

Dealmaking and differentiation in migraine's big new market

After safety issues dashed hopes several years ago, calcitonin-gene-related peptide has re-emerged as a prominent target, catalyzing deals and potentially reinvigorating the generic-dominated migraine market.

Chris Morrison

In 2011, Merck & Co. discontinued a once promising program to develop a new kind of drug to treat and prevent migraines. The biological rationale behind telcagepant—a small-molecule inhibitor of the receptor for calcitonin-gene-related peptide (CGRP)—was strong, and efficacy data from phase 3 trials were compelling. But long-term use resulted in liver toxicity that doomed the Merck compound. Other companies, including Boehringer Ingelheim and Bristol-Myers Squibb, also dropped their small-molecule CGRP inhibitors.

Five years later, monoclonal antibodies against CGRP from Eli Lilly, Alder Biopharmaceuticals and Teva, as well as a monoclonal antibody against the CGRP receptor from Amgen and partner Novartis, are jostling to fulfill the blockbuster potential of CGRP inhibition. With phase 3 programs in full swing, the antibodies appear to be safe and effective—in some cases dramatically so—in preventing frequent or chronic migraine attacks. More than 5,000 patients have been treated in clinical trials of the CGRP inhibitors, and the safety profiles of all the antibodies are fairly similar and benign, said Stephen Silberstein, director of the Jefferson Headache Center at Thomas Jefferson University Hospital. So far it looks like the liver problems Merck saw were due to the chemical structure of its drug, and not to CGRP inhibition.

One or more of the antibody candidates could be approved as soon as 2018, and, notably, their long half-lives are ideally suited for preventative therapy. Whereas acute migraine can sometimes be treated by a class of generic medicines called triptans, individuals with frequent episodic and chronic migraine conditions can endure headaches 15 days per month or more and require prophylactic treatment. However, they are served only partially by drugs repurposed for migraine such as Botox, beta blockers and the anticonvulsant topiramate, which often have various side effects that limit their use.

The hope is that targeting CGRP, a small neuromodulatory peptide that has a key role in migraine pathogenesis, could be more effective, at least for some individuals. CGRP is thought to regulate the sensitivity of pain-sensing neurons outside the brain, dialing up or down the nerve cells' response to particular signals that may set off migraine in some sufferers. Those particular migraineurs "seem to have CGRP as the primary underpinning for migraine causation," said Alder Biopharmaceuticals president and CEO Randall Schatzman.

The unmet need is significant: according to the Migraine Research Foundation, 38 million people in the United States alone suffer from migraine headaches. Of those, 4 million experience chronic migraine (more than 15 headaches per month, of which at least 8 are migraines). Consequently, the market for an effective drug is huge—analysts at Evercore ISI peg the CGRP opportunity at \$8–10 billion per year.

Risk reduction starts the race

Boosted by the changing clinical science and the large market opportunity, dealmaking around antibodies in the space has heated up since Merck abandoned its small-molecule CGRP program. Lilly's approach to developing its CGRP-specific antibody LY2951742 reflects the risk profile of the class over the past few years, and also highlights an emerging strategy for larger companies to manage the uncertainties of early-stage assets.

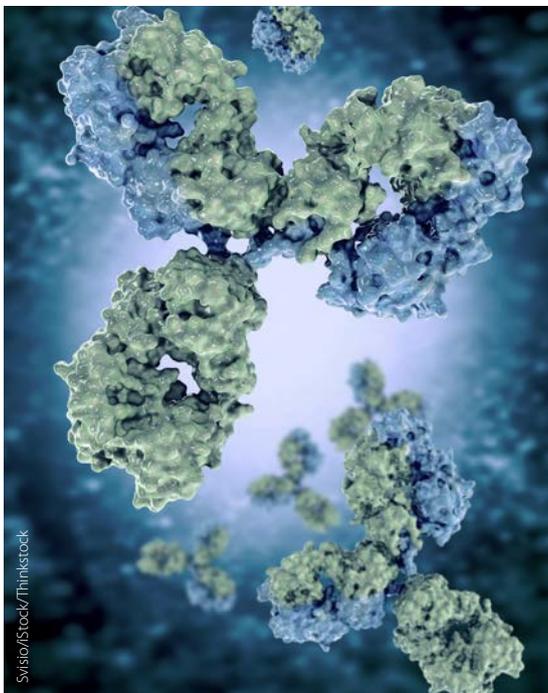
In 2011, Lilly decided to out-license the then preclinical candidate LY2951742 to Arteaus, a purpose-built biotech backed by Atlas and Orbimed, and keep an option to buy it back if and when proof-of-concept clinical data were positive. For assuming the risk that LY2951742 might fail, Arteaus' investors were able to pre-specify the terms of the potential buyout. At the time, the CGRP field was far from a "horse race," said Atlas Venture partner David Grayzel, who served as Arteaus' CEO. "When we first started this, there was only small-molecule data and there was still quite a lot of risk," he said. It was also unclear whether a CGRP-targeting therapeutic would need to penetrate the blood-brain barrier to be effective and whether it would be safe to inhibit CGRP for long periods of time.

The Arteaus arrangement provided a cost-efficient way to resolve these uncertainties and to share the risks of development between Lilly and Arteaus' investors. Arteaus was the first to show positive randomized phase 2 data for a CGRP-specific antibody in migraine prevention, in 2013, and "our data in part catalyzed the field," said Grayzel. These data also convinced Lilly to pull the trigger on its option to reacquire the antibody, paying \$57 million for Arteaus in January 2014.

Teva joined the CGRP fray not long after, with the June 2014 buyout of Labrys Biologics. Teva paid \$200 million up front and may owe Labrys investors up to \$625 million in milestone payments, depending on the success of the CGRP-specific antibody LBR-101 (now

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Roger Longman, CEO of Real Endpoints



TEV-48125). Teva becomes the antibody's fourth owner—an impressive tally that also illustrates the ebb and flow of interest in CGRP as a mechanism of action. First developed by Rinat Biosciences, the drug wound up at Pfizer when the big pharma acquired Rinat in 2006, in large part to land the biotech's preclinical-stage Alzheimer's disease antibody therapy (that deal was valued at approximately \$500 million and at the time was the richest takeout of a privately held biotech in industry history). Pfizer's R&D strategy shifted and it eventually spun off the CGRP-specific antibody to Labrys, which raised \$31 million to develop the then phase 1 candidate in 2013.

Amgen and Novartis are now codeveloping erenumab (originally known as AMG 334) as part of the two big companies' broader 2015 neuroscience collaboration that also involved Novartis' BACE inhibitor for Alzheimer's disease. Alder's program remains unpartnered, but the company says it's evaluating its partnership options. "We'll need commercial capabilities in the geographies we're not active in, and we keep exploring those opportunities," said Alder CBO Mark Litton. In the United States, the company thinks it has the wherewithal and the financial capability to push the drug across the regulatory finish line and market it alone.

And coming full circle, companies are reviving the small-molecule strategy for targeting CGRP: Merck agreed to license its remaining small-molecule CGRP antagonists to Allergan in mid-2015 for \$250 million up front; Lilly is developing in-house small molecules; and Teva teamed up with the biotech Heptares Therapeutics on that company's small-molecule CGRP drugs in November 2015. Heptares received a \$10 million upfront alliance payment and is eligible to receive up to \$400 million in milestones based on the programs' success, plus royalties on net sales.

Differentiation and payer pressure

The clinical success of the CGRP antibodies has analysts and executives dreaming about the next blockbuster biologics market, a rare feat for neuroscience candidates. Though other drugs will certainly be developed for CGRP non-responders, the class is unlikely to be supplanted by better therapies in the near term. "The data around the CGRP antibodies is so robust and startling in its efficacy that it will be a pretty high bar," said Grayzel.

But the ultimate market success of these drugs may be hindered by the fact that several are emerging in quick succession. "Payers will say, 'How do I prevent these drugs from becoming a huge, budget-busting class?'" said Roger Longman, CEO of Real Endpoints, which helps its payer and pharmaceutical customers assess the value of treatments. In other specialty drug markets with multiple entrants demonstrating similar efficacy, such as hepatitis C and the cholesterol-lowering antibodies that target PCSK9, payers drove down prices by signing exclusive deals with the company that offered the lowest price.

Although there is not yet a clear leader among the group, there are some potential differentiators, including the choice of targeting either CGRP or its receptor. Marcelo Bigal, SVP and head of global specialty development at Teva (and former CMO at Labrys), said that targeting CGRP with an antibody could bring high levels of the peptide closer to normal, whereas targeting the receptor may block the entire CGRP signal. Conversely, Rob Lenz, Amgen VP of global development in neuroscience, noted that targeting the CGRP receptor might mean the target could be saturated with a lower dose of drug, theoretically avoiding long-term side effects.

The route of administration is another possible differentiator. Alder's first formulation for its lead CGRP antibody ALD403 is an intravenous infusion given once every three months, whereas Amgen, Lilly and Teva are aiming for a monthly self-administered subcutaneous injection. Alder's approach "will allow for convenience for patients, better compliance and better disease management," argued Schatzman. "From a payer perspective, better disease management and compliance results in lower costs overall," he added.

Others point to the convenience of self-administration and the well-established self-injector technologies that have made the practice relatively simple in indications such as rheumatoid arthritis. Amgen's Lenz said a monthly home auto-injection "isn't onerous or burdensome" and would be preferred because it doesn't require a trip to a physician. Regardless, any formulation or dosing advantage might be relatively short-lived. "I suspect every company [in the field] will have both injectable and infusion formulations eventually," said Silberstein. Indeed, alternatives—including an injectable formulation of Alder's ALD403—are in early-stage development.

"The economics of payer-pharma dealmaking around CGRP will be crucial. Essentially this could be a marketplace dominated by one or two winners while everyone else gets shut out," said Longman. "These are highly innovative drugs, but if they can't figure out a way of differentiating themselves this will become a market access war in which rebates and contracting will be the ultimate decider on who wins."

Chris Morrison is a freelance writer for the pharmaceutical and biotech industry.