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PDAC gives qualified support to Lucemyra to help with opioid withdrawal

By Mari Serebrov, Regulatory Editor

U.S. Worldmeds LLC's Lucemyra (lofexidine) moved another step closer to the U.S. market Tuesday with an 11-1 advisory committee vote recommending FDA approval of the drug to mitigate symptoms of opioid withdrawal.

The vote came with some qualifications, as several members of the FDA's Psychopharmacologic Drug Advisory Committee (PDAC) expressed concerns about the drug's cardiac risks. Because of those

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All hands (or most) on I-O deck

Kineta crafting seaworthy RIG in cancer after Merck sets sail with German buy

By Randy Osborne, Staff Writer

Last year, after Merck & Co. Inc. "put this stake in the ground" to establish the importance of the retinoic acid-induced gene I (RIG-I) pathway by acquiring Rigontec GmbH, other pharma firms sat up and took notice, said Kristin Bedard, chief scientific officer of Kineta Inc.

Her Seattle-based firm, with a preclinical RIG-I program, was "approached by some pretty large pharmaceutical companies," Bedard told *BioWorld*. "They were interested in our RIG-I program but they wanted to test them in cancer," though Kineta first explored the pathway in infectious disease. "We decided we would raise a small round of financing, go into immuno-oncology [I-O] and see if the program had legs," she said. "That's what we've been doing for about the last 18 months."

Merck, of Kenilworth, N.J., paid €115 million (then US$137

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The BioWorld Biome

Tetherball

New approaches could broaden antibiotic space

By Anette Breindl, Senior Science Editor

Editor's note: This series highlights recent studies that have used novel approaches to identify antibiotic candidates.

As antibody developers can attest, many antibodies can bind to cells. But most of them don't do anything of therapeutic value after they do.

That same issue applies to the screening of antimicrobial peptides. Binding is comparatively easy to test with current assays, but figuring out

See Antibiotics, page 5

Australia opens provisional approval path, SAS to speed patient access to new drugs

By Tamra Sami, Staff Writer

PERTH, Australia – Pharmaceutical companies wanting to submit new drug applications in Australia now have additional pathways thanks to new drug legislation aimed at speeding access to therapies.

Australia's Therapeutic Goods Administration (TGA) released new details on how to apply for both the provisional approval pathway and the special access scheme.

Both pathways were praised by industry stakeholders during numerous consultations with

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Newco News

Year-old Caelum sharpens its 'chisel' against AL amyloidosis

By Marie Powers, News Editor

Caelum Biosciences Inc. enhanced its cachet with an analysis of data from the phase Ib trial of its chimeric fibril-reactive monoclonal antibody (MAb), CAEL-101 (11-1F4), that showed a correlation between sustained decrease in N-terminal pro-brain natriuretic peptide (NT-proBNP) levels and improvement in global longitudinal strain (GLS) in individuals with cardiac amyloid light chain (AL) amyloidosis. The data, presented during an oral session at the 16th International Symposium on Amyloidosis in Kumamoto, Japan, expanded the phase Ia/Ib findings reported in December at the American Society of Hematology (ASH) annual meeting in Atlanta showing that eight of 12 patients with relapsed and refractory AL amyloidosis who had cardiac involvement responded to CAEL-101 with a median time to response of 21 days and an overall organ response rate of 63 percent (14 of 24).

Evaluable patients in the study presented with cardiac amyloidosis at baseline (NT-proBNP ≥650 pg/mL) and at least one post-baseline NT-proBNP measure. CAEL-101 was administered to eight

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A note to readers

BioWorld has updated its format for clinical trial news to make the information easier to scan and more readily useable.

Read today's Clinical news

Other news to note

Arrevus Inc., of Raleigh, N.C., received a $300,000 grant from the National Institute of Allergy and Infectious Diseases to further research using one of its products, ARV-1502, for the treatment of antibiotic-resistant wound infections. The company recently closed a series A financing, which together with the grant is expected to help accelerate the development of its proline-rich antimicrobial peptide chaperone protein inhibitors.

Biostem Technologies Inc., of Pompano Beach, Fla., signed a letter of intent with CCM Pharma Solutions setting out plans to co-develop and seek 505(b)(2) approvals for several drugs in the cardiovascular, metabolic disease and CNS disease space. Four initial products have been identified for co-development with a currently expected market revenue potential up to $30 million to $35 million each in gross annual revenue sales per product, Biostem said.

Biotime Inc., of Alameda, Calif., said that IVT Holdings has acquired Ascendance Biotechnology Inc., a company in which Biotime subsidiary Agex Therapeutics Inc. owned a minority stake. Agex will receive up to $3.5 million in cash for its Ascendance shares, helping fund Agex programs and operational expenses as it continues to grow in the field of aging and age-related diseases, said Biotime. Ascendance was originally created in late 2015 by combining Hepregen Corp.'s cellular micropatterning drug and chemical screening technologies with certain noncore Biotime research products and pluripotent cell technologies.

Carna Biosciences Inc., of Kobe, Japan, has signed a joint research agreement with Osaka, Japan-based **Sumitomo Dainippon Pharma Co. Ltd.** The companies will work together to discover, develop and potentially commercialize kinase inhibitors for psychiatric and neurological disorders. Sumitomo Dainippon (SD) will provide up to ¥80 million (US$12.7 million) up front to Carna and milestone payments in each research phase. Should SD decide to transition to clinical development and marketing of the agent(s), it will pay about ¥10.6 billion (US$1.69 billion) in total to Carna with development milestone payments in each development phase, milestone payments on sales, and royalties.

Cyxone AB, of Stockholm, concluded the first phase of a pilot study investigating the effect of cyclotides against inflammatory bowel disease (IBD) in an acute animal model of the condition. Interim results demonstrated an effect on the lymph nodes, suggesting that the cyclotides mitigate T-cell activity, which could reduce inflammation for those suffering from IBD, the company said. The study design has not yet shown clinical benefit for IBD symptoms, which will be further investigated in the second phase using an animal model closer to the nature of IBD.

Nabriva Therapeutics plc, of Dublin, and Basel, Switzerland-based **Roivant Sciences GmbH** have agreed to work together to develop and commercialize Nabriva's lefamulin, a semisynthetic derivative of pleuromutilin, in greater China. Top-line data from a second pivotal, international phase III trial of lefamulin for the treatment of adults with moderate to severe community-acquired bacterial pneumonia (CABP) are expected in the spring of 2018. Nabriva will receive a $5 million up-front payment and will be eligible for up to $90 million in additional payments tied to the successful completion of certain regulatory and commercial milestones related to lefamulin for CABP. In addition, Nabriva will be eligible to receive low double-digit royalties on sales upon approval in the covered territories.

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PDAC

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concerns, most of the committee said the drug should be approved for a 2.4-mg/day regimen, with some flexibility allowed.

The Louisville, Ky.-based Worldmeds, which began developing the drug for U.S. approval 15 years ago, had pushed for a 3.2-mg/day regimen, but it had tested both regimens, which each involved taking the drug four times a day for five to seven days. Committee members noted similar efficacy in both regimens but a significant difference in the rates of adverse events at the higher dosage.

In casting the lone no vote, Kim Wictzak, PDAC's consumer representative, recognized the precedence that would be set in approving Lucemyra as the first nonopioid, nonaddictive drug to treat opioid withdrawal. "This is kind of setting the stage," she said.

Comparing the current public pressure to do something about the opioid epidemic gripping the nation with that seen in the 1990s when HIV was the dominating public health concern, Wictzak said, "I want to make sure we're doing the right thing."

Her concerns centered on what could happen when the drug is moved from an idealized clinical trial setting to the real world, given the cardiac risks and the unknowns about how those risks would play out in patients with existing cardiac issues or those who are taking other drugs that may have similar risks.

Dicing the indications

Coming into the meeting, Worldmeds proposed two indications – mitigating symptoms associated with opioid withdrawal and facilitating the completion of abrupt opioid discontinuation treatment. The first indication was an easier sell, as even the FDA questioned whether the second one should be a separate indication.

Celia Winchell, an FDA clinical team leader, said that as staff members went through the review, they began to appreciate how interwoven the two proposed indications were, giving rise to the question of whether they were parts of the same indication or two separate indications. Approved drugs can have a lot of effects that are not included as an indication, Winchell said. But since the FDA's action on Lucemyra will set the stage for future opioid treatment drugs, agency staff wanted to explore completion of treatment as an indication, even though it is not technically a disease or a condition.

Committee members ranged all over the issue, with some insisting that it shouldn't be an indication and others saying perhaps it could be discussed in other labeling sections. Some had problems with including the word "completion." "The word 'complete' is so loaded and so impossible with this population," said Kathleen Carroll, a psychiatry professor and director of the Psychosocial Research Division of Substance Abuse at Yale University School of Medicine.

Walter Dunn, staff psychiatrist and assistant clinical professor at the West Los Angeles Veterans Administration Medical Center and the University of California Los Angeles, suggested removing "completion," which he called ambiguous, from the indication.

Some of the concern over the indication, raised by panelists and people speaking during the public hearing, focused on the lack of long-term data to support the use of Lucemyra beyond seven days. Sharon Hertz, director pf the FDA's Division of Anesthesia, Analgesia and Addiction Products, reminded them that opioid withdrawal treatment is not the same as long-term management of opioid use disorder or maintenance of sobriety.

The proposed indication is a "very specific limited use," Hertz said. "There is no claim that this is going to have a benefit for long-term opioid use disorder."

When it came time to vote on recommending approval, Carroll said she would recommend both indications, but added that completing one detox successfully is not a predictor of a patient's long-term success against opioid addiction. She said some patients go through multiple withdrawals, and "you never know which detox will turn the tide for somebody."

In presenting Lucemyra to PDAC, Louis Baxter, executive medical director of the Professional Assistance Program of NJ Inc., stressed the need for more treatment options, citing a study that showed patients' desire to avoid withdrawal, with all of its unpleasantness, is the leading reason for their current opioid use.

"We have been caught unprepared for the issues we fight today," Baxter said of the national opioid epidemic. Although a few drugs are used off-label to help with opioid withdrawal, methadone – itself an opioid that can be addictive, diverted and abused – is the only FDA-approved therapy. A few other drugs are used off-label, including clonidine, which, like Lucemyra, is an alpha 2-adrenergic receptor agonist.

Lofexidine was approved in the U.K. in 1990 and has been marketed there since 1992 as Britlofex. According to the U.K. label, the tablets relieve withdrawal symptoms, but they do not alleviate the cravings that lead many opioid-dependent patients to relapse.

Looking forward, Mark Pirner, Worldmeds' senior medical director, said, "Today's favorable recommendation brings us one step closer to providing evidence-based medication, and hope for recovery, to people who want to discontinue opioid use and are struggling with the agonizing symptoms of opioid withdrawal, one of the most powerful factors driving opioid dependence and addictive behaviors."

The FDA granted Lucemyra priority review in November. ♦

Other news to note

Novartis AG, of Basel, Switzerland, has entered an agreement with London-based **Glaxosmithkline plc** to divest its 36.5 percent stake in its consumer health care joint venture to GSK for $13 billion. Novartis said the sale will enable it to further focus on the development and growth of its core businesses. GSK, which earlier in the week withdrew an effort to acquire New York-based **Pfizer Inc.**'s consumer health care business, said the move is expected to benefit its adjusted earnings and cash flows, helping the company accelerate efforts to improve its performance.

Kineta

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million) up front and up to €349 million more in potential milestone payments to take over Rigontec, of Munich. The latter, a 2014 spinout from the University of Bonn, is commercializing the work of co-founders Gunther Hartmann and Veit Hornung. They identified – around the same time as a group at University College London – an uncapped double-stranded viral RNA species, 5' triphosphate RNA (3pRNA), as the ligand for RIG-I, a widely expressed cytosolic pattern recognition receptor. It leads to a type I interferon response upon activation. Rigontec had reached phase I trials with a prospective I-O candidate when Merck made its move. (See *BioWorld*, Sept. 7, 2017.)

Because RIG-I's natural ligand is a viral RNA, part of the virus particle binds to that receptor, thereby mounting an innate immune response, which bridges to an adaptive immune response while also eliciting immunogenic cell death in tumor cells specifically. "You're not having general cell killing," Bedard said. "The tumor cells are dying, but they're dying in a way that they will be alerting the immune system. We're essentially tricking the cancer cells into thinking they're infected with a virus" by using small-molecule drugs.

The small-molecule factor differentiates Kineta from Rigontec, and the latter, with its RNA-based efforts, is "restricted to doing intratumoral injections of their product, most likely because of the stability," Bedard said.

Her firm's work is still early preclinical. "We've selected a lead and backup series out of the phenotypic screening platform that we developed at Kineta, and in parallel we're doing a structure-based design approach. Our goal is to develop, long-term, systemic products."

Research thus far suggests "very good oral bioavailability," though intratumoral (IT) dosing has been explored, too, she said, adding that "the quickest way for us to get into the clinic is to continue with that IT administration," but an oral therapy is worth shooting for.

This week at the Keystone Symposia on Molecular and Cellular Biology: Cancer Immunotherapy Combinations in Montreal, Kineta offered preclinical RIG-I data showing that, in mouse models, the agonists yielded significant reductions in tumor growth. Two models were tested: CT26 colon carcinoma and B16F10 melanoma. Also unveiled was a newly identified RIG-I lead candidate with potent innate immune activation and immunogenic cell death activities showing orthogonal confirmation around the lead series.

Kineta's "general concept is that we have small-molecule drugs that bind to the RIG-I receptor, and they basically turn on the pathway in cancer," Bedard said. "We're essentially mimicking a virus infection but in a tumor cell," an inflammatory condition that means "you can really mount a very strong response in the cancer cells." She noted that, in I-O, a "massive number of combination trials are going on, but if you look at them, it's a lot of the same thing, tweaking this and tweaking that. There's still a giant void in new targets and new approaches, [a fact] that I think bigger companies are coming around to."

> *"[A] massive number of combination trials are going on, but if you look at them, it's a lot of the same thing, tweaking this and tweaking that. There's still a giant void in new targets and new approaches.*
>
> Kristin Bedard
> CSO, Kineta

Conus a bonus, dalazatide on phase II ride

Thus far, checkpoint inhibitor combos have turned up only modest improvements, and "the Mercks and Pfizers of the world are looking at it and saying, 'We might need something else,'" Bedard said. "A lot of it comes down to that in vivo data. Being able to show that RIG-I agonists get complete regression of the tumor [is important], but the more interesting thing is that now the mouse is immune to the cancer. When you do a re-challenge, 100 percent of those mice are resistant, and it's a long-term response," lasting for up to six months, she said. "The most compelling part of the mechanism is that you can drive that type of response."

Kineta was founded in 2007 by biotech veterans Charles Magness and Shawn Iadonato, who previously co-founded Illumigen Biosciences Inc., a genetics/genomics company bought by Cubist Pharmaceuticals Inc. in 2007. Lexington, Mass.-based Cubist didn't need Illumigen's Seattle facility, so the two entrepreneurs brought other members of the team back together to form Kineta. Merck has since acquired Cubist. (See *BioWorld Today*, Sept. 21, 2011, and Dec. 9, 2014.)

Bedard was the first new scientist hired by Kineta, which has kept afloat with money from private investors, the NIH and the Department of Defense. The company put together a robust biodefense platform focused on antivirals and vaccine adjuvants in the space of biodefense, Bedard said. "We haven't taken any large institutional financing or venture capital money, so we have a lot of flexibility in terms of how we can conduct business and what types of deals we can do," she said. The idea is to collect just enough cash with each round to reach the next inflection point "where we think we'll be in a good spot for a partnering deal."

Raising funds for the I-O program has been "I don't want to say easy, but it's gone pretty smoothly," she said. "Each round that we've done, we've exceeded our target and closed out the round on our own, because we felt that we had enough funding."

Kineta has research underway with other candidates as well, including dalazatide, a Kv1.3 inhibitor for the treatment of inclusion body myositis, a rare progressive disease of the muscle. The compound was in-licensed from UC Irvine, and Kineta took it through formal preclinical and phase I work, "showing that we could operate in this translational development space," Bedard said. Dalazatide is ready for

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Antibiotics

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whether a bound peptide will be bactericidal is a much longer slog.

Now, researchers have developed a method to quickly screen peptides for bactericidal activities. They engineered the target bacteria themselves to first express peptide sequences as part of a fusion protein and then transport the fusion protein to their cell surface, where it remains connected to the bacterium via a flexible linker sequence. If the peptide has bactericidal activity once it is on the surface, the linker keeps it close enough for it to exert that bactericidal activity.

The team has called its approach, which it reported in *Cell* earlier this year, Surface Localized Antimicrobial Display, or SLAY for short.

Senior author Bryan Davies, an assistant professor of molecular biosciences at the University of Texas at Austin, told *BioWorld* that the approach can be thought of as a sometimes-deadly version of tetherball.

Using SLAY technology, Davies and his colleagues reported on more than 800,000 random peptide sequences in their *Cell* paper.

Not too surprisingly, more than 98 percent of those peptides had no antimicrobial activity whatsoever.

But even at a hit rate of less than 2 percent, the study identified nearly 8,000 peptides with potential antimicrobial activity in gram-negative bacteria.

More broadly, the research has shown, Davies said, that "there is a much wider range of peptide chemistry with antimicrobial properties than we previously recognized."

"Peptide research has been dominated by what nature gave us, which is predominantly cationic peptides," Davies said. But his team's work has shown that "we are not limited to what nature gave us."

The team plans to follow up on some of the leads it has identified both scientifically – "we now have peptides that have very unique chemistry that have antimicrobial activity, and we have no idea how they work," Davies said – and in terms of their potential as drug leads.

But the SLAY technology itself, he added, is "where I see the real win."

Davies has been working with Avalon Ventures to recently found startup Anexigen Inc. The company will optimize the promising initial leads toward producing clinical candidates and commercialize the platform itself.

The team is refreshingly straightforward in its take on resistance. While explaining why the chances for resistance are low is de rigueur in most antimicrobial discovery efforts, Davies and his co-authors wrote in their *Cell* paper, "Bacteria have gained resistance to every antibiotic clinically used. There is no doubt they would gain resistance to any antimicrobial peptide discovered."

But if and when such resistance starts to develop, Davies said, the now-resistant bacterium can be subjected to another round of tetherball to find a peptide it is not resistant to.

The SLAY screen, he said, "can be run over and over, and that's the beauty of it." ♦

> *"Bacteria have gained resistance to every antibiotic clinically used. There is no doubt they would gain resistance to any antimicrobial peptide discovered.*
>
> Bryan Davies and team
> University of Texas at Austin

Caelum

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patients through a single intravenous (I.V.) infusion at week one in the phase Ia portion of the trial and to 19 patients through one weekly I.V. infusion for four weeks during phase Ib portion of the study. The depth and magnitude of response continued through the once-weekly dosing, according to Caelum.

In the updated data, improvement in GLS, a measure of myocardial shortening during systole, was shown in eight patients with confirmed cardiac amyloidosis at baseline who were enrolled in the phase Ib portion of the trial, correlating with reduction in NT-proBNP (Pearson correlation coefficient 0.345).

Caelum plans to present a full analysis of the phase Ib cardiac data later in the year.

Heading into its second year of operations, Caelum has amassed quite a story.

Launched in January 2017 by Fortress Biotech Inc., of New York, in rapid succession Caelum inked an agreement with Columbia University to secure exclusive global rights to CAEL-101, completed the phase Ia/Ib study initiated by Columbia, inked a biopharmaceutical manufacturing agreement with Patheon NV to prepare for process development and cGMP production of CAEL-101 in phase II/III studies and generated buzz in December with its presentation at ASH. Not surprisingly, in January, Michael Spector, president and CEO, was booked solid for three days of meetings at the J.P. Morgan Healthcare Conference in San Francisco.

In addition to the back-office support provided by Fortress, Caelum is funded by $9.9 million raised in the first quarter of 2017 through a convertible offering.

Spector joined Fortress in 2015 as an entrepreneur in residence with the intention of forming a Fortress company. He'd been introduced to the Columbia investigators leading the development of CAEL-101, which was viewed at the time as an academic program rather than one with therapeutic potential. That value proposition changed when Columbia Technology Ventures, the university's seasoned tech transfer office, began looking for a licensee, giving Caelum the opportunity to acquire "the original compound that developed the hypothesis for anti-amyloid treatment," Spector said.

Them's fighting words, considering that CAEL-101 has only a phase I study under its belt, while Prothena Corp. plc has advanced birtamimab (NEOD-001), a conformation-specific humanized IgG1 kappa MAb, into a phase III program targeting systemic AL amyloidosis. The VITAL study, which caps a development program that collectively enrolled approximately 700 participants, is expected to report top-line data next year, according to Cortellis Clinical Trials Intelligence. In the meantime, data from the phase II PRONTO study in AL amyloidosis are expected in the second quarter.

Dublin-based Prothena, which has seen the price of its shares (NASDAQ:PRTA) meander over the past year, got a boost last week in a back-loaded $2.2 billion pact with Celgene Corp. that included $100 million up front and a $50 million equity investment. The collaboration centers on three proteins, including tau, a cleaved form of TAR DNA-binding protein 43 (TDP-43) and an undisclosed target. (See *BioWorld*, March 22, 2018.)

Caelum's Spector acknowledged Prothena's jump on the amyloid space but said the profile of Columbia's asset is superior. Considering that, at the time Prothena launched VITAL its valuation was north of $1.5 billion, Fortress saw in the anti-amyloid effort "a logical opportunity to build value in a company" and made the call to launch Caelum – Latin for "chisel," like the constellation of the same name, and a metaphor for the company's treatment, which consists of breaking up amyloid deposits in an organ.

'Investors get the story'

Current treatment for AL amyloidosis is much like that for multiple myeloma (MM), Spector pointed out. Existing treatment focuses on eliminating plasma cells that produce abnormal proteins, but pathologic amyloid deposits in the body's vital tissues often remain or progress, resulting in organ failure and even death. What's different about CAEL-101 is its ability to bind to amyloid and attack it directly at the organ rather than in bone marrow or plasma cells.

The data presented at ASH by Suzanne Lentzsch, professor of medicine and director of the multiple myeloma and amyloidosis service at New York Presbyterian Hospital/Columbia University Medical Center and chair of Caelum's scientific advisory board, focused on the ability of CAEL-101 to bind to light-chain amyloid fibrils and achieve early and clinically effective organ responses in individuals with AL amyloidosis. The study achieved its primary objective of establishing a maximum tolerated dose of up to 500 mg/m2.

In addition to the overall organ response rate, the Ia/Ib study showed overall cardiac response of 67 percent (eight of 12) and overall renal response of 50 percent (five of 10). All patients showed an organ response or were stable through duration of treatment, and no patients showed organ progression. No drug-related grade 4 or 5 adverse events or dose-limiting toxicities were seen in the trial, and no deaths occurred during the study. At a median follow-up period of 18.6 months, patients in the study had an overall survival rate of 93 percent.

The next step, provided the FDA gives its blessing, is to move CAEL-101 directly into a pivotal phase IIb/III trial, expected to begin in the second half of 2018 and run for about 18 months with another 24 to 32 months of follow-up. Caelum also is exploring the inclusion of populations that might provide earlier read-outs for possible accelerated review. Although the trial design is not yet set in stone, Caelum is in dialogue with the FDA and EMA with a view to filing in both regions, and "we're certainly interested in Asia," Spector added.

"We have a sense of what the FDA's agreed to in the past," he pointed out. "One of the benefits of being No. 2 is that you have a chance to see what the lead company has done and to learn from their program."

On the flip side, "the importance for us, with a company ahead

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TGA

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the regulator. (See *BioWorld*, Dec. 7, 2016.)

The provisional approval pathway applies to new medicines or new uses for registered medicines that offer treatment options for serious illnesses where none are currently available. If approved for that pathway, drugs could get to market two years sooner than they would under a standard approval.

The provisional approval pathway provides time-limited provisional registration on the basis of preliminary clinical data when there is the potential for substantial benefit to patients. Provisional registration is limited to a maximum six years, and registration will automatically lapse at the end of that period.

There are five steps in the provisional approval process. The first is a determination process that takes about three to six months. If the new drug is deemed appropriate for the pathway, sponsors would then submit a premarket application and, if approved, would receive a two-year provisional registration. The provisional registration can be extended twice for up to two years for each term for a maximum of six years. After that time, the sponsor can transition to full approval when sufficient clinical data confirm safety and efficacy of the drug.

To be eligible for the provisional approval pathway, therapies must meet all of the following conditions:

- New prescription medicine or new indication
- For treating a serious condition
- Favorable comparison compared to existing therapies
- Major therapeutic advance
- Evidence of a plan to submit comprehensive clinical data.

Sponsors considering applying for the provisional approval pathway should organize a pre-submission meeting with the TGA to discuss the application.

Special access scheme widened

The country's special access scheme allows patients to get access to therapies that are not included on the Australian Register of Therapeutic Goods (ARTG) through their doctors. The arrangement applies for the supply of an unapproved therapy for a single patient on a case-by-case basis.

Previously, access to unapproved drugs required pre-approval, and doctors needed to submit clinical justification for authorization. Now, however, patients in Australia can get access to certain drugs that have an established history of use in similar overseas markets via a simple notification process known as the special access scheme (SAS) Category C.

Category C is a notification pathway that allows access to a single patient on a case-by-case basis for certain therapeutic products that are deemed to have an established history of use. Those products are specified in a list along with their indications. There are separate lists for drugs, medical devices and biologics.

Under the rules, the practitioner must inform the patient that the product is not approved in Australia. Adverse events must be reported to the TGA and the drug sponsor.

The process remains the same for SAS Category A and Category B pathways. Category A is a notification pathway, which allows access to seriously ill patients who would likely die without treatment. Category B requires TGA approval to access an unapproved drug that is not deemed to have an established history of use and can't be accessed through Category C. An approval letter is required before a patient can access the therapy.

The TGA said that any unapproved therapy could potentially be supplied via the SAS pathway except for goods included in Schedule 9 of the Poisons Standard.

Drugs that are not listed on the ARTG are not subsidized via the Pharmaceutical Benefits Scheme (PBS). That means it is up to the sponsor to provide the therapy on a compassionate basis at a reduced cost or at no cost.

Applications will not be accepted for the SAS scheme that cite monetary reasons as justification for the unapproved therapy, the TGA said. The applicant must provide a clinical justification for the use of the therapy, including why any product on the ARTG and available in Australia is not appropriate for the patient.

The TGA also rolled out new priority review and orphan drug pathways in July 2017 as part of the overhaul of drug and device regulations. The priority review pathway shaves about three months off a standard application. (See *BioWorld*, July 3, 2017.) ♦

Kineta

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phase II. "We're doing another round of financing to bring that product forward," she said.

At the preclinical stage is a non-opioid pain program based on a derivative from the venom of the Conus regius, a small cone snail native to the Caribbean Sea. The conopeptide drugs are described as highly potent alpha9alpha10 nAChR antagonists that have shown robust analgesic, anti-inflammatory and neuroprotective effects across multiple animal chronic pain models. In-licensed from the University of Utah, the peptide candidate is "about six to nine months away from phase I studies," Bedard said. ♦

Caelum

Continued from page 6

of us in the category, is to demonstrate that our treatments are not the same," Spector said, citing the 21-day time to organ response as a key differentiator.

"AL amyloidosis, particularly cardiac amyloidosis, has high mortality, so if you're able to improve the organ faster, that could be a meaningful benefit both in organ function and patient functioning," he explained.

The differences between CAEL-101 and other agents in the space begin at the point of design, according to Spector, since the Caelum asset was rationally designed to bind to AL light chains while others – though they may have some binding effect – were not.

"The biotech industry is astute enough to know that being second sometimes has its benefits, and you often see that No. 2 outperforms the compound that may get a first approval," he said. "In a high mortality population, investors get the story." With a 21-day response, compared to 10 months in conventional chemotherapy, "we can see ourselves being the leader in newly diagnosed patients."

In a first take on parent company Fortress Biotech, H.C. Wainwright analyst Joseph Pantginis pronounced CAEL-101 "ready to go pivotal" based on the additional phase Ib analysis.

Caelum holds orphan drug designations for CAEL-101 for use as a therapeutic agent to treat AL amyloidosis and for use as a radio imaging agent in amyloidosis.

As to whether or at what point the company will seek to partner the program, "Caelum will take this as far as it makes sense for Caelum to oversee the development," Spector said. "It's quite possible that we could consider further licensing or acquisition, but at this point our goal is to finance the company and move into a phase III program."

A financing, expected by the third quarter, could be accomplished "through public or private means," Spector said. Though he declined to cite the target amount, the raise will be sufficient to develop the company's supply chain, complete additional studies to characterize the antibody and fund the phase IIb/III to completion.

Development and commercialization of CAEL-101 can be achieved by a small company like Caelum that can target MM specialists. But, assuming the phase IIb/III effort succeeds, once data are in hand, "I suspect that a lot of interested companies would come knocking down our door," he said.

CAEL-101 is Caelum's only candidate, for now, although "we're always looking for additional assets to populate around CAEL-101," Spector said, citing hematology, amyloidosis and rare disease candidates in "crossover" specialty groups as potential prospects.

The company's story, he added, will "play out over the next year, and we'll have a sense of where we are competitively and how our profile stacks up."

On Tuesday, Fortress shares (NASDAQ:FBIO) closed at $4.80, down 18 cents. ♦

Financings

Adagene Inc., of Suzhou, China, which is involved in antibody discovery and engineering, said it raised $50 million from a series C financing, led by Sequoia China, and backed by New World TMT, Avic Trust, King Star Capital and Gopher Asset Management as well as other investors. The company has developed a dynamic precision library that assists in the development of a pipeline of antibody therapeutics to advance into clinical trials.

Arena Pharmaceuticals Inc., of San Diego, said it completed its underwritten public offering of 9.77 million shares at $41.50 each. The total included 1.275 million shares sold from the exercise in full of the underwriters' option to purchase additional shares. The gross proceeds were approximately $405.7 million and the company anticipates using the net proceeds for the clinical and preclinical development of drug candidates, including its planned phase III programs for etrasimod for the treatment of ulcerative colitis and ralinepag for the treatment of pulmonary arterial hypertension. (See *BioWorld*, March 21, 2018.)

Aslan Pharmaceuticals Pte. Ltd., of Singapore, which is focused on targeting cancers that are both highly prevalent in Asia and orphan indications in the U.S. and Europe, said it filed a registration statement with the SEC to conduct a proposed IPO of its American depository shares (ADSs) in the U.S. The number of ADSs that will be offered, and the price range have yet to be determined. The company has applied to list its ADSs on Nasdaq under the symbol ASLN.

Briacell Therapeutics Corp., of Berkeley, Calif., said it completed a nonbrokered private placement of 43 million units, consisting of one common share and one common share purchase warrant, at C10 cents each for gross proceeds of C$4.3 million (US$3.34 million). Each warrant is exercisable for one common share at C14 cents. Concurrent with the unit offering, the company also announced it completed a brokered private placement for the purchase of 5 percent unsecured convertible notes of Briacell for $800,000. The company said it will use some of the proceeds to finance a phase IIa trial.

DBV Technologies Inc., of Montrouge, France, said it issued an additional 529,162 ordinary shares, including 208,802 ordinary shares in the form of 417,604 American depositary shares (ADSs), on the same terms and conditions as the securities previously sold in the global offering, for the exercise of the underwriters' option to purchase additional shares. Each ADS represents the right to receive one-half of one ordinary share. The gross proceeds now total approximately $172.5 million. The company plans to use the net proceeds to fund the development and commercialization of its Viaskin Peanut allergy therapy, to advance development of other product candidates and for working capital and general corporate purposes.

Hua Medicine Ltd., of Shanghai, said it closed a combined series D and series E financing of $117.4 million, which is expected to fully fund the company through completion of its two phase III trials and commercial launch in China for dorzagliatin (HMS-5552), a fourth-generation glucokinase activator that treats the impaired blood glucose sensor function, addressing the underlying cause of type 2 diabetes.

Financings

Macrogenics Inc., of Rockville, Md., said it has commenced an underwritten public offering of 4.5 million shares and also intends to grant the underwriters a 30-day option to purchase up to an additional 675,000 shares of common stock.

Sorrento Therapeutics Inc., of San Diego, is selling $120.5 million of unsecured convertible notes in a private placement to accredited investors. The notes will be convertible into shares of Sorrento common stock at a price of about $7.01 per share and will accrue 5 percent interest. Purchasers will also receive a warrant to purchase additional shares. Sorrento said the financing, together with cash on hand, will allow it to continue executing for the next 18 to 24 months on its long-term strategy.

Summit Therapeutics plc, of Oxford, U.K., is raising about £15 million (US$21.2 million) through a placement of shares to investors in Europe. The company will use the funds to accelerate its preparations for a placebo-controlled trial of its Duchenne muscular dystrophy candidate, ezutromid, and for a potential regulatory filing for the candidate based on receipt of 48-week results from the ongoing phase II trial, Phaseout DMD. Top-line 48-week results of that study are expected during the third quarter. Funds will also flow to continuing development of the company's utrophin modulator and infectious disease pipeline activities, and to support initiation of the phase III trials of ridinilazole for *C. difficile* infection, that are planned to start in the first quarter of 2019, the company said. Completion of the placement remains conditional upon the admission of the ordinary shares to trading on the AIM market of the London Stock Exchange, the company said.

Other news to note

Sinovac Biotech Ltd., of Beijing, entered amendment number one to the amalgamation agreement dated June 26, 2017, that was agreed upon by parent company Sinovac (Cayman) Ltd. and its wholly owned subsidiary, Sinovac Amalgamation Sub Ltd. Under the terms of the deal, the amalgamation agreement may be terminated by the company or parent if the amalgamation of Amalgamation Sub with the company has not occurred on or before March 26, 2018. The amendment extends the termination date to April 26, 2018.

Stelvio Therapeutics Inc., of San Francisco, joined the early drug discovery ecosystem of the i2020 Accelerator in San Diego. The accelerator deploys a worldwide network of well-established R&D resources, financial and business development capabilities designed to help Stelvio advance its epigenetic platform for glioblastoma therapies. The company's artificial intelligence-driven epigenetic signature-based platform, which identifies compounds that trigger differentiation of cancer stem cells into benign cell types, matches i2020's target profile well, the accelerator said.

Vifor Pharma Group, of Bern, Switzerland, granted **Zeria Pharmaceutical Co. Ltd.**, of Tokyo, rights to hyperkalemia treatment Veltassa (patiromer) in Japan. Under the terms of the agreement, Zeria will have the exclusive right to develop Veltassa for the Japanese market and, once marketing authorization has been granted, to commercialize it in Japan. Terms were not disclosed.

Clinical data for March 27, 2018

Company	Product	Description	Indication	Status
Phase I				
Altimmune Inc., of Gaithersburg, Md.	Heptcell	Targeted immunotherapy	Chronic hepatitis B infection	Showed it was well-tolerated at all doses, while unblinded T-cell immunogenicity results were inconclusive
Arrowhead Pharmaceuticals Inc., of Pasadena, Calif.	ARO-HBV	Targeted RNAi molecule	Chronic hepatitis B virus (HBV) infection	In the phase I/II, study dosed healthy subjects to evaluate safety in single ascending doses in one portion of the trial and the pharmacodynamic effects of multiple ascending doses in patients with chronic HBV in another portion
Phase II				
Altimmune Inc., of Gaithersburg, Md.	Nasovax	Intranasal influenza vaccine	Influenza	Showed 100% seroprotection in the mid- and high-dose groups in 60 phase IIa patients
Anaptysbio Inc., of San Diego	ANB-020	Antibody that binds and inhibits IL-33	Peanut allergy	Top-line data showed six of 13 (46%) patients with moderate to severe symptoms at baseline improved peanut tolerance to cumulative 500 mg at day 14 after a single dose, compared with 0 placebo patients; concomitant allergy symptoms occurred in 80% of placebo, 7% of treated; therapy was well tolerated
Caelum Biosciences Inc., of New York	CAEL-101 (mAb 11-1F4)	Chimeric fibril-reactive monoclonal antibody	Relapsed or refractory amyloid light chain amyloidosis	Demonstrated correlation between sustained decrease in natriuretic peptide-proBNP and improvement in global longitudinal strain in cardiac population following CAEL-101 treatment in the phase Ib study
Enterin Inc., of Philadelphia	ENT-01	Orally administered synthetic derivative of squalamine	Parkinson's disease	Completed enrollment of a two-stage phase IIa study in 50 patients
Esperion Therapeutics Inc., of Ann Arbor, Mich.	Bempedoic acid	Cholesterol biosynthesis blocker	Elevated low-density lipoprotein cholesterol	Study met primary endpoint with 30 percent additional LDL-C lowering ($p<0.001$); achieved a significantly greater reduction of 34 percent in high-sensitivity C-reactive protein; observed safe and well-tolerated when added to PCSK9 therapy
Miragen Therapeutics Inc., of Boulder, Colo., and Les Laboratoires Servier SAS, of Neuilly-sur-Seine, France	MRG-110 (S95010)	Locked nucleic acid modified oligonucleotide inhibitor of microRNA-92	Heart failure	Initiated trial to evaluate safety and tolerability in a systemic dosing protocol
Moleculin Biotech Inc., of Houston	Annamycin	Liposomal anthracycline	Relapsed or refractory acute myeloid leukemia	Enrollment has begun
Opthea Ltd., of Melbourne, Australia	OPT-302	VEGF-C/VEGF-D Trap therapy	Wet age-related macular degeneration	Began dosing patients in Europe in the ongoing phase IIb trial in combination with Lucentis
Tesaro Inc., of Waltham, Mass.	niraparib	PARP inhibitor	Ovarian cancer	TOPACIO trial in combination with pembrolizumab showed overall response rate of 25 percent and disease control rate of 68 percent; ORR was 24 percent in the platinum-refractory population; response rates were not dependent on biomarker status
Tyme Technologies Inc., of New York	SM-88	Tyrosine derivative	Metastatic pancreatic cancer	The first site is open for enrollment
Phase III				
Polyphor Ltd., of Allschwil, Switzerland	POL-7080	murepavadin	Ventilator-associated bacterial pneumonia	Enrolled the first patient in the PRISM-MDR trial in VAPB due to *Pseudomonas aeruginosa*

Company	Product	Description	Indication	Status
Recro Pharma Inc., of Malvern, Pa.	Intravenous meloxicam	Long-acting preferential COX-2 inhibitor	Pain after bunionectomy surgery	Achieved a statistically significant difference reduction in Summed Pain Intensity Difference over 48 hours (p = 0.0034) as well as statistically significant reductions in SPID valued at other times and intervals; an opioid-sparing effect was observed for I.V. meloxicam 30 mg, indicated longer time to first use of rescue (p = 0.0076.)
Notes For more information about individual companies and/or products, see Cortellis.				

Regulatory actions for March 27, 2018

Company	Product	Description	Indication	Status
Antares Pharma Inc., Ewing, N.J.	Xyosted	Testosterone enanthate	Testosterone replacement therapy	Based on type A meeting with FDA, plans to submit response to FDA CRL in the second quarter 2018
Avexis Inc., of Chicago	AVXS-101	Gene therapy	Spinal muscular atrophy type 1	Received Sakigake designation by Japan's MHLW
Bristol-Myers Squibb Co., of Princeton, N.J.	Opdivo	Nivolumab	Microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin and irinotecan	FDA accepted supplemental BLA for use in combination with Yervoy
Daiichi Sankyo Co. Ltd., Tokyo	DS-8201	HER2-targeting antibody-drug conjugate	HER2-positive gastric, gastroesophageal junction cancers	Received Sakigake designation by Japan's MHLW
Fennec Pharmaceuticals Inc., of Research Triangle Park, N.C.	Pedmark	Sodium thiosulfate	Cisplatin-related ototoxicity	FDA granted breakthrough therapy designation for use in pediatric patients with standard risk hepatoblastoma
Genetx Biotherapeutics LLC, of Downers Grove, Ill.	GTX-101	Antisense oligonucleotide	Angelman syndrome	Received FDA orphan drug designation
Krystal Biotech Inc., of Pittsburgh	KB-103	Gene therapy	Dystrophic epidermolysis bullosa	Filed an IND for a phase I/II trial
Merck KGaA, of Darmstadt, Germany	Tepotinib	c-Met receptor tyrosine kinase inhibitor	Non-small-cell lung cancer	Received Sakigake designation in Japan for use in patients with Met exon 14 skipping mutations
Shield Therapeutics plc, of London	Feraccru	Ferric carboxymaltose	Iron deficiency	EC approves extending approval to include patients with and without anemia
Notes For more information about individual companies and/or products, see Cortellis.				