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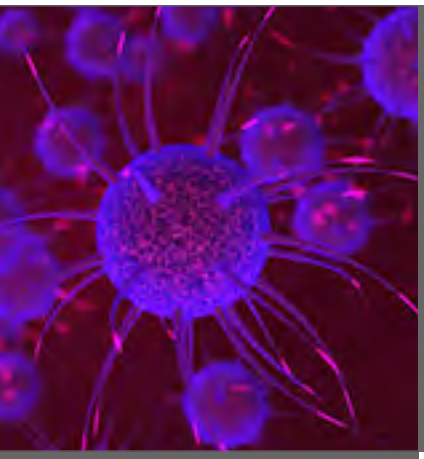

Active Biotech shares drop on laquinimod miss in Huntington's

By Cormac Sheridan, Staff Writer

DUBLIN – Shares in Active Biotech AB dropped 37 percent Tuesday on news that its lead drug laquinimod, which is licensed to Teva Pharmaceuticals Industries Ltd., missed the primary endpoint of a phase II trial in Huntington's disease.

The study randomized 352 patients to one of three dose arms (0.5 mg, 1.0 mg or 1.5 mg daily) or to a placebo group. The primary endpoint was a change in the Unified Huntington's Disease Rating Scale

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'Finding regimens that work'

No 'DED' zone in dry eye as midstage pipeline perks up

By Marie Powers, News Editor

To the layperson, dry eye disease (DED), technically xerophthalmia, often is dismissed as an innocuous nuisance that can be treated with over-the-counter eye drops. But Anat Galor, an ophthalmologist in Miami and clinical expert with the American Academy of Ophthalmology (AAO), said the disease name "is a little bit of a misnomer" for a chronic indication that encompasses a variety of symptoms and can have serious consequences for patients. The multifactorial disease of the tears and ocular surface can result not only in burning and aching but also in visual disturbances and tear film instability that have the potential to damage the ocular surface.

"This is probably not a disease that's going to make you legally blind, but it has a lot of implications for quality of life," Galor told *BioWorld*.

Indeed, research conducted by the AAO suggested that

See Dry eye, page 4

Still 'value' in HMA treatment

Strike one for ASTRAL as guadecitabine swings and misses in front-line AML

By Marie Powers, News Editor

Guadecitabine (SGI-110), the prize in Otsuka Pharmaceutical Co. Ltd.'s 2013 pick-up of Astex Pharmaceuticals Inc. for $886 million in cash, failed its first pivotal test.

Tokyo-based Otsuka and Astex, its wholly owned subsidiary, said the phase III ASTRAL-1 study, which was evaluating guadecitabine in adults with previously untreated acute myeloid leukemia (AML) who are ineligible for intense induction chemotherapy, fell short of its co-primary

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BPD fees decrease as U.S. biosimilar pathway comes of age

By Mari Serebrov, Regulatory Editor

While the cost of just about everything else seems to be going up, biosimilar sponsors are in for a bit of a break next year when it comes to FDA user fees.

According to the fiscal 2019 BsUFA fee schedule, which goes into effect Oct. 1, the annual biosimilar biological product development (BPD) fee will be $185,409. That's more than an 18 percent drop from this year's BDP fee of $227,213.

Unique to biosimilars, the BDP requires sponsors to pay a fee every year their product is in development. When sponsors submit a biologic license application, the BDP fees they've paid will

See Biosimilars, page 8

Azedra nod in ultra-orphan tumors early win for Progenics' radiopharmaceutical strategy

By Jennifer Boggs, Managing Editor

Progenics Pharmaceuticals Inc.'s newly approved Azedra (iobenguane I 131) arrives on the market with a nod for ultra-orphan neuroendocrine tumors, a hefty price tag and a label the New York-based firm hopes will lay the foundation for its broader radiopharmaceutical efforts.

On its PDUFA date Monday – extended from an initial April 30 PDUFA – Azedra won the nod as the first FDA-approved treatment specifically for patients, 12 and older, with iobenguane scan-positive, unresectable, locally advanced or metastatic pheochromocytoma or paraganglioma

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Researchers solve 'Newfoundland curse,' now looking to further develop device to stop it

By David Godkin, Staff Writer

Arrhythmogenic right ventricular cardiomyopathy (ARVC) affects one in 5,000 people worldwide and has been a perennial puzzle for clinicians as to its cause and treatment. Now a cardiologist with the research team that has won Canada's prestigious Governor General's Innovation Award for identifying the gene responsible for the condition is looking to California for assistance in repairing it.

"We've identified the gene defect that affects 50 percent of children in upwards of 20 families in Newfoundland and tracked them back for eight, nine generations," cardiologist Sean Connors told

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Earnings

Alimera Sciences Inc., of Atlanta, reported that for the three months ended June 30, 2018, its net revenue increased 5 percent to approximately $10.9 million. Its U.S. net revenue decreased by 1 percent to approximately $8 million, attributed to lower distributor orders compared to U.S. net revenue of approximately $8.1 million for the three months ended June 30, 2017. Net loss was approximately $4 million, compared to a net loss of approximately $2.8 million for the comparable three months period in 2017. Alimera had cash and cash equivalents of approximately $16.7 million.

Incyte Corp., of Wilmington, Del., reported for the quarter ended June 30, 2018, GAAP net product revenues of JAK inhibitor Jakafi (ruxolitinib) were $346 million as compared to $276 million for the same period in 2017. For the six month period, product revenues of Jakafi were $659 million as compared to $527 million for the same period in 2017. Net product revenues of Iclusig (ponatinib) were $20 million and $41 million for the three and six-month periods, respectively. Royalties for ex-U.S. sales of Jakavi, as reported by partner Novartis AG, of Basel, Switzerland, totaled $47 million and $88 million for the three and six-month periods, respectively, as compared to $34 million and $63 million for the same periods in 2017. For the quarter and six months ended June 30, 2018, GAAP product royalties from sales of Olumiant, which has been out-licensed to Lilly & Co. globally, were $9 million and $15 million, respectively, as compared to $1 million for the same periods in 2017. Incyte posted GAAP net income for the quarter of $52 million, and $0.24 per diluted share, as compared to a net loss of $12 million, or $0.06 per basic and diluted share for the same period in 2017. GAAP net income for the six months period was $11 million, or $0.05 per basic and diluted share, as compared to a net loss of $200 million, or $1 per basic and diluted share for the same period in 2017. The company had about $1.2 billion in cash, equivalents and marketable securities.

Shire plc, of Dublin, reported that for the three months ended June 30, 2018, it achieved product sales growth of 6 percent to $3.8 billion (Q2 2017: $3,592 million), driven primarily by product sales in immunology, internal medicine, and ophthalmology. It generated non-GAAP diluted earnings per ADS of $3.88, an increase of 4 percent. Total revenues were $3.9 billion representing a 5 percent growth. Non-GAAP operating income was unchanged from the 2017 Q2 period at $1.49 billion.

Takeda Pharmaceutical Co. Ltd., of Osaka, Japan, reported, for its first quarter 2018, a revenue growth of 6.4 percent led by sales in gastroenterology, oncology, neuroscience and emerging markets. Key product drivers were Entyvio (vedolizumab) for treatment of severe ulcerative colitis and moderate to severe Crohn's disease (34.1 percent) and Ninlaro (ixazomib) in relapsed or refractory multiple myeloma (43.3 percent). Its core earnings in the period grew 40.3 percent, reflecting strong revenue growth.

Financings

Delcath Systems Inc., of New York, said it has filed a registration statement with the SEC for the sale of up to 28.57 million shares at a subscription price of $1.75 per share. After its record date of Aug. 3, the company expects to distribute, at no charge, a non-transferable subscription right to purchase 500 shares of its common stock to holders of record for each share of common stock held on the record date, and to holders of its warrants to purchase common stock. Each basic subscription right will entitle the holder of record to purchase five hundred shares of common stock at the subscription price of $1.75 per share. Holders as of the record date that exercise their basic subscription rights in full will also have an over-subscription privilege, where they may subscribe to purchase additional shares at the subscription price to the extent that not all basic subscription rights are exercised.

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Active

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– Total Motor Score (UHDRS-TMS), which measures patients' motor abilities in multiple ways, including movement and control of the limbs, hands, eyes, neck and tongue. Although the drug showed no effect on this measure, it did attain a secondary endpoint, a reduction in brain atrophy. This provided some evidence that the drug was having a physiological effect in the brain, but it was obviously insufficient to have an impact on patients' symptoms.

Its cause was not helped by a decision to stop assigning patients to the high-dose arm in January 2016, following the emergence of cardiovascular symptoms in multiple sclerosis (MS) patients on 1.2 mg and 1.5 mg in a phase III trial. Laquinimod, which now has a long history of unsuccessful clinical development behind it, is a successor to roquinemex, an immunomodulatory compound originally developed by Pharmacia (now part of New York-based Pfizer Inc.), which was undone by its cardiotoxicity. Laquinimod was identified from a screening program designed to eliminate those issues, but they emerged late in the MS program – in a second phase III trial. (See *BioWorld Today*, Jan. 5, 2016.)

The drug had been an early front-runner in the contest to develop an oral MS drug. Like Sanofi SA's unexpected blockbuster Aubagio (teriflunomide), laquinimod had demonstrated moderate levels of efficacy in MS. Its positioning called for a clean safety profile, which, however, it proved unable to guarantee.

Teva, of Pitach Tikva, Israel, picked up the drug for very little outlay – just $5 million up front and up to $87 million in development, regulatory and commercial milestones – back in 2004. Active Biotech had favored a higher royalty rate along with more modest upfront and milestone payments. It has received just $22 million over the lifetime of the alliance. Teva has, obviously, invested a whole lot more in the compound's development. "Big pharma, when they do it, they do it in multiple indications," Hans Kolam, chief financial officer of Lund, Sweden-based Active Biotech, told *BioWorld*.

Teva had also conducted exploratory trials in systemic lupus erythematosus and Crohn's disease, but to no avail. The effort in Huntington's was always a longshot. "It's a tricky indication," Kolam said. "It's wrong to say that we were surprised to see it didn't hit its primary endpoint." Teva has not formally terminated the program yet. "They will need to finalize the analysis of the data before they decide what to do," Kolam said. The reaction from investors tells its own story, however.

Shifting to new approaches

Laquinimod is increasingly looking like biotech's past rather than its future. None of the traditional small-molecule drugs that have been tested in clinical trials have had any impact on the course of Huntington's. The autosomal dominant disorder is caused by an expansion of CAG repeats in the HTT huntingtin gene; the resulting misfolded proteins damage and ultimately kill neurons.

The research emphasis has recently shifted to newer approaches, following the dramatic, if preliminary, finding that an antisense oligonucleotide, IONIS-HTTRx, which Cambridge, Mass.-based Ionis Pharmaceuticals Inc. is developing in collaboration with Roche Holding AG, of Basel, Switzerland, lowered mutant huntingtin protein, the main molecular culprit in Huntington's disease, in the cerebrospinal fluid of patients. (See *BioWorld*, March 5, 2018.)

Wave Life Sciences and partner Takeda Pharmaceutical Co. Ltd. are in the clinic with two compounds, each of which silences expression of the HTT gene in an allele-specific fashion. Topline data from the two phase Ib/IIa studies are due in the first half of 2019.

The rest of Active Biotech's pipeline is curiously venerable while also being preclinical. Its best hope is tasquinimod, an oral immunomodulatory drug that has generated promising preclinical data in multiple myeloma, Kolam said. It is thought to act by targeting immunosuppressive cells within the tumor microenvironment. It improved progression-free survival in a phase III trial in prostate cancer, but development in that indication was terminated because of a failure to demonstrate an overall-survival benefit. Ipsens SA was the partner for that program. (See *BioWorld Today*, April 17, 2015.)

Active Biotech is now seeking a new deal in multiple myeloma. "It's an enormous market," Kolam said. "We need a partner that can add knowledge and competence in the multiple myeloma field." It has already secured a partner for its third clinical-stage program, Anyara. NeoTX Therapeutics Ltd., of Rehovot, Israel, is expected to begin a phase I trial of the tumor-targeting superantigen, in combination with a programmed cell death 1 (PD-1) inhibitor, later this year. The therapeutic vaccine was previously tested in several cancer indications over a decade ago.

Shares in Active Biotech (ACTI:Stockholm) closed Tuesday at SEK3.195 (US$0.36), down 37 percent on Monday's close. ♦

Financings

Insitu Biologics LLC, of Woodbury, Minn., said it launched a $10 million stock offering using Regulation A+. The company is targeting the pain control market with Anestagel that has been proven in preclinical studies as a long-lasting and fast-acting non-opiate painkiller, for use in post-operative regional pain management. The company plans to use the financing to fund phase I manufacturing, a phase I clinical study, and further preclinical studies of Anestagel.

Liquidia Technologies Inc., of Research Triangle Park, N.C., said it closed its IPO of 4.54 million shares of common stock at $11 each for gross proceeds of $50 million. The underwriters have been granted a 30-day option to purchase up to 681,818 additional shares at the IPO price. The company's shares are now trading on the Nasdaq Capital Market under the ticker symbol LQDA.

Dry eye

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fewer individuals diagnosed with DED actually present with dryness due to lack of sufficient tears as a symptom than from inflammation on the ocular surface or dysfunctional tear composition – lacrimal fluid that is too salty, insufficient in volume or displaying increased osmolarity.

Correspondingly, treatment for DED isn't a one-size-fits-all affair. Lifestyle modifications, including environmental strategies and dietary changes, often are recommended. Pharmacotherapy traditionally starts with artificial tears products, which vary in viscosity, composition and formulation. Other drug therapies include mucin production enhancers and, increasingly, anti-inflammatory agents. In 2016, the small-molecule LFA1/ICAM-1 antagonist Xiidra (lifitegrast) from Shire plc became the first FDA-approved integrin-targeted anti-inflammatory developed specifically for ocular use, though it first had to overcome a complete response letter requesting additional data from a phase III study that, fortuitously, was already underway. (See *BioWorld Today*, Oct. 20, 2015.)

The FDA had previously approved Restasis (cyclosporine) from Allergan Inc. (now Allergan plc) as the only other anti-inflammatory indicated to treat DED.

Xiidra contributed $259 million in revenues to Shire's bottom line during 2017, its first full year on the market, and the five-year consensus forecast is $1.1 billion, according to Cortellis Competitive Intelligence. Restasis pulled in $1.5 billion in 2017 sales, though revenues are expected to decline over the next five years as its patents begin to expire, despite last year's widely criticized and ultimately unsuccessful move by Allergan to shield the drug's intellectual property from inter partes review by offloading it to the Saint Regis Mohawk Tribe. (See *BioWorld*, Sept. 20, 2017, and Feb. 27, 2018.)

The anti-inflammatories approved to treat DED are low-risk, Galor said, but have their downsides. Restasis can cause a burning sensation in the eyes while Xiidra can cause an unpleasant taste – side effects that are poorly tolerated by some patients. However, the biggest problem with both medications is that, in many patients, they simply don't work.

Some turn to products that are generally but not specifically indicated for DED, such as Avenova, a pure hypochlorous acid developed by Novabay Pharmaceuticals Inc. A non-antibiotic designed to treat the underlying cause of bacterial dry eye, Avenova "is the only commercial product that is clinically proven to reduce bacteria on ocular skin surfaces, [so] sales of the product could continue to inch higher as the dry eye market grows with novel therapeutics, in our view, though the pace of market adoption could be slower than our original forecast," H.C. Wainwright analyst Raghuram Selvaraju wrote this month after Emeryville, Calif.-based Novabay expanded its marketing effort.

Research 'exploring many different pathways'

The dedicated DED pipeline also is alive and well, with nearly three dozen assets in the clinic and a dozen more in preclinical studies, according to Cortellis Competitive Intelligence.

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Dry eye

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"Researchers are exploring many different pathways," Galor said, citing efforts such as long-acting formulations, different anti-inflammatory mechanisms, nerve growth factor blockers and activators, ion channel inhibitors and cell-based therapies. Although most clinical candidates are not yet ready for prime time, some are moving through or toward pivotal trials.

At the head of the class is OTX-101, a cyclosporine nanomicellar solution developed by Sun Pharmaceuticals Industries Ltd., of Mumbai, India, which acquired the rights in 2016 from Auven Therapeutics Management LLLP, of St. Thomas, U.S. Virgin Islands, and filed for U.S. approval last year, according to Cortellis Disease Briefings.

A half-dozen agents also are in phase III development in DED. Kala Pharmaceuticals Inc. earlier this year reported outcomes from the phase III STRIDE 1 (Short Term Relief In Dry Eye) and STRIDE 2 trials of KPI-121 (loteprednol etabonate) 0.25 percent vs. placebo using the company's mucus-penetrating particle technology (MPP) to enhance delivery into target tissue of the eye. Those findings showed the drug met statistical significance in the primary endpoint of conjunctival hyperemia change, compared to placebo. But STRIDE 1 missed the mark for another pre-specified primary sign endpoint – inferior corneal staining change from baseline to day 15 (p=0.1128) – though a positive treatment effect for ocular discomfort was observed in the intent-to-treat population at day eight (p=0.0011). (See *BioWorld*, Jan. 8, 2018.)

Under the FDA's guidance, Kala disclosed Tuesday that the first patient was dosed in the third pivotal phase III STRIDE 3 trial of KPI-121 0.25 percent, expected to enroll 900 participants and designed to confirm the primary symptom endpoint of day 15 ocular discomfort severity. Data from the trial are expected to report in the fourth quarter of 2019, but Kala won't wait that long to move forward with regulatory plans. The Waltham, Mass.-based company plans to file a new drug application with the FDA during the second half of the year that includes data from one phase II, safety studies and the STRIDE 1 and 2 trials that, collectively, enrolled approximately 2,000 participants.

"We believe KPI-121 0.25 percent could obtain marketing approval for DED in 2020," Wainwright's Selvaraju wrote last month in a report initiating coverage on Kala with a buy and $35 price target, noting that the company's MPP technology "allows drugs loaded into specially designed nanoparticles to avoid the problem of washout that typically occurs via the mucus secreted at the ocular surface within the tear film. Through optimization of delivery, Kala's solutions permit lower concentrations of existing APIs to be used, enhancing safety and tolerability. More importantly, Kala's candidates can be dosed less frequently, meaningfully improving patient compliance and thus clinical outcome."

'Patients drop off pretty rapidly'

The richest portion of the DED pipeline belongs to midstage candidates. Oyster Point Pharma Inc. reported in July that the highest dose (2 percent) in its phase II PEARL trial of nicotine acetylcholine receptor (nAChR) agonist OC-02 showed a mean change in Schirmer's score of 19.3 mm compared to 2.6 mm for the control (p<0.0001). Mean change in Eye Dryness Scale score was -19 mm for the 2 percent dose compared to -6.8 mm for placebo (p=0.0006), and the 0.2 percent and 1 percent doses also were statistically significant on both measures, compared to placebo, in a dose-dependent manner.

The study was funded by a $22 million series A the Princeton, N.J.-based company landed last year in its effort to target the root cause of DED. At the time, CEO Jeffrey Nau told *BioWorld* that the potential to improve DED therapy loomed large.

"We have these two big drugs, [Restasis and Xiidra], a huge market, and big numbers behind both of these drugs, but those numbers should actually be exponentially higher, because patients drop off pretty rapidly," Nau pointed out. "The data we have say patients get their scripts filled for those drops two or three times" before they discontinue, he said. "These drugs are worth $1.5 billion, with [patients] only getting a couple of scripts filled." (See *BioWorld*, Nov. 8, 2017.)

Oyster Point has a second selective nAChR agonist, OC-1, in phase II development. In general, both compounds leverage the trigeminal parasympathetic pathway to activate the glands that comprise the lacrimal functional unit and promote tear film production, delivered either as a nasal spray or topical eye drop.

In July, Aldeyra Therapeutics Inc. said the last patient completed dosing in its 300-patient study comparing two doses of the topical formulation of reproxalap to vehicle over 12 weeks of treatment. The trial, designed to determine the optimal dose of the aldehyde scavenger to test in phase III and to assess the size of the next study, is expected to report top-line data in the second half of the year. The Lexington, Mass.-based firm also is testing the ocular version of reproxalap in allergic conjunctivitis and noninfectious anterior uveitis and the dermal version in ichthyosis associated with Sjögren-Larsson syndrome. (See *BioWorld*, July 25, 2018.)

Also last month, Aurinia Pharmaceuticals Inc., of Victoria, British Columbia, started a 90-patient phase II study designed to compare the tolerability of its calcineurin inhibitor, voclosporin, to Restasis after four weeks of treatment using the Ocular Surface Disease Index, System Assessment in Dry Eye, Individual Symptom Severity Assessments and Drop Discomfort Visual Analog Scale scores, along with fluorescein corneal staining and the Schirmer tear test. That trial also is expected to read out by year-end.

And Ocugen Inc., which is advancing its alpha-2 adrenergic agonist, OCU-300, into phase III development in ocular graft-vs.-host-disease using the 505(b)(2) pathway, has a separate candidate, OCU-310, with a different concentration of the active ingredient, brimonidine tartrate, in DED. In a phase II trial completed earlier this year, OCU-310 produced meaningful improvements across a number of endpoints related to the signs and symptoms of dry eye disease when compared to placebo. The company plans to move OCU-310 into phase III development this year. (See *BioWorld*, July 3, 2018.)

In all, 19 assets are in or have completed phase II development, according to Cortellis.

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Dry eye

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'Signs and symptoms don't correlate' in DED

The design of clinical trials in dry eye is, for now, a major obstacle to move new therapies to the finish line. To consider a filing for approval, the FDA wants to see pivotal trials that show improvement in one sign and one symptom of DED, Galor said, but there's more to that standard than meets the eye.

"One of the challenges of dry eye is that signs and symptoms don't correlate with each other due to the biology of the disease," she pointed out. "You can have a patient who feels much better but the eye surface looks the same, and you can have other patients where the surface looks much better but the patient doesn't notice any improvement. Because of that, many drugs that looked promising don't meet their primary efficacy endpoints when they get to large phase III studies."

She wasn't referring just to Kala. Another phase III victim was Rockville, Md.-based Regenerx Biopharmaceuticals Inc., which last year completed the phase III DED trial sponsored by its U.S. joint venture, Regentree LLC, of Princeton, N.J. Called ARISE-2, the trial investigated the safety and efficacy of RGN-259, a formulation of thymosin beta 4, compared to placebo in 601 patients. The experiment, conducted with Andover, Mass.-based Ora Inc., showed a number of statistically significant improvements in both signs and symptoms with 0.1 percent RGN-259 vs. placebo, along with good safety, comfort and tolerability profiles. Specifically, the ocular discomfort symptom showed a statistically significant reduction in the RGN-259-treated group at day 15 as compared to placebo (p=0.0149) in the change from baseline.

But ARISE-2 did not duplicate the results of the earlier ARISE-1 phase III study, which Wainwright's Selvaraju attributed to a more diversified patient population.

After meeting with the FDA, Regentree confirmed in April that the agency was insisting on an additional phase III trial (ARISE-3), expected to begin this year, to demonstrate efficacy in both signs and symptoms of DED in a larger patient population. The agency did, however, accept safety data from ARISE-1 and ARISE-2 and also said additional nonclinical efficacy and safety studies would not be required.

There's also the former Eleven Biotherapeutics Inc., now Sesen Bio Inc., whose lead candidate, EBI-005, failed to outperform a vehicle control, missing both co-primary endpoints in a phase III study in moderate to severe DED. Eleven called off an additional planned phase III study to concentrate instead on the drug's potential in allergic conjunctivitis, where it also proved a dud. (See *BioWorld Today*, May 19, 2015, and Jan. 20, 2016.)

The company's technology seemed sound – so much so that EBI-031, a humanized monoclonal antibody that Eleven said binds IL-6 and inhibits all known forms of IL-6 cytokine signaling, later sparked an exclusive licensing deal worth as much as $270 million with Roche Holding AG, granting the Basel, Switzerland-based pharma global rights to develop and commercialize EBI-031 and all other IL-6 antagonist antibody technology owned by Eleven. (See *BioWorld Today*, Aug. 18, 2016.)

> *"Right now it's a little bit of trial and error in trying to determine which patients will respond to which drugs."*
>
> Anat Galor, clinical expert,
> American Academy of Ophthalmology

A month later, the Cambridge, Mass.-based company engineered a merger with Viventia Bio Inc. to exploit its protein engineering platform in antibody-drug conjugates rather than ophthalmology. (See *BioWorld Today*, Sept. 22, 2016.)

Late-stage trial designs aren't the cause of every, or even most, drug failures across the board, and there's no reason to believe DED is any different. But in addition to the challenge of syncing up signs and symptoms in DED, the indication is notorious for its plethora of subtypes, and existing diagnostics fall short in parsing out differences among patients. So, while there's no shortage of DED patients, "right now it's a little bit of trial and error in trying to determine which patients will respond to which drugs," Galor acknowledged.

Companies in the DED space are working with the FDA to suggest adaptive trial designs that align better with the biology of the disease, Galor said, but progress has been slow.

Despite the challenges, "it's an exciting time" to be working in DED, she said. Although a curative approach is not yet in sight, Galor added, with so many candidates in development the odds are better than ever of "finding regimens that work for patients and give them back their lives." ♦

Astex

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endpoints of complete response (CR) rate (p>0.04) and overall survival (OS) (p>0.01), per protocol analysis, compared with the control arm of physician's choice of azacitidine, decitabine or low dose cytarabine.

Mohammad Azab, president and chief medical officer of Astex, in Pleasanton, Calif., declined to offer additional details until the full dataset is presented at a scientific meeting, which he did not name. The company continues to evaluate the data from ASTRAL-1, he said, and is committed to completing the ongoing global phase III ASTRAL-2 study evaluating guadecitabine in relapsed and refractory (r/r) AML and ASTRAL-3 in individuals with r/r myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia.

"From the data analysis that we have done, we certainly believe that guadecitabine is still an active drug, from an efficacy perspective," Azab told *BioWorld*. "The safety data are consistent with the safety profile that we had in phase II."

Guadecitabine is a next-generation DNA hypomethylating agent (HMA) designed to resist degradation by cytidine deaminase, in turn prolonging exposure of tumor cells to the active metabolite, decitabine, to ensure its uptake into the DNA of rapidly dividing cancer cells. Guadecitabine inhibits DNA methyl transferase and shows the potential to reverse aberrant DNA methylation, a characteristic of many cancer cells that results in silencing of critical genes. Through the re-expression of silenced genes, guadecitabine may offer the potential to sensitize tumor cells to other anticancer agents, including immunotherapeutics, and to re-sensitize cancer cells previously resistant to chemotherapeutics.

The candidate was designed to be administered subcutaneously (SC) as a low-volume, stable formulation. At the time of Otsuka's acquisition, Astex had just reported positive phase II data for SGI-110 in AML and MDS, and some investors groused that the purchase price was too low. (See *BioWorld*, Aug. 9, 2013, and Sept. 6, 2013.)

The compound was among the assets developed by cancer specialist Supergen Inc., which merged with its privately held counterpart, London-based Astex Therapeutics plc, in a 2011 cash and shares deal valued at $120 million. (See *BioWorld Today*, Apr. 8, 2011.)

ASTRAL-1 was the largest global prospective study conducted to date in treatment-naïve AML patients ineligible for intense induction chemotherapy, Azab said. The study enrolled 815 patients across 163 sites in 24 countries, with the goal of showing the superiority of guadecitabine, delivered SC 60mg/m2/day for five days, over standard of care azacitidine intravenously (I.V.) or SC 75 mg/m2/day for seven days, decitabine I.V. 20 mg/m2/day for five days or low dose cytarabine SC 20 mg bid for 10 days, all administered in 28-day cycles.

The study's criteria of ineligibility to receive intensive chemotherapy was based on age (over 75 years), ECOG performance status of two or three or comorbidities – a population of high unmet medical need, according to Azab.

"We still believe in the value of HMA treatment in that patient population for ASTRAL-1," he said. Decitabine and azacitidine are approved in the EU and widely used in the U.S. to treat this cohort of AML patients, he said, but not currently approved by the FDA.

'Analyses are still ongoing'

In addition to the co-primary endpoints of CR and OS, ASTRAL-1 evaluated multiple secondary endpoints. According to Cortellis Clinical Trials Intelligence, these included 30- and 60-day all-cause early mortality; progression-free survival; composite CR (CR plus complete response with incomplete blood count recovery and complete response with incomplete platelet recovery); number of days without overnight hospital stays; number of red cell or platelet transfusions during study treatment; health-related quality of life as assessed by the EQ-5D-5L descriptive system and the EQ Visual Analog Scale; duration of response and safety.

Astex and Otsuka will drill down into each endpoint to determine what lessons can be applied to other trials of guadecitabine. In addition to ASTRAL-2 and 3, those include more than 20 investigator- and company-sponsored tests in other hematological malignancies and in solid tumors, both as a single agent and in combination with chemotherapy or immunotherapy.

"With such a large trial of 815 patients, we're able to do a lot of substantial subgroup analysis that will give us some insights about the best patient population that could benefit from guadecitabine and whether there are any genetic markers that would show that guadecitabine might have an advantage," Azab pointed out. "All of these analyses are still ongoing."

Whether Astex and Otsuka would decide to make changes to the enrollment criteria in ASTRAL-2 and 3, which are still enrolling, is "an open question" until the ASTRAL-1 data analysis is complete, he added. The advice of key opinion leaders across the globe also will be sought before considering protocol changes in ongoing studies.

Although the miss on ASTRAL-1 likely takes the study out of contention for regulatory filings, "we still believe there is a good chance that we can achieve the primary endpoint" for ASTRAL-2 and 3, given differences in the demographics, the indications and the trial designs," Azab emphasized.

As for the impact of the ASTRAL-1 miss on guadecitabine's development and regulatory timetable, "we are not anticipating that ASTRAL-2 and 3 will report before 2020," he said.

AML is the most common form of acute leukemia in adults and is associated with the lowest survival rate, according to Cortellis Disease Briefings. The disease affects more men than women, and the median age at presentation is 70 years.

Although up to 80 percent of AML patients younger than 60 years may achieve a CR with standard intensive induction chemotherapy, response rates plunge below 50 percent for older patients, with cure rates following transplant of less

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Biosimilars

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be deducted from the application fee.

All other BsUFA fees will remain at their 2018 levels, according to the fee schedule published in Tuesday's *Federal Register*. Thus, the fee for applications requiring clinical data will be $1,746,745, and those not requiring clinical data will have a fee of $873,373. Sponsors with approved biosimilars will be invoiced a biosimilar biological product program fee of $304,162.

The reduction in the BDP and the stability of the other fees are signs that the biosimilar path is coming of age. The idea behind the BDP fee was to provide the FDA with the funding to get the new pathway up and running. But from the beginning, drug companies interested in the biosimilar path were adamant that the fee should be considered a stopgap measure that would end once the route was established.

While biosimilars are finally a reality in the U.S., the pathway has not advanced as quickly as expected. When the first BsUFA agreement was being hashed out in 2011, the Biotechnology Innovation Organization said the BDP fees should end in fiscal 2018. Instead, they've just been reduced. (See *BioWorld Today*, Dec. 19, 2011.)

In determining the fees, the FDA starts by calculating the total funding amount based on inflation and its likely workload for the BsUFA program in the coming year. BsUFA II set a base amount of $45 million, but the agency reduced that to $40.2 million for fiscal 2018 in light of its expected workload. (See *BioWorld*, Sept. 15, 2017.)

For 2019, the FDA is reducing the total even more – to $38,847,000 – in keeping with a commitment it made in BsUFA II to reduce its fee carryover to no more than 21 weeks of operating reserve by the end of fiscal 2022.

In breaking out the fees, the FDA expects to invoice 23 program fees for fiscal 2019. That estimate is based on currently approved products and those with pending applications with BsUFA goal dates before Oct. 1. But as of July 30, only 12 biosimilars had been approved. Last year, the program fee was based on nine biosimilars being approved. Only seven were approved by the beginning of the new fiscal year.

The FDA also expects sponsors will pay BPD fees for 87 candidates in the biosimilar development pipeline. That number includes 24 new products entering development in fiscal 2019 and the 63 products currently in development. ♦

Other news to note

Acticor Biotech SAS, of Paris, said it signed an asset transfer and licensing agreement covering a development and commercialization collaboration agreement with CMS Medical Ltd. as well as an investment agreement with CMS Medical Venture Investment Ltd., a wholly owned subsidiary of China Medical System Holdings Ltd. Acticor will collaborate with CMS, who will have the full rights in China and certain other Asian countries (excluding Japan and India), to enable the development and commercialization of the company's pipeline of drug candidates in the region. The parties will coordinate and share data from their respective clinical studies and Acticor will also receive commercial milestones and royalties based on the achievement of sales milestones by CMS and make a manufacturing margin on any product the company supplies.

Akcea Therapeutics Inc., of Cambridge, Mass., said that a study demonstrating the benefits of patient-to-patient connectivity in the management of familial chylomicronemia syndrome (FCS) found that patients who were regularly taking part in ongoing conversations with one or more patient groups were three times as likely to report "high" or "extremely high" motivation in managing their health. The company, a spinout of **Ionis Pharmaceuticals Inc.**, is developing Waylivra (volanesorsen), a potential treatment for FCS under regulatory review in the U.S., EU, and Canada.

Genkyotex SA, of Archamps, France, said the National Institutes of Health (NIH) has awarded an $8.9 million grant to Victor Thannickal at the University of Alabama at Birmingham to fund a multi-year research program evaluating the role of NOX enzymes in idiopathic pulmonary fibrosis (IPF). The core component of the program will be to conduct a 24-week phase II trial of the company's lead product candidate, GKT831, in patients with IPF. The patient enrollment is expected to begin during the first half of 2019.

Indivior plc, of Slough, U.K., has succeeded in blocking an effort by Hyderabad, India-based **Dr. Reddy's Laboratories Ltd.** to stay a preliminary injunction preventing it from using, importing, selling, or offering to sell its generic version of Suboxone (buprenorphine/naloxone) sublingual film, for now. The U.S. Court of Appeals for the Federal Circuit previously granted a motion by DRL to expedite its appeal of the preliminary injunction, and oral arguments will be held the first week of October 2018.

Innovate Biopharmaceuticals Inc., of Raleigh, N.C., agreed to collaborate with a professor at UVA Children's Hospital of the University of Virginia School of Medicine, whose research is focused on the study of enteric bacteria and their roles in health and disease. The company will work with James Nataro, director of Children's Services at the hospital, to research the effects of Innovate's lead candidate, larazotide, on environmental enteric dysfunction.

Intas Pharmaceuticals Ltd., of Ahmedabad, India, said that its wholly owned subsidiary, Accord Healthcare Ltd., will be the first to launch a pegfilgrastim biosimilar across Europe, following a positive opinion for Pelgraz (pegfilgrastim) from the EMA's Committee for Medicinal Products for Human Use. Intas, which said that it will manufacture the biologic in its own production facility, has 12 different biosimilars approved in various markets across the world.

Kane Biotech Inc., of Winnipeg, Manitoba, signed a three-year Cooperative Research and Development Agreement extension with the U.S. Army Institute of Surgical Research in Fort Sam Houston, Texas. The collaborators are developing an antibiofilm-antimicrobial wound gel formulation to address the needs of the U.S. Army Dental and Trauma Research Detachment's programs.

Progenics

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who require systemic cancer therapy. While precise patient numbers are difficult to estimate, given that the tumors are rare and often undiagnosed, literature suggests they affect between two and eight people per million in the U.S., said Bryce Tenbarge, senior vice president of commercial for Progenics.

That puts the addressable patient population in the U.S. at about 400 to 800 per year, he told investors on an early Tuesday conference call.

The good news for Progenics is that the complexities of treatment guidelines for patients with pheochromocytoma or paraganglioma (pheo or para) mean patients are referred to specialized centers, of which there are about 20 to 25 in the U.S. "This is where we plan to focus our initial efforts with our small, dedicated commercial team of 15 people," Tenbarge said. "We plan to launch our commercial efforts immediately."

As a treatment targeting ultra-rare indications, Azedra will have a price to match. Based on the average dose, the cost will be about $157,500 per dose. For patients receiving both doses of Azedra, the total cost of treatment comes to just under $300,000.

"We feel this price appropriately reflects the value" as the only approved therapy for pheo and para," Tenbarge said, adding later, "We've done our homework on this one."

According to Progenics, most patients do go on to receive the second dose. In the pivotal study, 74 percent of patients received the second dose. And real-world use is expected to offer treatment to patients with less advanced disease compared to those enrolled in the clinical study, which could increase that percentage.

The company has spent considerable time in discussions with payers, who "definitely recognize the unmet need," said CEO Mark Baker. Nor did payers raise issues with the pivotal study's primary endpoint – a reduction in antihypertensive treatment rather than the oft-sought overall survival.

"I think they accept this is an ultra-orphan drug and it is entitled to ultra-orphan pricing," Baker said. "We priced this to maximize access to the drug and, hopefully, to provide a good return" for shareholders.

The company is not yet providing sales guidance.

Progenics said it will supply an initial dosimetric dose – a necessary step to optimize the therapeutic dose for each patient – free of charge. In the pivotal study, Iobenguane I-131 was given to patients at dosimetric doses of 111 to 222 MBq. That was followed by the first therapeutic dose. Three months after the first dose, a second dose could be administered. In the pivotal phase II study, 50 of 68 patients went on to receive the second dose.

Data from the single-arm, open-label trial met the primary endpoint, showing that 17 (25 percent) experienced a 50 percent or greater reduction of all hypertensive medication for at least six months. "Importantly, this reduction was sustained, with a median duration of clinical benefit of 13.3 months," Baker said.

Overall tumor response measured via RECIST, a key secondary endpoint, showed confirmed overall tumor response of 22 percent (15 patients), with 53 percent of those experiencing durable responses lasting six months or longer.

Pheo and para, tumors arising in and around the adrenal gland, provoke increased levels of stress hormones epinephrine and norepinephrine, which can result in "dangerously high blood pressure and increased risk of heart attack and stroke," Baker said. "Controlling tumors and reducing these symptoms are the two goals."

Literature has suggested a five-year survival rate for malignant pheo and para as low as 12 percent, he added.

Detailed data disclosed at the American Society of Clinical Oncology meeting in June showed median overall survival time, as of the Dec. 4 data cut-off, was 37 months from first Azedra dosing in the overall study population. Patients receiving two therapeutic doses showed overall survival of 44 months, while patients receiving one dose had survival of 18 months.

PSMA programs to read out soon

The pivotal trial was conducted under a special protocol assessment (SPA) going back to 2009, when the drug was being developed by Molecular Insight Pharmaceuticals Inc. using technology designed to maximize delivery of the iobenguane I 131 molecules to tumors. A year after gaining the SPA, Molecular Insight filed for Chapter 11 and, in 2013, Progenics snagged that firm's assets in an all-stock deal. At that time, the prostate-specific membrane antigen (PSMA) assets for diagnosing and treating prostate cancer were the main attractions, with Azedra as a side note. Progenics pursued the planned pivotal study, however, and submitted an NDA late last year, accepted for priority review. (See *BioWorld Today*, Jan. 26, 2015.)

Azedra, which targets uptake by the norepinephrine transporter, was developed using Ultratrace, a technology designed to use less non-radioactive MIBG during enrichment for greater delivery of radiation to the tumor. The presence of so-called "carrier" iobenguane molecules can diminish uptake in target tumors, and preclinical studies showed significantly enhanced tumor kill in the absence of carrier iobenguane.

Treatment with Azedra also is specified for patients with MIBG-avid disease, with the label actually requiring an MIBG scan prior to treatment, an inclusion Baker said he found "intriguing" and one that "really fits with our strategy" of identifying patients, treating patients and then "really monitoring that treatment."

Progenics intends to look at expanding potential indications for Azedra, investigating other neuroendocrine and other tumors targeting the same molecular pathway. "We will explore a comprehensive Azedra life cycle management program," he told investors, though specifics will have to wait for a future date. "For now, the focus is on executing a successful launch."

Elsewhere in the pipeline, the firm is advancing its PSMA programs, having completed enrollment in June in the phase

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Newfoundland

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BioWorld. "What's so tragic is that some of these young men in their 20s and 30s, many of them fishermen with young families, just drop dead."

Connors, Daryl Pullman, Terry-Lynn Young and Kathy Hodgkinson, all from Memorial University in St. John's, Newfoundland, won the Governor General's Innovation Award for singling out the TMEM43 gene as the cause of the cardiac muscle disorder that often shows no symptoms before sudden cardiac arrest, discovering the gene that caused arrhythmogenic right ventricular cardiomyopathy, and helping introduce life-saving treatments for it.

No longer at sea

After identifying the gene responsible for the disease, the team developed a blood screening test for people at risk from the defect as well as a small defibrillator inserted into the heart that recognizes and corrects abnormal heart rhythm. Connors said he tells many of his patients it's like "having a lifesaver when they're out in a fishing boat." Ninety-nine percent of the time you'll never need it.

"It watches and records every single heartbeat, and as soon as it deviates from normal heart rhythm, it automatically intervenes in order to prevent a heart attack. I'm not aware of any other cardiac condition in which we base treatment solely on a genetic abnormality and a blood test."

Connors said implanting the device in healthy 18-year-old men was initially viewed by researchers and clinicians as highly unorthodox. All that changed when it was revealed the blood test and defibrillator "added, on average, 31 years to the life of a man with this gene," Connors said.

Elliptically shaped and about one-third of the size of a hockey puck (approximately 1 cm by 5 cm), the device is buried in the chest wall and connected to the heart by a very thin silicone lead. Signals from the heart travel from there back to a chip where the heart rhythms are recorded and transmitted to medical staff.

Follow the puck

Financed by up to C$15 million in public sector funding, the team's work may not end with recent miniaturization of the device and the supply of built-in battery power. Connors said he's in conversation with San Francisco-based researcher Jason Roberts about re-designing the device to repair the genetic defect. The object then would be to create a med-tech startup built around TMEM43 detection and personalized genetic repair for patients at risk of ARVC.

In the meantime, other questions abound, which if answered could benefit future generations with the genetic mutation. What is not known is the function the gene performs, why most people with the disease are men (four in five dead by age 50) and why some people with the gene live long and relatively normal lives.

Genetics researcher Kathy Hodgkinson likens that genetic variability to an ice hockey team. The bad gene can't skate or shoot the puck, but is surrounded by strong capable genes that can. Put that bad gene on the ice with weaker genes and the game is all but over.

"We've identified the gene defect that affects 50 percent of children in upwards of 20 families in Newfoundland and tracked them back for eight, nine generations.

Sean Connors, cardiologist
Memorial University in St. John's, Newfoundland

"The question is what other genes are there to help your heart work the way it's supposed to," Hodgkinson told *BioWorld*. "If you can start to understand that more clearly, you would be able to provide more personalized information and care." ♦

Astex

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than 10 percent and a median survival of less than one year, according to data from Astex.

New agents – mainly those targeting cancer metabolism – have emerged over recent years, however, raising the bar for additional entrants. They include Vyxeos (cytarabine/daunorubicin, Jazz Pharmaceuticals plc) and Idhifa (enasidenib mesylate, Celgene Corp., Agios Pharmaceuticals Inc.), both approved last year, and Tibsovo (ivosidenib) from Agios, green-lighted last month. (See *BioWorld*, Aug. 2, 2017, Aug. 4, 2017, and July 23, 2018).

Last year, the FDA also added Rydapt (midostaurin, Novartis AG) to the therapeutic toolkit to treat adults with newly diagnosed FLT3-mutated AML. (See *BioWorld Today*, May 1, 2017.)

On Tuesday, shares of parent company Otsuka Holdings Co. Ltd. (4768.T) closed at ¥5,150 (US$46.05) for a loss of ¥9 (8 cents). ♦

Progenics

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II/III OSPREY trial testing the diagnostic accuracy of PSMA-targeted PET/CT imaging agent, Pyl (18F-DCFPyL), in prostate cancer. Top-line data from the trial are expected in the fourth quarter of this year, with plans to initiate a second phase III study in patients with biochemical recurrence of prostate cancer by year-end.

In the third quarter, the company expects to report top-line results from the phase III study of 1404, a PSMA-targeted small-molecule SPECT/CT imaging agent designed to visualize prostate cancer. And in phase I, the firm has a small-molecule radiotherapeutic, 1095, in patients with metastatic castration-resistant prostate cancer.

Progenics, which reported second-quarter earnings after market close Tuesday, ended the quarter with $87.5 million on its balance sheet, which BTIG analyst Timothy Chiang wrote is "sufficient" for the U.S. launch of Azedra.

The company's shares (NASDAQ:PGNX) closed Tuesday at $7.99, down 33 cents. ♦

Other news to note

Merlion Pharmaceuticals Pte. Ltd., of Singapore, said that **Novartis AG** has terminated a license that Novartis subsidiary Alcon had to Merlion's Xtoro, an otic suspension of finafloxacin that is FDA-approved to treat swimmer's ear. The termination includes an undisclosed cash payment and all of Alcon's finafloxacin-related patents and know-how, along with Xtoro pharmaceutical product materials. David Dally, CEO of Merlion said that his company is "now well placed to progress the commercialization of Xtoro, either alone, or with partners."

Promis Neurosciences Inc., of Toronto, issued a white paper, titled "State of the Art at AAIC 2018," highlighting two major themes at this year's Alzheimer's Association International Conference in Chicago, including the potential treatment of Alzheimer's via targeting toxic amyloid beta oligomers and emerging data on the use of biomarkers to assess disease status and track the impact of treatment. A poster presentation showed the company's humanized PMN-310 demonstrated selectivity for native toxic amyloid beta oligomer derived from human Alzheimer's disease brains, with no off-target binding to amyloid beta monomers or plaque. PMN-310 is set to enter phase I testing in the second half of 2019.

Steadymed Ltd., of San Ramon, Calif., said its shareholders voted to approve the acquisition by **United Therapeutics Corp.**, of Silver Spring, Md. Shareholders also approved the nonbinding advisory proposal regarding executive compensation related to the acquisition. Upon completion of the acquisition, Steadymed shareholders will be entitled to receive $4.46 per share in cash and one contractual contingent value right per share, which will represent the right to receive $2.63 in cash upon the achievement of a milestone related to the commercialization of Trevyent (treprostinil sodium), a drug-device combination designed to deliver subcutaneous treatment for pulmonary arterial hypertension. The transaction is expected to close in the third quarter.

Takeda Pharmaceutical Co. Ltd., of Osaka, Japan, has acquired all outstanding ordinary shares and warrants of **Tigenix NV**, of Leuven, Belgium, following the expiration of the squeeze-out period. Takeda agreed to purchase the cell therapy specialist in January, in a deal valued at €520 million (US$626.7 million), which would give the Japanese pharma full ownership of Alofisel, an off-the-shelf allogeneic therapy for anal fistulas that was recommended for European marketing approval late last year. (See *BioWorld*, Dec. 18, 2017, and Jan. 8, 2018.)

Vasomune Therapeutics Inc., of Toronto, a spin-out of Sunnybrook Research Institute and MaRS Innovation, and **Anges Inc.**, of Tokyo, said they inked a global co-development deal to develop and commercialize therapeutics for diseases associated with blood vessel dysfunction and destabilization. The collaboration is designed to advance Vasomune's peptide-based Tie2 receptor agonist program, initially for the treatment of critical care indications, including acute respiratory distress syndrome, into clinical development. The parties expect to initiate clinical trials in 2020. The companies also have the option to co-develop the compounds for additional indications associated with vascular dysfunction and leakage. Those indications include asthma, atopic dermatitis, glaucoma and vascular complications of diabetes. Specific terms were not disclosed, but the companies said Anges will provide Vasomune with "multimillion-dollar co-development contributions," which will include up-front and clinical milestone fees. The parties will share equally in all expenses and all proceeds, including milestone and royalty payments from any third-party licensing transaction. Development and commercialization of the program will be managed through joint committees organized by the two companies.

Clinical data for July 31, 2018

Company	Product	Description	Indication	Status
Phase I				
Asterias Biotherapeutics Inc., of Fremont, Calif.	ASTOPC-1	Oligodendrocyte progenitor cell population derived from human embryonic stem cells	Severe cervical spinal cord injury	Cohorts 3 and 4 in the Scistar study reported results, showing no adverse events and 92% (11/12) of subjects with magnetic resonance imaging scans at 12 months consistent with the formation of a tissue matrix at the injury site; at 12 months, 100% (6/6) of cohort 3 subjects have recovered at least one motor level on at least one side, with one subject having recovered two motor levels on one side; at 12 months, 83% (5/6) of cohort 4 subjects have recovered at least one motor level on at least one side, with one subject having recovered two motor levels on one side
Moleculin Biotech Inc., of Houston	WP-1066	Targeter of STAT3 pathway	Glioblastoma and brain metastases in adults	Opened enrollment for a physician-sponsored trial
Provectus Pharmaceuticals Inc., of Knoxville, Tenn.	PV-10	Oncovirus	Multiple tumors	Its ongoing, multi-center, open-label phase I trial of PV-10 for patients with hepatic lesions has expanded to include a single-site cohort of 10 uveal melanoma patients with hepatic metastases
Purdue Pharma LP, of Stamford, Conn.	Potential first-in-class small molecule	Undisclosed	Insomnia associated with alcohol cessation	Proof of concept study planned
Regeneus Ltd., of Sydney, Australia	RGSH4K	Cancer vaccine	Solid tumors	Reported positive results from a phase I ACTIVATE trial of its cancer vaccine, which met the primary endpoint of safety and tolerability; 12 patients, heavily pretreated with chemotherapy or radiotherapy, with various advanced solid tumors received RGSH4K in 3 dose cohorts; 3 vaccines were administered in the treatment phase, given at 3-week intervals, and patients had the option to continue dosing in an extension phase; all dose levels were safe and well tolerated, achieving the safety primary endpoint with no dose-limiting toxicities and no serious adverse events related to the vaccine
Phase II				
180 Therapeutics LP, of Cambridge, Mass.	Adalimumab	Anti-TNF monoclonal antibody	Dupuytren's disease	At a dose of 40 mg, reduced expression of the fibrotic markers, α-smooth muscle actin and type I procollagen proteins at 2 weeks post-injection
Antibe Therapeutics Inc., of Toronto	ATB-346	Hydrogen sulfide-releasing derivative of naproxen	Acute and chronic pain	Dose-ranging efficacy study remains on track to commence this quarter
Arca Biopharma Inc., of Westminster, Colo.	Gencaro	Beta blocker	Atrial fibrillation in heart failure	Positive end-of-phase-II meeting with FDA, single phase III trial may be adequate for approval
Athersys Inc., of Cleveland	Multistem	Off-the-shelf stem cell therapy	Ischemic stroke	Enrollment begins in Masters 2 study
Biopharmx Corp., of Menlo Park, Calif.	BPX-04	Topical minocycline gel	Moderate-to-severe papulopustular rosacea	Received institutional review board approval
Novocure Ltd., of St. Helier, Jersey	Tumor treating fields combined with weekly paclitaxel	Low intensity, alternating electric fields that disrupt cell division for drug delivery	Ovarian cancer	*Gynecologic Oncology* published results of Innovate trial, showing progression-free survival of patients treated with tumor treating fields plus weekly paclitaxel was more than double that of weekly paclitaxel-treated historical controls

Company	Product	Description	Indication	Status
Phase III				
Kala Pharmaceuticals Inc., of Waltham, Mass.	KPI-121	Loteprednol etabonate	Dry eye disease	Dosed first patient in STRIDE 3
Lantheus Holdings Inc., of North Bellerica, Mass.	Flurpiridaz 18F	Imaging agent	Detection of coronary artery disease (CAD)	Began multicenter study, Aurora, to evaluate diagnostic efficacy of Flurpiridaz 18F Injection positron-emission tomography myocardial perfusion imaging to detect CAD
Pharmamar S.A., of Madrid, Spain	Zepsyre (lurbinectedin, PM-1183)	Inhibitor of RNA polymerase II	Small-cell lung cancer	Atlantis trial reached 600-patient recruitment goal
Notes For more information about individual companies and/or products, see Cortellis.				

Regulatory actions for July 31, 2018

Company	Product	Description	Indication	Status
Aegerion Pharmaceuticals Inc., of Windsor, England, a unit of Novelion Therapeutics Inc., of Vancouver, British Columbia	Myalepta (metreleptin)	Leptin replacement therapy	Lipodystrophy	European Commission granted marketing authorization
Ascletis Bioscience Co. Ltd., of Hangzhou, China	Ravidasvir	NS5A inhibitor	Hepatitis C	Filed a new drug application with the China FDA for use in combination with Ganovo
Bristol-Myers Squibb Co., of New York	Opdivo (nivolumab)	Anti-PD-1 antibody	Melanoma with involvement of lymph nodes or metastatic disease in patients who have undergone complete resection	European Commission granted marketing authorization
Bristol-Myers Squibb Co., of Princeton, N.J.	Sprycel	Dasatinib	Chronic myeloid leukemia	European Commission expanded the indication for Sprycel (dasatinib) to include the treatment of children and adolescents aged 1 year to 18 years with Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase and to include a powder for oral suspension formulation.
Clovis Oncology Inc., of Boulder, Colo.	Rubraca	Rucaparib	Epithelial ovarian, fallopian tube, or primary peritoneal cancer	EMA validated the application for a type II variation to the marketing authorization for Rubraca to include maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy
Eisai Co. Ltd., of Tokyo, and Merck & Co. Inc., of Kenilworth, N.J.	Lenvima (lenvatinib)	VEGFR1, VEGFR2 and VEGFR3 kinase inhibitor	Second-line or later advanced and/or metastatic non-microsatellite instability high/ proficient mismatch repair endometrial carcinoma	FDA granted breakthrough designation for use with Keytruda (pembrolizumab)

Company	Product	Description	Indication	Status
Helsinn Healthcare SA, of Lugano, Switzerland	Akynzeo (netupitant/ palonosetron)	NK1 receptor antagonist and 5-HT3 receptor antagonist	Nausea and vomiting associated with highly or moderately emetogenic cancer chemotherapy	Korean Ministry of Food and Drug Safety approved the drug for use
Immutep Ltd., of Sydney	Eftilagimod alpha	LAG-3Ig fusion protein	Non-small-cell lung carcinoma or head and neck carcinoma	FDA approved IND for TACTI-002 study testing drug in combination with Keytruda (pembrolizumab, Merck & Co. Inc.)
Novartis AG, of Basel, Switzerland	Aimovig (erenumab)	CGRP-R inhibitor	Prevention of migraine in adults experiencing 4 or more migraine days per month	European Commission granted marketing authorization
Pfizer Inc., of New York	Trazimera	Biosimilar to Herceptin (trastuzumab)	HER2 overexpressing breast cancer and HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma	European Commission granted marketing authorization
Progenics Pharmaceuticals Inc., of New York	Azedra (iobenguane I 131)	Radiolabeled guanidine analog	Lobenguane scan positive, unresectable, locally advanced or metastatic pheochromo-cytoma or paraganglioma	FDA approved new drug application
Puma Biotechnology Inc., of Los Angeles	Nerlynx (neratinib)	Pan-HER kinase inhibitor	Extended adjuvant treatment of early stage HER2-overexpressed/ amplified breast cancer following adjuvant trastuzumab-based therapy	Health Canada accepted the new drug submission for review
Sumitomo Dainippon Pharma Co. Ltd. and Nitto Denko Corp., both of Osaka, Japan	Lonasen (blonanserin)	Atypical antipsychotic	Schizophrenia	Submitted new drug application in Japan for a transdermal patch formulation of the drug
Theratechnologies Inc., of Montreal	Trogarzo	Ibalizumab-uiyk	HIV	EMA will review the application for marketing authorization of Trogarzo injection under the accelerated assessment procedure
United Therapeutics Corp., of Silver Spring, Md.	Remodulin (treprostinil)	Prostacyclin vasodilator	Pulmonary arterial hypertension	FDA approved new drug application

Notes

For more information about individual companies and/or products, see Cortellis.