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Article Reprint • Page 1 of 2

Product Development

Mineralizing success

By Michael Flanagan
Senior Writer

Enobia Pharma Inc. is seeking to improve on an earlier attempt to develop an enzyme replacement therapy for hypophosphatasia by using a fusion protein that combines the missing enzyme with a bone-targeting polyacidic sequence. Early results from a pair of studies of its ENB-0040 suggest that both infants and adults benefit from the treatment, and now the company plans to conduct additional Phase II trials this summer before entering pivotal testing.

In addition to determining the size and shape of its next study, the company eventually will have to decide between making itself a takeout target for one of the established players in the ERT space or going at it alone. The latter is a possibility given the limited marketing infrastructure required for targeting a world-wide population of little more than 2,000 patients.

Hypophosphatasia is an ultra-orphan disease in which a loss-of-function mutation results in defective TNSALP (tissue non-specific alkaline phosphatase), an enzyme that is responsible for mineralizing bone. The clinical presentation of the disease can range from stillbirth or early death to respiratory problems, motor deficits and increased fractures depending upon the age of onset. Earlier expression almost always correlated with a higher degree of morbidities and mortality.

In the 1980s, Michael Whyte, a professor of medicine at the **Washington University School of Medicine** who now consults to Enobia, attempted to make an ERT for hypophosphatasia using naked TNSALP. But not enough of the

enzyme made it to the bone where it was most needed.

Philippe Crine, VP of research and CSO, said Enobia believes it has found a way to address this problem by attaching TNSALP to a polyaspartic acid peptide sequence that has a high affinity for hydroxyapatite, an inorganic component of hard tissues such as bone. In between the catalytic domain of TNSALP and the bone-targeting polyacidic sequence, the company introduced the Fc region of IgG1, which Crine said increased the agent's half-life and makes purification during the manufacturing process much simpler.

"We have done *in vitro* studies taking ENB-0040 and comparing it with natural TNSALP and have shown that our compound binds 32-fold more potently to bone compared with the natural enzyme," said Hal Landy, VP of medical affairs and CMO.

The company evaluated the safety and activity of ENB-0040 in a knockout mouse model developed at the **Burnham Insti-**

tute for Medical Research that mimics the severe form of hypophosphatasia most often seen in infants.

"These animals are born with the bone demineralization and profound rickets that characterize the disease, which will eventually lead to death within a matter of weeks," said Landy. "We found that ENB-0040 administered subcutaneously successfully corrected the phenotype and significantly improved survival."

Based on these data, Enobia ran a Phase I trial in four adult patients and reported ENB-0040 had good bioavailability and achieved target serum levels. It then ran a Phase I/II trial in six infants with severe hypophosphatasia. Both open-label studies

See next page

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Hal Landy, Enobia Pharma

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Product Development,
from previous page

were designed to evaluate an initial IV infusion of ENB-0040 followed by repeated doses of subcutaneous ENB-0040.

Earlier this month, Enobia presented data from the studies at The Endocrine Society meeting in Washington, D.C.

“There were no drug-related adverse events. The subcutaneous product was well tolerated,” said Landy. “There were a couple of mild to moderate infusion site reactions from the IV infusion though, importantly, no patients developed antibodies” against ENB-0040.

One mother withdrew consent after her infant had an infusion reaction, but he said the attending physician described it as “moderate” in nature.

After 12 weeks of thrice-weekly dosing, according to Landy, several of the infants have shown marked respiratory and functional improvement, with radiographic evidence of mineralization at the metaphysis (the wide section at the end of a long bone).

“Based on short-term observations in a small group of infants, we are making tremendous progress in healing their rickets and at the same time seeing good evidence of growth and motor development,” he added.

Enobia plans to discuss the next phase of clinical development with global regulatory agencies after concluding the Phase II trial in infants this summer. It hopes to start the next study by year end.

Crine believes Enobia could use the same bone-targeting technology to deliver a variety of proteins, though he declined to provide any details as it is an endeavor the company has just begun to explore.

The company last raised money in September 2007 by way of a C\$40.1 million (\$38 million) series B round led by OrbiMed Advisors and CTI Life Sciences Fund, and plans to announce a series C round later this year, according to Julie Anne Smith, VP and chief commercial officer.

She declined to comment on the size of the C round, but said it will be designed to carry Enobia through the end of pivotal testing with ENB-0040.

Smith acknowledged that Enobia has received inquiries about ENB-0040 from potential partners and/or buyers, but she was coy about the company's plans.

“This is a rare opportunity because hypophosphatasia is a disease treated by specialty physicians who are relatively easy to target with a manageable sales infrastructure even for a company our size, and we have top tier investors willing to fund us through commercialization,” she said. “But at the same time, there has been tremendous interest in the program from companies in a position to partner or acquire the program.”

COMPANIES AND INSTITUTIONS MENTIONED

Burnham Institute for Medical Research, Santa Barbara, Calif.

Enobia Pharma Inc., Montreal, Quebec

Washington University School of Medicine, St. Louis, Mo.