Update Neurologia 2025

Claudio Gobbi

Neurocentro della Svizzera italiana

15.10.2025

Agenda

1.Stroke
2.Emicrania
3.Demenza

Terapia acuta
Terapia cronica

ChatGPT. 2025. IA-generated image of an intensive care unit with ECMO cannulation. Open IA

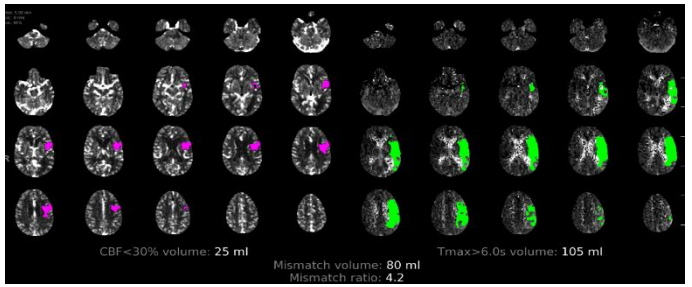
American Stroke Association.
International Stroke Conference

Alteplase for Ischemic Stroke at 4.5-24 Hours with Perfusion-imaging Selection

HOPE Trial (NCT04879615)

Ying Zhou, Yaode He, Bruce C.V. Campbell, Maarten G. Lansberg, David S. Liebeskind, Changzheng Yuan, Hui Chen, Yanxing Zhang, Tingyu Yi, Zhongyu Luo, Zuowen Zhang, Changcai Meng, Jianhua Cheng, Hezhong Ouyang, Jin Hu, Fei Wang, Sheng Zhang, Qi Fang, Haitao Hu, Xuting Zhang, Yi Chen, Wansi Zhong, Shenqiang Yan, Min Lou, on behalf of the HOPE Group

American Academy of Neurology, AAN, San Diego 2025



CONCLUSIONS

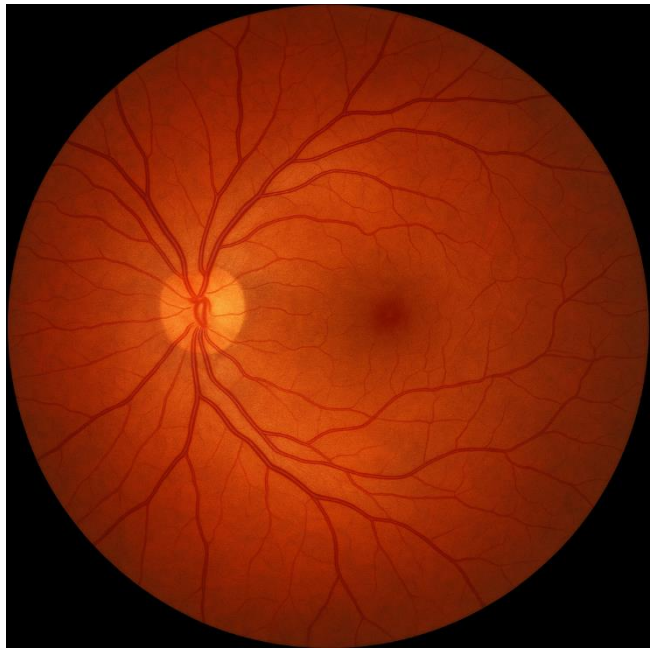
- The administration of intravenous alteplase between 4.5 and 24 hours after stroke onset in patients with imaging-confirmed salvageable tissue resulted in a greater proportion of non-disabled functional outcome compared with standard medical treatment

- Increase in symptomatic intracranial hemorrhage did not lead to a difference in mortality

Ischaemic stroke:
Central retinal artery occlusion (CRAO)

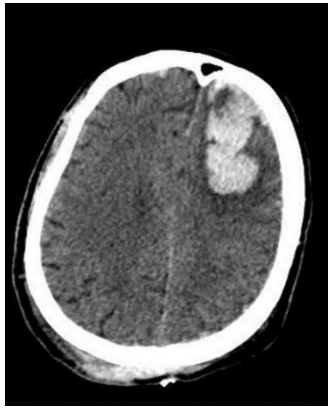
- THEIA: Randomised controlled trial of tPA (alteplase) for CRAO within 4.5 hours

tPA for CRAO is safe and improves visual outcomes in CRAO compared with aspirin alone.



American Academy of Neurology
2025

Endoscopic ICH evacuation, round 1 of 7

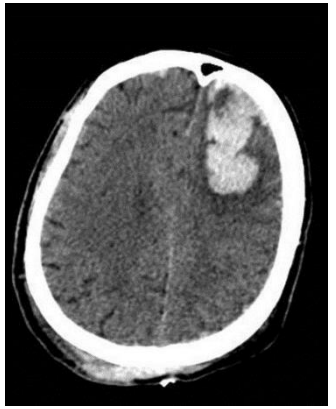


Trial of Early Minimally Invasive Removal of Intracerebral Hemorrhage

N Engl J Med 2024;390:1277-1289

- ICH evacuation by open craniotomy doesn't clear improve functional outcomes.
- After promising early phase data about minimally invasive surgical approaches, this is the first of 7 active trials testing the technique in phase 3 trials.
- Multicenter RCT with adaptive design testing trans-sulcal parafascicular minimally-invasive evacuation of moderate volume (30-80 ml) (1) anterior BG and (2) lobar ICH performed within 24 hours.
- Primary outcome: utility-weighted mRS @ 180 days.
- Enrollment of basal ganglia ICH stopped halfway.
- Patients in surgical arm has significantly better function at 180 days compared to medical. The difference was driven by patients with lobar ICH. Mortality was 9.3% in surgical group vs 18.0% in medical group. Surgery patients has less SAEs.

Safety and efficacy of early versus delayed acetylsalicylic acid after surgery for spontaneous intracerebral haemorrhage in China (E-start): a prospective, multicentre, open-label, blinded-endpoint, randomised trial

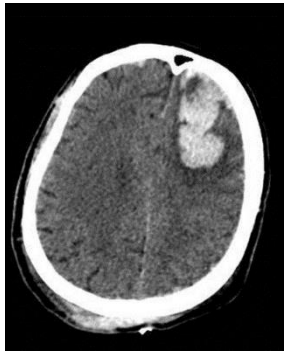


Qingyuan Liu, Shaohua Mo*, Jun Wu*, Xianzeng Tong*, Kaiwen Wang*, Xu Chen, Shanwen Chen, Shuaiwei Guo, Xiong Li, Mingde Li, Lei Peng,*

Interpretation Starting acetylsalicylic acid on the third day after surgery for spontaneous intracerebral haemorrhage in Chinese patients at high risk of postoperative ischaemic events resulted in fewer postoperative ischaemic major cardiovascular, cerebrovascular, or peripheral vascular events than starting acetylsalicylic acid therapy at 30 days, with no increased risk of intracranial bleeding. Whether early initiation of acetylsalicylic acid therapy is safe and improves clinical outcomes for broader populations of patients with spontaneous intracerebral haemorrhage requires further research.

Lancet Neurol 2024;
23: 1195–204

Ischaemic stroke: Preventative and chronic treatments



Direct oral anticoagulants versus no anticoagulation for the prevention of stroke in survivors of intracerebral haemorrhage with atrial fibrillation (PRESTIGE-AF): a multicentre, open-label, randomised, phase 3 trial

*Roland Veltkamp, Eleni Korompoki, Kirsten H Harvey, Emily R Harvey, Cornelia Fießler, Uwe Malzahn, Viktoria Rücker, Joan Montaner, Valeria Caso, Igor Sibon, Peter Ringleb, Omid Halse, Klemens Hügen, Sabine Ullmann, Carolin Schuhmann, Gabriele Putz Todd, Kirsten Haas, Elena Palà, Stéphanie Debette, Morgane Lachaize, Tim D'Aoust, Christian Enzinger, Stefan Ropele, Simon Fandler-Höfler, Melanie Haidegger, Yanzhong Wang, Hatem A Wafa, Virginia Cancelloni, Maria Giulia Mosconi, Gregory Y H Lip, Deirdre A Lane, Walter E Haefeli, Kathrin I Foerster, Viktoria S Wurmbach, Peter Brønnum Nielsen, Karim Hajjar, Patrick Müller, Sven Poli, Jan Purrucker, Mona Laible, Lucio D'Anna, Yolanda Silva, Reyes de Torres Chacon, Patricia Martínez-Sánchez, Marion Boulanger, Bo Norrving, Guillaume Paré, Rolf Wachter, George Ntaios, Charles D A Wolfe, Peter U Heuschmann, on behalf of the PRESTIGE-AF Consortium**

Summary

Background Direct oral anticoagulants (DOACs) reduce the rate of thromboembolism in patients with atrial fibrillation but the benefits and risks in survivors of intracerebral haemorrhage are uncertain. We aimed to determine whether DOACs reduce the risk of ischaemic stroke without substantially increasing the risk of recurrent intracerebral haemorrhage.

Methods PRESTIGE-AF is a multicentre, open-label, randomised, phase 3 trial conducted at 75 hospitals in six European countries. Eligible patients were aged 18 years or older with spontaneous intracerebral haemorrhage, atrial fibrillation, an indication for anticoagulation, and a score of 4 or less on the modified Rankin Scale. Patients were randomly assigned (1:1) to a DOAC or no anticoagulation, stratified by intracerebral haemorrhage location and sex. Only the events adjudication committee was masked to treatment allocation. The coprimary endpoints were first ischaemic stroke and first recurrent intracerebral haemorrhage. Hierarchical testing for superiority and non-inferiority, respectively, was performed in the intention-to-treat population. The margin to establish non-inferiority regarding intracerebral haemorrhage was less than 1·735. The safety analysis was done in the intention-to-treat population. The trial is registered with ClinicalTrials.gov, NCT03996772, and is complete.

Findings Between May 31, 2019, and Nov 30, 2023, 319 participants were enrolled and 158 were randomly assigned to the DOAC group and 161 to the no anticoagulant group. Patients' median age was 79 years (IQR 73–83). 113 (35%) of 319 patients were female and 206 (65%) were male. Median follow-up was 1·4 years (IQR 0·7–2·3). First ischaemic stroke occurred less frequently in the DOAC group than in the no anticoagulant group (hazard ratio [HR] 0·05 [95% CI 0·01–0·36]; log-rank p<0·0001). The rate of all ischaemic stroke events was 0·83 (95% CI 0·14–2·57) per 100 patient-years in the DOAC group versus 8·60 (5·43–12·80) per 100 patient-years in the no anticoagulant group. For first recurrent intracerebral haemorrhage, the DOAC group did not meet the prespecified HR for the non-inferiority margin of less than 1·735 (HR 10·89 [90% CI 1·95–60·72]; p=0·96). The event rate of all intracerebral haemorrhage was 5·00 (95% CI 2·68–8·39) per 100 patient-years in the DOAC group versus 0·82 (0·14–2·53) per 100 patient years in the no anticoagulant group. Serious adverse events occurred in 70 (44%) of 158 patients in the DOAC group and 89 (55%) of 161 patients in the no anticoagulant group. 16 (10%) patients in the DOAC group and 21 (13%) patients in the no anticoagulant group died.

Interpretation DOACs effectively prevent ischaemic strokes in survivors of intracerebral haemorrhage with atrial fibrillation but a part of this benefit is offset by a substantially increased risk of recurrent intracerebral haemorrhage. To optimise stroke prevention in these vulnerable patients, further evidence from ongoing trials and a meta-analysis of randomised data is needed, as well as the evaluation of safer medical or mechanical alternatives for selected patients.

Lancet 2025; 405: 927–36

Published Online February 26, 2025 https://doi.org/10.1016/S0140-6736(25)00333-2

This online publication has been corrected. The corrected version first appeared at thelancet.com on March 13, 2025

See Comment page 872

*Members of the PRESTIGE-AF Consortium are listed in the appendix (p 2)

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PRESTIGE-AF trial

In people with afib and recent haemorrhagic stroke, DOACs significantly reduced ischaemic stroke risk but also significantly increased recurrent intracranial haemorrhage and other major bleeding complications.

American Academy of Neurology

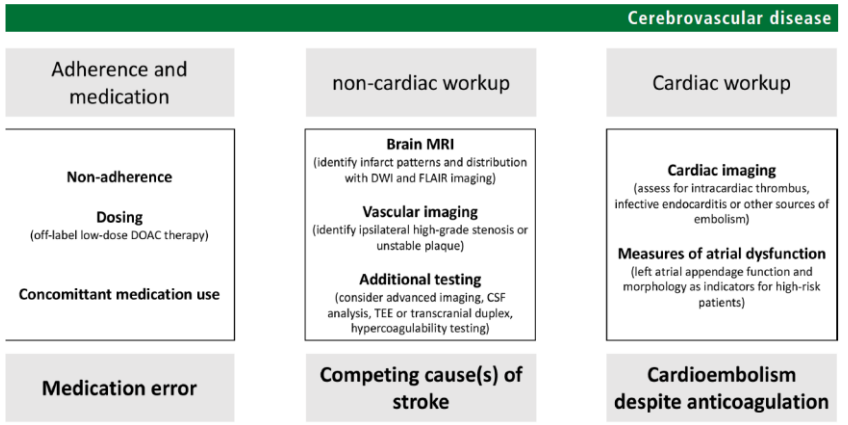
2025

RESEARCH ARTICLE

Anticoagulation Strategies Following Breakthrough Ischemic Stroke While on Direct Anticoagulants

A Meta-Analysis

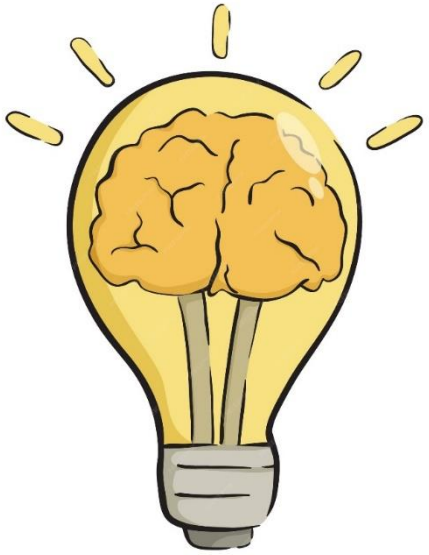
Neurology® 2025;105:e213964. doi:10.1212/WNL.0000000000213964



Results

We retrieved 2,171 results, with 8 observational studies reaching quantitative synthesis (n = 14,307 patients, mean age = 75 years, 48% female). Switching to warfarin was associated with a higher risk of ischemic stroke compared with keeping the same DOAC (RR 1.80, 95% CI 1.42–2.29, I^2 = 0%, $n_{studies}$ = 5) or changing DOAC dosage (RR 1.72, 95% CI 1.20–2.45, I^2 = 0%, $n_{studies}$ = 4). Switching to warfarin was also associated with higher ICH rates compared with keeping the same DOAC (RR 2.90, 95% CI 2.01–4.18, I^2 = 0%, $n_{studies}$ = 5) and DOAC-to-DOAC switch (RR 3.25, 95% CI 2.13–4.96, I^2 = 0%; $n_{studies}$ = 5). Keeping the same DOAC and switching to another DOAC, independently from mechanism, had similar rates of primary and secondary outcomes.

Ischemia cerebrale: «pearls»



- Anticoagulazione con DOAC dopo uno stroke
  - «Minor» stroke 2-3 giorni, «moderate/severe» stroke 5-7 giorn
  - DOAC >> Vit K antg
  - 8 settimane dopo una emorragia
- Anti-aggregazione dopo uno stroke
  - Doppia anti-aggregazione in TIA e minor stroke (NIHSS<5p) per 3 setttimane
  - Successivamente mono-antiaggregazione a vita (clopidrogel > ASS)
- Stroke e severa arteriopatia
  - Considerare ASS+ DOAC (Rivaroxaban 2.5 mg x2)

American Academy of Neurology, AAN, San Diego 2025

Agenda

1.Stroke
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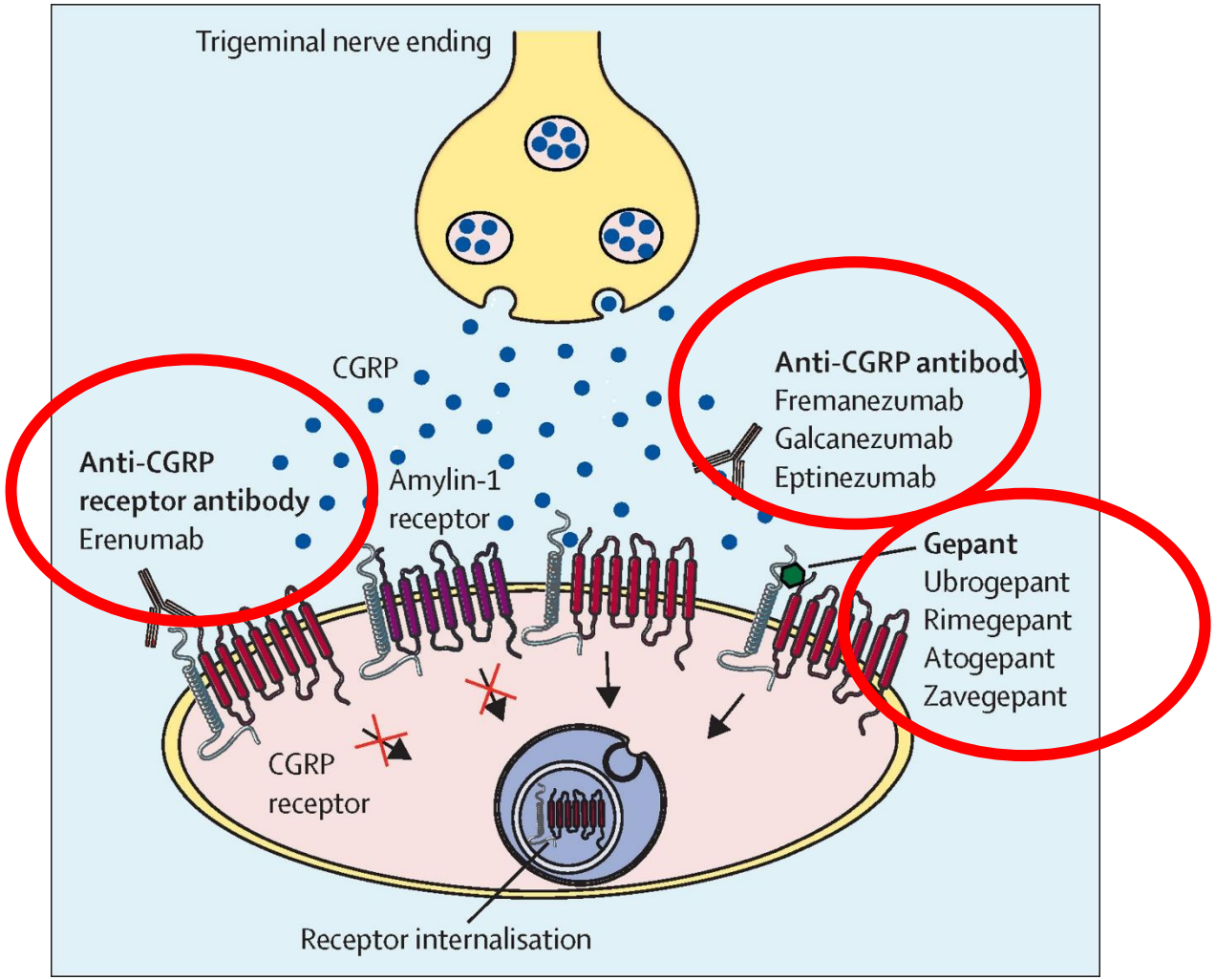
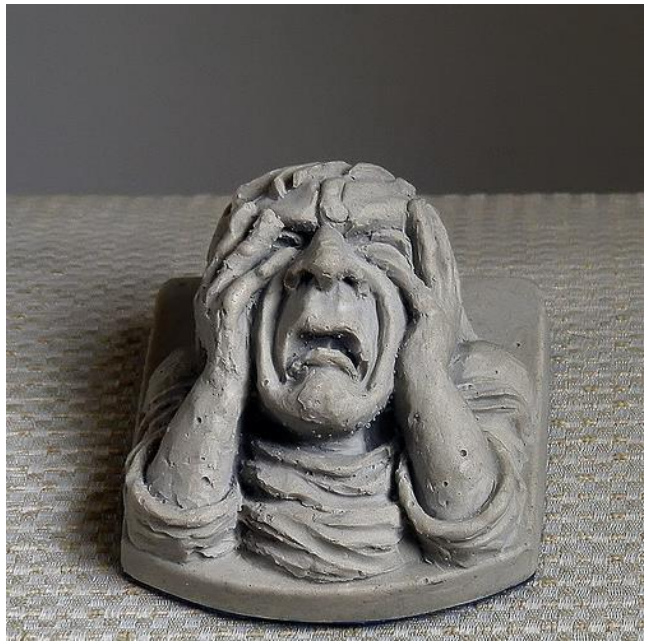
3.Demenza

ORALS TARGETING THE CGRP PATHWAY: GEPANTS

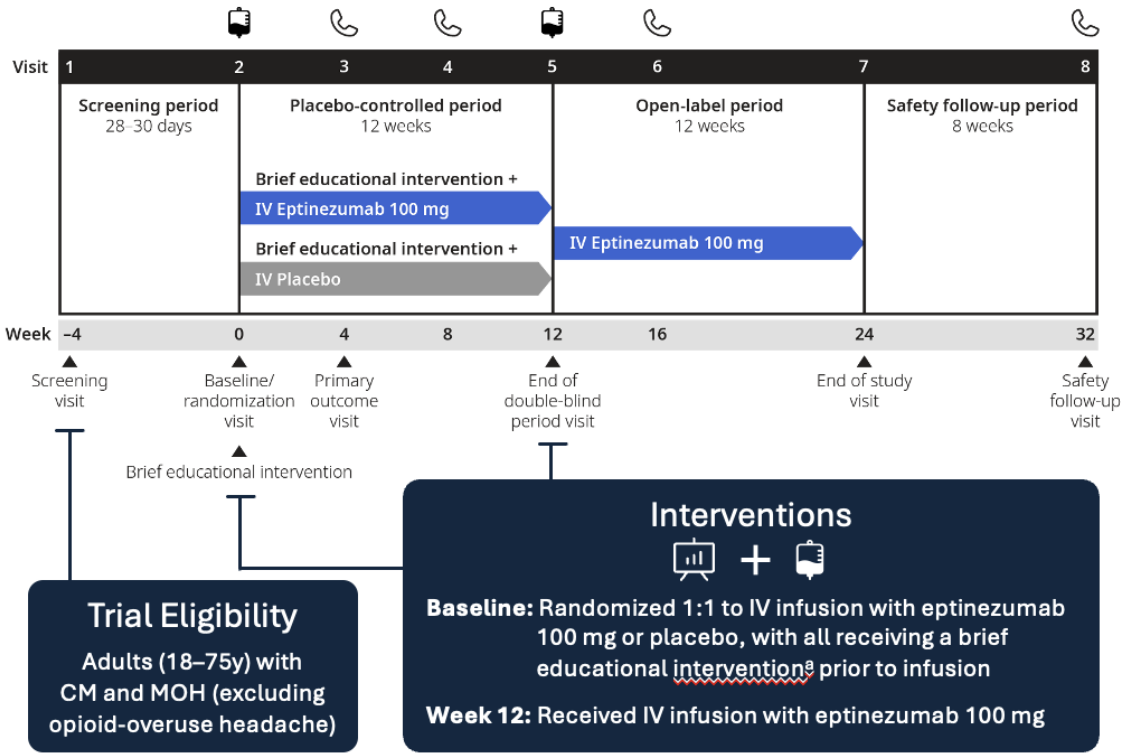




Al-Hassany et al. Lancet Neurol 2022; 21 (3):284-294.

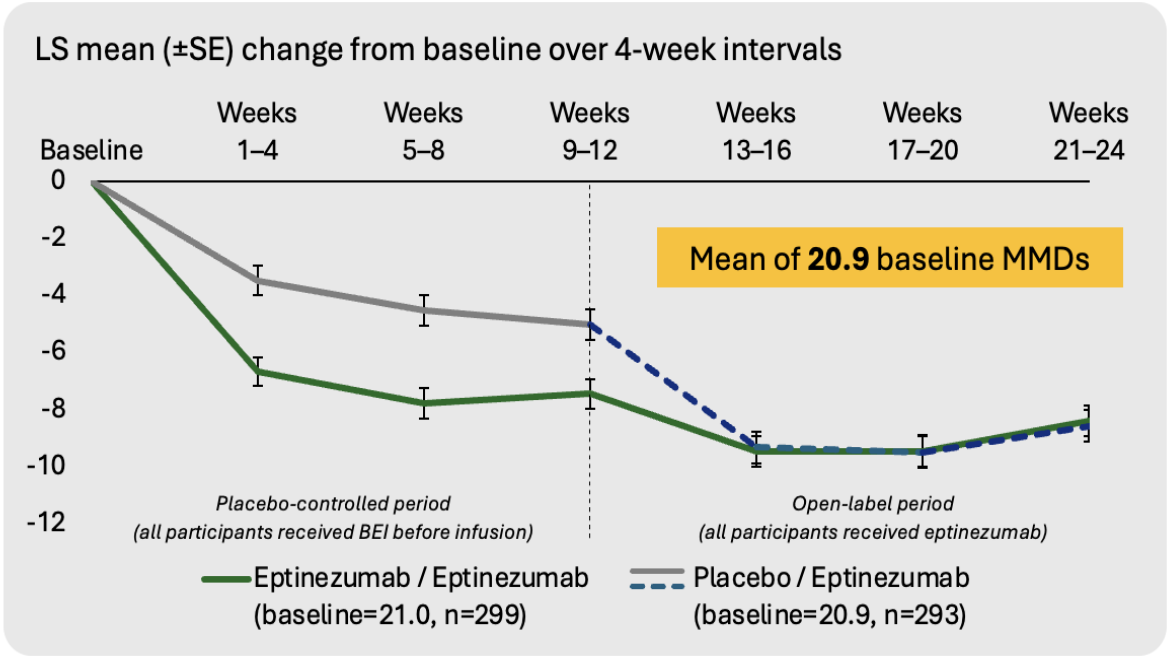
IHC25-LBA-015

Efficacy and safety of eptinezumab in adults with chronic migraine and medication-overuse headache: 24-week results of the RESOLUTION trial



608 CM+MOH

- Mean MMDs **20.9**
- Mean monthly days with acute medication use **20.1**



Presented at the 22nd Congress of the International Headache Society, September 10–13, 2025 (São Paulo, Brazil)

Fremanezumab Initiation at Early Disease Stages May Improve Migraine Outcomes: Post Hoc Analysis of the PEARL Study

Messoud Ashina,[1,2] Dimos D. Mitsikostas,[3] Patricia Pozo-Rosich,[4] Cristina Tassorelli,[5,6] Pinar Kokturk,[7] Hasan Akcicek[7]

[1]Department of Neurology, Danish Headache Center, Copenhagen University Hospital– Rigshospitalet Glostrup, Copenhagen, Denmark; [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [3]Department of First Neurology, Aeginition Hospital, National and Kapodistrian University of Athens, Athens, Greece; [4]Headache Unit and Research Group, Vall d'Hebron Hospital and Research Institute, Universitat Autonoma de Barcelona, Barcelona, Spain; [5]Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy; [6]IRCCS C. Mondino Foundation, Pavia, Italy; [7]Teva Pharmaceuticals Europe B.V., Haarlem, The Netherlands.

PEARL: Pan-European Real-Life Study (EUPAS35111)

24-month, observational, prospective Ph. 4 study

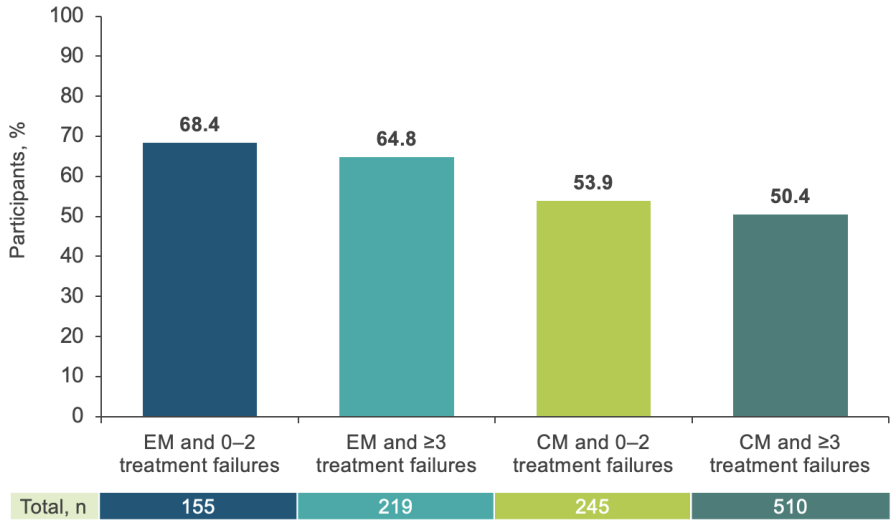
effectiveness and safety of fremanezumab

1140 adults with EM or CM

Post hoc analysis

Effectiveness in subgroups (migraine type, no. of prior preventive treatment failures)

Proportion achieving ≥50% reduction in MMD



Factors associated with a higher likelihood of 50% reduction in MMD

Variable	Odds Ratio	Lower 95% CI	Upper 95% CI	Wald Chi-Square	p-value
Migraine (EM/CM)	1.785	1.285	2.478	11.9646	**0.0005**
History of depression or anxiety (no/yes)	1.399	0.977	2.003	3.3664	**0.0665**
OnabotulinumtoxinA as premedication (no/yes)†	1.542	1.125	2.113	7.2644	**0.0070**

Trend towards enhanced effectiveness of fremanezumab in patients with EM and fewer prior treatment failures, compared with CM and more treatment failures

PO-277

A Phase 4 Randomized Double-blind Placebo-Controlled Study of Rimegepant for Acute Treatment of Migraine in Adults Unsuitable for Triptan Use

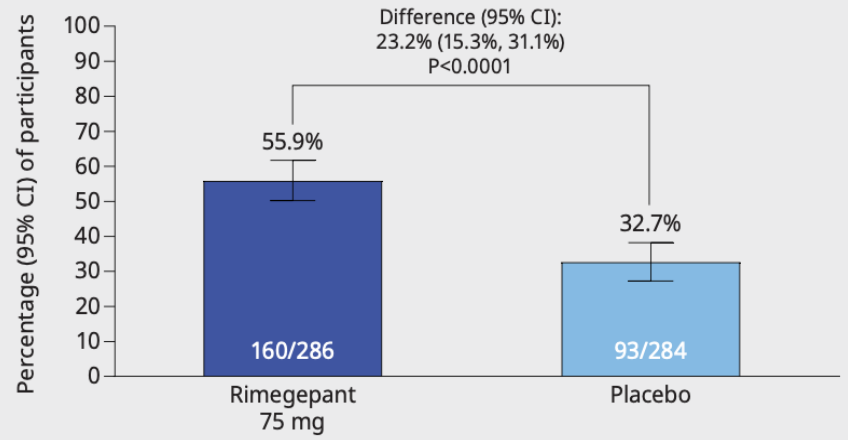
Messoud Ashina[1], Peter McAllister[2], Luz M Ramirez[3], Catherine Nalpas[4], Alexandra Thiry[5], Lucy Abraham[6], Robert Fountaine[5], Terence Fullerton[5]

[1]Danish Headache Center, Rigshospitalet, Copenhagen, Denmark; [2]New England Institute for Neurology and Headache, Stamford, CT, USA; [3]Pfizer Inc, Princeton, NJ, USA; [4]Pfizer Inc, Paris, France; [5]Pfizer Inc, Groton, CT, USA; [6]Pfizer R&D UK Ltd, Tadworth, UK

Unsuitable for triptan therapy due to:
(A) history of prior intolerance or lack of efficacy to ≥2 triptans *or*
(B) the presence of a contraindication.

Rimegepant n=295
Placebo n=290

Figure 2: Migraine pain relief at 2 h pose dose (primary endpoint)



Analyzed in all participants who were randomized only once, had a qualifying migraine attack at the time of dosing, took double-blind study intervention, and had post dose efficacy data. Groups were compared using Mantel–Haenszel risk estimation.

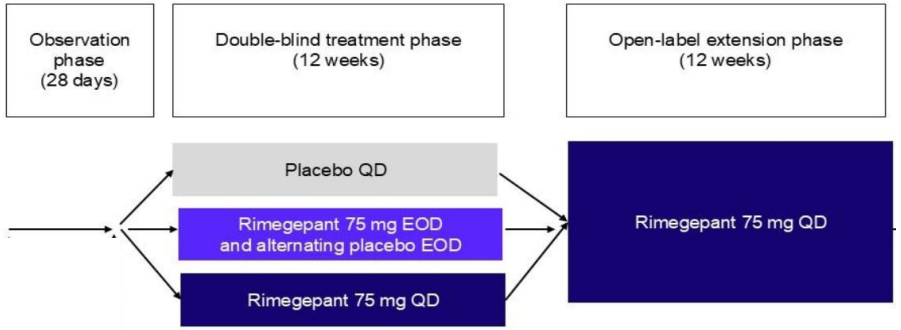
Table 2: Summary of on-treatment adverse events[a]

AE, n (%)	Rimegepant 75 mg n=295	Placebo n=290
Any AE	37 (12.5)	35 (12.1)
AE related to study drug	10 (3.4)	10 (3.4)
Mild AE[b]	31 (10.5)	19 (6.6)
Moderate AE[b]	6 (2.0)	15 (5.2)
Severe AE[b]	0	1 (0.3)
Serious AE	0	0
Hypertension AE	1 (0.3)	0
Raynaud's phenomenon AE	1 (0.3)	0

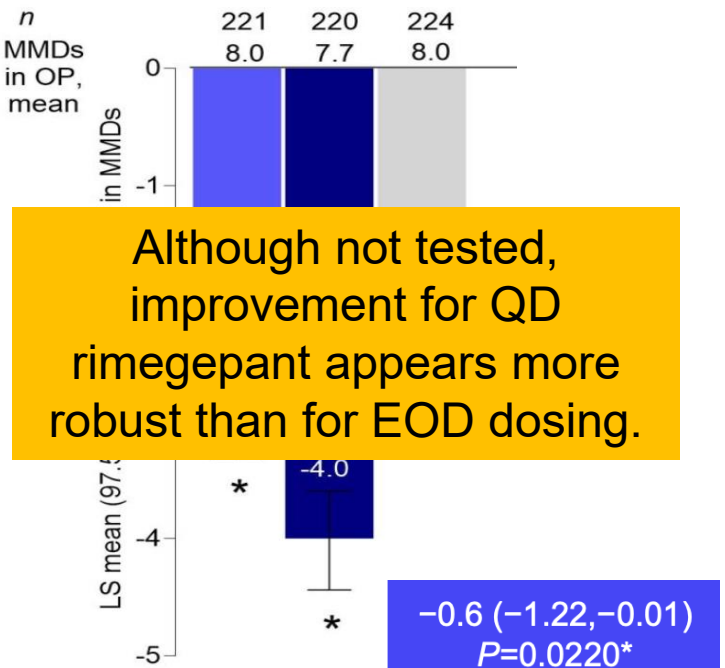
Efficacy and Safety of Two Rimegepant Dosing Regimens for the Prevention of Episodic Migraine: A Double-blind, Placebo-Controlled Study

Peter J Goadsby[1], Cristina Tassorelli[2], Robert J Fountaine[3], Jeremias Antinew[3], Patrizia de Besi[4], Sergey Dubrovin[5], Silvia Rosalia Kopf[4], Vittorio Loprinzo[3], Terence Fullerton[3]

[1]NIHR King's Clinical Research Facility, King's College London, UK & King Abdullah University of Science and Technology, Saudi Arabia; [2]University of Pavia, Pavia, Italy; [3]Pfizer, NY, USA; [4]Pfizer, Milan, Italy; [5]Pfizer, Moscow, Russia.



EP1: MMDs change



Although not tested, improvement for QD rimegepant appears more robust than for EOD dosing.

−0.6 (−1.22,−0.01)
P=0.0220*

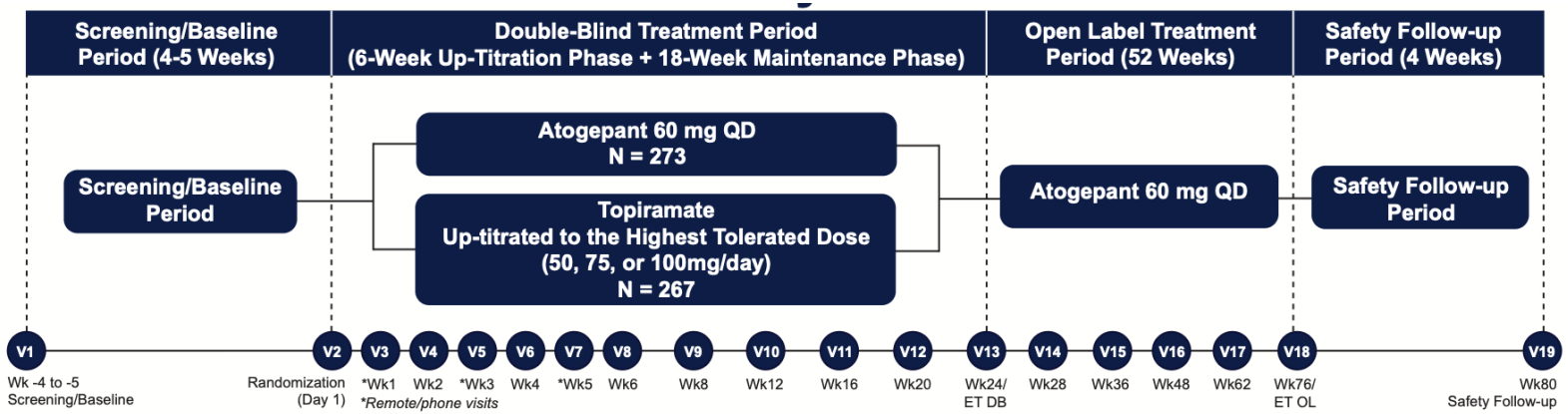
−1.8 (−2.35, −1.19)
P<0.0001*

Adverse events

Participants, *n* (%)	Double-blind treatment phase		
	Rimegepant EOD (*n* = 232)	Rimegepant QD (*n* = 229)	Placebo QD (*n* = 231)
Any AE	102 (44.0)	100 (43.7)	117 (50.6)
Mild AE	73 (31.5)	86 (37.6)	91 (39.4)
Moderate AE	42 (18.1)	22 (9.6)	43 (18.6)
Severe AE	4 (1.7)	3 (1.3)	2 (0.9)
AE related to study drug	35 (15.1)	39 (17.0)	44 (19.0)
AE leading to study drug discontinuation	6 (2.6)	1 (0.4)	4 (1.7)
Serious AE	3 (1.3)	2 (0.9)	1 (0.4)
Serious AE related to study drug	1 (0.4)	0	0
Hepatic-related AE	7 (3.0)	8 (3.5)	8 (3.5)
Hepatic-related AE leading to study drug discontinuation	4 (1.7)	1 (0.4)	2 (0.9)
Preferred terms (≥4% in any treatment group during double-blind treatment)			
Nasopharyngitis	13 (5.6)	13 (5.7)	13 (5.6)
Nausea	10 (4.3)	8 (3.5)	4 (1.7)

Tolerability, Safety, and Efficacy of Atogepant Versus Topiramate in Participants Requiring Preventive Treatment for Migraine: Results From the Head-To-Head TEMPLE Trial

Uwe Reuter, Annelies Van Dycke, Stewart Tepper, Mark Kristof Farkas, Giovanna Forero, Lei Luo, Hua Guo, Eric Cohen, Krisztian Nagy



CM/EM, MMDs 11 ATO 273 : TOP 277

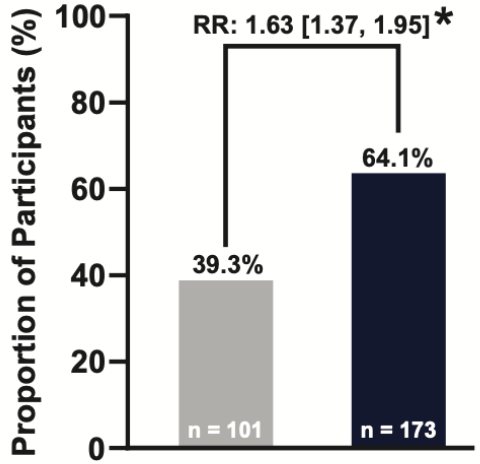
Primary Endpoint: Treatment Discontinuation Due to AEs Across 24 Weeks

	Topiramate (N = 267)	Atogepant (N = 273)
Number of Participants with AEs Leading to Treatment Discontinuation	79 (29.6)	33 (12.1)
Relative Risk (95% CI), Atogepant versus Topiramate		0.41 (0.28, 0.59)
		$P < 0.0001$

AEs, adverse events; N, number of participants from safety population.

- Atogepant demonstrated **superior tolerability with significantly fewer treatment discontinuations due to adverse events** across 24 weeks compared with topiramate

Achievement of ≥ 50% Reduction in Mean MMDs During Months 4-6



Topiramate (N = 257)

Atogepant (N = 270)

- **Significantly more participants in the atogepant group achieved a ≥ 50% reduction in mean MMDs** during Months 4-6 compared with topiramate

* $P < 0.0001$. MMDs, monthly migraine days; n, number of participants who achieved ≥ 50% improvement in mean MMDs; N, number of participants from modified intent-to-treat population.

Effectiveness and tolerability of the combination of onabotulinumtoxinA and atogepant for migraine prevention in Norway: the SYNERGY real-world study

Marina Romozzi, Luigi Francesco Iannone, Edoardo Caronna, Patricia Pozo-Rosich,

Ian Finkelstein, Dineo Seabi, Anne Hege Aamodt, Erling Andreas Tronvik, Christina Sundal

Objective

Atogepant, a small-molecule CGRP receptor antagonist, and botulinum toxin type A (BoNTA) may exert synergistic effects within the trigeminovascular system, with atogepant primarily targeting Aδ-fibers and BoNTA C-fibers. This study aimed to evaluate the effectiveness and safety of preventive treatment with atogepant added to a stable regimen of BoNTA after 24 weeks of dual therapy.

Methods

This **retrospective cohort** study, conducted at NeuroClinic (Norway), included adult patients with chronic migraine (CM) who had received **≥ three consecutive cycles of BoNTA and atogepant 60 mg daily in add-on**. Patients were evaluated at baseline (**M0) and 24 weeks (M6) after atogepant** start. Monthly migraine days (MMDs), monthly headache days (MHDs), monthly acute medication (MAMs), Headache Impact Test-6 (HIT-6) were assessed. Patients' Global Impression of Change (PGIC) scale was evaluated at M6.
The outcomes were MMDs change from M0 to M6, proportion of responders (≥50% reduction in MMDs (50%RR)) at M6, comparison between responders and non-responders, and comparison of patients naïve to monoclonal antibodies anti-CGRP (**anti-CGRP mAbs, naive) and not** (non-naive). Adverse events (AEs) were recorded.

Results

Eighty-two CM patients (93.9% females, mean age [±SD] 42.8±10.3 years) were included. **MMDs from baseline (16.4±6.8) to M6 (10.0±7.0)** achieved a reduction of 6.4±5.2 days (p<0.001). The **naive** group (n=20, 24.3%) achieved a **reduction of 6.1±5.4** MMDs (p<0.001), whereas the **non-naive** group (n=62, 75.6%) had a reduction of **6.5±5.**3 (p<0.001). At M6, 37 (45.1%) patients were 50%RR, and the mean PGIC was 5.6±1.1. A lower percentage of patients with 50%RR had used anti-CGRP mAbs (64.9% vs. 84.4%, p=0.040). Patients with 50%RR had fewer cycles of BoNTA (10.9±6.6 vs. 14.8±7.8, p=0.018), fewer prior ineffective preventive treatments (4.8±1.4 vs. 5.3±1.1, p=0.049), lower HIT-6 score (62.5±3.0 vs. 64.8±3.1, p<0.001) and higher MAMs (11.7±1.3 vs. 10.8±2.2, p=0.035) at baseline. Higher baseline MAMs increased the likelihood of 50%RR (OR=1.51, 95% CI:1.03-2.20, p=0.035), while higher HIT-6 scores (OR=0.76, 95% CI:0.63-0.92, p=0.004) and more BoNTA cycles (OR=0.92, 95% CI:0.85-1.00, p=0.049) reduced response likelihood.

Finally, 49/82 patients (59.7%) had at least one AE, all mild; none led to discontinuation.

Conclusion

The study demonstrates effectiveness, tolerability, and high PGIC scores for atogepant in add-on to BoNTA at 24 weeks in a real-world setting in a difficult-to-treat population.

IHC25-PO-317

Gepants in clinical practice

- Adverse events
  - Nausea, somnolence, (low rates), dysgeusia (nasal spray only)
- Gepant contraindications:
  - Pregnancy
  - Use with strong CYP3A4 inducers (ketaconazole, clarithromycin)
  - Ubrogepant dose should be limited to 50 mg in patients taking verapamil and in hepatic disease; avoid rimegepant
- Not believed to cause medication overuse headache
  - Rimegepant is FDA approved for prevention with every other day dosing

American Academy of Neurology

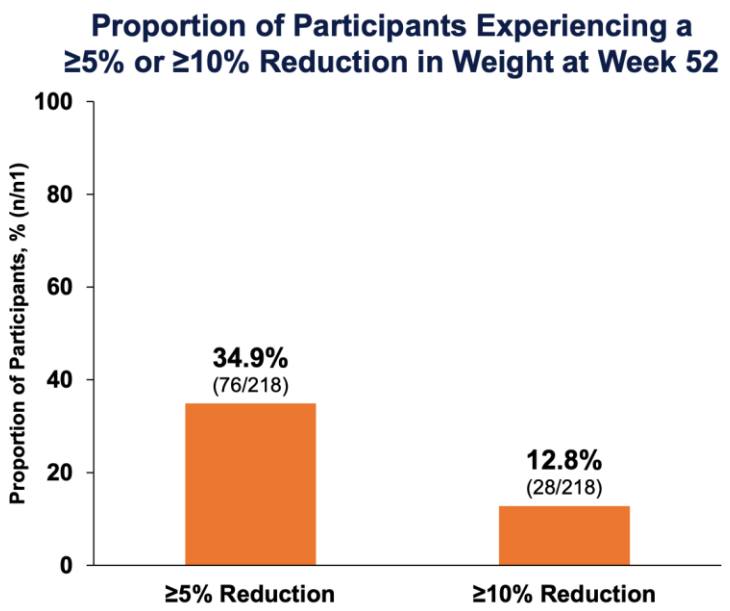
Dodick DW, et al. N Engl J Med. 2019 Dec 5;381(23):2230-2241; Lipton RB et al. JAMA. 2019 Nov 19;322(19):1887-1898; Lipton RB et al Lancet Neurol. 2023. Mar;22(3):209-217.

Weight Loss With Atogepant in Participants With Migraine and Overweight or Obesity: Interim Analysis of a Phase 3, Multicenter, Open-Label, 156-Week Extension Study

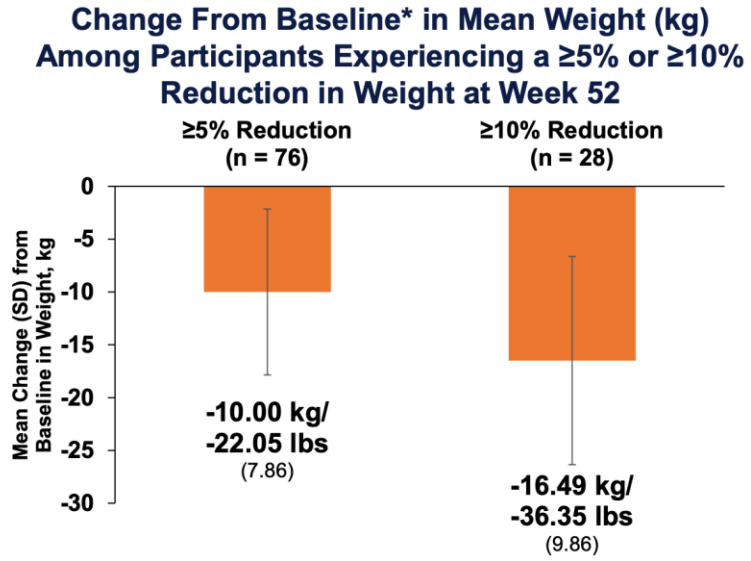
B. Lee Peterlin, Jonathan H. Smith, Jessica Ailani, Teshamae Monteith, Yingyi Liu, Eric Cohen, Krisztian Nagy, Brett Dabruzzo, Dale S. Bond

Overweight or obese participants to ELEVATE (NCT04740827; EM, failed by 2–4 preventives) or PROGRESS (NCT03855137; CM)

	N = 279
Age, mean (SD)	42.8 (11.7)
Female, n (%)	232 (83.2)
Monthly migraine days, mean (SD)	14.6 (6.1)
Weight (kg), mean (SD)	85.6 (14.6)
BMI (kg/m^2), mean (SD)	30.3 (4.8)
BMI Category, n (%)	
Overweight (25 kg/m² ≤ BMI < 30 kg/m²)	168 (60.2)
Class 1 obesity (30 kg/m² ≤ BMI < 35 kg/m²)	71 (25.4)
Class 2 obesity (35 kg/m² ≤ BMI < 40 kg/m²)	23 (8.2)
Class 3 obesity (BMI ≥ 40 kg/m²)	17 (6.1)
Number of cardiovascular risk factors, n (%)	
Only 1 Risk factor	104 (37.3)
2 Risk factors	146 (52.3)
≥2 Risk factors	175 (62.7)
≥3 Risk factors	29 (10.4)



- At Week 52, 34.9% of participants experienced a ≥5% weight reduction from baseline, while 12.8% experienced a ≥10% reduction

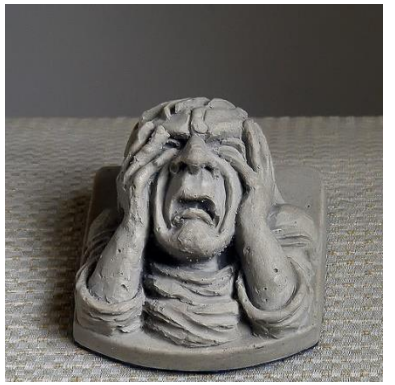


- For those who experienced a ≥5% weight reduction from baseline at Week 52, the mean weight loss was 10.00 kg (22.05 lbs)
- For those who experienced a ≥10% weight reduction from baseline at Week 52, the mean weight loss was 16.49 kg (36.35 lbs)

Candesartan versus placebo for migraine prevention in patients with episodic migraine: a randomised, triple-blind, placebo-controlled, phase 2 trial

Lise Rystad Øie, Tore Wergeland, Øyvind Salvesen, Gøril Bruvik Gravdahl, Irina Aschehoug, Sasha Gulati, Marte-Helene Bjørk, Christofer Lundqvist, Karl Bjørnar Alstadhaug, Bendik Slagsvold Winsvold, Anne Hege Aamodt, Iben Cornelia Larsen, Magne Geir Bøe, Mark Braschinsky, Bernd Müller, Kjersti Grøtta Vetvik, Kai Ivar Müller, Kjersti Aaseth, Andrej Netland Khanevski, Ane Bakke Øvrevik, Håkon Magne Vegrim, Jenny Lindroos, Karine Eid, Helene Engstrand, Burcu Bezgal, Martha Brakestad Larsen, Joakim Høgsteggen Østhus, Lars Jacob Stovner, Erling Tronvik**

IHC25-PO-307



Methods

In this **phase 2**, triple-blind, parallel group, randomized controlled trial, adults with **2 to 8 migraine** attacks per month were assigned to receive **16 mg candesartan, 8 mg candesartan, or placebo** once daily for **12 weeks**. The primary endpoint was the change in the mean number of migraine days per four weeks from baseline to weeks 9–12. Secondary endpoints included changes in headache days, triptan use, and the proportion of participants achieving a ≥50% reduction in migraine days. Safety and tolerability were also assessed.

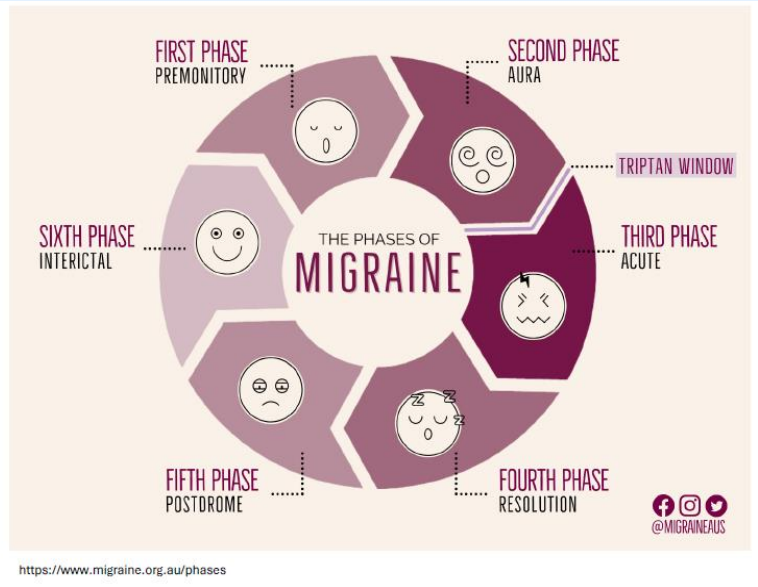
Results

A total of **458 parti**cipants were randomized (16 mg: n=156; 8 mg: n=150; placebo: n=152). At baseline, the mean number of migraine days per four weeks was **5.7.** By weeks 9–12, migraine **days decreased by 2.04 in the 16 mg group and 2.20 in the 8** mg group, compared to 0.82 in the placebo group (**P<0.001** for both candesartan groups vs. placebo; P=0.50 between candesartan doses). Both candesartan groups also showed significant reductions in headache days and triptan use (P<0.001). The ≥50% responder rate was 49% for 16 mg, 50% for 8 mg, and 25% for placebo (P<0.001). The frequency of adverse events was higher in the two treatment groups (60.9% in the 16 mg group and 60.7% in the 8 mg group) compared to the placebo group (43%). However, participants across all three groups reported minimal discomfort with the trial drug. The proportion of participants who **discontinued the trial due to inadequate tolerability was 2.2%.**

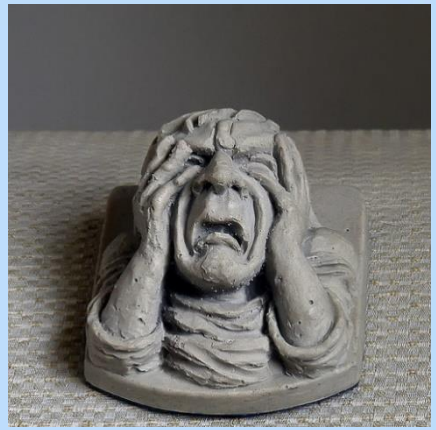
Conclusion

Candesartan 8 mg and 16 mg daily significantly reduced migraine frequency compared to placebo, with no significant difference between doses. These findings support candesartan as an effective and well-tolerated preventive treatment option for episodic migraine in both specialist and primary care settings.

Lancet Neurol 2025; 24: 817–27



https://www.migraine.org.au/phases



Interictal

The time between attacks

Sensitivity to light and sound

Nausea

Fatigue

Anxiety about another attack

Prodrome

Can be hours to days

Changes in mood, brain fog

Less appetite, or cravings

Increased thirst and urination

Muscle sti ness, neck pain

Fatigue or insomnia

Aura

'Warning' phase

Usually lasts 5-60 minutes

Visual: zig-zags, sparklers, tunnel vision

Sensory: numbness, tingling

Motor: weakness or paralysis of one side

Speech: troubl getting words out or slurring

Vestibular symptoms: vertigo, imbalance, tinnitus

Acute Phase

Lasts hours to days

Intense headache

Nausea, vomiting

Light, sound, smell sensitivity

Scalp feels tender (allodynia)

Vertigo

Fatigue

Body aches

Chills, hot ashes

Postdrome

Migraine "hangover"

May last up to 48 hours

Fatigue, brain fog

Elated or depressed mood

Trouble concentrating

Interictal

The time between attacks

Sensitivity to light and sound

Nausea

Fatigue

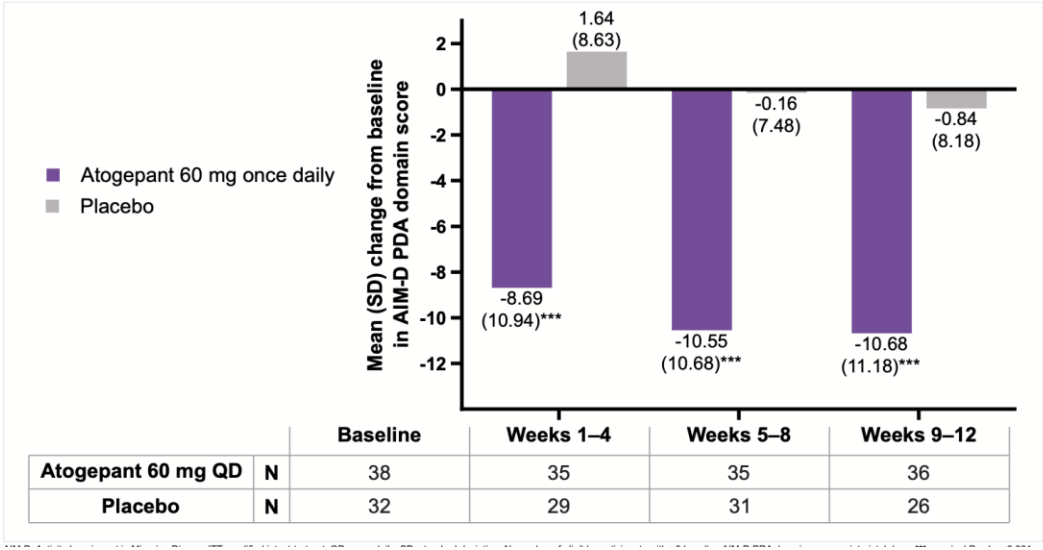
Anxiety about another attack

Atogepant Demonstrates Greater Improvement in Function Using the Activity Impairment in Migraine-Diary (AIM-D) During Interictal Days: Post-Hoc Analysis From the PROGRESS Chronic Migraine Trial

Richard B. Lipton, Pranav Gandhi, Antoinette Maassen van den Brink, Elizabeth Leroux, Rashmi Halker Singh, Molly Duan, Brett Dabruzzo, Kandavadivu Umashankar, Jonathan Stokes, Dawn C. Buse.

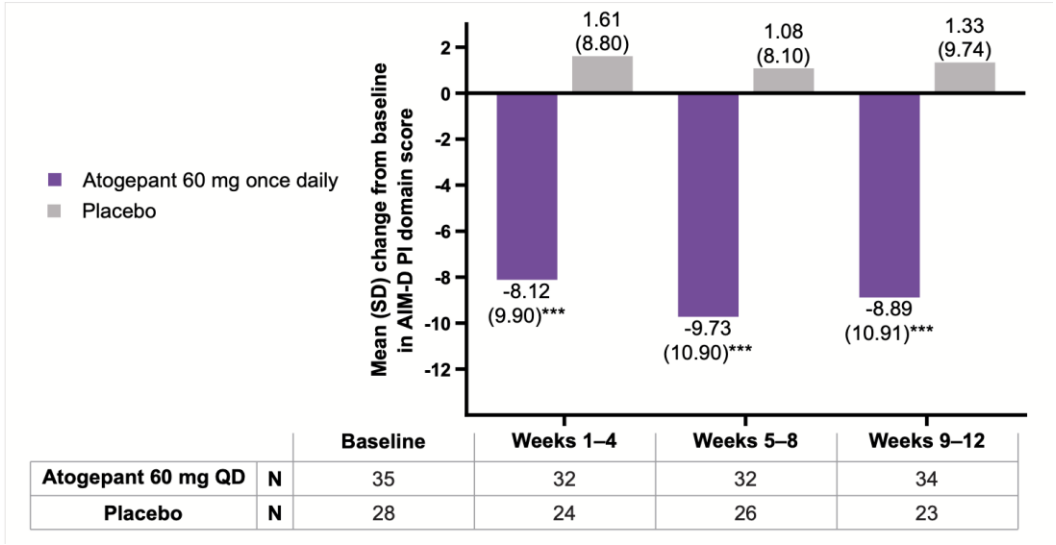
Headache day, premonitory / postdromal day (the day preceding/ following a headache day), **interictal day** (all other days).

Change From Baseline in the Performance of Daily Activities (PDA) Domain of the AIM-D at Weeks 1–4, Weeks 5–8, and Weeks 9–12 Among Participants With Chronic Migraine and at least a little Baseline Impairment on Interictal Days (mITT Population)



		Baseline	Weeks 1–4	Weeks 5–8	Weeks 9–12
Atogepant 60 mg QD	N	38	35	35	36
Placebo	N	32	29	31	26

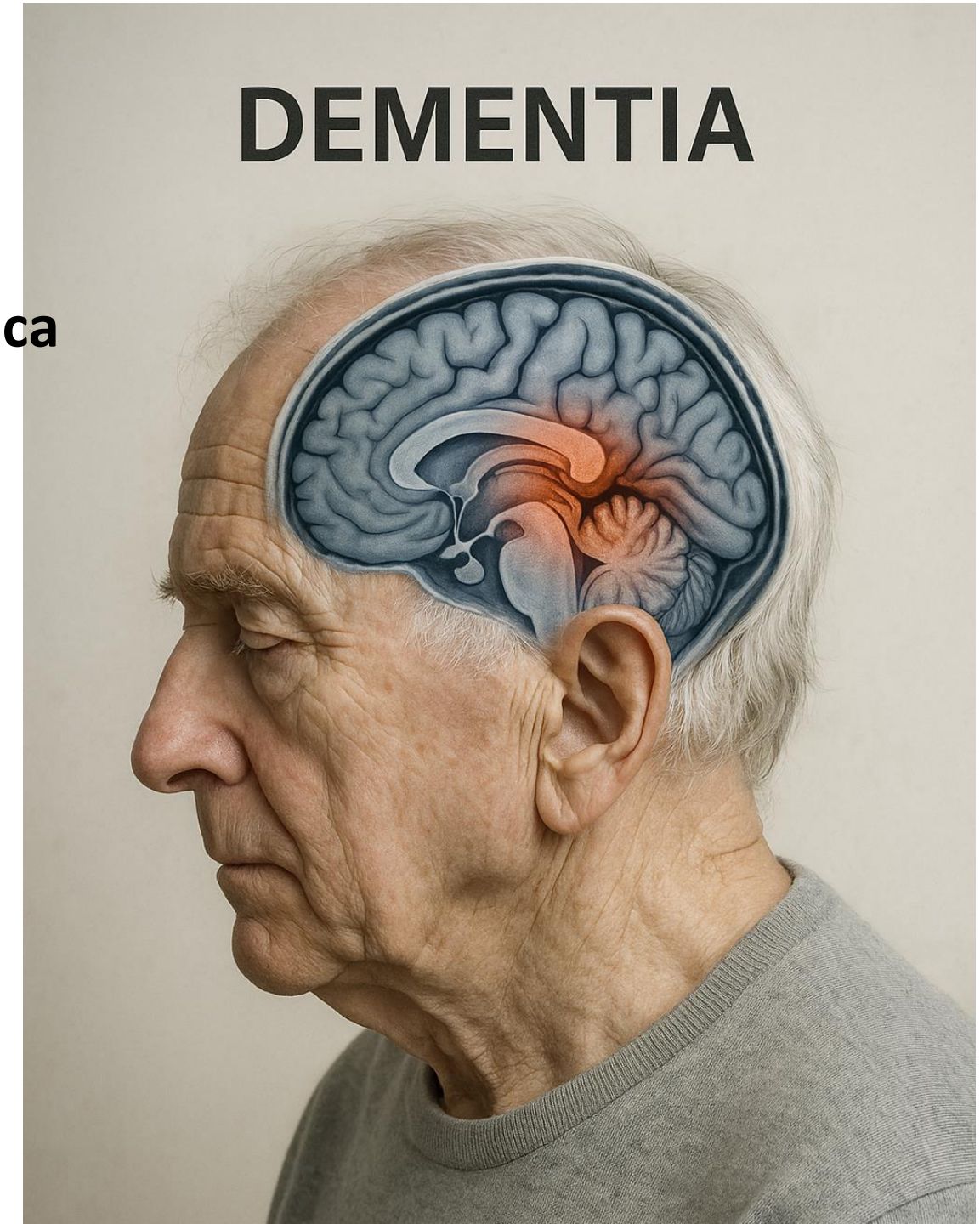
Change From Baseline in the Physical Impairment (PI) Domain of the AIM-D at Weeks 1–4, Weeks 5–8, and Weeks 9–12 Among Participants With Chronic Migraine and at least a little Baseline Impairment on Interictal Days (mITT Population)



		Baseline	Weeks 1–4	Weeks 5–8	Weeks 9–12
Atogepant 60 mg QD	N	35	32	32	34
Placebo	N	28	24	26	23

Performance of Daily Activities (PDA, 7 items): [ability to/ability to perform] chores, errands, leisure home, leisure outside, strenuous activities, concentrate, think clearly
Physical Impairment (PI, 4 items): walk, move body, bend forward, move head

Diagnostica
Terapia immunologica



AD Biomarkers

Aβ42 and tau are the core markers of AD pathophysiology

Blood phosphorylated tau for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis

Joseph Therriault, Waqner S Brum, Lydia Trudel, Arthur C Macedo, Fernando Valentim Bitencourt, Carolina Castro Martins-Pfeifer, Martin Nakouzi,

Interpretation Plasma p-tau217 is a highly sensitive and specific biomarker for Alzheimer's disease pathology, desp
high risk of bias of many studies. Prospective clinical implementation studies in real-world settings are nee
characterise the effect of plasma p-tau217 on Alzheimer's disease diagnosis and clinical management.

Lancet Neurol 2025; 24: 740–52

ocephalus)

- Seizures
- Autoimmune encephalitis

Are anti-amyloid antibodies available clinically? ...yes

Lecanemab: But does it work? Clinically...it seems so

- FDA approval in 20
  - Accelerat
  - Uses bion
  - Requirem
  - Removed
- FDA approva
  - Accelerat
  - Full FDA a
  - Also avail
- FDA approva
  - Also avail
- Indication or
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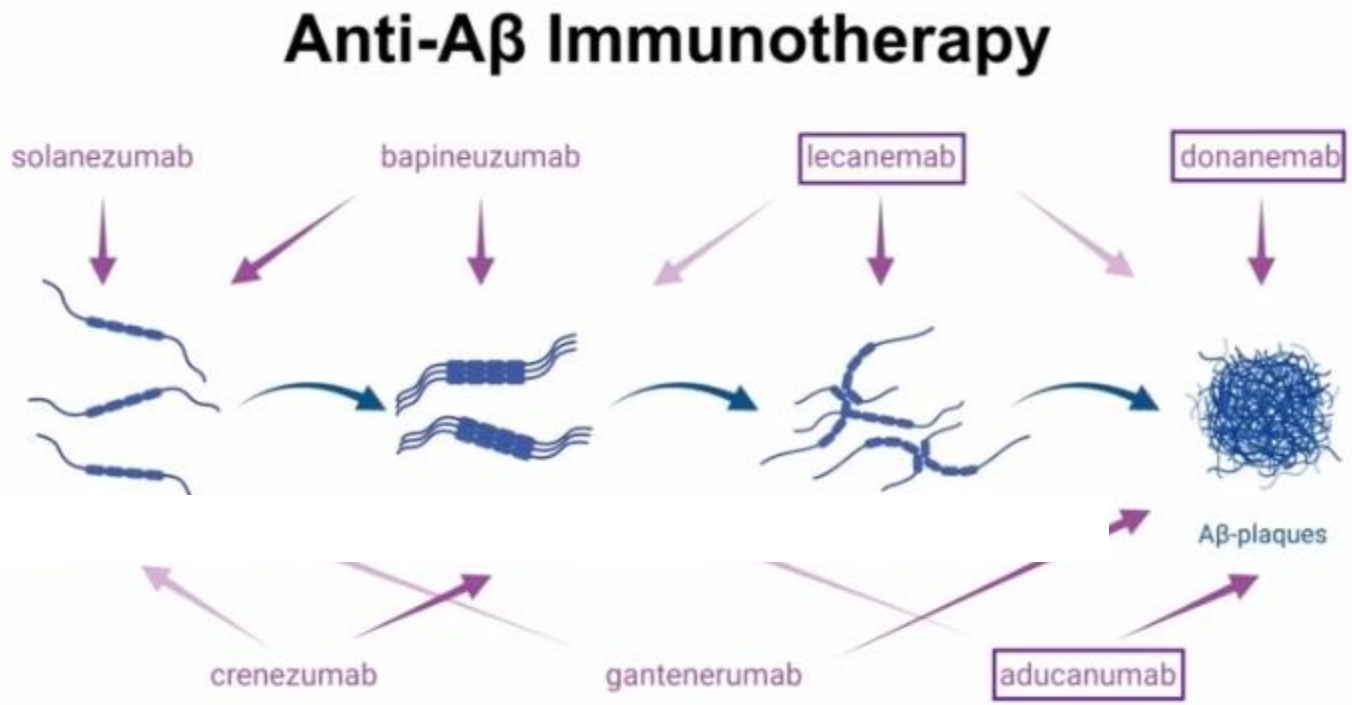


Perneczky R et al. Brain. 2023;146:842-849

LECANEMAB FOR THE TREATMENT OF EARLY ALZHEIMER'S DISEASE: THE EXTENSION OF EFFICACY RESULTS FROM CLARITY AD

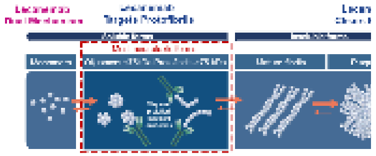
Christopher H. van Dyck,[1] David Li,[2] Shobha Dhadda,[2] Steven Hersch,[2] Larisa Reyderman,[2] Michael Irizarry,[2] Lynn Kramer[2]

1. *Yale University School of Medicine.* 2. *Eisai Inc.*

Introduction

- Lecanemab is an anti-amyloid monoclona... with highest affinity to soluble Aβ protofi... toxic than monomers or insoluble fibrils/p...
- In the 18-month phase 3 Clarity AD study, ... demonstrated a consistent slowing of dec... cognitive, functional, and quality of life) a... reduction in brain amyloid in early Alzhei...

Figure 1. Lecanemab Unique Dual Action Me...

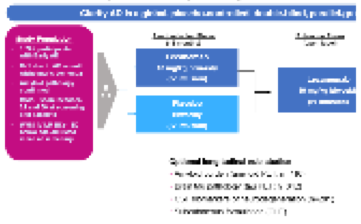


- Herein, we report the initial findings from ... Clarity AD open-label extension (OLE) stu... whether the treatment benefits were mai... in participants with early AD

Methods

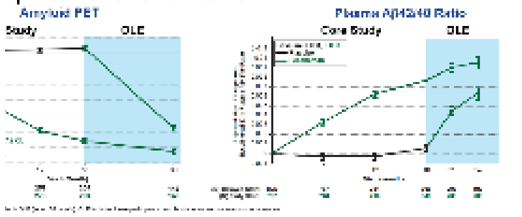
- Clarity AD is an 18-month, randomized st... with early AD, with an OLE phase where ... received open-label lecanemab (**Figure 2**)
- Clinical (CDR-SB, ADAS-Cog14, and ADCS ... (amyloid PET and plasma Aβ42/40 ratio) ... evaluated overall and by examining 'delay... followed by OLE:lecanemab) and 'early st... followed by OLE:lecanemab) cohorts
- A tau PET sub-study evaluated patients w... was conducted from patients who Time ... time to worsening were evaluated for CD...

Figure 2. Clarity AD Study Design



Results

...ity AD OLE: Biomarker Results



...mary of TEAE and ARIA (Exposure Adjusted)

- Early-stage participants (no/low tau subgroup) continue to benefit ...
- No new safety signals are observed with continued lecanemab treatment. After first six months, ARIA rates are low and similar to ...

Conclusions

- Lecanemab is a humanized IgG1 monoclonal antibody with a unique dual mechanism of action
- OLE results support disease-modifying effect and the importance of continued long-term lecanemab treatment
- Benefits accrue with lecanemab treatment through 36 months
- Early-stage patients (no/low tau or low amyloid) show stability or improvement over 18-36 months, supporting early initiation of treatment with lecanemab
- Amyloid pathway biomarkers improved at 3 months in newly treated participants and maintained/improved with continuous treatment
- No new safety signals are observed with continued lecanemab treatment, and ARIA rates are low and similar to ARIA rates on placebo after six months

REAL-WORLD EXPERIENCE WITH LONG-TERM LECANEMAB TREATMENT: A RETROSPECTIVE CHART REVIEW IN EARLY ALZHEIMER'S DISEASE

Intro

Lecanemab is a monoclonal anti
protofibrils and plaques, which
significantly slows clinical declin
measures in early Alzheimer's d
As lecanemab is an approved AD
there are limited real-world dat
profile, prescribers, and utilizati
The objective of our study was t
treatment of individuals with ea

Me

We conducted a single-center,
patients with confirmed early A
Clinical Trial Center of Abington
Data collection included patient
history, lecanemab treatment e
diagnosis to treatment
Assessments included N-psych
question survey by patients/car
Patient satisfaction participants
and therapy's burden on a scale
satisfied)

Re

A total of 94 patients with early
included (**Table 1**), with a mean

Table 1. Patient Characteristics

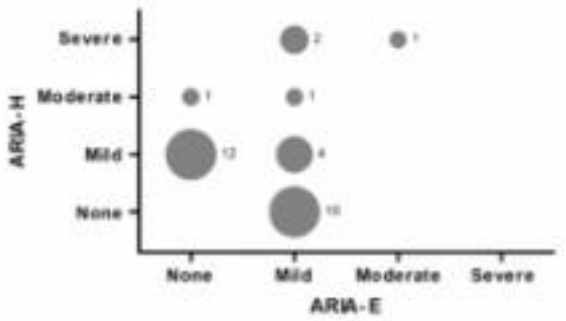
Characteristic	
Mean age, years	
Female, n (%)	
Race	
Caucasian	
Black	
Asian	
Other	
Clinical subgroup, n (%)	
Mild cognitive impairment due to to A	
Mild dementia due to Alzheimer's dise	
ApoE ε4 status, n (%)	
Noncarrier	
Carrier	68 (72)
Heterozygotes	57 (61)
Homozygotes	11(12)
Mean duration of disease, years (range)	2.9 (1-9)

Early Clinical Experience Suggests Limited Uptake and Safe Implementation of Aβ-Targeting Therapies

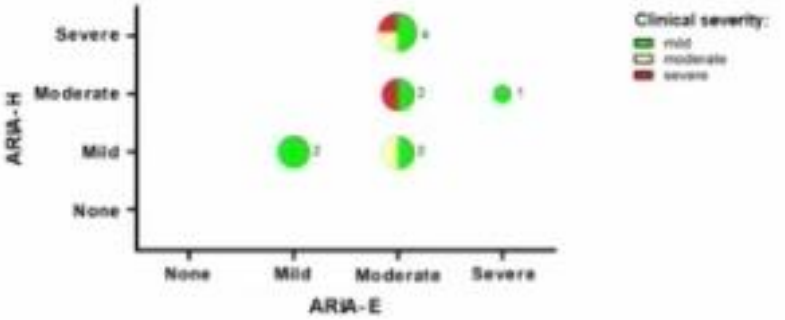
Washington University memory clinic Aug '23 – Sept '24

- **Limited uptake of treatment**
  - 234/4,060 patients seen (5.8%) initiated lecanemab
  - Represents 15.8% of all *eligible* patients
- **ARIA rates similar to clinical trials**
  - 21.6% overall , 5.7% symptomatic
  - 3 cases clinically severe, 1 case radiographically severe

a) ARIA radiographic severity- asymptomatic



b) ARIA radiographic severity- symptomatic



Data courtesy of Dr. Suzanne Schindler, Washington University

Acknowledgments / Disclosures

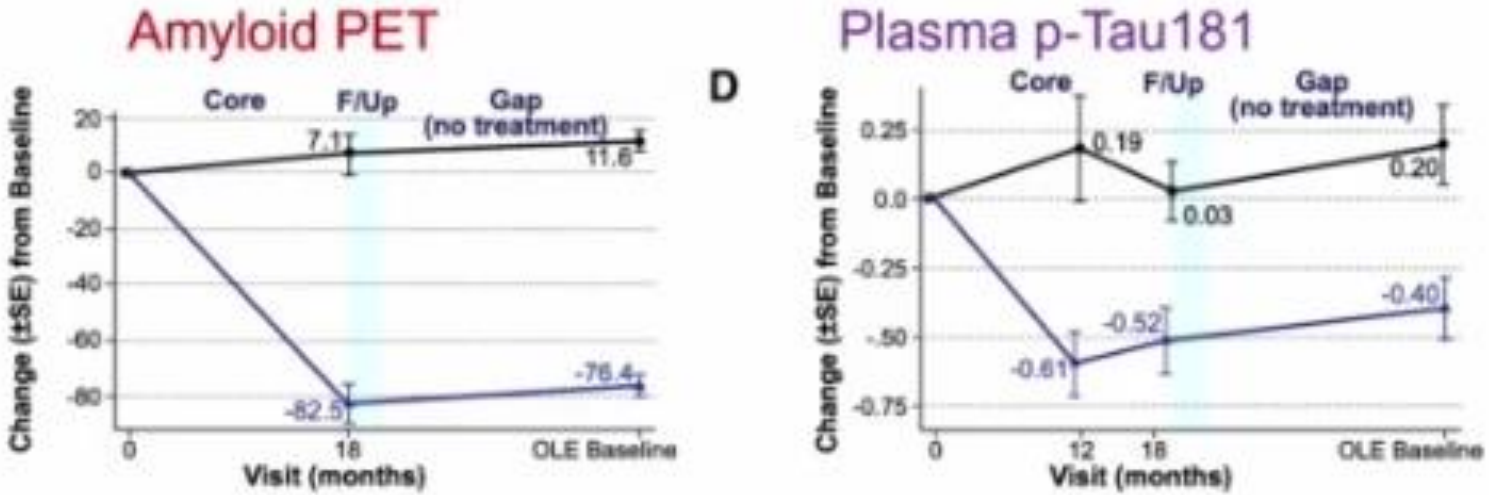
References
1. Söderberg L, et al. Neurotherapeutics. 2022 Oct 17. 2. van Dyck CH, et al. N Engl J Med. 2023;388:9-21. 3. Lecanemab prescribing information Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269s001lbl.pdf Accessed March 22, 2024. 4. Stern AM, et al. Neuron. 2023;111:2012-2020.e4. 5. Ono K, Hampel H. Int J Mol Sci. 2020;21:952. 6. Tucker S, et al. J Alzheimers Dis. 2015;43:575-88. 7. Lord A, et al. Neurobiol Dis. 2009;36:425–34. 8. Sehlin D, et al. PLoS One. 2012;7:e32014. 9. Sehlin D, et al. Neurodegener Dis. 2011;8:117–23. 10. Logovinsky V, et al. Alzheimer's Research & Therapy. 2016;8:14.

Presented at the American Academy of Neurology (AAN) 2025 Annual Meeting, April 5–9, 2025, San Diego, CA, USA. Poster 012.

If you have any questions about this poster, please email or call Eisai Medical Information at US_MedInfo@eisai.com or 888-274-2378

Lecanemab: Maintenance Treatment Approach

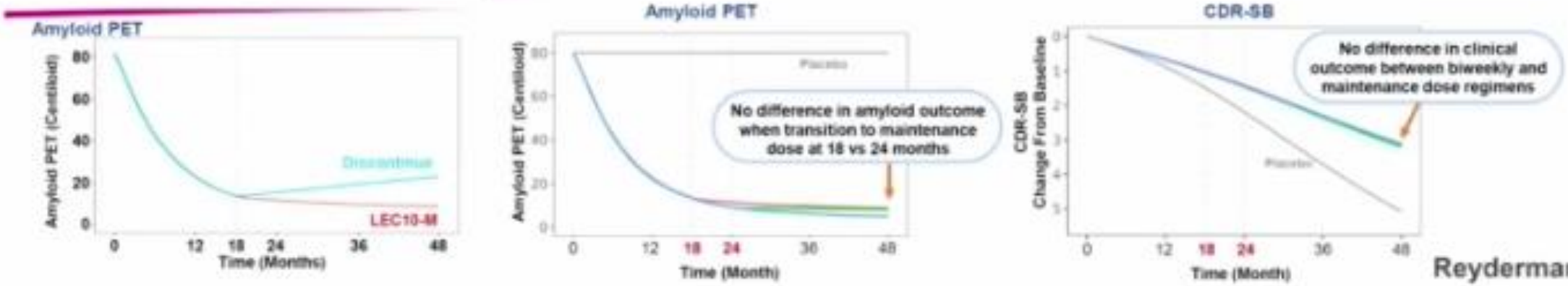
Lecanemab Open-Label Extension



McDade E et al. Alzheimers Res Ther Dec 2022;14(1)191

FDA Prescribing Information:
After 18 months, can continue 10 mg/kg every two weeks, or transition to maintenance dosing of 10 mg/kg every 4 weeks

Modeling maintenance dosing effects



Reyderman L et al. AAIC 2024

The Importance of Early Recognition and Treatment Initiation for Managing Alzheimer's Disease: Subpopulation Analysis of the TRAILBLAZER-ALZ 2 Randomized Trial

Raghavendra Vasudeva[1], Erin Doty[1], Fan E. Yang[1], Cynthia D. Evans[1], Jennifer A. Zimmer[1], Ming Lu[1], Peter McAllister[2], Jasdip Singh[1], John Sims[1]

[1]Eli Lilly and Company, Indianapolis, IN, USA
[2]New England Institute for Neurology and Headache, Stamford, CT, USA

American Academy of Neurology
San Diego, CA, and Online
April 5–9, 2025

TRAILBLAZER-ALZ 2 BACKGROUND AND METHODS

- Phase 3, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of donanemab
- TRAILBLAZER-ALZ 2 demonstrated treatment benefits of donanemab in participants with baseline clinical (MCI and mild dementia due to AD) and neuropathological (evidence of amyloid and tau pathology) characteristics.

Objectives and methods

- The efficacy and safety of donanemab were assessed in a pre-specified subpopulation of participants (placebo, N=105; donanemab, N=123) with MCI (baseline MMSE score ≥ 27) and low-medium tau neuropathology burden as measured by tau PET.

Abbreviations: MCI: mild cognitive impairment; MMSE: Mini-Mental Status Exam; PET: positron emission tomography

PHASE 3 PRIMARY OUTCOME: iADRS DISPLAYED 60% SLOWING IN THE MCI WITH LOW-MEDIUM TAU SUBPOPULATION

SUMMARY

JAMA Neurology | Original Investigation

Posttreatment Amyloid Levels and Clinical Outcomes Following Donanemab for Early Symptomatic Alzheimer Disease

A Secondary Analysis of the TRAILBLAZER-ALZ 2 Randomized Clinical Trial

Ming Lu, MD; Min Jung Kim, MS; Emily C. Collins, PhD; Sergey Shcherbinin, PhD; Amy K. Ellinwood, PhD; Yuma Yokoi, MD; Dawn A. Brooks, PhD; Oskar Hansson, MD, PhD; David S. Knopman, MD; John R. Sims, MD; Mark A. Mintun, MD

JAMA Neurol. doi:10.1001/jamaneurol.2025.3869
Published online October 13, 2025.

CONCLUSIONS AND RELEVANCE The findings in this secondary analysis of a randomized clinical trial demonstrating a correlation between posttreatment amyloid plaque level and clinical benefit support amyloid plaque removal as the mechanism of action for donanemab treatment and the level of amyloid plaque as a potential surrogate biomarker in amyloid-targeting therapies.

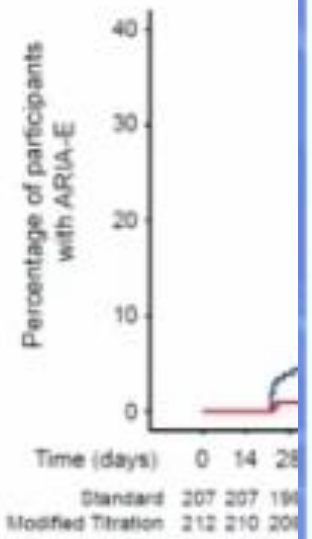
Mitigating ARIA: Donanemab Dose Titration
TRAILBLAZER-ALZ6 Trial

Standard Donan

Month 1: 700 mg | Month 2: 700 mg

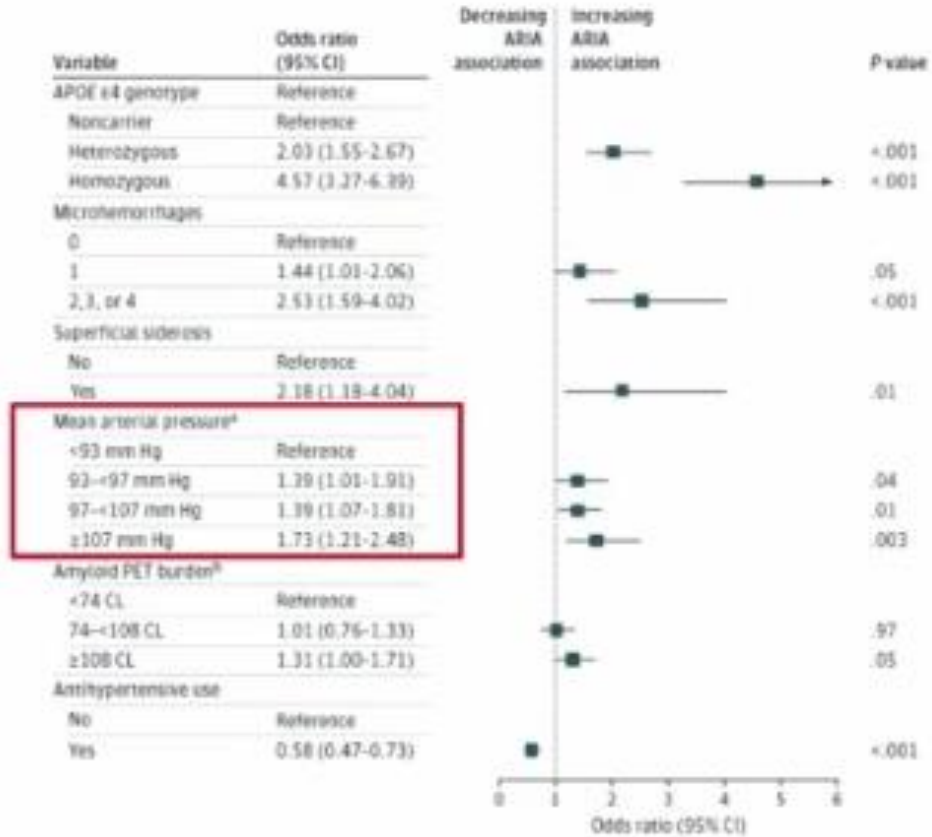
Modified Donan

Month 1: 350 mg | Month 2: 700 mg



Mitigating ARIA: What are the Risk Factors?

- Machine learning to identify predictors of ARIA-E in Donanemab clinical trials from 42 variables
  - Patient demographics
  - Weight, BP
  - Disease stage
  - Genetics (*APOE, BIN1*)
  - MRI, Amyloid/Tau PET
  - Blood Biomarkers



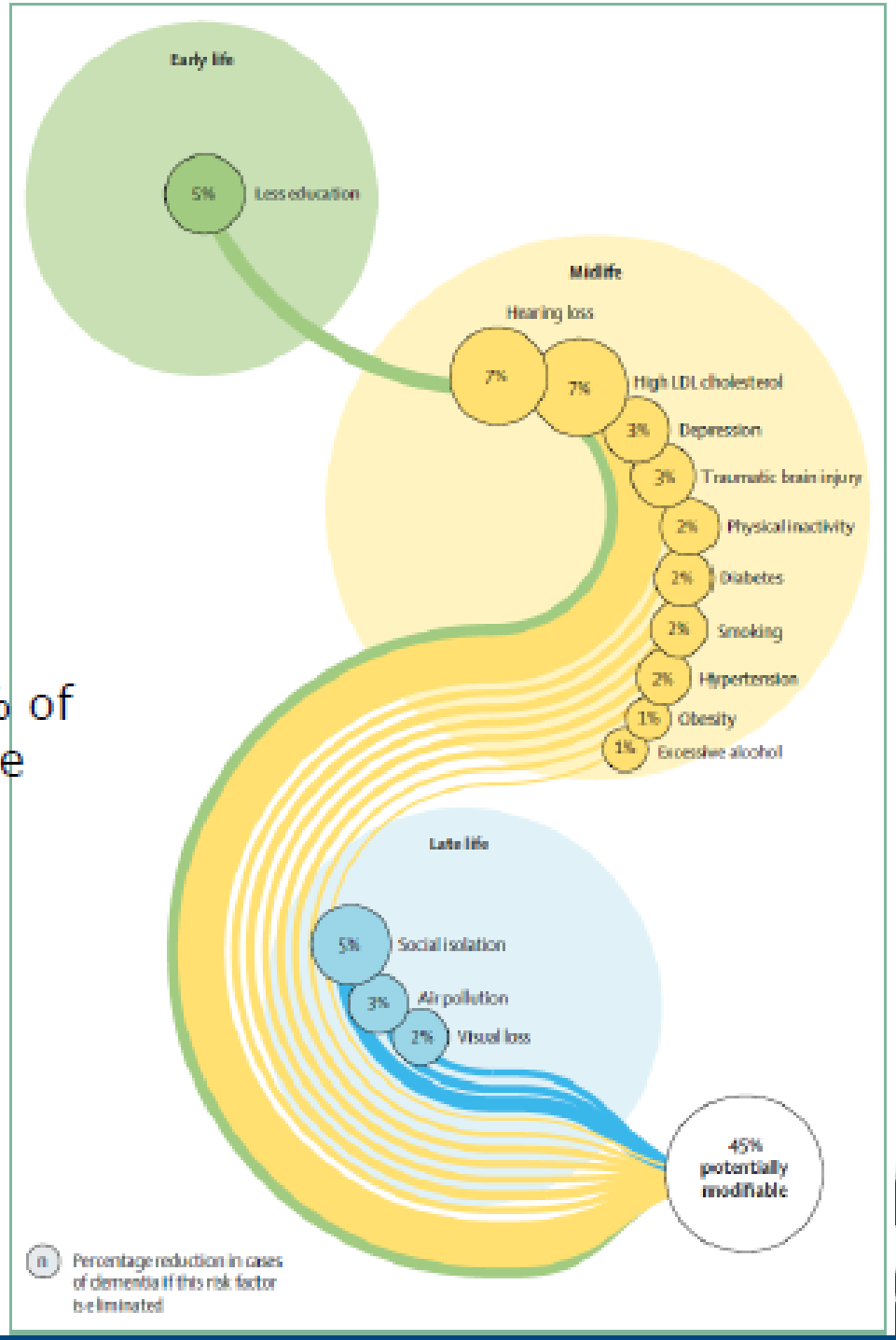
Zimmer JA et al. JAMA Neurol. 2025 10;e250065

Non-pharmacological treatments

with personalizesed activities, enjoyable exercice and environmental strategies improve apathy and depression

1. Cognitive activity
2. Depression
3. Mediterranean diet
4. Obesity
5. Hypertension
6. Smoking
7. High cholesterol
8. Type 2 diabetes
9. Physical inactivity

As much as 40% of dementia may be preventable



Livingston et al. Lancet. 2024

Take home message

Stroke sotto terapia anti-coagulante non cambiare DOAC

- ripresa DOAC (rischio/benefici) →8 settimane
- ripresa ASS → 1 settimana

Anti-CGRP e Gepants sono più efficaci delle terapie profilattiche standard e l'efficacia è confermatasul lungo termine

- terapie efficaci nel «post-drome»

Stadi precoci e di entità lieve di M. Alzheimer rispondono meglio ad una terapia immunologica

- plasma pTau 217 «game changer» nella diagnostica