Cefalee: novità in fatto di terapia

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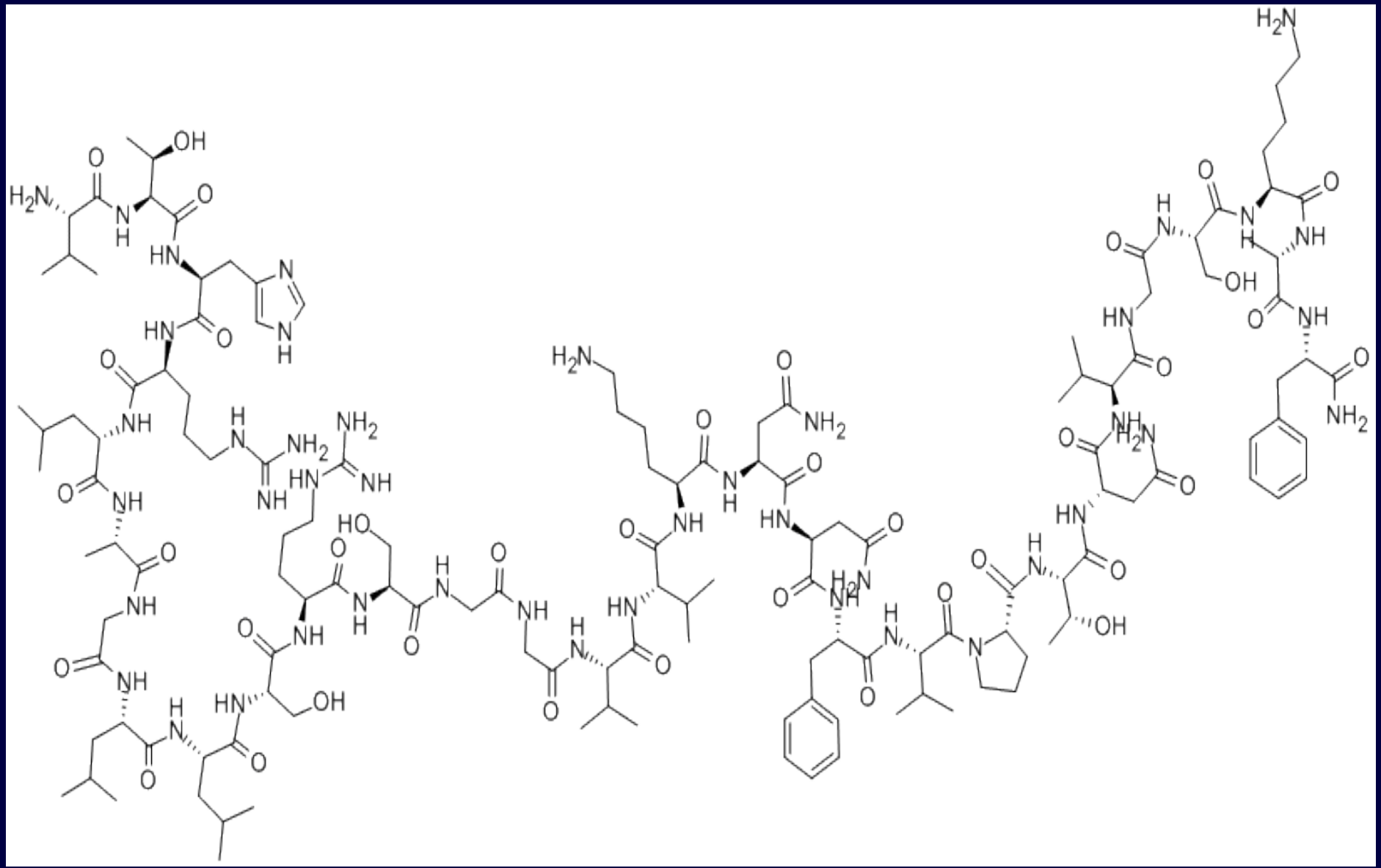
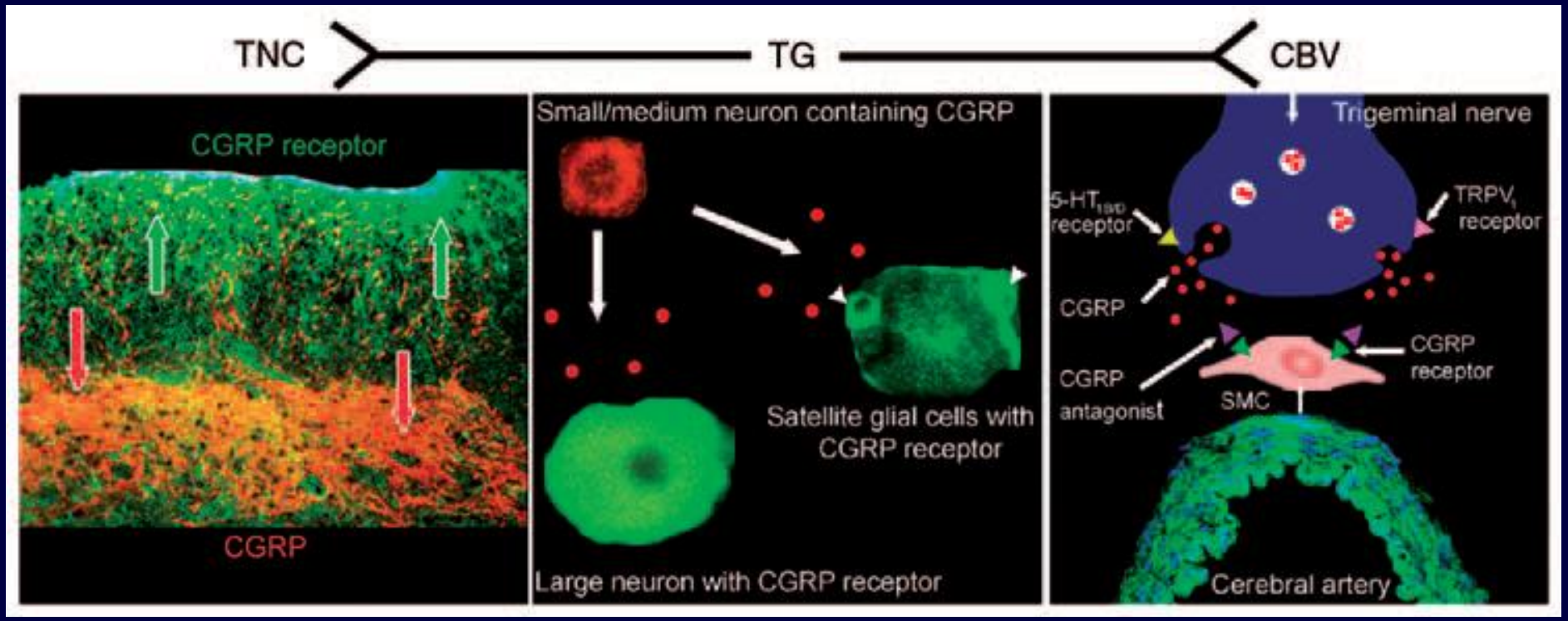
Roma, 1 marzo 2019



Migraine and CGRP



Ther Adv Neurol Dis 2010;3:369-378

CGRP antagonists (gepants)

Acute migraine treatment

Small molecules, non-peptides

Early molecules effective but not tolerable (raised liver enzymes)

Ubrogepant 25 & 50 mg effective and safe (ACHIEVE 2 phase III trial)

Planned extension study

CGRP antagonists (gepants)

Preventive migraine treatment

Statistic	Placebo (N=178)	Atogepant 10 mg QD (N=92)	Atogepant 30 mg QD (N=182)	Atogepant 60 mg QD (N=177)	Atogepant 30 mg BID (N=79)	Atogepant 60 mg BID (N=87)
Baseline						
Mean (Days)	7.81	7.63	7.64	7.74	7.38	7.62
Change from Baseline						
LS Mean (SE)	-2.85 (0.23)	-4.00 (0.32)	-3.76 (0.23)	-3.55 (0.23)	-4.23 (0.35)	-4.14 (0.33)
Atogepant vs Placebo						
Least Squares Mean Difference (SE)		-1.15 (0.40)	-0.91 (0.33)	-0.70 (0.33)	-1.39 (0.42)	-1.29 (0.41)
Adjusted p-value		0.0236	0.0390	0.0390	0.0034	0.0031

CGRP antagonists (gepants)

Parameter	Placebo (N=186)	Atogepant 10 mg QD (N=93)	Atogepant 30 mg QD (N=183)	Atogepant 60 mg QD (N=186)	Atogepant 30 mg BID (N=86)	Atogepant 60 mg BID (N=91)
ALT or AST (U/L)						
≥ 3 x ULN	3/179 (1.7 %)	2/92 (2.2%)	1/180 (0.6%)	3/181 (1.7%)	1/84 (1.2%)	1/88 (1.1%)
≥ 5 x ULN	3/179 (1.7%)	0	0	1/181 (0.6%)	0	0
≥ 10 x ULN	0	0	0	0	0	0
≥ 20 x ULN	0	0	0	0	0	0
Potential Hy's Law (ALT or AST ≥ 3XULN and Bilirubin Total ≥2XULN and ALP < 2XULN	0	0	0	0	0	0

Anti-CGRP(r) MoAbs

Efficacy

Episodic migraine	Mean monthly migraine days reduction vs placebo
Eptinezumab 1000 mg quarterly	-1.0 (-2.1 to 0.2)
Erenumab 70 mg monthly	-1.0 (-1.6 to -0.5) -1.4 (-1.9 to -0.9)
Erenumab 140 mg monthly	-1.9 (-2.3 to -1.4)
Fremanezumab 675 mg quarterly	-1.3 (-1.8 to -0.7)
Fremanezumab 225 mg monthly	-1.5 (-2.0 to -0.9)
Galcanezumab 120 mg monthly	-1.9 (-2.5 to -1.4) -2.0 (-2.3 to -1.7)
Galcanezumab 240 mg monthly	-1.8 (-2.3 to -1.2) -1.9 (-2.2 to -1.6)

J Headache Pain 2019;20:6

Anti-CGRP(r) MoAbs

Efficacy

Chronic migraine	Mean monthly migraine days reduction vs placebo
Erenumab 70 mg monthly	-2.5 (-3.5 to -1.4)
Erenumab 140 mg monthly	-2.5 (-3.5 to -1.4)
Fremanezumab 675 mg quarterly	-1.7 (-2.1 to -1.3)
Fremanezumab 225 mg monthly	-1.8 (-2.2 to -1.4)
Galcanezumab 120 mg monthly	-2.1 (-2.9 to -1.3)
Galcanezumab 240 mg monthly	-1.9 (-2.7 to -1.1)

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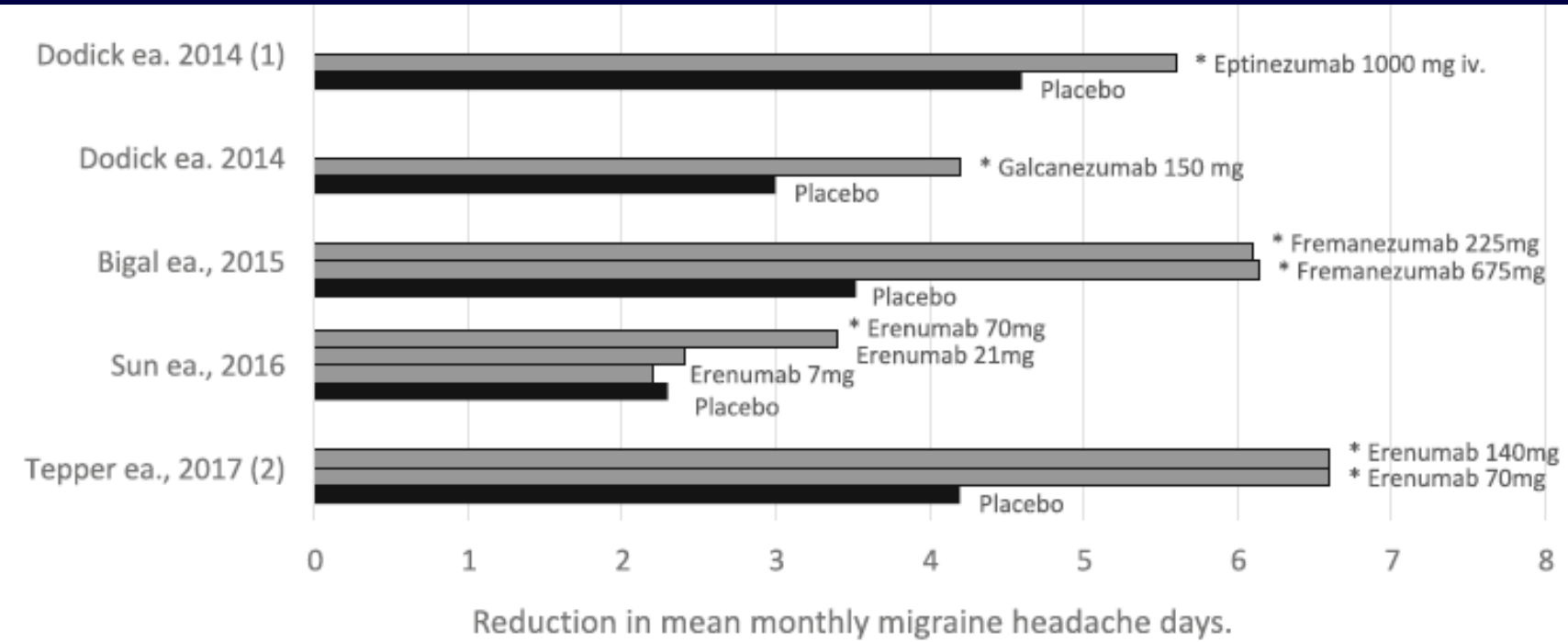
Anti-CGRP(r) MoAbs

Efficacy



J Headache Pain 2017;18:96

Anti-CGRP(r) MoAbs

Efficacy

Episodic migraine	50% response rate with MoAb, %	50% response rate with placebo, %	% difference
Eptinezumab 1000 mg quarterly	72.7	66.7	+10
Erenumab 70 mg monthly	42.2	28.3	+13
Erenumab 140 mg monthly	49.4	26.6	+23
Fremanezumab 675 mg quarterly	44.4	27.9	+17
Fremanezumab 225 mg monthly	47.4	26.9	+20
Galcanezumab 120 mg monthly	60.8	37.2	+24
Galcanezumab 240 mg monthly	58.6	37.2	+22

J Headache Pain 2019;20:6

Anti-CGRP(r) MoAbs

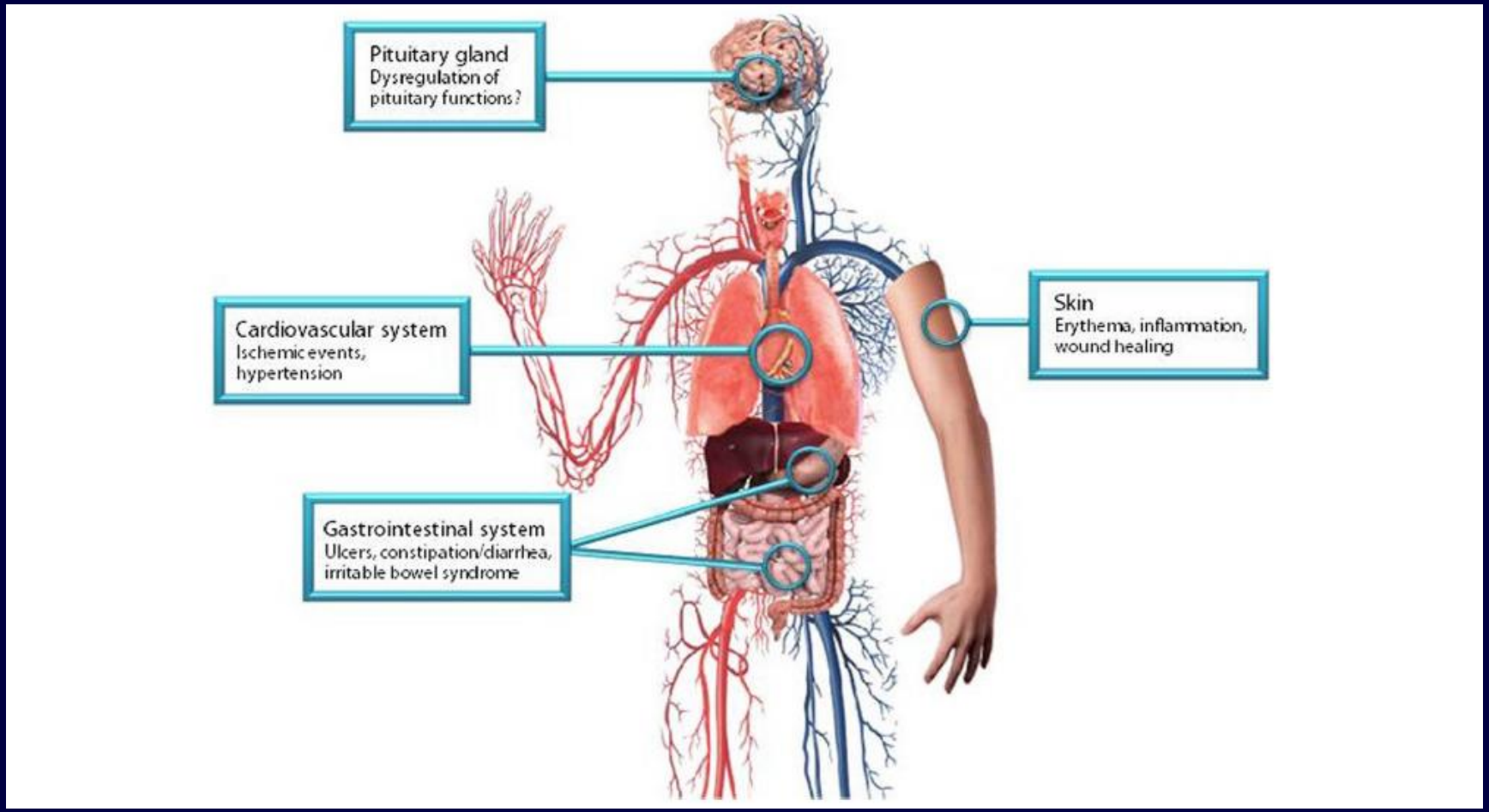
Efficacy

Chronic migraine	50% response rate with MoAb, %	50% response rate with placebo, %	% difference
Erenumab 70 mg monthly	39.9	23.5	+17
Erenumab 140 mg monthly	41.2	23.5	+18
Fremanezumab 675 mg quarterly	43.1	20.7	+20
Fremanezumab 225 mg monthly	37.6	18.1	+23
Galcanezumab 120 mg monthly	28.4	14.9	+12
Galcanezumab 240 mg monthly	28.5	14.9	+12

J Headache Pain 2019;20:6

Anti-CGRP(r) MoAbs

Safety



J Headache Pain 2017;18:96

Anti-CGRP(r) MoAbs

Safety

Episodic migraine	% SAE
Eptinezumab 1000 mg quarterly	2.4
Erenumab 70 mg monthly	1.7
Erenumab 140 mg monthly	1.9
Fremanezumab 675 mg quarterly	1.0
Fremanezumab 225 mg monthly	1.3
Galcanezumab 120 mg monthly	5.8
Galcanezumab 240 mg monthly	1.6

Chronic migraine	% SAE
Erenumab 70 mg monthly	3.1
Erenumab 140 mg monthly	1.1
Fremanezumab 675 mg quarterly	0.8
Fremanezumab 225 mg monthly	1.3
Galcanezumab 120 mg monthly	0.4
Galcanezumab 240 mg monthly	1.9

J Headache Pain 2019;20:6

Anti-CGRP(r) MoAbs

Use

Only erenumab approved for use (FDA, EMA)

Subcutaneous injection (iv for eptinezumab), monthly (or quarterly)

Any age, sex, aura status

Caution in patients with cardiovascular disease, hypertension, pulmonary disease, pregnancy

Possibility of concomitant use with other preventatives with the exception (?) of botulinum toxin

Effective also in patients with previous treatment failures

Tiseo et al., submitted

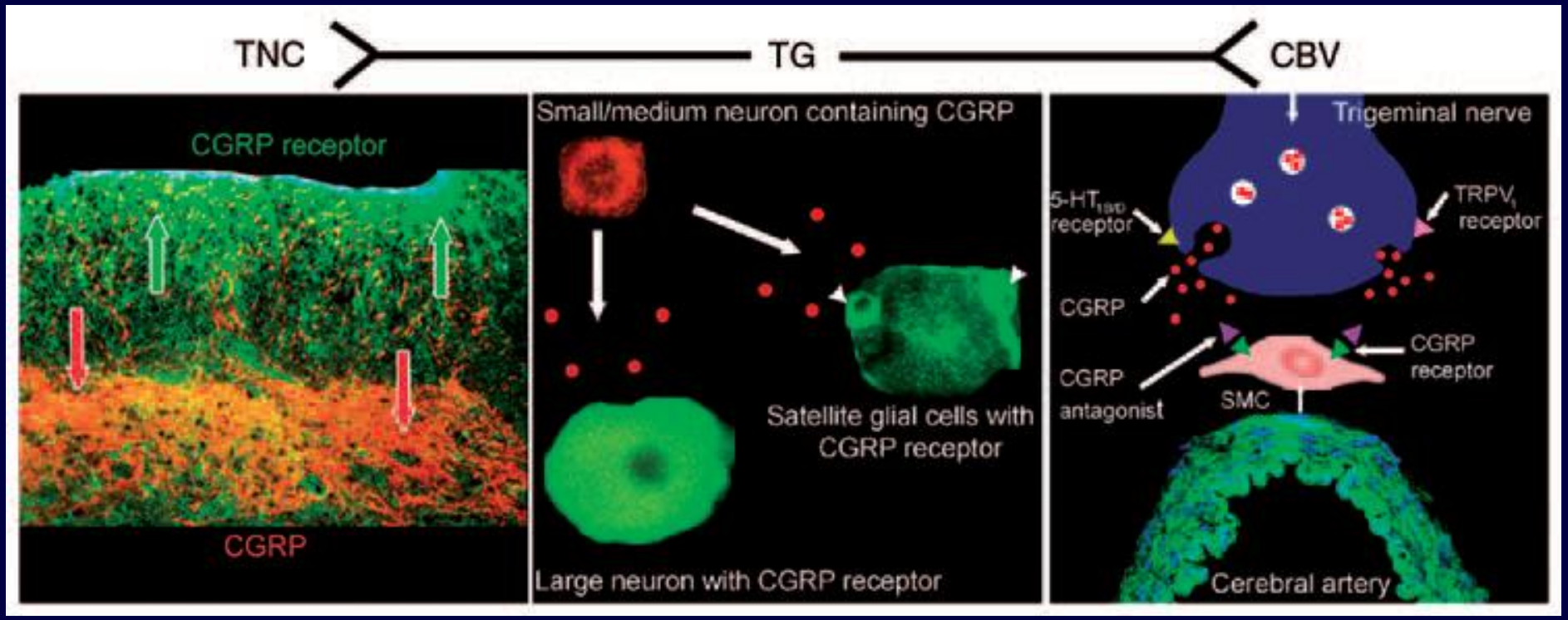
Anti-CGRP(r) MoAbs

Group	0 to 30% Improvement	30 to 70% Improvement	70 to 100% Improvement	*Subset 95 to 100% Improvement*
All Patients (n = 100)	31%	45%	24%	9%
All Women (n = 83)	35%	42%	23%	10%
Women Age 18 to 40 (n = 32)	38%	44%	19%	13%
Women Age 41 to 60 (n = 29)	34%	45%	21%	7%
Women age 61 and over; oldest was age 76 (n = 22)	32%	36%	32%	9%
All Men (n = 17)	12%	59%	30%	6%
Men Age 18 to 40 (n = 1)	100%	N/A	N/A	N/A
Men Age 41 to 60 (n = 5)	0%	60%	40%	20%
Men Age 61 and over; oldest was age 72 (n = 11)	9%	55%	36%	0%

Robbins and Phenicie, www.practicalpainmanagement.com, 2019

5-HT-1F receptor agonists (ditans)

No vasoconstriction → ideal for patients with cardiovascular risk



Neurology 2018;91:e2222-e2231

5-HT-1F receptor agonists (ditans)

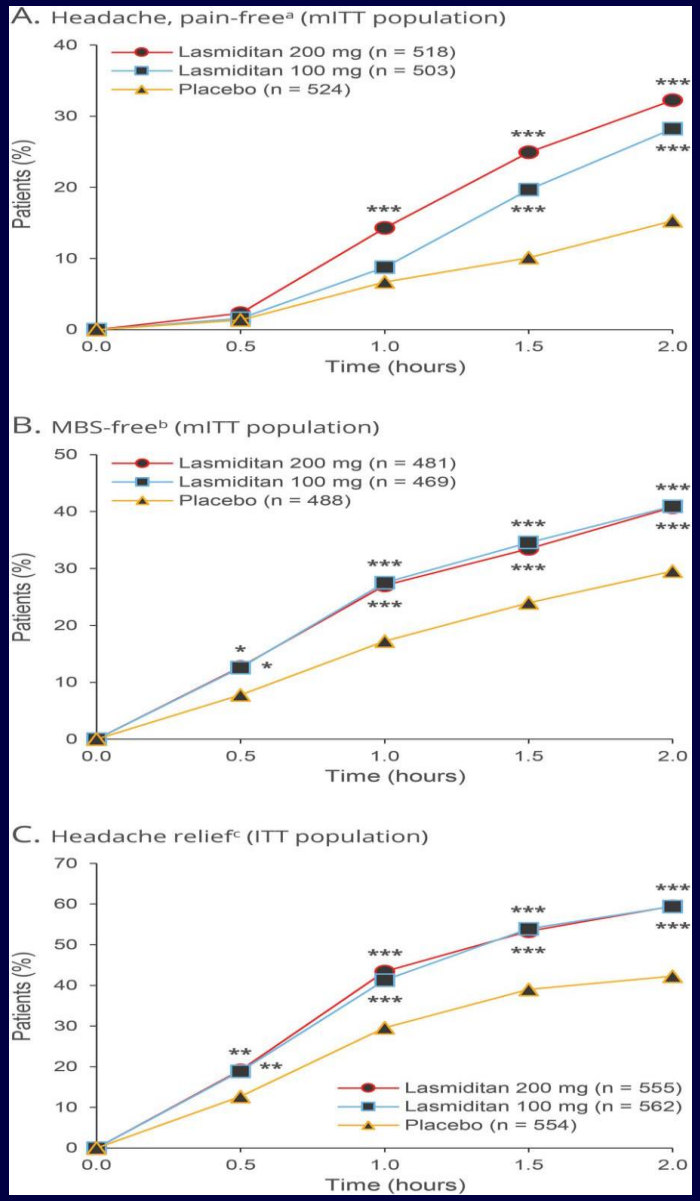


Table 4 Treatment-emergent adverse events (TEAEs) after the first dose

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)

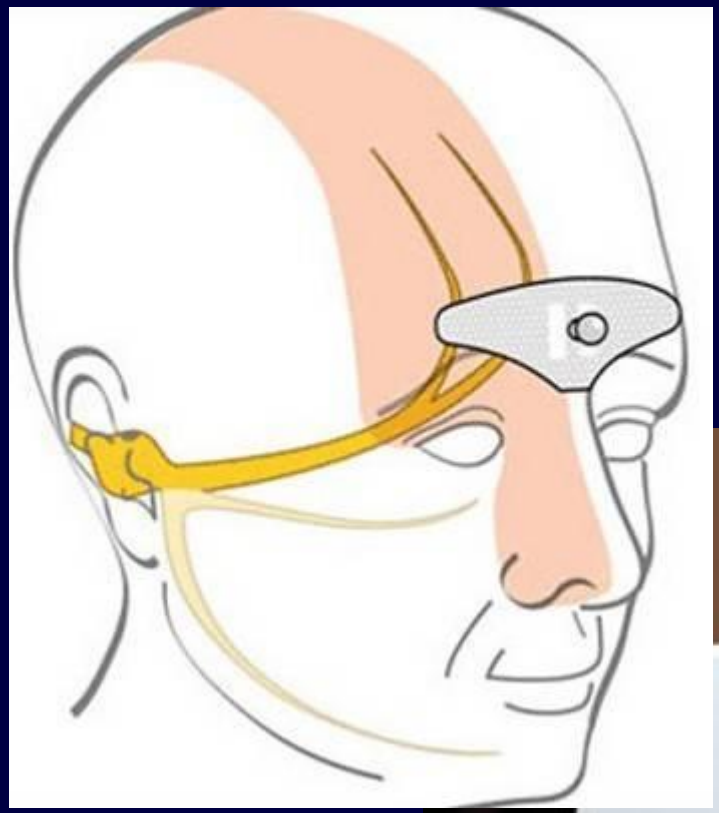
Abbreviation: TEAE = treatment-emergent adverse event (an event that started or worsened after the first dose of study medication [i.e., it did not present with the migraine] and occurred within 48 hours of dosing).

Neurology 2018;91:e2222-e2231

Noninvasive vagus nerve stimulation as acute therapy for migraine

The randomized PRESTO study

Neurology 2018;91:e364-e373



Other primary headaches

Anti-CGRP(r) MoAbs are currently being studies for cluster headache prophylaxis

Neurostimulation (invasive and non-invasive) for CH and intractable TACs

Conclusions

CGRP is the target of new acute and specific preventive treatments for migraine with good efficacy and excellent safety profile

New anti-migraine drugs are targeted towards neural rather than vascular structures

Real-world data will provide evidence for long-term management