Is there evidence…
for treating in the prodromal phase

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Disclosure

Company Name	*Honoraria/ Expenses*	*Consulting/ Advisory Board*	*Funded Research*	*Royalties/ Patent*	*Stock Options*	*Ownership/ Equity Position*	*Employee*
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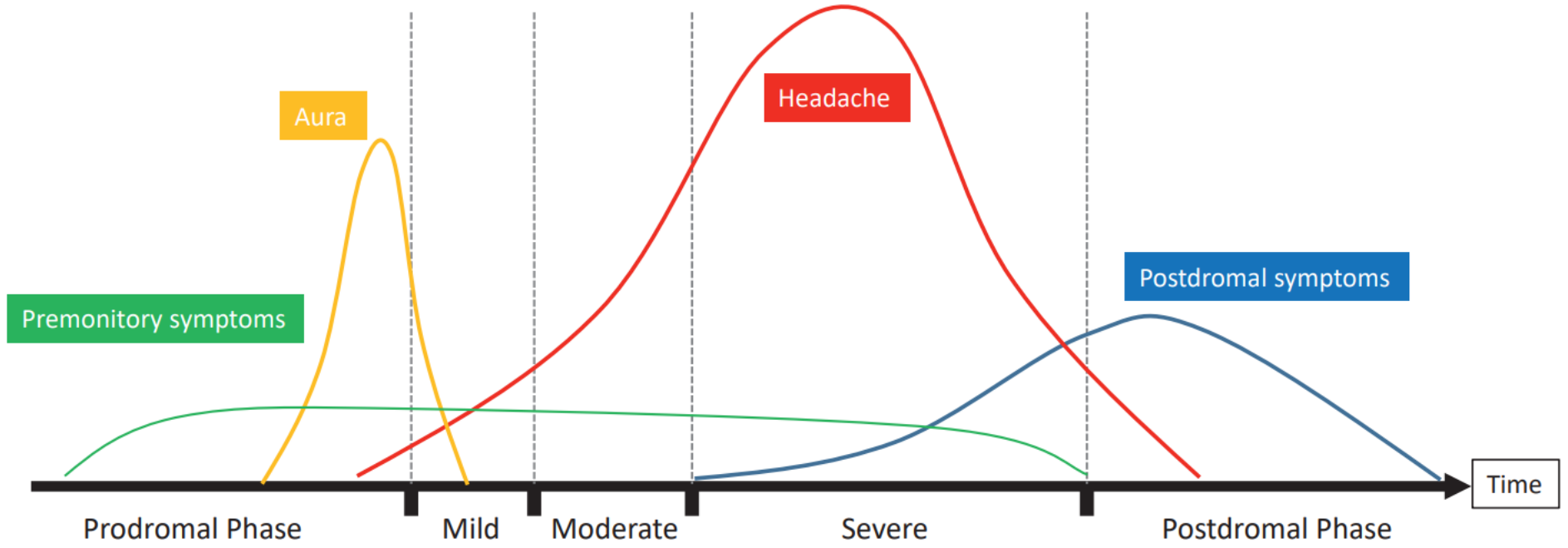
Prodromal phase



‘Based on available clinical/electrophysiological/neuroimaging data:
- preictal phase up to 48 hours before the headache attack
- postictal phase up to 24 hours following the ictal phase’

Handb Clin Neurol 2023;198:151-167
Cephalalgia 2020;40: 866–870

Premonitory symptoms

- neck stiffness
- tiredness
- cognitive dysfunction
- sensory sensitivities
- mood change
- homeostatic symptoms: yawning, thirst, food cravings

CNS Drugs 2024;38:533-546
Neurology 2003;60:935–40

Targets

- dopaminergic system
  - domperidon
- serotonergic system
  - naratriptan
  - dihydroergotamine
- CGRP system
  - ubrogepant

Ubrogepant not approved in EU

CNS Drugs 2024;38:533-546

Targeting the dopaminergic system

Domperidone (Tmax 30-60 min, t½ 7-9 hours)

D2/3 rec. antagonist (peripheral, CTZ)

prokinetic, antiemetic

placebo-controlled crossover trial

19 patients MA

4 attacks

domperidone 30 mg (2)

placebo (2)

Number of patients with complete classical migraine experiencing attacks after prophylactic treatment with domperidone 30 mg and placebo (n = 19)

No of attacks after administration of: Placebo	Domperidone 0	Domperidone 1	Domperidone 2
0	1	0	0
1	0	0	0
2	10	3	5

Statistically significant difference between drug and placebo, $p < 0{\cdot}001$ (Wilcoxon's matched-pairs signed ranks test).

Br Med J (Clin Res Ed) 1982;284:944

Targeting the serotonergic system

Dihydroergotamine (Tmax 30-60 min, t½ 9 hours)

[1]placebo-controlled crossover trial, 91 patients MO/MA, DHE 2 mg NS

4 prodromes/aura (2 X 2 design)

NS in prodrome or with aura superior to placebo

in preventing headache occurrence (36% vs 26%)

[2]open label study (abstract), 904 patients MO/MA, DHE 2 mg NS

NS in 'prodromal phase' (premonitory or aura) in 143 patients

'good efficacy' could be obtained by 63% of patients

[1]Cephalalgia 1987;7 (suppl): 440–41

[2]Schweiz Rundsch Med Prax 1990;79:914–7

Targeting the serotonergic system

Naratriptan (Tmax 2-3 hours, t½ 5-6 hours)

open label study, 20 patients MO/MA, 3 prodromes

instructed to use naratriptan 2.5 mg

during premonitory symptoms

reliably occurring 4–24 h preceding headache onset

when they felt headache was inevitable

to study effect on preventing headache/limiting headache severity:

- 60% headaches prevented (within 24 hours post-dosing)

more effective if taken early

- residual headaches reduced in severity

Cephalalgia 2000;20:122-6

Targeting the CGRP system

Ubrogepant (Tmax 90 min, t½ 5-7 hours)

μ

small molecule CGRP receptor antagonist, acute treatment of migraine

Ph3 RCT PRODROME (USA)

MO/MA, 2-8 attacks/month, moderate-severe headache

crossover design: ubrogepant 100 mg (1) ↔ placebo (1)

during prodrome, reliable (≥75%) prodomal symptoms

I^{ary} endpoint: abscence of moderate or severe headache

≤ 24 h after study drug during prodrome event

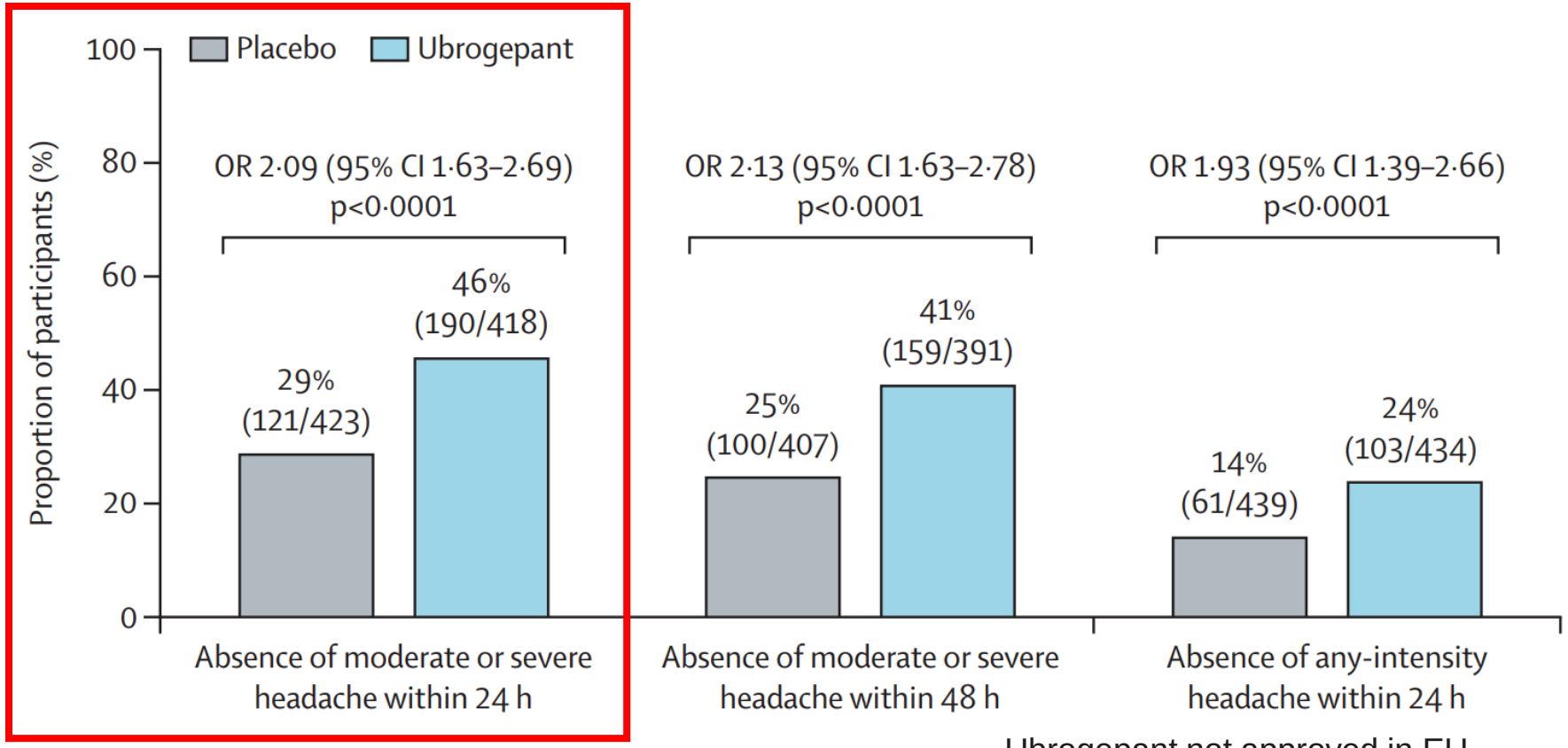
Ubrogepant not approved in EU

Lancet 2023; 402: 2307–16

Targeting the CGRP system

Randomized: 518

mITT population (at least 1 headache assessment ≤ 24 h): 477



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Targeting the CGRP system

Safety population (at least 1 administration of study drug): 480

	Placebo (n=462)	Ubrogepant 100 mg (n=456)
Any adverse event	55 (12%)	77 (17%)
Adverse event leading to discontinuation	0	0
Treatment-related adverse event	42 (9%)	60 (13%)
Serious adverse event	0	0
Serious treatment-related adverse event	0	0
Death	0	0
Most common adverse events (ie, occurred in ≥2% of participants)		
Nausea	15 (3%)	23 (5%)
Dizziness	12 (3%)	11 (2%)
Fatigue	7 (2%)	12 (3%)
Somnolence	5 (1%)	11 (2%)

Data are n (%).

Table 2: **Adverse events within 48 h after the study intervention in the safety population**

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Conclusion

- premonitory symptoms
  - are common
  - allow to reliably predict headache phase
  - provide an opportunity for early treatment
- 3 placebo-controlled trials evaluating the efficacy of an acute treatment administered during the prodrome
- trials with domperidone and DHE nasal spray
  - more than 30 years ago
  - small sample sizes
- recent large trial showed that ubrogepant is effective and well tolerated for the treatment of migraine attacks when taken during prodrome

Ubrogepant not approved in EU


The End