Alkermes jolted by dual phase III misses in ALKS 5461 depression program

By Michael Fitzhugh, Staff Writer

Missed efficacy endpoints in two phase III trials of Alkermes plc’s lead candidate, the once-daily depression medicine ALKS 5461, dragged company shares (NASDAQ:ALKS) down by 44.2 percent, or $26.71, to close at $33.71 on Thursday, as analysts deeply discounted the drug’s chances of success, cutting millions of dollars of projected revenue from the company’s future earnings.

Alkermes, which is pushing ahead with the program, said that in response it will increase trial enrollment and update its statistical analysis plan for a third late-stage

See Alkermes, page 3

Vasopham gets $22M for phase III traumatic brain injury trial

By Cormac Sheridan, Staff Writer

DUBLIN – Vasopham GmbH raised €20 million (US$21.7 million) in a new funding round to take its lead molecule, VAS203, into a European phase III registration trial in traumatic brain injury

See Vasopham, page 6

Oversight committee may offer Shkreli immunity for testimony

By Mari Serebrov, Regulatory Editor

A congressional committee is trying to force indicted pharma exec Martin Shkreli to appear at a hearing next week on two drug companies’ extreme price hikes for newly acquired drugs, even if it

See Price hikes, page 8

FORWARD’ MARCH?

Abingworth closes $105M fund for clinical co-development work

By Cormac Sheridan, Staff Writer

DUBLIN – Abingworth has raised $105 million for its first dedicated clinical co-development fund, which will extend its focus on putting up cash to help big pharma progress its pipeline without damaging its all-important P&L line.

The London-based venture capital firm has already been doing that for

See Abingworth, page 4

KEEN ON FUSION PROTEINS

Staging area: Philogen bid targets earlier melanoma, phase III injecting lesions

By Randy Osborne, Staff Writer

Philogen SpA’s “idea is to stop [melanoma] when you have metastases, but only at the skin,” co-founder Dario Neri told BioWorld Today, as his firm

See Philogen, page 5

IN THE CLINIC

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KEYTRUDA: KEY TO NEURODEGENERATION?

PD-1 blockers improve cognition in Alzheimer’s mice, study shows

By Anette Breindl, Senior Science Editor

Treating mouse models of Alzheimer’s disease with an antibody that blocks PD-1, the same molecule targeted by Merck & Co Inc.’s Keytruda (pembrolizumab), helped them clear amyloid plaque and improved their cognitive performance, scientists from the Israeli Weizmann Institute of Science reported in the Jan. 18, 2016, issue of Nature Medicine.

The approach is counterintuitive. Inflammation is a feature of Alzheimer’s as well as many other neurodegenerative disorders, and insofar as immunity has been a target in Alzheimer’s disease, the goal has been to reduce it, not increase it. Inflammation-reducing approaches, though, like many other things, have repeatedly failed in clinical trials.

Michal Schwartz, Maurice and Ilse Katz

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FINANCINGS

Beigene Co. Ltd., of Beijing, set terms for its IPO, which will seek to raise $126.5 million by offering 5.5 million American depositary shares, each representing 13 ordinary shares, priced in a range of $22 to $24. Filing with the SEC as a Cayman Islands-based emerging growth company, Beigene said two existing shareholders, Hillhouse BGN Holdings Ltd. and entities affiliated with Baker Bros. Advisors LP, expressed interest in purchasing 50 percent of the offering. Proceeds will fund ongoing and planned trials of BGB-3111, a Bruton’s tyrosine kinase inhibitor, in lymphoma; BGB-283, a small-molecule RAF kinase inhibitor; BGB-290, a highly selective PARP1 and PARP2 inhibitor; and BGB-A317, a PD-1 checkpoint inhibitor receptor. The company also intends to advance undisclosed preclinical candidates. Beigene plans to list on Nasdaq as BGNE. Goldman Sachs, Morgan Stanley and Cowen & Co. are joint bookrunners. (See BioWorld Today, Oct. 20, 2015.)

Moberg Pharma AB, of Stockholm, said it plans a bond issue, in part, to finance accretive acquisitions that will strengthen platforms for its strategic brands in the U.S. and allow for additional brands, increase international distribution and prepare for initiation of phase III studies for MOB-015, a topical formulation to treat nail fungus.

OTHER NEWS TO NOTE

Abbvie Inc., of North Chicago, is working with the University of Texas MD Anderson Cancer Center in a three-year collaboration focused on immuno-oncology. The agreement provides a framework for the two parties to choose and carry out preclinical and clinical studies. Abbvie and MD Anderson will each assign two scientists to a joint scientific committee, which decides on projects to pursue.

Abcellera Inc., of Vancouver, British Columbia, said it completed its first antibody discovery partnership with Massbiologics of the University of Massachusetts Medical School, funded by the Defense Advanced Research Project Agency under the ADEPT-PROTECT program and directed toward rapid human antibody discovery for infectious diseases. Screening of more than 10 million single B cells discovered a panel of hundreds of ultra-rare antibodies against multiple targets from enterotoxigenic Escherichia coli. In a separate element of the collaboration, Abcellera also identified hundreds of human anti-Ebola antibodies from a single blood sample obtained from a convalescent human patient, and provided sequences of a select subset of antibodies in less than a week.

Allergan plc, of Dublin, said the FDA approved its supplemental new drug application to update the label for Dalvance (dalbavancin) for injection. The expanded label will include a single dose administered as a 30-minute intravenous infusion for the treatment of acute bacterial skin and skin structure infections (ABSSSIs) caused by designated susceptible gram-positive bacteria in adults, including infections caused by methicillin-resistant Staphylococcus aureus. Dalvance was first approved in May 2014 for the treatment of ABSSSI in adults. (See BioWorld Today, May 27, 2014.)

Asterias Biotherapeutics Inc., of Fremont, Calif., said it completed the transfer of its manufacturing processes to produce AST-VAC2 to Cancer Research UK. AST-VAC2 is an immunotherapy product that contains mature dendritic cells derived from pluripotent stem cells, engineered to express a modified form of telomerase. Upon successful completion of AST-VAC2 production campaigns, Cancer Research UK’s Centre for Drug Development (CDD) will submit a clinical trial authorization application to the U.K. regulatory authorities for a phase I/II trial in non-small-cell lung cancer, which will be sponsored, managed and funded by CDD.

Basilea Pharmaceutica Ltd., of Basel, Switzerland, said it was informed that Claxosmithkline plc (GSK), of London, is discontinuing its U.S. Tocitno (alitretinoin) program. Global rights to Tocitno were transferred to Stiefel, a GSK company, in July 2012. Basilea has the option to reacquire the U.S. rights. GSK will continue to commercialize Tocitno in its current markets. (See BioWorld Today, June 13, 2012.)

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Alkermes

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study, called FORWARD-5.

Though there is precedent in Otsuka Pharmaceutical Co.
Ltd.'s Rexulti (brexpiprazole) for a depression drug to gain
FDA approval based on just one positive phase III study, “at
this point, (we) think the likelihood of success for the product
making it to the market is very low,” Credit Suisse analyst Vamil
Divan wrote. In step with analysts at Jefferies and JP Morgan,
Credit Suisse removed all potential sales for ALKS 5461 from its
models.

ALKS 5461 comprises a combination of samidorphan — an oral
opioid modulator formerly known as ALKS 33 — and the opioid
buprenorphine. Alkermes is developing it for the treatment of
major depressive disorder (MDD) in patients who have an
inadequate response to standard antidepressant therapies, an
indication for which it gained FDA fast track status in October
2013. MDD is the most common type of depression, with a
global point prevalence of 4.7 percent and a pooled annual
incidence of 3 percent, both based on a systematic review of
published epidemiological studies, according to Thomson
Reuters Cortellis.

Top-line results from FORWARD-1, an earlier phase III study,
confirmed the safety and tolerability of ALKS 5461 in one-week
and two-week dose-escalation schedules, also demonstrating
in exploratory analyses that patients who received it on either
schedule experienced a statistically significant reduction in
depressive symptoms from baseline. But that positive picture
is muddied by the two new trials, both of which compared
ALKS 5461 to placebo on the change from baseline on the
Montgomery–Åsberg Depression Rating Scale (MADRS). (See
BioWorld Today, March 7, 2014.)

One study, FORWARD-3, tested a formulation of ALKS 5461
containing 2 mg of buprenorphine and 2 mg of samidorphan
vs. placebo in 429 patients. It found no treatment effect for
the drug and a placebo response that was greater than that
observed in FORWARD-4, a trial that tested the same dose vs.
placebo in addition to a lower dose 0.5 mg/0.5 mg version of the
pill in 385 patients. Although the drug missed its endpoint in
FORWARD-4, too, Alkermes said there was “a clear trend
toward efficacy” with the 2 mg/2 mg dose in that study,
providing enough supportive evidence to move ahead with
FORWARD-5, the third pivotal efficacy study.

Ongoing now, FORWARD-5 is testing two dose levels of ALKS
5461 (2 mg/2 mg and 1 mg/1 mg). Though it shares common
design and analysis features with FORWARD-4, its enrollment will
now be increased and the statistical analysis plan will be updated,
Alkermes noted, though a representative of the company said no
further details of that change are being publicly disclosed now.
The company plans to provide an update later this quarter on the
projected timing of completion for the study.

“In the case of a clear positive outcome for FORWARD-5,
Alkermes believes that the evidence provided by it and the
previously completed successful, randomized, placebo-
controlled phase II study, together with supportive evidence
from FORWARD-4, collectively could provide substantial
evidence of efficacy for ALKS 5461 for the adjunctive treatment
of MDD,” it said in a statement.

PLACEBO EFFECTS

Alkermes’ experience with the placebo response in
FORWARD-3 is not wholly surprising. Studies testing
antidepressants against placebo suggest that 40 percent
of response is due to the placebo effect. (That’s part of
the reason there are so many trials in the FORWARD program.)
However, an additional element is at play in the study with the
inclusion of samidorphan, a mu-opioid antagonist intended
to control side effects associated with the opioid component:
Marta Pecina, a research assistant professor in the University of
Michigan department of psychiatry and the author of a recent
article proving the role of opioid mediated neurotransmission
in the formation of placebo effects in depression, told BioWorld
Today that “a potential limitation of samidorphan could be that,
in addition to reducing side effects it is also reducing placebo
effects in the drug arm, because of its mu-opioid antagonist
properties, and therefore it’s going to be harder to show a drug-
placebo difference.”

The failure of antidepressant responses to separate from
placebo has contributed to the reduction or discontinuation of
research on new treatments for depression, she wrote in her
recent study, published in the November 2015 issue of JAMA
Psychiatry. In parallel with efforts to develop new drugs, “we
need to put further efforts into developing ways to control for
placebo responses and effective ways to assess drug-placebo
interactions,” she said.

LOOKING LONG-TERM

While standing by Alkermes’ prospects in the long term, JP
Morgan analyst Cory Kasimov wrote that the company’s 2016
catalysts “aren’t convincing us to hang on in near-term.”
Over the course of the year ahead, he said his team expects
quarterly updates to provide insight into the launch of Aristada
(aripiprazole lauroxil), Alkermes’ extended-release injection to
treat adults with schizophrenia and on commercial progress
for Vivitrol (naltrexone), approved in the U.S. and Russia for
the treatment of alcohol dependence and for the prevention of
relapse to opioid dependence. (See BioWorld Today, April 17,
2006.)

Early data on two new candidates, ALKS 7119, a potential
treatment of agitation in patients with Alzheimer’s disease,
MDD and other central nervous system diseases and for the
immuno-oncology candidate RDB 1450 could also arrive this
year.

“One wildcard out there, in our view, is M&A, where ALKS could
conceivably be a player on either the buying or possibly even the
selling side,” Kasimov wrote. //
Abingworth
Continued from page 1

almost a decade through two co-development vehicles, SFJ Pharmaceuticals Group, of San Francisco, and London-based Avillion LLP, both of which it has jointly funded with Clarus Ventures. The offer to industry partners isn’t changing. “The plan is we’ll continue to use the portfolio companies,” Abingworth’s managing partner, Tim Haines, told BioWorld Today. Moreover, Abingworth’s venture funds will continue to invest in co-development deals as well, alongside Cambridge, Mass.-based Clarus, and, should the need arise, additional investors. Clarus closed its $500 million Clarus III fund last year, with the aim of investing about half of the cash in risk-sharing partnerships with biotech and pharmaceutical firms. (See BioWorld Today, June 9, 2015.)
The new fund, formally called Abingworth Clinical Co-Development Fund (ACCF), is Abingworth’s 11th life sciences fund. It has already completed its first deal, in an entity called SFJ Pharmaceuticals IX, which is developing an undisclosed asset for a third-party firm. The investment model offers the investors an opportunity to share some of the upside attached to big pharma’s – or big biotech’s – pipeline, by funding and, often executing, clinical development on their behalf. “This is not a cash issue, this is a P&L issue,” Haines said. Maintaining present and future profitability is a major preoccupation for big pharma management, so these deals allow development to continue by offloading the downside risk onto external partners. “It gives them more shots on goal,” Haines said. “They only pay when the put is exercised.” What they pay is pre-agreed – the exit terms are locked into the deal at the outset. “It’s really based on the value of the asset to the pharmaceutical company,” Haines said. “It’s really about market size and market opportunity.”
The new fund offers a different risk profile for investors, many of whom are also investors in Abingworth’s traditional venture funds. The clinical and regulatory risk is lower, as the assets involved are generally late stage or are already approved in a particular indication or geography. The timelines are much shorter than traditional clinical development timelines. The rewards are commensurately lower. “The rewards are pretty healthy. They’re not the 20x you occasionally see in venture and which we’ve occasionally had,” Haines said. But another positive from an investor perspective is that the deals do not require traditional venture capital exit routes, be it a trade sale or an IPO, which has begun to look increasingly risky of late. “Here it doesn’t matter what the public markets do,” Haines said.

Whether the current turbulence on public markets will affect deal sizes in privately held firms is another question – but one that is also of relevance to Abingworth. “It may do – and it may be no bad thing, because some of the valuations were probably getting ahead of themselves,” Haines said. But not all biotech stocks are overvalued, he added. “If you look at the PE numbers of the large-cap biotechs, we’re at five-year lows now.” //

Before going to press, Abingworth had completed three deals, in a public entity named SFJ Pharmaceuticals IX, which is developing an undisclosed asset for a third-party firm. The investment model offers the investors an opportunity to share some of the upside attached to big pharma’s – or big biotech’s – pipeline, by funding and executing clinical development on their behalf. “This is not a cash issue, this is a P&L issue,” Haines said. Maintaining present and future profitability is a major preoccupation for big pharma management, so these deals allow development to continue by offloading the downside risk onto external partners. “It gives them more shots on goal,” Haines said. “They only pay when the put is exercised.” What they pay is pre-agreed – the exit terms are locked into the deal at the outset.

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OTHER NEWS TO NOTE

Celleceutix Corp., of Beverly, Mass., said the FDA granted orphan designation to Kevetrin for the treatment of pancreatic cancer. Kevetrin is currently in a phase I trial at Harvard Cancer Centers’ Dana Farber Cancer Institute and Beth Israel Deaconess Medical Center.

Celltrion Inc., of Incheon, South Korea, said it adopted the technology platform from Medidata, a cloud-based solutions provider, to enhance the speed, efficiency and accuracy of clinical trials of its biosimilar candidates. Financial terms were not disclosed.

Cleveland Biolabs Inc., of Buffalo, N.Y., said the EMA granted orphan status to entolimod for treatment of acute radiation syndrome. The drug previously received orphan designation from the FDA for prevention of death following a potentially lethal dose of total body irradiation during or after a radiation disaster.

Eli Lilly and Co., of Indianapolis, said the FDA approved its Humulin R U-500 Kwipen (insulin human injection) 500 units/mL, a pre-filled device containing Humulin R U-500, a formulation of insulin that is five times more concentrated than standard U-100 insulin. It’s approved for treating high blood sugar in people with type 1 and type 2 diabetes who need more than 200 units of insulin per day.

Mannkind Corp., of Valencia, Calif., said it entered a collaboration and license agreement with newly formed Receptor Life Sciences Inc., of Seattle, in which they will explore multiple inhaled therapeutic products for the potential of treating conditions such as chronic pain, neurologic diseases and inflammatory disorders. Under the terms, Mannkind will perform initial formulation studies and will work with Receptor to develop inhaled versions of certain undisclosed compounds. Mannkind will also transfer manufacturing technology to Receptor, which will be responsible for manufacturing and commercialization activities. The parties will collaborate on clinical development, with Receptor being responsible for all development costs. Mannkind will be eligible to receive development and commercialization milestones of up to $102.25 million as well as mid-single to low double-digit royalties on net sales.

Mediwound Ltd., of Yavne, Israel, said it signed an agreement granting Avalon Pharmaceutical SA, of Bogota, Colombia, exclusive rights to market and distribute Nexobrid, a topically applied pharmaceutical product that removes dead or damaged tissue, in Colombia, Peru, Chile, Ecuador and Panama for the treatment of severe burns. Sales of Nexobrid in the new Latin American territories will commence after receipt of local regulatory approvals, which will be filed with the local regulatory authorities in each country by Avalon and is expected to be granted within a year or possibly longer. Financial terms were not disclosed.

Philogen
Continued from page 1

launched its pivotal trial in about 200 patients testing Darleukin against stage IIIb/c disease, which “almost invariably” worsens to often-fatal stage IV within two years.

Philogen, of Siena, Italy, based Darleukin on findings that the use of paired therapies (L19 with interleukin-2 [IL-2] as well as L19 with tumor necrosis factor [TNF]) are especially effective as immunotherapies. Inspired by a group of German researchers who tested IL-2 therapy in melanoma lesions for 10 years, Philogen constructed a protein that pairs IL-2, sold by Novartis AG, of Basel, Switzerland, as Proleukin, with the human vascular-targeting antibody L19. The firm genetically fused the genes coding for the antibody and the cytokine, so that the result contains both moieties and represents a new chemical entity. L19, which targets an antigen expressed during angiogenesis, was discovered in research carried out at the Swiss Federal Institute of Technology in Zurich, Switzerland, by Neri, who is also president of the company’s scientific advisory board. “The preclinical studies showed such a strong synergy [between L19 and IL-2] that it was very tempting for us to see whether the same effect could be observed in patients” with melanoma, he said.

“I think we have perfected the technology [pioneered by the German group] by giving a combination of two immunostimulatory drugs,” Neri said. “We saw not only disappearance of the lesions but most importantly effects on non-injected lesions,” suggesting an immune boost while reducing the dose from three times per week to once per week, and only four doses. In December, regulators in Italy and Germany gave their go-ahead for an international multicenter controlled phase III trial that will involve 15 European dermatological oncology centers, Philogen said.

The much-touted melanoma drugs already approved for marketing target mostly stage IV disease, Neri noted, although the FDA last fall expanded the label for New York-based Bristol-Myers Squibb Co.’s Yervoy (ipilimumab) to include adjuvant therapy in patients with stage III. The cytotoxic T-lymphocyte-associated antigen 4 blocker first won clearance in 2011 for late-stage patients not eligible for surgery. “Another thought behind the local-lesion application of Darleukin is that these [stage III] patients are actually doing fine,” he said. “They want to get rid of the disease, but also they want to stay as well as possible,” and avoiding more drastic treatment brings “potentially the advantage of good acceptance.” On paper, Darleukin is the most advanced candidate in the company’s pipeline, but he pointed out that the company has run many clinical trials with another prospect, Fibromun, a fusion protein that links L19 with recombinant TNF. The latter is sold by Ingelheim, Germany-based Boehringer Ingelheim GmbH as Beromun. Fibromun could prove strong in melanoma, colorectal cancer and soft-tissue tumors, though it’s a systemic therapy, he said.

Neri also has linked L19 and other antibodies that target antigens expressed during angiogenesis to marketed drugs, photosensitizers, radiolabels, procoagulants and cytokines such as IL-2. Research showed the entities can be targeted to tumor neovascularature, and also are relevant to other disorders related to angiogenesis, such as rheumatoid arthritis and age-related macular degeneration.

Four years ago, Philogen pulled its IPO on the Milan Stock Exchange after partner Bayer Schering Pharma AG (now Bayer Healthcare Pharmaceuticals, of Whippany, N.J.) terminated a licensing and collaboration deal between the two for the development of vascular-targeting antibodies in cancer. The IPO, in which Philogen had hopes of raising €65.3 million (then US$89.6 million), would have been the first European biotech listing of 2011, but didn’t happen because of what Philogen described as the “unexpected” notice of termination from Bayer. Philogen had tried to go public in early 2008, too, but backed away because of unfavorable market conditions. (See BioWorld Today, Feb. 10, 2011, and Feb. 18, 2011.)

The firm has an active deal with New York-based Pfizer Inc. to develop antibody-drug conjugates (ADCs), and disclosed news separately from the phase III trial that the pharma giant has exercised options in the arrangement. Details were not disclosed, but Neri said the field of ADCs is “clearly one of strong focus” for the company.

Other News to Note

Neovacs SA, of Paris, and Stellar Biotechnologies Inc., of Port Hueneme, Calif., said they entered a term sheet to form a joint venture (JV) for the manufacture of conjugated therapeutic vaccines using Stellar’s Keyhole Limpet Hemocyanin, or KLH, technology, with the purpose of producing Neovacs’ Kinoid candidates, including IFNa-Kinoid, as well as potentially other KLH-based immunotherapies on behalf of third-party customers. The parties anticipate that the JV will be owned initially 70 percent by Neovacs, with Stellar holding the remaining 30 percent.

Oxeia Biopharmaceuticals Inc., of San Diego, disclosed its lead program, OXE-103, which is designed to restore mitochondrial homeostasis via a well-characterized mechanism of action and may help curtail ongoing neurodegenerative processes. Research that led to the discovery of OXE-103 was exclusively licensed to Oxeia by the University of California, San Diego School of Medicine.

Roche AG, of Basel, Switzerland, and the Lead Discovery Center GmbH (LDC), of Dortmund, Germany, said they will collaborate to identify and leverage therapeutic opportunities addressing unmet needs across several disease areas. The partners will work together to advance projects from as early as target level up to the identification of a preclinical candidate. Over an initial three-year period, LDC will act as a translational incubator for Roche and carry out small-molecule projects in collaboration with the scientific inventors and their academic institutions. Upon attainment of a predefined milestone, Roche has option rights to an exclusive license, the terms of which will be agreed on a project-by-project basis.
Vasopharm

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(TBI). The study is due to begin in the coming months and is due to read out in 2019.

It’s been a long road for Würzburg, Germany-based Vasopharm, which first moved the compound into the clinic in January 2007. Even so, the evidence base supporting the drug is still quite thin. The upcoming study follows a 32-patient, placebo-controlled phase IIa trial, initially designed to demonstrate safety and tolerability. The EMA allowed the addition of an ex-protocol efficacy endpoint, following positive clinical effects seen in the first eight-patient cohort.

The phase III trial will follow a similar protocol – and the company hopes to see a similar outcome. The moderate to severe definition is determined by whether the treating physician decides to implant an intracranial pressure probe. “We are very firm believers that you draw up tight inclusion-exclusion criteria and you stick to them, particularly when going from phase II to phase III,” Vasopharm Chairman Andrew Clark told BioWorld Today. The study will recruit 220 patients, across 28 treatment centers. “If the effect we saw in the phase IIa is repeated, that number is more than sufficient to demonstrate it.”

In the phase IIa study, those in the drug treatment group achieved a two-point drop in the eight-point extended Glasgow Outcomes Scale at six months. Such an outcome in the phase III could be enough for the EMA’s purposes.

“It is a high barrier, but they have said they would consider an application based on a single study,” he said. Vasopharm is holding off from the U.S. for now. “We have never wanted to muddy the waters in the U.S. when we simply don’t have the resources or the capability to run a phase III study there,” Clark said. “There’s been no IND filed for this molecule,” he added. “As soon as you open that box it requires you to commit substantial resources to doing it properly.”

Potential pharma partners have shied away from the program – the history of drug development in TBI is not a happy one. Vasopharm remains open to a deal, but its main focus is on getting the phase III study done.

The study protocol allows but does not require the use of microdialysis to monitor local drug levels in situ. That removes a “mind-bendingly difficult” process – in the phase IIa trial it was performed on an hourly basis over 72 hours, using a system developed by Urban Ungerstedt at the Karolinska Hospital in Stockholm.

Originally, that was done to prove Vasopharm’s hypothesis – that the TBI causes the blood-brain barrier (BBB) to open, allowing the drug to cross into the injured area in pharmacologically relevant quantities. It does not do so in healthy volunteers. “The great strength of the microdialysis data is we know it’s happening,” Clark said. “If the blood-brain barrier is damaged, it gets into the brain where it’s needed – because it’s needed where the blood-brain barrier is damaged.”

VAS-203 is an analogue of biopterin, an endogenous co-factor required for nitric oxide synthase (NOS) activity. It relies on differing patterns of expression of the three NOS enzymes found in the brain, to inhibit selectively an inducible isoform of the enzyme (iNOS). The latter is only switched on when the BBB is compromised, whereas the two other forms, endothelial NOS and neuronal NOS, are constitutively expressed and remain complexed with biopterin for more than a week.

“We believe both endothelial and neuronal NOS have protective effects,” Clark said. The inducible isoform is highly active and more damaging. “You’re turning on a tsunami of nitric oxide,” he said. “This superdosing of nitric oxide synthase is triggering a whole cascade of events.” The iNOS requires de novo synthesis and therefore takes six to eight hours to become active in the brain, which provides a significant therapeutic window. “It gives us six to eight hours to get the patient into an ICU and stable,” Clark said.

The company has patent protection on the molecule until 2022, but it is relying on orphan drug status for European market exclusivity. Although the company sought orphan status for severe patients only, the difficulty in distinguishing moderate from severe brain injury led the EMA to grant orphan status for the wider indication. “Potentially, the numbers will exceed what is conventionally allowed for orphan,” Clark said. A complex manufacturing process – which required the development and patenting of proprietary technology – provides another layer of protection. “It’s a very, very difficult molecule to make,” he said.

TBI is also a very difficult indication, with plenty of casualties. Most recent large-scale trials have been conducted by academic investigators rather than for-profit companies. Two recent phase III trials of progesterone, Synapse and Protect, which recruited 1,195 and 882 patients, respectively, failed to demonstrate benefit. A placebo-controlled phase III trial of citicoline in 1,213 patients was stopped due to futility. The London School of Hygiene and Tropical Medicine is currently recruiting 10,000 TBI patients in a trial of the anti-hemorrhage treatment tranexamic acid.

OTHER NEWS TO NOTE

Sarepta Therapeutics Inc., of Cambridge, Mass., said the FDA’s Peripheral and Central Nervous System Advisory Committee meeting scheduled for Friday, Jan. 22, has been postponed due to an anticipated severe winter snowstorm forecasted to hit the Washington area. A future meeting date will be announced in the Federal Register. In the event of a change in the Feb. 26 PDUFA date, the company said it will provide an update at that time. The adcom was scheduled to review Sarepta’s new drug application for eteplirsen for the treatment of Duchenne muscular dystrophy amenable to exon 51 skipping. (See BioWorld Today, Jan. 19, 2016.)

Thetis Pharmaceuticals LLC, of Southport, Conn., said the FDA granted orphan designation to TP-252, its candidate for familial adenomatous polyposis, or FAP, a rare genetic disease characterized by the formation of numerous large polyps in the bowel in late childhood or adolescence.
Alzheimer’s
Continued from page 1
Professorial Chair in Neuroimmunology at the Weizmann Institute and the senior author of the work now published in *Nature Medicine*, is focused on the interplay between the nervous system and the immune system.

Previous findings by Schwartz’s lab suggested that the aging brain might be suffering from the consequences of reduced immune surveillance – that like tumors, which develop in part because the aging immune system can no longer control mutated cells, neurodegenerative disorders might be a form of immune escape.

In support of that hypothesis, the team had previously shown that depleting regulatory T cells could improve plaque clearance and cognitive symptoms in Alzheimer’s mice. (See *BioWorld Today*, Aug. 19, 2015.)

In the new study published in *Nature Medicine*, first author Kuti Baruch of Schwartz’s team, in collaboration with Ido Amit’s laboratory for immuno-genomics, treated two different types of mice with Alzheimer’s disease with systemic anti-PD-1 antibodies. The PD-1 receptor is expressed on T cells, and the antibody blocks the inhibition of T cells that occurs when they interact with other cells that express its ligand PD-L1.

That immune checkpoint shuts off the immune response after a time, preventing immune responses from becoming permanent. But it can be co-opted by tumor cells, which often express PD-L1 on their surfaces. And in the aging immune system, the interaction between PD-1 and PD-L1 may be more of a problem than a solution, preventing the immune system from its surveillance tasks.

Animals treated with PD-1 antibodies had fewer amyloid beta plaques, and the treatment improved their performance when their memories were tested in a maze.

The effects of the treatment were better when the mice received two doses of antibodies that were a month apart, though even then the effect of treatment disappeared over time. Schwartz said her team was not surprised by the necessity for continued treatment, and she expected such treatment would need to be repeated in diseases such as Alzheimer’s.

The details of the cellular mechanism that Schwartz and her colleagues observed also differed from those in cancer.

While the treatment empowers the individual immune system by releasing the T cells from some checkpoint restraints, the needed T cells in the case of Alzheimer’s disease are effector T cells unlike in cancer where killer cells are needed.

And the job of those helper cells is to open up a gateway into the brain for the cells that ultimately clear away the plaques, which are macrophages. The team also found a key requirement for a rise in levels of interferon-gamma for the approach to be successful.

For Schwartz, the differences in detail illustrate what to her is the key advantage of the immune-targeting approach – namely, that rather than targeting one aspect of Alzheimer’s disease, it aims for a systemwide reset by restoring immune surveillance, which is by its nature multifaceted.

The Weizmann Institute has filed method-of-use patents for immune checkpoint blockers in neurodegenerative disorders, and Schwartz and her team are both continuing their preclinical work to understand how PD-1 blockers would be most effective for neurodegenerative disorders and looking for partners that will take the approach into the clinic, where it could start as a phase II trial.

Schwartz said she believes the approach could have broader utility in neurodegenerative disorders, many of which are characterized by out-of-whack proteostasis.

The team is also testing PD-1 blockers in mouse models of dementia without Alzheimer’s disease, where early results look promising.

Other neurodegenerative diseases, she said, “will each need to be tested . . . but there is no reason to believe immunotherapy which activates the immune system wouldn’t work.”

REGULATORY FRONT

In its first untitled letter of the year, the FDA’s Office of Prescription Drug Promotion (OPDP) rapped Hospira Inc., a Pfizer Inc. company based in Lake Forest, Ill., for not submitting a promotional video touting Precedex (dexmedetomidine hydrochloride) before putting it on YouTube. The video also fails to include risk information and presents “arousability” as a benefit rather than a warning or precaution for the injected sedative labeled for use in surgery and other intensive care settings. In addition, the video doesn’t spell out pertinent usage information, including the fact that the drug should not be infused for more than 24 hours. OPDP instructed Hospira to remove the video immediately and to respond to the letter by Jan. 29.

James Feijo, owner and operator of Daniel Chapter One, of Portsmouth, R.I., was sentenced this week for marketing an unapproved drug and tax evasion. He is to serve six months in prison followed by six months of home confinement and three years of supervised release. Feijo, who pleaded guilty to the charges in September, also was ordered to pay more than $218,000 in restitution to the IRS, according to the Department of Justice. Feijo marketed unapproved cancer treatments online, in stores, through a call center and on his daily radio program. He avoided employment taxes by telling employees they were independent contractors and paying them with checks written out to cash.

APPOINTMENTS AND ADVANCEMENTS

Annexon Bioscience, of South San Francisco, named Mario Saltarelli chief medical officer, and Susan Kramer vice president, product development. Cellectis SA, of Paris, appointed of Loan Hoang-Sayag chief medical officer.
Price hikes
Continued from page 1
has to offer him immunity.

Jason Chaffetz (R-Utah), chairman of the House Oversight and Government Reform Committee, informed Shkreli’s attorney Wednesday that the founder and former CEO of Turing Pharmaceuticals AG could be criminally liable if he refuses to comply with a subpoena the committee issued last week. “Mr. Shkreli is uniquely qualified to answer questions about rising prescription drug prices,” Chaffetz said in a letter to Baruch Weiss, a partner with Arnold & Porter LLP.

Weiss had informed the committee that Shkreli would not appear at Tuesday’s hearing voluntarily and would “assert his constitutional privilege to remain silent if compelled to appear in light of his indictment on securities fraud and wire fraud charges,” according to the letter.

Chaffetz raised the possibility of hearing Shkreli’s testimony in an executive session or granting him immunity. He also pointed out that at least some of the questions to be asked in the hearing wouldn’t be related to Shkreli’s seven-count indictment, which stems from his management of hedge funds and Retrophin Inc. – not his time at Turing.

Shkreli, who is reportedly shopping for a different attorney, responded publicly to the subpoena Wednesday, tweeting a photo of the document with the comment, “Found this letter. Looks important.”

In addition to trying to get Shkreli in the witness chair, the House committee has requested information from New York-based Turing about the nearly 5,500 percent increase in the price of Daraprim (pyrimethamine), an anti-parasitic drug to treat toxoplasmosis, after the company bought the drug from Impax Laboratories for $55 million. The purchase and price hike occurred in August when Shkreli was at the helm of Turing, a private company.

The committee also is seeking information from Valeant Pharmaceuticals International Inc., of Laval, Quebec, relating to its hefty price hikes for heart drugs Isuprel (isoproterenol) and Nitropress (nitroprusside), both of which were acquired last February from Marathon Pharmaceuticals LLC, of Northbrook, Ill. Just a year earlier, Marathon had raised the prices 400 percent after purchasing the drugs from Hospira Inc., which has continued to manufacture the products despite the shifts in ownership.

While most of its attention is centered on Daraprim, Isuprel and Nitropress, the committee asked both Turing and Valeant to provide lists of all their drugs that have seen at least 200 percent price hikes year over year.

PLEADING THE FIFTH
The House committee hearing follows on the heels of a similar hearing last month before the Senate Special Committee on Aging, which was billed as the first in a series of hearings to investigate “sudden, aggressive price spikes of decades-old prescription drugs whose patents had expired long ago.”

As part of its ongoing investigation, the Senate committee subpoenaed Shkreli Dec. 24, requesting Turing business records relating to the Daraprim price hike that were housed on Shkreli’s personal electronic devices. (See BioWorld Today, Dec. 11, 2015.)

Sens. Susan Collins (R-Maine) and Claire McCaskill (D-Mo.), the chairwoman and ranking member of the Special Committee on Aging, reported Wednesday on the Senate floor that Shkreli has invoked the Fifth Amendment and refused to produce the documents. Turing also has not cooperated in securing the documents, Collins said.

Noting that the requested documents have no apparent connection to the criminal proceedings against the former CEO, the Senate committee is asking Shkreli to explain how producing and authenticating the documents would be incriminating.

The documents likely include information that’s essential for the Special Committee on Aging to fully understand why companies can impose egregious price increases on older prescription drugs and what policies should be considered to end the practice, Collins said.

“Absent a valid justification for the grounds for invoking the Fifth Amendment, Mr. Shkreli’s assertion could hinder our important investigation,” she added.

HURTING THE CANCER MOONSHOT?
Although the Senate committee is focusing on the pricing schemes of a few drugmakers, its investigation has received push-back from lobbyists and insiders. “One industry lobbyist even said if we wanted to cure cancer, we better leave the drug companies alone,” McCaskill said. “Well, that’s absurd.

“We want to encourage innovation and protect those investing in research and development, but we can do so while also taking a hard look at price gouging and the hedge-fund like behavior of some pharmaceutical companies,” she noted.

The senator observed that even as the committee investigation proceeded, some major drug companies raised drug prices by double digits just last month.

Altogether, prescription drug prices increased by 13 percent last year and are up 76 percent over the past five years — more than eight times the rate of inflation, McCaskill said. She cited a recent national poll showing that the affordability of prescription drugs is the top health care concern in the U.S.

APPOINTMENTS AND ADVANCEMENTS


Ocera Therapeutics Inc., of Palo Alto, Calif., named Stan Bukofzer chief medical officer.
Hundreds of academics, health care professionals and AIDS advocates from around the world are calling on President Barack Obama to essentially by-step Congress to deliver on his proposal to increase funding for HIV/AIDS research in the NIH’s final fiscal 2016 operating budget. In his budget proposal last February, the president called for an additional $100 million in NIH funding for HIV/AIDS. The president’s annual spending proposal is the opening bid in the budget negotiations with Congress, which put together the final funding bills passed in December. While the NIH got a sizable bump in funding, lawmakers spelled out how the money was to be distributed. “This is a time to prioritize, not cut or flat fund HIV/AIDS research,” the AIDS advocates said in a letter to the president this week. (See BioWorld Today, Feb. 3, 2015.)

Allergan plc, of Dublin, said findings from two randomized, multicenter, placebo-controlled phase III trials of Viberzi (eluxadoline) in irritable bowel syndrome with diarrhea were published in The New England Journal of Medicine. In those trials, significantly more patients treated with Viberzi experienced improvements in diarrhea and abdominal pain, as compared with placebo. Efficacy was defined as simultaneous reductions in the daily worst abdominal pain score by > 30 percent as compared to the baseline weekly average and a reduction in the Bristol Stool Scale to < 5, on at least 50 percent of the days within a 12-week treatment interval. The oral drug, which has mixed opioid receptor activity, was approved last year by the FDA. (See BioWorld Today, May 29, 2015.)

Agenus Inc., of Lexington, Mass., said the FDA cleared its investigational new drug (IND) application for AGEN1884, an immune checkpoint modulator antibody that binds to cytotoxic T-lymphocyte antigen-4, or CTLA-4. The FDA also cleared the IND for a second checkpoint antibody partnered with Incyte Corp., of Wilmington, Del., for INCAGN1876, which targets glucocorticoid-induced tumor necrosis factor receptor, or TNFR-related protein. Both candidates are expected to move into trials by midyear. Recepta Biopharma, of São Paulo, Brazil, was involved in the collaboration that led to the discovery of AGEN1884, which is partnered with Recepta for certain South American rights. (See BioWorld Today, Jan. 12, 2015.)

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**IN THE CLINIC**

**BTG plc,** of London, said additional data on Vistogard (uridine triacetate) were presented at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium 2016 in San Francisco. The drug was approved by the FDA last month as an antidote to overdose and early onset, severe or life-threatening toxicities from chemotherapy drugs 5-fluorouracil or capecitabine. The data, which were included in the Vistogard new drug application, showed that 96 percent of patients treated with the agent recovered fully within 30 days of treatment. Additionally, 38 percent of overdose patients resumed chemotherapy within 30 days. In comparison, 19 percent of historical cases employing standard supportive care measures survived. Generally mild adverse events of vomiting, nausea and diarrhea were attributed infrequently and, in most cases, as possibly related to Vistogard.

**Collegium Pharmaceutical Inc.** said the FDA accepted the company’s investigational new drug application to begin a clinical trial of Hydrocodone Deterx, an abuse-deterrent, extended-release analgesic for the treatment of chronic pain. The proof-of-concept trial is intended to evaluate the safety, bioavailability and abuse deterrence properties of Hydrocodone Deterx.

**Cytori Therapeutics Inc.** of San Diego, said licensee Kerastem Technologies LLC, of Solana Beach, Calif., has expanded STYLE, its U.S. phase II trial investigating early stage female and male pattern hair loss. In the expansion, Kerastem has added new trial sites in New York and New Jersey to complement the currently enrolling sites in Los Angeles and Miami. STYLE is approved to enroll up to 70 patients to test Kerastem, a treatment described as focusing on the relationship between adipose tissue and hair, highlighting the increasingly important role that adipose plays in driving the hair growth cycle.

**Five Prime Therapeutics Inc.** of South San Francisco, reported preliminary data from part 1 of the ongoing phase I trial of FPA144 in patients with solid tumors, including gastric cancer, during a poster presentation at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium 2016 in San Francisco. Safety data from 27 patients and pharmacokinetic (PK) data from 23 patients from part la (3+3 dose escalation in solid tumor patients) and part lb (parallel escalating doses in gastric cancer patients) suggested FPA144 was well tolerated in patients with advanced solid tumors up to 15 mg/kg, with no dose-limiting toxicities observed. A maximum tolerated dose was not reached in part 1. The most common treatment-emergent adverse events were grades 1 or 2 and self-limiting, including fatigue, nausea, diarrhea, dizziness and dry eye. The company said PK characteristics support once every other week or less frequent dosing. Five Prime also reported that FPA144 showed preliminary antitumor activity in patients with gastric cancer whose tumors overexpress the FGFR2b protein – the initial target patient population for the compound – including two partial responses and three patients with stable disease. The agent also showed antitumor activity in a patient with urothelial bladder cancer.

**Halozyme Therapeutics Inc.** of San Diego, said Abbvie Inc., of North Chicago, has dosed the first subject in a trial evaluating the safety and pharmacokinetics of Humira (adalimumab) with Halozyme’s Enhanze technology. Adalimumab, a therapy for arthritis, ankylosing spondylitis and Crohn’s disease, binds specifically to tumor necrosis factor (TNF)-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors. Enhanze is based on a proprietary recombinant human enzyme (rHuPH20) that temporarily degrades hyaluronan, a glycosaminoglycan or chain of natural sugars in the body, to aid in the dispersion and absorption of other injected therapeutic drugs. The start of clinical evaluation triggered a $5 million milestone payment to Halozyme under the collaboration and license agreement between the companies.

**Merrimack Pharmaceuticals Inc.** of Cambridge, Mass., said an updated overall survival analysis of the phase III NAPOLI-1 study of topoisomerase inhibitor Onivyde (irinotecan liposome injection) in combination with fluorouracil (5-FU) and leucovorin achieved a substantial improvement in 12-month overall survival in patients with post-gemcitabine metastatic pancreatic adenocarcinoma when compared to 5-FU and leucovorin alone. Analysis of the updated data supports the overall survival benefit of the Onivyde combination therapy observed in the primary analysis of the NAPOLI-1 trial. Updated findings showed one in four patients treated with Onivyde survived a milestone of one year or more: 12-month overall survival estimates of 26 percent for Onivyde in combination with 5-FU and leucovorin, a 63 percent improvement when compared to 16 percent for 5-FU and leucovorin alone. No new safety or tolerability concerns were noted in the updated analysis, the firm said.

**Oncoceutics Inc.** of Philadelphia, said patient enrollment has commenced for a trial at the Massachusetts General Hospital of the company’s lead compound, ONC201, in glioblastoma multiforme. The phase II trial will investigate the use of single-agent ONC201 in adult patients with glioblastoma who have relapsed or are refractory to other therapies and have not been treated with Avastin (bevacizumab, Roche AG). ONC201 is described as a small-molecule inducer of the human tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) gene that improves efficacy-limiting properties of recombinant TRAIL.

**APPOINTMENTS AND ADVANCEMENTS**

**Zosano Pharma Corp.** of Fremont, Calif., appointed Konstantinos Alataris president and CEO.
**IN THE CLINIC**

**Oncogenex Pharmaceuticals Inc., of Vancouver, British Columbia**, reported that its combination of apatorsen with carboplatin and pemetrexed failed to demonstrate a statistically significant progression-free survival (PFS) benefit in untreated metastatic non-small-cell lung cancer during the placebo-controlled, double-blind, randomized phase II Spruce trial. The company said a potential PFS benefit was observed in patients with high baseline serum Hsp27 status when treated with apatorsen and that the study is ongoing. Overall survival results are expected in the second half of 2016. Treatment and maintenance therapy with apatorsen was well tolerated, Oncogenex said. Adverse events were comparable between the arms and as expected for the study chemotherapy treatment.

**Precision Biologics Inc., of Rockville, Md., a member of the Cancer Moonsshot 2020 consortium**, reported data from the phase II trial of ensituximab, a neo-epitope-targeting antibody, in patients with refractory metastatic colorectal cancer who failed all standards of care. Preliminary results demonstrated a 35 percent improvement in overall survival compared to historical controls in a similar population. The primary endpoint was achieved, and more than 30 percent of patients in the trial remain alive, with the longest current survivor more than two years out from the start of treatment. Up to 60 percent of colorectal cancer patients screened for the study had a tumor containing the neo-epitope target for ensituximab. Of those enrolled in the study, 48 percent showed stabilization of target lesions after two months of therapy. Representatives from the company and the consortium plan to present the data at the American Society of Clinical Oncology Gastrointestinal Cancers Symposium in San Francisco.

**Regulus Therapeutics Inc., of La Jolla, Calif., said it plans to evaluate its phase II hepatitis C virus (HCV) candidate RG-101 in combination studies with different approved direct-acting anti-HCV agents (DAAs), including in combination with an investigational oral DAA that can be formulated into a long-acting parenteral formulation for injection providing the potential for a single-visit therapy, and in certain underserved HCV patient populations. Patient enrollment is complete in an ongoing phase II study evaluating the microRNA therapeutic in combination with Harvoni (sofosbuvir + ledipasvir, Gilead Sciences Inc.), Olysio (simeprevir, Janssen Pharmaceuticals Inc./Johnson & Johnson) or Daklinza (daclatasvir, Bristol-Myers Squibb Co.). In March, Regulus plans to initiate an open-label phase II study evaluating the combination of a single subcutaneous injection of 4 mg/kg of RG-101 and daily oral administrations of 20 mg of GSK2878175, an investigational non-nucleoside NS5B polymerase inhibitor, for up to 12 weeks in treatment-naïve patients chronically infected with HCV genotypes 1 and 3. Safety and efficacy readouts from that study are due by year-end. Regulus also said enrollment has started for an open-label, nonrandomized phase I study of 2 mg/kg of RG-101 in subjects with severe renal insufficiency or end-stage renal disease. It will compare those patients to healthy control subjects.

**Summit Therapeutics plc, of Oxford, U.K., received approval from the U.K. Medicines and Healthcare products Regulatory Agency and the Research Ethics Committee to start Phaseout DMD (Duchenne muscular dystrophy), a phase II proof-of-concept trial of the oral small-molecule utrophin modulator SMT C1100 in patients with DMD. Summit expects to report data from the first group of patients enrolled in the trial periodically from the second half of 2016 onward, with the first set of 24-week muscle biopsy data expected to be available before the end of 2016. It also expects to submit an investigational new drug application to the FDA to allow Phaseout DMD to also enroll patients in the U.S.

**Vtv Therapeutics Inc., of High Point, N.C., said it is enrolling the first patients in the company’s phase II LOGRA (aLlosteric Oral Gip1 Receptor Agonist) study, a randomized, double-blind, placebo-controlled, parallel group trial of TTP273, an oral, small-molecule GLP-1R agonist. The study will assess the safety and efficacy of TTP273 in type 2 diabetic patients on stable doses of metformin. Its primary endpoint is change in baseline in Hba1c at three months, with secondary endpoints including body weight, plasma glucose, lipids insulin, lactate, C-peptide, glucagon and GLP. The company anticipates enrolling 156 patients at 26 trial sites throughout the U.S. Top-line results are expected at the end of 2016.**

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