Review: New Treatment and Prevention Agents for Migraine

2Q2020 P&T DUR Education, April 9, 2020

Presented by Shannon Lee, PharmD

4/24/2020

Migraine Epidemiology

Migraines are estimated to affect up to12% of the US population

- Up to 17% of adult women and 6% of adult men
- Most commonly affects those aged 30-39

Major cause of disability

- Ranked 2nd worldwide in 2016 among all diseases for years of life lived with disability
- Accounts for more than $29 billion in expenses annually in the US
  - Between $5.6 and $17.2 billion in lost work productivity

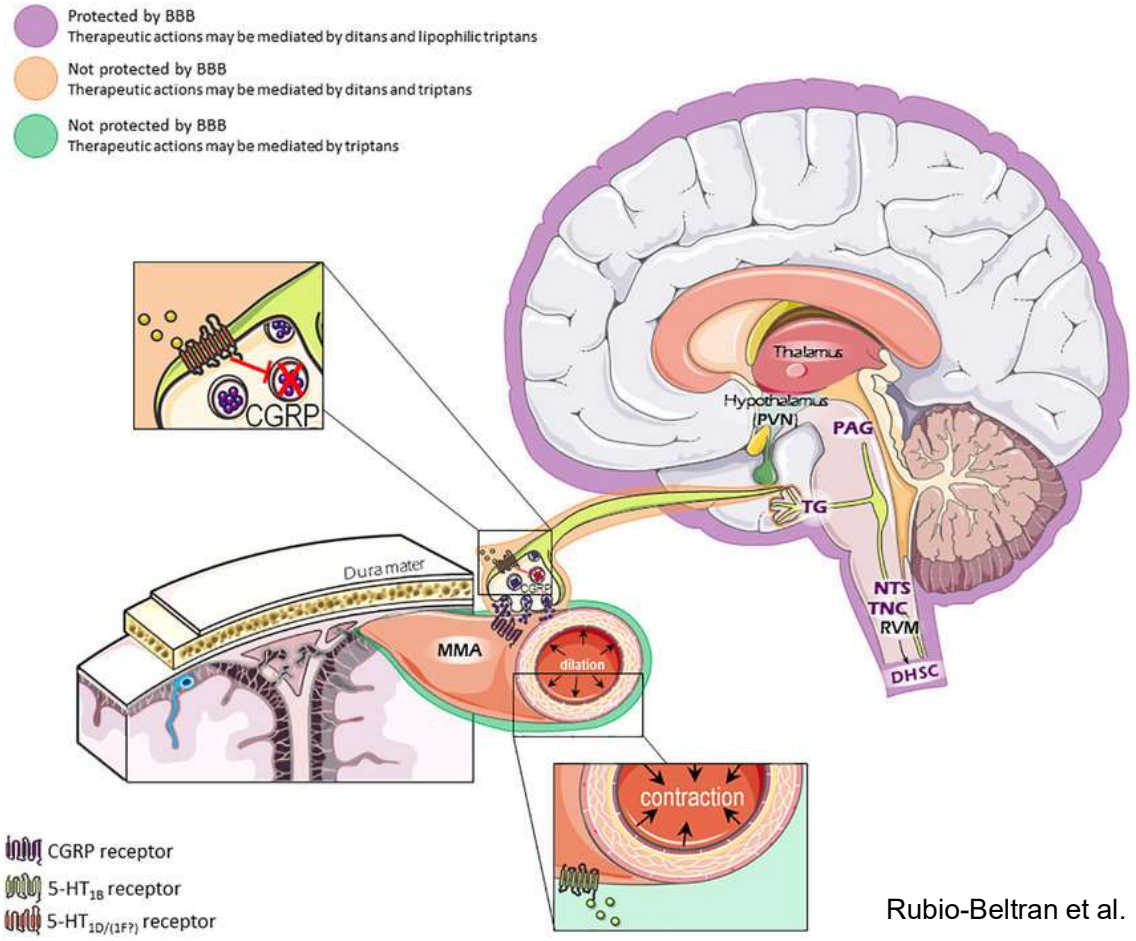
Two main classifications of migraine frequency

- Episodic: less than 15 headache days per month
- Chronic: at least 15 headache days per month

- Over 25% have more than 3 headache days per month

Migraine Pathology

- Migraine is a whole nervous system disease
- Spontaneous pain and sensory amplification
- Trigger is unknown and likely varies between individuals
- Neurovascular disorder caused by activation of the trigeminovascular system and cranial vasodilation
- Mediated by release of calcitonin gene-related peptide (CGRP)



Rubio-Beltran et al.

New Agents

Drug Name	MOA
Acute Treatment Agents	
Reyvow (lasmiditan)	Selective serotonin 1F receptor agonist
Ubrelvy (ubrogepant)	Calcitonin gene-related peptide (CGRP) receptor antagonist (peptide)
Nurtec (rimegepant)	
Prophylaxis Agents	
Aimovig (erenumab-aooe)	CGRP receptor antagonist (monoclonal antibody)
Ajovy (fremanezumab-vfrm)	
Emgality (galcenezumab-gnlm)	
Vyepti (eptinezumab-jjmr)	

Acute Treatment Agents

4/24/2020

Triptans are Mainstay of Acute Treatment

Table.—Strength of the Evidence

Level A	Level B	Level C	Level U	Others
Analgesic Acetaminophen 1000 mg (for non-incapacitating attacks)	**Antiemetics** *Chlorpromazine IV 12.5 mg Droperidol IV 2.75 mg *Metoclopramide IV 10 mg *Prochlorperazine IV/IM 10 mg; PR 25 mg	**Antiepileptic** Valproate IV 400-1000 mg	**NSAIDs** Celecoxib 400 mg	**Level B negative Other** Octreotide SC 100 μg
Ergots DHE *Nasal spray 2 mg Pulmonary inhaler 1 mg	**Ergots** DHE * IV, IM, SC 1 mg *Ergotamine/caffeine 1/100 mg	**Ergot** *Ergotamine 1-2 mg	**Others** *Lidocaine IV *Hydrocortisone IV 50 mg	**Level C negative Antiemetics** *Chlorpromazine IM 1 mg/kg *Granisetron IV 40-80 μg/kg
NSAIDs *Aspirin 500 mg Diclofenac 50, 100 mg Ibuprofen 200, 400 mg *Naproxen 500, 550 mg	**NSAIDs** *Flurbiprofen 100 mg Ketoprofen 100 mg Ketorolac IV/IM 30-60 mg	**NSAIDs** Phenazone 1000 mg		**NSAIDs** Ketorolac tromethamine nasal spray
Opioids *Butorphanol nasal spray 1 mg		**Opioid** *Butorphanol IM 2 mg *Codeine 30 mg PO *Meperidine IM 75 mg *Methadone IM 10 mg *Tramadol IV 100 mg		**Analgesic** Acetaminophen IV 1000 mg
Triptans Almotriptan 12.5 mg Eletriptan 20, 40, 80 mg Frovatriptan 2.5 mg *Naratriptan 1, 2.5 mg *Rizatriptan 5, 10 mg Sumatriptan *Oral 25, 50, 100 mg *Nasal spray 10, 20 mg Patch 6.5 mg *SC 4, 6 mg Zolmitriptan nasal spray 2.5, 5 mg *Oral 2.5, 5 mg	**Others** $MgSO_4$ IV (migraine with aura) 1-2 g *Isometheptene 65 mg	**Steroid** Dexamethasone IV 4-16 mg		
Combinations *Acetaminophen/aspirin/caffeine 500/500/130 mg Sumatriptan/naproxen 85/500 mg	**Combinations** *Codeine/acetaminophen 25/400 mg Tramadol/acetaminophen 75/650 mg	**Others** *Butalbital 50 mg *Lidocaine intranasal		
		Combinations		

*Based on 2000 American Academy of Neurology evidence review.
Level A: Medications are established as effective for acute migraine treatment based on available evidence.
Level B: Medications are probably effective for acute migraine treatment based on available evidence.
Level C: Medications are possibly effective for acute migraine treatment based on available evidence.
Level U: Evidence is conflicting or inadequate to support or refute the efficacy of the following medications for acute migraine.
Level B negative: Medication is probably ineffective for acute migraine.
Level C negative: Medication is possibly ineffective for acute migraine.

Marmura et al.

Utilize migraine specific agents (i.e. tripans) after failure of non-specific pain agents (APAP & NSAIDs)

- Limit to 2 treatment days per week per American Headache Society (AHS) 2018

Triptan use has many limitations

- MOA: Serotonin 1B/1D/(1F) receptor agonist
- High expression of serotonin 1B receptors in the cranial blood vessels but also present in peripheral blood vessels
  - Contraindicated in vascular disease
  - Use is consistently shown to increase blood pressure

New Acute Treatment Agents

- Three new non-triptan oral agents recently approved
- Indicated for acute treatment of migraine with or without aura in adults

Brand Name	FDA Approval Date	Coverage Guidelines
Reyvow	October 11, 2019	CP.PMN.218 Lasmiditan (Reyvow) • Approved 1Q2020 and went into effect 4.1.2020
Ubrelvy	December 23, 2019	CP.PMN.476 Ubrelvy (Ubrogepant) • Under 2Q2020 review; will go into effect 7.1.2020
Nurtec	February 27, 2020	In development; expect to see in 3Q2020 materials

- All agents are currently non-formulary

Reyvow (Lasmiditan)

FDA Approved Dosing: 50mg, 100mg, or 200mg as needed

- Not to exceed one dose in 24 hours
- Safety of treating more than 4 migraine episodes in 30 day period is not established

Available Strengths: 50mg, 100mg oral tablets

Clinically Significant Side Effects:

- Dizziness
- Fatigue
- Paresthesia
- Sedation

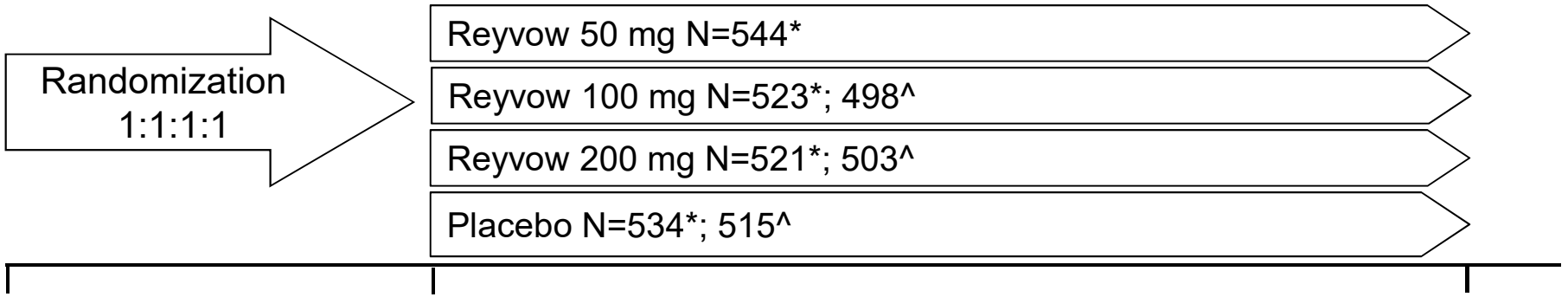
Additional Warnings and Precautions:

- Driving impairment
- Central nervous system depression
- Serotonin syndrome
- Medication overuse headache

Regulatory Status: Schedule 5 controlled substance classification; may cause euphoria

SAMURAI & SPARTAN:

R, DB, PC, Phase 3 Trials



Patient eligibility criteria:

- Dx of migraine with or w/o aura
- ≥ 18 years of age
- H/o disabling migraine for ≥ 1 yr
- MIDAS# total score of ≥ 11
- H/o 3-8 migraine attacks/month (<15 headache days/month)

Exclusion criteria :

- H/o chronic migraine or chronic headache w/in the prior 12 months
- Medication-overuse headache
- Initiation/change in migraine preventive meds w/in 3 months before screening
- Increased seizure risk
- Known coronary artery disease, clinically significant arrhythmia, or uncontrolled hypertension^

Efficacy endpoints:

At 2 hrs post-dose

- Pain free
- Free of MBS (most bothersome symptom)
- Pain relief**

Primary analysis

*SPARTAN only; ^SAMURAI only; #MIDAS=Migraine Disability Assessment; **defined as a reduction in migraine pain from “moderate or severe” to “mild or none”

SAMURAI: Results

	Reyvow 100mg	Reyvow 200mg	Placebo
Pain Free at 2 hrs			
% Responders	28.3	31.8	15.3
Difference from Placebo (%)	13	16.5	n/a
p-value (vs. Placebo)	< 0.001	< 0.001	n/a
MBS Free at 2 hrs			
% Responders	41.2	40.7	29.6
Difference from Placebo (%)	11.6	11.1	n/a
p-value (vs. Placebo)	< 0.001	< 0.001	n/a
Pain Relief at 2 hrs			
% Responders	54.0	55.3	40.0
Difference from Placebo (%)	14.0	15.3	n/a

Conclusion: Reyvow demonstrated a statistically significant reduction in migraine pain and symptoms when compared to placebo.

Number Needed to Treat (NNT):

- Primary outcome: 7 or 8 patients must be treated with Reyvow 200 mg or 100 mg, respectively, for every one patient who achieves freedom from pain at 2 hours after study medication, relative to placebo.
- Secondary outcomes: 9 or 10 patients must be treated with Reyvow 100 mg or 200 mg, respectively, for every one patient who achieves freedom from their MBS at 2 hours after study medication, relative to placebo. 7 or 8 patients must be treated with Reyvow 200 mg or 100 mg, respectively, for every one patient who achieves migraine pain relief at 2 hours after study medication, relative to placebo.

Number Needed to Harm (NNH):

- For every 625 patients treated for acute migraines with Reyvow, one patient discontinued Reyvow due to adverse effects, relative to placebo.

SPARTAN: Results

	Reyvow 50mg	Reyvow 100mg	Reyvow 200mg	Placebo
Pain Free at 2 hrs				
% Responders	28.3	31.4	38.8	21.0
Difference from Placebo (%)	7.3	10.4	17.8	n/a
p-value (vs. Placebo)	0.006	< 0.001	< 0.001	n/a
MBS Free at 2 hrs				
% Responders	40.8	44.0	48.7	33.2
Difference from Placebo (%)	7.6	10.8	15.5	n/a
p-value (vs. Placebo)	0.014	< 0.001	< 0.001	n/a
Pain Relief at 2 hrs				
% Responders	55.9	61.4	61.0	45.1
Difference from Placebo (%)	10.8	16.3	15.9	n/a

Conclusion: Reyvow demonstrated a statistically significant reduction in migraine pain and symptoms when compared to placebo.

Number Needed to Treat (NNT):

- Primary outcome: 6, 10, or 14 patients must be treated with Reyvow 200 mg, 100 mg, or Reyvow 50 mg respectively, for every one patient who achieves freedom from pain at 2 hours after study medication, relative to placebo. 7, 10, or 14 patients must be treated with Reyvow 200 mg, 100 mg, or Reyvow 50 mg respectively, for every one patient who achieves freedom from their MBS at 2 hours after study medication, relative to placebo.
- Secondary outcomes: 7, 7, or 10 patients must be treated with Reyvow 200 mg, 100 mg, or Reyvow 50 mg respectively, for every one patient who achieves migraine pain relief at 2 hours after study medication, relative to placebo.

Number Needed to Harm (NNH):

- For every 384 patients treated for acute migraines with Reyvow, one patient discontinued Reyvow due to adverse effects, relative to placebo.

Ubrelvy (Ubrogepant)

FDA Approved Dosing: 50 mg or 100 mg taken orally, as needed.

- If needed, a second dose may be administered at least 2 hours after the initial dose.
- Maximum dose in a 24-hour period is 200 mg.

- The safety of treating more than 8 migraines in a 30-day period has not been established.

Available Strengths: 50mg and 100mg oral tablets

Clinically Significant Side Effects:

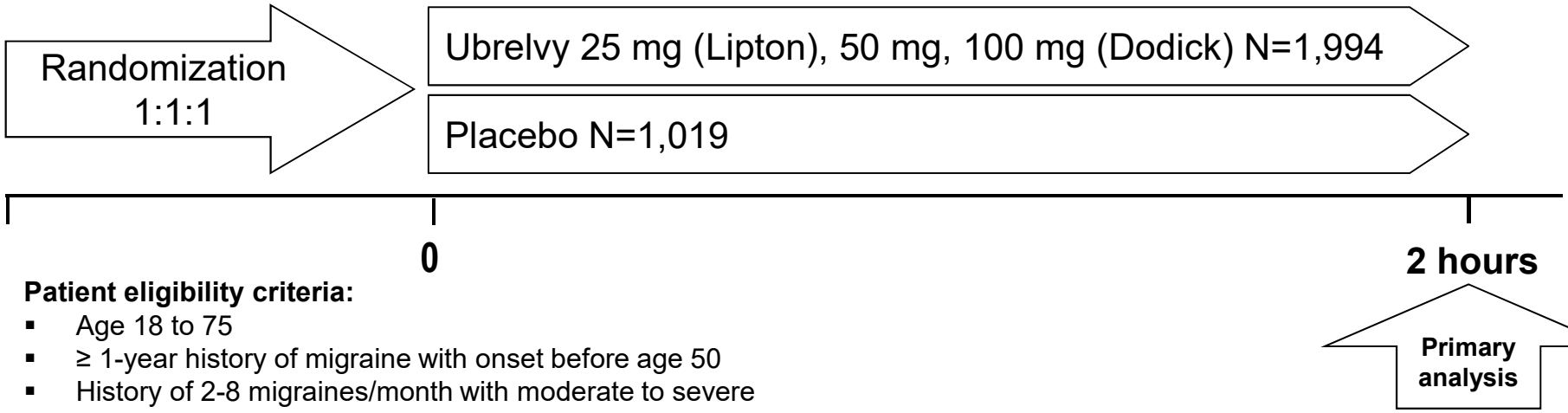
- Nausea
- Somnolence
- Dry mouth

Additional Warnings and Precautions:

- Drug-Drug Interactions Impact Use:
  - Concomitant use with strong CYP3A4 inhibitors is **contraindicated**
  - Avoid concomitant use with strong CYP3A4 inducers
  - Dose adjustment recommended with: moderate CYP3A inhibitors; strong, moderate and weak CYP3A inducers; BCRP inhibitors; P-gp inhibitors

Dodick/Lipton et al.,

R, MC, DB, PC Phase 3 Trials



Patient eligibility criteria:

- Age 18 to 75
- ≥ 1-year history of migraine with onset before age 50
- History of 2-8 migraines/month with moderate to severe headache pain
- Migraines lasted between 4 and 72 hours with attacks separated by ≥ 48 hours of freedom from headache pain

Exclusion criteria :

- Chronic migraine
- Acute migraine treatment on 10 or more days/month
- Cardiovascular or cerebrovascular disease

Efficacy endpoints: assessed 2 hours after initial dose

- Co-primary: freedom from pain; absence of MBS
- Secondary: pain relief

Dodick et al.: Results

	Ubrelvy 50mg	Ubrelvy 100mg	Placebo
Pain Free at 2 hours			
% Responders	19.2	21.1	11.8
Difference from Placebo (%)	7.4	9.4	n/a
p-value (vs. Placebo)	0.002	< 0.001	n/a
MBS Free at 2 hours			
% Responders	38.6	37.7	27.8
Difference from Placebo (%)	10.8	9.9	n/a
p-value (vs. Placebo)	0.002	0.002	n/a
Pain Relief at 2 hours			
% Responders	60.7	61.4	49.1
Difference from Placebo (%)	11.6	12.3	n/a
p-value (vs. Placebo)	0.002	0.002	n/a

Conclusion: Ubrelvey demonstrated a statistically significant reduction in migraine pain and symptoms when compared to placebo.

Number Needed to Treat (NNT):

- Primary outcome: Fourteen or 11 patients must be treated with Ubrelvy 50 mg or 100 mg, respectively, for one additional patient to achieve freedom from pain at 2 hours after study medication, relative to placebo. Ten or 11 patients must be treated with Ubrelvy 50 mg or 100 mg, respectively, for one additional patient to achieve freedom from their MBS at 2 hours after study medication, relative to placebo.
- Secondary outcomes: Nine patients must be treated with Ubrelvy 50 mg or 100 mg, for one additional patient to achieve migraine pain relief at 2 hours after study medication, relative to placebo.

Number Needed to Harm (NNH):

- For every 277 patients treated with Ubrelvy, one patient discontinued the study drug due to adverse effects.

Lipton et al.: Results

	Ubrelvy 50mg	Ubrelvy 25mg	Placebo
Pain Free at 2 hours			
% Responders	21.8	20.7	14.3
Difference from Placebo (%)	7.5	6.4	n/a
p-value (vs. Placebo)	0.01	0.03	n/a
MBS Free at 2 hours			
% Responders	38.9	34.1	27.4
Difference from Placebo (%)	11.5	6.7	n/a
p-value (vs. Placebo)	0.01	0.07	n/a
Pain Relief at 2 hours			
% Responders	62.7	60.5	48.2
Difference from Placebo (%)	14.5	12.3	n/a
p-value (vs. Placebo)	0.01	Not reported	n/a

Conclusion: Ubrelvey demonstrated a statistically significant reduction in migraine pain and symptoms when compared to placebo.

Number Needed to Treat (NNT):

- Co-primary outcomes: Fourteen or 16 patients must be treated with Ubrelvy 50 mg or 25 mg, respectively, for one additional patient to achieve freedom from pain at 2 hours after study medication, relative to placebo. Nine or 15 patients must be treated with Ubrelvy 50 mg or 25 mg, respectively, for one additional patient to achieve freedom from their MBS at 2 hours after study medication, relative to placebo.
- Secondary outcomes: Seven or 9 patients must be treated with Ubrelvy 50 mg or 25 mg, respectively, for one additional patient to achieve migraine pain relief at 2 hours after study medication, relative to placebo.

Number Needed to Harm (NNH):

- For every 1,111 patients treated for acute migraines with Ubrelvy, one patient discontinued Ubrelvy due to adverse effects, relative to placebo.

Nurtec (rimegepant)

FDA Approved Dosing: 75 mg orally [PRN; swallowed or placed under tongue].

- Maximum dose in 24-hour period: 75 mg.
- Safety of treating > 15 migraines in 30-day period not established.

Available Strengths: 75mg ODT

Clinically Significant Side Effects:

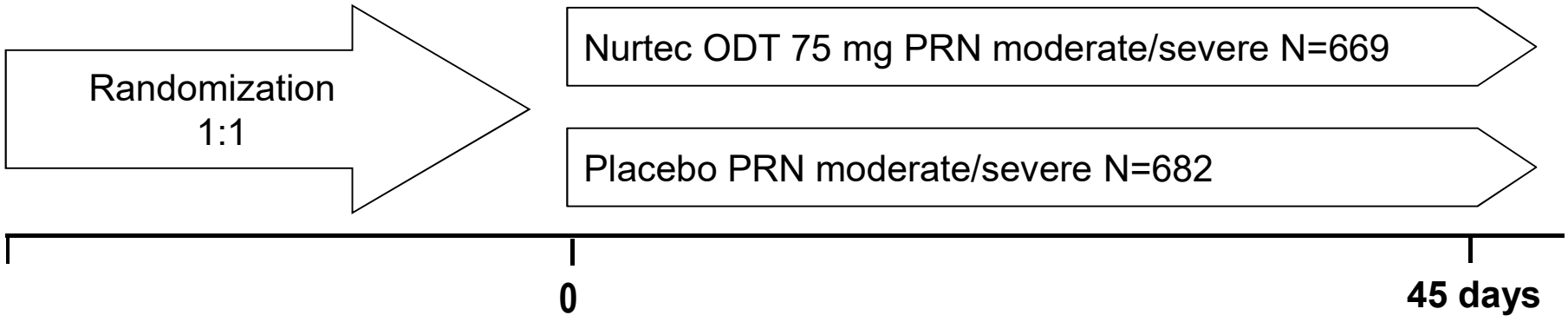
- Nausea

Additional Warnings and Precautions:

- Drug-Drug Interactions Impact Use
  - Avoid with strong/moderate CYP3A4 inhibitors, strong/moderate CYP3A inducers, P-gp/BCRP inhibitors: avoid

Croop R, et al.,

RCT, CB, PC, Phase 3



Patient eligibility criteria:

- Adults, 1-year history of migraine, 2-8 moderate/severe migraines/month.
- Stable preventive medication for 3 months.

Exclusion criteria:

- Medical conditions with undue risk, recent alcohol/drug abuse, relevant allergies, ECG/lab findings that raised concerns re safety and tolerability.

Efficacy endpoints:

- Primary: 2 hours post dose: freedom from pain and most bothersome symptom – times one migraine

Croop R, et al,: Results

Endpoints	Nurtec ODT 75 mg	Placebo
Pain Free at 2 hours		
% Responders	21.2	10.9
Difference from placebo (%)	10.3	
p-value		<0.001
MBS Free at 2 hours		
% Responders	35.1	26.8
Difference from placebo (%)	8.3	
p-value		0.001
*n=number of responders/N=number of patients in the treatment group		

Conclusion: Nurtec ODT 75 mg demonstrated an effect on pain freedom and most bothersome symptom (MBS) freedom at two hours after dosing compared to placebo. Among patients who selected an MBS, the most commonly selected symptom was photophobia (54%), followed by nausea (28%), and phonophobia (15%).

Number Needed to Treat (NNT):

- Primary outcome: Ten patients must be treated with Nurtec ODT for one patient to achieve a pain freedom outcome at 2 hours after study medication (defined as a reduction of moderate or severe headache pain to no headache pain), relative to placebo.
- Secondary outcomes: Thirteen patients must be treated with Nurtec ODT for one patient to achieve freedom from their MBS at 2 hours after study medication (defined as the absence of the self-identified MBS (i.e., photophobia, phonophobia, or nausea)), relative to placebo.

Number Needed to Harm (NNH):

- Not applicable

Place in Therapy

Study Limitations:

- Long-term data needed to determine safety and tolerability
- Studies did not compare with existing acute migraine therapies (eg triptans)
  - CPAC Review: Fairly equal therapeutic outcomes anticipated with new agents and triptans however efficacy outcomes are better with triptans

Reyvow study showed low frequency of likely CV treatment-emergent adverse events

- Good option for those with CV risk factors contraindicating use of triptans

Cost is ~3x as much as generic oral triptans

New agents are appropriate after trial and failure or contraindication to triptans

New Prophylaxis Agents

4/24/2020

Prophylaxis Treatment of Migraines

Consider prophylaxis when at least 4 migraines on average a month, or when frequency/severity significantly interferes with daily activities.

- No preference for a specific preventative medication and choice should be based on patient-specific factors

Prophylaxis Agents:

Oral Agents:

- Antiepileptics (e.g., divalproex sodium, topiramate)
- Beta-blockers (e.g., metoprolol, propranolol, timolol)
- Antidepressants (e.g., amitriptyline, venlafaxine)

Injectable Agents:

- Botox *Only indicated for chronic migraine
- CGRP antagonists (e.g., Aimovig, Ajovy, Emgality)

Menstrual Migraines: The use of hormone-based interventions to stabilize estrogen levels may eliminate or sufficiently minimize migraines when standard treatment for acute attacks is inadequate

- **Note:** estrogen containing contraceptive use may be limited in individuals who have migraine with aura

New Prophylaxis Agents

Three Injectable Agents Approved in 2018 and another early 2020

- Indicated for preventative treatment of migraine in adults
  - Approved for use in both episodic AND chronic migraine

Brand Name	FDA Approval Date	Coverage Criteria in Place
Aimovig	May 17, 2018	CP.PMN.128 Erenumab-aaoe (Aimovig)
Ajovy	September 18, 2018	CP.PHAR.403/CP.PCH.17 Fremanezumab-vfrm (Ajovy)
Emgality	October 6, 2018	CP.PHAR.404/CP.PPA.344 Galcanezumab-gnlm (Emgality)
Vyepti	February 21, 2020	In development; expect to see in 3Q2020 materials

- Trillium OHP Preferred Agent (PA required): Aimovig

Aimovig (Erenumab)

FDA Approved Dosing: 70 mg SC once monthly.

- Dose may be increased to 140 mg SC once monthly

Dosage Forms:

- 70 mg/ml single-dose autoinjector or prefilled syringe

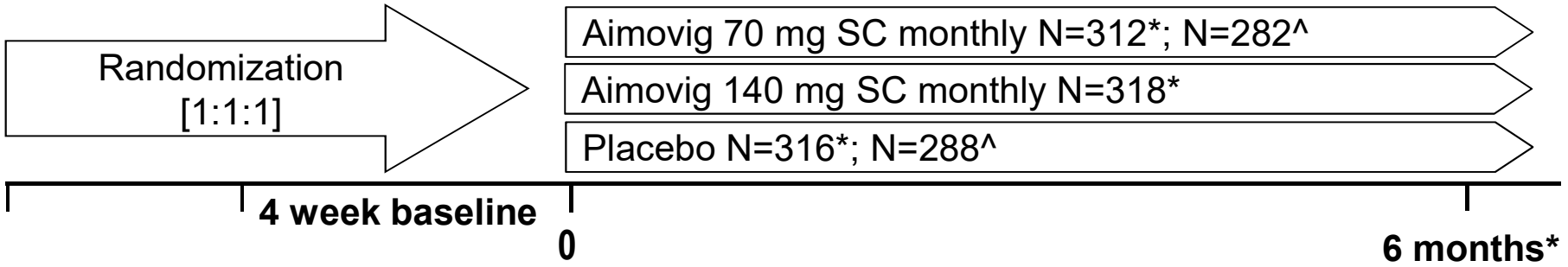
Clinically Significant Side Effects:

- Injection site reactions
- Constipation

STRIVE/ARISE:

(Episodic Migraine Prophylaxis)

P3, MC, R, DB, PC study



Patient eligibility criteria:

- Age 18 to 65
- 12 month history of migraine (with or without aura)
- Episodic migraine

Exclusion criteria:

- Age >50 at migraine onset
- History of hemiplegic migraine or cluster headache
- Botulinum toxin use last 4 months; migraine prophylaxis device or procedure last 2 months
- No response to >2 migraine-preventative treatments

Efficacy endpoints:

- Primary: migraine days/month
- Secondary: ≥50% reduction in migraine days/month, number of acute migraine-specific medication use days

*STRIVE only
^ARISE only

STRIVE: Results

Outcome	Placebo	Aimovig 70 mg†	Aimovig 140 mg†
Migraine days per month			
Change from baseline	−1.8 ± 0.2	−3.2 ± 0.2	−3.7 ± 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)	-	2.13 (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 ± 0.1	−1.1 ± 0.1	−1.6 ± 0.1
Difference vs. placebo (95% CI)	-	−0.9 (−1.2 to −0.6)	−1.4 (−1.7 to −1.1)
†P<0.001 for all pairwise comparisons between erenumab and placebo			

Conclusion: Aimovig demonstrated a statistically significant reduction in migraine days per month when compared to placebo.

Number Needed to Treat (NNT):

- Primary outcome: not applicable
- Secondary outcomes: 6 or 4 patients must be treated with Aimovig 70mg or Aimovig 140 monthly for one additional patient to experience a ≥ 50% reduction from baseline in migraine days per month.

Number Needed to Harm (NNH):

- For every 333 patients treated with either Aimovig 70mg or Aimovig 140mg, one patient discontinued the study drug due to adverse effects.

ARISE: Results

Outcome	Placebo	Aimovig 70 mg	P-value
Migraine days per month			
Change from baseline	−1.8 ± 0.2	−2.9 ± 0.2	Not applicable
Difference vs. placebo (95% CI)	-	−1.0 (−1.6 to −0.5)	<0.001
≥50% Reduction from baseline in migraine days per month			
No. of patients (%)	85 (29.5)	112 (39.7)	Not applicable
Odds ratio (95% CI)	-	1.59 (1.12 to 2.27)	0.010
Days of use of acute migraine–specific medication per month			
Change from baseline	−0.6 ± 0.1	−1.2 ± 0.1	Not applicable
Difference vs. placebo (95% CI)	-	−0.6 (−1.0 to −0.2)	0.002

Conclusion: Aimovig demonstrated a statistically significant reduction in migraine days per month when compared to placebo.

Number Needed to Treat (NNT):

- Primary outcome: not applicable
- Secondary outcomes: 10 patients must be treated with Aimovig 70mg monthly for one additional patient to experience a ≥ 50% reduction from baseline in migraine days per month.

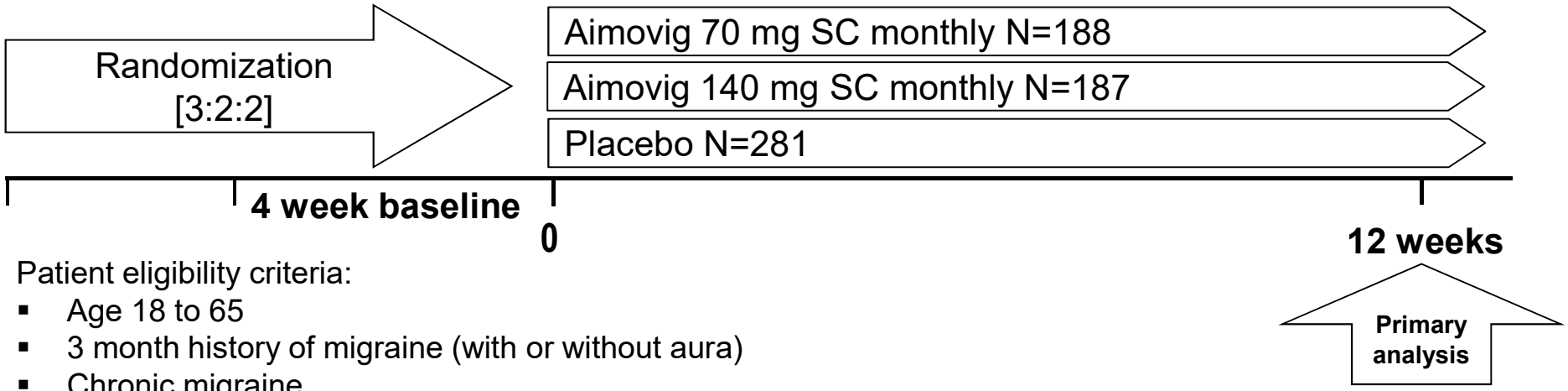
Number Needed to Harm (NNH):

- For every 67 patients treated with either Aimovig 70mg or Aimovig 140mg, one patient discontinued the study drug due to adverse effects.

Tepper S, et al.:

(Chronic Migraine Prophylaxis)

Phase 2, MC, R, DB, PC study



Patient eligibility criteria:

- Age 18 to 65
- 3 month history of migraine (with or without aura)
- Chronic migraine

Exclusion criteria:

- Age >50 at migraine onset
- History of hemiplegic migraine or cluster headache
- Botulinum toxin use last 4 months; migraine prophylaxis drugs last 2 months
- No response to >3 migraine-preventative treatments

Efficacy endpoints:

- Primary: migraine days/month
- Secondary: ≥50% reduction in migraine days/month, number of acute migraine-specific medication use days, cumulative headache days

Tepper S, et al.: Results

Outcome†	Placebo	Aimovig 70 mg†	Aimovig 140 mg†
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 to 7.9)	−19.3 (−36.7 to −1.9)
†P≤0.001 for all pairwise comparisons between Aimovig and placebo, except for cumulative monthly headache hours, where only Aimovig 140 mg demonstrated a significant reduction compared to placebo (P=0.0296)			

Conclusion: Aimovig demonstrated a statistically significant reduction in migraine days per month when compared to placebo.

Number Needed to Treat (NNT):

- Primary outcome: not applicable
- Secondary outcomes: 6 patients must be treated with Aimovig 70mg or Aimovig 140mg monthly for one additional patient to experience a ≥ 50% reduction from baseline in migraine days per month.

Number Needed to Harm (NNH):

- Aimovig 70mg: not applicable. For every 333 patients treated with Aimovig 140mg, one patient discontinued the study drug due to adverse effects.

Ajovy (Fremanezumab-vfrm)

FDA Approved Dosing: 225 mg SC once monthly or 675 mg SC every three months

Dosage Forms:

- 225 mg/1.5 mL single-dose prefilled syringe

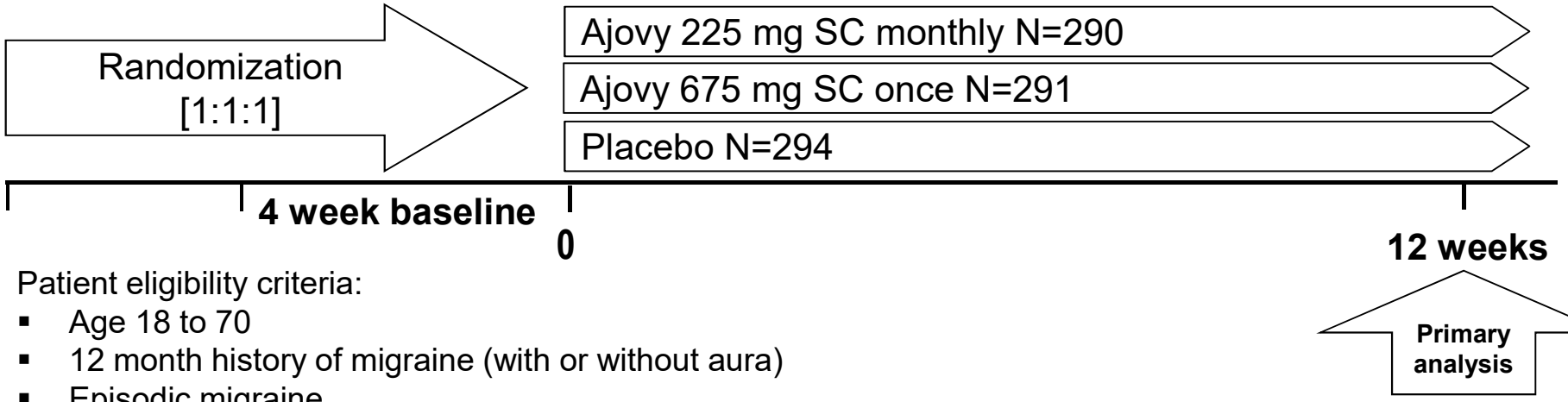
Clinically Significant Side Effects (≥5%):

- Injection site reactions

Dodick, et al.

(Episodic Migraine Prophylaxis):

P3, MC, R, DB, PC Trial



Patient eligibility criteria:

- Age 18 to 70
- 12 month history of migraine (with or without aura)
- Episodic migraine

Exclusion criteria:

- Age >50 at migraine onset
- Botulinum toxin use last 4 months; migraine prophylaxis device or procedure last 2 months
- No response to >2 migraine-preventative treatments

Efficacy endpoints:

- Primary: migraine days/month
- Secondary: ≥50% reduction in migraine days/month, number of acute migraine-specific medication use days

Dodick, et al.: Result

Outcome*	Placebo (N =294)	Ajovy 225 mg (N = 290)	Ajovy 675 mg (N = 291)
Migraine days per month			
Change from baseline	−2.2	−3.7	−3.4
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 to 27.6)	16.5 (8.9 to 24.1)
Days of use of acute migraine–specific medication per month			
Change from baseline	−1.6	−3.0	−2.9
Difference vs. placebo (95% CI)	-	−1.4 (−1.84 to −0.89)	−1.3 (−1.76 to −0.82)
*p < 0.001 for all pairwise comparisons between Ajovy and placebo			

Conclusion: Ajovy demonstrated a statistically significant reduction in migraine days per month when compared to placebo.

Number Needed to Treat (NNT):

- Primary Outcome: not applicable
- Secondary Outcome(s): 6 patients must be treated with Ajovy 225 mg monthly (7 patients with Ajovy 675 mg every 3 months) for one additional patient to experience a ≥ 50% reduction from baseline in migraine days per month.

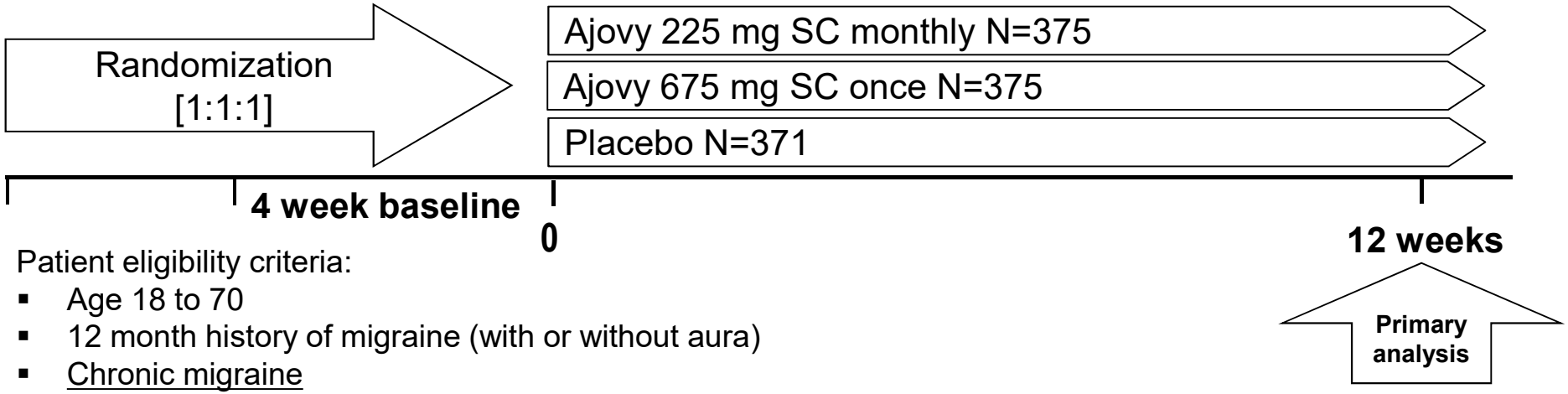
Number Needed to Harm (NNH):

- For episodic migraine prophylaxis, 99 patients treated with Ajovy 225 mg (151 patients treated with Ajovy 675 mg) to avoid one additional patient discontinuing the study drug due to adverse effects.

Silberstein, et al.

(Chronic Migraine Prophylaxis):

P3, MC, R, DB, PC Trial



Patient eligibility criteria:

- Age 18 to 70
- 12 month history of migraine (with or without aura)
- Chronic migraine

Exclusion criteria:

- Age >50 at migraine onset
- Botulinum toxin use last 4 months; migraine prophylaxis device or procedure last 2 months
- No response to >2 migraine-preventative treatments

Efficacy endpoints:

- Primary: headache days/month
- Secondary: migraine days/month, ≥50% reduction in headache days/month, number of acute migraine-specific medication use days

Silberstein, et al.: Results

Outcome*	Placebo	Ajovy 225 mg	Ajovy 675 mg
Headache days per month			
Change from baseline	−2.5 ± 0.3	−4.6 ± 0.3	−4.3 ± 0.3
Difference vs. placebo	-	−2.1 ± 0.3	−1.8 ± 0.3
Migraine days per month			
Change from baseline	−3.2 ± 0.4	−5.0 ± 0.4	−4.9 ± 0.4
Difference vs. placebo	-	−1.8 ± 0.4	−1.7 ± 0.4
≥50% Reduction from baseline in headache days per month			
No. of patients (%)	67 (18)	153 (41)	141 (38)
Days of use of acute migraine–specific medication per month			
Change from baseline	−1.9 ± 0.3	−4.2 ± 0.3	−3.7 ± 0.3
Difference vs. placebo	-	−2.3 ± 0.3	−1.8 ± 0.3
*p < 0.001 for all pairwise comparisons between Ajovy and placebo			

Conclusion: Ajovy demonstrated a statistically significant reduction in migraine days per month when compared to placebo.

Number Needed to Treat (NNT):

- Primary Outcome: not applicable
- Secondary Outcome(s): 5 patients must be treated with monthly or quarterly Ajovy for one additional patient to experience a ≥ 50% reduction from baseline in migraine days per month.

Number Needed to Harm (NNH):

- For chronic migraine prophylaxis, 344 patients treated with monthly Ajovy (120 patients treated with quarterly Ajovy) to avoid one additional patient discontinuing the study drug due to adverse effects

Emgality (Galcanezumab-gnlm)

FDA Approved Dosing: One time loading dose of 240 mg, followed by monthly 120 mg dose injected subcutaneously.

Dosage Forms:

- 120 mg/mL single-dose prefilled pen
- 120 mg/mL single-dose prefilled syringe

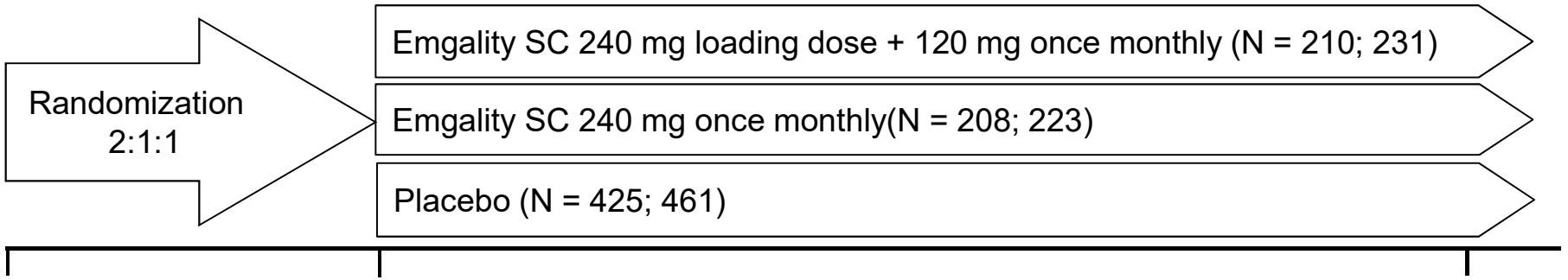
Clinically Significant Side Effects:

- Injection site reactions
- Anaphylaxis - Postmarketing

EVOLVE-1 & 2:

(Episodic Migraine Prophylaxis):

MC, DB, R, PC, P3 Studies



Patient eligibility criteria:

- Age 18 to 65 years
- Diagnosis of migraine for at least 1 year prior to enrollment
- Experienced 4 to 14 migraine headache days (MHDs) and ≥ 2 migraine attacks per month during baseline period
- Migraine onset prior to age 50 years

Exclusion criteria:

- History of failure to 3 or more classes of migraine preventive treatments
- Currently receiving preventive migraine medication within 30 days of the baseline period (4 months for botulinum toxin-A or toxin-B)

Efficacy endpoints:

- Primary: Mean change of monthly MHDs from baseline to month 6
- Secondary: Proportion of patients with reduction in monthly MHDs (≥ 50%, 75%, and 100% response rates), MHDs requiring acute medication use

Primary analysis

EVOLVE-1: Results

Outcome	Placebo	Emgality 120 mg†	Emgality 240 mg†
Migraine days per month			
LS mean change from baseline	-2.8	-4.7	-4.6
LS mean change difference vs. placebo (95% CI)	-	-1.9 (-2.5 to -1.4)	-1.8 (-2.3 to -1.2)
≥ 50% Reduction from baseline in migraine days per month			
Proportion of patients, %	38.6	62.3	60.9
Odds ratio (95% CI)	-	2.6 (2.0 to 3.4)	2.5 (1.9 to 3.2)
Days of use of acute migraine–specific medication per month			
LS mean change from baseline	-2.2	-4.0	-3.8
LS mean change difference vs. placebo (95% CI)	-	-1.8 (-2.3 to -1.3)	-1.6 (-2.1 to -1.1)
†P<0.001 for all pairwise comparisons between Emgality and placebo			

Conclusion: Emgality demonstrated a statistically significant reduction in migraine days per month compared to placebo.
Number Needed to Treat (NNT):
Primary Outcome: not applicable
Secondary outcome(s):

- Five patients must be treated with Emgality for one additional patient to experience at least a 50% reduction in migraine days per month. Six patients must be treated with Emgality for one additional patient to experience at least a 75% reduction in migraine days per month.Eleven patients must be treated with Emgality 120 mg and 12 patients must be treated with Emgality 240 mg for one additional patient to experience a 100% reduction in migraine days per month.

Number Needed to Harm (NNH):

- For every 52 patients treated for episodic migraine, one patient discontinued Emgality 120 mg due to adverse effects. For every 100 patients treated for episodic migraine, one patient discontinued Emgality 240 mg due to adverse effects.

EVOLVE-2: Results

Outcome	Placebo	Emgality 120 mg†	Emgality 240 mg†
Migraine days per month			
LS mean change from baseline (95% CI)	-2.3 (-2.7 to -1.9)	-4.3 (-4.8 to -3.8)	-4.2 (-4.7 to -3.7)
LS mean change difference vs. placebo (95% CI)	-	-2.0 (-2.6 to -1.5)	-1.9 (-2.4 to -1.4)
≥ 50% Reduction from baseline in migraine days per month			
Proportion of patients, % (95% CI)	36 (33 to 39)	59.3 (55 to 64)	56.5 (52 to 61)
Days of use of acute migraine–specific medication per month			
LS mean change from baseline (95% CI)	-1.9 (-2.2 to -1.5)	-3.7 (-4.1 to -3.2)	-3.6 (-4.1 to -3.2)
†P<0.001 for all pairwise comparisons between Emgality and placebo			

Conclusion: Emgality demonstrated a statistically significant reduction in migraine days per month compared to placebo.

Number Needed to Treat (NNT):

- Primary Outcome: not applicable
- Secondary outcome(s): Five patients must be treated with Emgality for one additional patient to experience at least a 50% reduction in migraine days per month. Seven patients must be treated with Emgality for one additional patient to experience at least a 75% reduction in migraine days per month. Eighteen patients must be treated with Emgality 120 mg and 13 patients must be treated with Emgality 240 mg for one additional patient to experience a 100% reduction in migraine days per month.

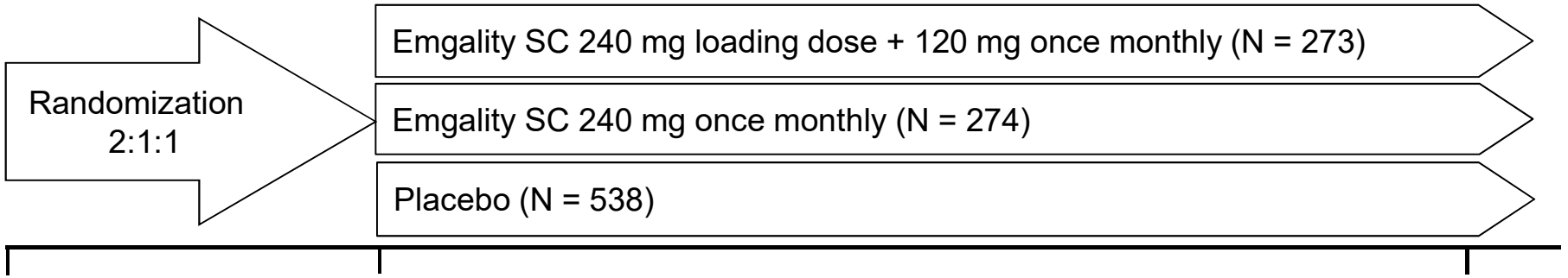
Number Needed to Harm (NNH):

- For every 238 patients treated for episodic migraine, one patient discontinued Emgality 120 mg due to adverse effects.
- For every 43 patients treated for episodic migraine, one patient discontinued Emgality 240 mg due to adverse effects.

REGAIN:

(Chronic Migraine Prophylaxis)

MC, DB, R, PC, P3 Study



Patient eligibility criteria:

- Age 18 to 65 years
- Diagnosis of migraine for at least 1 year prior to enrollment
- Chronic migraine defined as ≥ 15 headache days per month, of which at least 8 are MHDs
- Migraine onset prior to age 50 years

Exclusion criteria:

- History of persistent daily headache, cluster headache, or migraine subtypes including hemiplegic (sporadic or familial) migraine, ophthalmoplegic migraine and migraine with brainstem aura (basilar-type migraine)

Efficacy endpoints:

- Primary: Mean change of monthly MHDs from baseline to month 3
- Secondary: Proportion of patients with reduction in monthly MHDs (≥ 50%, 75%, and 100% response rates), MHDs requiring acute medication use

REGAIN: Results

Outcome	Placebo	Emgality 120 mg†	Emgality 240 mg†
Migraine days per month			
LS mean change from baseline	-2.74	-4.83	-4.62
LS mean change difference vs. placebo	-	-2.09	-1.88
≥ 50% Reduction from baseline in migraine days per month			
Proportion of patients, %	15.4	27.6	27.5
Days of use of acute migraine–specific medication per month			
LS mean change from baseline	-2.23	-4.74	-4.25
†P<0.001 for all pairwise comparisons between Emgality and placebo			

Conclusion: Emgality demonstrated a statistically significant reduction in migraine days per month compared to placebo.
Number Needed to Treat (NNT):
Primary Outcome: not applicable
Secondary outcome(s): Nine patients must be treated with Emgality for one additional patient to experience at least a 50% reduction in migraine days per month. Forty patients must be treated with Emgality 120 mg and 24 patients must be treated with Emgality 240 mg for one additional patient to experience at least a 75% reduction in migraine days per month.
Number Needed to Harm (NNH):
Emgality 120 mg: not applicable. For every 277 patients treated for episodic migraine, one patient discontinued Emgality 240 mg due to adverse effects.

Vyepti (eptinezumab-jjmr)

FDA Approved Dosing: 100 mg IV every 3 months.

- Some patients may benefit from a dosage of 300 mg IV every 3 months.

Dosage Forms:

- Single-dose vial: 100 mg/mL

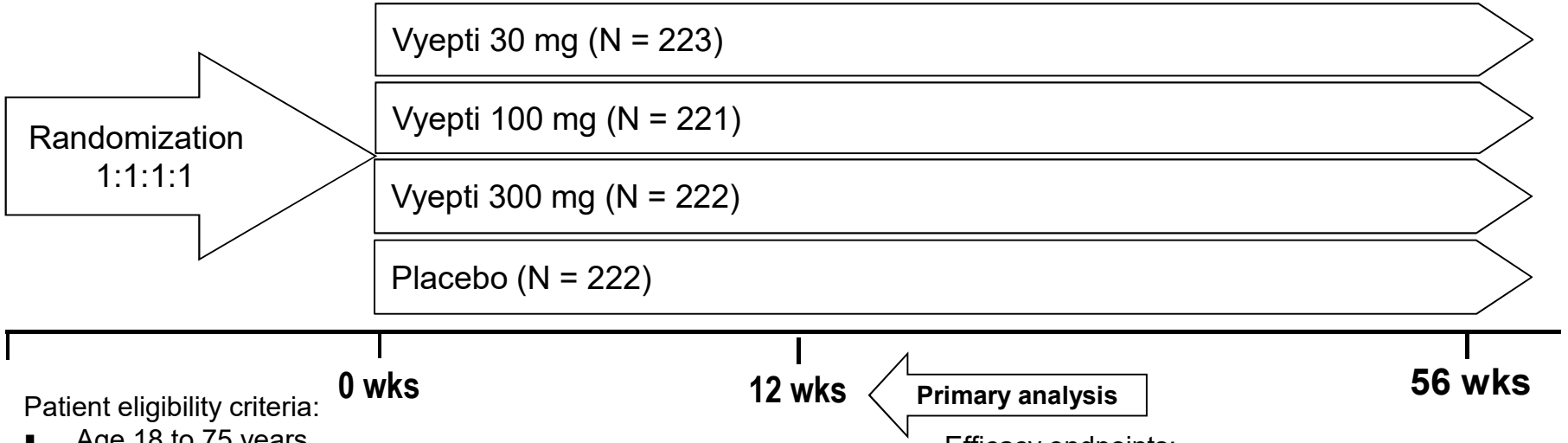
Clinically Significant Side Effects:

- Nasopharyngitis
- Hypersensitivity

PROMISE-I:

(Episodic Migraine Prophylaxis)

MC, DB, R, PC, P3 Study



Patient eligibility criteria:

- Age 18 to 75 years
- Diagnosis of migraine for at least 1 year prior to enrollment
- Experienced ≤ 14 headache days per month and ≥ 4 monthly migraine days (MMDs) during pre-screening period
- Migraine onset prior to age 50 years
- Allowed use of acute migraine medication

Exclusion criteria:

- Regular use (>7 days) prophylactic headache medication within 3 months prior to randomization
- Botulinum toxin injections in the head, face, or neck within 5 months of randomization

Efficacy endpoints:

- Primary: Mean change in MMDs over weeks 1-12
- Secondary: Proportion of patients with reduction in migraine (≥ 75% MRR over weeks 1-4, ≥ 75% MRR over weeks 1-12, ≥ 50% MRR over weeks 1-12), and proportion of patients with a migraine on the day after dosing

MMD: monthly migraine days
MRR: migraine responder rate

PROMISE-I: Results

Trillium Community Health Plan

Outcome*	Placebo	Vyepti 100 mg	Vyepti 300 mg
Mean Monthly Migraine Days (MMDs), weeks 1-12			
Mean change from baseline	-3.2	-3.9	-4.3
Difference vs. placebo (95% CI)	-	-0.7 (-1.3 to -0.1)	-1.1 (-1.7 to -0.5)
≥ 75% Reduction from baseline in migraine days per month, weeks 1-4			
Proportion of patients, %	20.3	30.8	31.5
Difference vs. placebo (95% CI)	-	10.5 (2.4 to 18.6)	11.2 (3.2 to 19.3)
≥ 75% Reduction from baseline in migraine days per month, weeks 1-12			
Proportion of patients, %	16.2	22.2	29.7
Difference vs. placebo (95% CI)	-	6.0 (-1.4 to 13.3)	13.5 (5.8 to 21.2)
50% Reduction from baseline in migraine days per month, weeks 1-12			
Proportion of patients, %	37.4	49.8	56.3
Difference vs. placebo (95% CI)	-	12.4 (3.2 to 21.5)†	18.9 (9.8 to 28.0)

*** Vyepti 30 mg outcomes & secondary endpoint of proportion of patients with a migraine on the day after dosing outcomes not reported as they failed to be statistically significant; † endpoints failed to be statistically significant due to a failed test earlier in the serial testing algorithm (based on serial procedure used to account for multiplicity in doses and endpoints, in line with industry guidance issued by US FDA**

Conclusion: Vyepti demonstrated a statistically significant reduction in MMDs compared to placebo.

Number Needed to Treat (NNT):

- Primary outcome: Not applicable
- Secondary outcomes: Ten patients must be treated with Vyepti 100 mg and 9 patients with Vyepti 300 mg for one additional patient to experience at least a 75% reduction in migraine days per month in the first month after treatment. Eight patients must be treated with Vyepti 300 mg for one additional patient to experience at least a 75% reduction in migraine days per month within 3 months after treatment. Nine patients must be treated with Vyepti 100 mg and 6 patients with Vyepti 300 mg for one additional patient to experience at least a 50% reduction in migraine days per month within 3 months after treatment.

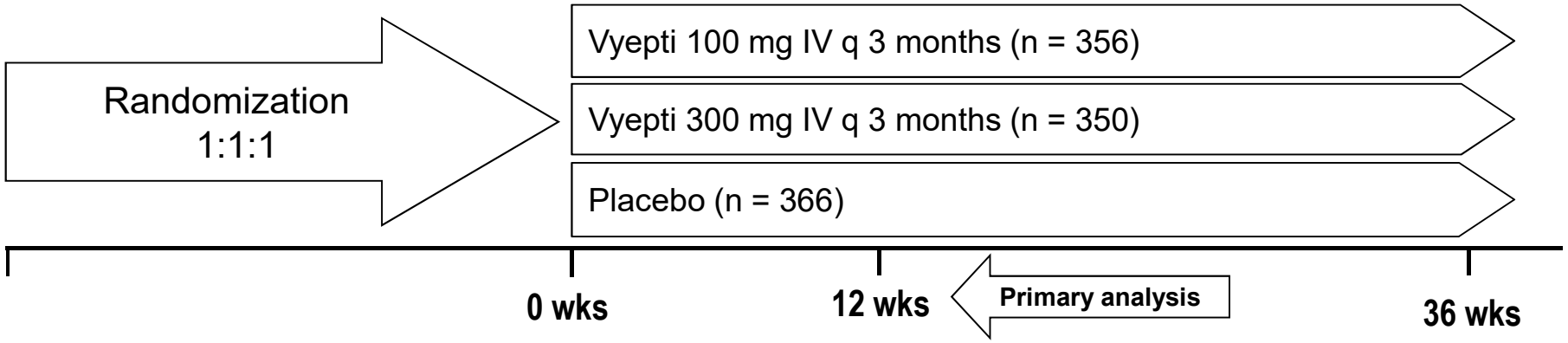
Number Needed to Harm (NNH):

- For every 37 patients treated for episodic migraine, one patient discontinued Vyepti 30 mg due to adverse effects. For every 8134 patients treated for episodic migraine, one patient discontinued Vyepti 100 mg due to adverse effects. For every 222 patients treated for episodic migraine, one patient discontinued Vyepti 300 mg due to adverse effects.

PROMISE-II

(Chronic Migraine Prophylaxis):

P3, MC, DB, R, PC Study



Patient eligibility criteria:

- Age 18 to 65 years
- Diagnosis of migraine for ≥1 year prior to enrollment
- Experienced ≥ 15 to ≤ 26 headache days per month and ≥ 8 MMDs during screening period
- Migraine onset prior to age 50 years
- Allowed use and continuation of an established stable regimen of acute migraine or headache preventive medication

Exclusion criteria:

- Botulinum toxin injections in the head or neck within 5 months of randomization

Primary Efficacy endpoint:

- Mean change from baseline in MMDs over months 1 through 3

Secondary Efficacy endpoints:

- Proportion of patients with a ≥ 75% reduction from baseline in MMDs over months 1 through 3
- Proportion of patients with a ≥ 50% reduction from baseline in MMDs over months 1 through 3

PROMISE-II: Results

Outcome	Placebo	Vyepti 100 mg†	Vyepti 300 mg†
Mean Monthly Migraine Days (MMDs), months 1-3			
Mean change from baseline	-5.6	-7.7	-8.2
Difference vs. placebo	-	-2.0	-2.6
≥ 75% Reduction from baseline in migraine days per month, months 1-3			
Proportion of patients, %	15.0	26.7	33.1
Difference vs. placebo	-	11.7	18.1
50% Reduction from baseline in migraine days per month, months 1-3			
Proportion of patients, %	39.3	57.6	61.4
Difference vs. placebo	-	18.2	22.1
† $p < 0.001$ for all pairwise comparisons between Vyepti and placebo			

Conclusion: Vyepti demonstrated a statistically significant reduction in MMDs compared to placebo.

Number Needed to Treat (NNT):

- Primary outcome: Not applicable
- Secondary outcomes: Nine patients must be treated with Vyepti 100 mg and 6 patients with Vyepti 300 mg for one additional patient to experience at least a 75% reduction in migraine days per month in the first month after treatment. Six patients must be treated with Vyepti 100 mg and 5 patients with Vyepti 300 mg for one additional patient to experience at least a 50% reduction in migraine days per month within 3 months after treatment.

Number Needed to Harm (NNH):

- Not calculable

Trillium OHP Utilization

- 1st Quarter 2020 Paid Claims:
  - New Acute Treatment Agents: None
  - New Prophylactic Treatment Agents:
    - Aimovig: 31 paid claims for 17 utilizers
    - Ajovy: 2 paid claims for 1 utilizer
    - Emgality: 8 paid claims for 4 utilizers
- 1st Quarter 2020 PA Requests:
  - New Acute Treatment Agents: None
  - New Prophylactic Treatment Agents:
    - Aimovig: 19 requests; 63% approval rate
    - Ajovy: 2 requests; 100% approval rate
    - Emgality: 3 requests; 100% approval rate

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