

A New Class of Drugs for Migraine Prevention: Calcitonin Gene-Related Peptide (CGRP)- Directed Treatments

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DISCLOSURE

- Dr. Otto-Meyer
 - I have no actual or potential conflicts of interest in relation to this activity.
- Dr. Djuric Kachlic
 - I have no actual or potential conflicts of interest in relation to this activity.

OBJECTIVES

- Explain the mechanism of action of calcitonin gene-related peptide (CGRP)-directed treatments for migraine.
- Discuss published safety and efficacy data for approved CGRP monoclonal antibodies.
- Describe the current place in therapy of the anti-CGRP medications.
- Explain the role of the pharmacist in educating patients on the use of the CGRP products.

Pre-Test 1: Which of the following best describes the proposed role of calcitonin gene-related peptide (CGRP) in migraine?

- A. It causes aura through the vasoconstriction of dural blood vessels.
- B. It increases pain signaling and causes vasoconstriction of the dural blood vessels.
- C. It causes vasodilation of the dural blood vessels, plasma extravasation, and inflammation.
- D. It decreases pain signaling and causes vasodilation of the dural blood vessels.

Pre-Test 2: Which of the following outcome measures did all CPRG treatments consistently demonstrate in episodic migraine patients?

- A. Reduction in number of migraine days
- B. High rate of adverse cardiovascular effects
- C. Long term efficacy in migraine reduction (>12 months)
- D. Improvement in MIDAS scores

Pre-Test 3: Which of the following is/are currently impacting the CPRG medications' place in therapy? (Select all that apply)

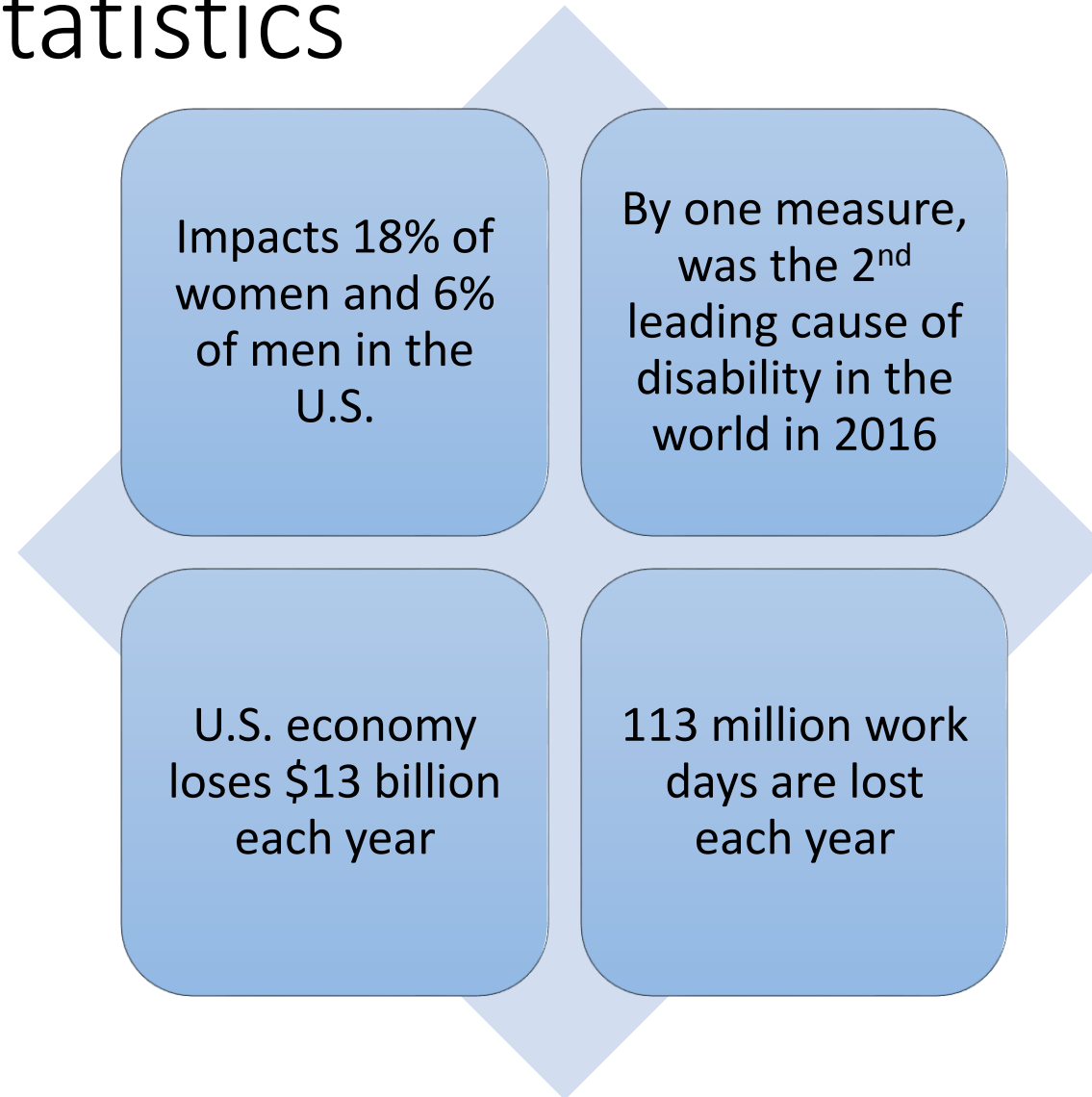
- A. Concerns regarding its long-term safety
- B. Concerns regarding its poor side effect profile
- C. Contradictory guideline recommendations
- D. Concerns regarding cost

Pre-Test 4: Which of the following is an important counseling point for any of the CPRG medications?

- A. Shake vigorously prior to injection
- B. If the syringe is dropped on a hard surface, it is still ok to use
- C. The medication can be injected IM if preferred by the patient
- D. Allow to sit at room temperature for 30 minutes prior to injection

Migraine Background

Migraine Statistics



1. Lipton RB. *Headache*. 2001;41(7):646-57.
2. GBD Collaborators. *Lancet*. 2017;390(10100):1211-1259.
3. Migraine Research Foundation. www.migraineresearchfoundation.org

Migraine Definition

- Is a chronic neurological disorder
- Characterized by
 - Attacks of moderate/severe headache
 - Reversible neurological and systemic symptoms
- Two subclasses
 - Migraine without aura
 - Migraine with aura
- Two duration classifications
 - Episodic migraine
 - Chronic migraine

Migraine Without Aura

- More common form of migraine headache
- IHS diagnostic criteria:
 - A. At least 5 attacks fulfilling criteria B-D
 - B. Headache attacks lasting 4-72 hours
 - C. Headache has at least 2 of the following characteristics:
 - Unilateral location
 - Pulsating quality
 - Moderate or severe pain intensity
 - Aggravation by or causing avoidance of routine physical activity
 - D. During headache, at least 1 of the following:
 - Nausea and/or vomiting
 - Photophobia and phonophobia
 - E. Not better accounted for by another ICHD-3 diagnosis

Migraine With Aura

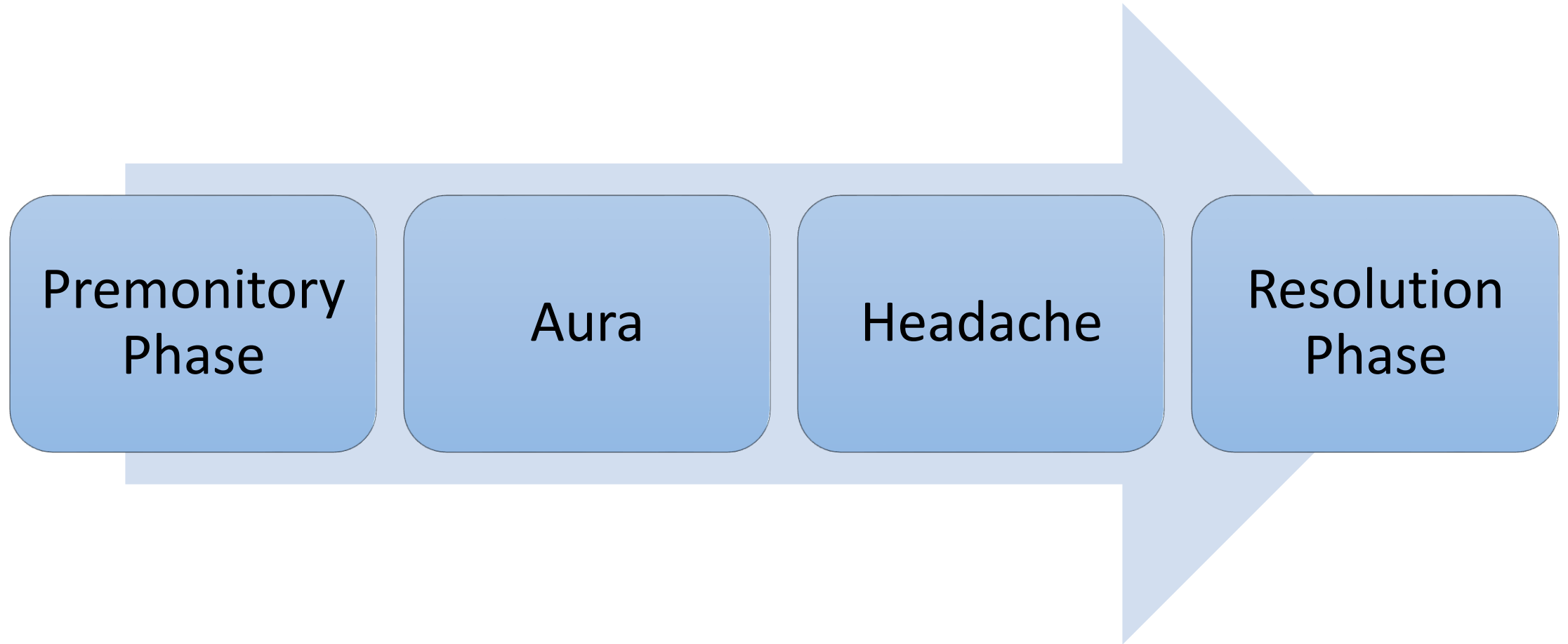
- Experienced by approximately 1/3 of migraine sufferers
- IHS diagnostic criteria:
 - A. At least 2 attacks fulfilling criteria B and C
 - B. One or more of the following fully reversible aura symptoms:
Visual, Sensory, Speech and/or language, Motor, Brainstem, Retinal
 - C. At least 3 of the following characteristics
 - At least 1 aura symptom spreads gradually over ≥ 5 minutes
 - Two or more aura symptoms occur in succession
 - Each individual aura symptom lasts 5-60 minutes
 - At least 1 aura symptom is unilateral
 - At least one aura symptom is positive
 - The aura is accompanied by, or followed within 60 minutes, by headache
 - D. Not better accounted for by another ICHD-3 diagnosis

Chronic Versus Episodic Migraine

- Chronic migraine:
 - Approximately 8% of the migraine patient population
 - Headaches occur on > 15 days/month for > 3 months AND
 - On at least 8 days/month, the headache has the features of migraine headache
- Episodic migraine:
 - Not formally defined by IHS
 - Includes headaches that meet the diagnostic criteria for migraine but do not meet the definition of chronic migraine

What happens during a
migraine?

Migraine Phases

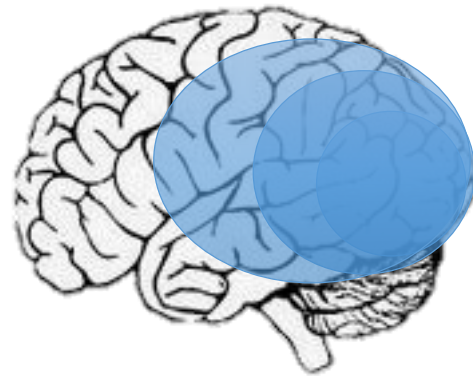


Pathophysiology

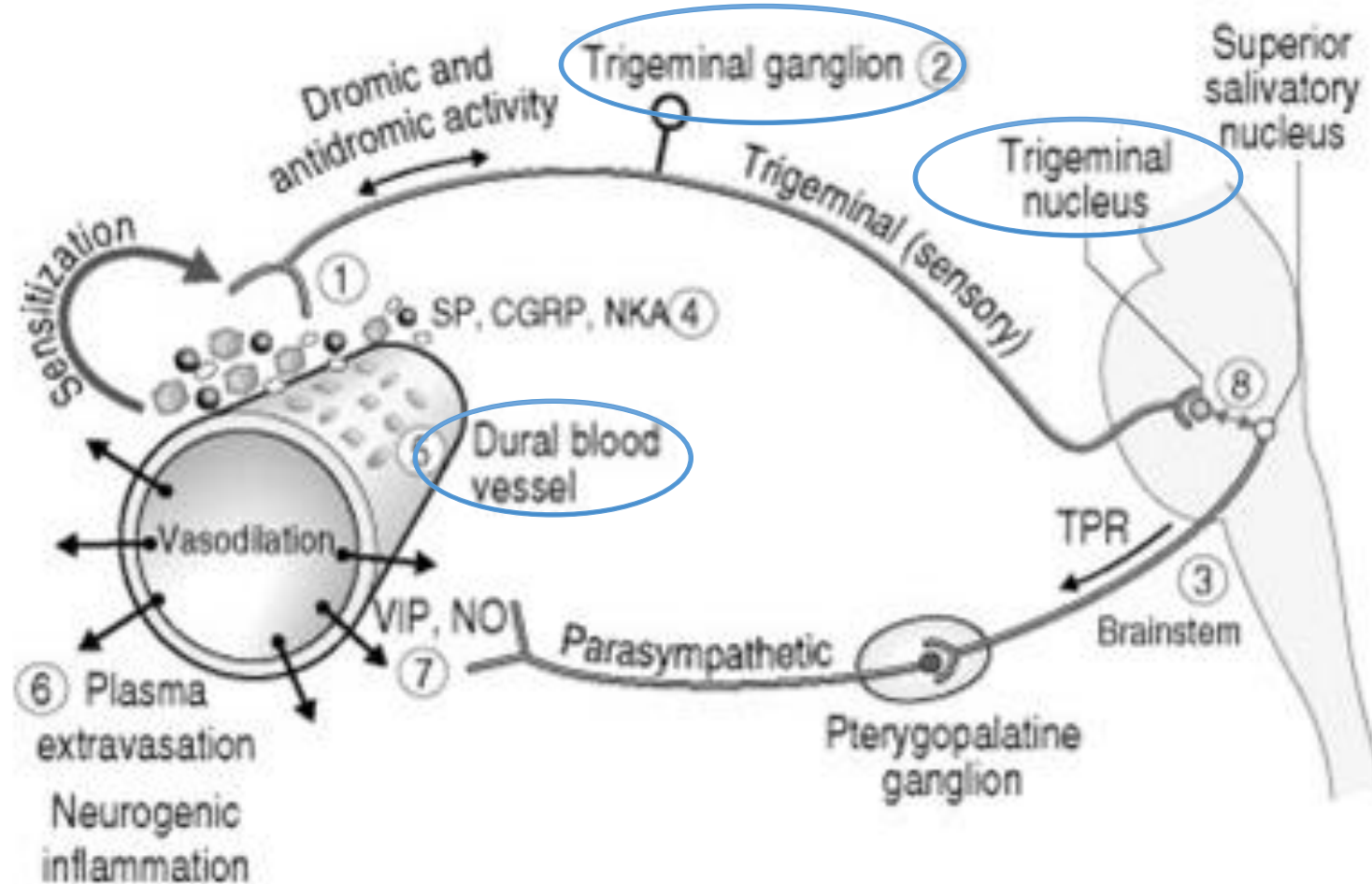
- Not completely understood
- Vasoconstriction/vasodilation theory no longer supported
- Key processes involved:
 - Cortical spreading depression
 - Trigeminovascular system activation
 - Neuronal sensitization
 - Involvement of serotonin and dopamine

1. Cortical Spreading Depression

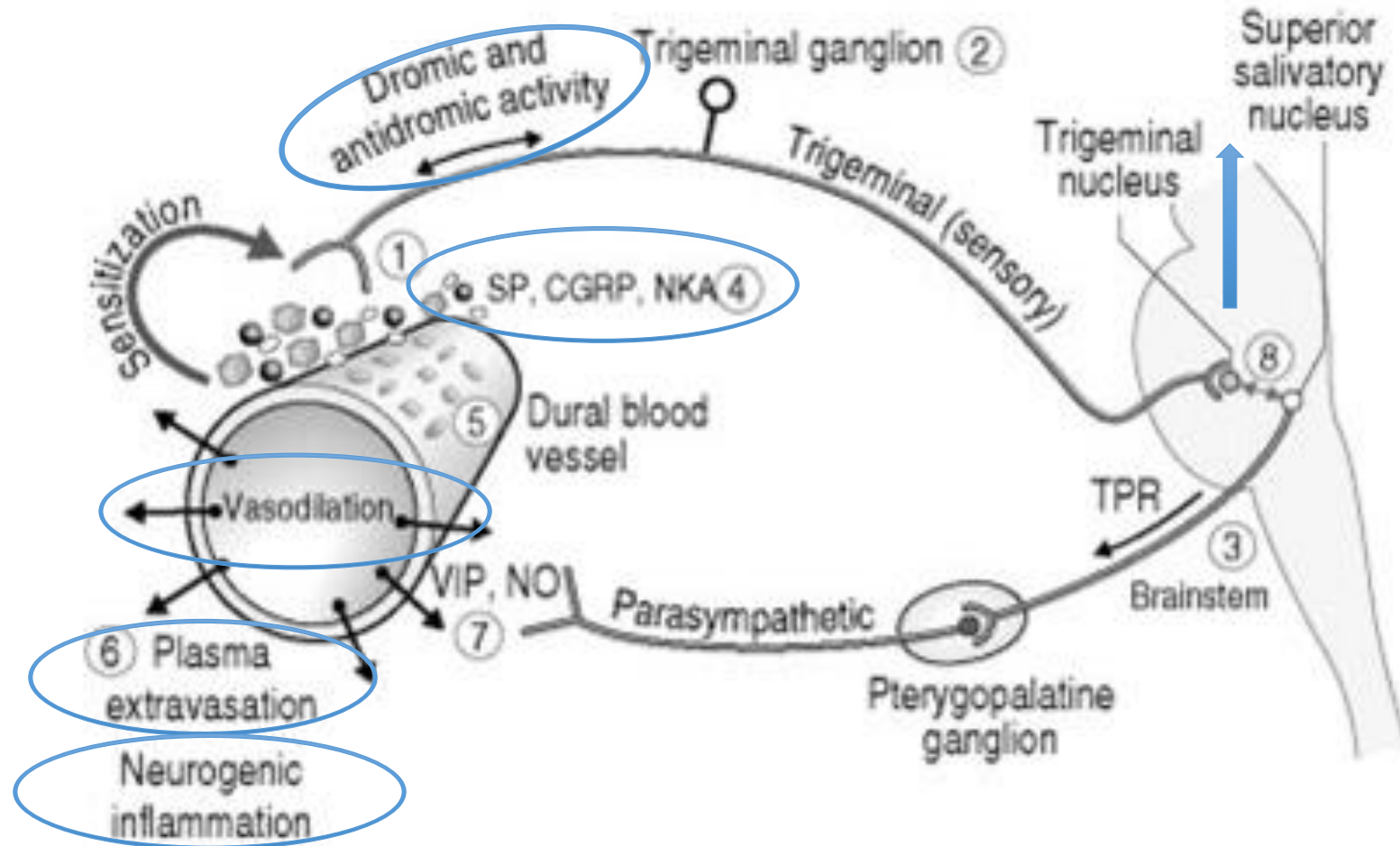
- Hypothesized trigger of migraines and cause of aura
- Wave of depolarization followed by depressed electrical activity
- Travels across the cortex at the same rate aura symptoms spread
- Causes inflammation and activation of the trigeminal nucleus caudalis



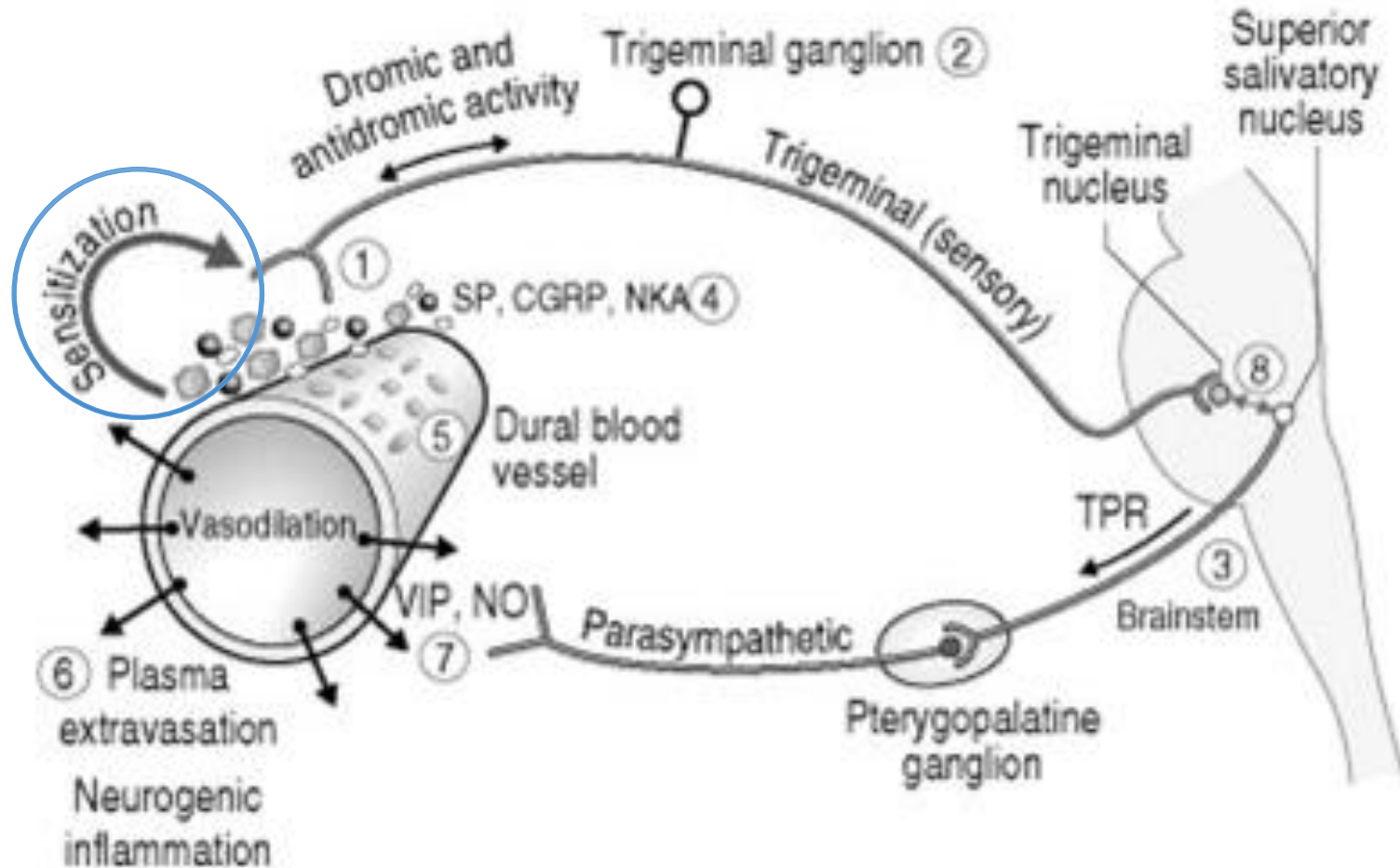
2. Trigeminovascular System – Location and Function



2. Trigeminovascular System Activation – Vasoactive Peptide Release



3. Neuronal Sensitization



4. Involvement of Serotonin and Dopamine

- Serotonin and dopamine play a role in migraine, but their exact role is not well understood
- Agonists of certain 5-HT₁ receptor subtypes help treat migraines by:
 - Causing vasoconstriction of meningeal blood vessels
 - Inhibiting vasoactive neuropeptide release and pain signal transmission
- Dopamine receptor antagonists are also useful migraine treatment agents

Migraine Treatment Options

Acute Versus Preventative Treatments

- Acute Treatments

- Taken at the headache's onset
- Include:
 - Analgesics
 - Non-steroidal anti-inflammatory drugs (NSAIDs)
 - Triptans
 - Ergot alkaloids
 - Dopamine receptor antagonists

- Preventative Treatment

- Taken on a regular basis
- Historically reserved for patients with frequent and/or severe migraines
- Include:
 - Beta blockers
 - Antidepressants
 - Antiepileptics
 - OnabotulinumtoxinA
 - (for chronic migraine only)

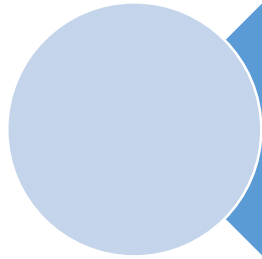
Problems with Preventative Treatment Options

- Medications:
 - Historically not migraine-specific
 - Frequently have unwanted side effects
 - Take several weeks to show substantial benefit
- The benefit is relatively low
 - A reduction in headache frequency of 50% is generally considered successful
- Utilization rates are low

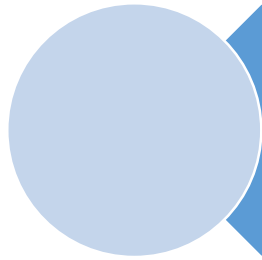
Calcitonin Gene-Related Peptide (CGRP) Monoclonal Antibodies

- CGRP is released during trigeminovascular system activation and causes vasodilation, plasma extravasation, and inflammation during migraines
- Prior to 2018, there were no FDA-approved medications that targeted this migraine component
- CGRP monoclonal antibodies represent a new class of medications
 - Target either CGRP directly or its receptor to prevent binding
 - Are the first drugs developed since the 1960s specifically for migraine prevention

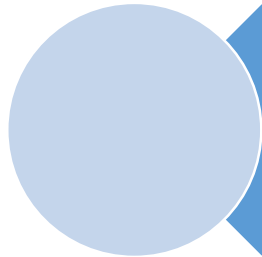
FDA Approved CPRG Monoclonal Antibodies



Erenumab (Aimovig)



Fremanezumab (Ajovy)



Galcanezumab (Emgality)

Erenumab Trials

Study to Evaluate the Efficacy and Safety of Erenumab in Migraine Prevention (STRIVE)

- Objective: To compare erenumab to placebo for the prevention of episodic migraine
- Multicenter, randomized, double-blind, placebo controlled, parallel-group phase 3 trial
- Study phases: Screening (< 3 weeks and a 4-week baseline phase) and double-blind treatment phase (24 weeks)
- Study groups: Random assignment to erenumab 70 mg, erenumab 140 mg, or placebo injected subcutaneously monthly over 6 months

STRIVE Inclusion/Exclusion Criteria

- Inclusion criteria:

- Adults 18-65 years old with a history of migraine for at least 12 months before screening
- Experienced 4 to < 15 migraine days/month and < 15 headache days/month on average
- Demonstrated 80% reporting adherence to daily handheld electronic diary completion

- Exclusion criteria:

- Age > 50 at migraine onset
- History of hemiplegic migraine or cluster headache
- Recent treatment with botulinum toxin or prophylactic devices/procedures
- **Had no therapeutic response to > 2 migraine-prevention treatment categories**
- **Use of > 1 concomitant migraine preventive medication or use of 1 at an unstable dose**

STRIVE Endpoints

- Primary endpoint:
 - Change from baseline to months 4-6 in the mean number of migraine days/month
- Secondary endpoints:
 - 50% or greater reduction in mean migraine days/month
 - Change in the number of days of acute migraine-specific medication use
 - Change in scores on the physical-impairment and everyday-activities domains of the Migraine Physical Function Impact Diary
- Safety
 - Monitored through the reporting of adverse events

STRIVE Baseline Patient Characteristics

	Placebo (N = 319)	Erenumab 70 mg (N = 317)	Erenumab 140 mg (N = 319)
Age - years (range)	41.3 \pm 11.2 (18-65)	41.1 \pm 11.3 (18-63)	40.4 \pm 11.1 (19-65)
Female sex – no. (%)	274 (85.9)	268 (84.5)	272 (85.3)
White race – no. (%)	277 (86.8)	281 (88.6)	293 (91.8)
Migraine-specific medication use – no. (%)	191 (59.9)	179 (56.5)	192 (60.2)
Preventive medication use – no. (%)			
No current or previous use	178 (55.8)	175 (55.2)	187 (58.6)
Previous use only	131 (41.1)	133 (42.0)	124 (38.9)
Current use	10 (3.1)	9 (2.8)	8 (2.5)

STRIVE Baseline Patient Characteristics

	Placebo (N = 319)	Erenumab 70 mg (N = 317)	Erenumab 140 mg (N = 319)
Assessment of migraine during baseline phase – mean\pmSD			
Migraine days per month	8.2 \pm 2.5	8.3 \pm 2.5	8.3 \pm 2.5
Headache days per month	9.3 \pm 2.6	9.1 \pm 2.6	9.3 \pm 2.5
Days of use of acute migraine-specific medication per month	3.4 \pm 3.4	3.2 \pm 3.4	3.4 \pm 3.5
Monthly everyday activities score	13.7 \pm 9.1	14.0 \pm 8.9	13.1 \pm 8.3
Monthly physical-impairment score	12.2 \pm 9.4	12.6 \pm 9.6	12.0 \pm 9.0

STRIVE Results

*P < 0.001

	Placebo (N = 316)	Erenumab 70 mg (N = 312)	Erenumab 140 mg (N = 318)
Migraine days per month*			
Change from baseline	-1.8 \pm 0.2	-3.2 \pm 0.2	-3.7 \pm 0.2
Difference vs. placebo (95% CI)		-1.4 (-1.9 to -0.9)	-1.9 (-2.3 to -1.4)
50% reduction from baseline in migraine days per month*			
No. of patients (%)	84 (26.6)	135 (43.3)	159 (50.0)
Odds ratio (95% CI)		2.12 (1.52 to 2.98)	2.81 (2.01 to 3.94)
Days of use of acute migraine-specific medication per month*			
Change from baseline	-0.2 \pm 0.1	-1.1 \pm 0.1	-1.6 \pm 0.1
Difference vs. placebo (95% CI)		-0.9 (-1.2 to -0.6)	-1.4 (-1.7 to -1.1)
Monthly everyday activities score*			
Change from baseline	-3.3 \pm 0.4	-5.5 \pm 0.4	-5.9 \pm 0.4
Difference vs. placebo (95% CI)		-2.2 (-3.3 to -1.2)	-2.6 (-3.6 to -1.5)
Monthly physical-impairment score*			
Change from baseline	-2.4 \pm 0.4	-4.2 \pm 0.4	-4.8 \pm 0.4
Difference vs. placebo (95% CI)		-1.9 (-3.0 to -0.8)	-2.4 (-3.5 to -1.4)

Strive Results

	Placebo (N = 319)	Erenumab 70 mg (N = 314)	Erenumab 140 mg (N = 319)
Adverse event – no.(%)	201 (63.0)	180 (57.3)	117 (55.5)
Nasopharyngitis	32 (10.0)	31 (9.9)	35 (11.0)
Upper respiratory tract infection	18 (5.6)	21 (6.7)	15 (4.7)
Sinusitis	7 (2.2)	7 (2.2)	11 (3.4)
Constipation	4 (1.3)	5 (1.6)	11 (3.4)
Arthralgia	6 (1.9)	7 (2.2)	7 (2.2)
Fatigue	8 (2.5)	6 (1.9)	7 (2.2)
Influenza	6 (1.9)	4 (1.3)	8 (2.5)
Injection-site pain	1 (0.3)	10 (3.2)	1 (0.3)
Hypertension	8 (2.5)	5 (1.6)	0
Adverse event leading to discontinuation	8 (2.5)	7 (2.2)	7 (2.2)
Serious adverse event	7 (2.2)	8 (2.5)	6 (1.9)

STRIVE Conclusions and Limitations

- Conclusion: Over a period of 6 months, erenumab 70 mg or 140 mg injected subcutaneously monthly significantly reduced:
 - Migraine frequency
 - The effects of migraines on daily activities
 - The use of acute migraine-specific medications in patients with episodic migraine
- Limitations:
 - Durability of response not explored
 - Looked at 6 month timeframe
 - Did not analyze 70 mg versus 140 mg results
 - Exclusion criteria
 - External validity

Safety and Efficacy of Erenumab for Preventive Treatment of Chronic Migraine: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Trial

- Objective: To compare erenumab to placebo for the prevention of chronic migraine
- Multicenter, randomized, double-blind, placebo controlled, parallel-group phase 2 trial
- Study phases: Screening (< 3 weeks), baseline phase (4 weeks), double-blind treatment phase (12 weeks), and safety follow-up (12 weeks)
- Study groups: Random assignment to erenumab 70 mg, erenumab 140 mg, or placebo injected subcutaneously monthly over 3 months

Inclusion/Exclusion

- Inclusion criteria:

- Adults 18-65 years old with a history of chronic migraine
- Experienced > 15 headache days/month, of which > 8 were migraine days
- Demonstrated 80% reporting adherence to daily handheld electronic diary completion

- Exclusion criteria:

- Age > 50 at migraine onset
- History of hemiplegic migraine, cluster headache, or **chronic migraine with continuous pain**
- Recent botulinum toxin use
- **Had no therapeutic response to \geq 3 migraine-prevention treatment categories**
- **Use of any migraine preventive medication within 2 months before baseline**

Endpoints

- Primary endpoint:
 - Change from baseline to weeks 9-12 in the mean number of migraine days/month
- Secondary endpoints:
 - 50% or greater reduction in mean migraine days/month
 - Change in the number of days of acute migraine-specific medication use
 - Change from baseline in cumulative headache hours
- Safety
 - Monitored through the reporting of adverse events

Baseline Characteristics

	Placebo (N = 286)	Erenumab 70 mg (N = 191)	Erenumab 140 mg (N = 190)
Age - years (range)	42.1±11.3 (18-66)	41.4±11.3 (18-64)	42.9±11.1 (18-64)
Female sex – no. (%)	116 (79%)	166 (87%)	160 (84%)
White race – no. (%)	268 (94%)	176 (92%)	184 (97%)
History of preventative treatment failures – no. (%)			
None	86 (30%)	64 (34%)	64 (34%)
Failed ≥ 1 drug	200 (70%)	127 (67%)	126 (66%)
Failed > 2 drugs	142 (50%)	93 (49%)	92 (48%)
Migraine with aura – no. (%)	124 (43%)	81 (42%)	71 (37%)
Medication overuse – no. (%)	117 (41%)	79 (41%)	78 (41%)

Baseline Characteristics

	Placebo (N = 286)	Erenumab 70 mg (N = 191)	Erenumab 140 mg (N = 190)
Assessment of migraine during baseline phase – mean (SD)			
Migraine days per month	18.2 (4.7)	17.9 (4.4)	17.8 (4.7)
Headache days per month	21.1 (3.9)	20.5 (3.8)	20.7 (3.8)
Days of use of acute migraine-specific medication per month	9.5 (7.6)	8.8 (7.2)	9.7 (7.0)
Monthly headache hours	235.3 (126.1)	223.6 (126.6)	215.1 (123.5)

Results

	Placebo (N = 281)	Erenumab 70 mg (N = 188)	Erenumab 140 mg (N = 187)
Migraine days per month*			
Change from baseline	-4.2 (0.4)	-6.6 (0.4)	-6.6 (0.4)
Difference vs. placebo (95% CI)		-2.5 (-3.5 to -1.4)	-2.5 (-3.5 to -1.4)
50% reduction from baseline in migraine days per month*			
No. of patients (%)	66 (23%)	75 (40%)	77 (41%)
Odds ratio (95% CI)		2.2 (1.5 to 3.3)	2.3 (1.6 to 3.5)
Days of use of acute migraine-specific medication per month*			
Change from baseline	-1.6 (0.2)	-3.5 (0.3)	-4.1 (0.3)
Difference vs. placebo (95% CI)		-1.9 (-2.6 to -1.1)	-2.6 (-3.3 to -1.8)
Cumulative monthly headache hours			
Change from baseline	-55.2 (5.7)	-64.8 (6.9)	-74.5 (6.9)
Difference vs. placebo (95% CI)		-9.5 (-27.0 to 7.9)	-19.3 (-36.7 to -1.9)

*P ≤ 0.0001

Results

	Placebo (N = 282)	Erenumab 70 mg (N = 190)	Erenumab 140 mg (N = 188)
Adverse event – no.(%)	110 (39%)	83 (44%)	88 (47%)
Injection-site pain	3 (1%)	7 (4%)	7 (4%)
Upper respiratory tract infection	4 (1%)	5 (3%)	6 (3%)
Nausea	7 (2%)	4 (2%)	6 (3%)
Nasopharyngitis	16 (6%)	6 (3%)	3 (2%)
Constipation	1 (<1%)	0	8 (4%)
Muscle spasms	4 (1%)	0	8 (4%)
Migraine	3 (1%)	3 (2%)	5 (3%)
Adverse event leading to discontinuation	2 (<1%)	0	2 (1%)
Serious adverse event	7 (2%)	6 (3%)	2 (1%)

Conclusion and Limitations

- Conclusion: Over a period of 3 months, erenumab 70 mg and 140 mg injected subcutaneously monthly significantly reduced migraine frequency in patients with chronic migraine
- Limitations:
 - Durability of response not explored
 - Looked at 3 month timeframe
 - Did not analyze 70 mg versus 140 mg results
 - Exclusion criteria
 - External validity

Fremanezumab Trials

Effect of Fremanezumab Compared with Placebo for Prevention of Episodic Migraine

- Objective: To compare fremanezumab to placebo for the prevention of episodic migraine
- Multicenter, randomized, double-blind, placebo controlled, parallel-group phase 3 trial
- Study phases: 28-day pretreatment period; 12-week treatment period; final evaluation
- Study groups: Random assignment to fremanezumab 225mg (monthly), fremanezumab 675mg (quarterly), or placebo injected subcutaneously monthly over 12 weeks

Inclusion/Exclusion Criteria

- Inclusion criteria:

- Adults 18-70 years old with a history of migraine for at least 12 months before screening
- Experienced 6-14 migraine days/month and at least 4 days of headache fulfilling criteria of migraine

- Exclusion criteria:

- Age > 50 at migraine onset
- Use of opioids or barbiturates during pre-treatment
- Recent treatment with botulinum toxin or prophylactic devices/procedures
- Had no therapeutic response to > 2 migraine-prevention treatment categories

Endpoints

- Primary endpoint:
 - Mean change from baseline in mean number of monthly migraine days during a 12-week period after first injection
- Secondary endpoints:
 - 50% or greater reduction in mean number of monthly migraine days
 - Mean change in monthly mean number of monthly days with use of any headache medications
 - Mean change from baseline to week 4 in number of migraine days
 - Mean change in mean number of monthly migraine days in patient not receiving concomitant migraine preventative medications
 - Mean change in MIDAS score
- Safety
 - Monitored through the reporting of adverse events, vital signs, ECG, labs, physical exam, concomitant medication use, suicidal ideation, injection sites, serum anti-drug antibodies

Baseline Patient Characteristics

	Placebo (N = 294)	Fremanezumab 225mg (N = 290)	Fremanezumab 675mg (N = 291)
Age - years \pmSD	41.3 \pm 12.0	42.9 \pm 12.7	41.1 \pm 11.4
Female sex – no. (%)	247 (84.0)	244 (84.1)	251 (86.3)
Current acute medication use – no. (%)	280 (95.2)	279 (96.2)	281 (96.6)
Preventive medication use – no. (%)	62 (21.1)	62 (21.4)	58 (19.9)
Prior topiramate use – no. (%)	53 (18.0)	64 (22.1)	51 (17.5)

Baseline Patient Characteristics

	Placebo (N = 294)	Fremanezumab 225mg (N = 290)	Fremanezumab 675mg (N = 291)
Assessment of migraine during pretreatment period – mean\pmSD			
Migraine days	9.1 \pm 2.7	8.9 \pm 2.6	9.3 \pm 2.7
Headache days of moderate severity	6.9 \pm 3.1	6.8 \pm 2.9	7.2 \pm 3.1
Days with use of any acute headache medications	7.7 \pm 3.6	7.7 \pm 3.4	7.8 \pm 3.7
Days with use of acute migraine-specific medications	7.1 \pm 3.0	6.1 \pm 3.1	6.6 \pm 3.0
MIDAS score	37.3 \pm 27.6	38.0 \pm 33.2	41.7 \pm 33.0

Results

*P < 0.001

	Placebo (N = 290)	Fremanezumab 225 mg (N = 287)	Fremanezumab 675mg (N = 288)
Migraine days per month			
Change from baseline (LSM)	-2.2 (-2.68 to -1.71)	--3.7 (-4.15 to -3.18)	-3.4 (-3.94 to -2.96)
Difference vs. placebo (95% CI)		-1.5 (-2.01 to -0.93)*	-1.3 (-1.79 to -0.72)*
50% reduction from baseline in migraine days per month			
No. of patients (%)	81 (27.9)	137 (47.7)	128 (44.4)
Difference vs. placebo (95% CI)%		19.8 (12.0 to 27.6)*	16.5 (8.9 to 24.1)*
Mean monthly days with use of acute medication from baseline to week 12			
Change from baseline (LSM)	-1.6 (-2.04 to -1.20)	-3.0 (-3.41 to -2.56)	-2.9 (-3.34 to -2.48)
Difference vs. placebo (95% CI)		-1.4 (-1.84 to -0.89)*	-1.3 (-1.76 to -0.82)*
Mean monthly migraine days in patients with no preventive medications from baseline to week 12			
Change from baseline (LSM)	-2.4 (-2.91 to -1.88)	-3.7 (-4.23 to -3.17)	-3.5 (-4.06 to -3.01)
Difference vs. placebo (95% CI)		-1.3 (-1.92 to -0.70)*	-1.1 (-1.75 to -0.54)*
MIDAS score			
Change from baseline (LSM)	-17.5 (-20.62 to -14.47)	-24.6 (-27.68 to -21.45)	-23.0 (-26.10 to -19.82)
Difference vs. placebo (95% CI)		-7.0 (-10.51 to -3.53)*	-5.4 (-8.90 to -1.93)

Results

	Placebo (N = 293)	Fremanezumab 225mg (N = 290)	Fremanezumab 675mg (N = 291)
Adverse event – no.(%)	171 (58.4)	192 (66.2)	193 (66.3)
Upper respiratory tract infection	15 (5.1)	16 (5.5)	11 (3.8)
Nasopharyngitis	9 (3.1)	11 (3.8)	11 (3.8)
Injection site pain	76 (25.9)	87 (30.0)	86 (29.6)
Injection site induration	45 (15.4)	71 (24.50)	57 (19.6)
Injection site erythema	41 (14.0)	52 (17.9)	55 (18.9)
Nausea	5 (1.7)	4 (1.4)	7 (2.4)
Adverse event leading to discontinuation	5 (1.7)	5 (1.7)	5 (1.7)
Serious adverse event	7 (2.4)	3 (1.0)	3 (1.0)

Conclusions and Limitations

- Conclusion: Over a period of 12 week period, fremanezumab 225 mg or 675 mg injected subcutaneously significantly reduced:
 - Mean number of migraine days/month
 - Improved MIDAS scores
- Limitations:
 - Power
 - Various patient confounders
 - Length of study
 - Role of acute medications
 - Not compared to other drugs available in the class

Fremanezumab for the Preventive Treatment of Chronic Migraine

- Objective: To compare fremanezumab to placebo for the prevention of chronic migraine
- Multicenter, randomized, double-blind, placebo controlled, parallel-group phase 3 trial
- Study phases: 28-day pretreatment period; 12-week treatment period; final evaluation
- Study groups: Random assignment to fremanezumab 225mg (monthly), fremanezumab 675mg (quarterly), or placebo injected subcutaneously monthly over 12 weeks

Inclusion/Exclusion Criteria

- Inclusion criteria:

- Adults 18-70 years old with a history of migraine for at least 12 months before screening
- Experienced > 15 headache days/month, of which > 8 were migraine days

- Exclusion criteria:

- Use of opioids or barbiturates during pre-treatment
- Recent treatment with botulinum toxin or prophylactic devices/procedures
- Had no therapeutic response to > 2 migraine-prevention treatment categories

Endpoints

- Primary endpoint:
 - Mean change in average number of headache days per month (baseline to week 12)
- Secondary endpoints:
 - Mean change from baseline in average number of migraine days per month
 - Percentage of patients with reduction of at least 50% in the average number of headache days per month
 - Mean change from baseline in average number of days per month which acute headache medication was used during the study period
 - Mean change from baseline in number of headache days during the 4-week period and the 12-week period after the first dose in patients not receiving concomitant preventive medication
 - Mean change in HIT-6 scores
- Safety
 - Monitored through the reporting of adverse events, vital signs, ECG, labs, physical exam, concomitant medication use, suicidal ideation, injection sites, serum anti-drug antibodies

Baseline Patient Characteristics

	Placebo (N = 371)	Fremanezumab 225mg (N = 375)	Fremanezumab 675mg (N = 375)
Age - years \pmSD	41.4 \pm 12.0	40.6 \pm 12.0	42.0 \pm 12.4
Female sex – no. (%)	330 (88)	330 (87)	331 (88)
Current acute medication use – no. (%)	358 (95)	360 (95)	359 (95)
Preventive medication use – no. (%)	77 (21.)	85 (22)	77 (20)
Prior topiramate use – no. (%)	117 (31)	117 (31)	106 (28)
Prior onabotulinumtoxinA use – no. (%)	49 (13)	50 (13)	66 (18)

Baseline Patient Characteristics

	Placebo (N = 371)	Fremanezumab 225mg (N = 375)	Fremanezumab 675mg (N = 375)
Assessment of migraine during pretreatment period – mean\pmSD			
Headache days	13.3 \pm 5.8	12.8 \pm 5.8	13.2 \pm 5.5
Migraine days	16.4 \pm 5.2	16.0 \pm 5.2	16.2 \pm 4.9
Headache days of ANY severity/duration	20.3 \pm 4.2	20.3 \pm 4.3	20.4 \pm 3.9
Days with use of any acute headache medications	13.0 \pm 6.9	13.1 \pm 7.2	13.1 \pm 6.8
Days with use of acute migraine-specific medications	10.7 \pm 6.3	11.1 \pm 6.0	11.3 \pm 6.2
HIT-6 score	64.1 \pm 4.8	64.6 \pm 4.4	64.3 \pm 4.7

	Placebo (N = 371)	Fremanezumab 225mg (N = 375)	Fremanezumab 675mg (N = 375)
Average headache days per month			
Change from baseline (LSM)	-2.5±0.3	-4.6±0.3	-4.3±0.3
Difference vs. placebo (±SE)		-2.1±0.3*	-1.8±0.3*
Average migraine days per month			
Change from baseline (LSM)	-3.2±0.4	-5.0±0.4	-4.9±0.4
Difference vs. placebo (±SE)		-1.8±0.4*	-1.7±0.4*
50% or greater reduction from baseline in average number of headache days per month			
No. of patients (%)	67 (18)	153 (41)*	141 (38)*
Average number of days with use of acute medication per month from baseline to week 12			
Change from baseline (LSM)	-1.9±0.3	-4.2±0.3	-3.7±0.3
Difference vs. placebo (±SE)		-2.3±0.3*	-1.8±0.3*
Average number of headache days per month in patients with no preventive medications from baseline to week 12			
Change from baseline (LSM)	-2.6±0.3 (N=294)	-4.8±0.3 (N=290)	-4.6±0.3 (N=298)
Difference vs. placebo (±SE)		-2.2±0.4*	-1.9±0.4*
HIT-6 score change from baseline to week 4			
Change from baseline (LSM)	-4.5±0.5	-6.8±0.4	-6.4±0.5
Difference vs. placebo (±SE)		-2.4±0.5*	-1.9±0.5*

Results

	Placebo (N = 375)	Erenumab 70 mg (N = 379)	Erenumab 140 mg (N = 376)
Adverse event – no.(%)	240 (64)	270 (71)	265 (70)
Upper respiratory tract infection	15 (4)	16 (4)	18 (5)
Nasopharyngitis	20 (5)	15 (4)	19 (5)
Sinusitis	10 (3)	4 (1)	10 (3)
Injection site pain	104 (28)	99 (26)	114 (30)
Injection site induration	68 (18)	90 (24)	74 (20)
Injection site erythema	60 (16)	75 (20)	80 (21)
Injection site hemorrhage	10 (3)	8 (2)	7 (2)
Dizziness	5 (1)	11 (3)	9 (2)
Nausea	11 (3)	6 (2)	(1)
Adverse event leading to discontinuation	8 (2)	7 (2)	5 (1)
Serious adverse event	6 (2)	5 (1)	3 (<1)

Conclusions and Limitations

- Conclusion: Over a period of 12 week period, fremanezumab 225 mg or 675 mg injected subcutaneously significantly reduced:
 - Average number of migraine days/month
 - Number of migraine days
 - Improved HIT-6 scores
- Limitations:
 - Various patient confounders
 - Length of study
 - Long-term safety

Galcanezumab Trials

Efficacy and safety of galcanezumab for the prevention of episodic migraine (EVOLVE-2)

- Objective: To demonstrate superiority of galcanezumab to placebo in prevention of episodic migraine
- Multicenter, randomized, double-blind, placebo controlled, phase 3 trial
- Study phases: initial screening and washout period (3-45 days); prospective lead-in period (30-40 days); 6-month treatment period; 4 month post-treatment period
- Study groups: Random assignment to galcanezumab 120mg (after 240mg loading dose), galcanezumab 240mg, or placebo injected subcutaneously monthly over 6 months

Inclusion/Exclusion Criteria

- Inclusion criteria:

- Adults 18-65 years old with a history of migraine for at least 12 months before screening
- Experienced 4-14 migraine days/month and at least 2 migraine attacks per month during baseline period

- Exclusion criteria:

- Age > 50 at migraine onset
- Had no therapeutic response to 3 or more migraine-prevention treatment categories
- Prior exposure to any CGRP antibody
- Receiving preventive migraine medication within 30days of baseline period
- Certain medical conditions

Endpoints

- Primary endpoint:
 - Whether at least 1 dose of galcanezumab was superior to placebo in overall mean change from baseline of monthly migraine days
- Secondary endpoints:
 - 50%, 75%, and 100% reduction in monthly migraine days
 - Reduction of number of migraine days with use of any headache medications
 - Reduction in
 - MSQ scores
 - PGI-S scores
 - MIDAS scores
- Safety
 - Monitored through the reporting of adverse events, deaths, discontinuation rates, vital signs, weight, immunogenicity

Baseline Patient Characteristics

	Placebo (N = 461)	Galcanezumab 120mg (N = 231)	Galcanezumab 240mg (N = 223)
Age - years \pmSD	42.3 \pm 11.3	40.9 \pm 11.2	41.9 \pm 10.8
Female sex – %	85.3	85.3	85.7
White race/ethnicity – %	70.5	71.9	68.2
MIDAS score – mean\pmSD	34.3 \pm 31.0	30.9 \pm 27.9	32.8 \pm 28.8
MSQ RF-R score – mean\pmSD	51.4 \pm 15.7	52.5 \pm 14.8	51.7 \pm 16.3
PGI-S score – mean\pmSD	4.3 \pm 1.2	4.1 \pm 1.2	4.2 \pm 1.2
Prior preventive treatment - %	64.6	68.0	64.6

Baseline Patient Characteristics

	Placebo (N = 461)	Galcanezumab 120mg (N = 231)	Galcanezumab 240mg (N = 223)
Assessment of migraine during pretreatment period – mean\pmSD			
Migraine days per month	9.2 \pm 3.0	9.07 \pm 2.9	9.06 \pm 2.9
Migraine attacks per month	5.7 \pm 1.8	5.54 \pm 1.8	5.66 \pm 1.8
Headache days per month	10.7 \pm 3.5	10.56 \pm 3.4	10.74 \pm 3.7
Migraine days with use of any acute medications per month	7.6 \pm 3.4	7.47 \pm 3.3	7.47 \pm 3.3
≥ 2 failed preventive treatments	63 \pm 13.7	34 \pm 14.7	34 \pm 15.3

	Placebo (N = 461)	Galcanezumab 120mg (N = 231)	Galcanezumab 240mg (N = 223)
Overall change in migraine days per month*			
From baseline (LSM) (95% CI)	-2.3 (-2.7 to -1.9)	-4.3 (-4.8 to -3.8)	-4.2 (-4.7 to -3.7)
≥50% reduction from baseline in migraine days per month*			
% (95% CI)	36 (33 to 39)	59.3 (55 to 64)	56.5 (52 to 61)
≥75% reduction from baseline in migraine days per month*			
% (95% CI)	17.8 (15 to 21)	33.5 (29 to 38)	34.3 (30 to 39)
100% reduction from baseline in migraine days per month*			
% (95% CI)	5.7 (4.4 to 7.3)	11.5 (9 to 15)	13.8 (11 to 17)
Change in migraine days with use of acute migraine-specific medication*			
From baseline (LSM) (95% CI)	-1.9 (-2.2 to -1.5)	-3.7 (-4.1 to -3.2)	-3.6 (-4.1 to -3.2)
MSQ RF-R score*			
Change (LSM) (95% CI)	19.7 (17.9 to 21.5)	28.5 (26.2 to 30.7)	27 (24.7 to 29.3)
MIDAS total score*			
Change (LSM) (95% CI)	-12 (-14.5 to -9.5)	-21.2 (-24.3 to -18.1)	-20.2 (-23.4 to -17.1)
PGI-S score			
Change (LSM) (95% CI)	-0.9 (-1.1 to -0.8)	-1.2 (-1.4 to -1.1)	-1.2 (-1.3 to -1.0)

Results

	Placebo (N = 461)	Galcanezumab 120mg (N = 231)	Galcanezumab 240mg (N = 223)
Adverse event – no.(%)	287 (62.3)	147 (65.0)	163 (71.5)
Nasopharyngitis	41 (8.9)	19 (8.4)	16 (7.0)
Upper respiratory tract infection	16 (3.5)	13 (5.8)	12 (5.3)
Injection site pain	39 (8.5)	21 (9.3)	20 (8.8)
Injection site reaction	0	7 (3.1)	18 (7.9)
Injection site erythema	4 (0.9)	6 (2.7)	7 (3.1)
Injection site pruritus	0	6 (2.7)	7 (3.1)
Injection site swelling	0	5 (2.2)	1 (0.4)
Dizziness	10 (2.2)	8 (3.5)	7 (3.1)
Adverse event leading to discontinuation	8 (1.7)	5 (2.2)	9 (4.0)
Serious adverse event	5 (1.1)	5 (2.2)	7 (3.1)

Conclusions and Limitations

- Conclusion: Over a 6 month period, galcanezumab 120mg or 240mg was superior to placebo in:
 - Reduction of monthly migraine days
 - Reduction of migraine frequency
 - Reduction of migraine-related disability and improved patient functioning
 - Statistically significant reduction of 50%, 75%, and 100% in monthly migraine days
- Limitations:
 - Not known if effective as adjunct treatment
 - Generalizability
 - Caution in patients with certain CV comorbid conditions

Evaluation of Galcanezumab in the Prevention of Chronic Migraine (REGAIN)

- Objective: To evaluate the efficacy of galcanezumab in patients with chronic migraine
- Multicenter, randomized, double-blind, placebo controlled, phase 3 trial
- Study phases: 3 month treatment period
- Study groups: Random assignment to galcanezumab 120mg (after 240mg loading dose), galcanezumab 240mg, or placebo injected subcutaneously monthly over 3 months

Inclusion/Exclusion Criteria

- Inclusion criteria:

- Adults 18-65 years old with a diagnosis of chronic migraine for at least 12 months before screening

- Exclusion criteria:

- Age > 50 at migraine onset
- History of persistent daily headache, cluster headache or certain migraine subtypes
- Prior exposure to any CGRP antibody
- Known hypersensitivity

Endpoints

- Primary endpoint:
 - Mean change from baseline in number of monthly migraine days
- Secondary endpoints:
 - 50%, 75%, and 100% reduction in monthly migraine days
 - Mean change from baseline in number of migraine days with use of any headache medications
 - Mean change from baseline in
 - MSQ scores
 - PGI-S scores
 - MIDAS scores
- Study completion date: May 2021

Future Considerations

Long-term safety data

- Cardiac concerns

Excluded patients

- Treatment failures
- Elderly

Use in more diverse patient populations

Unclear dosing

Real-world use

Stop and Think Patient Case Scenario

- TM is 32-year-old woman with no significant past medical history is suffering from severe episodic migraines causing her to miss work 6 days a month. She has tried and failed several preventative medications due to side effect intolerance and would now like to try one of the new CPRG monoclonal antibodies.
- Is a CPRG monoclonal antibody a potential treatment option for TM based on the information provided?
- What additional information might change your mind?

Dosage and Administration

	Erenumab	Fremanezumab	Galcanezumab
Dose	70mg – 140mg SC monthly	225mg SC monthly 675mg SC quarterly	240mg SC loading dose 120mg SC monthly
How supplied	Prefilled syringe Autoinjector	Prefilled syringe	Prefilled syringe Autoinjector
Solution description	clear; colorless to light yellow	clear; colorless to light yellow	clear; colorless to light yellow/light brown
Contraindications	none	hypersensitivity to drug or component	hypersensitivity to drug or component
Precautions	Latex allergy, immunogenicity	hypersensitivity reactions, immunogenicity	hypersensitivity reactions
Adverse reactions	Injection site reactions; constipation, cramps, muscle spasms	Injection site reactions; antibody development; hypersensitivity	Injection site reactions; antibody development; hypersensitivity

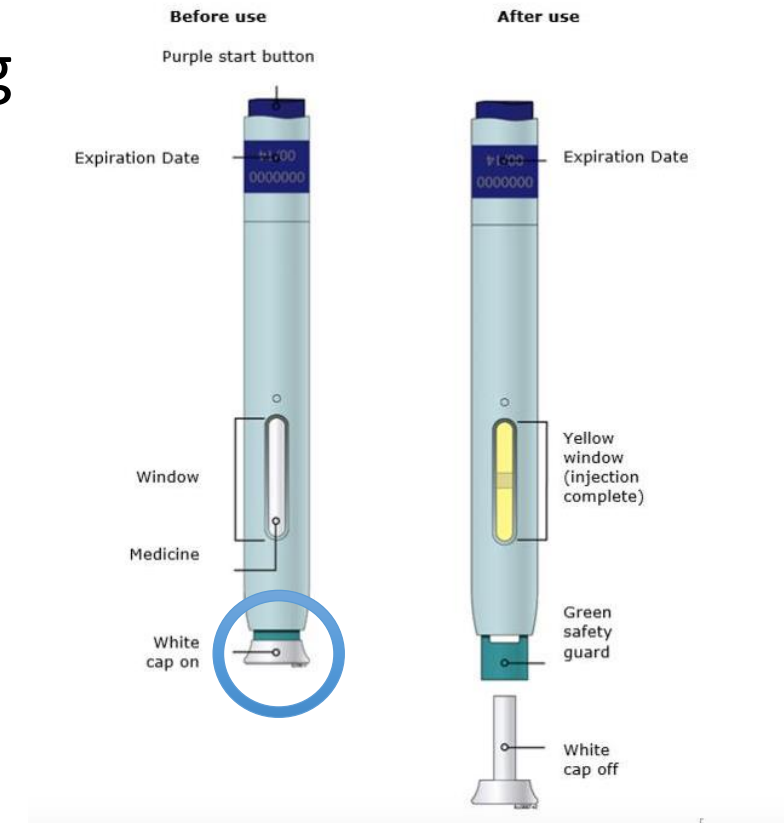
Aimovig [Package Insert]. Ajovy [Package Insert]. Emgality [Package Insert].

Patient Counseling Points - Administration

- Intended for patient self-administration
- Prior to administering:
 - Allow to sit at room temperature for at least 30 minutes
 - Visually inspect for particulates and discoloration
- Do not shake
- Do not use if it has been dropped on a hard surface
- Administer the entire contents subcutaneously into the abdomen, thigh, or upper arm

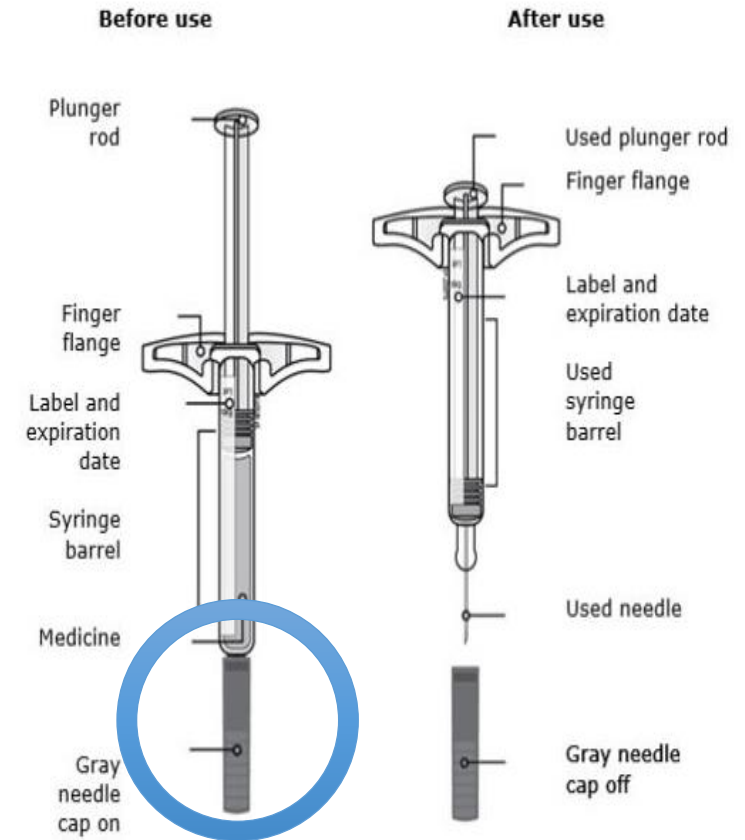
Autoinjector Administration (Aimovig)

- Pull the white cap straight off just prior to injecting
- Place on the skin at 90 degrees and firmly push it down until the autoinjector stops moving
- Press the top button to begin injecting
- Keep pushing down on your skin until you hear or feel a click and the window turns yellow
 - This will take about 15 seconds
- The needle will be automatically covered when removed from the skin



Syringe Administration (Aimovig)

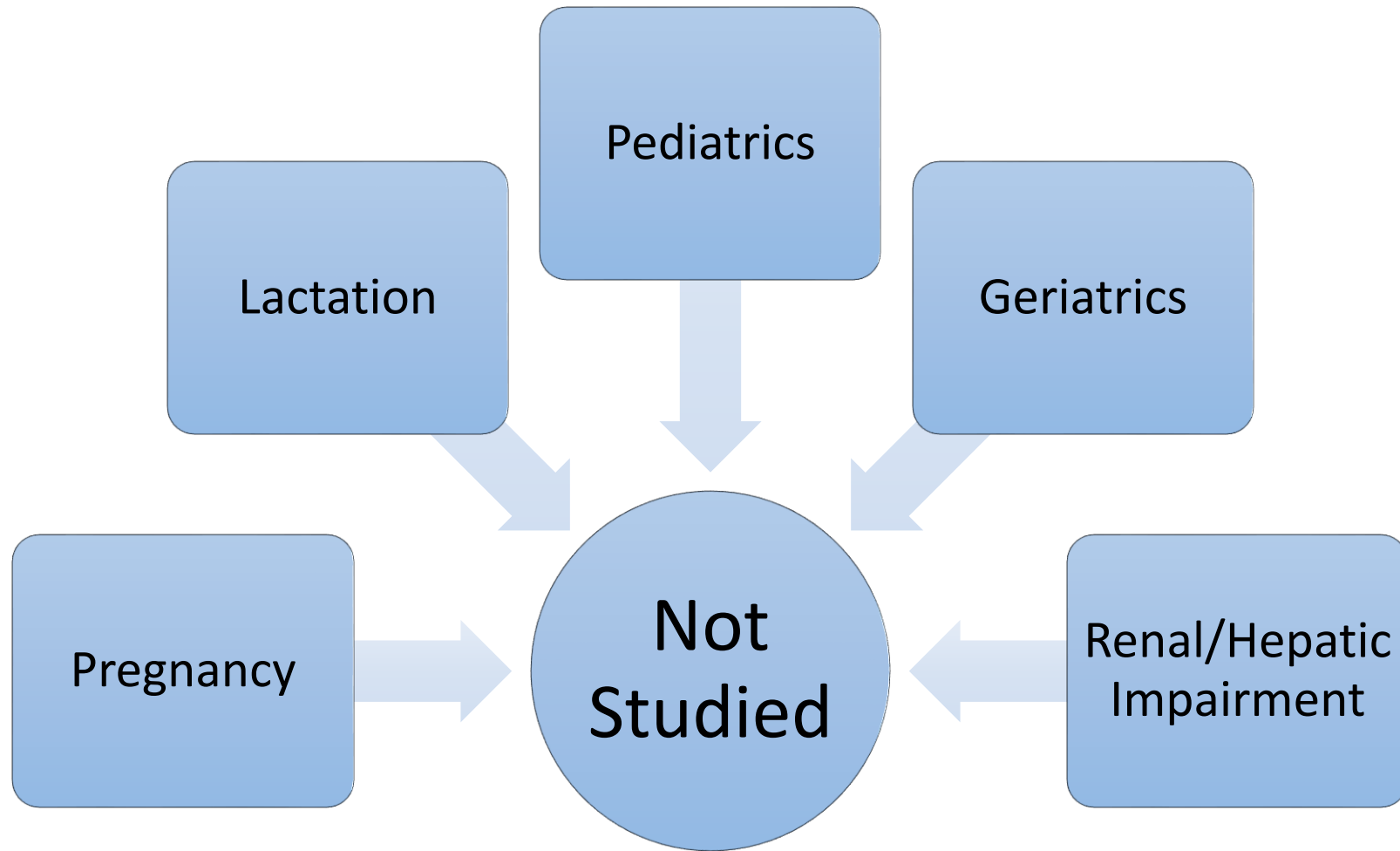
- Always hold the syringe by the syringe barrel
- Pull the gray needle cap off just prior to injecting
- Insert the syringe into the skin at 45 to 90 degrees
- Use slow and constant pressure to push the plunger until the syringe stops moving
- Once removed, check for remaining medication in



Patient Counseling Points - Storage and Handling

- Store refrigerated in the original carton to protect from light until time of use
- If removed from the refrigerator, keep at room temperature in the original carton for up to 7 days (erenumab and galcanezumab) or 24 hours (fremanezumab)
 - Do not put back into the refrigerator
 - Discard if left at room temperature for more than specified time
- Do not freeze

Use in Specific Populations



Place In Therapy

Stop and Think

- In general, what are some factors to take into account when assigning a medication a place in therapy?
 - Professional association guidelines
 - Trial results
 - Trial limitations
 - Continuing research
 - Classical treatment options
 - Benefits
 - Risks
 - Cost, coverage, and competition

Guidelines

- U.S. guidelines from the American Academy of Neurology and the American Headache Society are currently being updated to include CGRP monoclonal antibodies
- General indications for migraine prophylaxis:
 - Chronic migraine patients
 - Episodic migraine patients when
 - Recurrent migraine attacks are causing considerable disability despite optimal acute drug therapy
 - Frequency of acute medication use could put the patient at risk for medication-overuse headache
 - > 10 days/month for triptans, ergots, opioids, and combination analgesics
 - > 15 days/month for acetaminophen and NSAIDs
 - Recurrent attacks with prolonged aura are occurring
 - Contraindications to acute medications make management difficult

Trial Results, Limitations, and Continuing Research

Results

- Demonstrated reduction in migraine days/month for episodic and chronic migraine
- Showed favorable side effect profile

Limitations

- Long-term safety data
- Excluded patients
- Use in more diverse patient populations
- Unclear if benefit justifies cost in real-world use

Continuing research

Classical Treatment Options

- Beta blockers
- Antidepressants
- Antiepileptics
- OnabotulinumtoxinA
- (for chronic migraine only)

Pros:

- Generally cheaper
- Have longer treatment experience
- Can be effective for patients

Cons:

- Side effect profiles
- Variability in response
- Frequency of dosing
- Drug interaction potential
- Administration

Cost

\$6,900 per year

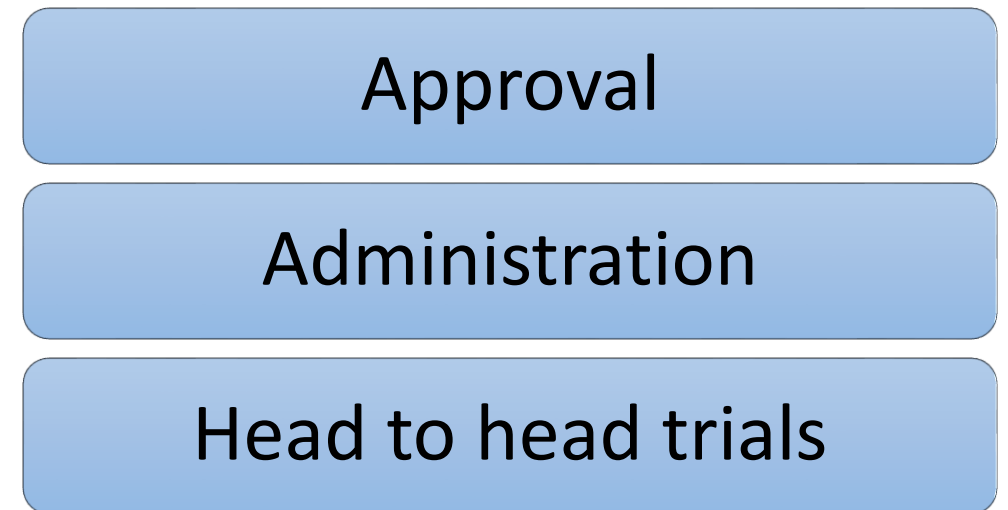
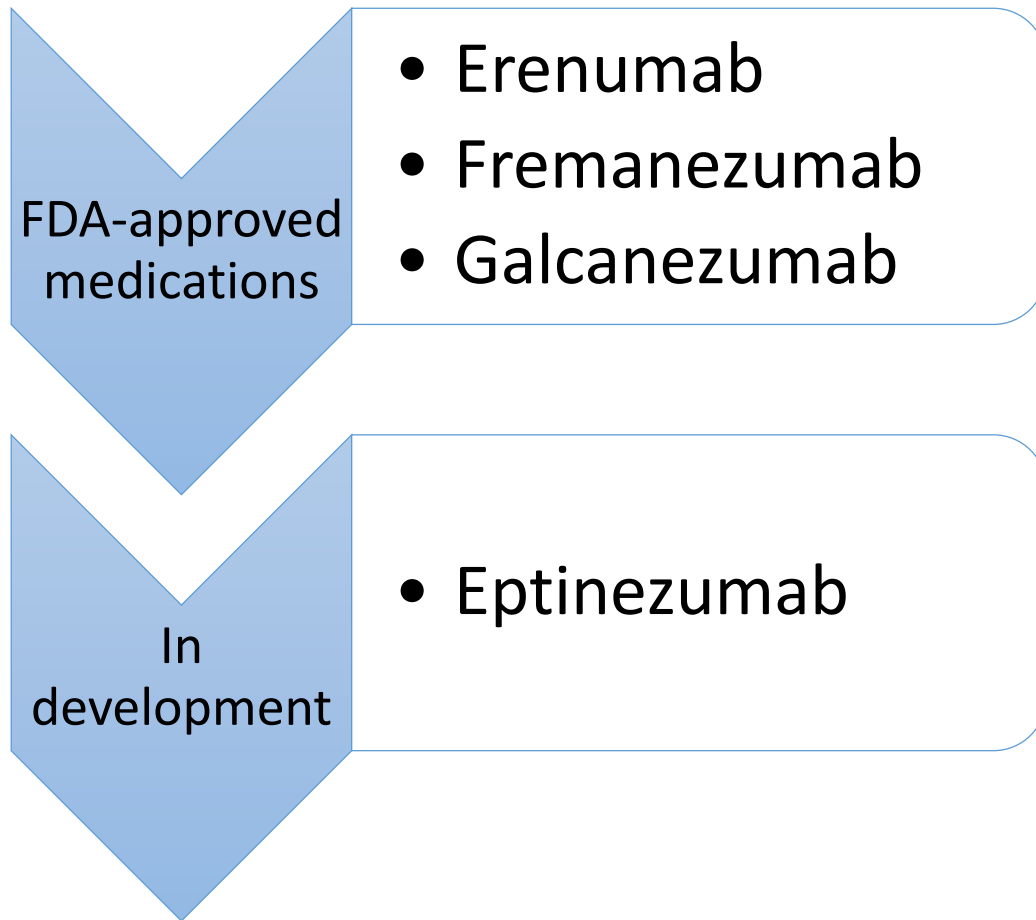
Many modifying factors

- Insurance coverage
- Patient assistance programs
- Competition (approval of new drugs)
- Approval in other markets

Results of recent cost-effectiveness analysis

Continuing emergence of new data

Competition – CGRP Inhibitors



Place in Therapy Conclusion

- CPRG monoclonal antibodies' place in therapy is not yet well established
- Factors to consider:
 - Chronic versus episodic migraine
 - Guideline revisions
 - Patient-specific factors
 - How well they fit study populations
 - Pros and cons of alternative treatment options
 - Cost/competition

Patient Case Pro/Con Grid

- Thinking back to patient TM, how do these new variables impact our opinion of the what the best treatment option is for her?

Pros

Cons

Patient Case Pro/Con Grid

- Thinking back to patient TM, how do these new variables impact our opinion of the what the best treatment option is for her?

Pros		Cons
Cost	<ul style="list-style-type: none">• Patient assistance programs	<ul style="list-style-type: none">• High cash price• Patient assistance program limitations
Existing preventative migraine treatments	<ul style="list-style-type: none">• Concurrent medical condition treatment• Generally lower costs	<ul style="list-style-type: none">• Side effect profile
Emerging competition	<ul style="list-style-type: none">• Could help drive costs down	<ul style="list-style-type: none">• Could complicate medication decisions

Post-Test 1: Which of the following best describes the proposed role of calcitonin gene-related peptide (CGRP) in migraine?

- A. It causes aura through the vasoconstriction of dural blood vessels.
- B. It increases pain signaling and causes vasoconstriction of the dural blood vessels.
- C. It causes vasodilation of the dural blood vessels, plasma extravasation, and inflammation.
- D. It decreases pain signaling and causes vasodilation of the dural blood vessels.

Post-Test 2: Which of the following outcome measures did all CPRG treatments consistently demonstrate in episodic migraine patients?

- A. Reduction in number of migraine days
- B. High rate of adverse cardiovascular effects
- C. Long term efficacy in migraine reduction (>12 months)
- D. Improvement in MIDAS scores

Post-Test 3: Which of the following is/are currently impacting the CPRG medications' place in therapy? (Select all that apply)

- A. Concerns regarding its long-term safety
- B. Concerns regarding its poor side effect profile
- C. Contradictory guideline recommendations
- D. Concerns regarding cost

Post-Test 4: Which of the following is an important counseling point for any of the CPRG medications?

- A. Shake vigorously prior to injection
- B. If the syringe is dropped on a hard surface, it is still ok to use
- C. The medication can be injected IM if preferred by the patient
- D. Allow to sit at room temperature for 30 minutes prior to injection

SUMMARY

- CGRP monoclonal antibodies represent a new class of medication that target either CGRP directly or its receptor to prevent binding
- The existing safety and efficacy data for these drugs suggest they are a promising treatment for chronic and episodic migraine
- Various factors including cost, a lack of long-term safety data, and competition are impacting CGRP monoclonal antibodies' current place in therapy
- Pharmacists, particularly those working in specialty pharmacy, should be equipped to train patients on administering these medications.

SUPPLEMENTAL RESOURCES

- National Headache Foundation
 - <https://headaches.org/resources/>
- American Headache Society
 - <https://americanheadachesociety.org/resources/information-for-clinicians/>
- American Academy of Neurology
 - <https://www.aan.com/policy-and-guidelines/guidelines/>
- International Headache Society
 - <http://www.ihs-headache.org/>

Questions?

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