NEW ABORTIVE AND PREVENTIVE THERAPIES FOR MIGRAINE

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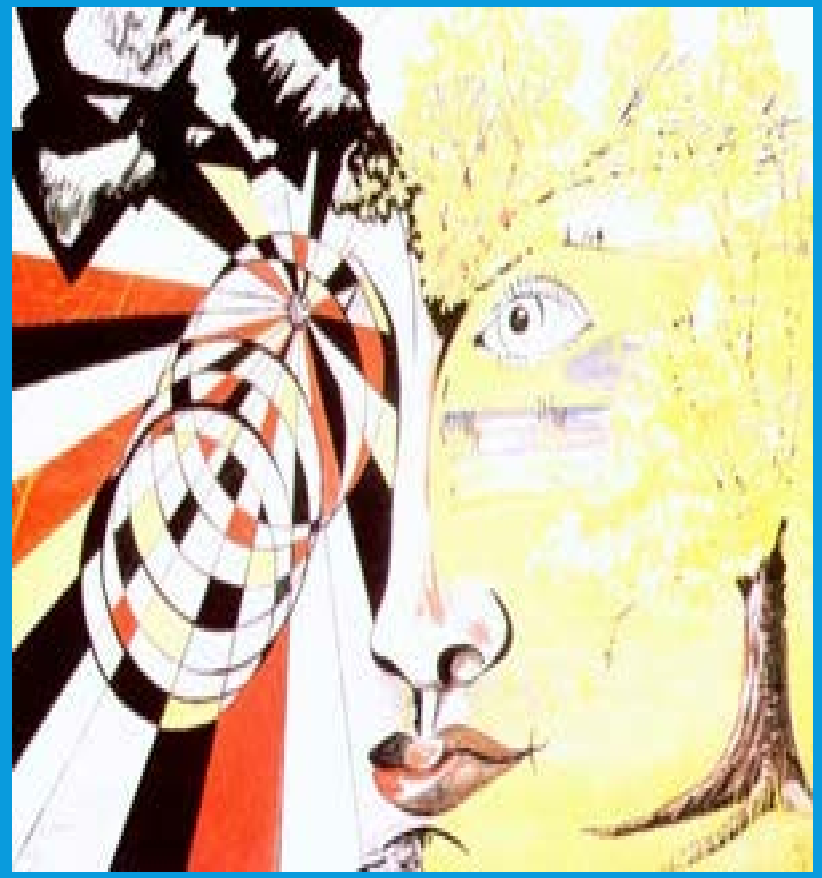
OVERVIEW

- Review of Migraine Assessment
- CGRP and Migraine
- Available CGRP Monoclonal Antibodies
- Available GPANTS
- Upcoming Therapies

COMMON MIGRAINE



- Lasting 4 to 72 hours
- One of the following:
  - Nausea and/or vomiting
  - Photophobia and photophobia
- At least two of the following:
  - Unilateral
  - Pulsating
  - Moderate to severe in intensity
  - Aggravated by increased activity

CLASSIC MIGRAINE

- At least three of the following:
  - One or more fully reversible aura
  - At least one aura developing > 4 min.
  - No single aura lasting > 60 minutes
  - Headache following aura within 60 min.

TAKE THE ID MIGRAINE TEST

In the last 3 months...

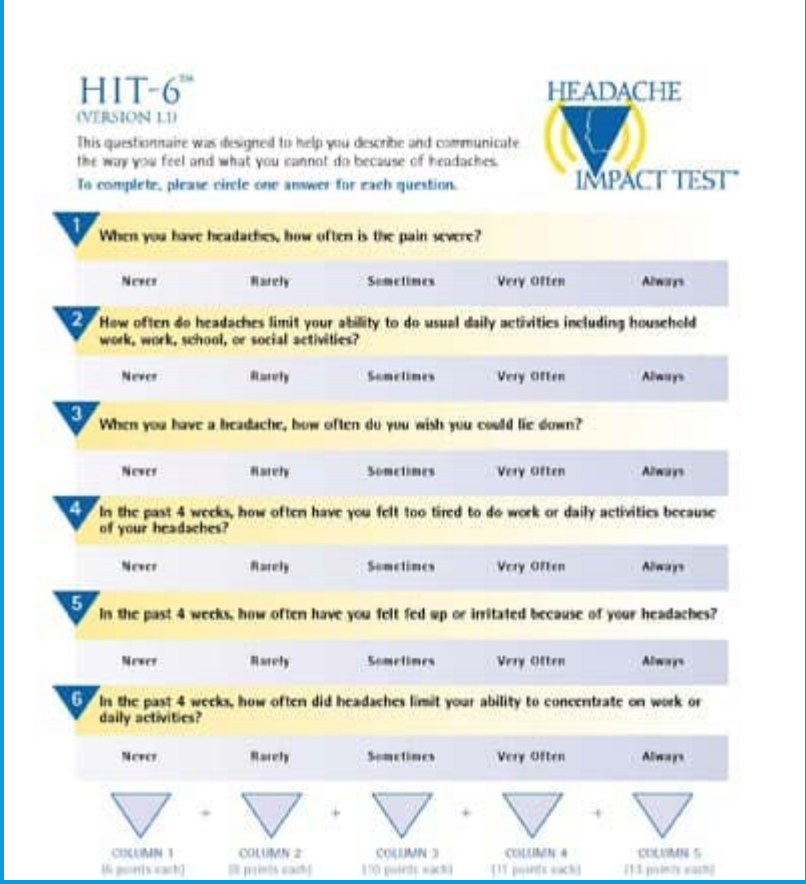
Has a headache limited your activities for a day or more?

Have you been nauseous or sick in your stomach when you have a headache?

Has light bothered you when you have a headache?

If you answered YES to 2 or more questions, then you may suffer from migraines. Make an appointment to see your doctor for further help

OBJECTIVE ASSESMENT



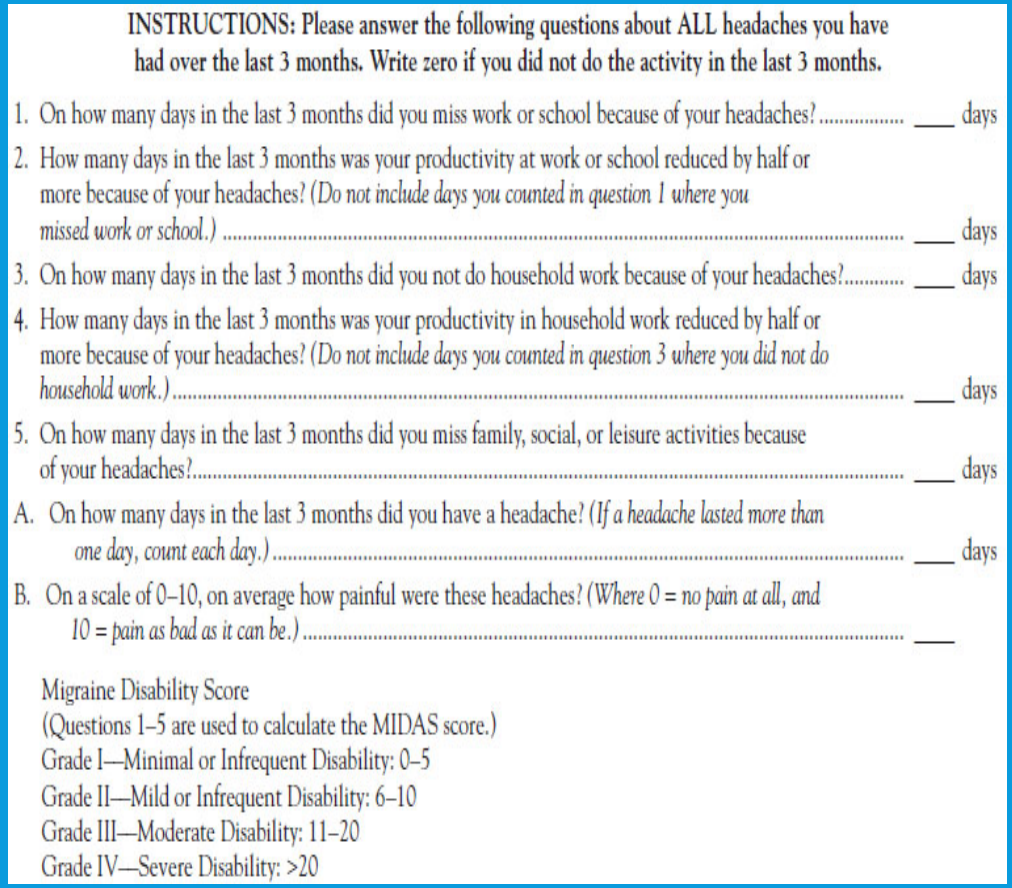
HIT-6™
(VERSION 1.1)

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.
To complete, please circle one answer for each question.

HEADACHE IMPACT TEST™

1. When you have headaches, how often is the pain severe?
   Never | Rarely | Sometimes | Very Often | Always
2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?
   Never | Rarely | Sometimes | Very Often | Always
3. When you have a headache, how often do you wish you could lie down?
   Never | Rarely | Sometimes | Very Often | Always
4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?
   Never | Rarely | Sometimes | Very Often | Always
5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?
   Never | Rarely | Sometimes | Very Often | Always
6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?
   Never | Rarely | Sometimes | Very Often | Always

COLUMN 1 + COLUMN 2 + COLUMN 3 + COLUMN 4 + COLUMN 5



INSTRUCTIONS: Please answer the following questions about ALL headaches you have had over the last 3 months. Write zero if you did not do the activity in the last 3 months.

1. On how many days in the last 3 months did you miss work or school because of your headaches? ..... ___ days
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (*Do not include days you counted in question 1 where you missed work or school.*) ..... ___ days
3. On how many days in the last 3 months did you not do household work because of your headaches? ..... ___ days
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches? (*Do not include days you counted in question 3 where you did not do household work.*) ..... ___ days
5. On how many days in the last 3 months did you miss family, social, or leisure activities because of your headaches? ..... ___ days

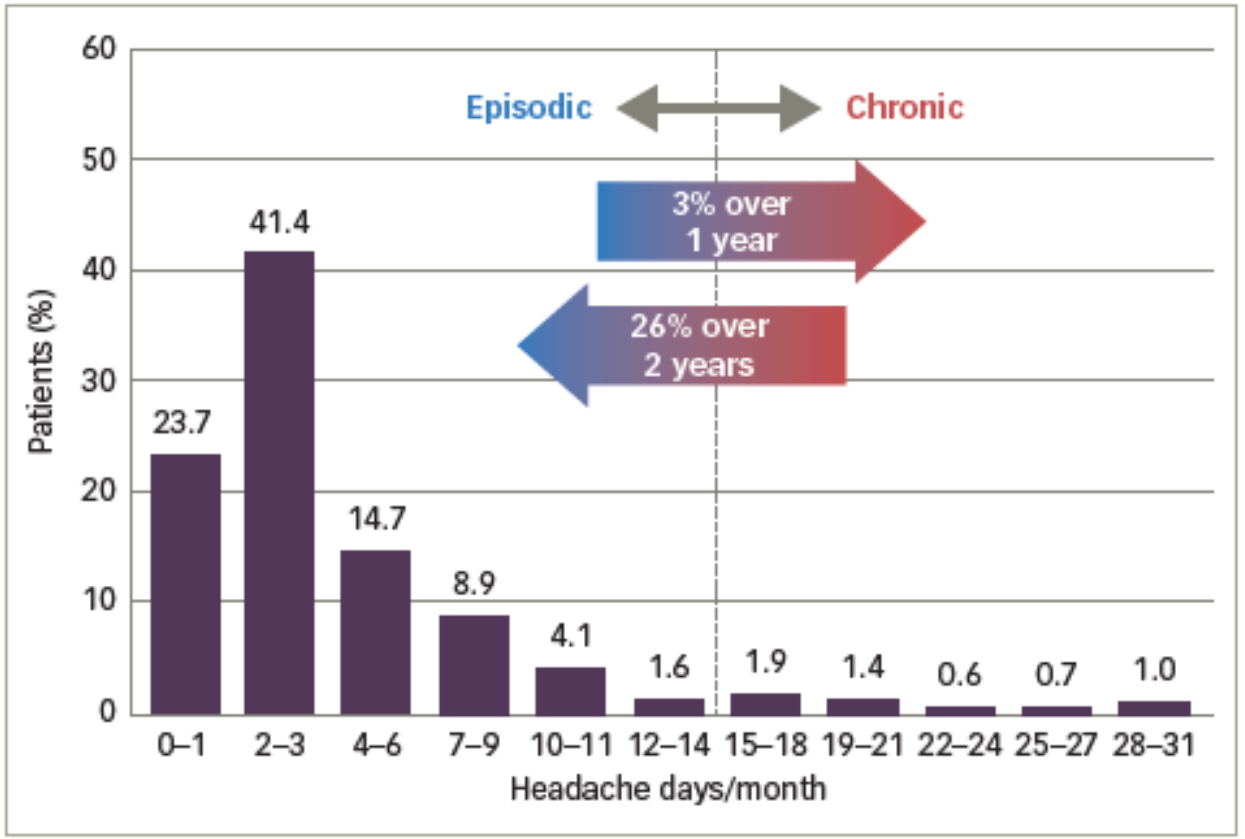
A. On how many days in the last 3 months did you have a headache? (*If a headache lasted more than one day, count each day.*) ..... ___ days

B. On a scale of 0–10, on average how painful were these headaches? (*Where 0 = no pain at all, and 10 = pain as bad as it can be.*) ..... ___

Migraine Disability Score
(Questions 1–5 are used to calculate the MIDAS score.)
Grade I—Minimal or Infrequent Disability: 0–5
Grade II—Mild or Infrequent Disability: 6–10
Grade III—Moderate Disability: 11–20
Grade IV—Severe Disability: >20

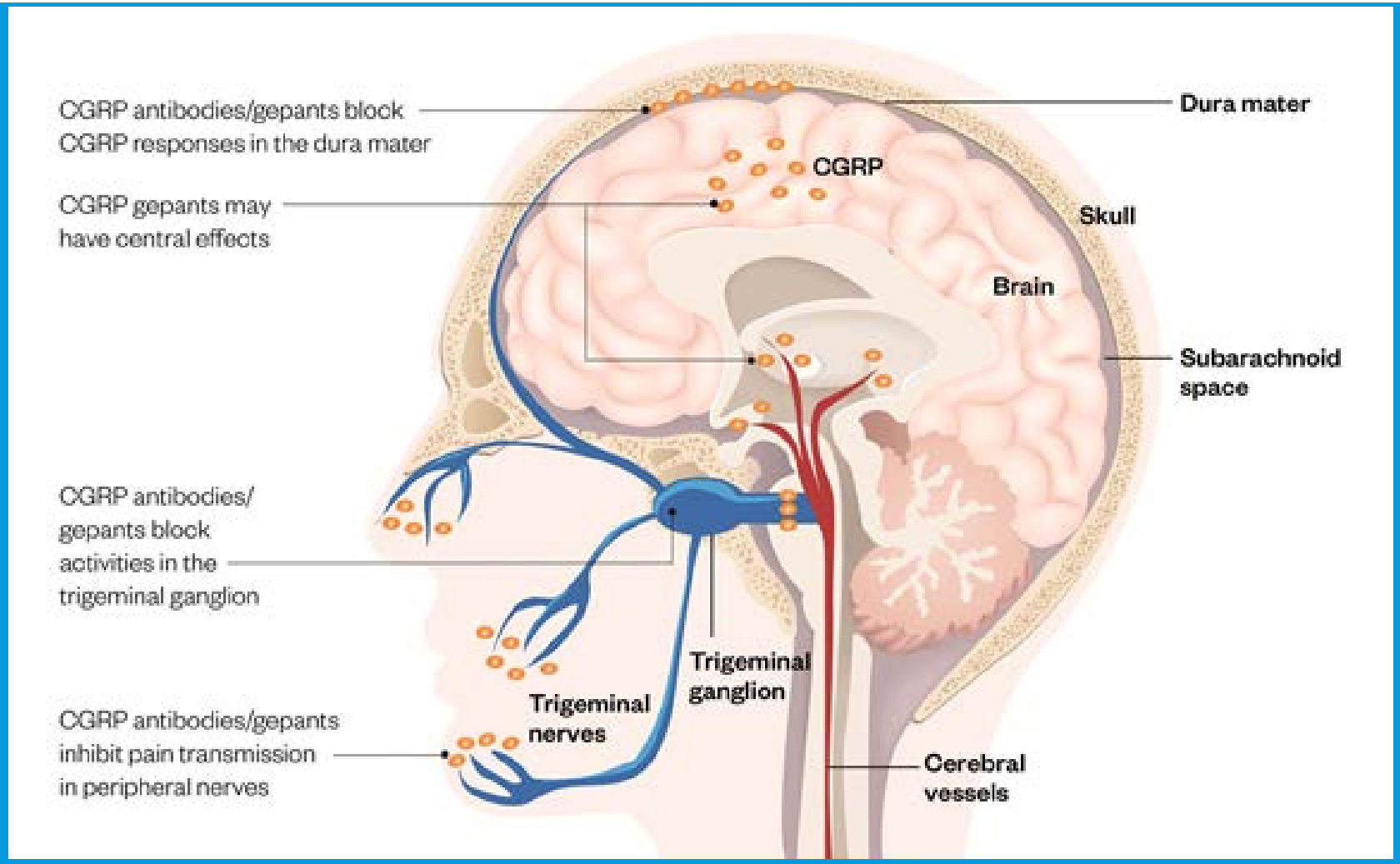
EPISODIC VS CHRONIC MIGRAINE

Figure 1. The frequency of headache days in patients with migraine (n=8,281)[8]



Data source: Bigal M, Krymchantowski AV, Lipton RB, 2008;[16] Blumenfeld AM et al., 2011;[8] Manack A et al., 2011.[11]

CGRP AND MIGRAINE



MONOCLONAL ANTIBODIES VS GEPANTS

TABLE. PROPERTIES OF -GEPANTS VS MONOCLONAL ANTIBODIES		
	-gepants	Monoclonal Abs
Size	Small	Large
Route of administration	Oral	Injection/infusion
Indication	Acute treatment	Preventive treatment
Onset of effect	Hours	Days
Half-life	8-12 hours	3-6 weeks

CGRP MONOCLONAL ANTIBODIES FOR MIGRAINE PROPHYLAXIS

CGRP MONOCLONAL ANTIBODIES FOR MIGRAINE PROPHYLAXIS

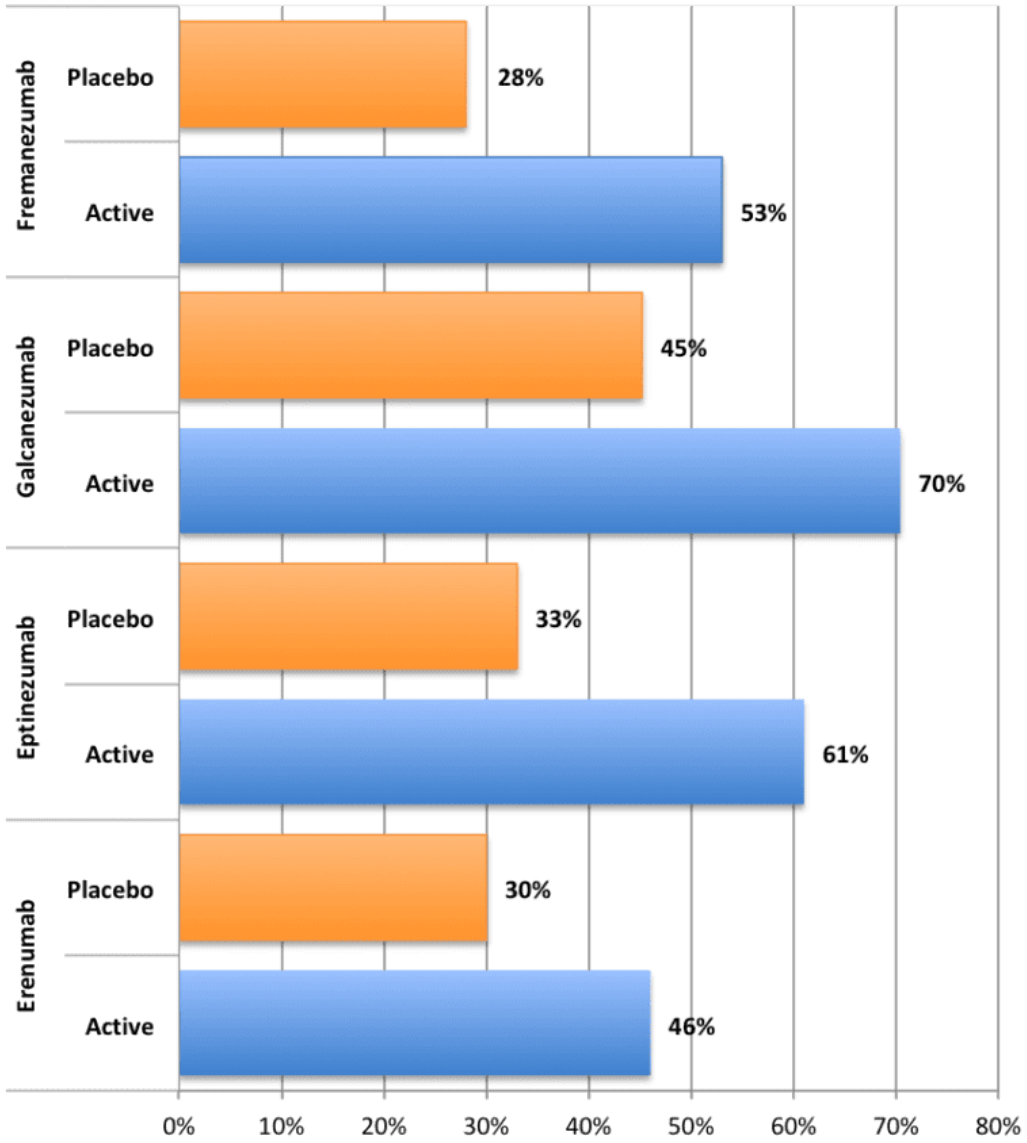
Generic name	Sponsor	Patient population	Target	Route	Dose (mg)	IgG Type	$t_{1/2}$ (days)	T_{max}
Eptinezumab[a] (ALD403)	Alder Biopharmaceuticals	Episodic and chronic migraine	CGRP-α CGRP-β	IV	30 mg QTLY 100 mg QTLY 300 mg QTLY	IgG 1	26	3 hours
Erenumab[b] (AMG 334)	Novartis and Amgen	Episodic and chronic migraine	CGRP receptor	SC	70 mg QM 140 mg QM	IgG 2	28	6 days
Fremanezumab[b] (TEV-48125)	Teva Pharmaceutical Industries	Episodic and chronic migraine	CGRP-α CGRP-β	SC	225 mg QM with 675 mg LD	IgG 2	32	5 days
Galcanezumab[b] (LY2951742)	Eli Lilly and Company	Episodic and chronic migraine	CGRP-α CGRP-β	SC	240 mg LD followed by 120 mg QM	IgG 4	27	5 days

CGRP: calcitonin gene-related peptide; IV: intravenous; SC: subcutaneous; QM: once monthly; LD: loading dose; QTLY: quarterly; $t_{1/2}$: half-life; T_{max}: time of maximum observed drug concentration.

[a]Currently in Phase 3 trials.

[b]Approved by the FDA.

Over 50% reduction in migraine days (% of patients)



50% REDUCTION IN MIGRAINE DAYS THERAPEUTIC GAIN

- Ajovy (fremanezumab): Approved Sept 14, 2018 25%
- Emgality (galcanezumab): Approved Sept 27, 2018 25%
- Vyepti (eptinezumab): Approved Feb 21, 2020 25%
- Aimovig (erenumab): Approved May 17, 2018 16%

CGRP MONOCLONAL ANTIBODIES
POTENTIAL SIDE EFFECTS

- Local skin reaction
- Hypersenstivity
- Contipation
- Hypertension
- No cardiovascular contraindication

CGRP RECEPTOR ANTAGONIST (GEPANT) FOR MIGRAINE PROPHYLAXIS

- Olcegepant (Boehinger Inglehim)
  - First gepant studies. IV only. Found effective
- Telcagepant (Merk)
  - Never FDA approved 11 of 660 subjects with elevated ALT
- Atogepant (Allergan)
  - Phase 3 data positive with 10, 30, and 60 mg
  - Most common side effects: Constipation, Nausea, URI

ATOGEPANT FOR MIGRAINE PROPHYLAXIS

- Goadsby PJ, Dodick DW, Ailani J, Trugman JM, Finnegan M, Lu K, Szegedi A. Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. Lancet Neurol. 2020 Sep;19(9):727-737. doi: 10.1016/S1474-4422(20)30234-9. Erratum in: Lancet Neurol. 2020 Nov;19(11):e10. PMID: 32822633.

ATOGEPANT FOR MIGRAINE PROPHYLAXIS

- 4-14 migraine days per month
- 834 subjects
- placebo vs atogepant
  - 10 mg once daily, 30 mg once daily, 60 mg once daily
  - 30 mg twice daily, or 60 mg twice daily

ATOGEPANT FOR MIGRAINE PROPHYLAXIS

Primary Outcome Measure

- Change From Baseline in Mean Monthly Migraine Days (Migraine/Probable Migraine Headache Days) Across the 12-Week Treatment Period

Secondary Outcome Measures

- Change From Baseline in Mean Monthly Headache Days Across the 12-Week Treatment
- Percentage of Participants With at Least a 50% Reduction in Mean Monthly Migraine Days (Migraine/Probable Migraine Headache Days) Across the 12-Week Treatment Period
- Change From Baseline in Mean Monthly Acute Medication Use Days Across the 12-Week Treatment Period

ATOGEPANT FOR MIGRAINE PROPHYLAXIS

- Mean Monthly Migraine Days Across the 12-Week Treatment Period
- placebo -2·9
- 10 mg once daily -4·0 (p=0·024)
- 30 mg once daily -3·8 (p=0·039),
- 60 mg once daily -3·6 (p=0·039),
- 30 mg twice daily -4·2 (p=0·0034)
- 60 mg twice daily -4·1 (p=0·0031)

ATOGEPANT FOR MIGRAINE PROPHYLAXIS

- Percentage of Participants With at Least a 50% Reduction in Mean Monthly Migraine Days Across the 12-Week Treatment Period

- Placebo 29.0%
- 10 mg arm 55.6%
- 30 mg arm 58.7%
- 60 mg arm 60.8%
- (all *P* <.0001).

ATOGEPANT FOR MIGRAINE PROPHYLAXIS

- Most Common Adverse Events
- constipation (6.9% to 7.7% across all doses; 0.5% for placebo)
- nausea (4.4% to 6.1% across all doses; 1.8% for placebo)
- upper respiratory tract infection (3.9% to 5.7% across all doses; 4.5% for placebo).

- The majority of cases were deemed mild or moderate in severity and did not lead to discontinuation. No hepatic safety issues were identified.

NURTEC (RIMEGEPANT) FOR MIGRAINE PROPHYLAXIS

- Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM, Stock EG, Coric V, Goadsby PJ. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomized, double-blind, placebo-controlled trial. Lancet. 2021 Jan 2;397(10268):51-60. doi: 10.1016/S0140-6736(20)32544-7. Epub 2020 Dec 15. PMID: 33338437.

NURTEC (RIMEGEPANT) FOR MIGRAINE PROPHYLAXIS

- 747 subjects
- Oral rimegepant 75 mg or matching placebo every other day for 12 weeks

NURTEC (RIMEGEPANT) FOR MIGRAINE PROPHYLAXIS

- Primary Outcome Measure

- change from the 4-week observation period in the mean number of migraine days per month in the last 4 weeks of the double-blind treatment phase (weeks 9–12).

NURTEC (RIMEGEPANT) FOR MIGRAINE PROPHYLAXIS

- Change from the observation period in mean number of migraine days per month during weeks 9–12

- –4·3 days (95% CI –4·8 to –3·9) with rimegepant and
- –3·5 days (–4·0 to –3·0) with placebo

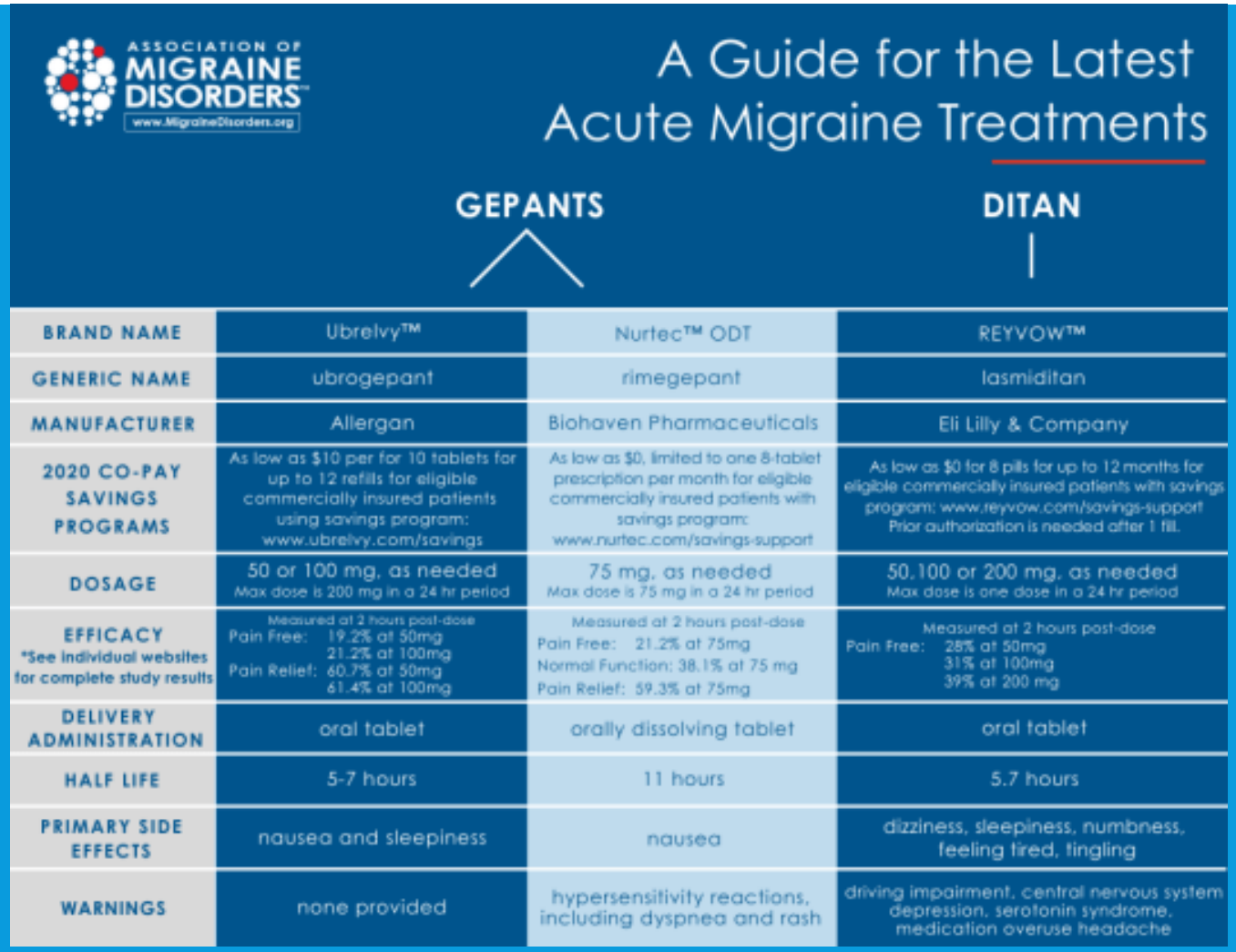
(least squares mean difference −0·8 days, 95% CI −1·46 to −0·20; p=0·0099).

- Seven (2%) participants who received rimegepant and four (1%) who received placebo discontinued the study due to an adverse event; no patients died.

ABORTIVE THERAPY EXPECTATIONS

- Fast relief
- Headache resolution
- Low recurrence
- No to low side effects
- Limited or no contraindications

CGRP RECEPTOR ANTAGONIST (GEPANT) AND DITAN FOR MIGRAINE ATTACKS



ASSOCIATION OF MIGRAINE DISORDERS
www.MigraineDisorders.org

A Guide for the Latest Acute Migraine Treatments

	GEPANTS		DITAN
BRAND NAME	Ubrelvy™	Nurtec™ ODT	REYVOW™
GENERIC NAME	ubrogepant	rimegepant	lasmiditan
MANUFACTURER	Allergan	Biohaven Pharmaceuticals	Eli Lilly & Company
2020 CO-PAY SAVINGS PROGRAMS	As low as $10 per for 10 tablets for up to 12 refills for eligible commercially insured patients using savings program: www.ubrelvy.com/savings	As low as $0, limited to one 8-tablet prescription per month for eligible commercially insured patients with savings program: www.nurtec.com/savings-support	As low as $0 for 8 pills for up to 12 months for eligible commercially insured patients with savings program: www.reyvow.com/savings-support Prior authorization is needed after 1 fill.
DOSAGE	50 or 100 mg, as needed Max dose is 200 mg in a 24 hr period	75 mg, as needed Max dose is 75 mg in a 24 hr period	50,100 or 200 mg, as needed Max dose is one dose in a 24 hr period
EFFICACY *See individual websites for complete study results	Measured at 2 hours post-dose Pain Free: 19.2% at 50mg, 21.2% at 100mg Pain Relief: 60.7% at 50mg, 61.4% at 100mg	Measured at 2 hours post-dose Pain Free: 21.2% at 75mg Normal Function: 38.1% at 75 mg Pain Relief: 59.3% at 75mg	Measured at 2 hours post-dose Pain Free: 28% at 50mg, 31% at 100mg, 39% at 200 mg
DELIVERY ADMINISTRATION	oral tablet	orally dissolving tablet	oral tablet
HALF LIFE	5-7 hours	11 hours	5.7 hours
PRIMARY SIDE EFFECTS	nausea and sleepiness	nausea	dizziness, sleepiness, numbness, feeling tired, tingling
WARNINGS	none provided	hypersensitivity reactions, including dyspnea and rash	driving impairment, central nervous system depression, serotonin syndrome, medication overuse headache

NEWEST GEPANT FOR ABORTIVE TREATMENT

- Vazegepant(Biohaven)
  - Intranasal
  - Positive phase 2 trial

NEW TREATMENTS FOR MIGRAINE
SUMMARY

Prophylaxis

- CGRP Monoclonal Antibody Antagonists
  - erenumab, galcanezumab, fremenezumab, epinezumab
- gepants: atogepant, rimegepant

Abortives

- gepants: ubrogepant and rimegepant
- ditan: lasmiditan

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