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MERCK'S GRASTEK FOLLOWING FAST

Greer Laboratories' Oralair gets FDA nod in hay fever; $10M to Stallergenes

By Michael Fitzhugh, Staff Writer

Hay fever sufferers will have a new option this spring with Wednesday's FDA approval of Greer Laboratories Inc.'s Oralair, the first under-the-tongue allergen extract approved in the U.S. to treat allergic rhinitis with or without conjunctivitis.

The oral immunotherapy will provide to U.S. patients an at-home alternative to injection treatments that has been available in Europe for years.

Oralair will be available nationwide in May, said John Roby, Greer's CEO and president. But final pricing for the new drug is still a week or two away as the

See Oralair, page 3

Celltrion hopes to blaze path for first U.S. biosimilar MAb

By Mari Serebrov, Washington Editor

Anticipating FDA approval early next year of its infliximab biosimilar, Celltrion Inc. is trying to clear the patent path so it can launch Remsima in the U.S. as soon as the approval comes down.

With Remsima posed to become the first biosimilar monoclonal antibody (MAb) approved for the U.S. market, the Korean

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DEALS AND M&A

Hemophilia heats up: Baxter snags Chatham Therapeutics for $70M

By Marie Powers, Staff Writer

Days after the FDA approved Biogen Idec Inc.'s Alprolix (coagulation factor IX [recombinant], Fc fusion protein) as the first recombinant, DNA-derived hemophilia B therapy with prolonged circulation, Baxter International Inc. moved to strengthen

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IN THIS ISSUE

THE BIOWORLD BIOME

'Completely new' cancer treatment strategy will start clinical trials in 2015

By Sharon Kingman, Staff Writer

LONDON – The discovery of an enzyme that is vital to the survival of cancer cells, but which normal cells do not seem to need at all, is pointing to entirely new ways of treating cancer.

Screening studies already have identified small-molecule inhibitors of the enzyme, and the Swedish team of researchers who made the discovery hopes to begin clinical trials with those compounds next year.

So far, studies suggest that inhibiting the enzyme causes all types of cancer cells to die. It seems unlikely that the inhibitors will have side effects on a scale seen with most chemotherapy drugs: Knock-out mice that lack the ability to synthesize the enzyme appear normal.

Thomas Helleday, Söderberg Professor at the Karolinska Institute in Stockholm,

See Cancer, page 6

FOUNDATIONS

KALYDECO SCOPE INSPIRES

'Gate' foundation? Enter here for early de-risking and add-on indications

By Randy Osborne, Staff Writer

The once-popular image of disease foundations as "old ladies in tennis shoes" busy mainly with direct patient care is going away, said Annette Bakker, president and chief scientific officer of the Children's Tumor Foundation (CTF). And that's good news.

Such groups were viewed as only moderate financers of research. "They would act like micro-National Institutes of Health, a funding agent helping out a little bit here and there, and giving some seed money to labs," Bakker said. Thanks to Cambridge, Mass.-based Vertex Pharmaceuticals Inc.'s win with Kalydeco (ivacaftor) for cystic fibrosis (CF), "that era is almost over."

Approved in 2012, Kalydeco was helped mightily by the CF Foundation, which

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FINANCINGS ROUNDUP

Intercept Pharmaceuticals Inc., of New York, said it commenced an underwritten public offering of 1 million shares of common stock, with 600,000 shares offered by the company and the remaining 400,000 to be sold by certain institutional selling stockholders. The company will use its share of the proceeds to fund work supporting the anticipated filings for marketing approval of obeticholic acid (OCA) in primary biliary cirrhosis (PBC), expected at the end of this year, as well as to fund the long-term safety extension portion of the POISE trial and its planned clinical outcomes trial in PBC patients. Proceeds also will be used to develop OCA in nonalcoholic steatohepatitis (NASH). Intercept will not receive any proceeds from the sale of shares by selling stockholders. BofA Merrill Lynch, Citigroup, Goldman, Sachs & Co. and Deutsche Bank Securities are acting as joint book-running managers, while BMO Capital Markets serves as lead manager and Needham & Co. LLC, Oppenheimer & Co., Wedbush Pacgrow Life Sciences, JMP Securities LLC and Summer Street Research Partners are acting as co-managers. The selling stockholders intend to grant underwriters a 30-day option to purchase up to an additional 150,000 shares. Shares of Intercept (NASDAQ:ICPT), which have soared nearly 400 percent since the beginning of the year, mostly on the back of promising phase IIb data with OCA in NASH, fell $3.54 Wednesday, to close at $330.65. (See *BioWorld Today*, Jan. 10, 2014.)

OTHER NEWS TO NOTE

Abcheck sro, of Plzen, Czech Republic, said it entered a research collaboration with **Pierre Fabre Group**, of Castres, France, in which Abcheck's Absieve discovery platform, which combines the firm's phage and yeast display technologies, will deliver antibodies against an undisclosed number of targets provided by Pierre Fabre. Specific terms were not disclosed, but Abcheck will receive discovery fees and milestone payments while Pierre Fabre retains full rights to any antibodies selected.

Acceleron Pharma Inc., of Cambridge, Mass., reported in an 8-K filing that partner **Celgene Corp.**, of Summit, N.J., agreed to purchase an aggregate of 1.1 million shares of common stock from five of Acceleron's current stockholders – Advanced Technology Ventures, Flagship Ventures, Polaris Venture Partners, Venrock and Alkermes Inc. – for an aggregate purchase price of $47.1 million. The addition of those shares will give Celgene about a 14.8 percent stake in Acceleron. The two companies have been working together since 2008, inking a new collaboration in 2011. Celgene also added $10 million in a private placement last year, concurrent with Acceleron's initial public offering. Shares of Acceleron (NASDAQ:XLRN) gained $4.46, or 13.2 percent, to close Wednesday at $38.33. (See *BioWorld Today*, Aug. 4, 2011, and Sept. 20, 2013.)

Alnylam Pharmaceuticals Inc., of Cambridge, Mass., said the EMA's Committee for Orphan Medicinal Products adopted a positive opinion recommending ALN-TTRsc for designation as an orphan product for the treatment of transthyretin (TTR)-mediated amyloidosis (ATTR). The RNAi drug is in a pilot phase II trial for the treatment of ATTR patients with TTR cardiac amyloidosis, with the aim of assessing tolerability and preliminary clinical activity.

Bioalliance Pharma SA, of Paris, said it inked a supply and license deal for Sitavig (acyclovir Lauriad) with **Daewoong Pharmaceutical Co. Ltd.**, of Seoul, South Korea, for commercialization rights in South Korea. Daewoong also will take over registering the drug, for use in recurrent labial herpes, in that region. Bioalliance is eligible for up-front and milestone payments, and the deal also includes a double-digit royalty rate. Specific financial terms were not disclosed.

STOCK MOVERS 4/2/2014

Company	Stock in $	Change in %
Nasdaq Biotechnology	+$3.30	+0.13%
Mannkind Corp.	+$2.97	+73.86%
Rexahn Pharmaceuticals	+$0.14	+12.28%
Acceleron Pharma Inc.	+$4.45	+13.17%

Biotechs showing significant stock changes Wwednesday

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Oralair

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company continues to negotiate with managed care providers.

"It's a process of education, introducing immunotherapy to them, and educating them around both the short-term or long-term benefits," Roby told *BioWorld Today*.

Lenoir, N.C.-based Greer is ramping up its marketing staff for the launch, but Roby said that as an allergy-focused company, it already had most of the sales infrastructure and relationships it will need in place.

The FDA approval triggers a $10 million payment to Greer's manufacturing partner and Oralair's originator, Stallergenes SA. The Antony, France-based company could receive up to $120 million in regulatory and sales-based milestones from its U.S. commercialization agreement with Greer. Stallergenes will receive an undisclosed transfer price for the tablets and stands to receive sales royalties on the product as well. (See *BioWorld Today*, Nov. 1, 2013.)

Though Oralair launches without immediate U.S. competition, before long it will likely face down Alk-Abello A/S and Merck & Co. Inc.'s Grastek sublingual tablet, an investigational therapy that received unanimous backing from the FDA's Allergenic Products Advisory Committee just a day after the committee considered Oralair. (See *BioWorld Today*, Dec. 13, 2013.)

Both therapies have been approved in Europe for years, with Stallergenes gaining approval for Oralair in 2008 and Grazax (Grastek's European trade name) approved in 2006.

In 2013, Stallergenes reported that sales of Oralair hit €22.2 million (US$30.6 million), with the drug gaining a global market share of 45 percent in the grass pollen tablet segment, according to IMS data for countries where both Oralair and Grazax are available. Projected sales of Grazax climbed to $37 million in 2013, according to Thomson Reuters Cortellis Competitive Intelligence.

There are about 30 million people in the U.S. with allergic rhinitis with or without conjunctivitis, with about 3 million of them using immunotherapy injections. Grass allergies are the most common seasonal allergy in the U.S. and most people are allergic to more than one type of grass. That could give Oralair an advantage over products that incorporate just one grass type, such as Grastek, Roby suggested.

During treatment for one grass pollen season, patients taking Oralair experienced a 16 percent to 30 percent reduction in symptoms and the need for medications compared to those who received a placebo.

Oralair is the only FDA-approved oral allergy immunotherapy tablet that includes a five-grass, mixed-pollens allergen extract. It contains extracts from sweet vernal grass (*Anthoxanthum odoratum)*, orchard grass (*Dactylis glomerata*), perennial rye grass (*Lolium perenne*), Timothy grass (*Phleum pratense*) and Kentucky bluegrass (*Poa pratensis*). The active ingredient in Grastek is extract from Timothy grass pollen.

Patients prescribed Oralair will need to start taking the once-daily tablet four months before the start of the grass pollen season, which generally runs May to August in the U.S., and continue using it throughout the season. The first dose is taken at the health care provider's office, where the patient is to be observed for at least 30 minutes for potential adverse reactions. Patients will also be prescribed an auto-injectable epinephrine pen as an extra precaution.

Oralair's prescribing information includes a boxed warning that severe allergic reactions (such as anaphylaxis, which can be life-threatening) can occur. Roby said that was expected and prudent, given that the product is in a new class. Within the year, Stallergenes will initiate a postmarketing safety study.

The most common adverse reactions to Oralair reported by

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Celltrion

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company filed suit this week in a federal court in Massachusetts seeking declaratory judgment that Janssen Biotech Inc.'s remaining patents on the reference drug Remicade (infliximab) are invalid and unenforceable.

The two drugmakers are on an "inevitable collision course" and relief is needed sooner rather than later, Celltrion said in its complaint. That sense of urgency underlies the entire complaint, as Celltrion hopes to avoid the delay Sandoz Inc. encountered when it tried to clear the patent path for an Enbrel (etanercept) biosimilar still in development.

Sandoz sought a declaratory judgment last year that its etanercept biosimilar doesn't infringe two patents owned by Roche AG and exclusively licensed to Amgen Inc. A federal judge in California denied Sandoz's complaint, saying it was premature. (See *BioWorld Today*, Nov. 15, 2013.)

Before parties can take a biosimilar patent challenge to court, they must first follow the steps of the information exchange Congress laid out in the Biologics Price Competition and Innovation Act, the judge ruled. They can only start clearing the path after the FDA approves the biosimilar, she told Sandoz, which is appealing the decision.

With its final pre-filing meeting scheduled with the FDA this month, Remsima is closer to approval than the Sandoz biosimilar. If everything's a go, Celltrion plans to file its biologic license application (BLA) for Remsima shortly after that meeting, giving the biosimilar a PDUFA date in the first quarter of 2015.

If Celltrion has to wait for the FDA's approval of Remsima before it can litigate declaratory judgment claims, it would be forced into launching the biosimilar without the benefit of discoverable information regarding Janssen's patents and legal positions or delaying the launch until what could be a lengthy legal process is played out.

"An at-risk launch without the benefit of discovery could create serious risks and exposure for Celltrion and could subject it to substantial damages and significant commercial harm," according to the complaint. Delaying the launch would hurt Celltrion financially as it is gearing up to manufacture several months' supply of Remsima ahead of its U.S. launch. A delay also would harm the public interest, because drug costs would remain high if Remicade were the only available treatment on the U.S. market.

Remicade was approved in 1998 to treat Crohn's disease. Since then, it has been approved for plaque psoriasis, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis and ulcerative colitis. The blockbuster biologic is based on the cA2 molecule, which is a murine-human MAb capable of binding to TNF-alpha. While it has faced competition from newer biologics, it has not had to compete with lower-priced follow-ons.

According to Celltrion's complaint, Janssen's predecessor Centocor Inc. applied for patents describing Remicade in March 1991, with the first being granted in 1997. "Since then, Janssen has applied for dozens of patents that all claim the same purported invention covering cA2 and its uses, or obvious variations of that purported invention," Celltrion said. Some of those were granted as recently as 2008.

At least three Remicade patents extend beyond this year, and Janssen has said its MAb has patent protection into 2018. As part of its legal challenge, Celltrion said Janssen purposefully delayed prosecution of one of the patents to improperly extend its term. The patent application was filed 24 years ago. Over the following seven years before the patent was granted, the claims were amended numerous times, and claims that were covered by an earlier patent were added.

Celltrion also accused Janssen, a Johnson & Johnson company, of inequitable conduct before the Patent and Trademark Office in obtaining another Remicade-related patent, because it didn't disclose prior art.

A BIOSIMILAR PATH

Aside from laying out Celltrion's case against Janssen's patents, the complaint provides a behind-the-scenes glimpse at biosimilar development and the brand company's global efforts to fight competition.

Celltrion began work on Remsima in 2008, investing more than $112 million in out-of-pocket external costs plus significant internal manpower and other corporate resources. In the process, it produced several technological breakthroughs, including a patented system for introducing the "instructions" for its biologic products into the cells that produce the drugs, proprietary cell lines, and manufacturing and purification processes.

Remsima began global trials in 2010. The phase I and III trials enrolled a total of 1,471 subjects in 20 countries and at 115 sites. On the strength of those trials, Remsima was first approved in 2012 in Korea, making it the world's first follow-on biologic to be approved on a biosimilar regulatory path. It was approved in the EU the following year. Today, Remsima is approved in 47 countries and marketing applications are pending in another 23 countries. (See *BioWorld Today*, Aug. 9, 2012, and Sept. 11, 2013.)

The company's current focus is on U.S. approval. Celltrion had a data review meeting with the FDA in July 2013. At that meeting, the FDA received the global trial results favorably, Celltrion said, and recommended that the drugmaker conduct a short follow-up clinical trial. That bridging study was completed last month. Before submitting its BLA, the company will discuss the format and content of the application at its final meeting with the FDA this month.

LEGAL CHALLENGES

While it's been pursuing Remsima approval all over the world, Celltrion has been fighting Janssen at almost every step of

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Chatham

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its own hemophilia franchise by snapping up the assets of Chatham Therapeutics LLC in a $70 million deal plus potential development, regulatory and commercial milestone payments. The acquisition gives Baxter full access to Chatham's gene therapy platform, including a hemophilia B (FIX) program that was part of a 2012 collaboration between the companies to evaluate Baxter's BAX 335, a preclinical hemophilia A program and potential future application to additional hemophilia treatments.

The move also comes less than a week after Baxter, of Deerfield, Ill., said it plans to separate the development and commercialization of biopharmaceuticals and medical products into two distinct companies next year, with Ludwig N. Hantson, president of Baxter's Bioscience unit, set to become CEO of the as-yet unnamed biopharmaceuticals firm. (See *BioWorld Today*, March 28, 2014.)

During Baxter's conference call about the corporate split, Hantson made clear that the new biopharma will seek to tighten its grip on the global hemophilia market. The company will start off with a portfolio of recombinant and plasma-based proteins to treat hemophilia and other bleeding disorders, capped by market leader Advate [antihemophilic factor (recombinant) plasma/albumin-free method, or octocog alfa)] in hemophilia A and follow-on BAX 855, a full-length, longer-acting recombinant factor VIII (rFVIII) antagonist partnered with Nektar Therapeutics Inc. (See *BioWorld Today*, Jan. 24, 2014.)

In hemophilia B, Baxter has Rixubis (coagulation factor IX [recombinant]), approved by the FDA last year for routine prophylaxis treatment, control of bleeding episodes and perioperative management in adults. The company filed for the pediatric indication in the U.S. and submitted applications in the European Union (EU), Japan and Australia.

The relationship between Baxter and Chatham dates to 2012, when they inked a collaboration to evaluate Chatham's Biological Nano Particle, or BNP, platform, which is an advanced recombinant adeno-associated virus (rAAV)-based gene therapy technology. Baxter picked up global rights to market and commercialize the treatment, paying $25 million up front to advance the program through early trials. The idea was to integrate the technology into the development of BAX 335, now in a phase I/II study.

The Chatham platform "will be highly complementary to Baxter's expanding pipeline of innovative solutions for a range of bleeding disorders," Baxter spokesman Brian Kyhos told *BioWorld Today*. "It also allows us to gain more experience with gene therapy, which has significant potential for the future of care."

Baxter will continue the ongoing open-label trial to assess the safety and optimal dosing schedule of BAX 335. The BNP technology is designed to provide a mechanism for the patient's own liver to begin producing FIX following a single dose of the genetically engineered treatment. The design of the vector allows for more targeted delivery of the FIX therapeutic cargo into the natural site of FIX synthesis, which may permit effective therapy with low quantities of the vector. The phase I/II trial is expected to enroll up to 16 hemophilia B patients.

"We believe it has a competitive advantage over alternative technologies and thus the ability to reach the market in a timely manner," according to Chatham spokesman Luke Roberts.

Going forward, Baxter will integrate Chatham's technology into its ongoing development activities, according to Kyhos.

'VALIDATING FOR OTHER HEMOPHILIA GENE THERAPY'

Chatham, of Chapel Hill, N.C., is an affiliate of Asklepios Biopharmaceutical Inc. (AskBio), also of Chapel Hill. The two will maintain their licensing and development relationship for hemophilia therapeutic gene therapy candidates using the BNP platform. AskBio is developing the BNP gene delivery technology for therapies targeting heart, central nervous system, muscle, ocular and liver diseases.

AskBio was co-founded by R. Jude Samulski, professor of pharmacology and director of the Gene Therapy Center at the University of North Carolina. Samulski demonstrated the first use of AAV as a viral vector, culminating in the first U.S. patent involving non-AAV genes inserted into AAV. He co-founded Merlin Pharmaceutical Corp., an AAV-based gene therapy company. In 1995, the company was acquired by Somatix Therapy Corp., which also teamed up with Baxter in multiple hemophilia gene therapy deals. Somatix subsequently merged in 1997 with Cell Genesys Inc. in a $115 million stock swap. (See *BioWorld Today*, Nov. 4, 1993, Nov. 10, 1994, Dec. 21, 1994, Feb. 15, 1995, and Jan. 14, 1997.)

Baxter also enhanced its hemophilia A portfolio last year, picking up global rights to OBI-1 (recombinant porcine factor VIII), the lead hemophilia program at Inspiration Biopharmaceuticals Inc., of Cambridge, Mass., as part of that company's Chapter 11 bankruptcy proceeding. After completing phase II/III studies in acquired hemophilia A and in congenital hemophilia A with inhibitors against human FVIII, Baxter filed for U.S. approval of the drug, previously partnered with Ipsen SA, of Paris, in the fourth quarter of 2013. OBI-1 has orphan drug designation both in the U.S. and EU. (See *BioWorld Today*, Jan. 25, 2013.)

Baxter's moves send a signal to Biogen, of Cambridge, Mass., and others that hemophilia remains a high priority. FDA approval of Alprolix, following an earlier nod by Health Canada, represents the first big win for Biogen's hemophilia pipeline. That approval was based on findings from the global, phase III B-LONG study and interim pharmacokinetic and safety data from the phase III Kids B-LONG study.

In December 2013, Biogen also disclosed positive findings from A-LONG, a phase III trial that evaluated a long-lasting clotting factor candidate in people with hemophilia A. Top-line results for long-lasting rFVIIIFc fusion protein, partnered with Swedish

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Cancer

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told *BioWorld Today*: "I have never come across, and no one I have talked to has ever come across, an enzyme that is not used in mammalian cells, but that is critically required for survival of cancer cells. We have taken a completely new step, for this work means that we have identified a new protein family that we can inhibit and target in order to treat cancer."

A drug that targets the enzyme, which is called MTH1, could in theory be a "magic bullet" for all cancers, he said. "On the other hand, we won't know that until we are in the clinic and, realistically, we think we will need to work with combinations of drugs."

Seven chemists, working for more than three years in Helleday's lab, have been synthesizing small molecules that inhibit MTH1 and then optimizing them so that they are effective at nanomolar and picomolar concentrations.

"To accelerate the development of this treatment principle, and to proceed with clinical trials in patients as quickly as possible, we are working with an open innovation model," Helleday explained. "Even before publication, we have sent out MTH1 inhibitors to a range of research groups worldwide."

In a paper in the April 2, 2014, issue of *Nature*, Helleday and his team described how they elucidated the role of MTH1 in cancer cells, validating it as a potential target for cancer therapy. The title of their paper is "MTH1 inhibition eradicates cancer by preventing sanitation of the dNTP pool."

In cancer cells, due to oxidative stress, the pool of nucleotides available for building DNA includes molecules that have become oxidized. When oxidized nucleotides are incorporated in DNA, the DNA breaks and the cell dies. MTH1, which is a member of the nudix hydrolase family of enzymes, "cleans up" those molecules, converting them back to the non-oxidized form and ensuring that the cancer cells live and can replicate.

In contrast, normal cells do not need MTH1, as their metabolism already includes ways of preventing damage to the nucleotides that are the building blocks of DNA.

Helleday and his colleagues summarized in *Nature* how they purified the enzyme, determined its crystal structure and screened small-molecule libraries for hits and then optimized them to produce inhibitors. In additional experiments, they took mice bearing xenografts of multiresistant melanoma tumors from patients and gave the animals one of the MTH1 inhibitors, with a "good" response, Helleday said.

Roger Olofsson Bagge, a surgeon at Sahlgrenska University Hospital who is affiliated with the Sahlgrenska Academy at the University of Gothenburg in Sweden, said: "When we saw that the tumor from one of my melanoma patients who has developed resistance to all the current treatment actually responded very well to the treatment, we were extremely happy. It's rare that you get to experience and witness such a breakthrough."

In a paper in the same issue of *Nature*, Giulio Superti-Furga, of the CeMM Research Centre for Molecular Medicine of the Austrian Academy of Sciences in Vienna, together with collaborators from the University of Oxford in the UK and the Karolinska Institute in Sweden, reported that previously identified substances that kill cancer cells also work by inhibiting MTH1. In that paper, titled "Stereospecific targeting of MTH1 by (S)-crizotinib as an anticancer strategy," Superti-Furga and his colleagues described how an experimental cancer agent, a kinase inhibitor called crizotinib, has its effect by suppressing MTH1 activity.

Helleday, who is also one of the authors of the second paper, said: "The fact that existing anticancer agents hit MTH1 shows that the concept really works. Now that we understand the mechanism, we can develop very selective inhibitors. We are continually identifying novel compounds in the lab and trying out the variants, to see which have the best properties." //

Oralair

Continued from page 3

adults were itching in the ears and mouth and of the tongue, as well as swelling of the mouth and throat irritation. In children, the most commonly reported adverse reactions were itching and swelling in the mouth and throat irritation. //

OTHER NEWS TO NOTE

Biondvax Pharmaceuticals Ltd., of Nes Ziona, Israel, said its board approved initiation of the process to list the company's shares in the U.S. through American depository receipt (ADR). Biondvax, which is developing a universal flu vaccine, will act to register an ADR Level 1 Over-the-Counter, which does not include the option for public offerings in the U.S., without additional registration. The goal is to increase the company's visibility to the public and facilitate access to professional and institutional investors.

Envivo Pharmaceuticals Inc., of Watertown, Mass., said it changed its name to Forum Pharmaceuticals Inc. to better reflect the company's position as a late-stage, purpose-built organization focused on treating brain diseases such as schizophrenia and Alzheimer's disease.

Erytech Pharma SA, of Lyon, France, said lead product Graspa/Ery-asp was granted orphan drug designation by the FDA for the treatment of acute myeloid leukemia (AML). The product, an enzyme formulation of L-asparaginase, is in a phase III trial in acute lymphoblastic leukemia and in a phase IIb trial in AML in Europe.

CTF

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continues to benefit, with "$160 million of the foundation coming from that one molecule," Bakker said. "It's a huge thing." (See *BioWorld Today*, Feb. 1, 2012.)

Hoping to emulate and improve upon that success is Bakker's New York-based CTF, taking on neurofibromatosis (NF), a set of genetic disorders that causes tumors to grow along the nerves.

NF1 occurs once in every 3,000 births. The afflicted show multiple cafe-au-lait spots and neurofibromas on or under the skin, sometimes with enlargement and deformation of bones and curvature of the spine (scoliosis). About half exhibit learning disabilities.

NF2 is much rarer at one in 25,000 births. Multiple tumors appear on the cranial and spinal nerves, along with lesions of the brain and spinal cord. The hallmark: tumors affecting both of the auditory nerves, with hearing loss in the teens or early 20s manifesting as the first symptom.

A third type is schwannomatosis, hitting about one in 40,000 people. It's much less studied than NF1 or NF2, and looks different from patient to patient.

Bakker described the CTF business model. "If, for example, Pfizer has a MEK inhibitor, and they develop it for the typical malignant cancer indication, what I can do for them as a foundation – and this is actually what we're doing – is that I can de-risk [the molecule enough for them in NF]," she said. "We have the infrastructure in place to do preclinical testing pretty quickly. Then, they can go to their executive management and say, 'You know, this MEK inhibitor is working really well in this rare but not so rare indication. We could be first in class here, so let's include some NF patients in a phase II trial.'" CTF can provide patients quickly through its open registry. (See graph.)

The approach is already working – and with a MEK inhibitor, since the pathways in oncology and NF are similar. CTF has an agreement with London-based Astrazeneca plc around clinical-stage AZD6244 (selumetinib), Bakker told *BioWorld Today*. "We have been funding the preclinical work, and now the molecule is in phase I, and ready to go into phase II, I think," she said. "It looks very promising." Last October, Boulder, Colo.-based Array Biopharma Inc. earned a $5 million milestone payment

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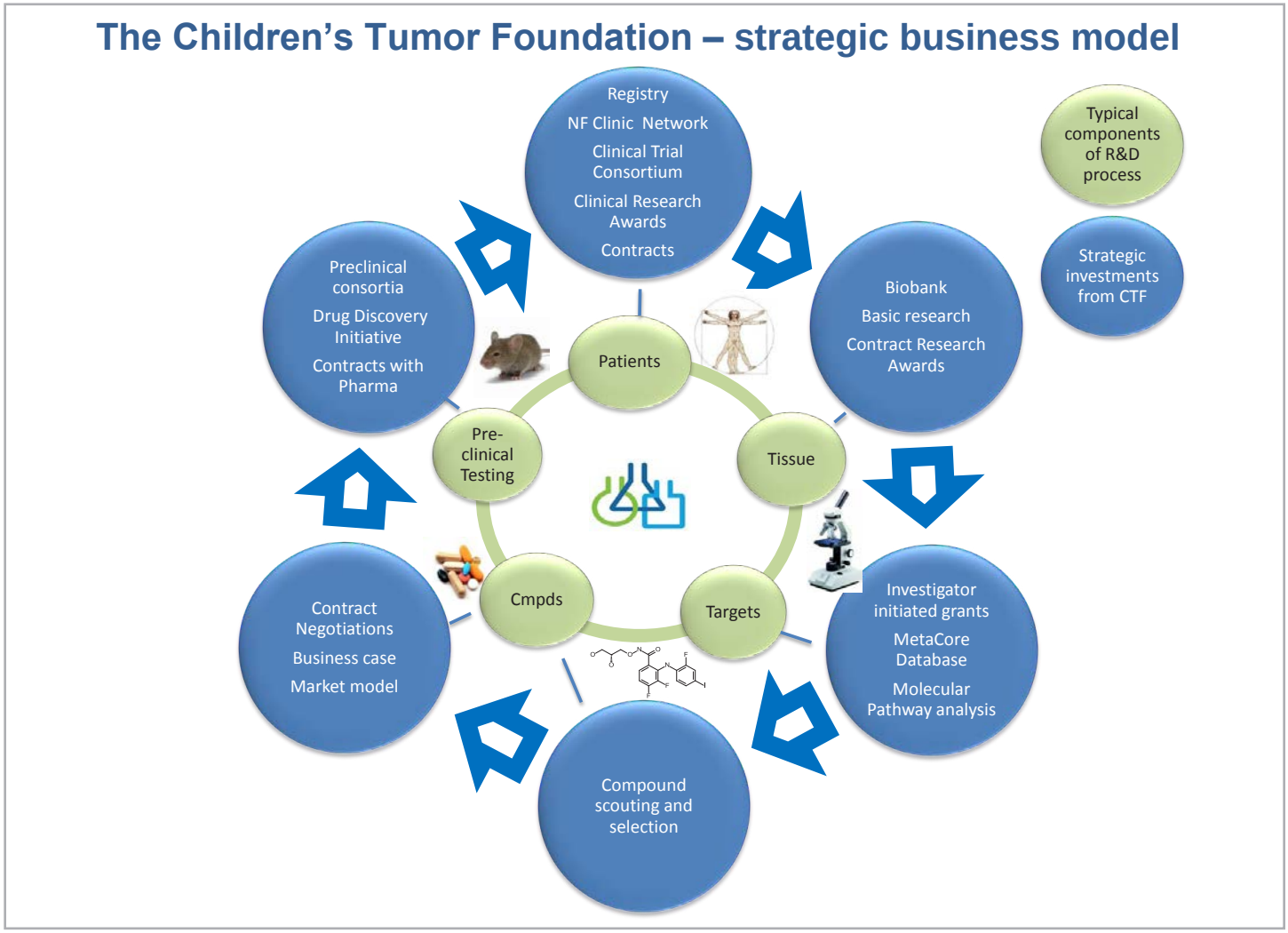

CTF

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when Astrazeneca began a phase III trial with oral selumetinib in patients with metastatic non-small-cell lung cancer whose tumors are KRAS mutation-positive. (See *BioWorld Today*, Oct. 23, 2013.)

Another study, entirely sponsored by CTF, is testing the combination of an MTOR inhibitor and an Hsp90 inhibitor, the latter provided by Synta Pharmaceuticals Corp., of Lexington, Mass. And the foundation is "trying to negotiate now a deal with a company that has a molecule for NF2," Bakker said. "We are investing in the complete preclinical testing, and the condition is that they will make sure the molecule is available for clinical testing, if the molecule works."

Bakker called the ongoing talks "a tough negotiation. If they don't want to take it into clinical trials, we will find the funding to do it," but if the company elects not to proceed, then CTF must be paid back its costs. "We have made huge progress, and we're close to signature now," she said. Meanwhile, "they can pursue the molecule in their malignant setting – they're doing that, it's in the clinical phase already – and we can add on the NF indication for our patients."

'A KIND OF SWITZERLAND'

Bakker said she is "trying to get some [more] deals to the table. I would almost view that as a fundraising opportunity to get donors more excited and add money to the pot. The advantage of having some real wealthy donors who are kind of butterflying around the foundation is that when they see that it's happening, I'm pretty sure we will get way more money."

To de-risk compounds costs about $200,000 each. CTF has done about 60 projects so far, and Bakker wants to work directly with more pharma and biotech firms. "During the preclinical study, we connect with the company and the company will provide us with formulation data, some pharmacokinetic data, some pharmacodynamic data," she said. "Some companies are even willing to help us with analysis."

The first stage also serves as a testing ground for the company "to see how serious they are," Bakker added. "If they don't want to give us any of their privileged information, then we know this is just one of those exercises. They're never going to [follow through]."

With a background in pharma, Bakker knows the routines. She spent six years at Janssen Pharmaceutica NV, of Beerse, Belgium, and more than seven years as head of oncology research and development for Siena Biotech SpA, of Siena, Italy. Neither industry nor academia seemed just right to get the job done.

"In academia, the only thing people want to do is publish as quickly as possible, to be able to get access to their funding, and in industry, they want to keep stuff secret for as long as possible" in order not to tip off competitors, Bakker said. She sought "a kind of Switzerland situation. That's why I left both academia and industry."

At CTF, "we don't want patents, we don't care about publication," she said. "The only thing I really care about is that the stuff gets from the research lab into the patient."

Bakker, who also lobbies on behalf of NF in Washington, said she showed a graphically created version of her business model to politicians there. "It was really funny to see their reactions. They said, 'This is awesome. I haven't seen this for many years, a foundation that comes with a strategy.'"

For tightly focused research on a specific disease, foundations such as CTF can be just the ticket, as Vertex found with Kalydeco and as more are attempting to do. Last September, CureDuchenne Ventures, a nonprofit organization dedicated to funding drug efforts in Duchenne muscular dystrophy, committed to raise $5 million for Lexicon Pharmaceuticals Inc., of The Woodlands, Texas, to develop its candidate, LX2931. (See *BioWorld Today*, Sept. 27, 2013.)

CTF's "biggest roadblock today is letting the world know that we're a [prospective] business partner," Bakker said. "We're not yet the big enchilada," she acknowledged, and hooking up with deep pockets might not bring the foundation to the $100 million mark, "but it's going to bring us to $30 million, and that will give us the discovery that will bring us to $100 million." //

Celltrion

Continued from page 4

the way. Janssen opposed Celltrion's trademarks for Remsima in Argentina, Australia, Bolivia, Brazil, Canada, Chile, India, Korea, the Philippines, South Africa and Uruguay, and brought invalidation proceedings in Korea and Paraguay. Most of those cases were decided in Celltrion's favor, according to the complaint.

Janssen also opposed Remsima's approval in Mexico on the grounds of data exclusivity, which Mexico doesn't grant. "Janssen asserted [it] anyway knowing that any challenge, no matter how frivolous, would automatically result in a stay of a pending market application," Celltrion said. A stay was granted, delaying Remsima's launch in Mexico.

Janssen had another legal victory in Peru after regulators approved Remsima. The Peruvian court suspended the approval, agreeing with Janssen's charge that the drug was approved hastily before biosimilar guidelines were established.

When it looked like Celltrion and its partner, Hospira Inc., were going to succeed with a patent challenge in the UK, the Mathilda and Terrence Kennedy Institute of Rheumatology Trust negotiated a licensing agreement with Celltrion. As part of the negotiations, the trust – which holds title to some patents relating to uses of cA2 – discussed giving Celltrion a global license, including licenses to its Canadian and U.S. patents.

However, Janssen, which has a nonexclusive license to the Kennedy patents, demanded that Celltrion not be given a license in Canada and the U.S., Celltrion said in its complaint. Kennedy and Janssen then asserted infringement against Celltrion in Canada. As part of those proceedings, Janssen refused to discuss the possibility of granting Celltrion a U.S. license. //

Chatham

Continued from page 5

Orphan Biovitrum AB, of Stockholm, showed the candidate, branded Eloctate, was effective in the control and prevention of bleeding, routine prophylaxis and perioperative management, and was generally well tolerated. (See *BioWorld Today*, Nov. 1, 2012, July 9, 2013, and Oct. 29, 2013.)

In a note, Piper Jaffray & Co. analyst Joshua Schimmer wrote that "BAX's current commercial presence is primarily in hemophilia A; its foray into hemophilia B highlights the factor replacement players' interest in both preserving and extending their franchises in the hemophilia domain. We see this as validating for other hemophilia gene therapy programs in development." //

OTHER NEWS TO NOTE

Evotec AG, of Hamburg, Germany, and **Debiopharm Group**, of Lausanne, Switzerland, inked a research and licensing deal to identify and develop compounds having the potential to treat multiple forms of solid tumors and leukemias with defined genetic alterations. Discovery and preclinical efforts will be driven by Evotec, while Debiopharm will manage clinical development. Evotec will receive R&D funding and high double-digit total payments triggered by clinical, regulatory and commercial milestones, plus royalties on sales of any resulting projects. Specific financial terms were not disclosed.

Keryx Biopharmaceuticals Inc., of New York, said the EMA determined that the firm's marketing authorization application seeking approval of Zerenex (ferric citrate coordination complex) as a treatment for hyperphosphatemia in patients with chronic kidney disease (CKD), including dialysis- and nondialysis-dependent CKD, is valid. The agency's review will follow the centralized marketing authorization procedure. If approved by the EMA, Zerenex will receive authorization in all 27 member states of the European Union, as well as in Norway, Liechtenstein and Iceland. Zerenex also is under review in the U.S., with an FDA PDUFA date of June 7. (See *BioWorld Today*, Aug. 9, 2013.)

Patrys Ltd., of Melbourne, Australia, said data on production of PAT-SM6 in an easy-to-grow plant manufacturing system were published in *Proceedings of the National Academy of Sciences*, showing that relatively high quantities of the IgM antibody can be made. Data also showed that by modulating the properties of the plants, a process called *in planta* glycoengineering, that plant expression system can produce fully functional antibodies similar to antibodies generated by the human body.

Pharmathene Inc., of Annapolis, said data from its Sparvax next-generation anthrax vaccine program presented at the New Technologies, New Vaccines conference demonstrated the firm's achievements in developing analytical assays for use to monitor the stability and potency of Sparvax. Data showed how the addition of phosphate alters the surface chemistry of the immune-stimulating adjuvant, Alhydrogel, in such a way that the stability profile of the recombinant protective antigen is improved and potency is increased, as compared to vaccine formulations with less phosphate. The phosphate/Alhydrogel formulation also demonstrated fivefold higher potency than a comparable low phosphate formulation, as tested in the mouse challenge assay.

Prometic Life Sciences Inc., of Laval, Quebec, said it has a pre-investigational new drug application (IND) meeting with the FDA for a plasma-derived biopharmaceutical under development with the Nantpro LLC joint venture. The company said the production of GMP bioequivalence clinical trial material is scheduled to occur during the second quarter, and patients are expected to start enrolling in the clinical trial in the fourth quarter. Following the pre-IND meeting, Prometic is targeting possible market approval for the product in the second half of 2017.

OTHER NEWS TO NOTE

Rosetta Genomics Ltd., of Rehovot, Israel, and **Marina Biotech Inc.**, of Boston, said they established an alliance to identify and develop microRNA-based products designed to diagnose and treat various neuromuscular diseases and dystrophies, starting with Becker and Duchenne muscular dystrophies and myotonic dystrophy. Rosetta will apply its microRNA discovery expertise and, if it is determined to be correlative to the disease, may further develop the microRNA as a diagnostic. If the microRNA is determined to be involved in the disease pathology, Marina may develop the resulting therapeutic for clinical development. Financial terms were not disclosed, but the deal leaves both companies free to develop and collaborate outside the fields of those two disease areas.

Synthon Biopharmaceuticals, of Nijmegen, the Netherlands, reported results of a head-to-head comparative program of its antibody-drug conjugate (ADC), SYD985, with Basel, Switzerland-based **Roche AG**'s anti-HER2 ADC drug Kadcyla (ado-trastuzumab emtansine), with in vivo data showing that SYD985 demonstrated unprecedented antitumor activity and outperformed Kadcyla, particularly where there was low expression of HER2. The study used patient-derived xenograft models in mice.

Tetraphase Pharmaceuticals Inc., of Watertown, Mass., said the FDA granted fast-track designation for both the intravenous (I.V.) and oral formulations of the company's lead antibiotic candidate, eravacycline. The company is testing the drug in a global phase III program, testing the I.V. formulation for the treatment of complicated intra-abdominal infections in IGNITE 1 and testing the drug as an I.V.-to-oral stepdown therapy for the treatment of complicated urinary tract infections in IGNITE 2.

TI Pharma, of Leiden, the Netherlands, reported that five academic institutions, two governmental institutes and two small and medium enterprises from Europe, Africa and Latin America are collaborating to develop drugs against parasites. The four-year, EU-funded project, dubbed PDE4NPD: PhosphoDiEsterase inhibitors for Neglected Parasitic Diseases, is led by VU University Amsterdam. The consortium has received funding of €7.8 million (US$10.7 million.)

CLINIC ROUNDUP

Agenus Inc., of Lexington, Mass., said partner **Glaxosmithkline plc** (GSK), of London, plans to terminate the phase III MAGRITi study of its MAGE-A3ii cancer immunotherapeutic, which contains Agenus' QS-21 Stimulon adjuvant, in non-small-cell lung cancer (NSCLC). GSK said it will not be able to identify a subpopulation of gene-signature-positive NSCLC patients who might benefit from the treatment. The companies reported last month that the trial missed both the first and second co-primary endpoints, failing to significantly extend disease-free survival compared to placebo in either the overall MAGE-A3-positive population or in MAGE-A3-positive patients who did not receive chemotherapy. GSK is continuing the phase III DERMA trial to evaluate whether a gene signature can identify a subpopulation of melanoma patients who would benefit from the MAGE-A3 cancer immunotherapeutic. The outcome of that trial is expected next year. (See *BioWorld Today*, Sept. 6, 2013, and March 21, 2014.)

Cardiocell LLC, of San Diego, received investigational new drug approval from the FDA for a phase IIa study using its allogeneic stem cell therapy to treat patients with chronic heart failure (CHF). The single-blind, placebo-controlled, crossover, multicenter, randomized study will assess the safety, tolerability and preliminary efficacy of a single intravenous dose of ischemia-tolerant allogeneic mesenchymal bone marrow cells at three U.S. sites. Cardiocell has an exclusive license to use ischemia-tolerant mesenchymal stem cells, or itMSCs, from parent company **Stemedica Cell Technologies Inc.**, of San Diego, which are grown under hypoxic conditions that more closely resemble the environment in which they live in the body. The CHF study was designed to determine if Cardiocell's itMSC-based therapies stimulate the transition of viable but nonfunctioning myocardium into functioning myocardium.

Corcept Therapeutics Inc., of Menlo Park, Calif., and US Oncology Research said two sites affiliated with US Oncology Research will participate in Corcept's phase I study of mifepristone in combination with chemotherapy drug Halaven (eribulin, Eisai Inc.) in patients with metastatic or locally advanced unresectable breast cancer. Up to 20 patients will be enrolled in the first phase of the trial, which is designed to determine the maximum tolerated dose of the combination regimen. The subsequent expansion phase will enroll up to an additional 20 patients with glucocorticoid receptor-positive metastatic triple-negative breast cancer and will include efficacy endpoints.

Cynapsus Therapeutics Inc., of Toronto, said interim data from its recently completed healthy volunteer pilot study of a single 25-mg sublingual strip (APL-130277) dose of apomorphine indicated that a higher load of drug on the strip does result in a higher amount of drug entering the bloodstream. Apomorphine is a dopamine agonist used in treating Parkinson's patients. Cynapsus is aiming to develop its drug under the 505(b)(2) pathway.

CLINIC ROUNDUP

Hepatera Ltd., of Moscow, initiated a trial investigating Myrcludex B in patients with chronic hepatitis B virus (HBV) who also are infected with hepatitis delta virus (HDV). Myrcludex B inhibits the entry mechanism of HBV and HDV, which affects 5 percent to 10 percent of patients with chronic HBV infection. Hepatera is co-developing the drug with **Myr GmbH**, of Burgwedel, Germany. The study is investigating the effects of Myrcludex in combination with pegylated interferon and the use of the entry inhibitor as pre-treatment before interferon therapy is initiated. Patient enrollment is expected to be completed in April, with top-line data expected in the third quarter.

Medivir AB, of Huddinge, Sweden, reported that two phase III trials are recruiting patients to examine the efficacy and safety of the NS3/4A protease inhibitor simeprevir in combination with the nucleotide inhibitor sofosbuvir for the treatment of chronic genotype 1 hepatitis C virus (HCV) infection in treatment-naïve and treatment-experienced patients with and without cirrhosis. The first trial, called OPTIMIST-1, will investigate the efficacy and safety of simeprevir 150 mg in combination with sofosbuvir 400 mg. The combination will be administered once daily for eight weeks or 12 weeks in chronic HCV genotype 1-infected patients without cirrhosis who are HCV treatment-naïve or treatment-experienced. This study will enroll approximately 300 patients in the U.S. and Canada. OPTIMIST-2 will study the efficacy and safety of simeprevir 150 mg in combination with sofosbuvir 400 mg. The combination will be administered once daily for 12 weeks in HCV genotype 1-infected patients with cirrhosis who are HCV treatment-naïve or treatment-experienced. That study will enroll approximately 100 patients in the U.S. and Canada. Ribavirin will not be administered in the trials. The primary efficacy endpoint in each study is the proportion of patients achieving sustained virologic response 12 weeks after the end of treatment.

Pozen Inc., of Chapel Hill, N.C., said it submitted the final study report for the phase I study comparing the pharmacokinetic profile of the omeprazole component of PA8140 tablets to that of PA32540 tablets as agreed with the FDA. (See *BioWorld Today*, Dec. 24, 2013.)

PHARMA: OTHER NEWS TO NOTE

Daiichi Sankyo Co. Ltd., of Tokyo, said its European subsidiary would add data on 5,000 new patients to a registry it designed to provide insight into the characteristics and management of atrial fibrillation (AF), with a focus on the prevention of thromboembolic events, such as stroke. The company's "Prevention of thromboembolic events European registry in atrial fibrillation" initially included data from 7,000 patients in seven European countries. The extended registry will add patients from Belgium and the Netherlands. It will also place a special focus on reviewing the use of novel oral anticoagulants (NOACs) and reasons for switching AF patients to NOACs, such as Daiichi's investigational, once-daily factor Xa inhibitor, edoxaban, from vitamin K antagonists, such as warfarin. Edoxaban is currently being evaluated for the prevention of stroke and systemic embolic events in patients with AF, as well as for preventing recurrent venous thromboembolism complications in patients with deep vein thrombosis and/or pulmonary embolism.

PHARMA: CLINIC ROUNDUP

Bayer HealthCare Pharmaceuticals Inc., of Whippany, N.J., began enrollment in a trial studying Xofigo (radium Ra 223 dichloride) injection in combination with abiraterone acetate and prednisone/prednisolone for the treatment of asymptomatic or mildly symptomatic chemotherapy-naive patients with bone predominant metastatic castration-resistant prostate cancer. The randomized, double-blind, placebo-controlled phase III trial is designed to determine the effects of this combination treatment on symptomatic skeletal event-free survival.

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