Appetite suppressor? Atox flesh-eating bug phase III dials down immune reply

By Randy Osborne

Staff Writer

To wipe out the varied flesh-eating bacteria that cause what are scientifically known as necrotizing soft tissue infections (NSTIs) is "not the main objective of treatment" in the phase III trial with the world's first-ever drug candidate, Dan Teleman, CEO of Atox Bio Inc., told *BioWorld Today*. "Obviously, we do want to eradicate the bacteria – that's one of the goals – but the major issue in these infections is the immune response that those bacteria trigger at the local and systemic levels," he said. "Although "the bacteria will eventually be killed with antibiotics, it usually takes a few days, and with this type of infection, the patient doesn't really have a few days," he said.

Enter AB103, a rationally designed short peptide that modulates the inflammatory response by binding to the CD28 dimer interface. Ness Ziona, Israel-based Atox has just launched the phase III study called ACCUTE, a rough acronym for "AB103 Clinical Composite endpoint StUdy in necrotizing soft Tissue InfEctions." Conducted at 40 centers in the U.S., the experiment will enroll 290 patients given round-the-clock support and treatment. Data should be available by the end of 2017.

Caused by bacteria such as streptococcus, staphylococcus and others that enter the body via a minor cut, surgery, insect bite or other route, NSTIs quickly spread to the layer of connective tissue below the skin, destroying it and potentially leading to multiple organ dysfunctions.

"If you look at different types of infections, this one is probably one of the smaller ones in terms of patient numbers," Teleman said, as compared to skin infections, pneumonia and urinary tract infections. Although rare, with about 29,000 patients per year in the U.S. at the upper estimate range, NSTIs are virulent, proving fatal in as many as 20 percent of cases. Atox is the first player in the niche because "most big pharma companies have gotten out of the infectious disease space pretty much altogether," he said, although some are "slowly getting back into" it. Those with programs are typically "mid-tier pharma or biotech companies focusing [their] development on traditional antibacterials, which do one thing and one thing well, which is kill the bacteria," he said. AB103 is designed to make the immune system back off just enough to protect tissues while the antibiotics do their work. (See *BioWorld Today*, July 8, 2013.)

"There are a lot of areas where acute inflammation plays a key role," Teleman said. "We, as a company, are focusing on this interface between infectious diseases and critical-care illnesses. We're thinking about going into acute kidney injury as a result of severe intra-abdominal infections," which offers "a very similar pathophysiology" to NSTIs and similar treatment approaches, involving surgical intervention plus antibiotics, he said.

Down the road, Teleman said, AB103 might be tried in sepsis, one of biopharma's top bêtes noires. "Sepsis is pie-in-the-sky," he said. "This is how we look at it." Attempts to come up with effective therapies for the deadly condition have been "not very successful, to say the least," he noted. The only drug to win approval for sepsis was Xigris (drotrecogin alfa), given the FDA's nod in November 2001 but yanked from the market in 2011 by Indianapolis-based Eli Lilly and Co., after a study showed the recombinant form activated protein C worked no better than placebo. Xigris had taken lumps from an advisory panel but U.S. regulators cleared it anyway. (See *BioWorld Today*, Oct. 17, 2001.)

"We think about sepsis all the time," Teleman said. The patient population is made up of "a very

heterogeneous group," often older people with assorted co-morbidities, their sepsis caused by hard-to-figure originating trouble, he said. "Sepsis essentially is a syndrome," and brings "various time points" at which it's correctly diagnosed, a challenge made worse by the fact that the approval endpoint is all-cause mortality at 28 days, he said, a high bar that "usually requires [trials with] a very large number of patients, hundreds and even thousands." Though the disease is "something we would aspire to" and may eventually try, "our strategy is to take a more step-wise approach" meanwhile and begin with NSTIs, where "we can identify the patients early," he said. "They don't linger at home a long period of time. Usually they have very clear symptoms. They get into the hospital and go to the operating room very quickly."

Spun out from the Hebrew University of Jerusalem, Atox was co-founded in 2003 by molecular biologist Raymond Kaempfer, who serves as the company's chief scientific officer, and colleague Gila Arad. The two worked to identify the mechanism of action for toxins secreted by virulent bacteria that were involved in the pathogenesis of NSTI and other severe infections, such as toxic shock. Because such toxins could be used as biological weapons, the scientists' findings drew interest from the U.S. Army, the Defense Advanced Research Projects Agency and the National Institutes of Health. Atox, which raised $23 million last summer, is fully funded through the phase III trial with AB103, which has orphan-drug and fast-track status from the FDA. Asked about marketing and partnerships, Teleman said the company is "leaving all those options open. The focus is on getting the phase III done and done appropriately – get good results and get it approved."