BIOWORLD™ TODAY
THE DAILY BIOPHARMACEUTICAL NEWS SOURCE
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NOVEMBER 19, 2015
VOLUME 26, NO. 222
SPECIAL REPRINT

Pledpharma keeps steady development pace, plots partnering

By Marie Powers, News Editor

Although it was founded in 2006, the roots of Swedish biotech Pledpharma AB go back almost 20 years earlier, to the discovery of a class of compounds known as pyridoxyl ethyldiamine, or "PLED," derivatives, which were discovered in the U.S. in the late 1980s by Salutar Inc. and used as MRI contrast agents.

During its development as a clinical diagnostic, investigators discovered that the PLED derivative mangafodipir, if injected too rapidly, caused patients to blush. Initially, the effect was viewed as detrimental to use as a clinical diagnostic. Upon further study, Pledpharma co-founder Jan Olof Karlsson, then a senior research scientist at Nycomed Imaging AS, in Oslo, Norway, realized the blushing effect was, instead, due to compound's mimicry of superoxide dismutase (SOD) – one of the body's most important antioxidant enzymes.

"The fact that we have a low-molecular enzyme mimetic against oxidative stress is one of our unique features," Pledpharma CEO Jacques Näsström told *BioWorld Today*. "This enzyme is central in all of our cells, and its function is to take care of free radicals."

Abundance of free radicals, of course, can lead to any number of problems, including nerve damage during chemotherapy, acute liver failure and reperfusion injuries. Although pharmas had long examined the SOD enzyme as a druggable target, "this compound was discovered by serendipity and shown to be safe and well-tolerated," Näsström said.

But proving efficacy would take a few more years. At the time of Karlsson's discovery, Pledpharma's co-founders were scattered across a handful of business and academic entities. Karlsson and Rob Towart were in separate Nycomed units. Per Jynge was a researcher at Trondheim University. Torsten Almén was at the University of Lund, Sweden, while Ingemar Lundström was at Sweden's Linköping University, Heidi Brurok was at Norwegian University of Science and Technology and Nobel Prize winner Louis Ignarro was at the University of California Los Angeles.

Rights to the underlying technology also changed hands several times before Karlsson and colleagues were able to license the original patents and form Pledpharma.

The Stockholm-based company made "small but ingenious chemical modifications" in the parent compound – which had been safely used as a diagnostic on some 240,000 patients – to extend its intellectual property (IP) protection on therapeutic use of PLED-derivatives from four in-licensed patents, according to Näsström.

"We recently presented phase IIb data, yet we still have patent protection for almost 20 more years," he said. In fact, the U.S. Patent and Trademark Office recently issued a notice of allowance for the key compound patent for calmangafodipir, which Näsström called "the centerpiece of our broad patent portfolio," extending its term through December 2032.

'WE'RE QUITE OPEN WHEN IT COMES TO BUSINESS MODELS'

Näsström took the reins of Pledpharma in 2010 as its first full-time CEO. A year later, the company listed on the Nasdaq OMX First North, where it continues to trade as PLED.ST.

Pledpharma has three candidates based on PLED substances. Earlier this year, the company reported that lead compound Pledox (calmangafodipir), dosed in combination with FOLFOX in patients with metastatic colorectal cancer, outperformed placebo plus FOLFOX in the global phase IIb PLIANT study.

The study enrolled 173 patients, and top-line data – confirmed in subsequent analyses – showed a clinically relevant reduction in the incidence of sensory nerve damage of 43 percent for patients treated with Pledox compared to placebo, without affecting the anti-cancer activity of the FOLFOX regimen. Symptoms of neuropathy also occurred later and were of shorter duration in patients treated with Pledox.

"This was the first time, to our knowledge, that someone has shown that you can actually prevent chemotherapy-induced neuropathy without interfering with the cancer therapy," Näsström said.

The findings prompted Pledpharma to step up partnering efforts and begin discussing the design of a pivotal program with the FDA.

"That is our business strategy," Näsström explained. "We are running clinical programs up to phase IIb and then looking for a partner for continued development."

The company also has Aladote in preclinical testing to treat acute acetaminophen poisoning and prevent liver damage – the not infrequent consequence of suicide attempts, Näsström pointed out – and has preparations underway for a phase II study. The third asset, PP-099, is designed to prevent reperfusion injury in acute myocardial infarction patients undergoing angioplasty. In 2013, Pledpharma completed a phase IIa study in 20 patients showing that PP-099 was well tolerated without side effects. In patients who received the compound, MRI showed a tendency of smaller infarcts (26 percent vs. 32 percent for the placebo group) and improved cardiac pump function (48 percent vs. 42 percent for the placebo group), according to Cortellis Clinical Trials Intelligence.

For the time being, however, Pledpharma is mainly focused on Pledox, which it estimates could achieve peak sales of $1 billion as a standard pre-treatment for traditional chemotherapy regimens in colorectal, breast, lung and other cancers. At a recent health care seminar in Stockholm sponsored by Pareto Securities, the CEO told analysts and investors that the company made a conscious decision to refrain from negotiating terms ahead of phase IIb results and an end-of-phase II meeting with the FDA.

In an update last week following disclosure of Pledpharma's third quarter financials, Redeye AB analyst Klas Palin wrote that "all eyes are now completely focused" on the FDA meeting, "which is expected to clarify the authority's view of the documentation and provide a recommendation regarding which studies are needed to achieve registration of Pledox in the US. With this in hand, discussions with partners can commence in earnest, and we expect this will considerably increase the temperature of the stock market with regard to the company."

Although Pledpharma is open to partnering, "our preferred strategy is to hand this off completely to a pharma," Näsström said. Pledpharma has remained virtual since its inception, with just four employees and a low burn rate. All told, the company has raised approximately SEK 240 million (US$28.8 million). For the quarter ending Sept. 30, the company reported cash and equivalents of approximately SEK 59.3 million, which Näsström judged sufficient to partner the programs, given that research costs related to PLIANT are decreasing.

"We don't have any fixed assets, so it could be attractive for a partner to acquire the whole company and all programs," he added. "We're quite open when it comes to business models."