**CASI's turnaround turns eastward; firm seeks to be Celgene of China**

By Shannon Ellis Staff Writer Friday, February 27, 2015

SHANGHAI – The evolving story of CASI Pharmaceuticals Inc. is about a Nasadaq-listed firm hoping for a fresh start as a China-focused oncology company without letting go of its American roots.

Back in 2012, with new investors on board, the U.S. biotech with more than 20 years history as Entremed Inc. changed its name to CASI (China America Strategy Integration) to highlight its focus eastward.

"Take everything you knew about Entremed and take that out of your mind," Cynthia Wu, chief operating officer of CASI, told BioWorld Today.

IDG Ventures became CASI's largest shareholder, the same folks that astutely invested in search engine Baidu (otherwise known as China's answer to Google) before it was cool. Predictably, IDG was keen to see CASI make a pivot to China. Other investors with board seats include Kleiner Perkins Caufield Byers China.

Headquartered in Rockville, Md., CASI has a wholly owned subsidiary and R&D operations in Beijing.

According to CASI CEO Ken K. Ren, the aspiration is that CASI will become the Celgene Corp. of China, much like Baidu has become the Google of China.

Ren tells the basic big-picture China story well: that China holds the promise of becoming the largest market for oncology products in the world and enables drug development at a lower cost. However, that promise, which has attracted companies to China like bees to honey, is no guarantee of success. For a small-cap company with seven products in development, the need to find a cost-effective, risk-mitigating strategy is great.

Moving past the China enthusiasms, it turns out CASI's approach is to shake things up with an opportunistic three-prong strategy that includes development of new drugs, a delivery platform for oncology drugs and partnering on late-stage or FDA-approved drugs for commercialization in China.

To bolster the pipeline, six months ago the company licensed the Greater China

rights to three drugs from Spectrum Pharmaceuticals Inc., two of which are FDA-approved oncology drugs – Zevalin (ibritumomab tiuxetan) used in the treatment of non-Hodgkin's lymphoma and Marqibo (vincristine sulfate lipsome injection) used in the treatment of acute lymphoblastic leukemia. Like other drugs that take the imported drug license path, they will have to go through human trials in China, though Zevalin may have a shortcut, allowing CASI to collect data during the 12-month wait period for getting clinical trial approval in China.

"Zavelin has been approved in Hong Kong, although the market is relatively small; it is important for our China strategy," Ren told BioWorld Today. "It will be the first time for the drug to collect data in a Chinese patient population.

"We intend to launch in the second quarter of this year," he added. "We intend to build up a China oncology network and establish relations between Hong Kong and China."

Marquibo, approved in the U.S. under an orphan indication for the rare type of leukemia that it treats, is a second-line treatment. According to Ren, it is expected to bring in peak sales of $50 million in China.

"For China, our current plan is to do two clinical trials while building a close relationship with oncologists in China," he said. "We are going to focus on science-based promotions and researchers."

**IN THE DEVELOPMENT PIPELINE**

CASI's lead candidate, ENMD-2076, is an orally active, Aurora A/angiogenic kinase inhibitor with multiple mechanisms of action, and multiple trials are ongoing in the U.S. and Canada with plans for three more in China.

ENMD-2076 was invented by well-respected immunologist Tak Mak, of the University of Toronto and Campbell Family Institute for Breast Cancer Research at the Princess Margaret Hospital, who holds a seat on CASI's board. The drug has gone through multiple phase I studies for solid tumor cancers, including ovarian, breast, liver, renal and sarcoma as well as leukemia and multiple myeloma.

A phase II trial in advanced ovarian cancer has been completed, while the company will continue to investigate the drug in triple-negative breast cancer (TNBC),

advanced/metastatic soft-tissue sarcoma and in advanced ovarian clear cell carcinomas in North America.

There are plans to expand those trials to China as part of global trials and they will be under U.S. investigational new drug application protocols. China has already granted trial approval for two indications, TNBC and sarcoma.

ENMD-2076 was inherited from Entremed's more cost-intensive drug development days, but Ren said CASI has developed a new nexus of relationships to develop the drug at a lower cost, with the support of institutes and government grants to run trials and by working with contract research organizations in a leaner manner. The plan also involves finding biomarkers for each indication and, once proof of concept is reached, partnering with other companies outside of China, while keeping the right to commercialize within China.

The drug might have applications in other types of cancer, too. After years of research, the most exciting development could be the recent finding that ENMD-2076 may be potentially efficacious for fibrolamellar carcinoma (FLC), a rare form of liver cancer.

According to Ren, ENMD-2076 showed remarkable results in one FLC patient who had continuously relapsed after multiple local chemotherapy treatments, treatment with Nexavar (sorafenib, Amgen Inc. and Bayer AG) and even liver transplantation. After 12 months on ENMD-2076, the tumor shrank by 50 percent and the patient had maintained stable disease at 15 months.

Earlier in February, CASI and the FDA came to an agreement on a clinical pathway for ENMD-2076, holding out the potential of the treatment to be a first-in-line therapy for FLC.

The company will conduct a Simon two-stage study in 16 FLC patients to evaluate overall response rate to ENMD-2076. If none of the patients respond to treatment, the study will be terminated, but if one or more patients show a response (according to RECIST 1.1 criteria) the study will continue with additional patients.

ENMD-2076 has received orphan drug designation for hepatocellular carcinoma from the FDA, and the company said the plan is to file for orphan drug designation for FLC in the EU and for the FDA's breakthrough therapy designation whenever clinical data

meet the appropriate criteria.

**DRUG DELIVERY EXPERTISE**

Lastly, another prong in the company's diversified strategy is the development of a drug delivery technology that has reformulated 2-ME2 (2-methoxyestradiol), a product that underwent multiple phase II trials before its bioavailability was determined to be a roadblock. (See BioWorld Today, March 14, 2008.)

"We applied technology to solve the solubility and bioavailability problems of 2-ME2," explained Ren. "We have screened multiple other products and so far have identified two additional candidates, but because of competitive reasons we have not disclosed the product names."

One of the products is off-patent and the other soon to go off patent globally, with only one drug currently available in China. The current combined sales of the two drugs is valued at more than $1 billion dollars.

"If our product can replace the current products, to go from injectable to oral, and we have patent protection, we believe there is the potential for several hundred million in sales. It will be easier to use, with less toxicity. We can develop it in China, to be competitive, with better stability." said Ren.

"And because of the bioavailability problem with oncology drugs we believe this can be applied to multiple drugs."

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