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ANALYSTS SURPRISED AS CLINICAL PIPELINE KAPUT POST-FDA HOLD

'EX1'-skipping: Primates frustrate bid in HBV, Arrowhead's delivery dead; subcu effort next

By Randy Osborne, Staff Writer

After toxicology problems led RNA interference (RNAi) specialist Arrowhead Pharmaceuticals Inc. to give up on its clinical pipeline that deploys the EX1 delivery method, worries turned to whether the subcutaneous platform might run into similar woes, though the firm's chief operating officer, Bruce Given, said that "we see bigger safety margins and it just doesn't look at all like the EX1 program."

Shares of Pasadena, Calif.-based Arrowhead (NASDAQ:ARWR) ended Wednesday $1.44, down $2.95, or 67.2 percent as Wall Street reacted to word that all pipeline

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Mendelian randomization tempers expectations for PCSK9 inhibitors

By Cormac Sheridan, Staff Writer

DUBLIN – Proprotein convertase subtilisin–kexin type 9 (PCSK9) inhibitors are as good as but no better than statins in reducing the risk of cardiovascular events in patients with cardiovascular disease, according to a large-scale Mendelian randomization study published this week in the *New England*

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IN THE CLINIC

Failed depression drug trial topples Cerecor shares

By Michael Fitzhugh, Staff Writer

Cerecor Inc. shares (NASDAQ:CERC) lost more than half their value Wednesday after the company reported that its fast-acting antidepressant candidate, CERC-301, failed to help patients with

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THE BIOWORLD BIOME

LIKE MAGIC

Psilocybin treats depression, anxiety, existential distress

By Anette Breindl, Senior Science Editor

A single dose of psilocybin, better known as the active ingredient in "magic mushrooms," had "substantial and possibly enduring antidepressant and

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IN THE CLINIC

FDA clears IND for first China-made biologic: Alphamab's KN035

By Shannon Ellis, Staff Writer

SHANGHAI – More than five years in the making, the FDA has granted Suzhou Alphamab Co. Ltd. clinical trial approval in the U.S. for KN035, an anti-PD-L1 single-domain agent discovered, developed and manufactured in China.

"It might sound trivial for someone in the U.S. to claim they can file an IND, but this is a first for our company, and I believe it is the first FDA IND approval for a China-made biologic," Ting Xu, chairman and CEO of Alphamab, told *BioWorld Today*. "It shows the FDA has confidence in our CMC and preclinical studies.

"In a sense, it opens a window. In the next year or so, there will be more Chinese companies looking to get IND approval from the FDA," he added.

In March, Alphamab filed KN035 with the CFDA for clinical trial approval –

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IN THIS ISSUE

BIOFIT 2016

Mind the gap: European efforts spur translation

By Cormac Sheridan, Staff Writer

LILLE, France – Academia's position as the major source of new innovation for pharma and biotech has, arguably, never been more secure. But the process of transferring innovation from an academic to an industry environment remains suboptimal, particularly in Europe, where

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Alphamab

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months before the FDA – and is expecting a greenlight from the Chinese regulators within the next few weeks.

Alphamab has a pipeline of 20 biologics programs in immune-oncology, infertility, infectious diseases and other areas and is looking to develop first-in-class or best-in-class medicines.

The firm has financed its novel pipeline ambitions by licensing out biosimilars to Chinese pharmaceutical companies and, before that, from CRO services. Alphamab has invested heavily in biologics manufacturing in China. Earlier this month, it announced a plant in Suzhou. (See *BioWorld Today*, July 11, 2014, and Nov. 2, 2016.)

GOOD THINGS COME IN SMALL PACKAGES

From the outset, Xu knew his firm would have to find a point of differentiation to tackle programed death-ligand 1 (PD-L1), a hot target in the even hotter category of immunotherapy, and spent five years defining the target product profile. Without something meaningful for patients, it would be tough to compete against Tecentriq (atezolizumab, Roche Holding AG) the only PD-L1 therapy on the market, or the multitude of competitors looking to launch their own PD-1 and PD-L1 drugs, particularly in China where it is thought there are more than 100 companies looking to develop PD-1/PD-L1 molecules.

As Xu explained, KN035 is better by design; it is a fusion protein of PD-L1 domain antibody and Fc domain of regular antibody. Compared to conventional PD-1 or PD-L1 antibodies, KN035 has better tumor tissue penetration in animal model studies, subcutaneous injection, high affinity, stability, low immunogenicity, mutated Fc domain to eliminate ADCC/CDC activity, and similarity in vivo half-life.

Using a single antibody domain derived from the immune system in camels, KN035 could be considered a nanobody, weighing 13 kDa, and it can be administered in a 200-mg/mL high-concentration formulation for subcutaneous injection. At half the size of an antibody, it has been shown to penetrate animal melanoma tumor cells easier and faster than regular antibodies.

Subcutaneous injections offer numerous benefits to patients over the current method of infusion because "the compliance is easier and patients don't need to go to the hospital for infusion," said Xu. As patients live longer on immunotherapy treatments, infusions will be harder to manage and patients will need maintenance treatments they can administer from home.

Those benefits have made it relatively easier to recruit patients in the U.S. to participate in the trial. According to Xu, key opinion leaders have warmly received the idea of subcutaneous injection in part because patients may not be eligible for infusions after second- or third-line therapies due to complications with veins. In those cases, subcutaneous injection is preferred. In addition, Alphamab is working with 3D Medicines, a Shanghai-based precision medicine company with offices in Beijing, Shenzhen, Hangzhou and Suzhou, to develop a diagnostics tool.

PARALLEL DEVELOPMENT IN U.S. AND CHINA

Alphamab will pursue a parallel development strategy between the U.S. and China. In China, the likely indications will be liver cancer, non-small-cell lung cancer (NSCLC), colorectal cancer, pancreatic cancer and bladder cancer. In the U.S., the firm will likely study KN035 in NSCLC and bladder cancer.

It will be entering relatively new territory as the changes to the CFDA guidelines make it possible the regulators will more willing than before to look at early data from the U.S.

Xu is anticipating that, for phase I and phase Ia, the regulatory requirements for tolerance and safety monitoring will largely be the same in the two countries. If Alphamab is able to complete the dose-escalation study in the U.S. first, and meet all ethical requirements in China, "with some data in hand, we may have a case to talk with the CFDA about an abbreviated phase I in China," theorized Xu.

Xu said he expects the real challenge will come later as possibly the first biologic to be co-developed in the U.S. and China. "There will may be a lot of three-party discussions between us, the FDA and the CFDA, to see how we can do a simultaneous multicenter clinical trial that will satisfy the FDA and CFDA requirements."

But Alphamab is not the only China-based company pursuing biologics in the U.S. Jiangsu Hengrui Medicine Co. Ltd. has been very active in the U.S. but has yet to be granted an IND for a PD-1/PD-L1. Beigene Co. Ltd., of Beijing, has studied its PD-L1, manufactured by CMO Boehringer Ingelheim, in U.S. patients as well as those in Australia and China. Shanghai-based Cstone Pharmaceuticals Co. Ltd. is another company to watch in the space. (See *BioWorld Today*, July 6, 2016, Sept. 14, 2016, and Oct. 26, 2016.)

Although filing in the U.S. is a complicated task for Alphamab, the company is strategizing; it will speed up its overall time to market by taking advantage of the both systems. Ultimately, the market in the U.S. is still currently the biggest for biologics.

"The China market is booming, but it will take time for it to develop," said Xu. "The profit for new drugs comes six or more years after approval. We are confident in our quality; that is why we have made a move to the U.S., to capture this market." //

OTHER NEWS TO NOTE

Celldex Therapeutics Inc., of Hampton, N.J., said it completed its acquisition of **Kolltan Pharmaceuticals Inc.**, of New Haven, Conn., a privately held firm developing antibody-based drugs targeting receptor tyrosine kinases. Among the drugs added to Celldex's pipeline are CEDX-0158 (formerly KTN0158), a humanized monoclonal antibody designed to inhibit KIT activation and receptor dimerization in tumor cells and mast cells that is in phase I testing in refractory gastrointestinal stromal tumors, and CDX-3379 (formerly KTN3379), a human monoclonal antibody designed to block the activity of ErbB3, which recently completed a phase Ib study.