Specific Issues of Anti-CGRP Treatment:

Safety, tolerability & wearing-off

Dagny Holle-Lee

Conflicts of interest

Advisory boards:	Allergan ● Lilly ● Teva ● Amgen ● Novartis
Educational boards:	Allergan ● Bayer ● Lilly ● Teva ● Novartis ● Hormosan
Speaking engagements:	Allergan ● Bayer ● Lilly ● Teva ● Amgen ● Novartis ● Hormosan ● Zuellig Pharma

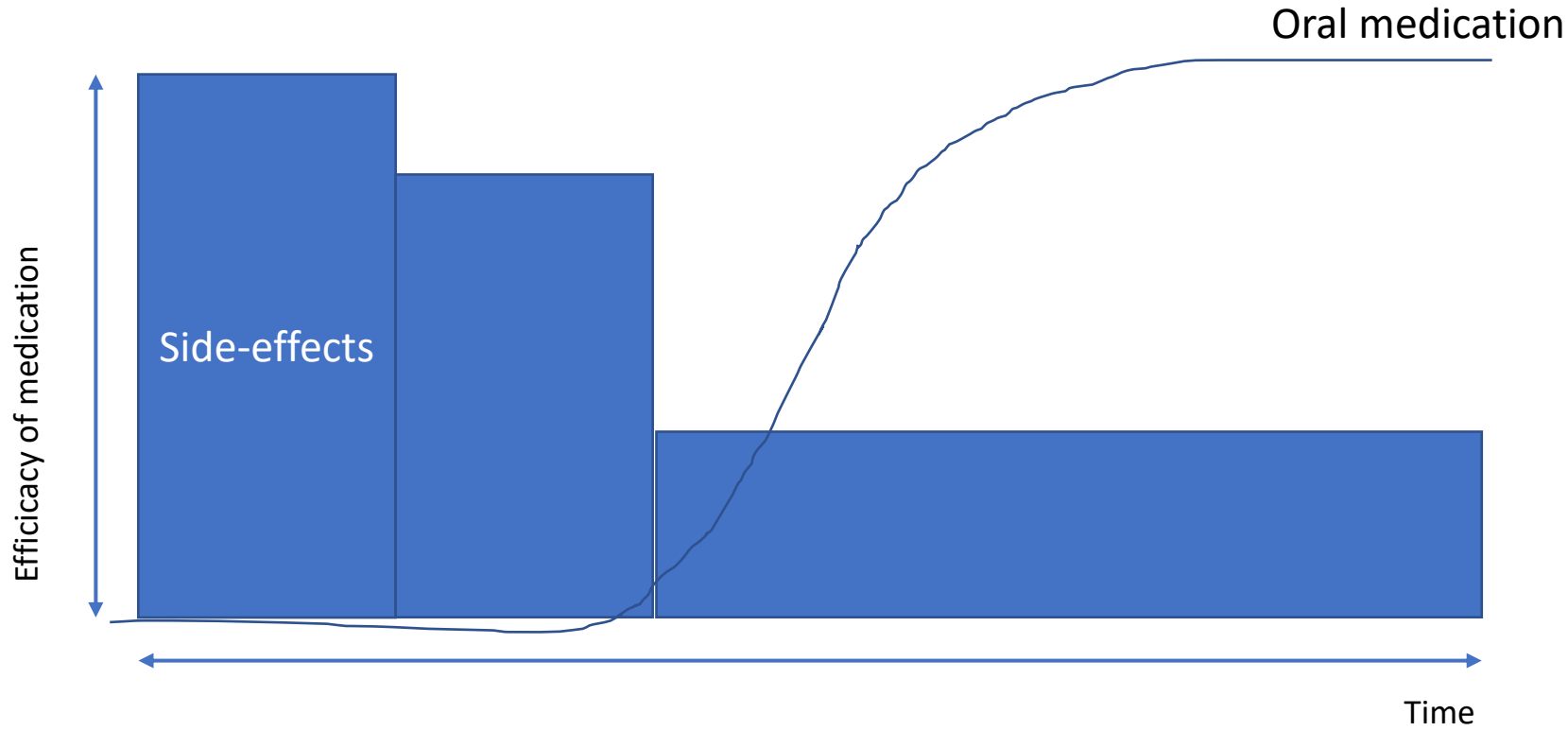
Tolerability?

Side effects and tolerability of oral first line prophylactic medication

- Cognitive dysfunction
- Weight gain
- Fatigue, sleepiness
- Reduction of blood pressure
- Disturbances of heart rhythm

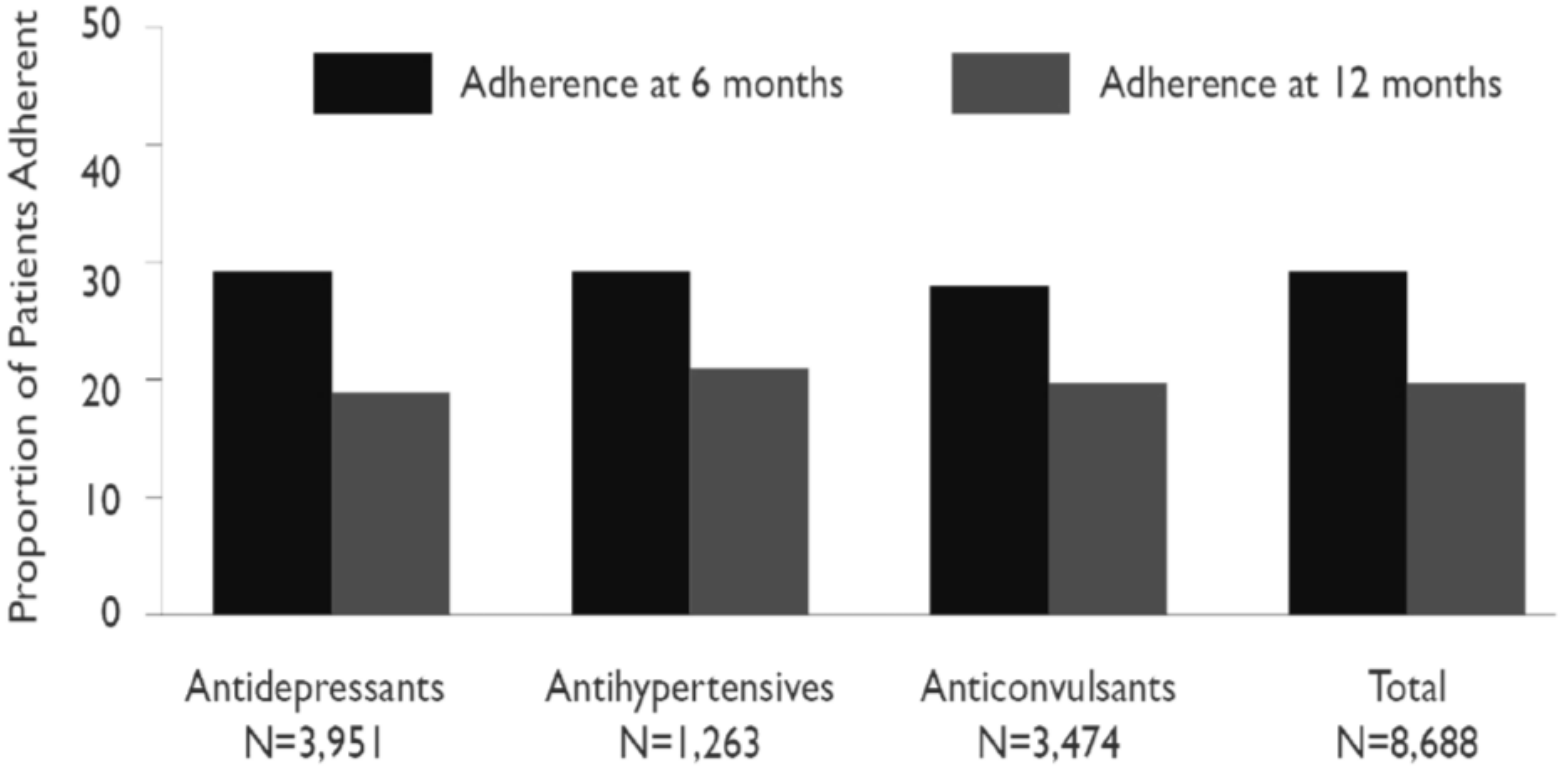
Many patients do not start with oral migraine prophylactic medication or complain about the medication because of tolerability problems

Side effects occur first in oral migraine prophylactic treatment



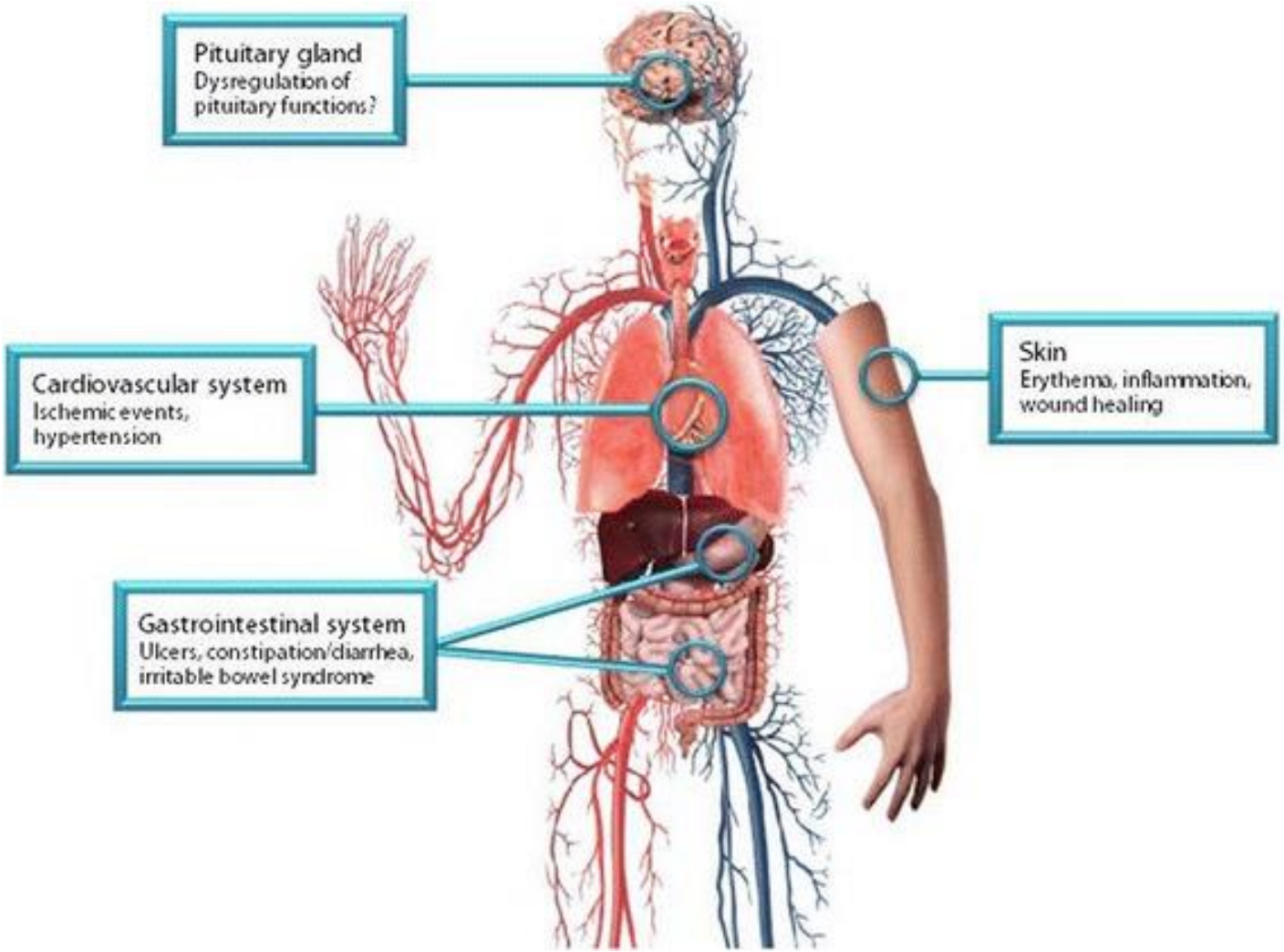
Efficicacy occurs second

Adherence of migraine prophylactic medication



Hepp et al. Adgerence to oral migraine-preventive medications among patients with chronic migraine; Cephalalgia 2015

Possible (adverse) effects of CGRP therapy



Deen et a. Blocking CGRP in migraine patients- a review of pros and cons. J Headache Pain 2017

Anti-CGRP mAbs are generally well tolerated

THE TOLERABILITY OF ANTI-CGRP mAbs HAS BEEN DEMONSTRATED IN PHASE 3 RCTS[1–4]

Injection site reactions and nasopharyngitis among most common AEs[1–10]

Few patients discontinued treatment as a result of AEs[1–10]

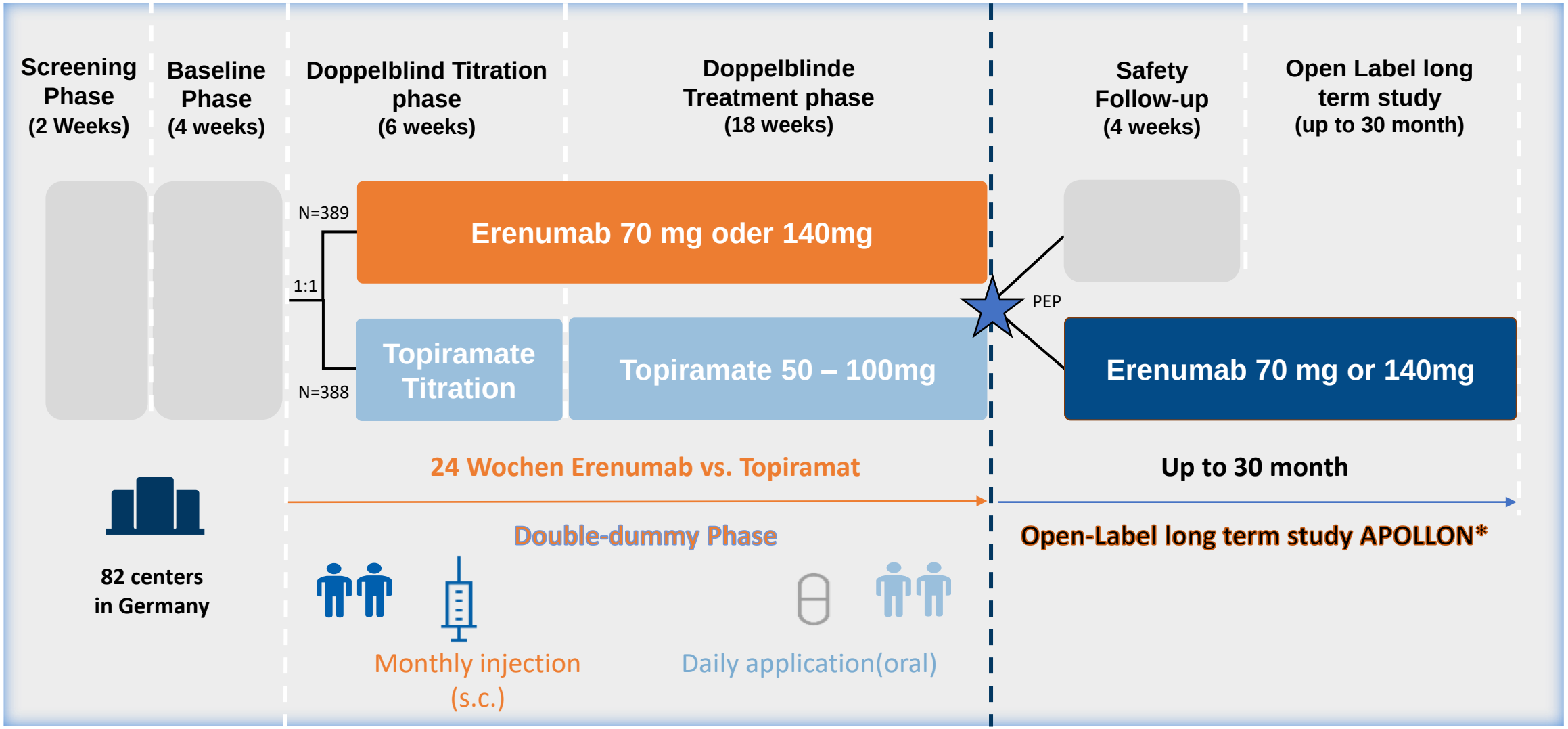
No meaningful changes in vital signs, physical-examination findings, or ECG results[6,8]

Low rates of ADA development and adverse events related to ADAs[11]

ADA, anti-drug antibody; AE, adverse event;
ECG, electrocardiogram;
RCT, randomized controlled trial

1. Dodick DW, et al. JAMA 2018;319:1999–2008; 2. Dodick DW, et al. Cephalalgia 2018;38:1026–37; 3. Goadsby PJ, et al. N Engl J Med 2017;377:2123–32;
4. Stauffer VL, et al. JAMA Neurol 2018;75:1080–8; 5. Skljarevski V, et al. Cephalalgia 2018;38:1442–54. 6. Silberstein S, et al. N Engl J Med 2017;377:2113–22;
7. Tepper S, et al. Lancet Neurol. 2017;16:425–34. 8. Detke H, et al. Neurology 2018;91:e2211–e2221; 9. Ashina M, et al. Cephalalgia 2020;40:241–254;
10. Lipton RB, et al. Neurology 2020;94: e1365–e1377; 11. Cohen J, et al. J Headache Pain 2021;22:3.

The HERMES Study: Tolerability of Erenumab compared to topiramate



PEP, primary endpoint

The Journal of Headache and Pain 2021, 22(Suppl 1):103

Primary outcome: Treatment break

Randomised (1:1)

Erenumab
(70 /140 mg), s.c.
N = 388

Under treatment

Topiramate
(50–100 mg), oral
N = 388

Under treatment

Treatment break because of AEs in the Erenumab group

10.6 %*

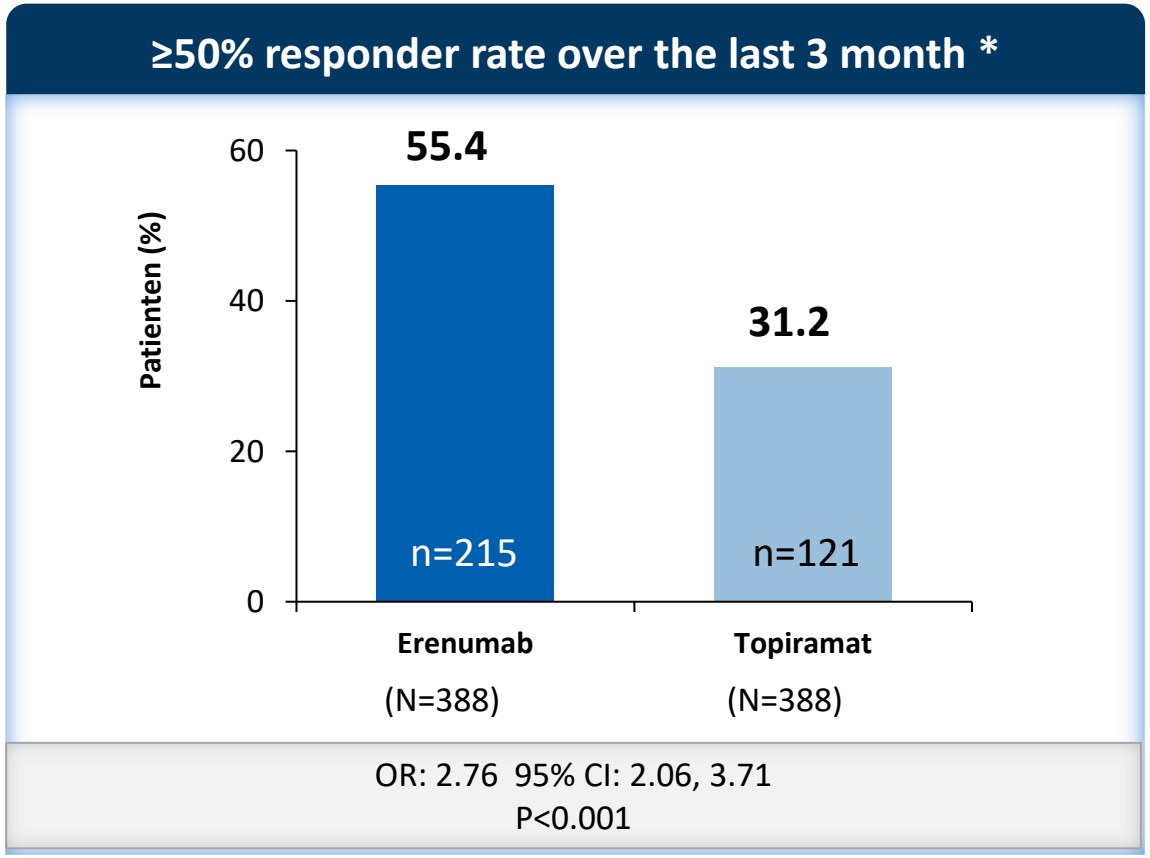
38.9 %*

Treatment break because of AEs in the Topiramat group

AE, *adverse event ;* *OR: 0.19 95% CI: 0.13, 0.27, P<0.001
Headache, June 2021, Volume 61, Issue S1

Erenumab is tolerated better and more efficious than topiramat

Phase 4 (HER-MES)



Patients treated with erenumab had a 3 times higher risk (OR=2.76) of reduktion of her MMD by 50% or more compared to patients taking topiramate.

* month 4 – 6

CI, *confidence interval*; MMT, monthly migraine days; OR, *odds ratio*

Headache, June 2021, Volume 61, Issue S1

Safety?

Arterial hypertension?

CGRP and blood pressure

- Vasodilative properties
- Effects on the renin-angiotensin-system

Erenumab and blood pressure

- Preclinical data demonstrated that supratherapeutic concentrations of erenumab affected neither the vascular tone of isolated human coronary arteries
- Combination of sumatriptan and erenumab showed no vasoconstrictive effects
- In telemeterized cynomolgus monkeys, no biologically significant changes in systolic, diastolic, or mean arterial pressures were observed with a single dose of erenumab at 225 mg/kg (yielding a systemic exposure 150 times higher than that in humans at the 140 mg dose level).

Bussiere JL et al. Nonclinical safety evaluation of erenumab, a CGRP receptor inhibitor for the prevention of migraine. Regul Toxicol Pharmacol. 2019

Pooled analysis of hypertension AEs and antihypertensive medication use during 12 DBTP

	Placebo (*N* = 1043)	Erenumab 70 mg (*N* = 893)	Erenumab 140 mg (*N* = 507)
Incidence of hypertension AEs, *n* (%)[7]	9 (0.9)	7 (0.8)	1 (0.2)
Serious hypertension AEs, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)
Exposure-adjusted incidence rates of hypertension, per 100 patient-years	3.6	3.3	0.8
Patients without antihypertensive medication at baseline, *n*	972	859	485
Patients initiating antihypertensive medication[a] during 12-week DBTP, *n* (%)[b]	12 (1.2)	7 (0.8)	1 (0.2)

Dodick et al. Risk of hypertension in erenumab-treated patients with migraine: Analyses of clinical trial and postmarketing data. Headache 2021

Postmarketing studies

	N = 355 cases
Sex, *n* (%)	
Female	261 (73.5)
Male	45 (12.7)
Unknown	49 (13.8)
Age,[a] years	
Mean	53.1
Median (range)	53 (24–87)
Age group,[a] years, *n* (%)	
24–30	12 (4.8)
31–40	25 (9.9)
41–50	58 (23.0)
51–60	80 (31.7)
61–70	55 (21.8)
71–80	17 (6.7)
81–87	5 (2.0)

[a] Based on data available for 252 cases.

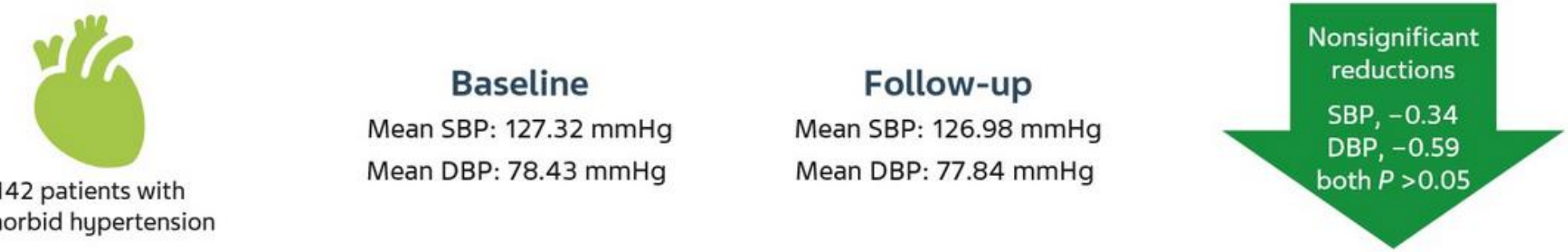
	Containing verbatim terms hypertension, hypertensive, or preeclampsia/eclampsia (44 events), *n* (%)	Describing change or increase in blood pressure only (318 events), *n* (%)
Number of SAEs	17 (38.6)	78 (24.5)
Medically confirmed (initial or follow-up from HCP)	38 (80.9)	129 (40.6)
With medical history of hypertension	9 (20.5)	53 (16.7)
Without medical history of hypertension, but with other risk factors for hypertension	9 (20.5)	85 (26.7)
Number of cases with only one reported instance of BP elevation	27 (61.4)	305 (95.9)
Started antihypertension medication(s)	6 (13.6)	20 (6.3)
Restarted or changed dose of previous antihypertension medication(s)	4 (9.1)	11 (3.4)

Abbreviations: BP, blood pressure; HCP, heathcare provider; SAE, serious adverse event.

Dodick et al. Risk of hypertension in erenumab-treated patients with migraine: Analyses of clinical trial and postmarketing data. Headache 2021

Impact of fremanezumab on migraine patients with arterial hypertension in a Real-world setting

- Change from baseline to follow-up in SBP and DBP in patients with migraine and comorbid hypertension

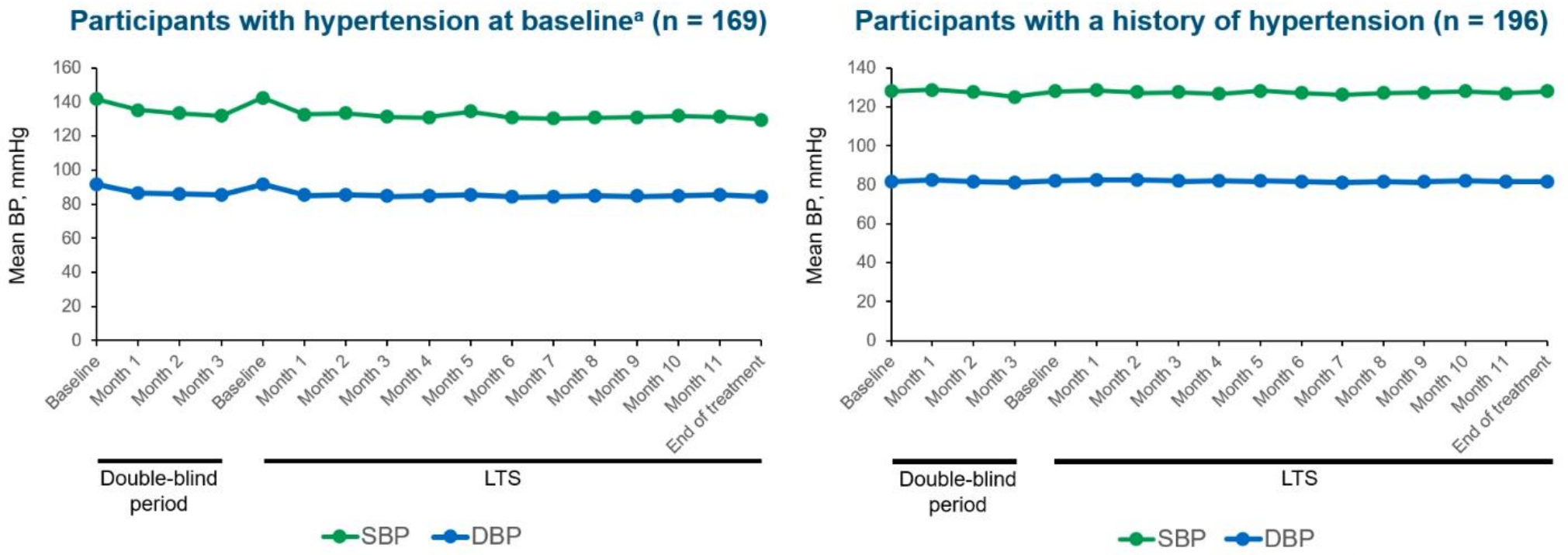


SBP, systolic blood pressure; DBP, diastolic blood pressure.

- Nonsignificant reductions from baseline to follow-up in SBP and DBP were observed in patients with migraine and comorbid hypertension (**Figure 3**); similar nonsignificant reductions in SBP and DBP were observed for patients with episodic and chronic migraine

Cephalalgia **2021 41:10:1075-1088**.

No significant changes in BP values were observed during the HALO LTS in partcipants with hypertension

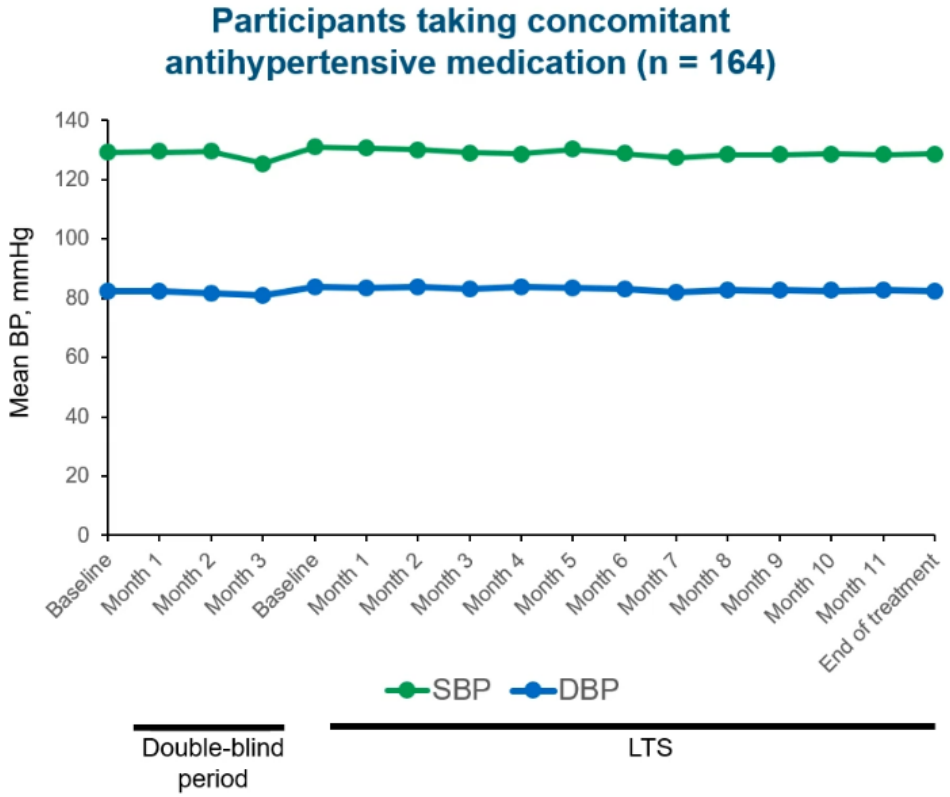


SBP and DBP values showed no meaningful changes for particpants with hypertension at baseline or histpry of hypertension from HALO LTS

BP, blood pressure; LTS, long-term study; SBP, systolic blood pressure; DBP, diastolic blood pressure.
[a]SBP ≥140 mmHg and DBP ≥90 mmHg.

***Cephalalgia* 2021 41:10:1075-1088.**

BP related AEs were infrequent and no significant changes in BP values were observed in participants taking antihypertensive in the HALO LTS



BP-related AEs in HALO LTS:

- 1 paticipant had increased DBP
- 1 participant had decreased SBP
- Both participants were receiving quaterly fremanezumab

BP, blood pressure; AE, adverse event; LTS, long-term study; SBP, systolic blood pressure; DBP, diastolic blood pressure.

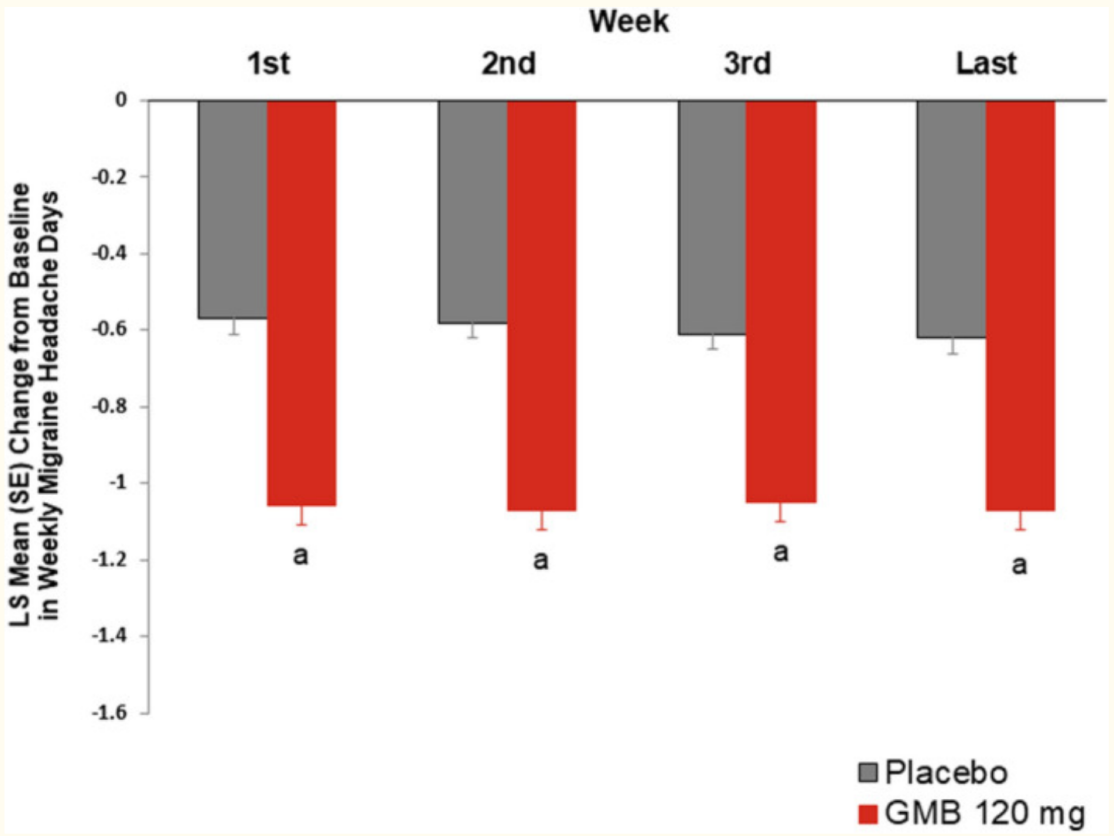
Cephalalgia 2021, 41:10: 1075-1088.

CGRP antibodies and Arterial hypertension

- Clinical trials did not demonstrate an increased risk of hypertension in patients with migraine treated with erenumab or other CGRP antibodies compared with placebo.
- In the postmarketing setting, hypertension AEs have been reported following the use of erenumab, many of which occurred in patients who had preexisting hypertension or risk factors for hypertension.
- Additional data are needed to fully characterize those at risk, as well as the nature, timing, and extent to which hypertension is a risk associated with erenumab and other CGRP-pathway antagonists.

Wearing off?

No wearing off in the 4 week injection intervall of Galcanezumab



- Post hoc analysis of clinical trial data from episodic (EVOLVE-1; EVOLVE-2; and chronic (REGAIN)
- Adults with episodic (placebo, *n* = 894; galcanezumab, *n* = 444) or chronic migraine (placebo, *n* = 558; galcanezumab, *n* = 278) were included.

Pozo-Rosich et al. J. Neurol. 2021 268:10 (3789-3798)

Wearing off in Real-World-Setting: Erenumab

- Wearing-off was self-reported in 34.7% (25/72)
- 80% one week before the next injection
- Sometime variable pattern to how often wearing-off occurred, but 32.0% (8/25) reported that it occurred with all injections.

→ 12%(3/25) of patients reported having no pattern

→20.0% (5/25) reporting it during months 1-2

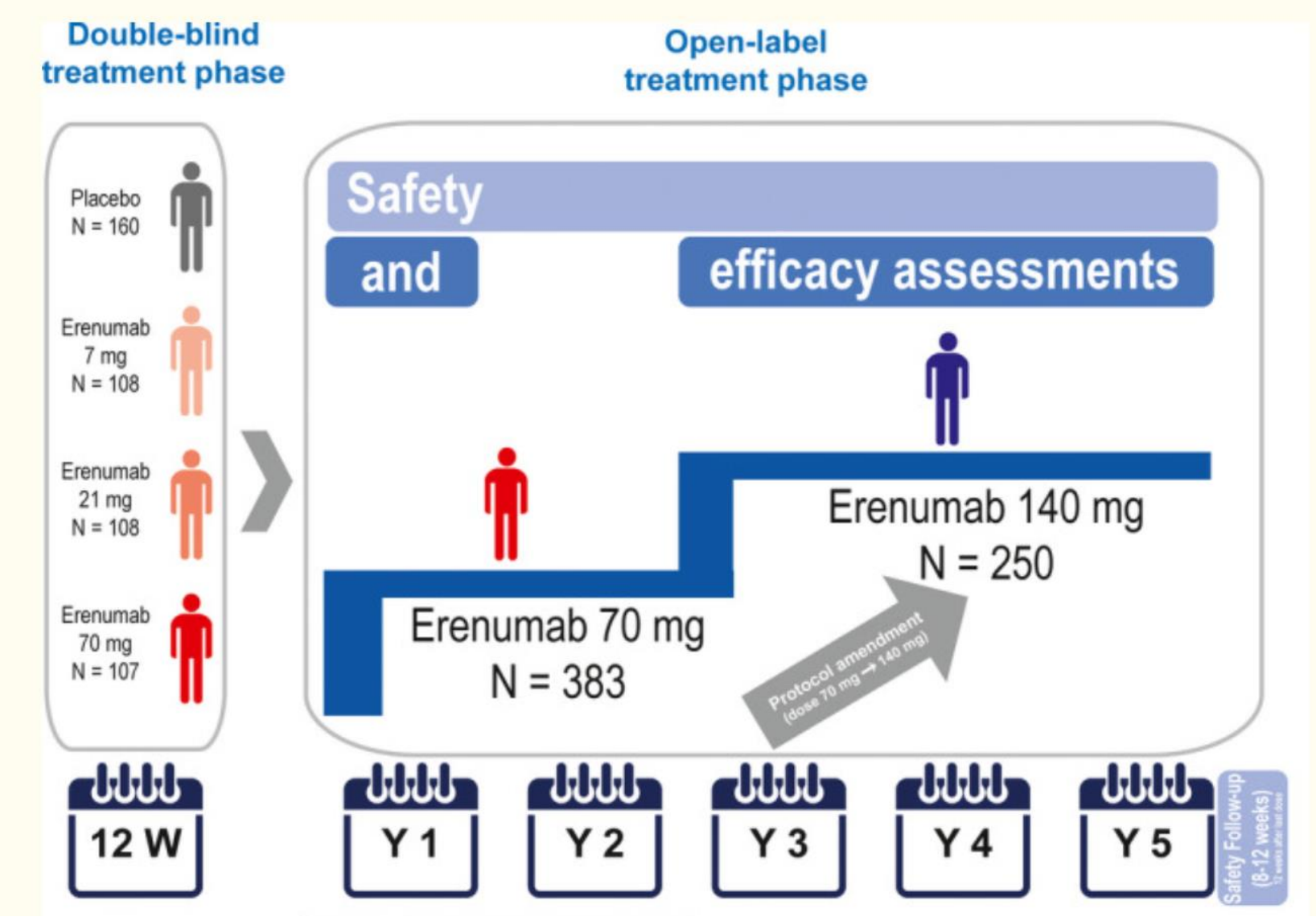
→ 8.0% (2/25) reported it during months 3-4

→20.0% (5/25) reported it during months 5-6

→One person noted wearing-off in the middle and late months, but not during the first 2 months.

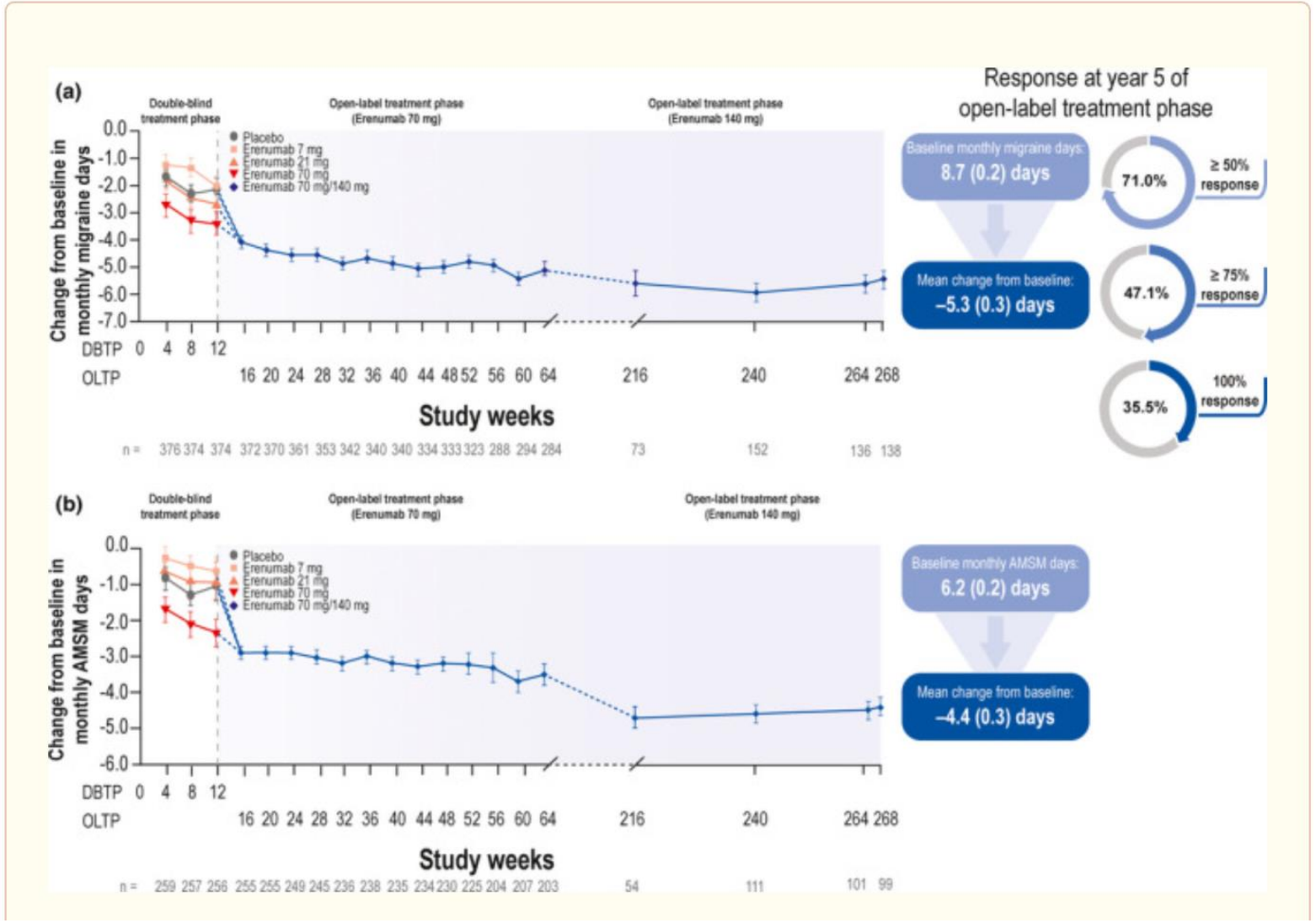
Robblee et al. *Headache* 2020 60:9 (2014-2025) .

5 years data on erenumab



Ashina et al. Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial Euro J Neurol. 2021

Erenumab is efficious over 5y of treatment



No Wearing off effects were observed!

Ashina et al. Long-term efficacy and safety of erenumab in migraine prevention: Results from a 5-year, open-label treatment phase of a randomized clinical trial Euro J Neurol. 2021

Take home messages

- CGRP (receptor) antibody therapy is safe
- CGRP (receptor) antibody therapy is well tolerated
- There are no significant wearing off effect regarding the treatment effects

Thanks for your attention!