

BIOTECHNOLOGY

Omthera Pharmaceuticals

Betting a “free” form of omega-3 will prove best

Like many other start-up companies these days, Omthera Pharmaceuticals Inc. aims to develop a slightly different and potentially better form of an existing product recognized as both safe and medically beneficial. In this case, the avatar is omega-3 fatty acid and, specifically, Lovaza, as yet the only prescription formulation of the substance found in warm and cold water fish oils. The US Food and Drug Administration approved the drug in 2005 as a treatment for reducing very high blood levels of triglycerides (<500 mg/dL). Then sold as Omacor by Reliant Pharmaceuticals, the drug drove GlaxoSmithKline PLC's acquisition of the smaller company in November 2007 for \$1.65 billion, in which it received US-only rights.

Lovaza currently generates about \$0.9 billion in annual sales for GSK, and sales are increasing rapidly. The success of this relatively simple, low-risk product has inspired companies besides Omthera to develop various forms of omega-3 fatty acid for disorders affecting large numbers of people. An Irish public company with offices in Mystic, CT, Amarin Corp. PLC is closest to market, with an ongoing Phase III clinical trial testing its ethyl ester of eicosapentaenoic acid (ethyl-EPA). Amarin believes its “ultra-pure” omega-3 form will be better than Lovaza in cardiovascular disorders. Meanwhile, Catabasis Pharmaceuticals Inc. believes that linking its own preferred form of omega-3 fatty acid (also an ethyl ester) to salicylate will yield a synergistic effect beneficial to treatment of diabetes and other disorders with inflammation as an underlying cause. Catabasis aims to begin clinical testing in humans in the latter half of 2011.

For its part, Omthera is convinced that its so-called free fatty acid form of omega-3 will prove superior to other companies' ethyl ester versions at reducing blood triglyceride levels. An ethyl ester is a free fatty acid with an ethanol bond on it; that bond is broken in the intestines by pancreatic lipase, an enzyme specialized in breaking down fat. In Omthera's version of omega-3 fatty acid, that bond is broken already. The company is betting that the difference will allow the free form to more effectively reduce blood triglyceride levels. Omthera calls its drug candidate Epanova, a name likely chosen to highlight the fact that the form contains 55% EPA and 20% of the omega-3 fatty acid form known as DHA. Lovaza contains approximately 46% EPA and 38% DHA, while Amarin's AMR101 is 96% EPA.

Omthera disclosed the results of its ECLIPSE (Epanova Compared to Lovaza In a Pharmacokinetic Single-dose Evaluation) trial on January 7, 2011. Company co-founder and chief medical officer Michael Davidson, MD, stated that the trial found that Epanova demonstrated a 13-fold increase in bioavailability of EPA over Lovaza in people following the kind of low-fat diet generally prescribed for cardiovascular patients. If the attribute bears out through Phase III clinical trials, he says the drug might achieve a similar effect to Lovaza at a lower dose and a more consistent and predictable absorption profile than the ethyl ester prescription omega-3s.

Lower pill burden could permit marketing of Epanova at a lower cost than Lovaza, Davidson believes, noting that Omthera intends to develop a starting dose of Epanova at 2 grams, in expectation that it would

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Business: Omega-3 fatty acid for very high triglycerides

Founded: December 2008

Founders: Jerry Wisler; Michael Davidson, MD

Employees: 6

Financing to Date: \$9 million

Investor: Sofinnova Partners

Board of Directors: George Horner, Chairman; Graziano Seghezzi (Sofinnova Partners); Jerry Wisler

Scientific Advisory Board: Daniel Rader, MD (University of Pennsylvania School of Medicine); Christie M. Ballantyne, MD (Baylor College of Medicine); William Harris, PhD (Director of the Cardiovascular Health Research Center, Sanford School of Medicine, University of South Dakota); John Kastelein, MD, PhD (University of Amsterdam); Kevin Maki, PhD (Provident Clinical Research & Consulting)

likely equal the function of a 4-gram dose of Lovaza. Doctors seeking tighter control over patients' triglyceride levels could simply titrate up the dosing, “as they are already comfortable doing,” he says.

Omthera obtained worldwide rights to Epanova from Tillotts Pharma AG, a private Swiss drug company acquired in September 2009 by the Japanese company Zeria Pharmaceutical Co. Ltd. Tillotts had sought to develop Epanova for Crohn's disease as a complement to the approved therapy Asacol (mesalamine), to which it had European marketing rights. Knowing that the natural form of omega-3 fatty acid had been reported as beneficial to individuals with gastrointestinal disorders, Tillotts' execs set out to develop a free fatty acid form that might be shown even more beneficial to Crohn's patients, who by the

nature of that disease have difficulty absorbing dietary nutrients. Unfortunately, Tillotts' two Phase III trials of Epanova, of 52- and 58-week duration, both failed to meet the clinical endpoints set for Crohn's disease. The costly failures put the asset and the company itself in play.

Davidson was intrigued by the data indicating the free fatty acid was better absorbed than the native form found in fish oils, especially in people on a low-fat diet, and he alerted Jerry Wisler to the opportunity at Tillotts. Having served as a VP of marketing at both Merck & Co. Inc. (where he oversaw products including the cholesterol-lowering blockbuster *Zocor* [simvastatin]) and Novartis AG (where *Diovan* [valsartan], *Lotrel* [amlodipine/benazepril], and *Starlix* [nateglinide] were among his responsibilities), Wisler was keen to take a crack at developing and marketing Epanova. He and Davidson co-founded Omthera in December 2008. Wisler was previously the founding CEO of Aegerion Pharmaceuticals Inc.

"Tillotts did great development work," Wisler asserts, noting that the Swiss company's tenacity in overcoming obstacles helped make Epanova a drug candidate capable of attracting investment even in a gloomy economy. The free fatty acid form of omega-3 fatty acid is more volatile than the ethyl ester form other companies have chosen to develop, he says, and so caused some GI disturbance in early drug trials. Tillotts conquered that problem, Wisler points out, by developing a capsule and enteric coating formulation that ferries the compound into the lower gastrointestinal tract, instead of the stomach, before the capsule is broken down. "That innovation means the compound causes much less fishy burping than is common with the natural product and potentially even with Lovaza," Wisler declares. He says Tillotts also overcame some manufacturing issues that previously made manufacturing the free fatty acid form of omega-3 fatty acid "much trickier" than producing an ethyl ester form.

Omthera aims to begin Phase III clinical testing of Epanova as a treatment for hypertriglyceridemia at some point in 2011, so that it can submit data in support of a marketing petition to FDA during the first half of 2012. Because the FDA has already approved one version of omega-3 fatty acid

for this indication and ushered others into late-phase testing, the regulatory pathway is well established. Omthera has already received permission to go ahead with a 12-week Phase III trial involving 330 patients. The company also plans to conduct a supportive trial of the drug candidate in combination with a statin. That trial would be open to a broader group of people with triglyceride (TG) levels between 200 and 500 mg/dL. Statins are the most frequently prescribed form of cholesterol-lowering medications.

There is no exact target for TG levels, Davidson acknowledges, but he says "over 150 is considered to be high" by the American Diabetes Association and others. He notes that primary care physicians as well as heart specialists "look at TG and target high levels for treatment." In the US, he says the estimate is that some five million people have TG levels over 500 mg/dL, and that the condition is known to put people at risk for pancreatitis. In the US, 35 to 50 million people are presently thought to have blood TG levels over 200 mg/dL. That is the kind of market size that can give rise to blockbuster drugs. Omthera clearly has that idea in mind: "We want to be the add-on therapy for statins, to continue to reduce risk for patients," Wisler asserts.

Blood chemistry testing, so vital to the success of cholesterol-lowering drugs, could one day also boost prescriptions of Omthera's drug candidate. Several companies sell kits to enable testing of omega-3 fatty acid levels, including an outfit founded by Omthera scientific advisory board member William S. Harris. OmegaQuant Analytics, a subsidiary of Omega Biostatus LLC, of which Harris is the president and CEO, produces The HS-Omega-3 Index. "This is the kind of biomarker we could use to show you can modify risk with treatment," Davidson declares. Wisler says Omthera has not yet used OmegaQuant's test, but is considering a study where it would be used to compare Epanova's effect on blood chemistry with that of Lovaza. "It may become part of our development program, a nice thing to have access to," he says.

Although omega-3 blood levels are not yet established as a biomarker relevant to disease, data suggesting improved levels could ultimately help marketing efforts

if Omthera's candidate is approved for sale. Wisler clearly knows how to leverage such data. He says he well remembers when **Pfizer Inc.**'s *Lipitor* (atorvastatin) launched and overtook his own company's former market-leading drug *Zocor* within 12 months. "They had some advantages they capitalized on, not even as significant as we believe we have with Epanova," he declares, explaining, "They had greater efficacy at the top dose, a little advantage in the packaging label, and they did a good job in targeting physicians."

If Epanova's Phase III trial is successful, Big Pharmas are likely to be interested in in-licensing, Wisler asserts. But as he sees it, Omthera may not need a larger pharma partner to succeed in the huge cardiovascular market. More recent evidence specific to omega-3 fatty acids bodes well for Omthera, he says, and the prescription trend line for Lovaza did not change much when ownership of the drug shifted to GSK from much-smaller Reliant. Consequently, "I think we can reach doctors in a targeted way, with a specialty sales force," he declares.

In the near term, Omthera needs to attract more financing to support a Phase III trial, which Davidson reckons can be completed for around \$25 million. Like many start-ups these days, the company is running lean – bringing few individuals on staff and making sure that independent consultants have absolutely pertinent experience. A few members of the clinical team worked at Reliant on Lovaza, whereas Omthera's consulting network includes people who formerly worked at FDA advising on preclinical and clinical development, plus a former senior regulatory expert from Merck.

The seasoned guidance of lead investor Graziano Seghezzi of Sofinnova Partners is likewise benefiting Omthera, Wisler asserts: "There has never been any pressure on us to partner early on. Graziano tells us, 'Invest the money in the appropriate clinical programs. If the product is as good as we think it is, all else will go well.'"

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— DEBORAH ERICKSON