

# BioCentury

WEEK OF SEPTEMBER 19, 2016

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## GETTING AHEAD OF HEADACHE

BY EMILY CUKIER-MEISNER, SENIOR WRITER

After several false starts, investments in CGRP inhibitors are bearing fruit in the clinic — if not exactly the prize pumpkins once hoped for from the class. Still, if the sponsors developing these products can convince payers to reimburse them, anti-CGRP mAbs could grab a slice of a potentially large market.

So far, three mAbs in advanced clinical testing that target calcitonin gene-related peptide and one targeting its receptor appear to offer efficacy equal to or modestly better than generics, without the side effects that hinder generic use.

The efficacy data reported to date also appear similar to data for [Allergan plc's](#) Botox onabotulinumtoxinA, the only patented treatment that has a label for prevention of chronic migraine.

But Botox hasn't appeared to be effective in preventing episodic migraines, where the new candidates from [Amgen Inc.](#), [Alder Biopharmaceuticals Inc.](#), [Eli Lilly and Co.](#) and [Teva Pharmaceutical Industries Ltd.](#) have shown small improvements in Phase II.

In a note dated July 12, Leerink analyst Jason Gerberry estimated the CGRP class could achieve \$4-\$5 billion in sales on the assumption that they are priced at \$10,000-\$12,000 per year, which works out to treating 400,000-417,000 patients annually.

The total market could be much larger if the companies could expand it to patients who are not currently diagnosed or treated.

But that could be tricky. Payers may balk at spending more for newer therapies that haven't shown a large efficacy boost over generic alternatives. And in similar situations where higher-cost therapies are not highly differentiated from each other, such as with some autoimmune drugs, HCV combinations and PCSK9 inhibitors, pitting sponsors against each other to

extract discounts in exchange for exclusive formulary access has become U.S. payers' go-to move.

Most of the sponsors are using their trials to measure healthcare utilization, productivity and quality of life outcomes that could make the case that the class brings greater value to the system.

## ROOM FOR IMPROVEMENT

Migraine prevention comprises two distinct indications: chronic and episodic migraine.

Chronic migraine is defined as headaches occurring on at least 15 days per month for more than three months.

Episodic migraine is defined as any number of migraines occurring on fewer than 15 days per month; episodic migraineurs may be candidates for prevention depending on the frequency and severity of headaches.

Standard of care for both indications includes generic topiramate, divalproex and beta blockers.

Mark Green, a professor of neurology, anesthesiology and rehabilitation medicine at the [Icahn School of Medicine at Mount Sinai](#), told BioCentury these drugs leave much to be desired. They reduce the frequency of migraines by half in only half of patients, and most have side effects that are difficult to tolerate in a chronic setting, such as weight gain or sedation.

## CONSIDERING CGRP

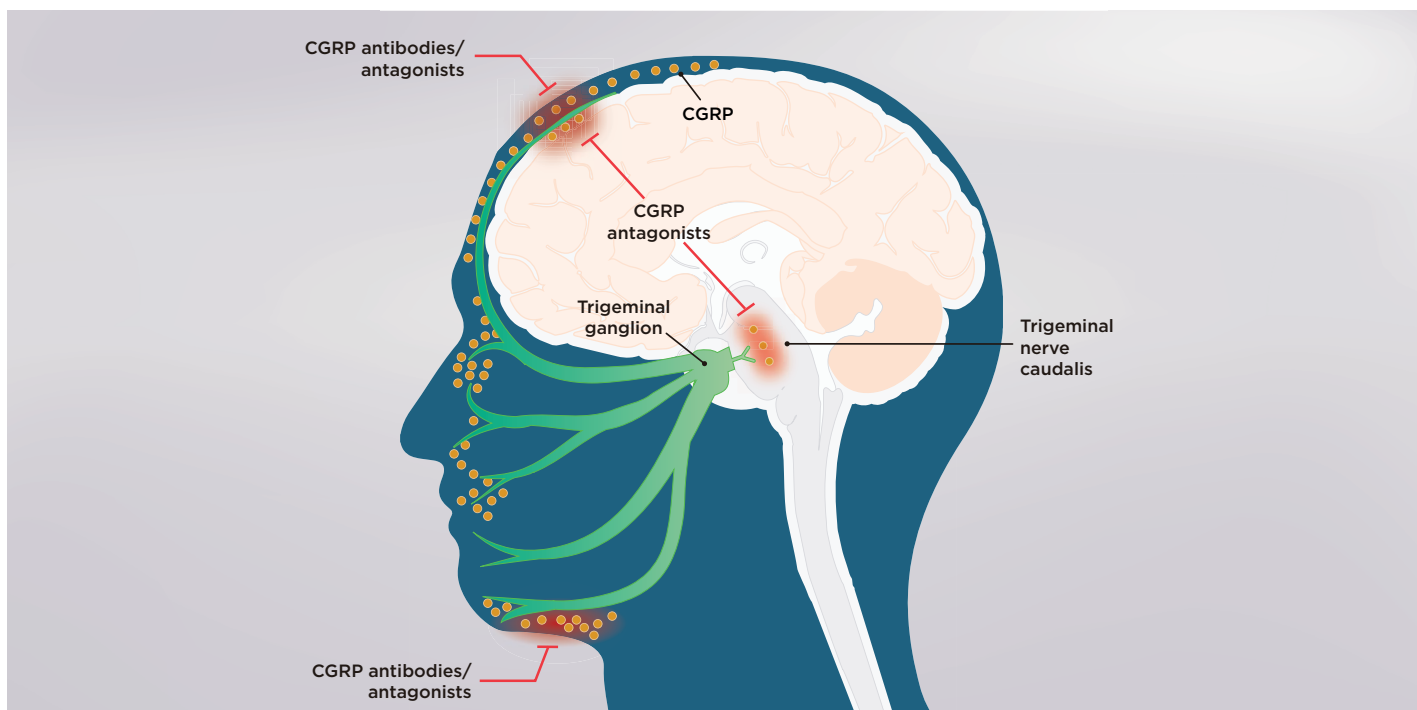
Migraine is associated with elevated levels of calcitonin gene-related peptide (CGRP), a multifunctional neuropeptide that plays multiple roles in the central and peripheral nervous system. Its exact biologic role in migraine is not fully known, but blocking CGRP activity could help alleviate migraine symptoms or prevent attacks by reducing vasodilation, neurogenic inflammation and pain perception.

Because they are thought to be poorly CNS-penetrant, anti-CGRP mAbs are thought to act by targeting CGRP released from trigeminal afferent nerve fibers during a migraine. Erenumab from **Amgen Inc.** (NASDAQ:AMGN) and **Novartis AG** (NYSE:NVS; SIX:NOVN) is in Phase III testing to prevent episodic migraine and has completed a Phase IIb study to prevent chronic migraine; it is the only one of the four late-stage anti-CGRP mAbs that target the receptor rather than the ligand.

Galcanezumab from **Eli Lilly and Co.** (NYSE:LLY) and TEV-48125 from **Teva Pharmaceutical**

**Industries Ltd.** (NYSE:TEVA) are in Phase III testing to prevent chronic and episodic migraine. **Alder Biopharmaceuticals Inc.** (NASDAQ:ALDR) has ALD403 in Phase III testing to prevent episodic migraine and plans to begin a Phase III study in chronic migraine this year.

Small molecule antagonists of CGRP that cross the BBB can also act on sites of CGRP action within the CNS, though it is not known how this may contribute to the molecules' safety or efficacy. **Allergan plc** (NYSE:AGN) has small molecule CGRP antagonist ubrogepant in Phase III testing to treat migraine, and small molecule CGRP receptor antagonist atogepant in Phase I for prevention. Teva and Lilly also have preclinical small molecule CGRP antagonist programs, though Lilly has not said whether its molecules can cross the BBB, and neither would say if they plan to develop them for prevention, treatment or both.



Topiramate reduced migraine days 1.3 and 1.6 days more than placebo did in two separate studies in patients with a history of migraine and 3-12 migraines in a four-week baseline period. Roughly half the patients in each study had at least 50% fewer monthly migraine episodes, compared with less than a quarter of placebo patients (54% vs. 23% and 49% vs. 23%).

Botox is part of standard of care to prevent chronic migraine only. The drug reduced monthly migraine days by 2 vs. placebo across its two Phase III trials. The proportion of patients who had at least 50% fewer monthly headache days was 47%, compared with 35% for placebo.

In episodic migraine, a meta-analysis of 10 randomized, placebo-controlled trials failed to show a significant reduction in frequency of

migraine episodes vs. placebo. Data were published in the *Journal of the American Medical Association* in 2012.

Few patients eligible for migraine prevention are actually on therapy.

The Migraine Research Foundation (MRF) estimates that 25%, or 9.5 million, of the 38 million U.S. migraineurs may be candidates for prevention therapy, although only 12% (4.6 million) receive it. About half of MRF's estimate of total migraineurs are patients who are undiagnosed and do not seek physicians' help for their pain.

According to the Chronic Migraine Epidemiology and Outcomes (CaMEO) study published in May in *Headache*, less than 5% of the total chronic migraine population is seeking and receiving preventive therapy.

## CHRONIC MIGRAINE COMPS

In chronic migraine prevention, differences in study designs used by developers of mAbs against calcitonin gene-related peptide (CGRP) or its receptor make it difficult to compare performance. However, the 12-week data from Phase II trials appear roughly similar across four mAbs and Botox onabotulinumtoxinA from **Allergan plc** (NYSE:AGN), which is approved for the indication.

In 24-week Phase III trials, Botox reduced monthly migraine days by two more than placebo, about the same as results from 12-week trials of erenumab from **Amgen Inc.** (NASDAQ:AMGN) and **Novartis AG** (NYSE:NVS; SIX:NOVN), and TEV-48125 from **Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA).

Alder Biopharmaceuticals Inc. (NASDAQ:ALDR) measured and met a different endpoint, with two doses of ALD403 that showed 31% and 33% of patients experienced a 75% reduction in migraine days compared with 21% for placebo. NS=not significant; NA=not available (A) Least squares mean (LSM) difference from placebo; (B) Change from baseline to weeks 9-12 in days of moderate to severe headache. Source: *Headache, Lancet Neurology, company press releases and presentations.*

Company	Product	Trial	Primary endpoint	Dosage	Chg in migraine days during last 4 weeks of primary analysis period	% pts w/>50% reduction in migraine days at 12 weeks	% pts w/>75% reduction in migraine days at 12 weeks	% pts w/100% reduction in migraine days at 12 weeks
<b>Allergan plc</b> (NYSE:AGN)	Botox onabotulinumtoxinA	2 pooled Ph III studies, 24 weeks	Change in monthly headache days from baseline to weeks 21-24 (met)	155 or 195 units SQ / 12 weeks (n=688)	-8.2 (p<0.001)	47.1% (p<0.001)	NA	NA
				placebo (n=696)	-6.2	35.1%	NA	NA
<b>Alder Biopharmaceuticals Inc.</b> (NASDAQ:ALDR)	ALD403	Ph IIb, 12 weeks	Percentage of patients with 75% reduction in monthly migraine days over 12 weeks (met)	300 IV (n=114)	NA	57% (p<0.01)	33% (p<0.05)	8% (NS)
				100 mg IV (n=118)	NA	54% (p<0.05)	31% (p<0.05)	5% (NS)
				30 mg IV (n=117)	NA	55% (p<0.05)	28% (NS)	4% (NS)
				10 mg IV (n=123)	NA	44% (NS)	27% (NS)	8% (NS)
				placebo (n=116)	NA	41%	21%	3%
<b>Amgen Inc.</b> (NASDAQ:AMGN) / <b>Novartis AG</b> (NYSE:NVS; SIX:NOVN)	erenumab (AMG 334)	Ph II, 12 weeks	Change in monthly migraine days from baseline to weeks 9-12 (met)	140 mg SQ / month (n=190)	-6.6 (p<0.001)	41% (p<0.001)	NA	NA
				70 mg SQ / month (n=191)	-6.6 (p<0.001)	40% (p<0.001)	NA	NA
				placebo (n=286)	-4.2	24%	NA	NA
<b>Teva Pharmaceutical Industries Ltd.</b> (NYSE:TEVA)	TEV-48125	Ph IIb, 12 weeks	Change from baseline in number of headache hours in weeks 9-12 (met)	900 mg SQ / 4 weeks (n=85)	-2.0 (p=0.04) (A)	55% (p=0.001) (B)	32% (p=0.01) (B)	NA
				675 mg SQ in cycle 1, 225 mg SQ in cycles 2-3 (4 week cycle) (n=87)	-1.72 (p=0.08) (A)	53% (p=0.004) (B)	29% (p=0.04) (B)	NA
				placebo (n=89)	NA	31% (B)	16% (B)	NA

# “OPPORTUNITY FOR GROWTH OF THE MARKET I THINK IS A BIGGER PART OF THE STORY HERE.”

BILL RATNER, LILLY

The authors said three main barriers contributed to that figure: talking to a healthcare professional about migraine, being diagnosed and being prescribed appropriate treatment.

Thus part of the opportunity for new prophylactics is not only to take share from Botox and generics, but also to expand the total market.

“Opportunity for growth of the market I think is a bigger part of the story here,” said Lilly Senior Director of Global Headache Marketing Bill Ratner.

## GETTING TO CGRP

CGRP has been known to play a role in migraine pain for at least three decades, although the earliest attempts to target it were focused on the acute setting rather than prevention.

Under normal conditions, CGRP regulates neuronal synapses and neuron interactions and maintains vascular tone in the brain. During migraines, CGRP levels are elevated peripherally and centrally, and CGRP receptors are found throughout the trigeminal nerve pathways involved in migraine headaches.

The exact mechanisms by which CGRP contributes to migraine — and how blocking it could relieve migraine symptoms — are not known, but they could involve the peptide’s roles in vasodilation, neurogenic inflammation and peripheral sensitization.

Many of the symptoms of migraine appear to arise from inflammation outside of the brain, according to Green (see “Considering CGRP,” page 2).

Botox is believed to work by non-selectively blocking CGRP.

Amgen VP of Neuroscience Global Development Robert Lenz said the receptor initially proved difficult to target because two different proteins must dimerize in the cell membrane to form a functional receptor.

Several small molecule antagonists have fallen by the wayside.

Telcagepant, a small molecule CGRP receptor antagonist from [Merck & Co. Inc.](#), showed that blocking CGRP reduced symptoms in acute migraine. But Merck shelved the compound in 2011 after seeing elevated liver enzymes in the clinic.

The cause of hepatotoxicity is not known, but one hypothesis is that it was a consequence of the molecular scaffolds that were used. Several companies are now developing small molecule CGRP antagonists for both acute and chronic migraine, including one in Phase III (see “Oral Persistence,” page 6).

Meanwhile, mAbs targeting CGRP or its receptor to prevent migraines have leapfrogged the small molecules in clinical trials.

Peter Goadsby, a professor of neurology at King’s College London, said R&D shifted from small molecules to longer-lived mAbs after it became apparent that CGRP could be a target for migraine prevention as well as acute therapy.

Companies developing anti-CGRP mAbs have hypothesized that because the molecules don’t enter the brain, they could be safer than small molecules that could compromise CGRP’s normal functions in the CNS. mAbs also are not expected to be hepatotoxic because they are not metabolized by the liver, and so far have not shown signs of hepatotoxicity in the clinic.

Amgen and partner [Novartis AG](#) expect to have data from two Phase III trials this year on erenumab to prevent episodic migraine. Lenz said those data, combined with Phase IIb chronic migraine data reported last week at the European Headache and Migraine Trust International Congress could support approval in both indications.

Lenz declined to say when Amgen plans to submit regulatory applications. Erenumab is the only candidate that targets the CGRP receptor.

Alder expects Phase III data for ALD403 for episodic migraine in 1H17 and for chronic migraine in early 2018.

Phase III data for a set of galcanezumab (LY2951742) studies in episodic and chronic migraine from Lilly are due in 2017. And Teva expects to complete Phase III studies of TEV-48125 for chronic and episodic migraine in 3Q17 and to report top-line data “shortly after.”

## LEVEL FIELD?

Differences in study designs for the four mAbs make it difficult to compare their performance; however, there do not appear to be any standouts.

In chronic migraine, Amgen and Novartis' erenumab and Teva's TEV-48125 have cut about 2 more monthly migraine days than placebo at weeks 9-12, the primary endpoint (see "Chronic Migraine Comps," page 3).

Alder used a different primary endpoint: the percentage of patients who experienced at least a 75% reduction in migraine days. Two doses met that endpoint, with 31% and 33% of patients vs. 21% for placebo.

Lilly has not reported Phase II data in chronic migraine.

In episodic migraine, all four companies have reported 12-week Phase II or IIb data on the primary endpoint of change in monthly migraine days; however, Alder measured the endpoint at weeks 5-8, while the others measured it at weeks 9-12 (see "Episodic Migraine Comps").

Erenumab, ALD403 and Lilly's galcanezumab spared patients about one more monthly migraine day than placebo did. TEV-48125 cut about 2.5-3 days compared with placebo.

Side effect rates for all the mAbs in both indications were generally low and similar to placebo, with injection site pain the most common across the programs. All of the companies have reported AEs related to

infections in treatment and placebo arms, including upper respiratory infection, nasopharyngitis and sinusitis.

None of the companies have reported any SAEs related to treatment. And none of the programs have shown cognition problems, weight gain or sedation, which are some of the most troublesome side effects of generic migraine prevention agents.

### WORTH A TRY

None of four neurologists who spoke to BioCentury saw meaningful differences across the mAbs' data, and all four said the class appears to provide only an incremental improvement in efficacy compared with Botox or generics.

Still, all four said the anti-CGRP mAbs have a clear place in the arsenal because even a modest reduction in headache days would be clinically meaningful, and because they appear more tolerable than most available migraine prophylactics. All four have experience treating migraine.

Green said a 50% reduction in headache days is a good standard, but even cutting them by less than half would be worthwhile for chronic migraine.

## EPISODIC MIGRAINE COMPS

Data from 12-week Phase II trials to prevent episodic migraine do not show any obvious differentiation among four mAbs targeting calcitonin gene-related peptide (CGRP) or its receptor. Erenumab from **Amgen Inc.** (NASDAQ:AMGN) and **Novartis AG** (NYSE:NVS; SIX:NOVN) and galcanezumab from **Eli Lilly and Co.** (NYSE:LLY) reduced the number of days of migraine by about one more day than placebo did during weeks 9-12. TEV-48125 from **Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA) reduced the measure by about two and a half to three days more than placebo.

ALD403 from **Alder Biopharmaceuticals Inc.** (NASDAQ:ALDR) saved patients one more migraine day than placebo during weeks 5-8. It also is the only mAb with prospective data showing a statistically significant 100% reduction in migraine days. The study showed 16% of patients were migraine free, compared with no placebo patients. A post hoc analysis showed galcanezumab produced a 100% reduction in 31.6% of patients compared with 17.3% for placebo, but the company did not provide a p-value. (A) No p-value given; (B) Post hoc analysis with no p-value given; NS=not significant; NA=not available Source: *Lancet Neurology, company press releases and presentations*

Company	Product	Trial	Primary endpoint	Dosage	Chg in migraine days during weeks 9-12	% pts w/>50% reduction in migraine days at 12 weeks	% pts w/>75% reduction in migraine days 12 weeks	% pts w/100% reduction in migraine days at 12 weeks
<b>Alder Biopharmaceuticals Inc.</b> (NASDAQ:ALDR)	ALD403	Ph IIb	Change from baseline in monthly migraine days at weeks 5-8 (met)	1,000 mg IV (n=73)	-5.6 (p=0.07)	61% (p<0.001)	33% (p<0.001)	16% (p<0.001)
				placebo (n=78)	-4.6	33%	9%	0%
<b>Amgen Inc.</b> (NASDAQ:AMGN) / <b>Novartis AG</b> (NYSE:NVS; SIX:NOVN)	erenumab (AMG 334)	Ph II	Change from baseline in monthly migraine days at weeks 9-12 (met)	70 mg SQ / month (n=104)	-3.4 (p=0.02)	46% (p=0.01)	NA	NA
				21 mg SQ / month (n=102)	-2.4 (p=0.8)	34% (p=0.4)	NA	NA
				7 mg SQ / month (n=107)	-2.2 (p=0.8)	29% (p=0.8)	NA	NA
				placebo (n=153)	-2.3	30%	NA	NA
<b>Eli Lilly and Co.</b> (NYSE:LLY)	galcanezumab (LY2951742)	Ph II	Change from baseline in monthly migraine days at weeks 9-12 (met)	150 mg SQ / 2 weeks (107)	-4.2 (p=0.003)	70.4% (A)	49% (B)	31.6% (B)
				placebo (n=110)	-3.0	45.2%	26.9%	17.3%
<b>Teva Pharmaceutical Industries Ltd.</b> (NYSE:TEVA)	TEV-48125	Ph IIb	Change from baseline in monthly migraine days at weeks 9-12 (met)	675 mg SQ / 4 weeks (n=96)	-6.09 (p<0.0001)	59% (p<0.0001)	31% (p=0.0008)	NA
				225 mg SQ / 4 weeks (n=95)	-6.27 (p<0.0001)	53% (p=0.0005)	34% (p=0.0001)	NA
				placebo (n=104)	-3.46	28%	11%	NA

## ORAL PERSISTENCE

Several companies are developing small molecule antagonists of calcitonin gene-related peptide for migraine treatment and prevention.

Peter Goadsby, a King's College London neurology professor, said a preventative oral anti-CGRP could be a game-changer because primary care providers may be more willing to prescribe tablets than injectable biologics. He did not expect the two modalities to have great differences in efficacy, or in the patient populations that respond to treatment.

The most advanced oral small molecule CGRP receptor antagonist is [Allergan plc's](#) ubrogepant. Allergan acquired ubrogepant and the oral CGRP receptor antagonist atogepant from [Merck & Co. Inc.](#) last year. Ubrogapant is in Phase III testing for acute migraine. Allergan plans to begin a Phase IIb study of atogepant to prevent episodic migraine this year.

Merck designed the molecules to avoid the liver toxicity that led the pharma to discontinue telcagepant, an earlier CGRP antagonist. Allergan and others have hypothesized that the liver toxicity was due to reactive chemical intermediates that form when the compound is metabolized.

"The chemical modifications that were introduced into ubrogepant and atogepant means those reactive chemical intermediates are unlikely to be formed," Allergan Chief R&D Officer David Nicholson told BioCentury.

He said preclinical and early studies have not shown hepatotoxicity, but that the question won't be fully answered until development is complete.

He said even if ubrogepant doesn't show an efficacy advantage over acute migraine treatments like triptans, it could still treat triptan non-responders — and so far it appears the CGRP class won't have the same cardiovascular liability as triptans.

Nicholson said ubrogepant and atogepant can cross the blood-brain barrier, and that so far Allergan has not seen side effects related to that activity.

He declined to discuss a timeline for regulatory submissions, but Allergan's November 2015 R&D day presentation projected a 2021 launch for atogepant.

[Teva Pharmaceutical Industries Ltd.](#) and [Eli Lilly and Co.](#) also are developing small molecule CGRP antagonists.

Senior Director of Global Headache Marketing Bill Ratner said Lilly thinks its compounds will avoid telcagepant's hepatotoxicity. The compounds are slated to enter the clinic this year, though Ratner would not say whether they will be studied for prevention or treatment.

Teva licensed its small molecules from [Sosei Group Corp.'s Heptares Therapeutics Ltd.](#) in 2015. SVP and Head of Global Specialty Development Marcelo Bigal said the programs used a different backbone than telcagepant did. They may cross the blood-brain barrier, which he added could be a route to enhanced efficacy compared to mAbs. He declined to disclose their development status or the specific indications they will be studied in.

— *Emily Cukier-Meisner*

In chronic migraine, about 40% of patients receiving erenumab experienced at least a 50% reduction in migraine episodes, compared with 24% of patients who received placebo. For high-dose TEV-48125, 55% of patients had at least a 50% reduction in days of moderate to severe headache compared with 31% of placebo patients.

Alder reported that 54-57% of patients in the three higher dose cohorts of ALD403 experienced a 50% reduction, compared with 41% of placebo patients. The lowest dose was considered subtherapeutic.

Stephen Peroutka estimated that a 30% reduction in migraine days from baseline would be clinically meaningful. Peroutka is VP and global therapeutic head of neuroscience and pain at [inVentiv Health Inc.](#) and a neurologist in private practice.

He considered the anti-CGRP mAbs an incremental improvement over current therapies, but thought they'd get used because most patients taking migraine prophylactics are still not headache free.

"Even though all these other drugs do exist, it's rare anybody goes to zero. If approved, there will be a lot of interest in trying," he said.

Only Alder has reported prospective data on the proportion of patients who became headache-free. In its Phase II episodic migraine trial, 16% of patients receiving ALD403 had a 100% reduction in migraines after 12 weeks, compared to none receiving placebo. ALD403 did not significantly improve the proportion of migraine-free patients vs. placebo in a Phase IIb trial to prevent chronic migraine.

Lilly has published a *post hoc* analysis of its Phase II trial to prevent episodic migraine that showed 32% of patients receiving galcanezumab had a 100% reduction in migraines after 12 weeks, compared to 17% receiving placebo. A p-value was not reported.

Peroutka expected physicians and patients would experiment with anti-CGRP monotherapy and combinations with other modalities to further reduce migraine severity, duration or frequency.

Stephen Silberstein, director of the Jefferson Headache Center and professor of neurology at [Thomas Jefferson University](#), said even without a substantial efficacy improvement, infrequent dosing and a "very benign side effect profile" could be advantageous over oral generics.

"All of the monoclonal antibodies seem effective for preventive treatment of migraine, with no side effects distinct from placebo seen so far," said Silberstein.

He said without real-life experience with the agents, he would likely reach for Botox first for his chronic migraine patients because he expects the newer treatments to cost more.

Goadsby thought the anti-CGRP mAbs might be more effective than Botox on the basis of higher proportions of chronic migraine patients achieving a 50% reduction in headaches, and because unlike Botox they did significantly reduce episodic migraines. He said he would likely recommend them over Botox because administering the toxin requires injections at 31 distinct places on the skin.

# “MY GUT SAYS THAT THIS IS GOING TO BE ONE OF THOSE MARKET SEGMENTS WHERE PBMS ARE GOING TO CHOOSE ONE OF THE DRUGS, AND THE OTHERS WILL BE EXCLUDED.”

ROGER LONGMAN, REAL ENDPOINTS

All of the CGRP companies have tested monthly dose regimens, and Alder and Teva are also studying quarterly administration. Lilly is studying monthly dosing in its Phase III programs, and Amgen declined to comment on the dose frequency it is studying in Phase III.

Goadsby thought quarterly rather than monthly injections would appeal to patients, but he did not think dosing frequency would be the deciding factor for which anti-CGRP mAb to use.

Goadsby has been a clinical investigator in trials of erenumab and galcanezumab. Silberstein has been a clinical investigator for all four mAbs. Green and Peroutka have not been clinical investigators for any anti-CGRP mAbs.

## PAYER HEADACHES

The CGRP companies have been somewhat tight-lipped about the details of their Phase III trials, — but what details are available do not suggest the data will be any easier to compare, which could make it harder to tease out advantages in efficacy or safety across the class.

In the absence of compelling differentiation, payers will probably require step therapy and pit the sponsors against each other for formulary access — depending on how expensive the drugs are.

Alder President and CEO Randy Schatzman said Alder may be able to command “a little bit of a bump” in pricing above Botox based on better efficacy, but he declined to give details. The average wholesale price (AWP) for Botox is about \$6,000 per year.

The other three companies declined to discuss pricing.

Ratner said Lilly expects patients may have to try at least one generic before moving on to galcanezumab.

Roger Longman, CEO of reimbursement consultancy Real Endpoints LLC, said step therapy with generics is likely, and maybe with Botox if it is “significantly cheaper.”

He added: “My gut says that this is going to be one of those market segments where PBMs are going to choose one of the drugs, and the others will be excluded.”

Silberstein said even if patients are required to fail multiple therapies, the impact could be minimal because a “large number of patients” have already done so.

Caroline Pearson, SVP at healthcare consultancy Avalere Health LLC, was less sure that payers will insist on step therapy.

“I think there’s a clear clinical benefit for the new products, and they look — optimistically — to represent an improvement over current treatment options,” she said.

But she said history suggests payers will likely try to counter companies’ efforts to expand the migraine prevention market, at least initially.

“When you had a large population suddenly become eligible for a new treatment, we saw strong efforts from payers to try to limit access to those medications as a cost management issue in the beginning. But those restrictions have loosened over time,” she said.

Both Longman and Pearson thought functional and economic outcomes would be important to make the case for the therapies.

Longman added that a significant fraction of migraine patients are covered by Medicaid, which would be even more reluctant to pay for anti-CGRP agents over cheaper alternatives than other insurers.

“In general, this group is under the strictest utilization management and formulary control,” Longman said.

Under the Affordable Care Act, individuals that make less than 133% of the poverty level are eligible for Medicaid. According to a 2015 report, 21.7% of adults who said they had experienced severe headache or migraine in the prior three months were in households making below 100% of the poverty level. The report was compiled by the Centers for Disease Control and Prevention (CDC) based on population interviews conducted from 1997-2014.

## BEYOND CLINICAL OUTCOMES

At least three of the companies are trying to build the case for reimbursing the mAbs over cheaper alternatives by developing data on functional and/or economic outcomes like reduced use of other healthcare products and services, increased productivity and quality of life.

Marcelo Bigal, SVP and head of global specialty development at Teva, said patients in Phase II and III trials were allowed to remain on stable background therapy with preventive agents like topiramate to show TEV-48125 can also work as an add-on to standard preventive care while reducing use of acute rescue medications.

Lilly, Alder and Teva are collecting resource utilization data in the hopes of showing improved cost effectiveness. Amgen declined to say whether it is doing so.

## “IF YOU’RE AN EMPLOYER PLAN, THE BENEFIT OF EFFECTIVE PREVENTIVE MIGRAINE MEDICINE IS VERY MEANINGFUL.”

CAROLINE PEARSON, AVALERE

Resource utilization outcomes related to migraine prevention include reduction in emergency room visits and reduction in approved acute migraine therapies as well as opioids, which are not recommended for migraine but are used in emergency settings.

And all the companies are also collecting patient-reported quality of life and functional outcomes data to show increases in work attendance and productivity, ability to do household chores and interaction with family members.


“Our trial has more functional and payer endpoints than any other I have worked with,” said Teva’s Bigal.

Longman said if the data bear out, companies could use outcomes data to make the case that alleviating severe migraines would make sufferers more able to work and thus reduce their reliance on Medicaid.

And Pearson said self-insuring employers would have a special interest in outcomes related to ability to work, compared with conventional insurers.

“Migraines are very closely linked to absenteeism, so if you’re an employer plan, the benefit of effective preventive migraine medicine is very meaningful,” she said.

But Longman cautioned that employer-sponsored plans are more likely to outsource formulary management to PBMs, who would be unlikely to tailor them to individual customers’ needs. He said even if the data do show fewer missed days of work in a real-world setting, the PBMs would

likely interpret it as a class effect rather than an argument for using a particular anti-CGRP agent. 

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### COMPANIES AND INSTITUTIONS MENTIONED

**Alder Biopharmaceuticals Inc.** (NASDAQ:ALDR), Bothell, Wash.  
**Allergan plc.** (NYSE:AGN), Dublin, Ireland  
**Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.  
**Avalere Health LLC.** Washington, D.C.  
**Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.  
**Icahn School of Medicine at Mount Sinai,** New York, N.Y.  
**inVentiv Health Inc.,** Burlington, Mass.  
**King’s College London,** London, U.K.  
**Merck & Co. Inc.** (NYSE:MRK), Kenilworth, N.J.  
**Migraine Research Foundation (MRF),** New York, N.Y.  
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland  
**Real Endpoints LLC,** Westport, Conn.  
**Sosei Group Corp.** (Tokyo:4565), Tokyo, Japan  
**Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA), Petah Tikva, Israel  
**Thomas Jefferson University,** Philadelphia, Pa.  
**U.S. Centers for Disease Control and Prevention (CDC),** Atlanta, Ga.

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