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'Great synergy' between the assets

Bristol-Myers Squibb shows the love for Nektar in potential $3.63B I-O pact

By Marie Powers, News Editor

Stressing the collaborative nature and "limited scope of exclusivity" of Nektar Therapeutics Inc.'s immuno-oncology (I-O) deal with Bristol-Myers Squibb Co. (BMS), Howard Robin, Nektar's president and CEO, touted the "transformative" nature of the potential $3.63 billion pact covering NKTR-214. The alliance provides Nektar with $1.85 billion up front – $1 billion in cash and the remainder through

See Nektar, page 3

Janssen wins FDA approval for significant new prostate cancer drug

By Michael Fitzhugh, Staff Writer

At least six weeks ahead of its assigned PDUFA date, Janssen Research & Development LLC's apalutamide has become the first FDA-approved therapy to treat patients with non-metastatic castration-resistant prostate cancer (nmCRPC), those whose disease has quit responding to medical or surgical treatments that lower testosterone but has yet to spread.

The approval, following a priority review at the agency, was based on pivotal data showing that the drug, to be marketed as Erleada, decreased the risk of distant metastasis or death by 72 percent vs. placebo while extending median metastasis-free survival by 24.3 months in nmCRPC patients.

Richard Pazdur, director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products, said the approval is the first to use the endpoint of metastasis-free survival and a demonstration

See Janssen, page 5

Reimagining HHS will be easier said than done

By Mari Serebrov, Regulatory Editor

In his second week on the job, Health and Human Services (HHS) Secretary Alex Azar got a crash course on why it's easier to imagine changes to 50-year-old U.S. government programs like Medicaid than it is to make them happen.

Welcoming the new secretary and former business

See HHS, page 6

Galmed shares tumble on phase IIa Aramchol trial read-out

By Michael Fitzhugh, Staff Writer

A mid-stage trial testing the Galmed Pharmaceuticals Ltd. candidate aramchol (arachidyl amido cholanoic acid) over 12 weeks found it made no apparent difference in liver fat for people with HIV-associated lipodystrophy

See Galmed, page 7

Abdominal 'whoa, man'

Tetraphase cUTI bid fails while agency mulls NDA

By Randy Osborne, Staff Writer

Inadequately concentrated drug may have caused Tetraphase Pharmaceuticals Inc.'s topline phase III blowup with intravenous (I.V.) eravacycline in complicated urinary tract infections (cUTI), and the company said the results bear no read-

See Tetraphase, page 8

Santen reports promising early data from carotuximab phase I/II study

By David Ho, Staff Writer

HONG KONG – Japan's Santen Inc. disclosed positive top line results from the phase I/II study of its carotuximab candidate, DE-122, for the treatment of wet age-related macular degeneration (AMD).

See Santen, page 9

The PD-1/PD-L1 antibody race in China is on

By Elise Mak, Staff Writer

HONG KONG – Talks of China's market for PD-1/PD-L1 antibodies got even more heated after the CFDA issued guidelines for the submission of new drug applications (NDA) for immunotherapy antibodies last week.

The announcement posted by the Center for Drug Evaluation (CDE) implies faster approval for

See China, page 10

The BioWorld Biome

GWAS in Chinese population implicates immune system in Alzheimer's disease

By John Fox, Staff Writer

A study has identified common genetic variants in the Chinese population contributing to the risk of developing Alzheimer's disease (AD) that possibly exert functional effects through the

See Alzheimer's, page 11

Financings

Avadel Pharmaceuticals plc, of Dublin, said its wholly-owned subsidiary, Avadel Finance Cayman Ltd., priced an offering of $125 million aggregate principal amount of 4.50 percent exchangeable senior notes due 2023 in a private placement to qualified institutional buyers. The initial purchasers of the notes will also receive a 30-day option to purchase up to an additional $18.75 million aggregate principal amount of the notes. The net proceeds will total approximately $119.6 million, or $137.7 million, if the initial purchasers exercise their option to purchase additional notes in full. The company said it currently expects to use the net proceeds for working capital and general corporate purposes. Concurrent to the pricing of the offering, Avadel also expects to use cash on-hand to purchase approximately $18 million of its American Depositary shares in privately negotiated transactions.

Celgene Corp., of Summit, N.J., said its board has authorized the repurchase of an additional $5 billion of the company's common stock, effective immediately. Purchases will be may be made in the open market or in privately negotiated transactions from time to time.

Elanix Biotechnologies AG, of Berlin, Germany, a developer of tissue regeneration products and specialty cosmetics in the field of dermatology and gynecology, said it raised €1.125 million (US$1.39 million) from the sale of 300,019 shares at €3.75 each. The additional funds will be used to launch Skinrepair, a dermatological cream, and advance the development of Firstcover, a bioresorbable and bioactive skin dressing derived from progenitor skin fibroblasts. In addition to the capital raise, the company says it has signed a term sheet providing access to a financing facility with a leading institutional investor of up to €11 million (US$13.6 million) over three years.

Merus N.V., of Utrecht, the Netherlands, is selling 3.1 million shares at $18 per share to Biotechnology Value Fund L.P. and certain of its affiliates, Aquilo Capital Management, Sofinnova Venture Partners L.P. and LSP Life Sciences Fund NV in a private placement. The offering, which is expected to close on or about Feb. 15, 2018, will gross approximately $55.8 million. The company plans to use the proceeds to fund development of its clinical and preclinical drug candidates and for general corporate purposes. Shares of Merus (NASDAQ:MRUS) closed up $1.04, 6.2 percent, to $17.79 on Wednesday.

Pieris Pharmaceuticals Inc., of Boston, said it priced its underwritten public offering of 5.5 million shares at $8 each for expected gross proceeds of $44 million. The underwriters have also been granted a 30-day option to purchase up to 825,000 additional shares of common stock at the public offering price. Pieris intends to use the proceeds for working capital and general corporate purposes.

Ra Pharmaceuticals Inc., of Cambridge, Mass., said it priced an underwritten public offering of 8.4 million shares of its common stock at $6 each. The underwriters in the transaction have been granted a 30-day option to purchase up to an additional 1.26 million shares of common stock. The gross proceeds, excluding any exercise of the underwriters' option to purchase additional shares, are expected to be $50.4 million. The net proceeds together with existing cash on hand, will be used to fund their phase II trial for RA101495 for generalized myasthenia gravis (gMG), other pipeline programs, and for working capital and general corporate purposes.

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Nektar

Continued from page 1

an $850 million purchase of approximately 8.28 million Nektar shares (NASDAQ:NKTR) at $102.60 apiece, a 35 percent premium to Tuesday's closing price of $75.66 per share.

The companies will evaluate the potential of NKTR-214 with Opdivo (nivolumab) or Opdivo plus Yervoy (ipilimumab) in registration-enabling trials in more than 20 indications across nine tumor types. BMS obtained exclusive rights in the indications included in the joint development plan for a specified time period. Targeted indications include melanoma and renal cell carcinoma (RCC), for which pivotal trials of the combination approach are expected to start mid-year, along with non-small-cell lung cancer (NSCLC), bladder and triple negative breast cancer.

Nektar, of San Francisco, is entitled to downstream milestones of $1.78 billion, including $1.43 billion in development and regulatory milestones, with the remainder linked to sales. Moreover, Nektar will book revenue for global sales of NKTR-214, recognizing a 65 percent split of global profits for NKTR-214, with BMS receiving the remaining 35 percent along with 100 percent of revenues for its own medicines.

BMS also will shoulder 67.5 percent of the development costs in the collaboration – 67.5 percent for joint NKTR-214/Opdivo development and 78 percent for trials that include NKTR-214 with Opdivo and Yervoy.

No matter how many trials are started in a given year, Nektar's expenses in the joint program are capped at $125 million annually, Robin said.

Nektar's stock started in the red Wednesday but gained lift as investors wrapped their arms around details of the deal, whose up-front economics set a new biopharma partnering standard – by a long shot, according to data from *BioWorld* and Cortellis Deals Intelligence. Shares closed at $84 for a gain of $8.34, or 11 percent.

Nektar and BMS inked their clinical collaboration in 2016 to evaluate the potential combination of Opdivo and NKTR-214. But BMS saw the potential in NKTR-214, which binds to the CD122 receptor on the surface of CD8-positive and CD4-positive immune cells, as far back as a phase I monotherapy study that included an extensive biomarker program, Stephen Doberstein, Nektar's senior vice president of research and development and chief R&D officer, told *BioWorld*. That program showed that NKTR-214, as a single agent, caused a large increase in tumor-infiltrating lymphocytes (TILs), effectively turning cold tumors hot. Secondly, the agent tended to increase the expression of PD-1 on T cells inside the tumor.

"Those two things made it really auspicious to think about combining with a checkpoint inhibitor," Doberstein said.

Subsequent data, presented first at the 2017 annual meeting of the American Society of Clinical Oncology (ASCO) with more mature findings in November at the Society of Immunotherapy of Cancer (SITC), showed the companies hypothesized correctly "that NKTR-214 would allow the checkpoint antibodies to do their job in a broader number of patients," he pointed out.

Data presented at SITC came from the ongoing phase I/II PIVOT-02 study on the combination of Opdivo and NKTR-214, showing a compelling objective response rate and impressive disease control rate across melanoma, RCC and NSCLC in PD-L1-positive as well as the more numerous PD-L1-negative patients. (See *BioWorld*, Nov. 14, 2017.)

"At that point, it was very clear to us that there was great synergy" between the assets, Doberstein said. "We'd been talking all along, but this idea of reaching this very broad collaboration agreement emerged from that data."

'An exceptional set of features'

Even preclinically, NKTR-214 had an effect on the immune systems of animals with tumors that suggested "an exceptional set of features with biological changes that you just didn't see with standard immunotherapy," added Jonathan Zalevsky, Nektar's senior vice president of research and chief scientific officer. "The ability to act on the immune system the way that NKTR-214 does, even preclinically, was a missing gap in immunotherapy regimens."

In fact, the preclinical findings were confirmed "from the very first patient that we enrolled in the monotherapy," Zalevsky said, when the individual's biopsy findings showed a "massive" increase in TILs. "Right from that first patient, companies like BMS started to take notice of NKTR-214," he told *BioWorld*.

Looking historically across the biopharma space, "none of the up-fronts come anywhere close" to the Nektar-BMS deal among partnerships that involve traditional biotechs, according to Karen Pihl-Carey, *BioWorld*'s analyst. In terms of total potential economics, the Nektar/BMS accord is the fifth largest biopharma collaboration on record. The others cited by Pihl-Carey were last year's $8.5 billion tie-up between Astrazeneca plc and Merck and Co. Inc. for Lynparza (olaparib); Merck's $6.3 billion preclinical I-O pact in 2015 with Ablynx NV; a potential €3.9 billion (US$4.25 billion) global diabetes deal in 2015 between Hanmi Pharmaceutical Co. Ltd. and Sanofi SA; and the potential $4.09 billion antisense therapies pact in 2015 between Ionis Pharmaceuticals Inc. (then known as Isis Pharmaceuticals Inc.) and Astrazeneca. (See *BioWorld Today*, July 23, 2015, Nov. 6, 2015, and Sept. 28, 2017.)

Most of these partnerships involved up-front payments in the neighborhood of several hundred million dollars or less. Even last year's arrangement between big pharmas Astrazeneca and Merck involved a smaller up front, at $1.6 billion, Pihl-Carey pointed out.

"If this [Nektar] is a deal in lieu of a potential M&A, it will be interesting to see if more follow suit," she said.

In a flash note on Nektar issued last week, Jefferies Group LLC analyst David Steinberg wrote that the company's reported evaluation of strategic options, potentially including a sale, was "not surprising in our view. Post the most recent '214 dataset three weeks ago we discussed NKTR fitting our M&A thesis now that ~90 percent of the valuation is derived from proprietary

See Nektar, page 4

Nektar

Continued from page 3

candidates. And with likely no additional '214 data until ASCO in June, the next key catalyst(s) likely will revolve around '181, partnering and corporate strategy."

Existing partner BMS "would make sense to be on the short list" of potential buyers, Steinberg added.

While deflecting talk about a rumored sale, Doberstein said Robin "has been very clear about the kind of deal that really made sense for us. Given that NKTR-214 has such broad potential applicability, we knew we couldn't do an out-licensing deal. It didn't make any sense. We knew we needed to maintain control of NKTR-214 – of the pricing, the distribution and the revenue from sales. Upon approval, this will have a Nektar label."

The partners plan to move combination trials forward apace.

"We want to get NKTR-214 developed as broadly and rapidly as possible," Robin emphasized on the company's conference call early Wednesday. "If these studies – all registrational studies – are not started within 14 months, they are not subject to exclusivity," enabling Nektar to move forward with other checkpoint combo relationships.

The next data from PIVOT-02 will, indeed, come in June at ASCO, for which abstracts were due Tuesday.

"By the time we are at ASCO, we should have approximately 150 patients' worth of data across all of our various expansion cohorts," including I-O naïve populations as well as some relapsed/refractory patient populations, Mary Tagliaferri, Nektar's senior vice president of clinical development and chief medical officer said. "We're not giving out the exact numbers of patients that will be enrolled to every cohort. Obviously, we're still enrolling, and enrollment is going on quite rapidly."

In the meantime, the BMS tie-up does not prevent Nektar from partnering NKTR-214 with other types of I-O assets, such as chimeric antigen receptor (CAR) T cell therapies – a combination with prospects that Robin described as "extremely interesting."

In a true win-win, the collaboration gives BMS "broad and rapid access" to the NKTR-214/Opdivo combinations "and leaves us a lot of green field to continue to develop" the asset, Doberstein said.

"Almost all of the I-O approaches that are showing any promise at all fundamentally come back to the activity of T cells to attack the tumor and to maintain that response," he pointed out.

The FDA just opened an IND for a combination study of NKTR-214 with NKTR-262, a small molecule agonist that Zalevsky invented that targets toll-like receptors found on innate immune cells. Nektar plans to move quickly into the phase I/II REVEAL study, which will evaluate the safety, tolerability and anti-tumor effect of the combination in patients with a variety of locally advanced or metastatic cancers.

Nektar will continue to advance the remainder of its pipeline, as well, including wholly owned asset NKTR-181, a mu-opioid agonist that proved its mettle last year in a phase III study in more than 600 patients with moderate to severe chronic low back pain who were new to opioid therapy. (See *BioWorld Today*, March 21, 2017.)

> *"Given that NKTR-214 has such broad potential applicability, we knew we couldn't do an out-licensing deal.*
>
> Stephen Doberstein, senior vice president of research and development/chief R&D officer, Nektar Therapeutics Inc.

Last year, Nektar also inked an autoimmune alliance with Eli Lilly and Co. to co-develop NKTR-358, which targets the interleukin (IL-2) receptor complex. That candidate was advanced from inception to the clinic in a mere 15 months. (See *BioWorld*, July 25, 2017.)

New York-based BMS agreed to certain lock-up, standstill and voting provisions on its share ownership for five years, subject to certain exceptions.

Jefferies' Steinberg was more than satisfied with what he called the "mega" collaboration and its prospects to accelerate development of NKTR-214 "significantly."

As Mizuho Securities USA analyst Difei Yang observed in a flash note, the deal could still lead to an outright acquisition.

"We believe BMS is valuating NKTR-214 at approximately $9-$10 [billion]," Yang wrote. "The main implication to us coming out of this transaction is that there is now the potential for a full take-out of Nektar by BMS as more data from NKTR-214 in combo with Opdivo becomes available, possibly when the phase III data on [the] first indication becomes available."

If the deal looked sweet for Nektar, Evercore ISI analyst Umer Raffat said terms were just as favorable for BMS.

"I think BMY got a very good deal structure on this I-O program," he wrote in an email, by retaining 35 percent of the economics "and yet not bet $16 [billion] up front," alluding to an outright purchase of Nektar. BMS also ensured its leadership in phase III I-O combination studies, Raffat pointed out.

The big pharma's interest in the Nektar program "goes beyond just the biology," he added, noting that BMS "was likely intrigued by the early response rate data coming out of NKTR … specifically in the PD-L1 [patients]."

Overall, "I like this addition to [the] BMY portfolio," Raffat concluded. ♦

Janssen

Continued from page 1

of "the agency's commitment to using novel endpoints to expedite important therapies to the American public."

Prostate cancer is the second most common form of cancer in American men, with about 161,360 men diagnosed with the condition in 2017 and 26,730 expected to die of the disease, according to the National Cancer Institute. About 10 percent to 20 percent of prostate cancer cases are castration-resistant, and up to 16 percent of those patients show no evidence that the cancer has spread at the time of the castration-resistant diagnosis.

According to a Clarivate Analytics Disease Forecast, the incidence of prostate cancer in G7 and BRIC countries is expected to grow at a rate of 0.036 per year for the foreseeable future.

"The strength of phase III data and a lack of adequate treatments for the target patient population suggest that apalutamide, like Zytiga, Imbruvica, and Darzalex, will eventually become a multibillion-dollar oncology brand," RBC Capital Markets analyst Glenn Novarro wrote, after Janssen released new findings from the pivotal phase III Spartan trial. Some estimates of the drug's potential sales suggest it could bring in as much as $2 billion annually by 2022.

Janssen representative Bernadette King told *BioWorld* that Erleada will be available in about one week at a wholesale acquisition cost $10,920 for a 30-day supply, consisting of 120 tablets, each containing 60 mg of the medicine. The label specifies that patients should take four tablets daily.

Janssen Biotech Inc., the official U.S. licensee of the drug, is owned by New Brunswick, N.J.-based Johnson & Johnson.

There is no recommended course of therapy with Erleada.

Patients stay on the drug until their disease progresses. At this point in our clinical study, the median duration of therapy is 16.9 months. However, 61 percent of patients are still on therapy today, according to the primary investigator for the Spartan trial.

Janssen picked up Erleada, a second-generation androgen receptor degrader also known as ARN-509, with its acquisition of Aragon Pharmaceuticals Inc. in the summer of 2013, a deal initially valued at $650 million up front, with $350 million more in potential milestone payments. The drug was originally sourced from the University of California in 2009. (See *BioWorld Today*, June 18, 2013.)

Janssen-Cilag International NV, of Beerse, Belgium, submitted a marketing authorization application to the EMA for apalutamide, earlier this month, also for the treatment of patients with high-risk nmCRPC.

As explained by the drug's label, apalutamide works by binding directly to the ligand-binding domain of the androgen receptor (AR). It inhibits AR nuclear translocation, DNA binding, and impedes AR-mediated transcription. A major metabolite of the drug, N desmethyl apalutamide, also inhibits AR, exhibiting one third the activity of the drug in an in vitro transcriptional reporter assay.

The FDA said that common side effects of Erleada include fatigue, high blood pressure, rash, diarrhea, nausea, weight loss, joint pain, falls, hot flushes, decreased appetite, fractures and swelling in the limbs. Severe side effects include falls, fractures and seizures. Falls and fractures occurred in 16 percent and 12 percent of patients receiving Erleada, respectively. Seizure occurred in 0.2 percent of patients.

Editor's note: For more information about Clarivate Analytics' Disease Forecasts click here: http://bit.ly/2GdmLtM http://bit.ly/2GdmLtM ♦

HHS

Continued from page 1

executive to his first congressional budget hearing Wednesday, Rep. Bill Pascrell (D-N.J.) told Azar, "This is not business. This is government. Very different. So welcome to the combat zone."

> *"This is not business. This is government. Very different. So welcome to the combat zone.*
>
> Rep. Bill Pascrell (D-N.J.)

The hearing before the House Ways and Means Committee was a bit combative at times as Azar presented, and defended, President Donald Trump's fiscal 2019 budget proposal, which supports the administration's initiatives to reimagine HHS. "The president's budget makes significant strategic investments in HHS' work, boosting discretionary spending at the department by 11 percent in FY2019 to $95.4 billion," Azar said, noting that the investments prioritize tackling the opioid epidemic, addressing health insurance costs, reining in drug prices and making sustainable reforms to Medicare and Medicaid.

Not everyone was a believer. "This budget is dangerous and unrealistic . . . [It] is an indignity and an affront to the average person," Rep. John Lewis (D-Ga.) said. He claimed it would dismantle the social safety net for people living paycheck to paycheck.

Although Lewis' emotion-laden attack on the budget was grounded in the status quo of HHS programs, the concept of reimagining the department to make its programs more responsive to the needs of the nation has congressional support. The challenge is finding consensus on how to do it, or even on what needs to be changed. And, as was apparent at Wednesday's hearing, some lawmakers consider any cut in funding for an HHS program as being off the table, even if it is delivered through increased efficiency, a crackdown on fraud or a reduced program need.

The details of reimagining HHS also could prove troubling for drug and device companies and other industries whose business models thrive on the status quo. Rep. David Schweikert (R-Ariz.) warned Azar that health care industries are terrified of change and they will be hounding his door to keep HHS from taking steps that will impact their current business models. Instead of getting stuck in the door, Azar should push forward with innovation and new technologies, Schweikert said.

"How many times did you go to Blockbuster Video this past week? That's change," the congressman said, driving home his point that government programs and businesses must adapt as technologies evolve.

Quest for value

Reforms are needed to create incentives to encourage patients and insurers to "pay for health and outcomes rather than procedures and sickness," Azar said. To make such changes will entail leveraging the "tremendous power" Medicare has as the largest health care purchaser in the U.S., he added.

Business as usual won't suffice. "The future of Medicare must be driven by value, quality and outcomes – not the current thicket of opaque, unproductive incentives," Azar told the committee.

As for Medicaid, his written testimony noted that the 50-year-old-plus structure of the program "has failed to create a sustainable federal-state partnership that is capable of controlling costs. In fact, its outdated design incentivizes cost increases without delivering commensurate benefits or allowing for much needed local health innovation."

To address the deficiencies, the budget "recognizes the importance of focusing government spending on programs that work and reforming our nation's health care programs for a fast-changing world," Azar said. It includes legislative solutions intended to improve Medicare and Medicaid, promote greater efficiencies, advance patient-centered care and reduce the government-imposed burden on providers.

For instance, proposed changes to Medicare Part D would discourage current rebate and pricing strategies, straightening out incentives that benefit middlemen more than they do beneficiaries. At the same time, the budget would give plans more tools to negotiate prescription drug prices with manufacturers and cap out-of-pocket spending for beneficiaries facing especially high drug costs. (See *BioWorld*, Feb. 13, 2018.)

The budget also proposes the first steps toward price negotiations for Part B drugs. In addition, Azar said the Centers for Medicare & Medicaid Services is looking at ways to incentivize the use of biosimilars. These and other changes that Azar called commonsense would produce net savings of $493.7 billion for Medicare and more than $1.4 trillion in federal spending on Medicaid over 10 years.

Despite Azar's assurances that the Medicare savings wouldn't affect beneficiaries, Rep. Lloyd Doggett (D-Texas) wasn't convinced. He repeated reports that the budget would increase beneficiaries' premiums by as much as $44 per month – a move he said would take money from the patient and put it in the pockets of big pharma.

Wednesday was Azar's first stop on his congressional tour to present the president's budget. He is scheduled to testify Thursday before the House Energy and Commerce Subcommittee on Health. ♦

Galmed

Continued from page 1

and non-alcoholic fatty liver disease (NAFLD). While company shares (NASDAQ:GLMD) fell by 45.4 percent on the news, Galmed's chief scientific officer, Liat Hayardeny, told *BioWorld* that substantial differences in the pathogenesis of fatty liver in HIV and non-alcoholic steatohepatitis (NASH) – the focus of another aramchol trial due to read out next quarter – should quell concerns about any potential read-through.

At the time the investigator-initiated study started, in 2015, "the HIV pathogenesis was less known," Hayardeny said. Today, the scientific literature is more focused and the mechanisms are better known for HIV-induced NAFLD, the Teva Pharmaceutical Industries Ltd. veteran said.

Though sharing a common pathology, with both populations having fatty livers, the pathogenesis of NASH represents a completely different mechanism, she said. In NASH, fatty acid in the liver comes primarily from dietary glucose and serum, while in HIV, a more complex mix of etiologies is at play, attributable not just to the virus itself attacking hepatocytes and causing mitochondrial injury and apoptosis of activated collagen-producing cells, including fibrosis in the liver. HIV also has a directly cytopathic effect on hepatocytes, primarily triggering apoptosis via the HIV gp120 protein-receptor signaling pathway, she said. Further complicating matters, it appears that highly active antiretroviral therapy, or HAART, up-regulates fat in the liver, she said, concluding that the trial didn't have bearing on the company's NASH program.

The phase IIa trial, called Arrive, was conducted at the University of California San Diego by professor Rohit Loomba. Randomized, double-blind, and placebo-controlled, it sought proof-of-concept for aramchol at 600mg/day vs. placebo in 50 patients with HIV-associated lipodystrophy and NAFLD. The primary endpoint of the study was improvement of liver fat at 12 weeks, as measured by magnetic resonance spectroscopy-measured proton density fat fraction (MRS-PDFF). Liver biopsies, a more common measure in NASH studies, were not included as part of the evaluation.

The trial found no difference between HIV patients receiving aramchol for 12 weeks when compared with HIV patients in the placebo arm, but did find that aramchol showed a favorable safety and tolerability profile. Further analysis of the data is ongoing.

Aramchol modifies liver fat and cholesterol metabolism by down-regulating stearoyl-CoA desaturase 1 (SCD1), neutralize the damaging activity of ROS and maintain redox homeostasis, a mechanism of action that has been shown in preclinical studies and a phase II trial to significantly reduce liver fat content and improve metabolic parameters associated with fatty liver disease.

As reflected in the substantial reaction to new data on aramchol, relevant or not to Galmed's true focus on NASH, investors are keeping a keen eye on anything that might hint at the tenor of top-line data from Galmed's phase IIb Arrest study to come. Data from that trial, expected in the second quarter, will demonstrate the drug's performance in 248 NASH patients at both 400 mg/day and 600 mg/day following 52 weeks treatment. Endpoints will be measured by MRS and liver biopsies.

Galmed has reason to be optimistic about its chances. Though it didn't turn out to be a very good drug for treating gallstones – its initial application – in May 2014, it yielded positive results from a trial in 58 patients with NAFLD during a randomized, double-blind, placebo-controlled, parallel-assignment, phase IIa study. NAFLD is a precursor to NASH. The data demonstrated that aramchol decreased liver fat content in a dose-dependent manner by 12.57 percent +/- 22.14 percent at 300 mg/day and by 2.89 percent +/- 28.22 percent at 100 mg/day compared to placebo over three months of treatment.

With the global prevalence of NASH growing by 3 percent per year, according to a Clarivate Analytics Disease Forecast, need for workable therapies has only grown, attracting multiple players to the space, including both heavyweights such as Allergan plc, Bristol-Myers Squibb Co., and Boehringer Ingelheim GmbH, as well as smaller companies, such as Genfit SA, Madrigal Pharmaceuticals Inc., and Intercept Pharmaceuticals Inc. With understanding of the condition in constant evolution and the potential pay-off high for success, even small clinical readouts can draw outsize attention.

Allen Baharaff, Galmed's CEO told *BioWorld* that investors abandoning the shares Wednesday were "not comparing apples to apples" and making the wrong judgment. "It's not simple at all."

In terms of immediate impact, Galmed had a bit less than $20 million in the bank at the end of 2017, and is not planning to raise more at the moment. With the most costly parts of the Arrest study complete, the company has substantially lowered its burn rate, giving it "a very long runway" and enough funding to carry it through 2019, he said.

Galmed's shares closed Wednesday at $5.17, having fallen $4.29.

Editor's note: For more information about Clarivate Analytics' Disease Forecasts click here: http://bit.ly/2GdmLtM ♦

Earnings

Alkermes plc, of Dublin, reported that for the year ending Dec. 31, 2017 its total revenues were $903.4 million, compared to $745.7 million for the same period in the prior year. Net sales of Vivitrol (naltrexon), non-addictive, non-narcotic, once-monthly treatment for opioid dependence, increased to $269.3 million. Net sales of for the schizophrenia drug Aristada were $93.5 million. Non-GAAP net income was $27.8 million, or a non-GAAP basic earnings per share of $0.18 and non-GAAP diluted earnings per share of $0.17, for 2017. This compared to a net loss of $10.3 million, or a non-GAAP basic and diluted loss per share of $0.07, for 2016. At Dec. 31, 2017, Alkermes recorded cash, cash equivalents and total investments of $590.7 million, compared to $619.2 million at Dec. 31, 2016.

Tetraphase

Continued from page 1

through to the same compound's value in complicated intra-abdominal infections (cIAI), for which it's under review in the U.S. and Europe.

In any case, "it's hard to see any way forward" with an oral version of eravacycline in cUTI, given the I.V. outcome, though other indications might be possible, CEO Guy Macdonald said during a conference call with investors. "This is the second trial that hasn't worked. If something comes up in the data analysis that makes us think otherwise, we'll reconsider," he said, adding that company officials are "still shocked at the results of Ignite3, and we haven't had time to think through whether there is something else we could look at."

The failure surprised Wall Street, too. Shares of Watertown, Mass.-based Tetraphase (NASDAQ:TTPH) closed Wednesday $2.37, down $3.06, or 56 percent, on word about the trial, which tested the efficacy and safety of once-daily I.V. eravacycline compared to ertapenem (Invanz, Merck & Co. Inc.) for the treatment of patients.

Statistical non-inferiority of eravacycline to ertapenem was not established. Specifically, the study failed to meet the co-primary efficacy endpoints of responder rate (a combination of clinical cure and microbiological success) in the microbiological intent-to-treat (micro-ITT) population at the end-of-I.V. treatment visit and at the test-of-cure visit, which were evaluated using a 10 percent non-inferiority margin. The drug was well tolerated, with a safety profile consistent with prior studies, the company said.

In his Feb. 6 research report, H.C. Wainwright analyst Ed Arce predicted "a solid, clean win" for Ignite 3. During Wednesday's conference call, management offered what they could in terms of available results. In the micro-ITT the responder rate at the end-of-I.V. treatment visit turned up 84.8 percent for eravacycline (n=363/428) vs. 94.8 percent for ertapenem (n=382/403), -10 percent confidence interval (CI), -14.1 percent and -6.0 percent. The numbers at the test-of-cure visit were 68.5 percent for eravacycline (n=293/428) vs. 74.9 percent for ertapenem (n=302/403), -6.5 percent CI, -12.6 percent and -0.3 percent).

Analyst sees launches in 2019

More circumspect in a report yesterday, Arce said that he had "come to regard the oral formulation of eravacycline, as used in the prior Ignite2 study, as the primary driver of the drug's first failure in cUTI. Based in large part on the post-hoc analyses of Ignite2 conducted by Tetraphase, we had believed that the I.V. administration, by avoiding the lower systemic exposures of the oral, would likely prove to be successful." With the latest outcome, he "regard[s] the weak efficacy of eravacycline in cUTI to be an issue of limited target attainment, in other words, insufficient drug concentrations in the urine. This is a common feature of the pharmacokinetic profiles of tetracyclines, as a class [to which eravacycline belongs], and not readily addressed by simple approaches such a switching the mode of administration."

> *"This is the second trial that hasn't worked. If something comes up in the data analysis that makes us think otherwise, we'll reconsider.*
>
> Guy Macdonald
> CEO, Tetraphase Pharmaceuticals Inc.

Tetraphase's chief medical officer (CMO) Larry Tsai said the company thoroughly examined the results from Ignite2, which was an I.V.-to-oral, step-down dosing regimen in cUTI, when designing Ignite3, and will now "analyze [Ignite3] in the context of the Ignite2 data." In Ignite3, researchers have found "no reason to suspect there is any kind of data quality issue or study conduct issue. We believe the results are reliable and real," he said. More work needs to be done, but signs are suggesting a definite direction in which the company might investigate. "Any time you have an antibiotic that appears to be effective in vitro and fails to be effective in vivo, you have to be suspicious that the concentrations at the target site were not high enough," he said.

Piper Jaffray analyst Edward Tenthoff agreed about the probable cause of the latest fizzle, noting that Ignite3 had a narrower non-inferiority margin and was otherwise different from the phase III Ignite4 study in cIAI, where eravacycline proved non-inferior to meropenem. "We expect responsible pricing to drive frontline cIAI uptake in the hospital setting against multi-drug resistant gram-negative bacteria," he wrote in a report. Tetraphase ended the third quarter of last year with $161 million, which should fund the company through eravacycline launch, in his view. Removing value for cUTI reduced Tenthoff's price target to $8 from $14, though he maintained an overweight rating on the shares due to the prospects in the abdominal indication. CEO Macdonald said the 60-day acceptance period for the NDA in cIAI closes at the end of this month. "We're continuing to answer requests for information that [the FDA is] sending to us," he said. "It's moving smoothly at this point." (See *BioWorld*, July 27, 2017.)

CMO Tsai said "the proof is really in the pudding here. We have two successful phase III studies, Ignite1 and Ignite4, in the cIAI indication against two gold-standard comparators." Ertapenem was used in Ignite1, and data from both experiments were included in the NDA package.

Analyst Tenthoff said he expects approval and launch of eravacycline in Europe and the U.S. in 2019. Tetraphase has set the price of about $175-250 per day, which could mean global sales of $400 million by 2025, by his estimate. "Key opinion leader diligence points to the need for new agents to treat extended-spectrum beta-lactamase-producing gram-negative infections that are resistant to carbapenems," he wrote. "We believe there is a place for empiric front-line use of eravacycline, as well as a final-destination therapy in non-responders." ♦

Santen

Continued from page 1

DE-122 is the ophthalmic formulation of California-based Tracon Pharmaceuticals Inc.'s proprietary anti-endoglin antibody, TRC105. Santen is responsible for the global development of DE-122 as a potential treatment of wet AMD.

"The clinical study assessed the safety, tolerability, and bioactivity of a single intravitreal injection of DE-122 at four dose levels in 12 subjects (n=3 per dose) with wet AMD refractory to vascular endothelial growth factor (VEGF) inhibitors," Tanya Shnaydman, director of corporate communications for Santen, told *BioWorld*.

"DE-122 was well tolerated, with no serious adverse events, and the results suggested bioactivity as measured by mean change in central retinal subfield thickness based on the spectral domain optical coherence tomography," she said.

The data were presented at the 15th Annual Angiogenesis, Exudation, and Degeneration, a medical symposium presented by Bascom Palmer Eye Institute of the University of Miami Miller School of Medicine.

"Wet AMD continues to be a leading cause of blindness and is responsible for severe loss of vision in most patients," said Victor Gonzalez, a study investigator and founder of the Valley Retina Institute, in a statement. He felt there were opportunities in seeking new therapies to address this need.

Wet AMD is usually treated with VEGF inhibitors. But according to Santen, DE-122 is an anti-endoglin monoclonal antibody, which it said uses a different pathway.

Endoglin is a member of transforming growth factor (TGF) receptor superfamily, and a co-receptor with TGF-β and bone morphogenetic protein (BMP)-9 receptors in signaling pathways associated with inhibition and promotion of angiogenesis, the process of new blood vessel formation, respectively.

Endoglin is essential for angiogenesis. It is highly upregulated on endothelial cells during neovascularization and following treatment with anti-VEGF therapy.

Genetic downregulation or pharmacologic inhibition reverses resistance to VEGF inhibition. Endoglin sustains VEGF receptor 2 on the cell surface, preventing its degradation in lysosomes, and mediates escape from VEGF inhibition.

"Carotuximab potentiates VEGF inhibition, by inhibiting VEGF-induced signaling and promoting VEGFR2 degradation, to inhibit angiogenesis and tumor growth in vitro and in vivo," explained Shnaydman.

Jefferies Analyst Tom Tarrant noted that the study result is significant as it presents an evolution in understanding the mechanism of action for anti-endoglin in the treatment of wet AMD.

Tarrant pointed to a January 2018 study in *The FASEB Journal* that gave details of the underlying role of VEGF and endoglin in angiogenesis and provided supporting evidence for dual inhibition.

It characterized mechanistically how endoglin and VEGF mediate stabilization of VEGFR2 on the cell's surface, which promotes tip cell development and ultimately enhances angiogenesis supportive of tumor growth and survival.

Tarrant cited that publication, the growing body of oncology data, and the genetic link to Osler-Weber-Rendu symptoms as steps forward in approaching endoglin and VEGF.

The data garnered from the phase I/II study supported Santen's decision to advance DE-122 to a phase IIa study, which had already dosed its first patients since it began in July last year.

Shnaydman said that the phase IIa trial will be a multicenter, randomized, double-masked and active-controlled exploratory proof-of-concept study. It aims to assess the efficacy and safety of intravitreal injections of DE-122 in combination with Lucentis (ranibizumab, Genentech Inc./Novartis AG) injection treatment, compared to Lucentis monotherapy in patients with wet AMD.

About 51 patients will receive six monthly intravitreal injections, randomized into three arms: a low dose of Lucentis and DE-122, high dose of Lucentis and DE-122, and a Lucentis and sham dose.

Tarrant said the design and duration should isolate efficacy benefit.

"Trial sites in the Philippines could allow for some treatment-naive patients to enroll, and based on some of the phase I/II data, we would expect less advanced patients to benefit more from treatment," noted the Jefferies analyst. "Also, patients in the phase IIa study will be less severe at baseline compared with the phase I/II and may be more amenable to combo treatment, which could provide a more potent anti-angiogenesis effect."

Santen expects the results for that to be available sometime in the first half of 2019.

Tarrant said another phase II trial for Tracon's TRC105 might provide a catalyst ahead.

The study on carotuximab and Inlyta (axitinib, Pfizer Inc.) used in combination for patients with advanced or metastatic renal cell carcinoma is expected to yield some possible advancement of its use with a checkpoint inhibitor. The data for that study is expected to be revealed mid-2018. ♦

Earnings

Intercept Pharmaceuticals Inc., of New York, reported that it recorded $129.2 million of worldwide net Ocaliva (obeticholic acid) sales for the full year and $37.3 million for the fourth quarter of 2017. Net U.S. sales of Ocaliva, which is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA, reached $115.8 million for the full year and $32 million for the fourth quarter. The company recorded a net loss of $360.4 million. As of Dec. 31, 2017, Intercept had cash, cash equivalents and investment securities available for sale of approximately $414.9 million, compared to $689.4 million as of Dec. 31, 2016.

China

Continued from page 1

marketing the PD-1/PD-L1 antibodies – a development widely welcomed by the industry, especially ambitious players who have set sights in the field.

Some drug makers already have filed, or planned to file, NDAs for their PD-1/PD-L1 inhibitors. "We expect a potential NDA submission in China this year," Liza Heapes, director of corporate communications of Beigene Ltd., told *BioWorld*.

According to the CDE, single-arm trials with objective response rate (ORR) as the primary endpoint are sufficient for drug makers to submit rolling NDAs for checkpoint inhibitors.

The guidelines also stipulated that full safety data and results of at least two independent assessments are required for the first submission. Applicants will need to file at least six months of efficacy and safety data that show duration of response during the NDA review. Companies are also allowed to apply for priority reviews simultaneously.

PD-1/PD-L1 monoclonal antibodies, though available in the U.S., are not approved in China yet. According to the CDE, 16 products have obtained approval to enter clinical trials to target different kinds of tumors. In China, at least 10 drug makers are actively engaged in developing the immunotherapy antibodies, including Hengrui Medicine Co. Ltd., Innovent Biologics Inc., Shanghai Junshi Biosciences Co. Ltd., Suzhou Alphamab Co. Ltd. and Beigene.

Bristol-Myers Squibb Co. submitted a biologics license application (BLA) in November 2017 for its PD-1 inhibitor, Opdivo (nivolumab). The pharma giant may secure the first non-small-cell lung cancer approval for an immune-oncology therapy in a country where lung cancer is the leading cause of death caused by cancer.

Next in line is Suzhou-based Innovent. It became the first domestic company to file an NDA for its PD-1 inhibitor in December 2017, shortly after BMS' filing. Its investigational agent, IBI308 – a fully human anti-PD-1 antibody – aims to treat advanced solid tumors. Approval to initiate clinical trials in China was granted to Innovent in September 2016.

Beigene also is planning to file an NDA for its BGB-A317 (tislelizumab) candidate this year, Heapes told *BioWorld*. The inhibitor obtained clinical trial approval from the CFDA in September 2016. Two registrational trials of BGB-A317, in urothelial cancer and classical Hodgkin lymphoma, are currently ongoing in China. In January 2018, the company announced that the anti-PD-1 agent had entered a phase III clinical trial.

"Tislelizumab, an immune checkpoint inhibitor, was designed to bind to PD-1, a cell surface receptor that plays an important role in downregulating the immune system by preventing the activation of T-cells," said Heapes.

Alphamab, also from Suzhou, has skin in the game, too.

"Our PD-L1 antibody is entering phase Ib/IIa clinical trials in China. We expect to launch it in the fourth quarter in 2019," said Junhong Zhang, vice president at Alphamab.

"It is a small-molecule inhibitor with high activity, high tumor vascular permeability, high stability and low immunogenicity. It is injected subcutaneously," Zhang told *BioWorld*.

Another competitor is Hengrui's SHR1210, which is being investigated in a phase III trial that started in December 2017.

Shanghai Junshi's JS-001, a recombinant humanized monoclonal antibody to PD-1, was the first to be approved for clinical trials by the CFDA in January 2016. The compound is currently in a phase II clinical trial and was just granted clinical trial approval by the U.S. FDA on Jan. 9, 2018.

Other PD-1/PD-L1 agents that are being developed in China include Genor Biopharma Co. Ltd.'s GB226 (genolimzumab) for the treatment of autoimmune disease that got the phase I clinical trial approval from the CFDA at the end of 2016, and Cstone Pharmaceuticals Co.'s fully human full-length PD-L1 agent CS1001 that received approval for a clinical trial in July 2017.

Demand, cost hurdles abound

In China, the demand for tumor immunotherapy is high, prompting patients to seek therapy elsewhere such as in Hong Kong or India.

The high cost is also limiting access for clinical drugs. Local reports suggested that the treatment cost for taking 100 mg of the PD-1 or PD-L1 antibodies is around ¥25,000 (US$3,945) to ¥30,000 (US$4,734), which means more than ¥50,000 (US$7,890) for two treatment sessions in a week.

Market potential and fertile regulatory environment aside, there may be some inevitable drawbacks behind the PD-1 and PD-L1 antibody bloom in China.

"Many Chinese companies are looking at the oncology and immuno-oncology space, especially biosimilars," said Eugene Huang, equity analyst at investment banking firm Jefferies. "CAR-T therapy is promising, but the PD-1 and PD-L1 area is becoming overcrowded; it wouldn't be a good strategy to go into that area right now."

At present, a major share of the revenue of the global PD-1 and PDL-1 inhibitors market is currently concentrated in North America, Europe, and Japan, according to Coherent Market Insights.

Research and Markets' report noted that the PD-1 and PD-L1 inhibitors market is estimated at $4.9 billion in 2016, and it is expected to grow at a compound annual growth rate of 23.4 percent between 2017 and 2025.

Given its population and high demand, China has the potential to be a profitable market. PD-1 and PD-L1 antibodies that have entered the final stage of clinical trials are expected to receive marketing approval in 2018 and 2019. ♦

Alzheimer's

Continued from page 1

immune system, which could have important implications for AD management.

The search continues for promising biomarkers and effective disease-modifying therapies for AD. The current drug development approaches mainly target the disease's hallmark pathology of amyloid-beta (Abeta) protein accumulation in the brain leading to Abeta plaque deposition.

Even if a successful Abeta-targeting drug could be developed and pass clinical trials, it would likely only be useful in the early stages of AD, so adding other treatment modalities would probably be necessary.

Interestingly, when the search for Abeta-targeting therapies first began in the 1990s, there was no known link between the brain and the immune system, but these are now known to be closely interconnected.

Genetics studies, including genome-wide association studies (GWAS), have identified several disease genes and their variant forms or alleles associated with altered risk for AD. Among these risk factors, a substantial proportion of the genes are associated with immune pathways.

To date, most AD risk variants revealed by GWAS concern microglia, brain-specific innate immune cells. Targeting the immune system, particularly microglia, is an anti-AD approach currently being investigated by a number of companies. (See *BioWorld*, Dec. 29, 2017.)

However, the vast majority of GWAS have been performed in Caucasian populations and information for other ethnic populations is limited, despite susceptibility to certain genetic risk factors being known to vary among populations.

For example, even for APOE, the most consistent risk factor for late-onset AD, risk levels vary among ethnic groups. Moreover recent small studies in Chinese report that not all of the AD susceptibility single nucleotide polymorphisms (SNPs) identified in Caucasians can be replicated in Chinese patients.

Therefore researchers led by Nancy Y. Ip, Morningside Professor of Life Science at Hong Kong University of Science and Technology (HKUST) and director of the State Key Laboratory of Molecular Neuroscience at HKUST, performed a whole-genome sequencing study of AD in a Chinese population.

The study was published in the Feb. 5, 2018, early online edition of *Proceedings of the National Academy of Sciences*.

The study recruited a total of 1,222 subjects from Fudan University's Huashan Hospital in Shanghai, including 489 with AD, 260 with mild cognitive impairment, and 473 matched controls.

In addition to variants identified in or around the APOE locus, two common variants, GCH1 and KCNJ15, were identified and further verified for their possible risk effects for AD in three small cohorts of non-Asian subjects.

"Both intrinsic and extrinsic factors contribute to AD pathogenesis, but our genetic study was done at a single center in China. Therefore it was vital to replicate the new variants' effects in non-Asian cohorts, in order to validate our findings," Ip told *BioWorld*.

Genotype-phenotype analysis showed that KCNJ15 variant rs928771 G allele affected the age of onset of AD, with earlier disease onset being seen in minor allele carriers.

"Based on our present data, AD subjects with two copies of the rs928771 G allele will develop AD 2.2 years earlier that those AD subjects without the variant allele," explained Ip.

In addition, altered expression level of the KCNJ15 transcript could be observed in the blood of AD patients. "Altered expression of the KCNJ15 transcript in the blood of AD subjects suggests a possible strategy to diagnose the disease of to monitor its progression by examining subjects' blood," said Ip.

"Also, the findings suggest a possible involvement of the peripheral circulation system during the onset and progression of the disease," she added.

Moreover, the risk variants of GCH1 and KCNJ15 were shown to be associated with changes in their transcript levels in specific tissues, as well as changes of plasma biomarkers levels in patients with AD.

"The GCH1 risk variants primarily modulated expression of GCH1 transcript level in brain tissue, whereas the KCNJ15 variant modulated the KCNJ 15 transcript level in whole blood," noted Ip.

Importantly, network analysis of hippocampus and blood transcriptome datasets suggested risk variants in the APOE, GCH1, and KCNJ15 loci might exert their functions through their regulatory effects on immune-related pathways.

"The network analysis revealed the genes which are significantly modulated by the newly identified AD risk variants and these genes are found to be involved in the immune-related pathway," she explained.

These findings have important implications for AD management. "Our findings provide a comprehensive genetic database for AD, specifically for Chinese and other Asians who comprise a substantial proportion of the global population.

"Association of genetic risk factors and biomarkers allow development of assays for the monitoring of AD subjects and risk evaluation. By using different dataset platforms, identification of the association of different genetic variants with specific pathways will permit a better understanding of disease mechanisms," Ip added.

"Next, we aim to establish a comprehensive biomarker database for Chinese AD subjects including genetic, transcriptomic, proteomic and brain imaging data through a more extensive collaboration with academics and physicians in China.

"This will facilitate a deeper understanding of AD pathogenesis through systematic study of AD-associated biomarkers and provide insights into new strategies for improving the diagnosis and therapies for AD." ♦

Other news to note

Allecra Therapeutics GmbH, of Lörrach, Germany, said the FDA granted fast track designation to AAI101 when given in fixed dose combination with the antibiotic cefepime for serious hospital-acquired infections. Allecra plans to start a phase III trial this summer for AAI101, an extended spectrum beta-lactamase inhibitor.

Astellas Pharma Inc., of Tokyo, acquired Universal Cells Inc., of Seattle, for up to $102.5 million in up-front and milestone payments. In the acquisition, Astellas gets the company's Universal Donor Cell technology that's used to create cell therapy products that do not require Human Leukocyte Antigen matching. The companies were partners through a deal in which Astellas Institute for Regenerative Medicine licensed the technology for a single indication. (See BioWorld, Oct. 23, 2017.)

Celltrion Inc., of Incheon, South Korea, said the European Commission approved Herzuma (trastuzumab), a biosimilar to Herceptin (trastuzumab, Roche Holdings AG) for the treatment of patients with early breast cancer, metastatic breast cancer or metastatic gastric cancer whose tumors have either HER2 overexpression or HER2 gene amplification.

DBV Technologies SA, of Montrouge, France, said the company agreed with the FDA on the content of the clinical module of the BLA for its peanut allergy treatment Viaskin Peanut. In October, the phase III PEPITES trial for Viaskin Peanut failed to meet the pre-specified 15 percent threshold difference in the lower end of the 95 percent confidence intervals for responder rates between treated and placebo patients. Shares of DBV (NASDAQ:DBVT) closed up $5.37, 25.7 percent, to $26.23 on Wednesday.

Durect Corp., of Cupertino, Calif., said its partner Pain Therapeutics Inc., of Austin, Texas, submitted an NDA to the FDA for their abuse-deterrent extended-release oxycodone, Remoxy ER, as a treatment for pain. Pain Therapeutics expects a six-month review for the drug.

Ferring Pharmaceuticals SA, of Saint-Prex, Switzerland, plans to invest CHF 30 million (US$32.3 million) in the new Ferring Biotech Centre at its existing headquarters and manufacturing site in Saint-Prex. The center will have discovery and development capabilities for monoclonal antibodies and manufacturing capabilities for biologics, including producing the active pharmaceutical ingredient for its fertility treatment Rekovelle (follitropin delta).

GC Pharma Corp., formerly Green Cross Corp., of Yongin, South Korea, licensed rights to develop and commercialize GCC-4401C, a factor Xa inhibitor anticoagulant, in the greater China and South East Asian market to Lee's Pharmaceutical Ltd., a subsidiary of Hong Kong-based Lee's Pharmaceutical Holdings Ltd. GC Pharma will receive an undisclosed upfront payment and is eligible to receive milestone payments and royalties on future net sales.

Genentech Inc., of South San Francisco, a unit of **Roche Holdings AG**, said the FDA accepted the supplementary BLA for Rituxan (rituximab) as a treatment for pemphigus vulgaris. The marketing application, which was assigned a priority review, is supported by data from a trial that showed Rituxan plus a tapering regimen of low dose oral corticosteroid (CS) improved pemphigus vulgaris remission rates and successful tapering and/or cessation of CS therapy compared to the standard dose of CS.

Glaxosmithkline plc, of London, and Innoviva Inc., of Brisbane, Calif., submitted a type II variation to the EMA to support an expanded label for Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol, FF/UMEC/VI) as a maintenance treatment of moderate to severe chronic obstructive pulmonary disease. The application is supported by data from the IMPACT trial in which Trelegy Ellipta reduced the number of exacerbations and improved lung function and health related quality of life compared to Relvar/Breo (FF/VI) and Anoro (UMEC/VI). A supplementary NDA for Trelegy Ellipta for the same indication is under review by the FDA.

Immunoqure AG, of Dusseldorf, Germany, is partnering with Paris-based Les Laboratoires Servier SAS, to develop an autoantibody neutralizing interferon-alpha. The companies will jointly work to get the autoantibody through preclinical development, at which point Servier will take over clinical development to treat diseases with elevated levels of interferon-alpha, focusing on systemic lupus erythematosus and Sjögren's syndrome. Servier will pay Immunoqure up to 164 million Euros ($204 million) in upfront and milestone payments as well as royalties on net sales.

Incysus Ltd., of New York, reported preclinical data on its drug-resistant immunotherapy approach at the Immunobiology of Primary and Metastatic Central Nervous System Cancer conference in San Diego. In an orthotopic patient-derived xenograft model of temozolomide-resistant glioblastoma, cryopreserved and thawed γδ T cells plus temozolomide increased median survival by 37.9 percent compared to animals treated with temozolomide alone.

Novartis AG, of Basel, Switzerland, formed an alliance with the Bill & Melinda Gates Foundation to develop KDU731, an inhibitor of cryptosporidium's phosphatidylinositol-4-OH kinase, for the treatment of cryptosporidiosis. The foundation will contribute $6.5 million to support the development of KDU731 for the treatment of children by the Novartis Institute for Tropical Diseases.

Novoheart Holdings Inc., of Vancouver, British Colombia, will test drug candidates from Sumocor LLC, of New York, using its Myheart platform to provide preclinical assessment of efficacy and cardiotoxicity in preparation for filing Sumocor filing an IND. Sumocor will pay $380,000 for the screening service.

Oncobiologics Inc., of Cranbury, N.J. received notice that the Nasdaq Hearings panel granted its request to transfer its listing from The Nasdaq Global Market to The Nasdaq Capital Market. Shares and series A and series B warrants will begin trading under the new listing on Feb. 15, 2018. As part of the transfer, Oncobiologics gained an extension through May 15, 2018 to meet the $35 million market capitalization requirement.

Oncoceutics Inc., of Philadelphia, entered into its second product development and investment partnership with Calvert Research LLC, of Cary, N.C., to develop ONC206, an imipridone for the treatment of cancer. Calvert will conduct GLP animal safety and pharmacology studies on ONC206 and make another equity investment in Oncoceutics. The IND-enabling studies are expected to be complete by the end of 2018, facilitating the start of a clinical trial in 2019.

Other news to note

Ortho Dermatologics, a unit of **Valeant Pharmaceuticals International Inc**., of Laval, Quebec, said the FDA accepted an NDA for its topical steroid Jemdel (halobetasol propionate) as a treatment for plaque psoriasis. The agency assigned a Prescription Drug User Fee Act action date of Oct. 5, 2018.

Pfizer Inc., of New York, said the FDA granted breakthrough therapy designation to its janus kinase 1 inhibitor PF-04965842 for the treatment of patients with moderate-to-severe atopic dermatitis. The company started a phase III program for PF-04965842 in December.

Pharmamar SA, of Madrid, licensed rights to its payloads for the development, manufacture and commercialization of antibody-drug conjugates and/or other drug conjugates to Seattle Genetics Inc., of Bothell, Wash. Pharmamar will receive $5 million upfront and is eligible for undisclosed development, approval and sales milestones, as well as royalties on future sales.

Poseida Therapeutics Inc., of San Diego, reported preclinical results on P-PSMA-101, a stem cell memory CAR-T therapy, at the 2018 Keystone Symposia on Emerging Cellular Therapies: T Cells and Beyond. Using LNCaP, a highly aggressive castrate-resistant metastatic prostate cancer mouse xenograft model, mice survived for 114 days following treatment with P-PSMA-101 compared to 41 days for mice treated with a CAR-T using J591 as a binding molecule.

Scythian Biosciences Corp., of Toronto, said it received approval to list its common shares on the Nasdaq Capital Market. The shares will begin trading on Feb. 22 under the ticker SCYB.

Sensorion SA, of Montpellier, France, provided data from SENS-401 (R-azasetron besylate), its 5-HT 3 receptor antagonist, during multiple poster presentations at the Association for Research in Otolaryngology's annual midwinter meeting in San Diego. Among the findings, a preclinical study of twice vs. once daily oral dosing of SENS-401 for 28 days in rats with severe acoustic hearing loss suggested that daily duration of drug exposure is more important than maximum dose exposure for otoprotective efficacy. In preclinical testing of oral doses of SENS-401 vs. placebo in models of severe noise-induced hearing loss and cisplatin-induced ototoxicity, SENS-401 showed improvement of hearing and enhancement of outer hair cell survival vs placebo. SENS-401 also was well tolerated by patients in a phase I trial in the indication, which determined that the pharmacokinetic profile is consistent with the drug exposures needed for preclinical efficacy. Sensorion plans to initiate a phase II study with SENS-401 in the indication during the first half of the year. (See *BioWorld*, Dec. 20, 2017.)

Sumitomo Dainippon Pharma Co. Ltd., of Osaka, Japan, filed patent infringement lawsuits jointly with its U.S. subsidiary, **Sunovion Pharmaceuticals Inc.,** in the U.S. District Court for the District of New Jersey against **Emcure Pharmaceuticals Ltd**. and in the U.S. District Court for the District of Delaware against **Amneal Pharmaceuticals LLC** regarding their submissions of abbreviated new drug applications for generic copies of Latuda (lurasidone HCl), approved to treat schizophrenia and bipolar depression. The lawsuits allege infringement of Sumitomo Dainippon's U.S. Patent No. 9,815,827. Sumitomo Dainippon granted Sunovion an exclusive license in the U.S., and Sunovion has marketed lurasidone HCl in the U.S. under the brand name Latuda since its February 2011 launch. The companies said they will vigorously protect the drug's patent rights. Although the lawsuits will not materially affect Sumitomo Dainippon's consolidated financial results for the fiscal year ending March 31, the company is postponing disclosure of a business update for the five fiscal years beginning April 1.

TC Biopharm Ltd. (TCB), of Edinburgh, Scotland, expanded its Asia operations by opening an office in Tokyo. TCB, which is pursuing chimeric antigen receptor T-based therapies to treat cancer, includes Tokyo-based Medinet as an investor and collaborates with Cell Science & Technology Institute Inc., a subsidiary of Nipro Corp., of Osaka, which also invested in the company's series A round last year.

Vaxart Inc., of South San Francisco, completed its merger with **Aviragen Therapeutics Inc.**, of Atlanta, which changed its name to Vaxart Inc. and concluded a 1-for-11 reverse split of its common stock. On Feb. 14, the combined company began trading on the Nasdaq Global Select on a post-reverse split basis as VXRT.

Earnings

Neurocrine Biosciences Inc., of San Diego, reported that the net product sales for its selective vesicular monoamine transporter 2 (VMAT2) inhibitor Ingrezza (valbenazine), to treat adults with tardive dyskinesia (TD), were $64.5 million for the fourth quarter ended Dec. 31, 2017. Total revenues in the period were $94.5 million, which included a $30 million milestone payment received from Abbvie Inc. for the FDA acceptance of the elagolix endometriosis NDA filing. For the year, net product sales of Ingrezza were $116.6 million and total company revenues were $161.6 million. The company reported a net loss for 12 months of $142.5 million, or $1.62 loss per share, as compared to a net loss of $141.1 million, or $1.63 loss per share for 2016. Cash, investments and receivables at the end of December totaled $797.6 million.

Shire plc, of Dublin, reported its 2017 product sales increased 33 percent to $14.4 billion, which was primarily driven by the inclusion of a full year of legacy Baxalta Inc. product sales of $6.98 billion, with strong sales from their immunoglobulin therapies and biotherapeutics products; royalties and other revenues also increased 39 percent to $712 million. Non GAAP total revenues were $15 billion, up 32 percent over the prior year. Its operating income increased to $5.99 billion (2016: $4.4 billion). Diluted earnings per American Depositary Share increased to $14.05 (2016: $1.27). The company attributed the increase to a higher tax benefit in 2017 driven by U.S. tax reform, higher operating income, combined with lower discontinued operations losses relating to the divestment of their Dermagraft business.

In the clinic

Athenex Inc., of Buffalo, N.Y., disclosed the completion of patient enrollment for both phase III studies of KX2-391 ointment for actinic keratosis indications months ahead of schedule. KX2-391, also known as KX-01, is a dual Src kinase and tubulin polymerization inhibitor and a first-in-class topical treatment of actinic keratosis. Phase I and phase II studies showed excellent efficacy and safety results, the company said, and two randomized double-blind controlled phase III trials totaling 600 patients were initiated in September 2017 in the U.S.

Bioverativ Inc., of Waltham, Mass., disclosed the publication of a retrospective analysis investigating the use of Eloctate (antihemophilic factor (recombinant), Fc fusion protein) for immune tolerance induction (ITI). These data add to a growing body of evidence supporting the potential of Eloctate to induce tolerance in severe hemophilia A patients with inhibitors, the company said, and the analysis was published online as an early view manuscript in *Hemophilia*. Data from 19 patients (seven first-time ITI and 12 rescue patients) treated with Eloctate for ITI were evaluated. Findings show that four of the seven first-time ITI patients achieved tolerization in a median of 7.8 months. The remaining three patients have continued on Eloctate ITI treatment, with two patients showing a reduction in inhibitor levels. In the 12 patients where ITI had been attempted with other factor therapies and failed, seven patients initially achieved a negative inhibitor level in a median 3.3 months, and one patient demonstrated a reduction in inhibitor levels. The remaining four rescue patients did not show a response to ITI with Eloctate. At the time of analysis, 16 of 19 patients remained on Eloctate prophylaxis treatment or ITI, and no adverse events were reported, the company said.

Exelixis Inc., of South San Francisco, disclosed results from a phase II investigator-sponsored trial of cabozantinib for the first-line treatment of metastatic radioiodine (RAI)-refractory differentiated thyroid carcinoma (DTC). The results will be presented during an oral session at the 2018 Multidisciplinary Head and Neck Cancers Symposium in Scottsdale, Ariz. Patients with metastatic, RAI-refractory DTC were enrolled in the single-arm, open-label trial, and were administered oral cabozantinib 60 mg once daily. The primary endpoint is objective response rate. Among the 35 patients who were evaluable for response, partial response was achieved by 54 percent of patients (n=19), and stable disease was reported in 43 percent of patients (n=15) per RECIST 1.1 criteria. All but one evaluated patient experienced a decrease in tumor target lesions. Secondary endpoints of the trial include progression-free survival (PFS), time to progression (TTP), duration of response (DOR) and clinical benefit rate (CBR) defined as the number of patients achieving an objective response or stable disease for at least six months. The CBR at six months was 80 percent (n=28). With a median follow up for the study of 35 weeks the median PFS has not been reached. The median TTP among those patients who progressed was 35 weeks. As Cabometyx tablets, the tyrosine kinase inhibitor cabozantinib was approved in April 2016 in the U.S. for the treatment of patients with advanced renal cell carcinoma. It was approved earlier as Cometriq for medullary thyroid cancer.

Herantis Pharma plc, of Helsinki, Finland, said its first-in-human clinical study with the company's CDNF for the treatment of Parkinson's disease has proceeded to its first safety assessment by an independent data safety monitoring board, and the study continues as planned. Patient recruitment is opening at two new study sites: Helsinki University Hospital in Finland, and Skåne University Hospital in Lund, Sweden. The first study site, Karolinska University Hospital in Stockholm, Sweden, continues to recruit additional patients. The randomized, placebo-controlled clinical study of CDNF intends to recruit in total 18 patients with Parkinson's disease. The participating patients will also be offered a possibility to participate in an extension study in which all patients will receive CDNF treatment, subject to regulatory approval of the extension study. CDNF is described as a drug candidate for the treatment of neurodegenerative diseases. Naturally present in the human blood circulation and cerebrospinal fluid, CDNF is a protein with neuroprotective and neurorestorative properties, patented internationally by Herantis, the company said.

Irx Therapeutics Inc., of New York, said the first patient has been dosed in an investigator-sponsored phase II double-blind, randomized, placebo-controlled clinical trial of IRX-2 in women with squamous cervical intraepithelial neoplasia 3 (CIN3) or vulvar intraepithelial neoplasia 3 (VIN3). The trial is being conducted at the University of Southern California (USC) Comprehensive Cancer Center in Los Angeles, Calif. IRX-2 is a therapeutic containing numerous active cytokine components, which data suggest may restore and activate multiple immune cell types, including T cells, dendritic cells and natural killer cells, that are known to recognize and attack tumors. The IRX-2 regimen will include cyclophosphamide on day one (three days before the start of IRX-2), IRX-2 daily for four days; and indomethacin, zinc with multivitamins, and a proton pump inhibitor (omeprazole) for 21 days. All treatments will be repeated at six weeks, for a total of two cycles. Patients will be randomized 2:1 to the treatment arm with the goal of enrolling 30 patients in the CIN3 cohort and 30 patients in the VIN3 cohort. The primary endpoint is pathological objective response at week 25.

Mallinckrodt plc, of Staines-upon-Thames, U.K., confirmed enrollment of the first patient in the company's phase I study assessing the safety and tolerability of Expressgraft C9T1 skin tissue in the treatment of subjects with diabetic foot ulcers. Expressgraft-C9T1 skin tissue has been genetically modified to express elevated levels of the human cathelicidin host defense peptide. The study is a prospective, open-label trial focused on assessing the safety and tolerability of ExpressGraft-C9T1 skin tissue. Targeted enrollment is up to six subjects with a confirmed diagnosis of diabetes and who have foot ulcers. Subjects will each receive a single application of Expressgraft-C9T1 skin tissue on a single identified study case of ulcers following a 10-14 day run-in period. Any subjects requiring additional treatment will receive protocol-defined dressings as necessary. Enrollment is staged with a minimum of one week between each subject. Cathelicidin is a multifunctional human defense protein with broad-spectrum antimicrobial activity and is a mediator of wound healing through promotion of angiogenesis and epithelialization, the company said.

In the clinic

Merck & Co. Inc., of Kenilworth, N.J., said it will be stopping protocol 019, also known as the APECS study, a phase III trial evaluating verubecestat (MK-8931), a small molecule inhibitor of the beta-site amyloid precursor protein cleaving enzyme 1 (BACE1), in people with prodromal Alzheimer's disease. The decision to stop the study follows a recommendation by the external data monitoring committee, which assessed overall benefit/risk during a recent interim safety analysis and concluded that it was unlikely that positive benefit/risk could be established if the trial continued. Data will be presented at an upcoming medical meeting, Merck said.

Myokardia Inc., of South San Francisco, said that dosing of its **Sanofi SA**-partnered experimental therapy for dilated cardiomyopathy (DCM) has begun. The candidate, MYK-491, is an oral small molecule, allosteric activator of myosin designed to restore the inadequate output characteristic of a DCM heart by targeting the biomechanical defects underlying disease and improving cardiac contractility. The single-ascending dose phase Ib trial will evaluate the safety, tolerability and preliminary pharmacokinetics and pharmacodynamics of MYK-491. Pharmacodynamic measures will include changes in established echocardiographic measures of cardiac contractility. Topline results from the study are anticipated in the second half of 2018.

Sienna Biopharmaceuticals Inc., of Westlake Village, Calif., said that the first patient has been dosed in the company's phase I/II study of topical product candidate SNA-125 in the treatment of psoriasis and associated pruritus, or itch. SNA-125 is designed to inhibit janus kinase 3 (JAK3) and tropomyosin receptor kinase A (TrkA) with minimal to no systemic exposure. The randomized, double-blind, placebo- and comparator-controlled, intra-individual trial will evaluate the safety, tolerability and efficacy of SNA-125 compared to vehicle and other reference formulations in about 15 patients with chronic psoriasis. Sienna's president and CEO Frederick Beddingfield III said that the company plans to soon start a proof-of-concept trial testing SNA-125 against atopic dermatitis, a trial for which data is expected in the second half of 2018.

Sumitomo Dainippon Pharma Co. Ltd., of Osaka, Japan and Osaka-based **Nitto Denko Corp.** are planning to submit an application for manufacturing and marketing approval of blonanserin in Japan during the first half of fiscal 2018 after top-line results from a phase III study evaluating a transdermal patch formulation of the atypical antipsychotic met its primary endpoint. For change from baseline to week six in the Positive and Negative Syndrome Scale (PANSS) total score, the primary endpoint of the study, both blonanserin 40mg/day and 80 mg/day groups showed statistically significant improvement vs. placebo in the modified intention-to-treat population of 577 subjects. The difference in score change vs. placebo was -16.4 [adjusted p=0.007] for the 40 mg/day group and -21.3 [adjusted p<0.001] for the 80 mg/day group. The placebo group's PANSS score declined by 10.8 points. Blonanserin was generally well-tolerated and the adverse events observed in the study, including those related to the skin, were generally mild, the partners said.

Therachon AG, of Basel, Switzerland, said that the first subject in its phase I trial for TA-46, a soluble recombinant human fibroblast growth factor receptor ligand trap, has been dosed with the drug. It's being developed as a weekly subcutaneous treatment for children and adolescents living with achondroplasia, the most common form of short limb dwarfism. The investigational therapy has received orphan status from both FDA and EMA. The randomized, placebo-controlled, double-blind trial is designed to evaluate the safety, tolerability and pharmacokinetics of single and multiple ascending doses of TA-46 in about 70 healthy male and female volunteers. The trial will take place in the Netherlands.

Vertex Pharmaceuticals Inc., of Boston, said that a phase II study of its NaV1.8 inhibitor VX-150 in patients with acute pain following bunionectomy surgery showed that it provided statistically significant relief of acute pain vs. placebo, as determined by the time-weighted Sum of the Pain Intensity Difference over the first 24 hours of treatment (SPID24), a standard measure of acute pain relief. The SPID24 values for those treated with VX-150 and placebo were 36.14 and 6.64, respectively. The SPID24 value for treatment with hydrocodone+acetaminophen, representing a standard-of-care reference arm, was 40.16. It was the second proof-of-concept study for VX-150 and "provides further validation for the use of a NaV1.8 inhibitor for the treatment of pain," the company said. Based on the latest phase II data, Vertex said that it plans to initiate a phase I study of VX-150 using an I.V. formulation for the treatment of acute pain. That study is planned to begin in the second half of 2018. A third phase II study of the candidate is underway in neuropathic pain caused by small fiber neuropathy, with data expected in early 2019. Vertex also recently started a phase I study of a second NaV1.8 inhibitor, VX-128.