

BioCentury

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PRODUCT DEVELOPMENT

ADAPTING FOR SPEED

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The streamlined design of a Phase II study [AM-Pharma B.V.](#) started last week, combined with the smaller safety database required, should make up for time spent going back to the drawing board with a recombinant version of its alkaline phosphatase product.

The trial combines the dose-finding components of a Phase IIa and the efficacy components of a Phase IIb trial into a single study. It will enroll 290 patients to evaluate the use of iv recombinant alkaline phosphatase (recAP) to treat sepsis-associated acute kidney injury (AKI). According to CEO Erik van den Berg, the trial will be the largest ever conducted in AKI. The company expects data in 2H16, at which point it will seek a partner.

It has been a long road for the biotech to reach this point. The company began developing a bovine-derived AP in 2002. In 2010 the company reported that in a Phase II study, the bovine enzyme significantly improved renal function as measured by creatine clearance, serum creatine and dialysis requirement at day 28 vs. placebo ($p=0.005$).

Despite compelling efficacy and the lack of any safety concerns in that study, the company concluded a recombinant human product was necessary. "In our interactions with regulators we noticed that they were much more comfortable with a recombinant production process," van den Berg told BioCentury.

In addition, from a commercial perspective, the recombinant manufacturing process has a much lower cost of goods and more easily meets industry standards for quality.

Still, van den Berg said the company's choice to start over in preclinical development with a human version of AP did not add much to the development timeline, given that the bovine product would require a significantly larger safety database. "The overall impact would probably not be too much with respect to timelines and money," he said.

In 2011, AM-Pharma's investors ponied up €29.2 million (\$41.1 million) in a series D round with the express aim of bringing recAP through Phase II testing for AKI.

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ERIK VAN DEN BERG, AM-PHARMA

ADAPTIVE DESIGN

The first stage of the trial is for dose-finding and will enroll four 30-patient cohorts, three of which will receive different doses of IV recAP, and one of which will receive placebo.

A blinded interim analysis slated for mid-year will analyze data on the primary endpoint of creatinine clearance rate and secondary endpoints including duration of dialysis over 28 days and estimated glomerular filtration rate (eGFR), a measure of chronic kidney disease.

Stage two will enroll 170 more patients — two cohorts of 85 patients each — to receive either the best dose from stage one or placebo.

van den Berg said the design should shave more than a year off the timeline for recAP compared to doing separate Phase IIa and Phase IIb trials. "The aim of the adaptive design is of course to fast track your development," he said. "It is certainly faster and cheaper."

He added that although the company and investigators will be blinded to the dose selected for stage two of the trial, data from the patients receiving the best dose in stage one can be used in the final statistical analysis plan. "So there is also a savings in terms of the number of patients you would need to enroll. If you did two separate studies, the number of patients would be larger," he said.

Last September the company raised an additional €12.2 million (\$15.8 million) in a series E round for the main

purpose of adding an additional dose cohort to the trial, which van den Berg said would both improve the power of the trial and provide sufficient data to establish a good understanding of the dose-response curve for recAP.

van den Berg said there is the potential for regulators to accept the trial as a pivotal study, although he said this likely would not be known until the company holds end-of-Phase II meetings.

ADDING VALUE

Although AM-Pharma's primary focus is conducting the Phase II trial for recAP, part of the cash from the series E round has been used to start preclinical development of an oral formulation of recAP for ulcerative colitis (UC).


AM-Pharma already has Phase II data for an oral, bovine-derived product in UC. Completed in 2007, the uncontrolled Phase IIa trial in 21 patients met the primary endpoints with a response rate of 63% on the Truelove-Witts score, which measures disease severity, and 47% on the Mayo score, which measures clinical and endoscopic aspects of disease activity. Four patients (19%) achieved clinical remission on the Mayo score after 21 days, a secondary endpoint.

The data hint at a competitive profile for AP in UC. For instance, last October [Receptos Inc.](#) reported data from the Phase II TOUCHSTONE trial of RPC1063 that showed the oral selective sphingosine-1-phosphate receptor 1 (S1PR1; S1P1; EDG1) modulator met the primary endpoint of improving the proportion of patients in clinical remission as defined by Mayo score at week 8 vs. placebo (16.4% vs. 6.2%, $p < 0.05$). RPC1063 also met the secondary endpoint of clinical response defined by Mayo score at week 8 (58.2% vs. 36.9%, $p < 0.05$).

Like other oral GI therapeutics in development, van den Berg said the argument for developing recAP in UC is that it should provide similar efficacy to biologics like TNF-alpha inhibitors, but with a much better safety profile because there is little to no systemic exposure.

UC patients have reduced expression of intestinal alkaline phosphatase, which results in a decreased capability to "detoxify the vast amounts of LPS that are present from the Gram-negative bacteria in the gut," van den Berg said. AP acts as a barrier protein to prevent overstimulation of the immune system and the resulting inflammation of the epithelial layer of the gut, he added.

In December, AM-Pharma also reported preclinical data for IV recAP in the ultra-Orphan disease hypophosphatasia (HPP), a genetic mineralization disorder caused by a mutation in the gene encoding AP. In a mouse model of severe HPP, treatment with recAP led to a normal lifespan and body weight for mice, whereas untreated control mice died after 20 days. There was also evidence of improved mineralization in bone.

AM-Pharma is a ways behind [Alexion Pharmaceuticals Inc.](#) in HPP. Alexion's asfotase alfa is under review for the indication in the U.S., Europe and Japan. Alexion gained the fusion protein incorporating the catalytic domain of human tissue non-specific alkaline phosphatase (TNSALP; ALPL) and a bone-targeting peptide in 2012 through its acquisition of [Enobia Pharma Inc.](#) for \$610 million up front and \$470 million in milestones. 

COMPANIES AND INSTITUTIONS MENTIONED

[Alexion Pharmaceuticals Inc.](#) (NASDAQ:ALXN), Cheshire, Conn.

[AM-Pharma B.V.](#), Bunnik, the Netherlands

[Receptos Inc.](#) (NASDAQ:RCPT), San Diego, Calif.

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