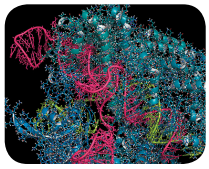
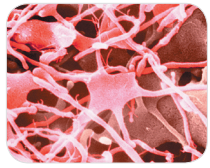
IN this section

Uncertainty surrounds liquid biopsy data p209



Preprint wipes millions off CRISPR stocks p211



Cell therapy for Crohn's disease fistulas nears approval in Europe p212

Migraine drug race turns its final corner, FDA decisions in sight

Over the next six months, the US Food and Drug Administration (FDA) is widely anticipated to approve a trio of monoclonal antibody (mAb) drugs for preventing migraine, in what could be a new era in the disease's treatment. The mAbs block calcitonin-gene-related peptide (CGRP), a neuropeptide that is active during migraine attacks and implicated in the transmission of pain signals and the sensory disturbances that define this common neurological disorder. All three companies developing anti-CGRP antibodies have blockbuster hopes for their migraine treatments—although, as observers do not expect to see much difference in efficacy between competitors, their advantages may largely be based on dosing and frequency.

First up will likely be erenumab (Aimovig). Its manufacturer, Amgen of Thousand Oaks, California, announced on January 22 that the drug outperformed placebo in a phase 3 trial of patients with episodic migraine who had previously tried and either not responded to or couldn't tolerate two to four other preventive treatments. A regulatory decision on erenumab is expected by mid-May.

Next, the FDA will likely rule on fremanezumab from Teva Pharmaceutical of Petach Tikva, Israel, in June; and a verdict should come by late September for galcanezumab from Eli Lilly of Indianapolis. A fourth anti-CGRP mAb, eptinezumab from Alder Biopharmaceuticals of Bothell, Washington, could then hit the market in 2019, and at least one prophylactic CGRP-antagonizing small molecule (and several others for acute treatment) might not be far behind (**Table 1**).

Anti-CGRP agents are the first drug class pursued by drug companies with the express purpose of preventing migraines. From beta-blockers and antidepressants to antiepileptics and botulinum neurotoxins, all existing prevention treatments were initially licensed for other indications and later repurposed as prophylactics against migraines. This new crop of antibody migraine drugs also stands apart in that their mechanisms of action are well understood—unlike triptans, which were developed to treat acute migraine attacks, on a molecular premise that later proved to be false. The antibodies provide migraine relief by blocking the blood vessel dilation and pain sensitization induced by CGRP on the trigeminal ganglion,

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Anti-CGRP antibodies are meeting phase 3 migraine endpoints, but observers predict no clear winner.

a group of sensory neurons that feed into the brainstem but are located outside of the central nervous system (CNS).

"These are really the first therapies, ever, that have been designed based on a specific laboratory understanding of the mechanisms of migraine," says Andrew Charles, a neurologist at the University of California, Los Angeles (who consults for Alder, Amgen and Lilly). "That, to me, is very exciting and compelling."

Not that there aren't biological details left to fill in. It's possible, for example, that CGRP signaling in the CNS might also contribute to migraine formation, as evidenced by recent mouse studies from Andrew Russo's lab at the University of Iowa in Iowa City (*J. Neurosci.* **37**, 204–216, 2017). "That does leave open the question of whether a centrally acting small-molecule antagonist would work better, or would it work for a different population of people"—because small molecules, unlike mAbs, can cross the blood–brain barrier and penetrate other difficult-to-reach areas of the body, such as smooth muscle cells within vessel walls—"and I think the answer is yes," says Russo, a molecular neuroscientist who consults for Alder.

Still, even with the brain penetrance question unanswered, physicians and patients can take comfort from the phase 3 trials of the CGRP-targeted mAbs reported to date. All antibodies seem to work about twice as well as placebos at reducing the number of days in which individuals experience migraine attacks, with few significant side effects among the 10,000 or so people treated with the therapies to date.

In fact, according to Peter Goadsby, a headache neurologist at the King's College London, who has been involved in trials of all four mAbs, and reported on two late last year (*NEJM* **377**, 2113–2122 and 2123–2132, 2017), there's little in the efficacy or tolerability data to indicate one anti-CGRP mAb might be better than any other. "I really defy people to show me any convincing evidence that they differentiate in any sort of way," he says.

For this reason, marketing, more so than clinical factors, will likely determine which, if any, drug comes to dominate the field, especially among the three products expected to win approval this calendar year. Amgen and its commercialization partner, Novartis of Basel, Switzerland, should have a small first-mover advantage—and the cost they establish for erenumab will undoubtedly set the bar for the entire field. Price projections begin at about $8,500 per year. But only Teva and Lilly are developing their drugs for the prevention of both migraines and cluster headaches. And Teva stands alone in its pursuit of yet-another indication: prevention of persistent post-traumatic headache.

Ultimately, however, most analysts expect all three agents will pull in about equal revenues, each earning in excess of $1 billion annually, with peak-year global sales for the entire class at around $6 billion. "Combined, we see it as a pretty big market," says Vamil Divan, a pharmaceuticals analyst at Credit Suisse in New York. And even eptinezumab, the Johnny-come-lately mAb from Alder, could reach blockbuster status, says Divan. That's because its distinct mode of delivery—intravenous infusions, whereas the others involve subcutaneous injections—could help eptinezumab find a niche.

More importantly to patients, Alder's eptinezumab can be dosed quarterly, because infusions allow high drug concentrations delivered less frequently. By comparison, erenumab and galcanezumab are both administered monthly, whereas fremanezumab has an unusually long half-life of more than 40 days, and seems to work with either single monthly injections or

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Table 1 CGRP-targeted therapies for migraine in clinical development

	Drug	Company	CGRP target	Route/dosing	Indications under investigation	Phase
Antibodies	Erenumab	Amgen	Receptor	Subcutaneous every 4 weeks	Prevention of migraines (EM, CM)	BLA
	Fremenezumab	Teva	Ligand	Subcutaneous every 4 or 12 weeks	Prevention of migraines (EM, CM, EC, CC, PPTH)	BLA
	Galcanezumab	Eli Lilly	Ligand	Subcutaneous every 4 weeks	Prevention of migraines (EM, CM, EC, CC)	BLA
	Eptinezumab	Alder	Ligand	Intravenous every 12 weeks	Prevention of migraines (HFEM, CM)	3
Small molecules	Rimegepant	Biohaven	Receptor	Oral as-needed	Acute treatment of migraines	3
	Ubrogepant	Allergan	Receptor	Oral as-needed	Acute treatment of migraines	3
	Atogepant	Allergan	Receptor	Oral once or twice daily	Prevention of migraines (EM)	2b
	BHV-3500	Biohaven	Receptor	Intranasal as-needed	Acute treatment of migraines	1

EM, episodic migraine; HFEM, high-frequency episodic migraine; CM, chronic migraine; EC, episodic cluster; CC, chronic cluster; PPTH, persistent post-traumatic headache; BLA, biologic license application.

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three shots every three months. According to Jaume Pons, who helped originate Teva's fremanezumab as head of protein engineering at Rinat Neuroscience in the mid-2000s (before Pfizer acquired Rinat, then licensed the drug to a company called Labrys Biologics, which Teva later bought), it is unclear what gives the product this unique feature. Pons is now CEO of Alexo Therapeutics, an immuno-oncology company based in S. San Francisco, California.

Injected mAbs still take a few weeks to kick in, however, whereas Alder's eptinezumab, because of its intravenous delivery, seems to have a much faster onset of action. The drug's effects are seen as soon as one day after the first infusion, according to phase 3 data. Eptinezumab might thus straddle—or perhaps even dismantle—the divide in the migraine field between medicines used to abort acute attacks and those taken for prevention. "This could conceivably knock out the headache you have that day and then keep them down for months," says Peter McAllister, medical director of the New England Institute for Neurology and Headache in Stamford, Connecticut, who has worked with all the companies in the CGRP space.

Perhaps the biggest difference between the various mAbs lies in the protein they target: erenumab (and the various small molecules under development) is directed against the CGRP receptor, the three other mAbs all block the CGRP ligand.

A few years back, molecular pharmacologists Debbie Hay and Christopher Walker of the University of Auckland in New Zealand showed that a second CGRP-activated receptor—the amylin 1 (AMY1) receptor—is also present at neural sites important for migraine pain (*Ann. Clin. Transl Neurol.* **2**, 595–608, 2015). That means the ligand-targeted mAbs may have an efficacy advantage over those blocking the receptor exclusively, because they block signaling through both the canonical CGRP receptor and the AMY1 receptor. Or, they may have some as-yet unnoticed side effect related to AMY1's metabolic function.

Small-molecule drugs mainly block the CGRP receptor, though Hay and Walker have found that many of them have a reasonably high affinity for the AMY1 receptor as well. "They are not nearly as selective as the literature would have you believe," says Hay. However, whether the AMY1 signaling inhibition matters for patients, given the redundancy of peptides and receptors in the trigeminal nerves, remains unclear. "We don't have complete understanding of this pathway," she adds.

The first small-molecule blockers of CGRP signaling to reach the market, perhaps as early as 2020, will likely be ubrogepant from Dublin-based Allergan and rimegepant from Biohaven Pharmaceuticals of New Haven, Connecticut. Both are in phase 3 testing for the treatment of acute migraine attacks, not prevention, with Allergan reporting last month that its pill helped around 20% of patients be pain-free two hours after dosing, besting placebo in its first of two pivotal trials. The only small molecule being pursued currently for prophylaxis is Allergan's atogepant, which is now the focus of an 810-person, phase 2b dose-finding study.

Small molecules have the advantage of oral delivery and, because they operate through a different mechanism than antibodies, they may still work in the brain to quell attacks, even in those patients taking anti-CGRP prophylaxis, notes Vlad Coric, Biohaven's CEO.

Casting a shadow over all these small molecules, though, is the specter of telcagepant, a drug from Merck of Kenilworth, New Jersey, that entered phase 3 development in the late 2000s but was abandoned after several patients developed significant elevations in liver enzymes levels. Given the overwhelming safety of the anti-CGRP mAbs, the problem is not thought to be due to on-target activity. Instead, it's suspected that either the breakdown of telcagepant in the body created toxic, reactive metabolites, or the drug had off-target effects on the liver's bile salt transporters.

Despite the unknowns, David Nicholson, chief R&D officer at Allergan, says the two CGRP receptors inhibiting small molecules acquired from Merck, ubrogepant and atogepant, "look safe no matter which hypothesis is actually correct." They were synthesized and selected to minimize the likelihood of liver toxicity, and although there were six cases of elevated liver enzymes in the phase 3 trial reported last month, an expert panel determined that the drug was not responsible for any of those adverse events. Coric makes essentially the same claims about the design of rimegepant, adding that the Biohaven pill and the company's phase 1 intranasal candidate BHV-3500 are both far more potent at the CGRP receptor than telcagepant, which allows for patients to take lower doses of the drugs for an added measure of safety.

But CGRP inhibitors still won't work for all migraine sufferers because CGRP is not the only neuropeptide involved in the disease process, and the neuropeptide seems to spur attacks in only around two-thirds of all migraineurs. Predictive biomarkers are therefore needed, although blood levels of CGRP itself don't seem to discriminate accurately between drug responders and non-responders.

Drug companies have also begun looking at additional targets for those who don't respond to CGRP inhibition or to layer on top in combination therapies—and according to Russo, "PACAP is leading the charge." Short for pituitary adenylate cyclase-activating peptide, PACAP is another signaling molecule involved in migraine pathophysiology. Amgen launched a phase 2 trial last year of a mAb that targets one of PACAP's receptors for migraine prophylaxis, and Alder has a preclinical candidate directed against a form of PACAP itself.

The laundry list of other potential targets includes amylin, neuropeptide Y, substance-P, angiotensin, adiponectin, orexin and both the corticotropin-releasing and melanin-concentrating hormones. "If we look at how many different receptors are actually expressed in trigeminal ganglia, it's nearly 200," Hay says. "How many of those are involved in migraine? It's very early days to say, but there are clearly, I think, lots of targets for the future."

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