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MID-STAGE 'FOUR PLAY' IN HEADACHE

Anti-neoteny botany: Alder takes on Lilly as migraine CGRPs reach maturity fast

By Randy Osborne, Staff Writer

Alder Biopharmaceuticals Inc. and Eli Lilly and Co. stand as the only developers of calcitonin gene-related peptide (CGRP) blockers that have generated human efficacy data in migraine patients, but Amgen Inc. and Teva Pharmaceuticals Ltd. are courting similar phase II success in the clinic.

"I'm not one to score [front-runners]," said Alder CEO Randall Schatzman, though he conceded that "we and Lilly are both in a very competitive position right now, with respect to everybody that's playing here."

Blocking CGRP could hold the key at last to a more widely effective and better tolerated migraine therapy, and Bothell, Wash.-based Alder made known Wednesday its plan to start phase IIb trials with the monoclonal antibody (MAb) ALD403 this year.

Teva's CGRP antibody, known as LRB-101, came aboard when the company took over Labrys Biologics Inc. in June. Indianapolis-based Lilly's anti-CGRP bullet is LY2951742. Amgen, of Thousand Oaks, Calif., is pursuing AMG 334, another MAb aimed at CGRP. (See *BioWorld Today*, Oct. 20, 2011, Jan. 4, 2013, and June 4, 2014.)

"Everybody is somewhere in the spectrum of phase II right now," Schatzman said.

Data from Bothell, Wash.-based Alder disclosed six-month phase IIa results at the American Headache Society meeting in June showing that, in any given month, ALD403 reduced migraine days by 100 percent in 27 percent to 40 percent of patients, by 75 percent in 45 percent to 53 percent of patients, and by 50 percent in 75 percent to 77 percent of patients. Efficacy of a single dose was maintained through the half-year period.

The phase IIb study lasting 12 weeks will test single doses of intravenous ALD403 in the chronic migraine population this year (from 1,000 mg downward), followed by a second phase IIb testing multiple doses administered subcutaneously in high-frequency episodic patients to start in the first half of next year. Both studies will be randomized, double-blind, and placebo controlled, and will have as their primary endpoints 75 percent migraine reductions over the length of the trial period.

Alder's next studies "are going to leverage off that earlier observation and ask what is the minimal amount of drug required to deliver that same level of efficacy," Schatzman said, calling the next work "an execution issue. We know what the endpoints are. It's about optimizing the amount of drug and how frequently we need to treat those patients to maintain that level of efficacy. Our goal is to have a label that would indicate the use of our drug for all patients with five or more migraine days every month."

Wells Fargo analyst Brian Abrahams found the phase IIb strategy with ALD403 "makes good strategic sense, and reflects FDA recognition of the agent's potential benefits." The phase IIb will let the company "gain experience in the more severely affected chronic migraine population, in anticipation of potentially incorporating these patients into a phase III program to achieve the broadest possible label (patients with five-plus headache days per month)." The size of the studies – about 100 subjects per arm – will help build the safety database, too.

Calling the phase IIa data "breakthrough therapy-like," Leerink Partners analyst Joseph Schwartz said ALD403 "has the potential to transform the migraine prevention treatment paradigm," and in a research report wrote that the firm's "discovery platform is differentiated by its unique yeast-based manufacturing technology Mabxpress, which we believe could enable a more efficient generation of monoclonal antibody therapeutics, potentially leading to higher yields, economies of scale and therefore pricing flexibility and/or a lower cost-of-goods-sold margin." Schwartz modeled peak revenues from the drug at $1.25 billion in the U.S. in 2025, and estimated ALD403's approval chances at 60 percent.

LIVER ENZYMES STALL MERCK, BI

Alder's platform gained a vote of confidence from licensor New York-based Bristol Myers Squibb Co. (BMS), which

in 2009 paid $85 million up front for exclusive global rights to develop and commercialize the rheumatoid arthritis candidate then known as ALD518 in all indications outside cancer. The deal also included $764 million in potential milestone payments and sales-based payments that could exceed $200 million, plus royalties.

Alder gained an option requiring that BMS make an equity investment of up to $20 million if the biotech goes public. Clazakizumab, as the compound is now called, is directed at the interleukin-6 cytokine molecule, rather than the receptor. (See *BioWorld Today*, Nov. 11, 2009.)

"After that we asked the question, 'What do we do for an encore? Do we leverage that by going into a biosimilar space, or do we go novel?'" Schatzman said. "In the biosimilar space even today, the regulatory environment is still risky. If you deliver the same molecule, be it Humira or Enbrel or whatever, and give patients the same efficacy and the same level of safety, but oh by the way, it's at a 20 percent discount, that just didn't seem like a very innovative approach for us. So we looked at an area where antibodies have not played a role previously, where pricing pressure would be an issue, and [where] there would be large markets where supply in mass scale would be required as well." Using an antibody against migraine was "a lot more exciting and a better proposition for investors than the biosimilar space," he said.

Mark Litton, Alder's chief business officer, said Alder's work settled important questions. "There was always this debate about did you need to get centrally activated to get past the blood-brain barrier, or could you affect this target peripherally? Before we had our clinical data, there was a lot of debate as to whether an antibody would work, knowing that an antibody doesn't cross the blood-brain barrier, for the most part."

The road wasn't easy at first, CEO Schatzman recalled. "As we were going out looking for funding, there was a lot of skepticism as to whether we would have the efficacy we saw, due to that [antibody] issue," he said. "We have felt all along that the events that initiate migraine are outside of the central nervous system [CNS]. CGRP acts both peripherally to initiate the biology that results in migraine, but it also acts as a neurotransmitter, if you will, to transmit that signal from the periphery through the trigeminal ganglia into the CNS."

CGRP has long been known as a migraine culprit – the start of headaches as well as their continuing – and big pharma has thrown plenty of money at the target. Telcagepant (MK-0974) from Whitehouse Station, N.J.-based Merck & Co. Inc. reached phase III but the company stopped trials in the summer of 2011, not providing a reason but saying the decision was "based on an assessment of data across the clinical program, including findings from a recently completed six-month phase III study."

Hopes had been high. Global Health Ventures Inc., of Vancouver, British Columbia, had even begun developing a sublingual form in 2010. Some hints of trouble had surfaced earlier, however; in 2009, Merck withdrew an FDA application because patients in telcagepant experiments were showing elevated liver enzymes.

Boehringer Ingelheim GmbH (BI), of Ingelheim, Germany, also has taken a stab at CGRP with olcegepant (BIBN4096BS), which showed promise in phase II trials, though clinicaltrials.gov listed no studies ongoing now. Schatzman and Litton said BI ended its work for the same reason as Merck: liver toxicity. Merck, Schatzman said, had almost 11,000 patients in its trial program and "had put a filing package together before they got off that bus."

Merck and BI "are really the ones that, I think, established this [CGRP] biology as being relevant," Schatzman told *BioWorld Today*. "They both had small molecules to the receptor. It is a complicated receptor in that it's a multi-chain protein, and to inhibit it, you've got to fill a fairly large gap in the structure." The small molecules they chose were, by necessity, also complicated.

PARTNER SOUGHT OUTSIDE U.S.

"The question for our program, as we were moving forward, was, 'Is that [liver toxicity] something that is mechanism-based, or was it an off-target effect?'" Schatzman said. "Clearly, today, we're all concluding it's an off-target effect because nobody's reporting that in the efficacy that we see by treating patients with a very specific antibody to these targets."

Teva, of Jerusalem, wanted San Mateo, Calif.-based Labrys' anti-CGRP therapy as an add-on to its marketed sumatriptan delivery patch, Zecuity, brought aboard in the buyout of Nupathe Inc., of Conshohocken, Pa. An intranasal powder version of sumatriptan, AVP-825, has been developed by Avanir Pharmaceuticals Inc., of Aliso Viejo, Calif., and Rohan Palekar, the firms' chief commercial officer, said during a conference call this week on earnings that "the team is moving forward rapidly on all marketing sales and medical affairs plans in anticipation of approval in late November" of this year. (See *BioWorld Today*, Jan. 9, 2014.)

"While there have been several new delivery systems and different formulation of sumatriptan launched in recent years, [key opinion leaders (KOLs)] view AVP-825 as different, given that it potentially offers rapid relief with a lower dose of medication resulting in a good tolerability profile," Palekar said, adding that the KOLs were impressed by the data from a study comparing the treatment with oral sumatriptan, a drug in the most commonly prescribed migraine class, triptans. That grouping includes sumatriptan (Imitrex, Glaxosmithkline plc), rizatriptan (Maxalt, Merck & Co. Inc.), zolmitriptan (Zomig, IPR Pharmaceuticals Inc.) and others.

Avanir's Palekar said the company was "encouraged [by the

KOL] feedback and we feel it supports our peak year sales estimate of between $150 million to $200 million."

With regard to new drugs, though, the migraine space has had its difficulties. About a month ago, the FDA smacked Irvine, Calif.-based Allergan Inc. with the firm's third complete response letter regarding Semprana (dihydroergotamine), the orally inhaled acute migraine candidate formerly called Levadex, which was the motive for Allergan's its $958 million acquisition of MAP Pharmaceuticals Inc., of Mountain View, Calif. (See *BioWorld Today*, Jan. 24, 2013, and July 1, 2014.)

"I don't think we understood the biology of migraine very well" until recently, Schatzman said. "The drugs we have used to date have been repurposed drugs that were approved for other uses. They seemed to have some kind of marginal benefit so we used them."

Business officer Litton said Alder "can [commercialize ALD403] ourselves in the U.S., but we've been in numerous discussions with people about finding a really good partner to help us with the rest of the world." Meanwhile, the company is mulling market penetration for an antibody in migraine.

"It's very similar to the PCSK9 story," Litton told *BioWorld Today*. "You're bringing an antibody to a marketplace that isn't used to antibody therapeutics.

One of the things we're watching is how Amgen and Sanofi deal with PCSK9 and that strategy." To market a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor for high cholesterol, Amgen with evolocumab is racing with Regeneron Pharmaceuticals Inc. and Paris-based Sanofi SA, partnered on alirocumab. (See *BioWorld Today*, July 30, 2014.)

Alder's stock (NASDAQ:ALDR) closed Wednesday at $15.22, down 44 cents. //