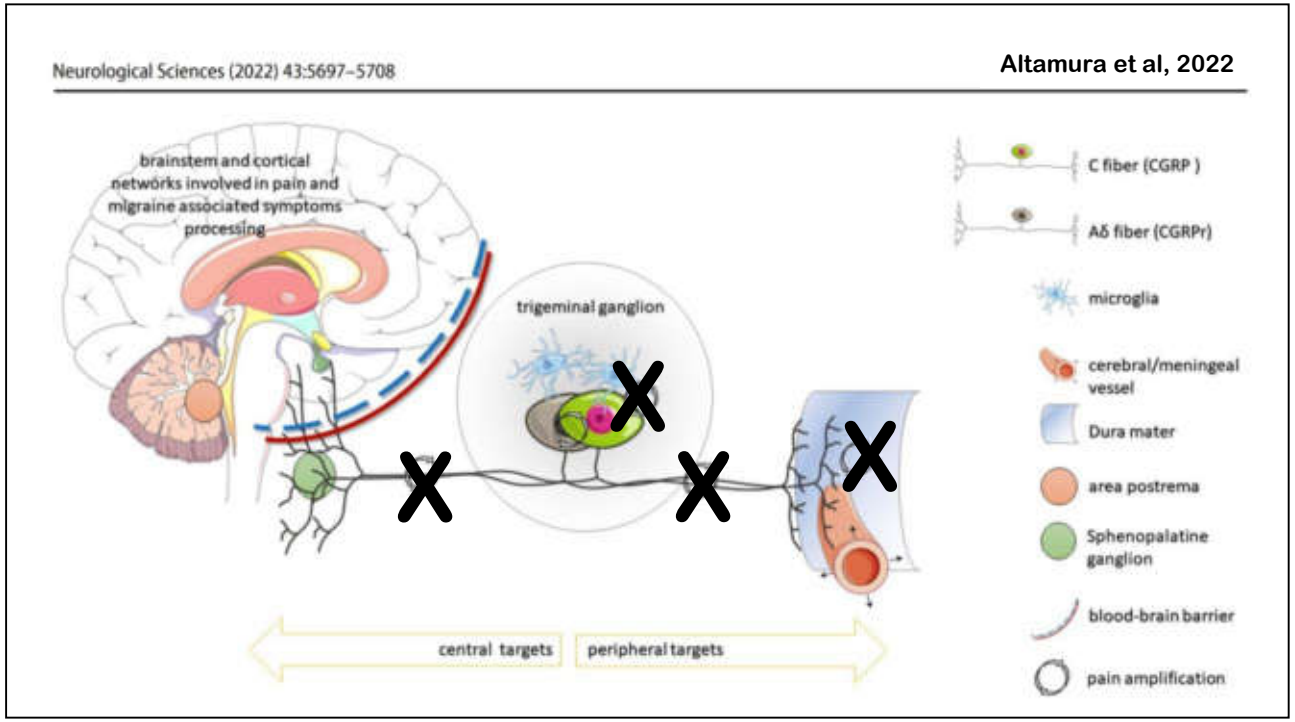


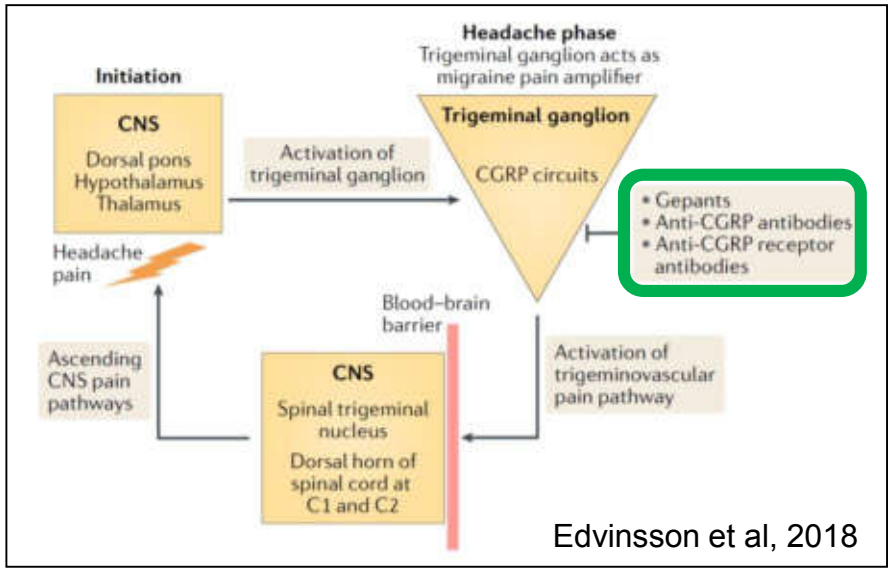


Edvinsson et al.

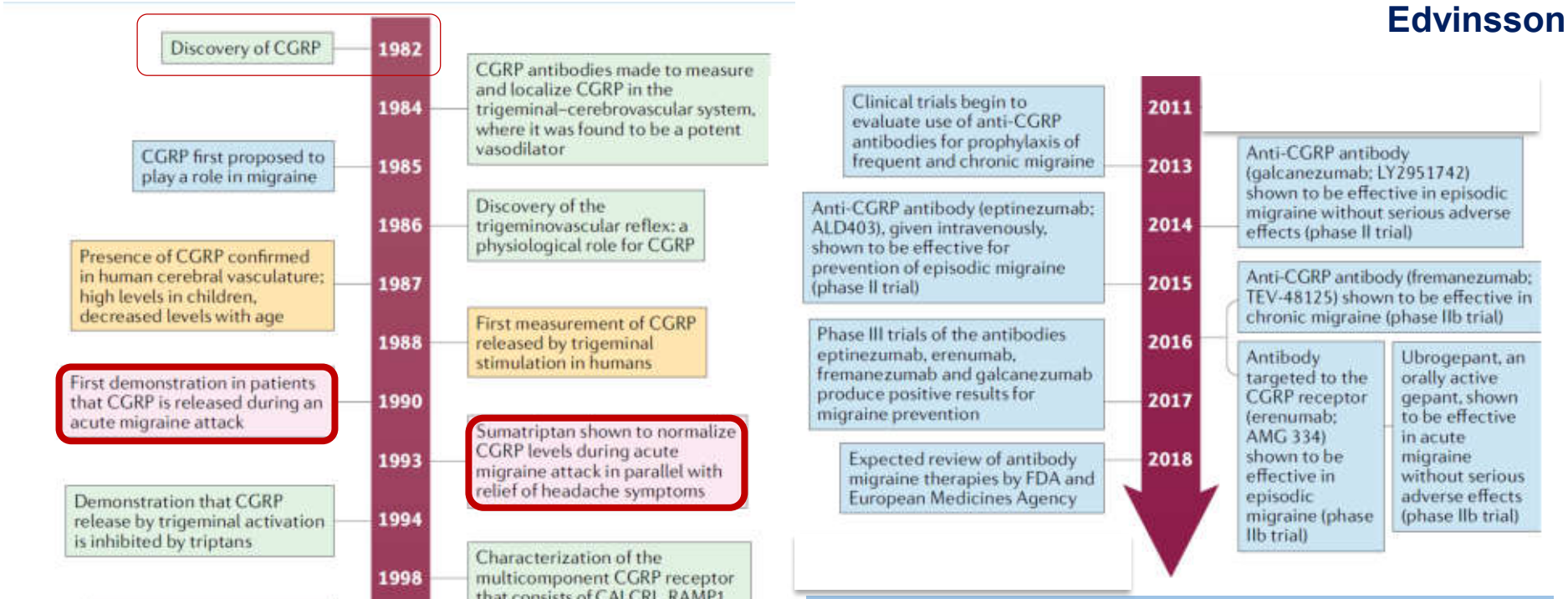
CGRP as the target of new migraine therapies - successful translation from bench to clinic

Nat Rev Neurol 2018


Neurological Sciences (2022) 43:5697–5708
Altamura et al, 2022
brainstem and cortical networks involved in pain and migraine associated symptoms processing
trigeminal ganglion
central targets
peripheral targets
C fiber (CGRP)
Aδ fiber (CGRPr)
microglia
cerebral/meningeal vessel
Dura mater
area postrema
Sphenopalatine ganglion
blood-brain barrier
pain amplification


Initiation
CNS
Dorsal pons
Hypothalamus
Thalamus
Activation of trigeminal ganglion
Headache phase
Trigeminal ganglion acts as migraine pain amplifier
Trigeminal ganglion
CGRP circuits
• Gepants
• Anti-CGRP antibodies
• Anti-CGRP receptor antibodies
Headache pain
Blood–brain barrier
Ascending CNS pain pathways
CNS
Spinal trigeminal nucleus
Dorsal horn of spinal cord at C1 and C2
Activation of trigeminovascular pain pathway
Edvinsson et al, 2018

Edvinsson et al, 2018



- **2018** – Approval of erenumab (May), fremanezumab, galcanezumab (September)
- 2019 - Phase III trials ubrogepant and rimegepant
- 2019 - Approval of ubrogepant (acute)
- 2020 - Approval of eptinezumab and rimegepant (acute)
- 2021 - phase III trials and approval of atogepant and rimegepant (both preventive); phase II trials zavegepant

- **2019-today: Real Life mAbs studies…**

Anticorpi monoclonali (mAbs) anti-CGRP

	Erenumab	Fremanezumab	Galcanezumab	Eptinezumab
Target	**CGRP recettore**	**CGRP ligando**	**CGRP ligando**	**CGRP ligando**
Dosaggio	**70 - 140 mg ogni 4 settimane**	**225 mg mese o 675 mg ogni 3 mesi**	**120 mg mese Loading dose 240 mg**	**100mg in 100 mL SF ogni 3 mesi**
Somministrazione	**s.c.**	**s.c.**	**s.c.**	**i.v. (infusione di 30')**
Autoiniettore	si	no (in italia)	si	N/A
$t_{1/2}$	21 gg	32 gg	~25–30 gg	~27 gg
Sottotipo IgG	IgG2	IgG2a	IgG4	IgG1
Sequences	Human (100%)	Fully humanized (>95%)	Humanized (>90%)	Humanized (>90%)
Tempo x massima concentrazione sierica (Tmax)	6 giorni	5-7 giorni	5 giorni	30 minuti* 3 ore**

Bigal et al, 2015 (modificata); Baker, 2020; El-Hassany et al. 2022***

mAbs anti-CGRP: Early onset di efficacia

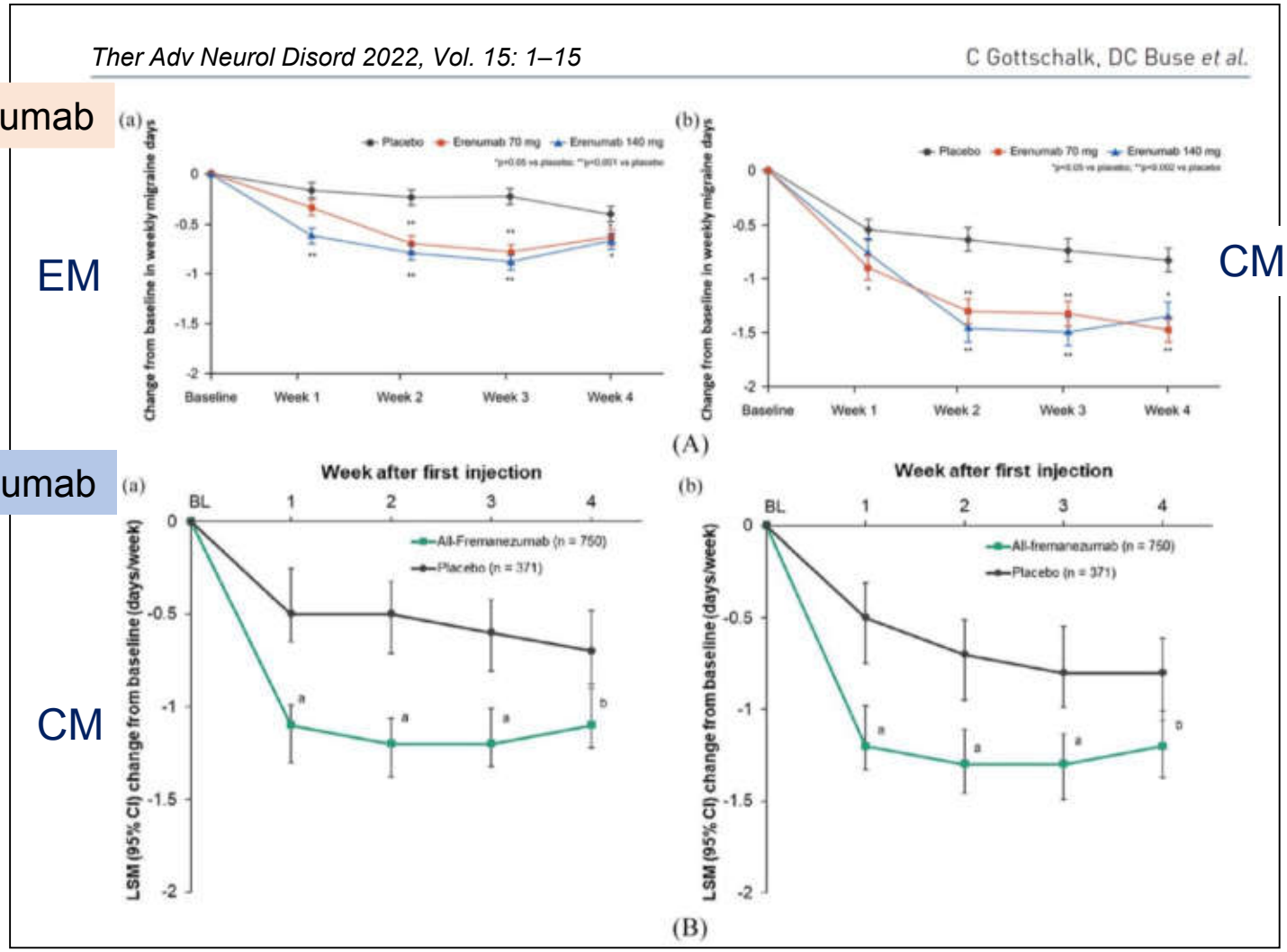
Erenumab

EM

CM

Fremanezumab

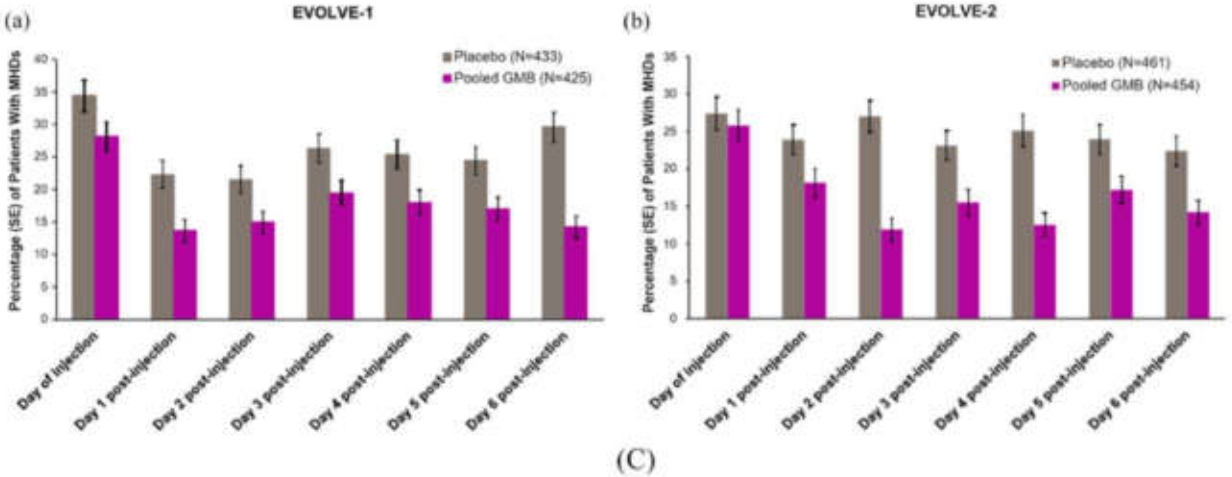
CM



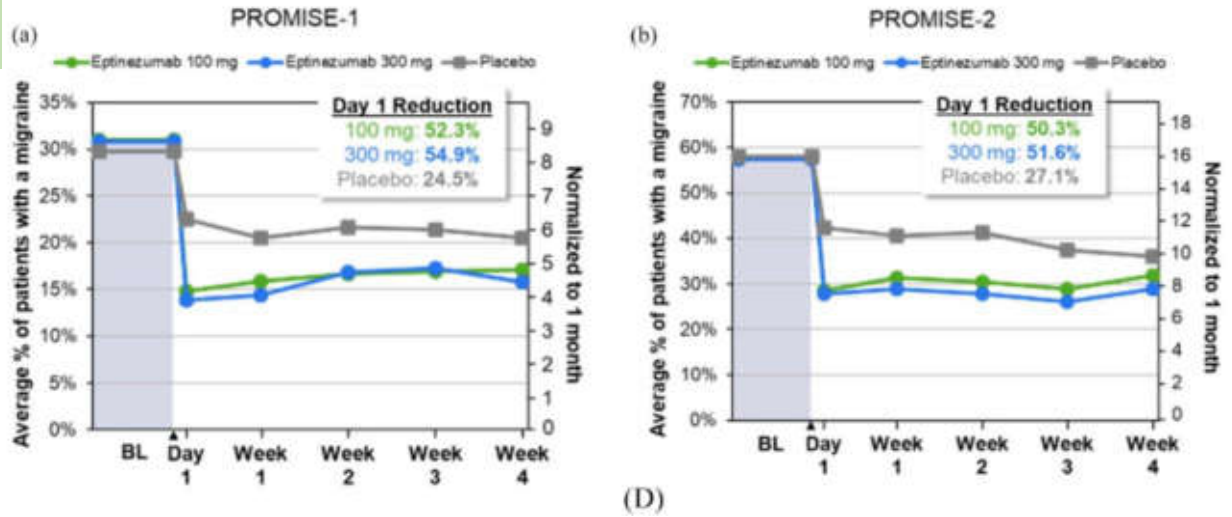
mAbs anti-CGRP: Early onset di efficacia

Galcanezumab

EM



Eptinezumab

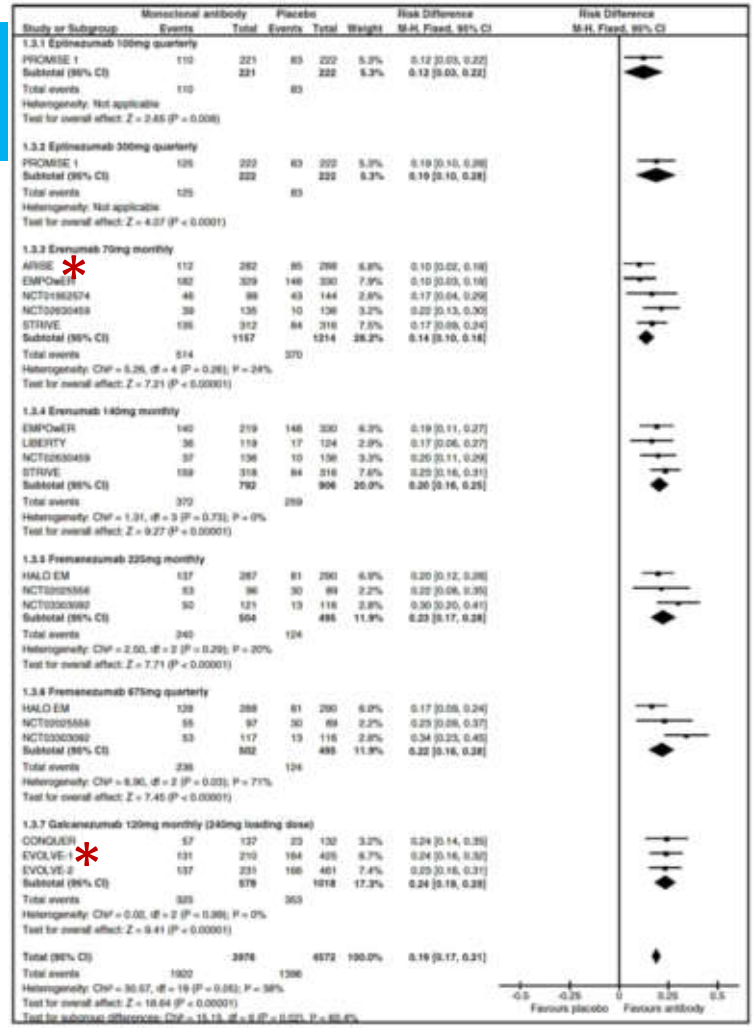


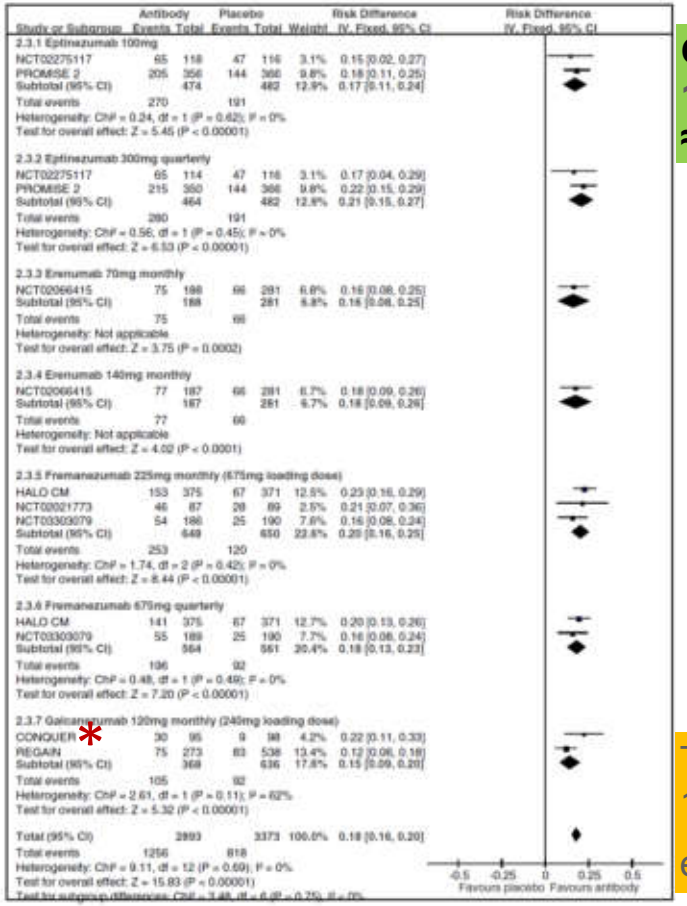
C Gottschalk, DC Buse et al., 2022; Dodick et al., 2020

European Headache Federation mAbs anti-CGRP Guideline

EM
15 studi
≈ 4000 pts

Forest plots of comparison: mAbs vs placebo
Episodic (L) and Chronic (R) migraine
At least 50% responder rate



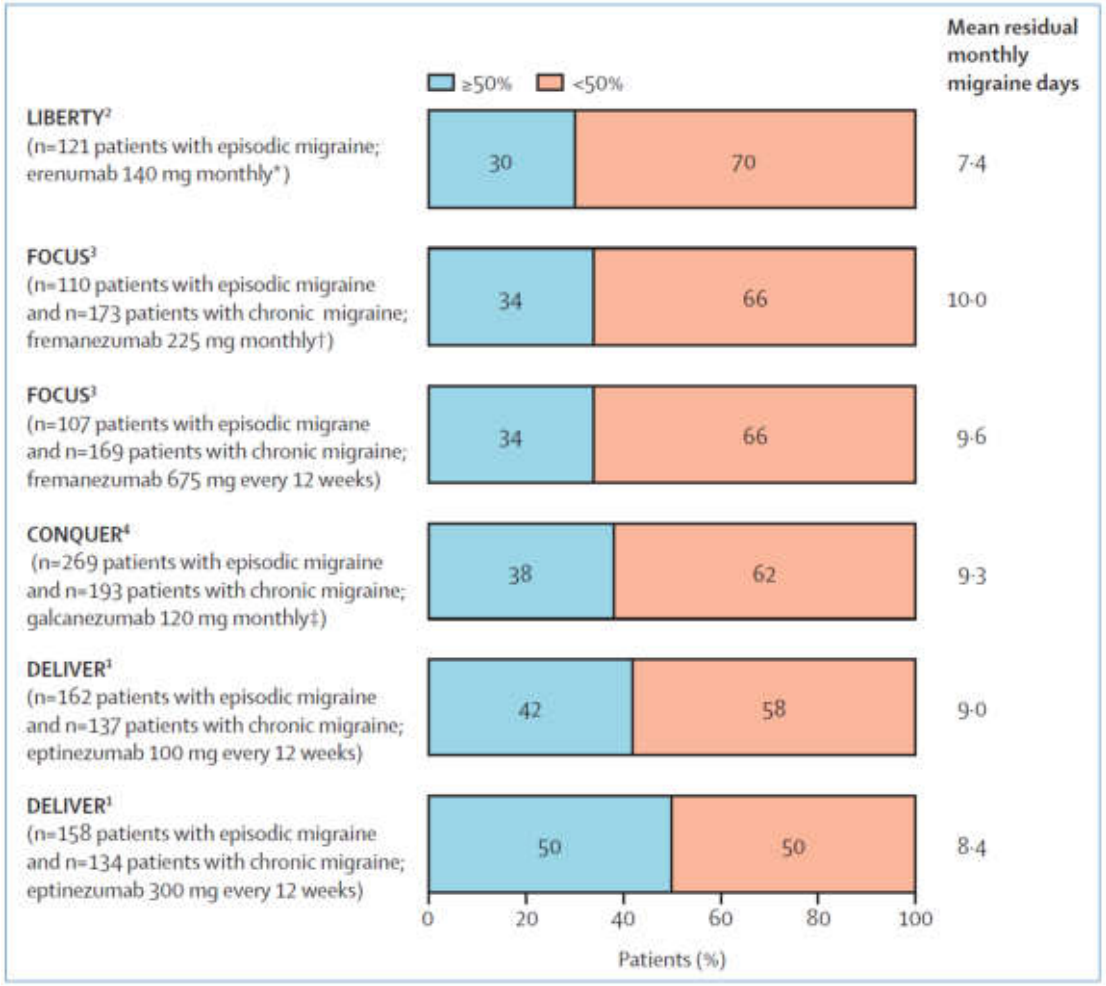


CM
10 studi
≈ 3000 pts

Tutti durata 12 settimane, eccetto*

Sacco et al. The Journal of Headache and Pain, June 2022

RCTs e studi Real Life in pazienti con EM e CM resistente

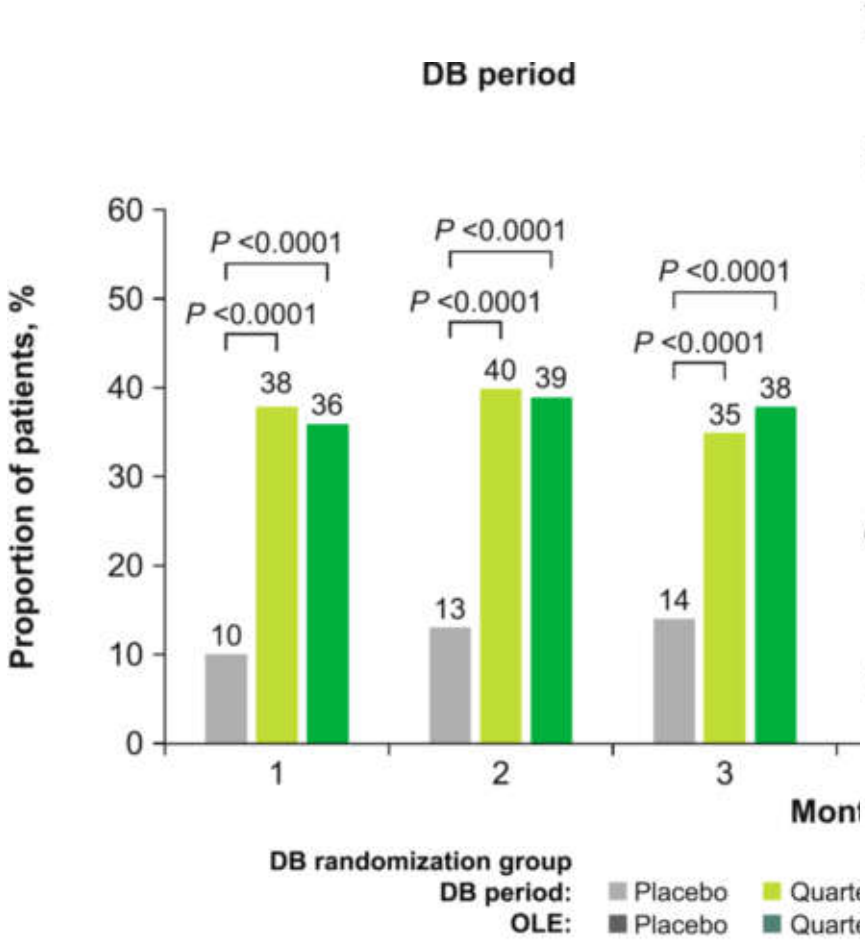


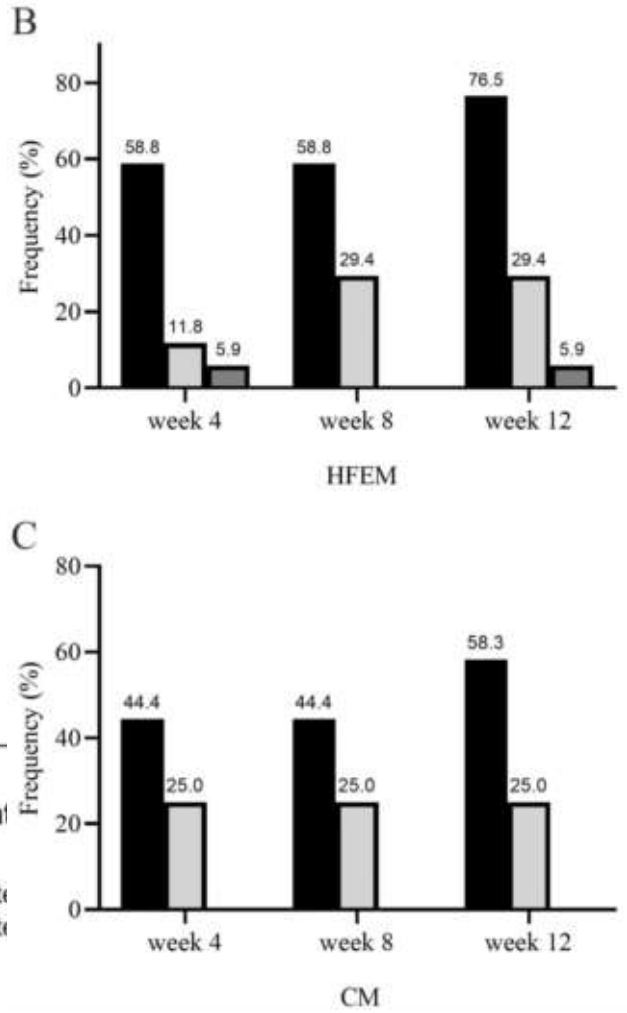
Ornello and Sacco, 2022

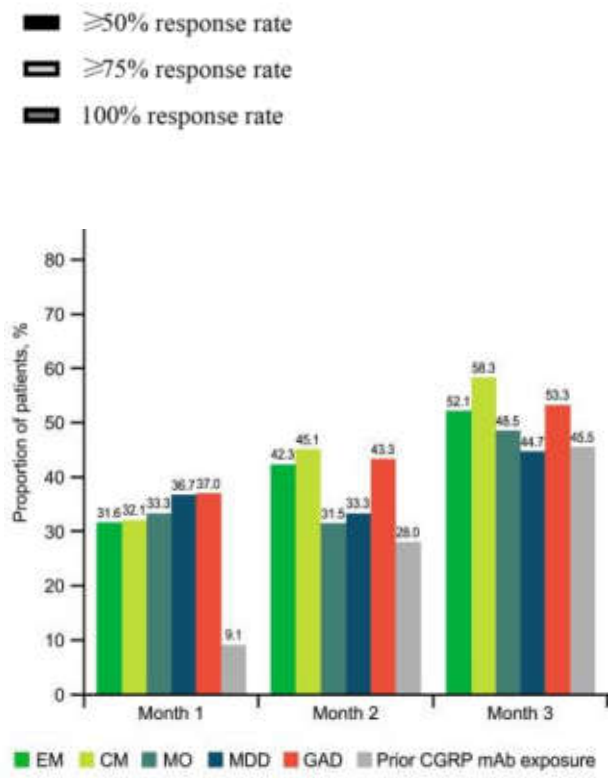
Studi Real Life	Studi osservazionali RL Data in corso (con aziende)
EARLY 1 3 mesi 50%RR: 59,4% in EM, 55,5% in CM (Barbanti et al. 2021)	APPRAISE, NEW-ERA
FRIEND 3 mesi 50%RR: 76,5% in EM, 58,3% in CM (Barbanti et al. 2022):	PEARL (analisi ad interim settembre 2022)
GARLIT 6 mesi: 50%RR: 76,5% in EM, 63,5% in CM (Vernieri et al. 2021)	TRIUMPH, REALITY

In phase II and phase III trials on CGRP-mAbs, 46.3% of individuals with migraine were treatment naive or without a previous history of drug failure *(Sacco et al. 2022)*

Studi Fremanezumab: RCTs vs Real Life







1. Ashina et al. FOCUS 6m, 2021; *2. Barbanti et al. FRIEND 2022;* *3. Driessen et al. 2022 (modif.)*

Erenumab: efficacia in RCTs e Real life

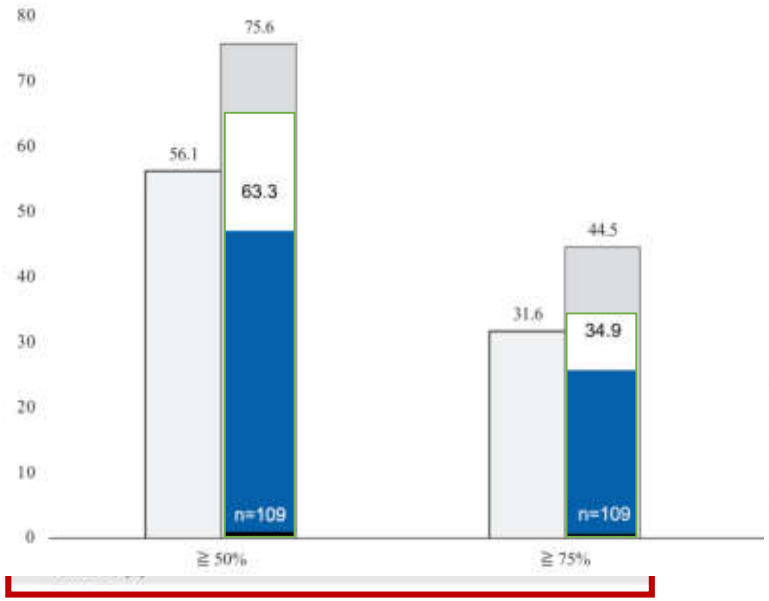
Long-term (48 weeks) effectiveness, safety, and tolerability of erenumab in the prevention of high-frequency episodic and chronic migraine in a real world: Results of the EARLY 2 study

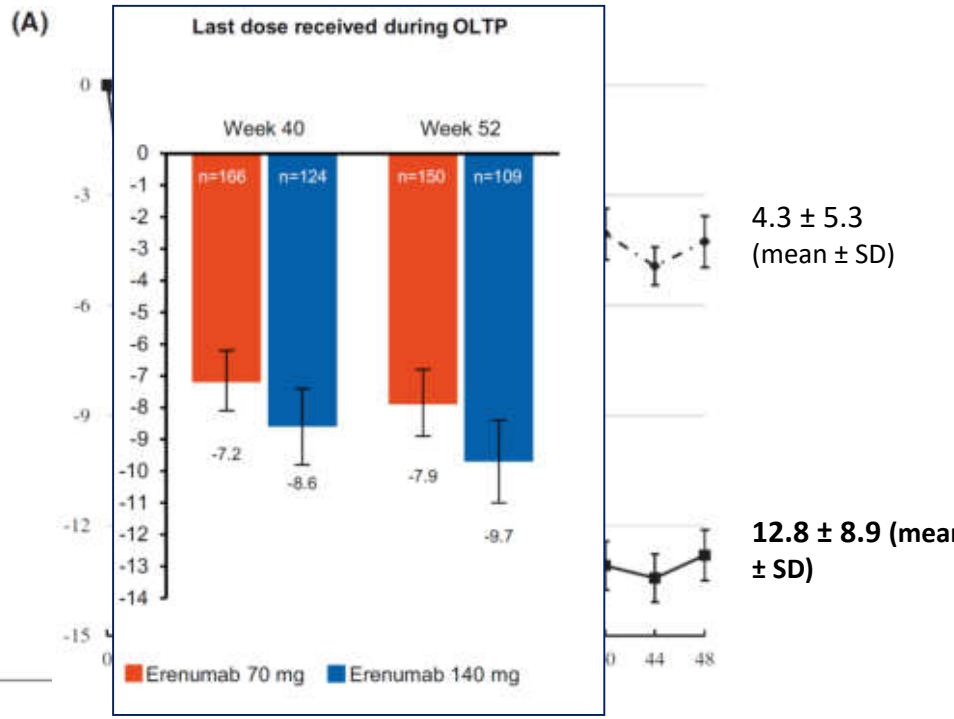
15 Centri Italiani, almeno 3 fallimenti terapeutici

Barbanti et al. Headache 2021

TABLE 1 Patient characteristics (*N* = 242)

	HFEM (*n* = 60)	CM (*n* = 182)
Female, n (%)	38 (63.3)	134 (73.6)





4.3 ± 5.3 (mean ± SD)

12.8 ± 8.9 (mean ± SD)

Ashina et al. Erenumab in CM, 2022

Erenumab: sicurezza e tollerabilità, confronto RCTs e RL

Exposure-adjusted patient incidence rates of TEAEs

≥1 TF	Erenumab 140 mg *n*(%)/*e*[*r*] (*N* = 174)[a]	Erenumab 70/140 mg *n*(%)/*e*[*r*] (*N* = 419)[a]
Any AE	116(66.7)/65.5[177.0]	288(68.7)/203.0[141.9]
Grade ≥2	85(48.9)/92.1[92.3]	238(56.8)/262.3[90.7]
Grade ≥3	6(3.4)/142.3[4.2]	28(6.7)/437.3[6.4]
Grade ≥4	0(0.0)/145.1[0.0]	0(0.0)/453.8[0.0]
TEAEs	32(18.4)/124.1[25.8]	90(21.5)/378.0[23.8]
SAEs	9(5.2)/141.1[6.4]	21(5.0)/442.3[4.7]
Discontinuation[b]	5(2.9)/143.1[3.5]	11(2.6)/450.0[2.4]
Fatal AEs	0(0.0)/145.1[0.0]	0(0.0)/453.8[0.0]

Long-term Erenumab in CM. Ashina et al. Headache 2022

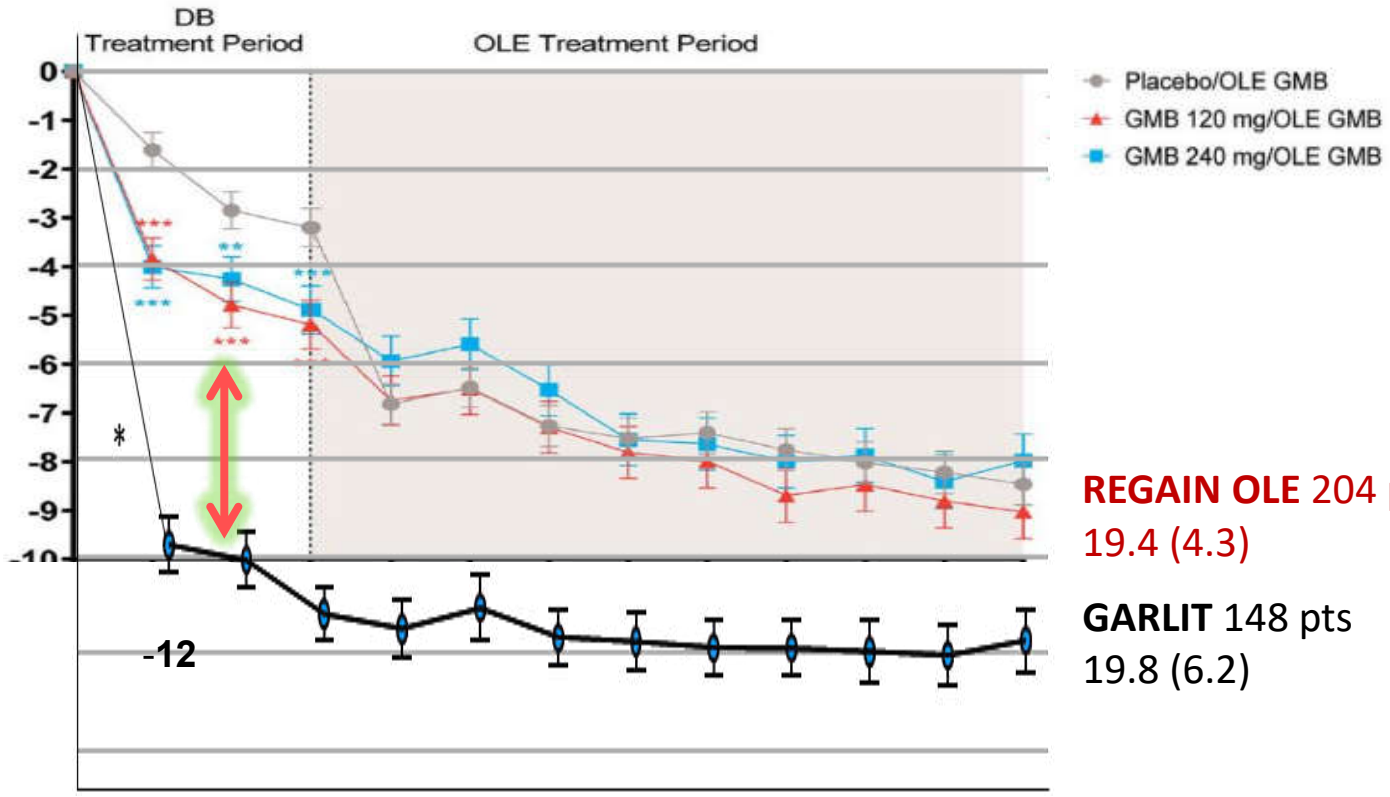
TABLE 2 Treatment-emergent adverse events (TEAEs) occurring at Weeks 4–48

	High-frequency episodic migraine	Chronic migraine
Patients, *n*	60	182
Patients with ≥1 TEAE	10 (16.7)	35 (19.2)
Serious TEAEs	1 (1.7)	2 (1.1)
Discontinuations	1 (0.6)	5 (1.6)
Constipation	6 (10)	19 (10.4)
Injection site erythema	3 (5)	5 (2.7)
Back pain	1 (1.7)	4 (2.2)
Flu	–	4 (2.2)
Paresthesias	–	3 (1.7)
Joint pain	1 (1.7)	2 (1.1)
Abdominal pain	1 (1.7)	2 (1.1)
Dyspepsia	1 (1.7)	1 (0.5)
Non-ST segment elevation myocardial infarction	–	2 (1.1)
Itch	–	1 (0.5)
Raynaud's phenomenon	–	1 (0.5)
Vomiting	–	1 (0.5)
Nervousness	–	1 (0.5)

Note: Data are presented as *n* (%).

Barbanti et al. Headache 2021

Galcanezumab: efficacia RCTs vs Real life (MMDs)
Lo studio GARLIT (16 centri cefalee italiani)

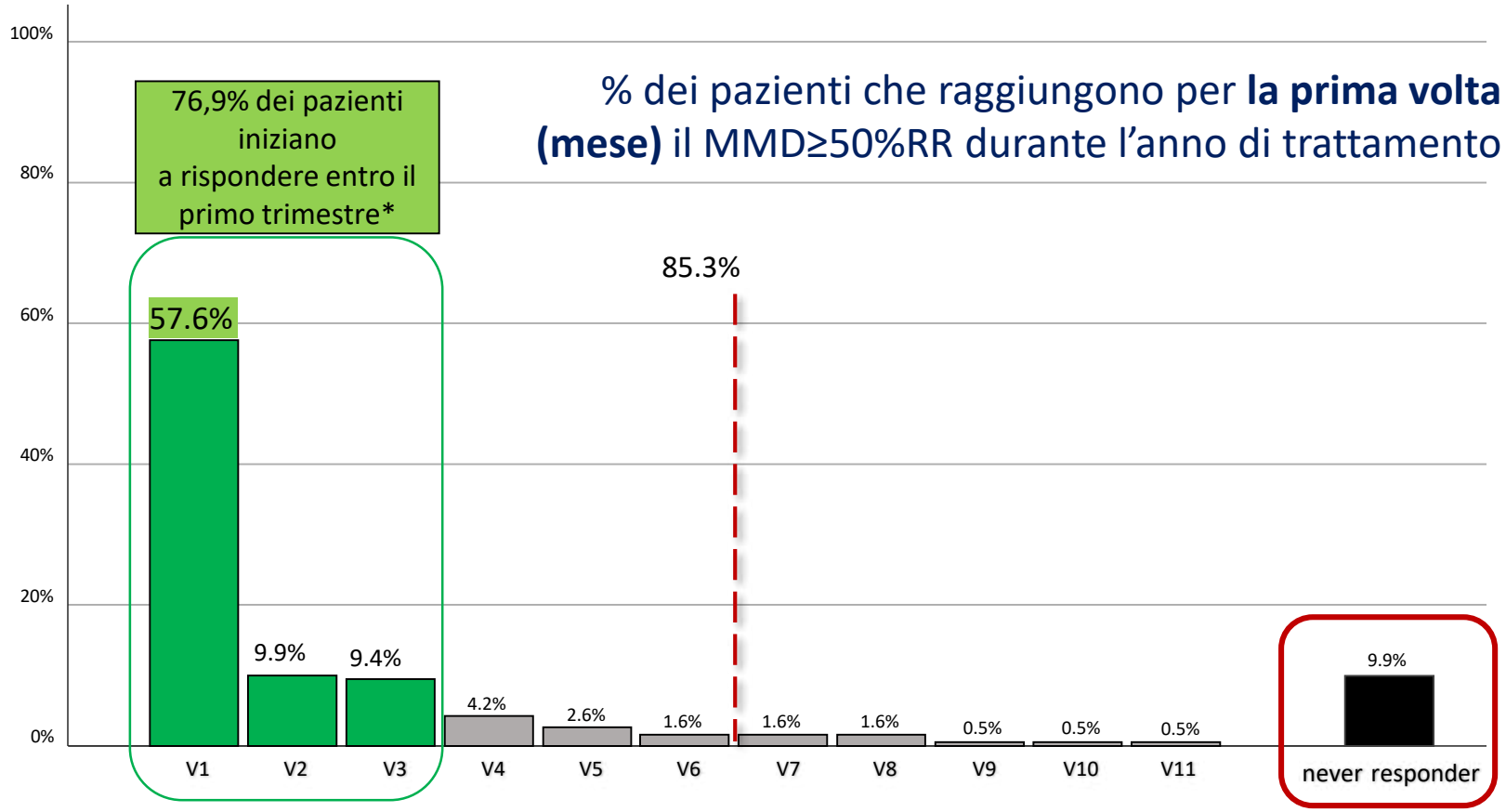


REGAIN OLE 204 pts
19.4 (4.3)

GARLIT 148 pts
19.8 (6.2)

Modified from Vernieri & the GARLIT STUDY GROUP, Eur J Neurol in press and Pozo-Rosich et al. Curr Med Res Opin, 2022

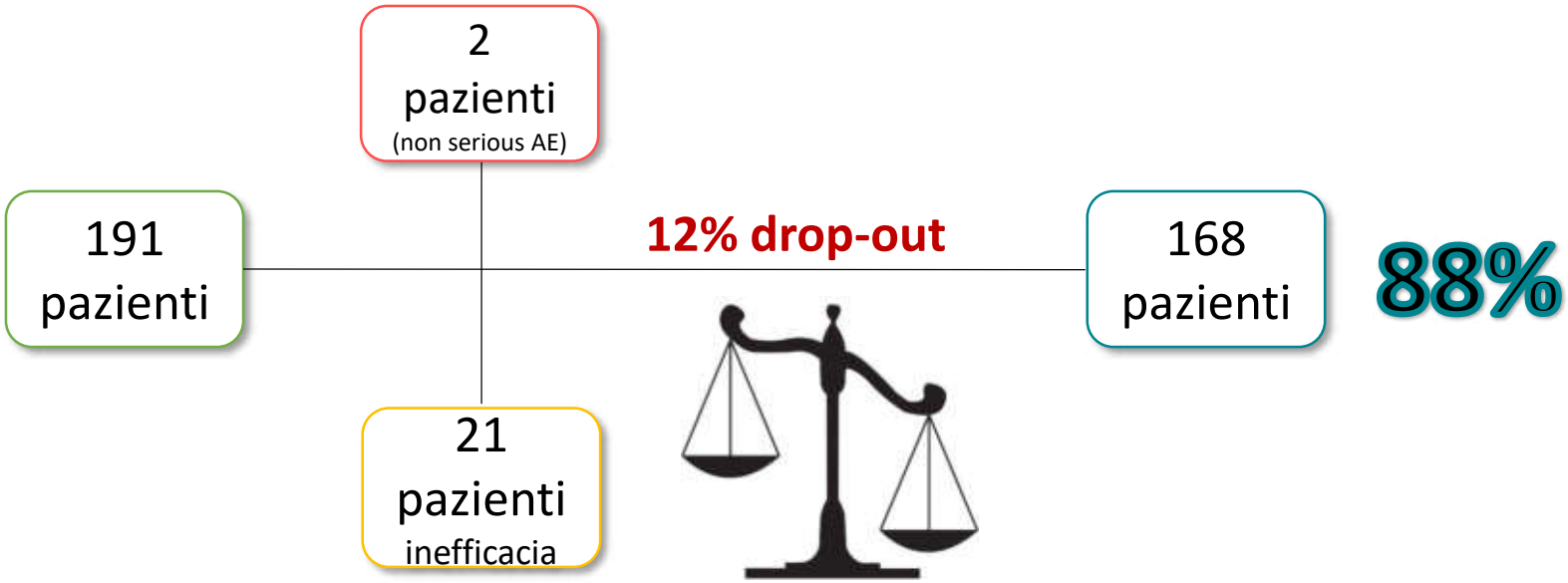
Valutazione dell'efficacia: GARLIT onset risposta 50% RR



Vernieri & the GARLIT study GROUP, Eur J Neurol in press

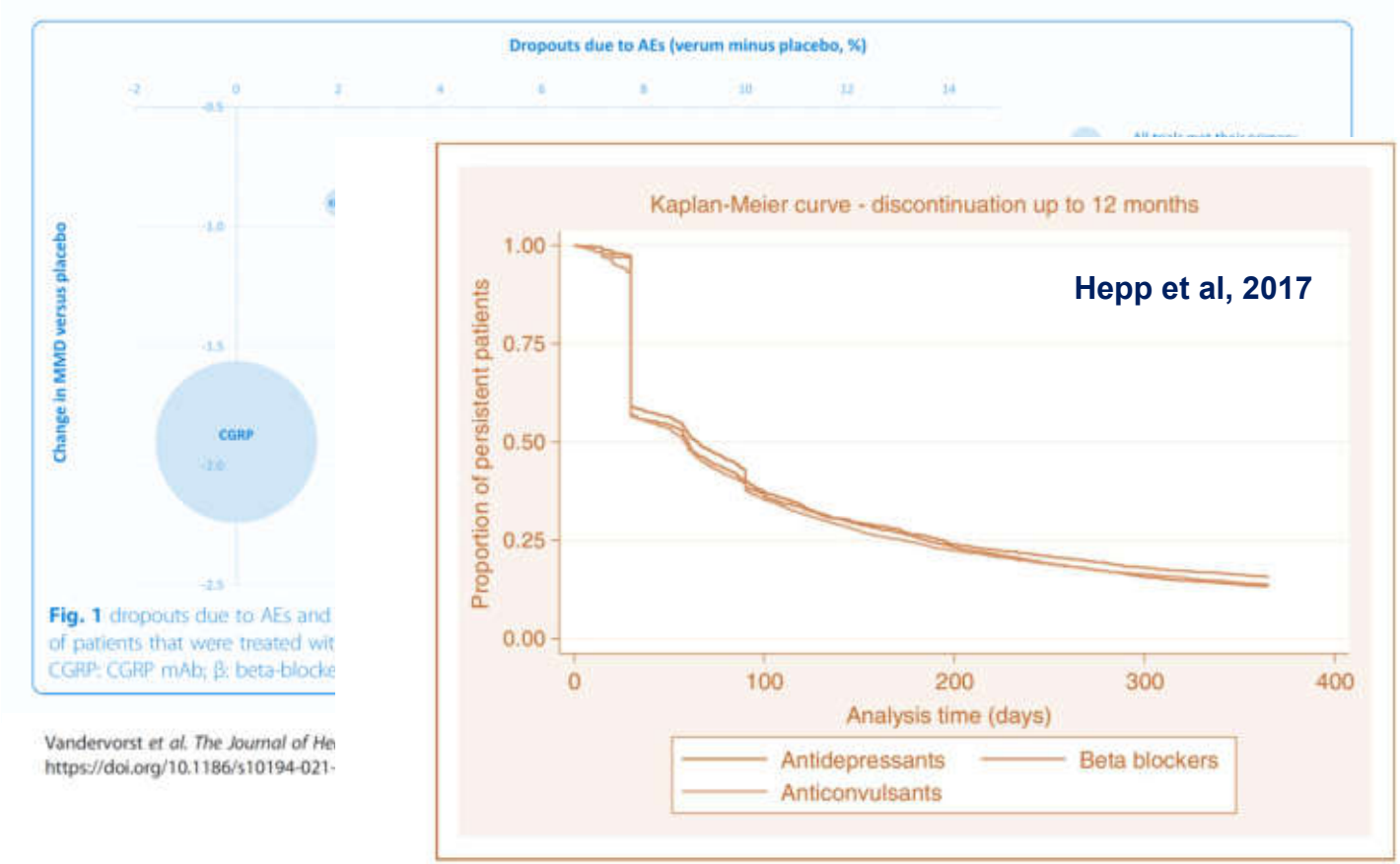
*Sono gli stessi pazienti che hanno maggiore risposta sostenuta nell'anno di trattamento

The GARLIT one-year study: discontinuazione



Vernieri & the GARLIT STUDY GROUP 2022, Eur J Neurol in press

Discontinuazione: confronto indiretto con terapie orali



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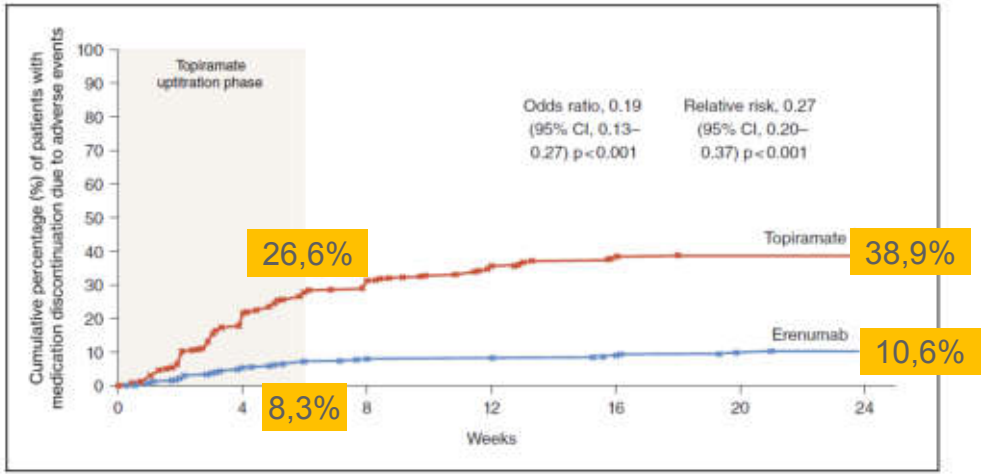

Figure 2. Cumulative percentage of patients who discontinued medication due to adverse events. Shading indicates the 6-week topiramate/placebo up-titration phase.

Table 2. Efficacy over months 4 to 6 of the double-blind treatment phase and patient reported outcomes (FAS).

	Erenumab (n = 388)	Topiramate (n = 388)	OR/RR or difference (95% CI)	p-value
Secondary efficacy endpoint				
≥50% reduction from baseline in migraine days per month	215 (55.4%)	121 (31.2%)	OR 2.76 (2.06–3.71) RR 1.78 (1.50–2.11)	<0.001 <0.001
Exploratory endpoints				
Monthly migraine days*	−5.86 (0.24)	−4.02 (0.24)	−1.84 (−2.43 to −1.25)	<0.001
HIT-6 (36–78)†	−10.9 (0.4)	−7.7 (0.4)	−3.2 (−4.3 to −2.1)	<0.001
SF-36v2 (0–100)‡				
Physical component	5.5 (0.4)	3.6 (0.4)	1.9 (1.0–2.8)	<0.001
Mental component	1.0 (0.5)	−1.2 (0.5)	2.2 (1.0–3.3)	<0.001

Original Article

Cephalalgia
International Headache Society

Cephalalgia
2022, Vol. 42(2) 108–118

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Erenumab versus topiramate for the prevention of migraine – a randomised, double-blind, active-controlled phase 4 trial

Uwe Reuter[1,2], Marc Ehrlich[3], Astrid Gendolla[4], Axel Heinze[5], Jan Klatt[6], Shihua Wen[7], Peggy Hours-Zesiger[6], Jacqueline Nickisch[3], Christian Sieder[3], Christian Hentschke[3] and Monika Maier-Peuschel[3]

Study treatment-related AEs were more frequent in the topiramate group than in the erenumab group (81.2% vs. 55.4% of patients)

In the **topiramate group**, the most frequent AEs that led to discontinuation of study medication were **paraesthesia, disturbance in attention, fatigue, and nausea**.

In the **erenumab group**, these were **fatigue, nausea, disturbance in attention and dizziness**.

Raccomandazioni EHF 2022

EHF mAbs antiCGRP Guideline

Table 2 Summary of the evidence-based recommendations

Recommendation	Quality of evidence[a]	Strength of the recommendation
In individuals with episodic migraine we recommend eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment	Eptinezumab 100 mg and 300 mg (q): moderate ⊕⊕⊕◯ Erenumab 70 mg (m) and 140 mg (m): high ⊕⊕⊕⊕ Fremanezumab 225 (m) and 675 (q): high ⊕⊕⊕⊕ Galcanezumab 120 mg (m) + 240 mg (ld): high ⊕⊕⊕⊕	Strong ↑↑
In individuals with chronic migraine we recommend eptinezumab, erenumab, fremanezumab and galcanezumab as preventive treatment	Eptinezumab 100 mg and 300 mg (q): high ⊕⊕⊕⊕ Erenumab 70 mg (m): high ⊕⊕⊕⊕ Erenumab 140 mg (m): moderate ⊕⊕⊕◯ Fremanezumab 225 mg (m): moderate ⊕⊕⊕◯ Fremanezumab 675 mg (q): high ⊕⊕⊕⊕ Galcanezumab 120 mg (m) + 240 mg (ld): high ⊕⊕⊕⊕	Strong ↑↑
In individuals with episodic or chronic migraine we recommend erenumab over topiramate as preventive treatment because of better tolerability	Low ⊕⊕◯◯	Strong ↑↑

(m) indicates monthly, *(q)* indicates quarterly, *ld* indicates loading dose

[a] For drugs with differences in the quality of evidence across the different outcomes we provided the overall rating according to the highest quality of evidence since the risk of bias was considered minor

Suggerimenti EHF (expert opinion)

EHF mAbs antiCGRP Guideline - Sacco et al. June 2022

Table 9 Summary of the expert consensus statements

Question	Statement
1. When should treatment with monoclonal antibodies targeting the CGRP pathway be offered to individuals with migraine?	In individuals with migraine who require preventive treatment, we suggest monoclonal antibodies targeting the CGRP pathway to be included as a first line treatment option.
2. How should other preventive treatments be managed when using monoclonal antibodies targeting the CGRP pathway in individuals with migraine?	In individuals with episodic or chronic migraine there is insufficient evidence to make suggestions regarding the combination of monoclonal antibodies targeting the CGRP with other preventatives to improve migraine clinical outcomes
3. When should treatment efficacy in individuals with migraine on treatment with anti-CGRP monoclonal antibodies be firstly evaluated?	In individuals with episodic or chronic migraine who start a new treatment with one monoclonal antibody targeting the CGRP pathway we suggest evaluating efficacy after a minimum of 3 consecutive months on treatment
4. When should treatment with anti-CGRP monoclonal antibodies be paused in individuals with migraine?	In individuals with episodic or chronic migraine we suggest considering a pause in the treatment with monoclonal antibodies targeting the CGRP pathway after 12-18 months of continuous treatment. If deemed necessary, treatment should be continued as long as needed. In individuals with migraine who pause treatment, we suggest restarting the treatment if migraine worsens after treatment withdrawal.
5. Should individuals with migraine and medication overuse offered treatment with monoclonal antibodies targeting the CGRP pathway?	In individuals with migraine and medication overuse, we suggest offering monoclonal antibodies targeting the CGRP pathway.
6. In individuals with migraine who are non-responders to one monoclonal antibody targeting the CGRP pathway, is switching to a different antibody an option?	In individuals with migraine with inadequate response to one monoclonal antibody targeting the CGRP pathway, there is insufficient evidence on the potential benefits of antibody switch but switching may be an option.
7. In which individuals with migraine is caution suggested when considering treatment with monoclonal antibodies targeting the CGRP pathway?	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 with history of severe constipation.

Prescrivibilità secondo AIFA e pazienti

Quali i criteri per migliorarla?

<u>Indicazione autorizzata</u>: indicato per la profilassi dell'emicrania in adulti che hanno almeno 4 giorni di emicrania al mese.

<u>Indicazione rimborsata SSN</u>: Trattamento dei pazienti adulti che negli ultimi 3 mesi abbiano presentato almeno 8 giorni di emicrania disabilitante al mese [definita come punteggio del questionario MIDAS >=11], già trattati con altre terapie di profilassi per l'emicrania e che abbiano mostrato una risposta insufficiente dopo almeno 6 settimane di trattamento o che siano intolleranti o che presentino chiare controindicazioni ad almeno 3 precedenti classi di farmaci per la profilassi dell'emicrania.

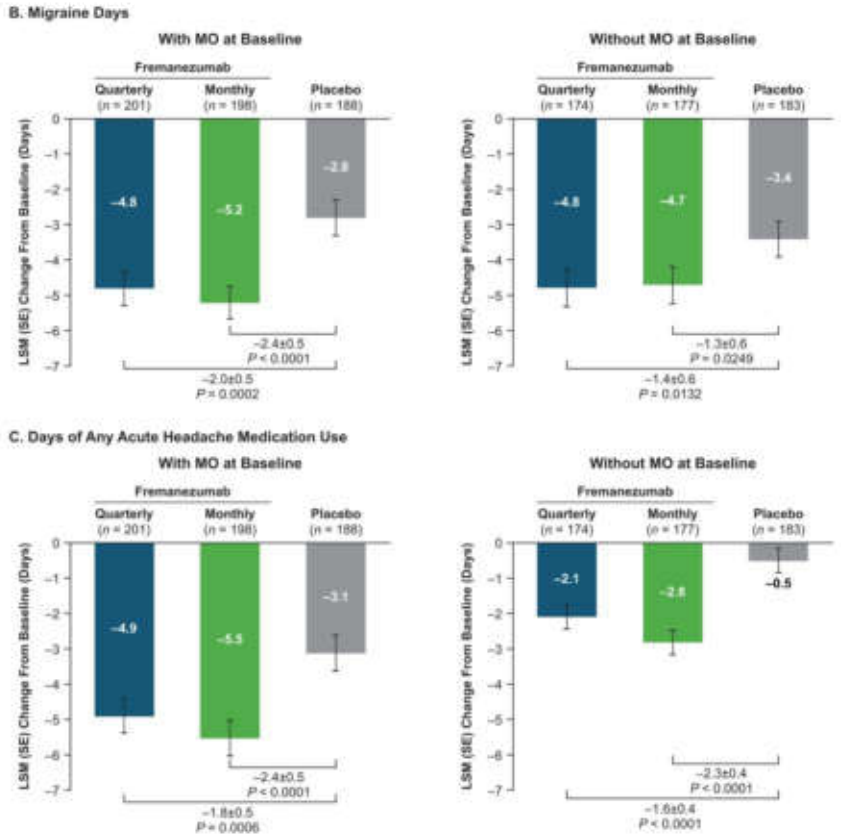
Predittori di risposta

Possono diventare un criterio di prescrivibilità?

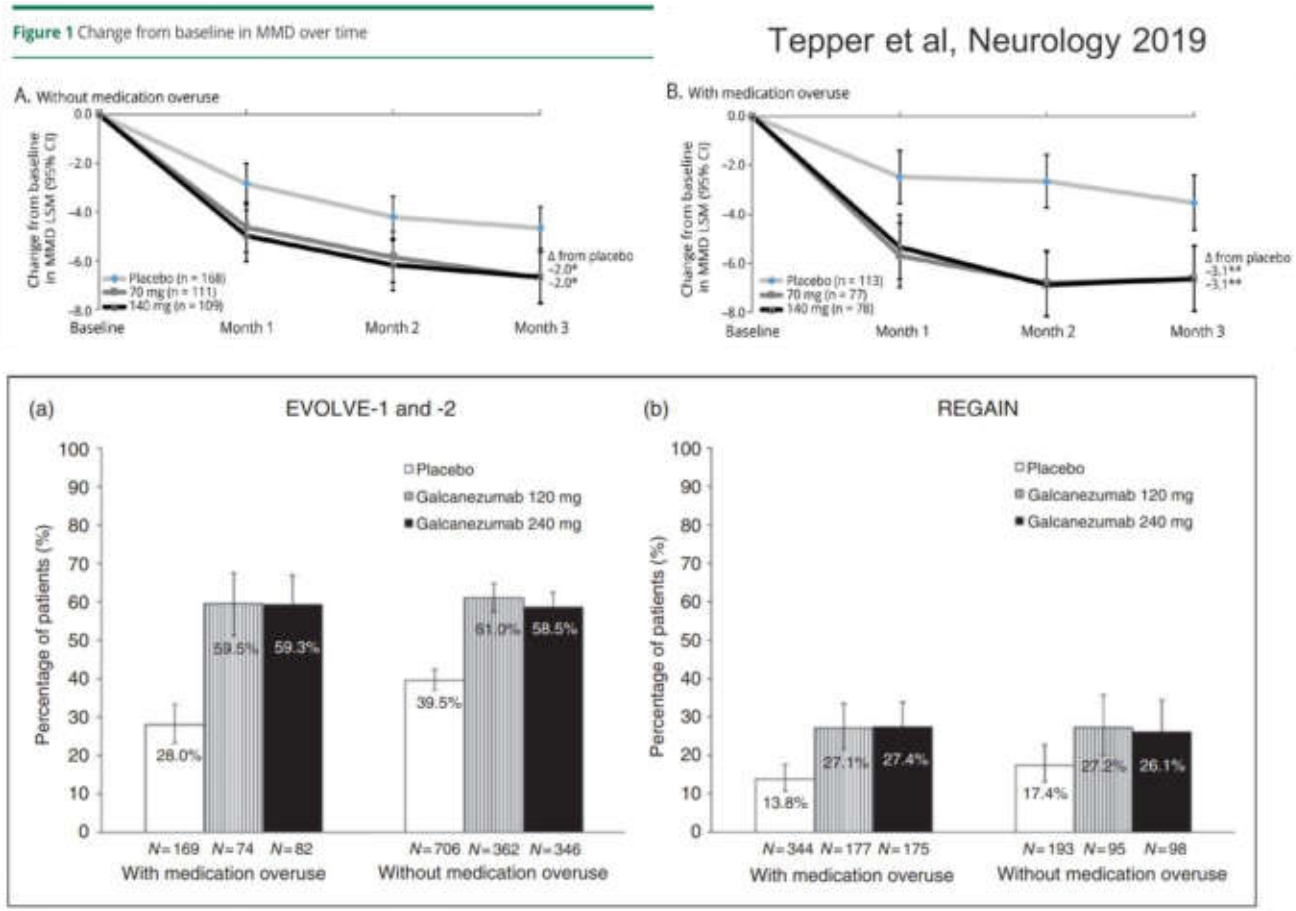
ERE*, GAL°	3 mesi	6 mesi	12 mesi
Barbanti et al, EARLY 1, 2021 (HFEM e CM)*	**Comorbidità psichiatriche** (CM)		
Barbanti et al, EARLY 2, 2021 (HFEM e CM)*			**Comorbidità psichiatriche**, **+ fallimenti profilassi** (CM)
Silvestro et al, Acta Neurol Scan 2021 (Ref-M)*		Alta frequenza, medication overuse, pain catastrophizing	
Bottiroli et al, TJHP 2021 (CM)*			Disturbo personalità Cluster C, Eventi vita 'almeno seri'
Vernieri et al, Eur J Neurol, 2021 (CM)°	**+ fallimenti profilassi, sovrappeso** (CM)		
Vernieri et al, TJHP, 2021 (HFEM e CM)°		**+ fallimenti profilassi, sovrappeso** (CM)	
Vernieri et al, Eur J Neurol, 2022°			**Sovrappeso**

Prescrivibilità: guardare al paziente, non solo ai criteri

CGRP mAbs RCTs and Medication Overuse: post-hoc analysis

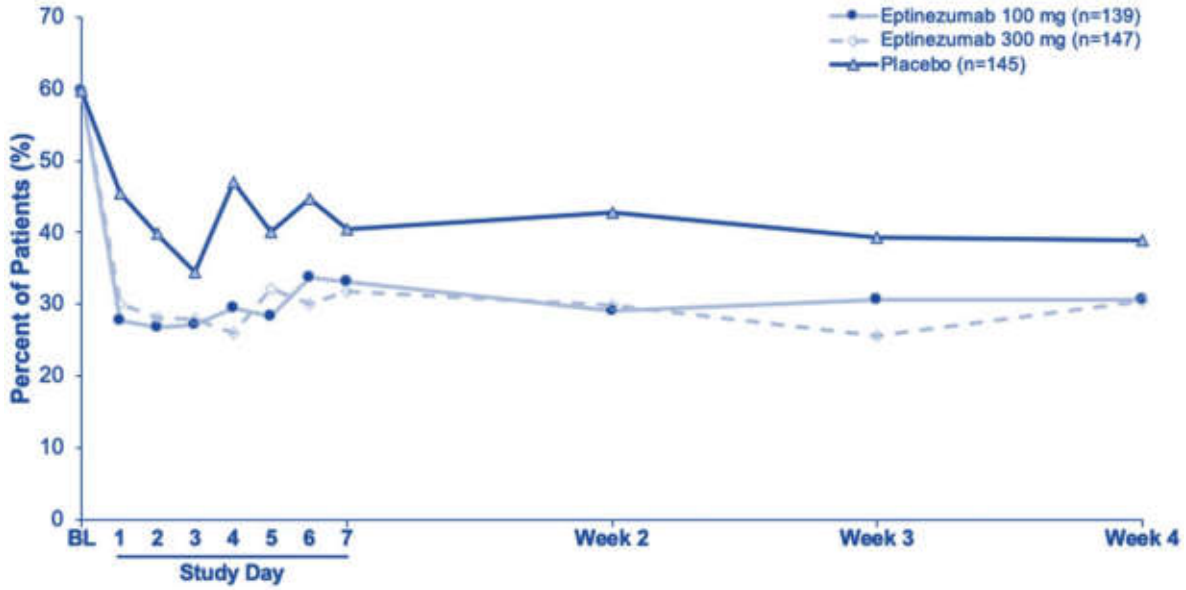


Silberstein et al. The Journal of Headache and Pain (2020)



Dodick et al. Cephalalgia 2020

Eptinezumab e MOH: rapidità e persistenza



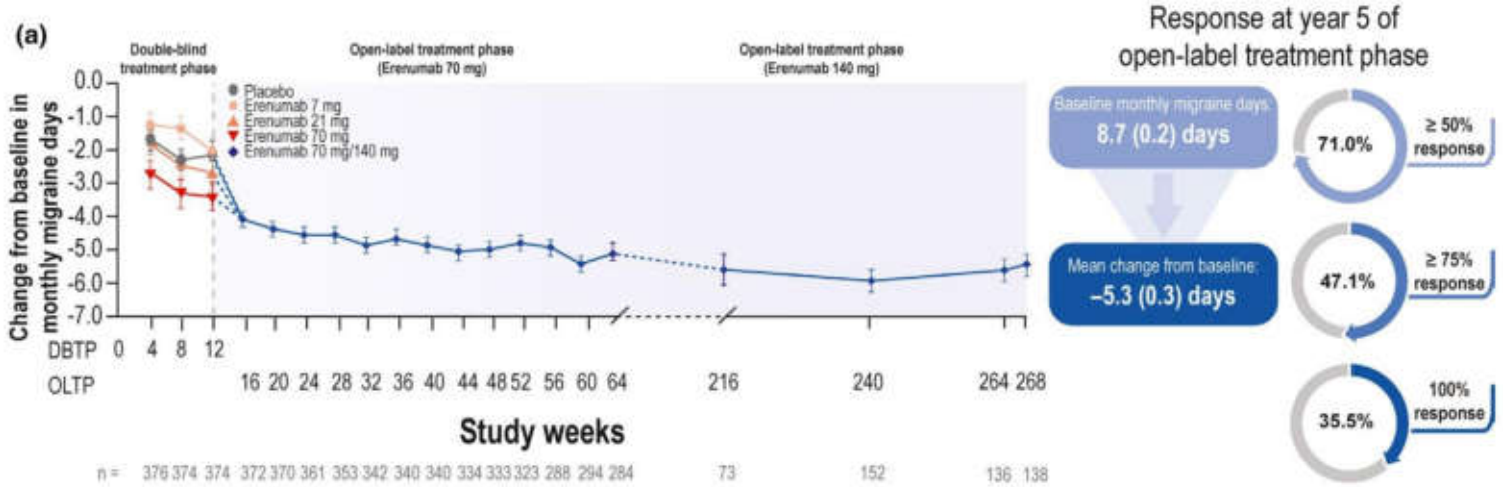
Percentage of patients with a dual diagnosis of CM and MOH with a migraine during the first 4 weeks after dosing.
The percentages that are based on more than one day (i.e., baseline and weeks 2–4) are based on the daily rates within these intervals. For example, the week 2 percentage is the average percentage over days 8–14.
Baseline is the average over the 28-day screening period prior to receiving treatment. BL, baseline; CM, chronic migraine; MOH, medication-overuse headache

Diener et al. Headache. 2021;61:125–136

	0	1	2	3	4	5	6
	Maximum number of months below CM diagnostic thresholds, *n* (%)[a]						
Eptinezumab 100 mg, *n* = 139	22 (15.8%)	5 (3.6%)	5 (3.6%)	11 (7.9%)	11 (7.9%)	14 (10.1%)	71 (51.1%)
Eptinezumab 300 mg, *n* = 147	22 (15.0%)	9 (6.1%)	4 (2.7%)	5 (3.4%)	9 (6.1%)	18 (12.2%)	80 (54.4%)
Placebo, *n* = 145	32 (22.1%)	14 (9.7%)	8 (5.5%)	12 (8.3%)	16 (11.0%)	16 (11.0%)	47 (32.4%)
	Maximum number of months below MOH levels of acute headache medication use, *n* (%)[b]						
Eptinezumab 100 mg, *n* = 93	12 (12.9%)	6 (6.5%)	2 (2.2%)	11 (11.8%)	6 (6.5%)	9 (9.7%)	47 (50.5%)
Eptinezumab 300 mg, *n* = 107	17 (15.9%)	6 (5.6%)	4 (3.7%)	3 (2.8%)	10 (9.3%)	14 (13.1%)	53 (49.5%)
Placebo, *n* = 96	22 (22.9%)	6 (6.3%)	10 (10.4%)	13 (13.5%)	6 (6.3%)	13 (13.5%)	26 (27.1%)

mAbs anti-CGRP: differenze farmacologiche e decisioni terapeutiche - **erenumab**

- First in class, studi fino a 5 anni di f-up *(Ashina et al. Eur J Neurol. 2021)*



- **Due dosaggi**, 70 e 140mg (con autoiniettore), preferito il secondo.
  - *The dose of erenumab was increased to 140 mg in 152/242 patients (62.8% CM) for ineffectiveness (n = 80) or loss of prior effectiveness (n = 72). No patient lowered the dose back to 70 mg for AEs or for other reasons (EARLY 2)*
- **Stipsi nel 10,3%** (EARLY 2), 3 x il dato di STRIVE 3,4% in EM (Goadsby 2017), **nel 15% nel NEW-ERA**
- A retrospective study reported one-third of patients experiencing **wearing off.**
  - *in most cases, these effects appeared approximately 1 week before the next injection (Robblee et al Headache 2020)*

mAbs anti-CGRP: differenze farmacologiche e decisioni terapeutiche - **fremanezumab**

- Due possibilità di somministrazione: 225mg monthly or 675mg quarterly
  - *Exposure-response evaluations showed that **both monthly (225 mg) and quarterly (675 mg) fremanezumab dosing regimens were appropriate in achieving clinical benefit** in adult patients with EM or CM (Fiedler-Kelly et al. Headache 2020)*
- **Lunga emivita e somministrazione trimestrale autonoma** (vs eptinezumab)
  - *Fremanezumab has the **lowest isoelectric point of all anti-CGRP-pathway** monoclonal antibodies, which would **limit its distribution outside the blood compartment**. Whether this underlies its longer half-life than other anti-CGRP antibodies potentially translating to longer efficacy and the **absence of the so-called wearing off effect**, is to be determined (Blumenfeld at al. 2020)*
- Abbiamo dati su pazienti over 60
  - *Fremanezumab treatment is efficacious and well tolerated over 12 weeks in participants aged ≥60 years with EM or CM (Nahas et al., TJHP 2021).*
- **Autoiniettore non disponibile in Italia**
  - *fremanezumab autoinjector presentation provides an easy-to-use bioequivalent PK profile with a similar safety and tolerability profile to that of the prefilled syringe (Cherniakov et al, 2021)*
- La somministrazione mensile in RL sembra preferita da medici e pazienti

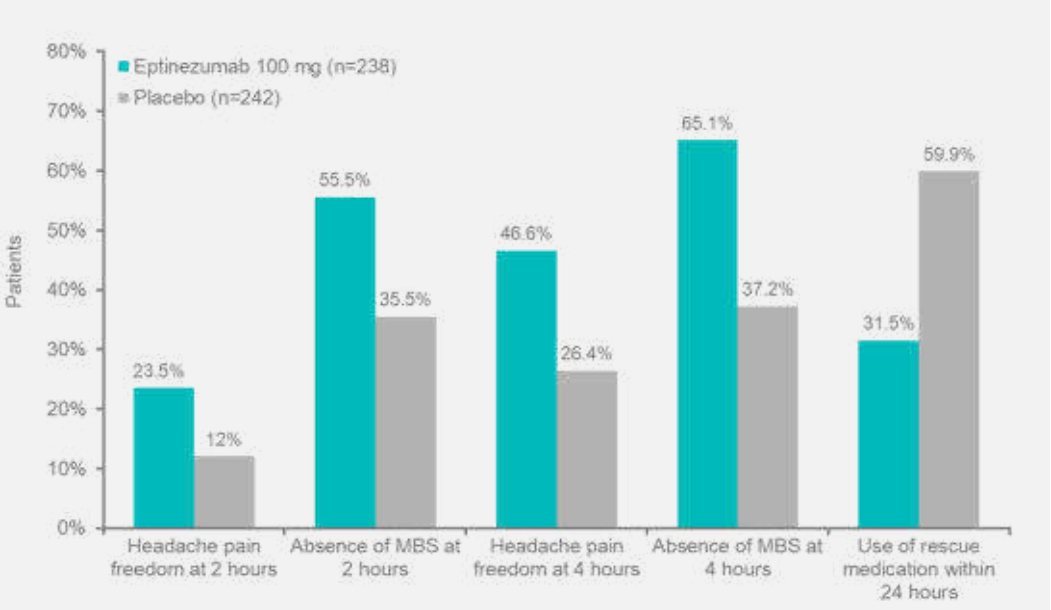
mAbs anti-CGRP: differenze farmacologiche e decisioni terapeutiche - **galcanezumab**

- **Unico dosaggio 120mg** con una **dose da carico 240mg, dati RCTs più omogenei**
- Autoiniettore
- Molti studi di real-life, anche in paesi asiatici
  - Besides being safe and effective in people of white ethnicity, galcanezumab is one of the few migraine drugs to have been tested in Japanese (Sakai et al. 2020) and South Korean (Kwon et al. 2022) patients with migraine.
- Dato su **Peso corporeo (Body Mass Index)**
  - *A post hoc pharmacokinetic analysis (Kielbasa and Quinlan, 2020) on 7 clinical trials with galcanezumab observed that **bodyweight modestly affected the pharmacokinetics of galcanezumab**, with median mAb concentrations being lower in the heaviest patients than in the lightest ones. As these effects were small no dose adjustments were recommended.*
    - A detrimental effect of a higher BMI has also been observed in post-hoc analyses of eptinezumab RCTs (Martin et al. 2022).
  - Dati Real Life dallo studio GARLIT a 3, 6 e 12 mesi di trattamento hanno dimostrato che **il sovrappeso costituisce un fattore prognostico negativo**
  - Utile studio ad hoc (?)

mAbs anti-CGRP: differenze farmacologiche e decisioni terapeutiche - **eptinezumab**

- **Unico a somministrazione endovenosa**: deve essere preparato e somministrato in regime ospedaliero (con PRO e CONs), da personale dedicato
- Garantisce l'**azione più rapida** (C^{max} al termine dell'infusione, 30 minuti)
- La somministrazione trimestrale può rappresentare un valore aggiunto
- **Opzione utile per pazienti difficili,** con **medication overuse**, **multipli fallimenti terapeutici**, **comorbilità psichiatriche**, che richiedono un setting dedicato *(Contextual effect, Forbes 2020)* e l'effetto più rapido possible (e sostenuto).

- **Possibile ruolo nell'emergenza?**



Studio RELIEF. Winner PK et al. JAMA. 2021;325:2348-2356

Gepanti: antagonisti del recettore CGRP

	Ubrogepant	Rimegepant	Atogepant	Zavegepant (Vazegepant)
Attacco	×	×		×
Profilassi		×	×	
fase	FDA approved	FDA and EMA approved	FDA approved EMA submitted	trial fase 3
somministrazione	orale	orale	orale	intranasale (orale)
dose	50 mg, 100 mg (max 200 mg / 24 h)	75 mg (max 75 mg / 24 h)	10 mg, 30 mg, 60 mg qd	5, 10, 20 mg (intranasali) 100, 200 mg (orali)
t_{max}	1.5 h	1.5 h	1.8 h	non disponibile
$t_{1/2}$	5-7 h	11 h	10-11 h	non disponibile
eliminazione	CYP3A4	CYP3A4 (CYP2C9)	CYP3A4	non disponibile

Drug Bank (go.drugbank.com) – Al-Hassany et al, 2022

Participants

- 18 years and older
- at least a 1-year history of migraine
- 1.1 and 1.2 according to ICHD-3 beta;
- migraine onset before age 50 years;
- at least two and not more than 8 migraine attacks of **moderate or severe intensity** per month
- fewer than 15 days per month with migraine or non migraine
- headache within the past 3 months.

Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial

Robert Croop, Peter J Goadsby, David A Stock, Charles M Conway, Micaela Forshaw, Elyse G Stock, Vladimir Coric, Richard B Lipton

Summary

Background Rimegepant, a small molecule calcitonin gene-related peptide receptor antagonist, has shown efficacy in the acute treatment of migraine using a standard tablet formulation. The objective of this trial was to compare the efficacy, safety, and tolerability of a novel orally disintegrating tablet formulation of rimegepant at 75 mg with placebo in the acute treatment of migraine.

Methods In this double-blind, randomised, placebo-controlled, multicentre phase 3 trial, adults aged 18 years or older with history of migraine of at least 1 year were recruited to 69 study centres in the USA. Participants were randomly assigned to receive rimegepant (75 mg orally disintegrating tablet) or placebo and instructed to treat a single migraine attack of moderate or severe pain intensity. The randomisation was stratified by the use of prophylactic medication (yes or no), and was carried out using an interactive web response system that was accessed by each clinical site. All participants, investigators, and the sponsor were masked to treatment group assignment. The coprimary endpoints were freedom from pain and freedom from the most bothersome symptom at 2 h postdose. The efficacy analyses used the modified intention-to-treat population, which included all patients who were randomly assigned, had a migraine attack with pain of moderate or severe intensity, took a dose of rimegepant or placebo, and had at least one

	Rimegepant 75 mg ODT (n=669)	Placebo (n=682)	Total (n=1351)
Most bothersome symptom, treated attack			
Photophobia	359 (54%)	374 (55%)	733 (54%)
Phonophobia	108 (16%)	101 (15%)	209 (15%)
Nausea	189 (28%)	195 (29%)	384 (28%)
Missing	13 (2%)	11 (2%)	24 (2%)

Data are mean (SD) or n (%). ODT=orally disintegrating tablet.

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See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(19)31611-3

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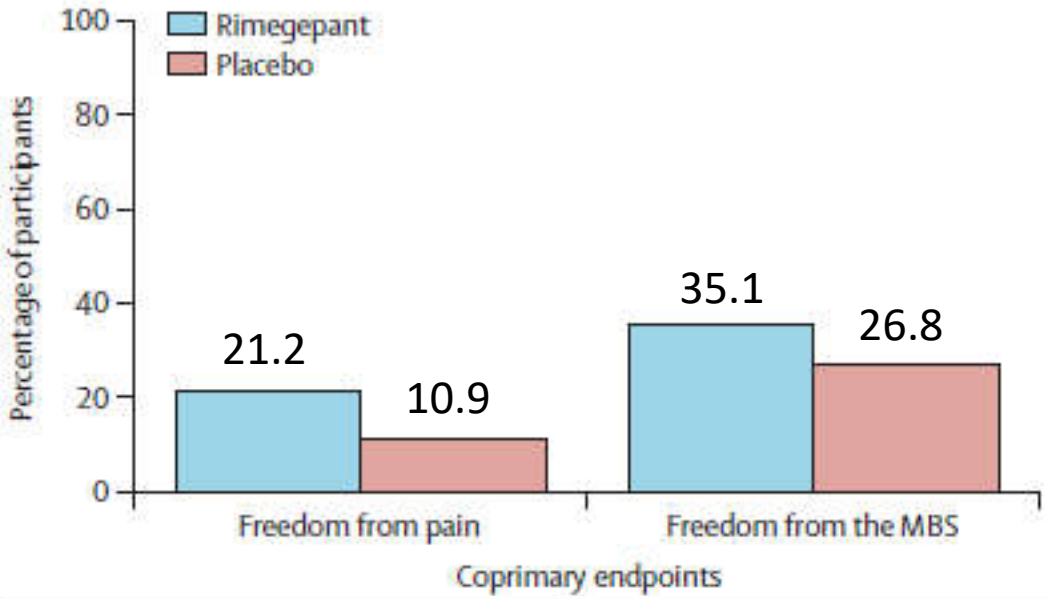
	Rimegepant	Placebo
	Events/patients (%)	Events/patients (%)
Primary endpoints		
Freedom from pain at 2 h postdose	142/669 (21·2)	74/682 (10·9)
Freedom from most bothersome symptom at 2 h postdose	235/669 (35·1)	183/682 (26·8)
Secondary endpoints		
Pain relief at 2 h postdose	397/669 (59·3)	295/682 (43·3)
Ability to function normally at 2 h postdose	255/669 (38·1)	176/682 (25·8)
Sustained pain relief from 2–24 h postdose	320/669 (47·8)	189/682 (27·7)
Sustained freedom from most bothersome symptom from 2–24 h postdose	181/669 (27·1)	121/682 (17·7)
No rescue medication within 24 h postdose	574/669 (85·8)	483/682 (70·8)
Sustained ability to function normally from 2–24 h postdose	198/669 (29·6)	115/682 (16·9)
Sustained pain relief from 2–48 h postdose	282/669 (42·2)	172/682 (25·2)
Sustained freedom from most bothersome symptom from 2–48 h postdose	155/669 (23·2)	112/682 (16·4)
Sustained ability to function normally from 2–48 h postdose	174/669 (26·0)	105/682 (15·4)
Freedom from photophobia at 2 h postdose	198/593 (33·4)	150/611 (24·5)
Ability to function normally at 90 min postdose	202/669 (30·2)	145/682 (21·3)
Pain relief at 90 min postdose	332/669 (49·6)	254/682 (37·2)
Sustained freedom from pain from 2–24 h postdose	105/669 (15·7)	38/682 (5·6)
Freedom from most bothersome symptom at 90 min postdose	183/669 (27·4)	147/682 (21·5)
Freedom from pain at 90 min postdose	101/669 (15·1)	50/682 (7·3)
Freedom from phonophobia at 2 h postdose	188/451 (41·7)	135/447 (30·2)
Sustained freedom from pain from 2–48 h postdose	90/669 (13·5)	37/682 (5·4)
Pain relief at 60 min postdose	246/669 (36·8)	213/682 (31·2)
Ability to function normally at 60 min postdose	149/669 (22·3)	108/682 (15·8)
Freedom from nausea at 2 h postdose	203/397 (51·0)	194/430 (45·2)
No pain relapse from 2–48 h postdose	90/142 (63·4)	37/74 (50·0)

-5 0

Favours placeb



	Rimegepant (n=682)	Placebo (n=693)
Participants with adverse event	90 (13%)	73 (11%)
Adverse events reported by ≥1% of participants in either treatment group		
Nausea	11 (2%)	3 (<1%)
Urinary tract infection	10 (1%)	4 (1%)
Dizziness	6 (1%)	7 (1%)
Adverse events related to treatment	47 (7%)	36 (5%)
Serious adverse events	0	0

Data are n (%). ODT=orally disintegrating tablet.

Table 2: **Adverse events with rimegepant 75 mg ODT and placebo**

Croop, JAMA 2019

ACHIEVE I Trial

- **Ubrogepant 50 or 100mg** vs placebo
- Single attack

PARTICIPANTS

- 18-75 years
- at least a 1-year history of migraine
- 1.1 and 1.2 according to ICHD-3 beta;
- migraine onset before age 50 years;
- Migraines lasting 4-72 hrs
- History of 2 to 8 migraines per month of **moderate or severe intensity**

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.

ABSTRACT

BACKGROUND

Ubrogepant is an oral, small-molecule calcitonin gene–related peptide receptor antagonist for acute migraine treatment.

METHODS

We conducted a randomized trial to evaluate the efficacy, safety, and side-effect profile of ubrogepant. We assigned adults with migraine, with or without aura, in a 1:1:1 ratio to receive an initial dose of placebo, ubrogepant at a dose of 50 mg, or ubrogepant at a dose of 100 mg for treatment of a single migraine attack, with the option to take a second dose. The coprimary efficacy end points were freedom from pain at 2 hours after the initial dose and absence of the most bothersome migraine-associated symptom at 2 hours. Secondary end points included pain relief (at 2 hours), sustained pain relief (from 2 to 24 hours), sustained freedom from pain (from 2 to 24 hours), and absence of symptoms associated with migraine (photophobia, phonophobia, and nausea) at 2 hours.

Table 2. Efficacy End Points (Modified Intention-to-Treat Population).*

End Point	Placebo (N=456)	Ubrogepant, 50 mg (N=423)	Ubrogepant, 100 mg (N=448)
Primary efficacy end points			
Freedom from pain at 2 hr — no./total no. (%)†	54/456 (11.8)	81/422 (19.2)	95/448 (21.2)
Odds ratio (95% CI)		1.83 (1.25–2.66)	2.04 (1.41–2.95)
Adjusted P value		0.002	<0.001
Absence of the most bothersome symptom at 2 hr — no./total no. (%)‡	126/454 (27.8)	162/420 (38.6)	169/448 (37.7)
Odds ratio (95% CI)		1.70 (1.27–2.28)	1.63 (1.22–2.17)
Adjusted P value		0.002	0.002
Secondary efficacy end points			
Pain relief at 2 hr — no./total no. (%)†	224/456 (49.1)	256/422 (60.7)	275/448 (61.4)
Odds ratio (95% CI)		1.69 (1.28–2.23)	1.69 (1.28–2.21)
Adjusted P value		0.002	0.002
Sustained pain relief, 2 to 24 hr — no./total no. (%)§	93/447 (20.8)	150/413 (36.3)	165/434 (38.0)
Odds ratio (95% CI)		2.25 (1.65–3.07)	2.39 (1.77–3.24)
Adjusted P value		0.002	0.002
Sustained freedom from pain, 2 to 24 hr — no./total no. (%)§	39/452 (8.6)	53/418 (12.7)	68/441 (15.4)
Odds ratio (95% CI)		1.57 (1.01–2.44)	1.95 (1.28–2.97)
Adjusted P value		NE	0.004
Absence of photophobia at 2 hr — no./total no. (%)‡	143/456 (31.4)	172/423 (40.7)	205/448 (45.8)
Odds ratio (95% CI)		1.63 (1.22–2.19)	1.81 (1.36–2.42)
Adjusted P value		NE	0.004

Table 3. Adverse Events According to Group (Safety Population).*

Event	Placebo (N=485)	Ubrogepant, 50 mg (N=466)	Ubrogepant, 100 mg (N=485)
		no. of participants (%)	
Adverse events that occurred within 30 days after any dose			
Any adverse event	113 (23.3)	126 (27.0)	139 (28.7)
Adverse events reported in ≥2% of participants in any group			
Nausea	12 (2.5)	9 (1.9)	23 (4.7)
Somnolence	4 (0.8)	4 (0.9)	12 (2.5)
Dry mouth	3 (0.6)	3 (0.6)	10 (2.1)
Upper respiratory tract infection	8 (1.6)	5 (1.1)	10 (2.1)
Any adverse event related to the trial regimen	49 (10.1)	36 (7.7)	68 (14.0)
Serious adverse events	0	3 (0.6)	2 (0.4)
Appendicitis	0	1 (0.2)	1 (0.2)
Pericardial effusion	0	1 (0.2)	0
Seizure	0	0	1 (0.2)
Spontaneous abortion	0	1 (0.2)	0
Death	0	0	0
Adverse event that led to discontinuation of the trial regimen	0	0	0

- Participants with clinically **significant cardiovascular or cerebrovascular disease** were **excluded**.
- Participants were also excluded if they had levels of alanine or aspartate aminotransferase that were more than 1.5 times the upper limit of the normal range.

6 participants had post baseline levels of ALT e AST at least 3 times the upper limit: considered not related to the trial regimen

Triptans therapeutic gain = 9-32%

Sumatriptan 16-21%

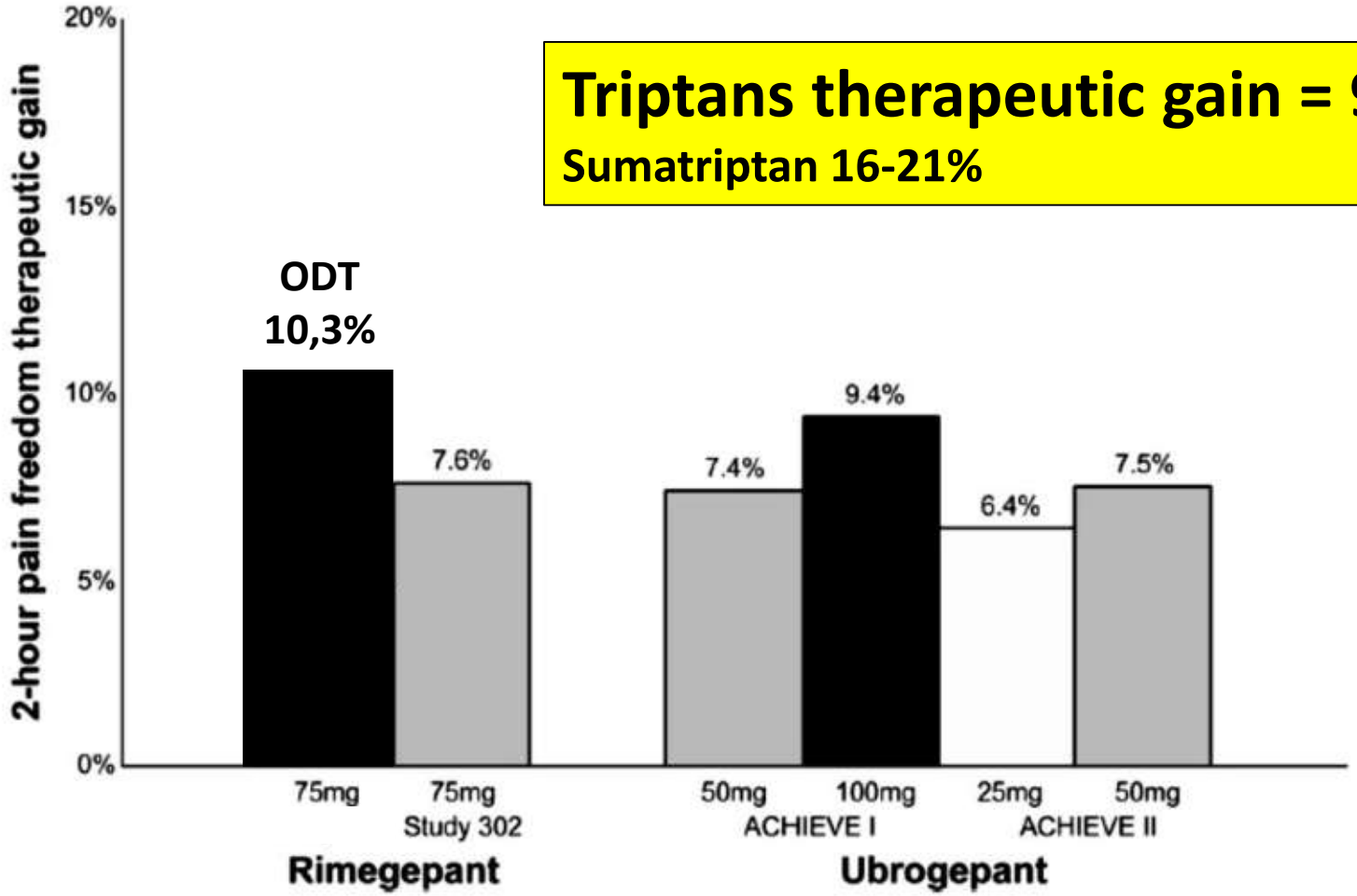


Fig. 6 Overview of the therapeutic gain* in 2-h pain freedom with gepants. A darker bar indicates a higher dose. *Therapeutic gain is defined as the difference between percentage of responders in active group compared to percentage of responders in placebo group

modificata

Do *et al. The Journal of Headache and Pain* (2019) 20:37

Gepanti – Considerazioni

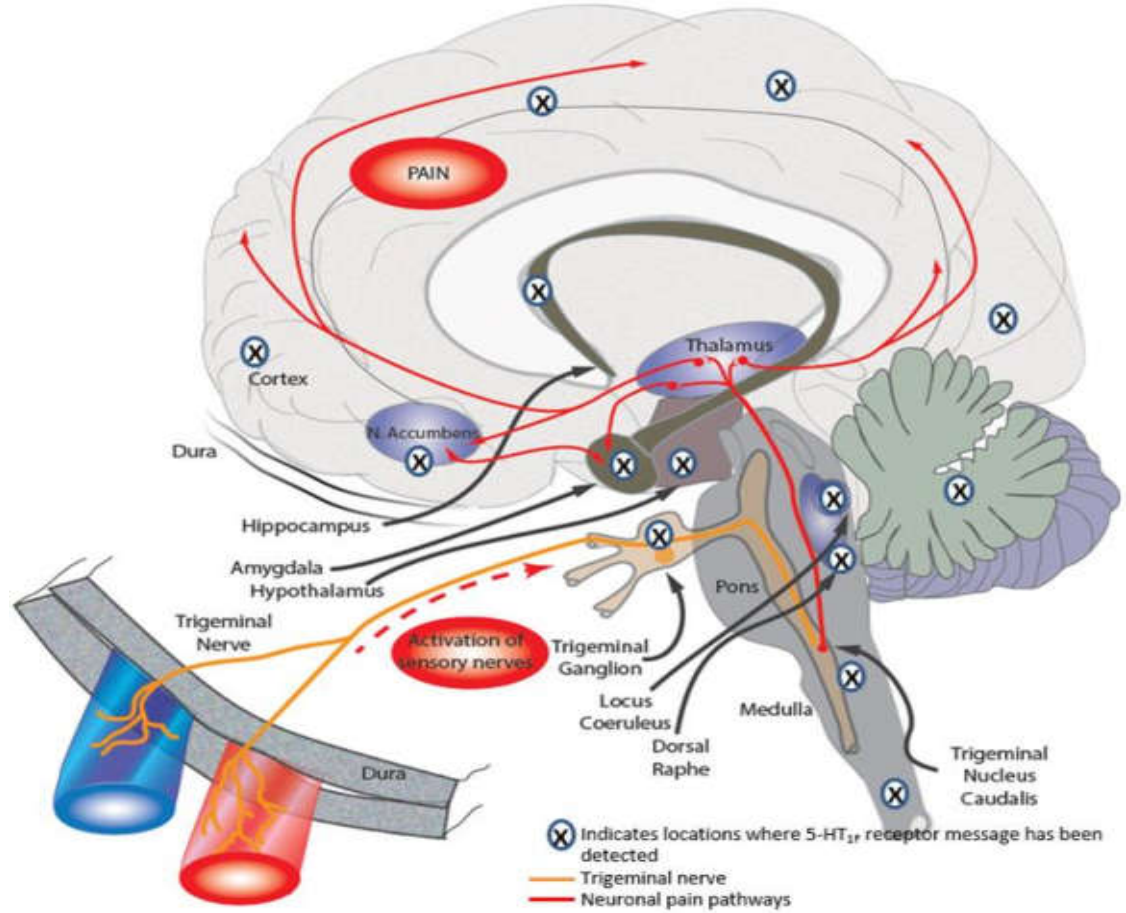
- I gepanti **non causano vasocostrizione**, pertanto possono essere usati in persone con cardiopatia o malattia cerebrovascolare ischemica
  - Non ci sono studi in gravidanza
- Seppure il **pain free a 2 h è più basso rispetto ai triptani, gli effetti collaterali sono nettamente inferiori**
- Gli study single attack hanno trattato intensità almeno ‘moderate’ (e severe in 1/3 dei casi) non ‘mild’: **necessità di evidenze per early treatment**
- L’uso frequente (finora solo in studi sulla profilassi) non ha evidenziato il rischio di uso eccessivo (vedi MOH per altri sintomatici)
- Il loro utilizzo nella profilassi è prossimo ma da verificare con altri studi.

Lasmiditan: meccanismo d'azione

Unique ability of lasmiditan to penetrate the blood–brain barrier rapidly due to its lipophilic nature.

Agonista (quasi puro, 90%) dei recettori 5-HT1F nella via trigeminale[1-4]

- **>470 volte più selettivo per il recettore 5-HT1F** rispetto a 5-HT1B e 5-HT1D
- **Riduce la trasmissione dolorifica nel Sistema TV**
- **Blocca l'infiammazione neurogenica nella dura**



1. Nelson DL, et al. Cephalalgia. 2010;30:1159-1169. 2. Goadsby PJ, et al. New Engl J Med. 2002;346:257-270. 4. Anderson CA, et al. In: Behavioral Neurology & Neuropsychiatry. 2013:12-31.

ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Lasmiditan is an effective acute treatment for migraine

Single attack, SAMURAI, Kuca et al, 2018

Table 2 Efficacy outcomes by treatment group

EM: 3-8 attacks/month, MIDAS ≥11, 77,9% had CV factors

mITT population	Lasmiditan 200 mg	Lasmiditan 100 mg	Placebo
Headache pain free, n[a]	518	503	524
At 2 h, n (%)	167 (32.2)	142 (28.2)	80 (15.3)
Odds ratio (95% CI)	2.6 (2.0–3.6)	2.2 (1.6–3.0)	
p Value vs placebo	<0.001	<0.001	
MBS free, n[b]	481	469	488
At 2 h, n (%)	196 (40.7)	192 (40.9)	144 (29.5)
Odds ratio (95% CI)	1.6 (1.3–2.1)	1.7 (1.3–2.2)	
p Value vs placebo	<0.001	<0.001	
Sustained pain freedom (ITT population), n[c]	555	562	554
At 24 h, n (%)	103 (18.6)	83 (14.8)	42 (7.6)
Odds ratio (95% CI)[d]	2.8 (1.9–4.1)	2.1 (1.4–3.1)	
p Value vs placebo[d]	<0.001	<0.001	

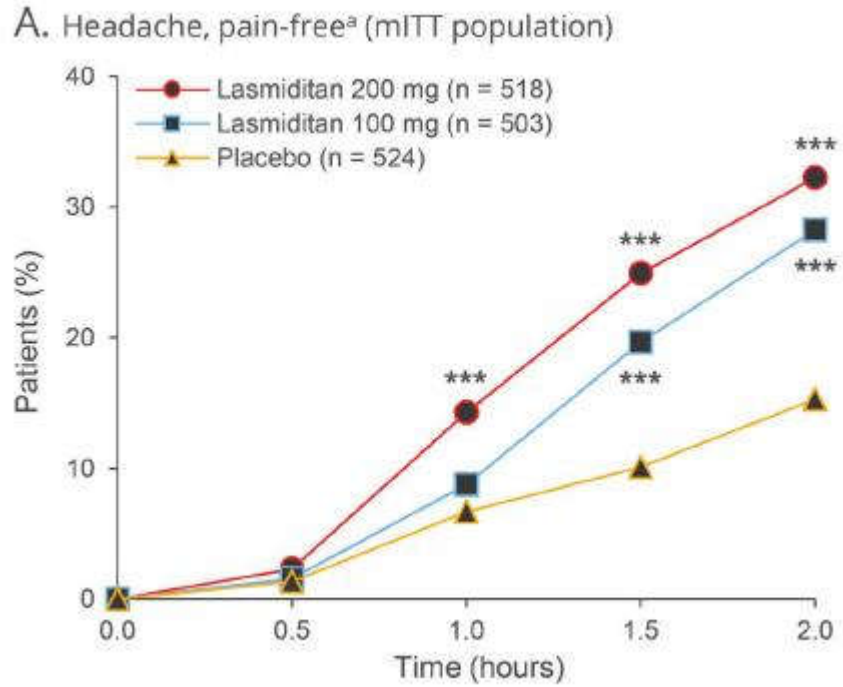
2x

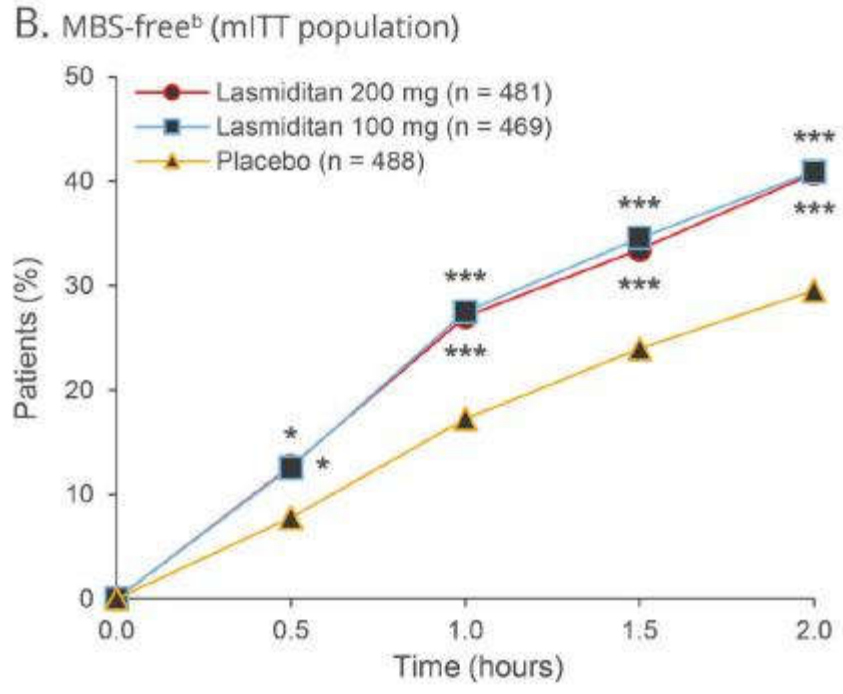
ARTICLE OPEN ACCESS CLASS OF EVIDENCE

Lasmiditan is an effective acute treatment for migraine

Table 2 Efficacy outcomes by treatment group

mITT population	Lasmiditan 200 mg	Lasmiditan 100 mg	Placebo





Kuca et al, 2018

Table 4 Treatment-emergent adverse events (TEAEs) after the first dose

Safety population	Lasmiditan 200 mg (n = 609), n (%)	Lasmiditan 100 mg (n = 630), n (%)	Placebo (n = 617), n (%)
At least 1 TEAE	260 (42.7)	229 (36.3)	101 (16.4)
At least 1 TEAE related to study medication	237 (38.9)	205 (32.5)	78 (12.6)
At least 1 serious TEAE	2 (0.3)	0 (0.0)	1 (0.2)
TEAEs with incidence ≥2% in any lasmiditan group and greater than placebo			
Dizziness	99 (16.3)	79 (12.5)	21 (3.4)
Paresthesia	48 (7.9)	36 (5.7)	13 (2.1)
Somnolence	33 (5.4)	36 (5.7)	14 (2.3)
Nausea	32 (5.3)	19 (3.0)	12 (1.9)
Fatigue	19 (3.1)	26 (4.1)	2 (0.3)
Lethargy	15 (2.5)	12 (1.9)	2 (0.3)
Incidence of cardiovascular TEAEs			
Palpitations	4 (0.7)	2 (0.3)	0 (0.0)
Sinus bradycardia	1 (0.2)	0 (0.0)	0 (0.0)
Bradycardia	0 (0.0)	1 (0.2)	1 (0.2)
Tachycardia	0 (0.0)	1 (0.2)	0 (0.0)
Left ventricular hypertrophy	0 (0.0)	0 (0.0)	1 (0.2)

Kuca et al, 2018

Table 1 Baseline demographics and clinical characteristics

2156 patients treated the migraine within 4 h

Characteristic	Lasmiditan 200 mg	Lasmiditan 100 mg	Lasmiditan 50 mg	Placebo
Safety population	*n* = 649	*n* = 635	*n* = 654	*n* = 645
Demographic characteristics				
Female, *n* (%)	536 (82.6)	539 (84.9)	554 (84.7)	545 (84.5)
Age, years, mean (SD)	41.8 (12.4)	43.4 (12.6)	42.8 (13.2)	42.6 (12.9)
Caucasian, *n* (%)	522 (80.4)	509 (80.2)	524 (80.1)	516 (80.0)
BMI (kg/m^2), mean (SD)	30.1 (8.2)	30.1 (8.3)	29.7 (7.6)	30.4 (11.1)
Clinical characteristics				
MIDAS total score, mean (SD)	32.9 (23.5)	31.3 (20.7)	33.2 (25.2)	31.5 (23.1)
Duration of migraine history, years, mean (SD)	17.6 (12.6)	19.2 (13.6)	18.6 (12.9)	17.9 (12.8)
Migraine attacks/month in past 3 months, mean (SD)	5.3 (1.9)	5.3 (1.9)	5.2 (2.0)	5.5 (2.4)
History of migraine with and without aura, *n* (%)				
With aura	229 (35.3)	238 (37.5)	226 (34.6)	244 (37.8)
Without aura	416 (64.1)	397 (62.5)	424 (64.8)	399 (61.9)
Background use of preventive migraine medication, *n* (%)	121 (18.6)	122 (19.2)	125 (19.1)	126 (19.5)
Presence of ≥1 cardiovascular risk factor[a], *n* (%)	528 (81.4)	510 (80.3)	508 (77.7)	517 (80.2)
History of ≥1 cardiac event	33 (5.1)	40 (6.3)	36 (5.5)	46 (7.1)
Full analysis set[b]	*n* = 528	*n* = 532	*n* = 556	*n* = 540

In contrast to the first phase 3 trial (Kuca et al., 2018), SPARTAN did not exclude individuals with known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension.

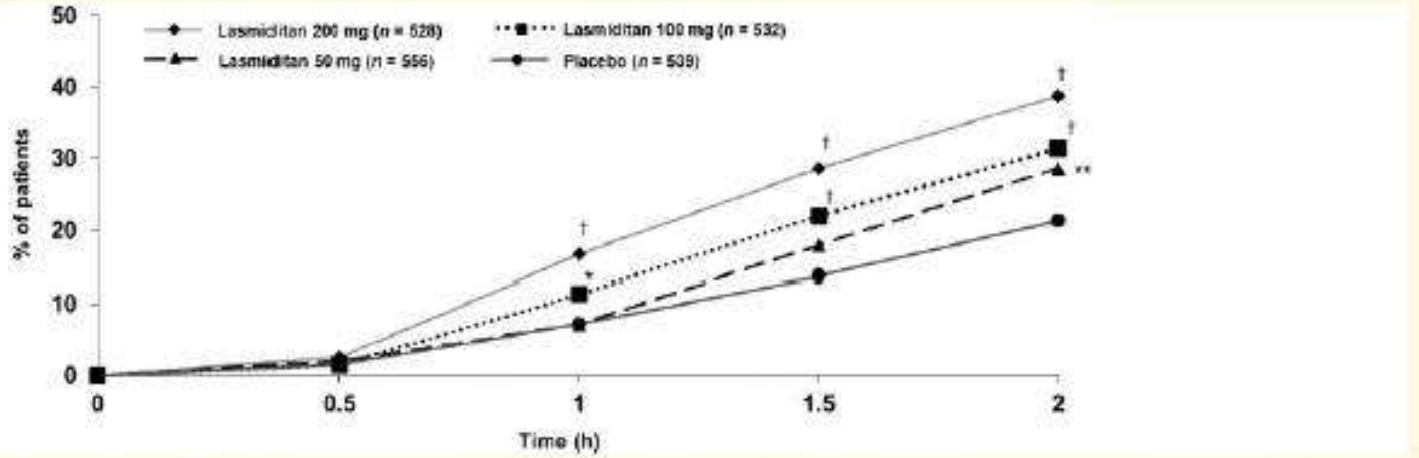


Figure 2 Headache pain-free after first dose. Full analysis set (originally referred to as the modified intent-to-treat population). $^{\dagger}P < 0.001$, $^{**}P < 0.01$, $^{*}P < 0.05$ versus placebo.

There was also no clear benefit of a second dose of lasmiditan as a rescue treatment.

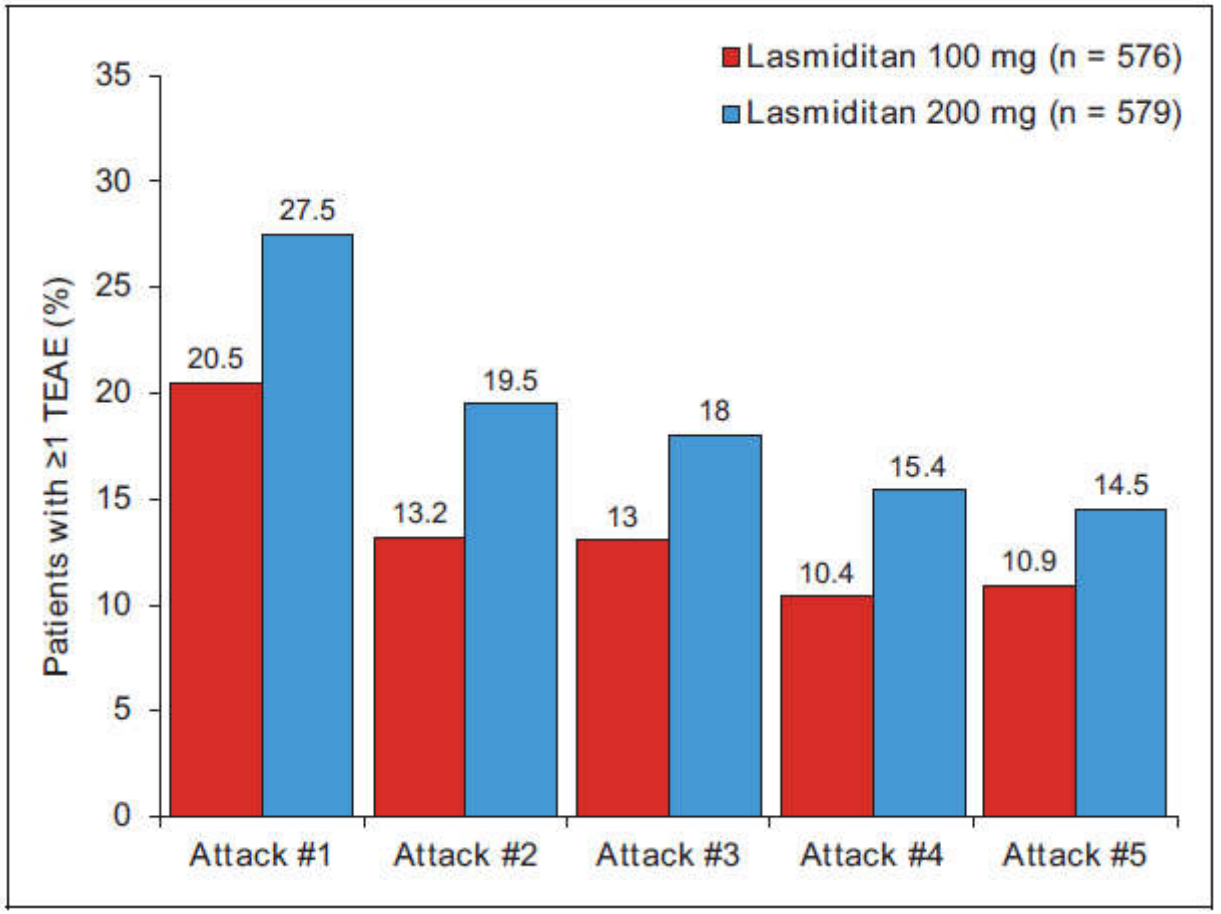
Table 4 Most commonly reported treatme afety population)

Preferred term	Lasmiditan 200 mg (*n* = 649)	Lasmiditan 100 mg (*n* = 635)	Lasmiditan 50 mg (*n* = 654)	Placebo (*n* = 645)
Subjects with at least one first-dose TEAE, *n* (%)	253 (39.0)	229 (36.1)	166 (25.4)	75 (11.6)
Dizziness	117 (18.0)	115 (18.1)	56 (8.6)	16 (2.5)
Somnolence	42 (6.5)	29 (4.6)	35 (5.4)	13 (2.0)
Paresthesia	43 (6.6)	37 (5.8)	16 (2.4)	6 (0.9)
Fatigue	31 (4.8)	26 (4.1)	18 (2.8)	6 (0.9)
Nausea	17 (2.6)	21 (3.3)	18 (2.8)	8 (1.2)
Lethargy	14 (2.2)	8 (1.3)	8 (1.2)	1 (0.2)
Incidence of cardiac disorder TEAEs, *n* (%)				
Palpitations	2 (0.3)	2 (0.3)	2 (0.3)	1 (0.2)
Tachycardia	2 (0.3)	2 (0.3)	1 (0.2)	0

Brandes et al. GLADIATOR study, 2020

Table 1. Common TEAEs (occurring in ≥2% of patients) in either treatment group by percentage of patients and percentage of attacks (safety population).

Because lasmiditan penetrates the blood–brain barrier easily and the most common side effects are central nervous system (CNS)-related events (e.g. dizziness, drowsiness, and fatigue), driving studies were necessary to evaluate a possible impairment of driving skills after substance intake. Two crossover studies revealed an impaired simulated driving performance at 1.5 h post-dose, but no clinically meaningful driving impairment was observed at 8, 12, or 24 h after the administration.[37] This led the FDA to the recommendation that patients should be advised not to drive or operate machinery for at least 8 h after taking lasmiditan.



Ditani (lasmiditan) - Considerazioni

- Lasmiditan approvato FDA ottobre 2019
- Nuova opzione terapeutica **per i pazienti emicranici che hanno controindicazioni di ordine vascolare ai triptani** ovvero che hanno presentato effetti collaterali con altri sintomatici
- Dosi raccomandate 50, 100 e 200mg (max 200mg die)
- Seconda dose non raccomandata (non beneficio)
- Primi effetti benefici dopo 30min, Tmax 2 h
- Efficacia pain free 2h simile ai triptani, migliore profilo di sicurezza
- **Importanti effetti collaterali**: dizziness, sonnolenza, nausea, parestesie, fatica: **divieto di guidare o usare macchinari per 8 ore!**

Le cefalee in emergenza

Percorso Cefalea Emilia-Romagna 2013

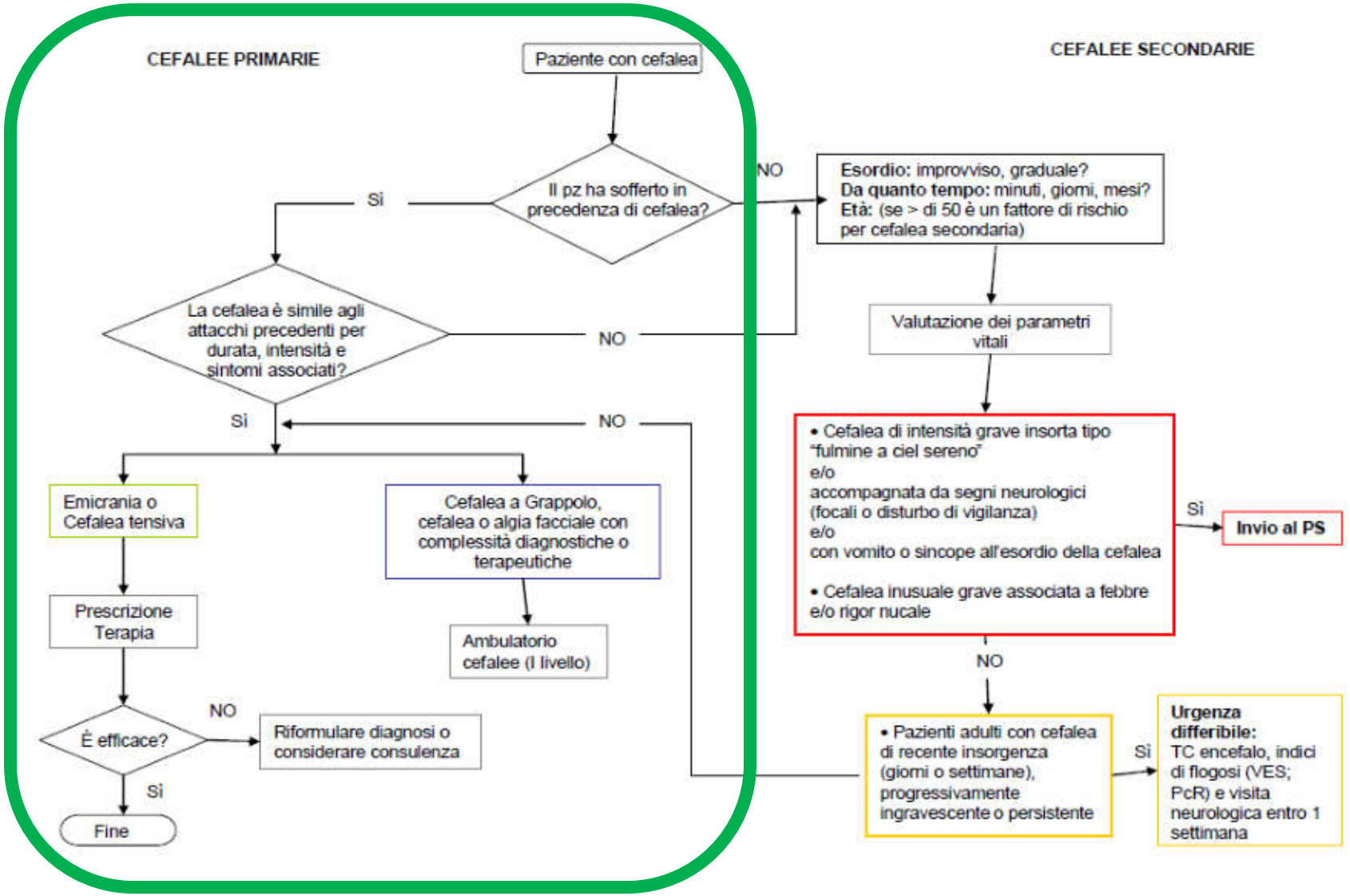
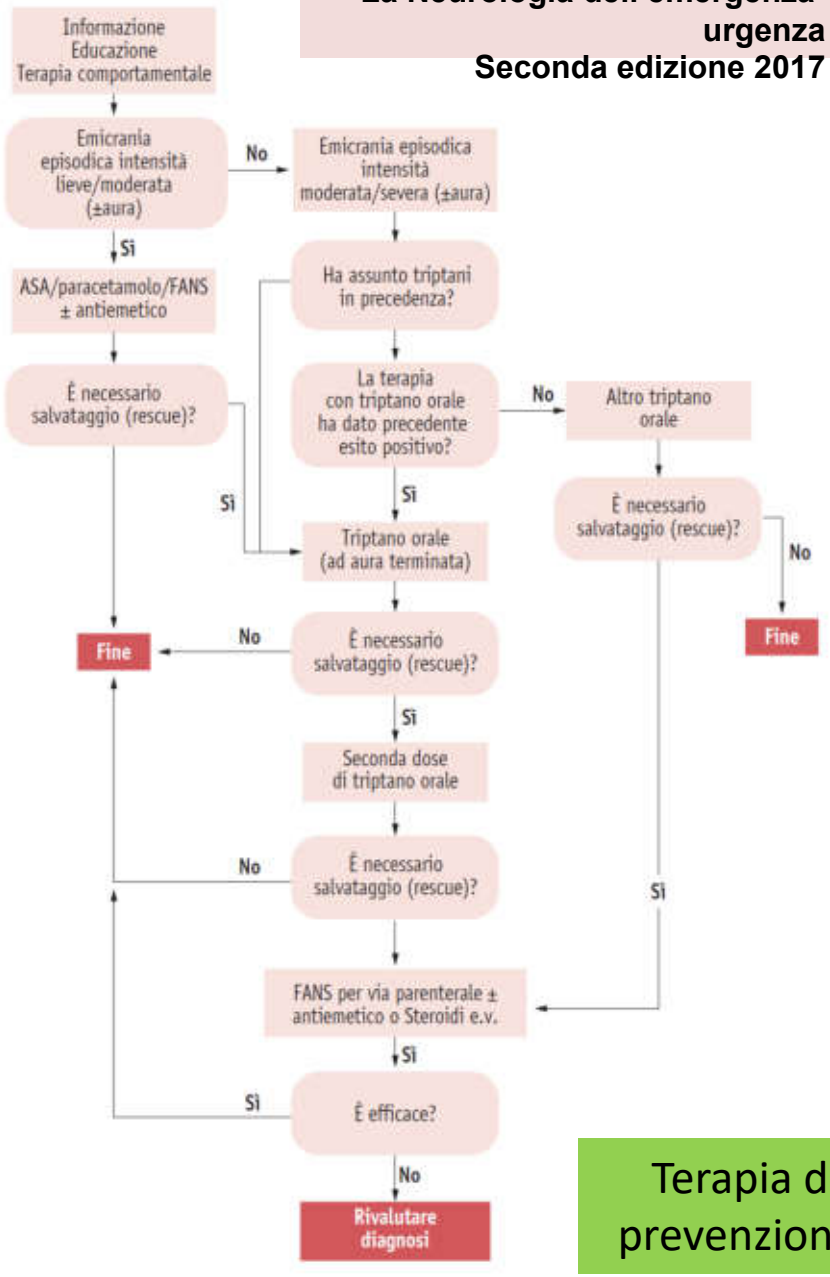


Figura 5.6 **Algoritmo terapeutico per l'attacco acuto di emicrania**

La Neurologia dell'emergenza-urgenza
Seconda edizione 2017



Terapia di prevenzione!

TABLE 5 Health resource use in patients with LF-CM and HF-CM frequency counts

Patients	Number (%) or mean ± SD		
	Total 866	LF-CM 430 (49.7%)	HF-CM 436 (50.3%)
Age at first headache center visit	35.3 ± 13.3	36.0 ± 12.7	34.7 ± 13.8
Hospitalization for migraine[b]	153 (19.6)	64 (16.7)	89 (22.4)
n. per patient	1.8 ± 1.4	1.5 ± 1.1	1.9 ± 1.5
Hospitalization for other diseases[b]	146 (18.9)	62 (16.3)	84 (21.2)
n. per patient	2.4 ± 2.5	2.4 ± 1.7	2.5 ± 2.9
Day hospital for migraine[b]	152 (19.5)	78 (20.4)	74 (18.6)
n. per patient	1.9 ± 2.2	1.7 ± 1.5	2.0 ± 2.7
Emergency room visits for migraine[c]	199 (25.3)	81 (21.0)	118 (29.5)
n. per patient	2.1 ± 2.1	2.1 ± 1.6	2.2 ± 2.3
Migraine medications, subsidized by			
NHS	516 (64.2)	271 (68.1)	245 (60.3)
Out of pocket	181 (22.5)	84 (21.6)	97 (23.9)
Both	107 (13.3)	43 (10.3)	64 (15.8)
Disabilityallowance for migraine	14 (1.8)	7 (1.8)	7 (1.8)
Disability allowance for other diseases	73 (9.4)	31 (8.1)	42 (10.6)
Migrainediagnosticinvestigation	661 (76.3)	325 (75.6)	336 (77.1)
n. per patient	1.6 ± 1.1	1.5 ± 1.0	1.6 ± 1.0
Types			
Brain imaging	618 (93.5)	305 (93.8)	313 (93.1)
Brain imaging *n.* per patient	1.3 ± 0.7	1.3 ± 0.6	1.4 ± 0.7
Spine imaging	71 (10.7)	29 (8.9)	42 (12.5)
Spine imaging *n.* per patient	1.0 ± 0.4	1.1 ± 0.6	1.0 ± 0.1
EEG	73 (11.0)	32 (9.8)	41 (12.2)
EEG *n.* per patient	1.0 ± 0.1	1.0 ± 0.0	1.0 ± 0.1

Italian chROnic migraiNe (IRON) project, Headache 2021

Terapie avanzate dell'emicrania nell'emergenza: conclusioni

- *Abbiamo* oggi **terapie di profilassi** efficaci, sicure e ben tollerate in grado di ridurre rapidamente la disabilità dei pazienti emicranici (**anticorpi monoclonali anti-CGRP**)
- Le terapie preventive sono risultate efficaci nel **ridurre l'uso eccessivo di sintomatici** (e **gli accessi in PS** per cefalea?)
- *Avremo* domani nuove opzioni per la **terapia dell'attacco** (**gepanti, ditani**), utili nel paziente con **comorbilità vascolare**
- Fondamentali restano la **diagnosi** (formazione adeguata) ed i **percorsi** di accesso per il paziente cefalalgico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