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I.V. and oral in the works

Cream of the clotbusters? Exithera 'teas' off at AHA with strong phase I data

By Randy Osborne, Staff Writer

Exithera Pharmaceuticals Inc. CEO Neil Hayward told *BioWorld* he's hoping to build a "continuum of care" around factor XIa inhibitor EP-7041, after phase I data showed the intravenous (I.V.) version of the antithrombotic safe and well-tolerated in healthy volunteers after single or multiple ascending intravenous doses – and even turned up some clues to efficacy.

"In the background, we've got an oral program that we're pounding as hard as we can, because we would like to have an I.V. and an oral," Hayward said. "In the hospital, [EP-7041] would be the procedural anticoagulant of choice, and then you would be put on our oral [version] as you go home."

CEO Neil Hayward

Describing the oral lineup, he "called them the Magnificent Seven, but I've cut it down to the Three Musketeers. We're finishing key studies at the moment. If all goes well, I expect to nominate the development candidate for the oral in about three months or less."

The phase I experiment showed that parenteral administration of EP-7041 resulted in a rapid, predictable increase in activated partial thromboplastin time (aPTT), a standard clinical measure of anticoagulation activity, without affecting partial thromboplastin (PT), indicating no unwanted/unintended effect on the extrinsic pathway, the company said. Circulating levels of the drug were rapidly achieved and quickly decreased when dosing stopped, with no bleeding observed or reported. The pharmacokinetic and pharmacodynamics profile make EP-7041 potentially ideal in acute-care hospital settings where patients are at risk of thromboembolic events.

Westborough, Mass.-based Exithera's results at the American Heart Association (AHA) Scientific Sessions in Anaheim, Calif., constituted "a bit of a coming-out party," Hayward said, noting the firm's virtual model. "I'm the only full-time employee."

The company was formed in August 2012, based on work started 15 years ago by Hayward and his team at Cambridge, Mass.-based Daiamed LLC. Daiamed's Japanese funder, Daiichi Pharmaceutical Co. Ltd., merged with Sankyo Co. Ltd., and "Sankyo laid us all off – they laid off America," he said, speaking from the AHA meeting. "We all lost our jobs." Researchers "basically had all these lead compounds that needed modifying. I felt strongly that within 50 compounds, we probably would have a development candidate."

EP-7041, as its name indicates, was the forty-first, so the goal was reached "a little bit quicker than I thought," he said.

At the time his work began, "there wasn't a ton of interest in factor XI, but we felt it could be a pretty sexy target," Hayward said. "We knew, everybody knew, that with new agents there's still a bleeding risk, and it's significant, so much so that you need a reversal agent," i.e., a direct-acting oral anticoagulant, or DOAC, such as the one "Portola is struggling to get through the FDA, but they'll get it through."

South San Francisco-based Portola Pharmaceuticals Inc. has factor Xa inhibitor antidote Andexxa (andexanet alfa) under review by U.S. regulators, and the compound's history includes a complete response letter. (See *BioWorld Today*, Feb. 6, 2017.)

"Our docs have been scared" by anticoagulants in general, Hayward said. "The poor docs see these patients come in and actually die in front of them. They can't do anything. The Holy Grail would be an antithrombotic without any bleeding risk," which EP-7041 may be. Sixty volunteers have so far taken the "very well-behaved small molecule" with no indication of bleeding.

EP-7041 could be useful in many settings, including cardiac operations. "They've got the patient on heparin, and when they go to close the chest, they sometimes have to give a reversal agent," which adds a lot of time to the procedure. "Clots, or a stroke, is an act of God, but bleeding is a mistake by the medic," he said. "That's how it's perceived, so the medic is very nervous to up the dose of the anticoagulant he's using."

'Do I think people are ahead of me? Maybe'

By pursuing factor XI so early, Exithera stole a march on big pharma, which was "focused on developing their factor Xs and thrombins to compete with the rat poison," Hayward said, referring to the first use of the active ingredient in the anticoagulant Coumadin (warfarin, Bristol-Myers Squibb Co.). Their efforts made sense, he conceded, likening the push to research by himself in gastric acid secretion at London-based Glaxosmithkline plc, and by others. "Everybody went for the proton pump inhibitor, the pivotal point in enzyme secretion in the stomach," he said, because they knew efficacy could be achieved.

Unlike factor X and thrombin, factor XI is "a bit in the corner of

the pathway. My concern [was], will it have enough potency?"

The answer so far seems to be yes. "We're designing the proof-of-concept study," Hayward said. "We could do total knee replacement, or we could go into a patient population that really has an unmet need, and since the bleeding rates are so high in these targets, the trials would be comparatively small. That's the debate we're going through at the moment."

With EP-7041, the firm "can go for an arena that's been contraindicated for these factor Xs and thrombins. We can go for anything where blood touches an artificial surface. These people can only get heparin and Coumadin." EP-7041 could prove useful with mechanical heart valves; extracorporeal membrane oxygenation, or ECMO, machines; and left ventricular assist devices, or LVADs. "We want to build a franchise on the indications that are unique to factor XI," he said.

"My investors are excited and willing to put more money into the company," Hayward said, but he's talking to big pharma and big biotech about partnerships as well. "Do we do it on our own or share some of this? We don't want to do a proof-of-concept study that's not going to blow away everybody, and the last thing I want is someone turning to me and saying, 'Nice study, Neil, but why didn't you do this?'"

Nowadays, Hayward said, most of the larger companies are looking into factor XI. In 2015, Isis Pharmaceuticals Inc. (which has since changed its name to Ionis Pharmaceuticals Inc.), of Carlsbad, Calif., signed a potential $155 million-plus deal with Berlin-based Bayer AG unit Bayer Healthcare for an alliance based on the antisense oligonucleotide ISIS-FXIrx, a factor XI inhibitor, following a phase II trial in patients with compromised kidney function. Beyond that, Ionis is eligible for milestone payments plus tiered royalties in the low to high 20 percent range. "The problem with the antisense is that you have to have multiple subcutaneous injections for about a month," Hayward said, adding that "there are safety concerns with these oligos." (See *BioWorld Today*, May 5, 2015.)

New York-based Pfizer Inc. has published its work with a factor XI antibody, Hayward noted. "Do I think people are ahead of me? Maybe," he said. "But we've got a lot of knowledge, and we had a lot of knowledge before anybody else did." ♦