STOCKWATCH

The glossing over of the totality of the data against eteplirsen's approval next month was not the most surprising aspect of the physicians' letter...

EXPERT VIEW

Don't panic! There is still money available for start-ups with innovative technology and robust science, claim venture capitalists...

SEC BARS BIOTECH'S BURRILL

Burrill accused of stealing money from a $283m venture capital fund to support his "lavish lifestyle"...

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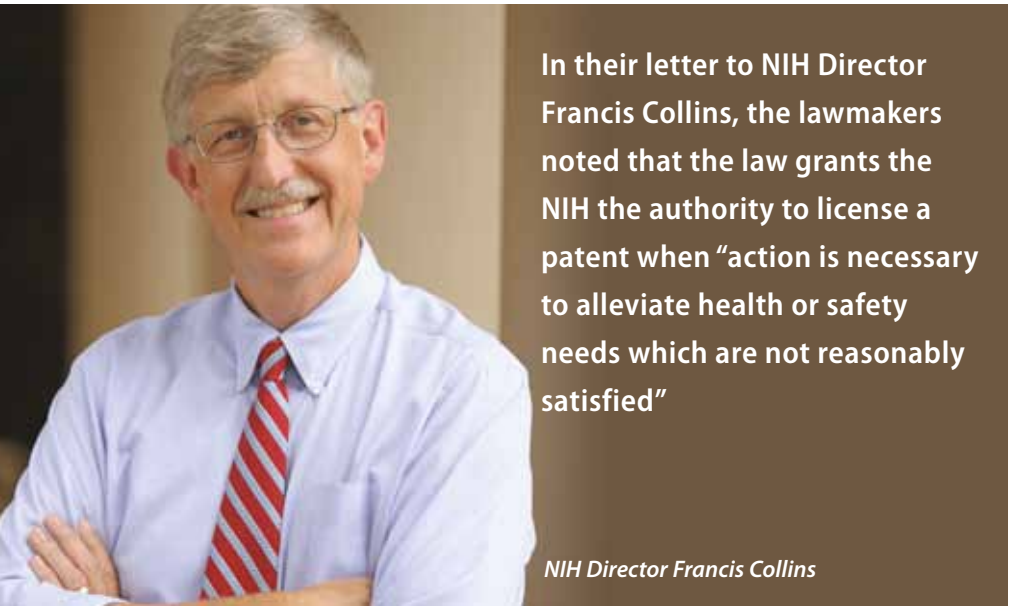

In their letter to NIH Director Francis Collins, the lawmakers noted that the law grants the NIH the authority to license a patent when "action is necessary to alleviate health or safety needs which are not reasonably satisfied"

NIH Director Francis Collins

Credit: National Institutes of Health

Analysts: Xtandi March-in Demands 'Noise,' 'Misguided'

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A demand by a group of lawmakers for the National Institutes of Health (NIH) to use its "march-in rights" authority as a way to bring down the US price of Medivation Inc.'s and Astellas Pharma Inc.'s prostate cancer drug *Xtandi* (enzalutamide) is simply "noise" and an action the agency is unlikely to take, analysts said on March 29.

Investors, however, took the potential threat seriously – driving shares of Medivation down about 14% on March 29, before closing at $38.75, a loss of $2.75, or 6%.

There were fears on Wall Street earlier in the day the panic over Medivation would spread to the whole biotech sector – much the way it did when presidential candidate Hillary Clinton declared war on drug prices this past fall.

But that didn't appear to play out – with the US biotech indices all ending the day in the green.

What has the lawmakers riled up is Xtandi's average wholesale price (AWP) in the US, which is about $129,000 a year, while the drug is sold for considerably less in other parts of the world, like Japan and Sweden, where its annual cost is $39,000, and in Canada, where it goes for $30,000 per year.

Xtandi was originally developed by the University of California at Los Angeles through taxpayer-supported research grants from the NIH and the US Army.

Under the Bayh-Dole Act of 1980, US universities, small businesses and nonprofits have control of their intellectual property that was funded by the US government.

But under the march-in rights provision in the law, the agency that funded an invention, such as the NIH, can choose to grant additional licenses to other applicants if certain criteria are met, including the failure by the licensee to satisfy the health and safety needs of US consumers.

Sens. Bernie Sanders (I-VT), Al Franken (D-MN), Sheldon Whitehouse (D-RI), Amy Klobuchar (D-MN), Patrick Leahy (D-VT) and Elizabeth Warren (D-MA) were joined by Reps. Elijah Cummings (D-MD), Lloyd Doggett (D-TX), Peter Welch (D-VT), Jan Schakowsky (D-IL), Rosa DeLauro (D-CT) and Mark Pocan (D-WI) in sending a letter to NIH Director Francis Collins calling on him to convene a public hearing to consider overriding the patent on Xtandi to make the drug available at a lower price.

In their letter, the lawmakers noted that the law grants the NIH the authority to license a patent when "action is necessary to alleviate health or safety needs which are not reasonably satisfied" or if the invention is not "available to the public on reasonable terms."

They insisted price can be a clear barrier to access for consumers.

A group of 50 Democrats in January had sent a similar letter to Collins about using march-in rights to control drug prices in the US, although at that time, they didn't specify any particular drugs.

The March letter from the dozen senators and representatives also follows a petition submitted in January to the NIH by the nonprofits the Knowledge Ecology International (KEI) and the Union for Affordable

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from the editor

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April is here and *Scrip* has had a spring-clean, ditching its tired old fonts and lay-outs and introducing fresh graphics, new formats and better signposting for our content. For those of you reading the weekly issue online, we've also made access to our exclusive online content via clickable links clearer and easier to find.

Not everything has changed, though. We're still bringing you the pick of our weekly coverage from our team of journalists across the globe, we're keeping our regular features like Stockwatch and Pipeline Watch... and we're still yellow.

The changes to the weekly issue prefigure more radical improvements for *Scrip*. By the end of this month we will launch our long-awaited new online platform, which promises to be a vast improvement on the current website. The new platform will be easier to navigate and interact with, and it will be responsive so you can enjoy accessing it from different devices. We've listened to readers and we've invested significantly, and we can't wait to show you the results.

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Five recent US and EU venture capital investments that did follow a more traditional path from the academic, startup or pharma lab to early-stage VC funding.

SEC Bars Biotech's Burrill, Settles VC Fund Theft Charges

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He may not be into buying $2m Wu-Tang Clan hip-hop albums, like another biotech executive that's recently found himself in hot water, but Steven Burrill apparently likes his vacations to St. Barts and Paris and spending cash, which allegedly wasn't his own, on private jets and Tiffany jewelry and other gifts for his wife – and his girlfriend, according to the Securities and Exchange Commission (SEC).

The SEC accused Burrill of stealing money from a $283m venture capital fund – Burrill Life Sciences Capital Fund III, formed in 2006 – to support his "lavish lifestyle" and to cover cash shortages at his VC businesses and pay employee salaries.

> All told, the SEC said, Burrill used about $4.6m of the money he misappropriated from Fund III to pay for his cash draws and personal expenses – including those lavish vacations and gifts.

"Burrill spent his fund's capital on whatever he pleased and elevated his own interests above those of investors," said Andrew Ceresney, director of the SECs Enforcement Division.

The SEC said the venture capitalist – one of the most well-known in the biotech community – and his company, Burrill Capital Management (BCM), agreed to pay back nearly $4.8m Burrill had pilfered from investors for personal use, plus a $1m penalty, to settle charges he misappropriated $18m.

Burrill has been up against lawsuits from investors and at least one former employee claiming the VC chief had depleted the fund – the latter of which was recently settled.

Under the SEC's settlement, Burrill – known mostly for his popular annual state of the biotech industry reports, which he presented each year at the BIO International Convention – is forever barred from the securities industry. Also barred were BCM's chief legal officer Victor Hebert and controller Helena Sen, who the SEC asserted were in on Burrill's scheme to steal cash from the fund – a plot that went as far back as 2007. Hebert also is paying penalties of $185,000, while Sen must pony up $90,000.

The SEC said Hebert led investment committee meetings and agreed to call in additional capital from fund investors while knowing the money would be spent on expenses unrelated to the fund.

On at least two occasions, Burrill and Sen delayed distribution of payments owed to fund investors so the money could instead be used to pay the VC boss' personal expenses and the salaries of his two accomplices, regulators said.

None of the three accused conspirators have fessed up to the charges – but they didn't deny them, either. The SEC said the three moved the $18m around by calling the cash "advanced management fees."

But in August 2013, several members of Fund III's investment committee had discovered the misappropriations and notified investors.

A CASH FLOW PROBLEM

The SEC said the scheme to take money from Fund III started in 2007, when BCM began to face cash flow shortages. According to BCMs accounting records, the expenses for the Burrill's business entities, along with his personal expenses, far exceeded the revenue his businesses were generating.

When Sen told Burrill in late 2007 that BCM was unable to make its payroll or pay its expenses for the period because of its cash deficit, he instructed her to take $400,000 from Fund III to make up the shortfall and to treat the transaction as an "advance on management fees," which he thought could be earned back in the first quarter of 2008, according to the SEC's settlement order.

Burrill insisted those "fees" were "strictly a timing issue," because BCM was entitled to take them four days later on Jan. 1, 2008. So Sen transferred the money from Fund III's bank account to the VC company and it as a "prepaid expense" in the fund's books and records.

The same type of shortfall came up again in mid-2008, so Burrill instructed Sen to cover it by again taking an advance on management fees from Fund III. They then repeated that cycle "on many occasions" when BCM fell short of cash – using the Fund III because it "had the most money available to it in the form of committed, but still-uncalled capital," the SEC said.

Hebert came into the plot when he joined Burrill & Co. in October 2008 as chief administrative officer, chief legal officer and managing director – becoming Sen's boss. By May 2013, the money Burrill had taken exceeded the total management fees that could be earned over Fund III's life by at least $13m – about four years worth of fees, the SEC said. Not only did Burrill misappropriate the Fund III's existing cash, he and his accomplices also asked investors for more money than was needed for follow-on investments so they could continue to fund BCM's operations, regulators said.

In February 2009, Sen began inflating the amounts included in the capital call demand letters above what the investment committee determined was needed for follow-on investments and the then due management fees and expenses – creating a "cushion" ranging from $50,000 to $1.5m, which was not disclosed to investors. But Burrill and his co-conspirators eventually got caught in late August 2013.

While Burrill admitted to the committee at an "emergency" meeting the next month he'd taken money from Fund III, he said it was to develop other venture funds under the his firm's brand – saying he only owed about $7.8m and hiding the fact he'd actually misappropriated a total of $18m.

All told, the SEC said, Burrill used about $4.6m of the money he misappropriated from Fund III to pay for his cash draws and personal expenses – including those lavish vacations and gifts.

Burrill, the SEC charged, "willfully violated" US investment laws through his deceit and Herbert and Sen aided and abetted him in the scheme.

FDA: Biosimilar Labeling Should Rely On Innovator Data

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The labeling for biosimilars should rely largely on the relevant safety and effectiveness data used by the corresponding US-licensed innovator medicines, with appropriate product-specific modifications, the FDA said in a new long-awaited draft guidance document issued on March 31 – declaring that's the best approach the agency could come up with after six years of trying.

The major drug industry lobbying groups – the Pharmaceutical Research and Manufacturers of American (PhRMA), the Biotechnology Industry Organization (BIO) and the Generics Pharmaceutical Association (GPhA) and its affiliated Biosimilars Council – all said they were not ready to comment on the labeling guidance, but it's unlikely they'll all be satisfied with the document, particularly the organizations representing the innovators.

The Biosimilars Forum, which consists of a mixed bag of brand-name and generic firms, said it also wanted more time to scrutinize the guidance, but said it was at least glad to see the FDA had produced something that would provide greater clarity.

The document comes six years after President Barack Obama signed the Biologics Price, Competition and Innovation Act into law, giving the FDA the authority to approve biosimilars.

The FDA said it's still working on its much-anticipated interchangeability guidance – declaring the agency is still mulling over the types of data and information needed to support a demonstration that a biosimilar is interchangeable with a reference product. But in the FDA's aptly named Labeling for Biosimilar Products guidance, regulators said information and data from a biosimilar's clinical study should only be described in that product's labeling when it's necessary to inform safe and effective use by a health care practitioner – a recommendation which likely won't sit well with PhRMA and BIO.

The FDA insisted there was no need for biosimilar labeling to include a description of the copycat product's studies, since those trials were not generally designed to independently demonstrate safety and efficacy, but were instead conducted to show there were no clinically meaningful differences between it and the innovator drug.

The biosimilar data, the agency contended, would not likely to be relevant or useful to prescribers and may in fact cause confusion – "resulting in an inaccurate understanding of the risk-benefit profile of the product."

BIOSIMILARITY STATEMENT

PhRMA and BIO should be thrilled over the "biosimilarity statement" the FDA has called for in the "Highlights" section of the labeling, which is intended to describe the product's relationship to the brand-name biologic – a recommendation the two big lobbying groups had insisted on in comments to the agency.

Using the fictitious product name "Nexsymeo," the FDA explained the biosimilarity statement would read something like: "*Nexsymeo* (replicamab-cznm) is biosimilar* to *Junexant* (replicamab-hjxf) for the indications listed."

An asterisk placed after the word "biosimilar" would direct prescribers and patients to a footnote explaining that a "Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product."

Leah Christl, associate director for therapeutic biologics and lead of the therapeutic biologics and biosimilars staff in the agency's Office of New Drugs, emphasized biosimilars are not required to have the same labeling as their referenced innovator drugs.

The FDA said a biosimilar medicine's labeling should be specific to the conditions of use, like the indications and dosing regimens, and should be consistent with language previously approved for the reference medicine. But in some cases where a biosimilar is licensed for fewer conditions of use than the innovator, it may be necessary to include information in the biosimilar labeling relating to indications for which it's not approved to help ensure safe use, like when information specific to only the biosimilar's indications cannot be easily extracted, the FDA said. Regulators emphasized that such text should not imply the biosimilar is approved for a reference product's indications or uses for which the biosimilar is not licensed.

NAME USE

In the guidance, the FDA recommended the name used in the biosimilar's labeling text should be specific to that product or refer solely to it, like in the "Indications and Usage," or "Dosage and Administration," or for directive statements and recommendations for preventing, monitoring, managing or mitigating risks, such as those used in black-box warnings or contraindications.

If a biosimilar has a proprietary name, like Sandoz Inc.'s Zarxio, then it should be used. If it doesn't have a proprietary name, its "proper," or nonproprietary, name should be used.

The proper name for biological products would include a designated suffix composed of four lowercase letters attached to the "core" name with a hyphen.

For instance, "filgrastim" and "epoetin alfa" are core names. So for Zarxio, its full proper name – at least for now – is filgrastim-sndz.

The FDA said the innovator's proper names should be used when clinical studies or data derived from trials with those products are described in the biosimilar labeling, such as in "Adverse Reactions" or "Clinical Studies" sections.

Additionally, the reference product name should be included within the biosimilarity statement. But in biosimilar labeling sections where the risk applies to the copycat and its referenced drug, like black-box warnings or contraindications, the FDA said the core name of the innovator followed by the word "products" should be used – like "replicamab products."

And there may be times when the proprietary, proper and core names are all used in a biosimilar's labeling, the FDA said. The FDA acknowledged there's likely going to be a need to make changes to the labeling over the lifecycle of a biosimilar and its reference product.

Endo Accused Of Antitrust Pay-For-Delay Schemes

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Endo International PLC became the latest target of the US Federal Trade Commission (FTC) in the agency's battle to stop what it says are anticompetitive reverse-payment settlements – commonly called pay-for-delay deals – between brand-name drug makers and their potential generic rivals. Shares of Endo took an 8.6% hit on March 31, before closing at $28.15, down 30 cents, or about 1%.

In a complaint filed at the US District Court for the Eastern District of Pennsylvania, the FTC said Endo and generic drug makers **Impax Laboratories Inc.**, Watson Laboratories Inc., part of **Allergan PLC**, and Teikoku Seiyaku Co. Ltd. and its US subsidiary violated antitrust laws by using pay-for-delay settlements to block consumers' access to lower-cost versions of *Opana ER* (oxymorphone hydrochloride) and Lidoderm, a lidocaine patch.

The FTC said the case is the first time it's challenged a deal in which a branded firm has agreed not to market its own "authorized" generic (AG).

Under US law, the first generic applicant to challenge a branded pharmaceutical's patent – the first-filer – may be entitled on FDA approval to 180 days of exclusivity protection against other generics.

But brand-name drug makers are permitted to market their own generic versions of their drugs – the AGs – at any time, including during the 180-day period after the first copycat competitor enters the US market.

The FTC alleged that Endo made deals in which it paid the first-filers to keep their products off the market for a period of time, while the branded company also agreed not to market its AG versions until some months after the generic entered the market.

Under the "no-AG commitments," both parties are winners because the generic firm is pocketing some cash in the interim, while the branded company is maintaining its monopoly for a longer period.

The FTC, however, said those deals violate antitrust laws. Specifically, the FTC said Endo entered into an illegal agreement in 2010 in which it paid Impax $112m to keep its generic of Opana ER off the market. Endo also agreed not to put its own AG on the market until January 2013.

The FTC asserted that Endo used that delay to transition patients to a new formulation of Opana ER, whose US sales exceeded $250m in 2010.

Endo and its partner Teikoku made a similar deal with Watson in 2012, under which the latter company committed to not market a generic of Lidoderm until after September 2013 in exchange for "hundreds of millions of dollars," including $96m worth of the branded product for free that Endo and Teikoku gave to Watson and the possibility for an additional free product worth up to $240m through 2015, the FTC said in its complaint.

The agency noted US Lidoderm sales approached $1bn in 2012 alone.

Endo then agreed not to put its Lidoderm AG on the market for more than seven months after September 2013, allowing Watson to have the only generic version of the product on the market during that period.

As a result, Watson made "hundreds of millions of dollars" more in generic Lidoderm sales, the federal agency said.

The FTC ended up settling with Teikoku and its US subsidiary, under which the firms are prohibited for 20 years from engaging in certain types of reverse-payment agreements, including settlements containing no-AG commitments.

While three of the FTC commissioners backed filing the complaint against Endo and the generic drug makers, Commissioner Maureen Ohlhausen dissented – declaring that while she agreed there was reason to believe the defendants violated the law by entering into the pay-for-delay agreements, she didn't think it served the public interest to seek disgorgement in the case as a proper remedy.

ENDING PAY-FOR-DELAY A PRIORITY

The FTC said it has made putting an end to pay-for-delay deals a top priority and has sought legal action against several companies – accusing them of being anticompetitive.

The regulatory agency, however, has mostly ended up on the losing side of the challenges, getting the thumbs down by US appeals courts at the Eleventh, Second and Federal Circuits, which all ruled the agreements are permissible so long as they do not exceed the potential exclusionary scope of the patent.

But the US Court of Appeals for the Third Circuit sided with the FTC in one case – declaring that the "scope of the patent test" improperly restricts the application of antitrust laws and is contrary to the policies underlying the Hatch-Waxman Act and a long line of Supreme Court precedent on patent litigation and competition. It was the Eleventh Circuit's ruling, however, the Supreme Court decided to hear in March 2013.

That case involved patent settlement agreements between Solvay Pharmaceuticals, now part of **AbbVie Inc.**, and Watson, Paddock Laboratories and its partner Par Pharmaceutical. Those deals involved AbbVie's testosterone-replacement drug AndroGel. But in that case, the FTC came out the big winner – with the Supreme Court ruling 5-3 that pay-for-delay agreements can be subject to antitrust scrutiny.

Although the Supreme Court did not declare pay-for-delay deals presumptively illegal in its June 2013 decision in FTC v Actavis, the court said the agreements have the potential for genuine anticompetitive effects because they permit a brand-name drug company to eliminate the risk of competition, maintain a monopoly and share the benefits of the monopoly with its potential competitor.

Since the Actavis decision, potentially unlawful reverse-payment settlements appear to be declining, said Jamie Towey of the FTC's Bureau of Competition.

Even though the number of overall patent settlements filed in fiscal year 2014 was higher than ever before, the percentage of settlements containing reverse payments dropped, Towey said in a blog posted on the FTC's website.

Indeed, he noted that in the vast majority – more than 80% – pharma companies settled patent disputes without any compensation to the generic firm, he said.

Alder Readies To Take On Teva, Others In Migraine

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Alder Biopharmaceuticals is gearing up to wage a commercial battle against some of the world's largest pharmaceutical companies in a market that could be worth billions if any of the companies can get it right. Alder is hoping dosing and administration will give it an advantage over the likes of Teva Pharmaceuticals, Eli Lilly & Co. and Amgen.

The biotech is set up to be a strong foe in the upcoming commercial landscape. It announced March 28 that its lead product candidate, ALD403, has shown positive progress in an ongoing Phase IIb study of 600 chronic migraine patients.

The study is comparing four different doses – 300mg, 100mg, 30mg, and 10mg – of ALD403 given via intravenous infusion to a placebo. Alder announced topline data that showed the two highest doses had a statistically significant impact on the number of migraines patients had each month.

Patients with chronic migraines have headaches 15 days per month and have severe migraines at least eight days per month. The 300mg dose of the drug was able to reduce migraine days by half for 57% of patients and achieved a 75% reduction in migraine days in as many as 33% of patients.

Meanwhile, 54% of patients taking the 100mg dose had a 50% reduction in migraines, while 31% achieved a 75% reduction over the course of the first 12 weeks.

A small percentage of the patients in the study showed a 100% reduction in migraines, meaning they remained migraine-free for the entire three months.

The study continues and patients will be observed again at 24 weeks and 48 weeks. Further results from the study will be announced later in the year at an upcoming medical meeting.

Alder currently had another study in episodic migraines that is ongoing and expected to report out in 2017. The company intends to begin a second pivotal study in chronic migraines later this year. Data from this study will help inform the doses that will be brought forward in clinical studies.

"We will have a discussion with the FDA in terms of what that next study will be, and what we can actually move into at this point in time. Our strategy would be to accelerate this and go right into a pivotal study if that makes sense, and as such, we would obviously keep the pace with the competitors that are out there. I think the discussion we've had on this end is that we would move more than one dose into that study versus placebo just to make sure that we've covered the dose response that we want to capture at the end of the day," Alder CEO Randall Schatzman in a March 28 conference call with analysts.

"Of those 13 million, we see about 3 million are the most severe or chronic migraine patients. And we believe that those are the most likely candidates for an IV presentation in this case," said Schatzman.

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SETTING IT APART

The biotech is hoping that its dosing schedule and form of administration will help set its drug apart from the competing drugs currently being developed by Teva, Lilly and Amgen, all of which are developing monthly subcutaneous injections. All of the drugs have entered or are ready to enter Phase III and could face FDA scrutiny in the next two years. All four drugs inhibit the calcitonin gene-related peptide (CGRP) protein, which plays a role in inflammation and pain. Other companies have abandoned CGRP-targeted drugs in the past due to safety concerns, most notably an oral CGRP inhibitor that was abandoned by Merck & Co. in 2011. This latest generation of the inhibitors have been able to skirt those issues thus far and have relatively benign safety profiles.

Alder also announced the results from a Phase I study in healthy volunteers that tested the pharmacokinetics and pharmacodynamics of ALD403 when given different ways. The study compared the intravenous infusion with a subcutaneous injection and an intramuscular injection. It showed that all forms of the drug were comparable – a major boon for Alder, which is hoping to market ALD403 as a drug that can be self-administered instead of patients having to go to the doctor's office.

There are currently 13 million Americans that suffer from migraines and as many as 3 million that suffer from the chronic affliction. There are currently treatments for migraines, but most are given after the pain begins and only work to mute the pain, not prevent it. Patients are often given triptans, but the drugs are associated with a range of side effects.

"Of those 13 million, we see about 3 million are the most severe or chronic migraine patients. And we believe that those are the most likely candidates for an IV presentation in this case," said Schatzman. "These are patients that, by and large, are going into the neurologist suites. They have said to us that they would prefer less frequent dosing and if we can dose them four times a year as opposed to 12 times a year with a subcutaneous injection, that's where they would go," he added.

Evercore ISI analyst Umer Raffat estimates this could be an $8bn to $10bn market in the US. Alder has said it intends to commercialize ALD403 on its own with the help of 75 to 100 sales reps, but that it would potentially seek partnerships in Europe and Asia in the future.

Analysts believe this sets up Alder to have a potential best-in-class molecule. Jefferies analyst Brian Abrahams wrote in a same day note that this study provide Alder with a differentiating factor from the other competition.

CONTINUED FROM COVER

Cancer Treatment (UACT), which also asked the agency to use the march-in authority and convene the public hearing.

Earlier this month, 11 groups, which mostly represent consumers, also sent a letter to NIH's Collins supporting KEI's and UACT's petition.

The NIH, however, has never used its march-in authority and analysts were skeptical the agency would start now with the Medivation/Astellas drug.

In a statement to *Scrip*, Medivation said it believed the KEI-UACT petition to grant march-in rights for Xtandi "does not meet the criteria" laid out in Bayh-Dole, "nor is it an appropriate way to address perceived pricing disparities in different health care systems."

The company pointed out NIH's Collins already has stated the march-in authority is an "extraordinary solution" not appropriate for controlling drug prices.

"We believe taking measures such as exercising march-in rights would stifle the kind of innovation and collaborations with public institutions which have resulted in innovative medicines, such as Xtandi, that have made meaningful clinical improvements in the lives of patients," Medivation asserted.

What's not accounted for in the KEI-UACT petition, the company insisted, is that "Xtandi, a standard of care for advanced metastatic cancer, already is widely available to patients."

"A large majority of patients paid a standard co-payment for Xtandi in 2015," Medivation said. "In addition, we provide a number of avenues for those without insurance or who are underinsured to get this lifesaving medicine for free."

Physician checks have not hinted at any barrier to access in the US, said Credit-Suisse analyst Kennen MacKay.

With the financial assistance and other programs offered for Xtandi, MacKay said, the lawmakers' letter "appears misguided."

He noted that Xtandi has demonstrated a five-month extension in lifespan of prostate cancer patients in clinical trials.

"I implore our senators and representatives to question the value of five months of extended lifespan of their constituents, friends and family members," he said.

MacKay argued Medivation represents an innovative biotechnology company focused on improving patient lives with heavy investment in R&D "at the cost of its bottom line."

"As such, Medivation hardly represents corporate profiteering and tax-payer 'price-gouging' to inflate profits," he asserted.

MacKay said he doubted the NIH would exercise its march-in rights on Xtandi, given the "significant" existing access programs.

And, he added, the use of march-in rights could have "significant negative ramifications" to innovative drug development from NIH-funded laboratories.

Canaccord Genuity analyst John Newman called the congressional letter "noise," declaring that even at $129,000 per year, the public's health is not at risk.

"Quite the contrary," Newman said. "Xtandi improves public health."

Even if the NIH grants a hearing on Xtandi, he said there was "minimal likelihood for changes" in the drug's US price.

And, Newman said, "We do not expect any meaningful price changes for Xtandi based on a request" from the lawmakers.

Oral Fabry Drug Clears CHMP

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Amicus Therapeutics Inc., which is having a roller coaster ride with its oral Fabry disease treatment, is now in touching distance of getting the drug approved in Europe. The EMA's advisory committee, CHMP, gave migalastat (*Galafold*) a positive recommendation on April 1, 2016 for the treatment of Fabry disease in all patients who have amenable genetic mutations.

Amicus said a final decision was expected during the second quarter.

The company conducted two Phase III global registration studies (the FACETS Study, Study 011, and the ATTRACT Study, Study 012) of migalastat monotherapy. Both studies enrolled patients with Fabry disease who have alpha-galactosidase A (alpha-Gal A) mutations that are amenable to chaperone monotherapy.

In the US, Amicus has been working on completing an integrated safety summary across all of migalastat's clinical studies as well as additional data analyses from the two Phase III studies, as requested by the US FDA in October.

Amicus had initially expected to be able to file the NDA in the US by the end of 2015, but the FDA surprised the company and analysts alike by requesting the extra analyses.

Amicus said it had collected and analyzed additional histopathology data and gastrointestinal symptom data, as well as longer-term renal and cardiac data across both Phase III clinical studies. It expects to meet with the FDA in the second quarter of 2016 to present these data and discuss a potential pathway to submitting the NDA.

"This is certainly an important lesson for us in perseverance," said Amicus CEO John Crowley in a conference call following the CHMP's decision.

AMENABILITY WEBSITE

Amicus has set up a "very unique and first of its kind searchable genetic website, an amenability website," Crowley said. "This website will enable physicians to quickly and accurately determine if a Fabry patient has an amenable mutation. The amenable mutations [269 have been listed in the label] represent 35% to 50% of the diagnosed Fabry population in a market that generated $1.2bn in global sales in 2015, and which continues to grow at a double-digit rate annually as new patients are diagnosed."

Management declined to lay out a full commercialization schedule "for competitive reasons" but revealed that migalastat would be launched in Germany first, once approval is secured. While every country has its own reimbursement process, Amicus chief operating officer Bradley Campbell said that in the UK, the product has been "selected to go through the highly specialized technology process that was designed for orphan diseases with unmet need; the reimbursement [in the UK] will not be determined by quality adjusted life."

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http://bit.ly/1UY9pH1

Tweaks In Indian Biosimilar Guidelines Target 'Residual Risk'

India's latest set of guidelines for biosimilars seeking market authorization in the country has specified additional post marketing study requirements to "further" reduce the "residual risk" of similar biologics. The new guidelines, which largely build on the 2012 guidance in the area, notes that additional safety data "may need to be collected" after market approval through a predefined single arm study of "generally more than 200 evaluable patients" and compared to historical data of the reference product. "The study should be completed preferably within two years of the marketing permission/manufacturing license unless otherwise justified," it says. The new guidance also suggests that the package insert of the similar biologic shall be based on "data generated by the manufacturer or from verifiable publicly available data."

April Cuts Signal Earlier Price Erosion For Originator Drugs In Australia

Originator pharmaceutical companies in Australia stand to take a hit on April 1 when the prices of 900 brand drugs reimbursed under the Pharmaceutical Benefits Scheme fall by 5% as a result of the first instalment of the new statutory price reduction (SPR), which affects medicines on the single-brand F1 formulary that have been listed on the PBS for at least five years. Among the products affected by the cut are many high-profile and expensive brand medicines in various presentations, including adalimumab (AbbVie's *Humira*), etanercept (Amgen's *Enbrel*), and ustekinumab (Janssen's *Stelara*). The SPR was announced last year as part of a package of measures designed to bring net savings of around A$3.7bn ($2.7bn) over five years, improve patient access to newer medicines, and help ensure the sustainability of the PBS. The move means that innovator drugs are now likely to face price erosion earlier and more systematically than before – i.e., once they have been on the PBS for five years, rather than when a product is moved from the F1 formulary to the F2 (multi-source) formulary as the result of the listing of a second brand. It will also add to the burgeoning pressure on Australian drug prices this year as a result of other measures such as applying price disclosure reductions for single ingredient drugs to combination items, and removing originator brands from the calculation of the average weighted price of PBS-funded drugs after they have been listed on the F2 formulary for three or more years.

Europe Set To Get Live Pandemic Bird Flu Vaccine Protection

Europe looks set to get its first pandemic live attenuated influenza vaccine for fighting H5N1-strain bird flu after EMA's top advisory panel backed use of AstraZeneca PLC's version in an officially declared pandemic situation in children and adolescents. The greenlight for MedImmune LLC's Pandemic Live Attenuated Influenza Vaccine (P/LAIV) from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), announced Apr 1, would allow a vaccine containing a strain of pandemic potential to be developed and authorized in advance of an emergency being declared. MedImmune is AstraZeneca's US-based biologics arm. The CHMP's opinion will now be advanced to the European Commission for adoption of a decision on EU-wide marketing authorization of the vaccine as a pandemic preparedness vaccine. The final decision, expected within months, will be applicable to all 28 European Union member countries plus Iceland, Norway and Liechtenstein.

GSK CHMP Nod For 'Bubble Boy' Gene Therapy

GlaxoSmithKline PLC's 'bubble boy' treatment has been given a positive opinion by the European Medicines Agency's advisory committee. The Committee for Medicinal Products for Human Use (CHMP), in conjunction with the Committee for Advanced Therapies (CAT), recommends marketing approval for GSK2696273, which will be sold under the brand name Strimvelis. It has been developed to treat patients with the very rare disease ADA-SCID (severe combined immunodeficiency due to adenosine deaminase [ADA] deficiency) for whom no suitable human leukocyte antigen (HLA)-matched related stem cell donor is available. "Strimvelis is a one-time treatment and its cost will reflect the value that it delivers in an ultra-rare condition," GSK said. GSK added it is exploring "different pricing options, including both traditional reimbursement routes as well as more innovative approaches."

Latest Indian Price Caps Face Early Industry Dissent

The Indian regulator's latest move capping prices of over 100 formulations appears to be facing some dissent with industry moving a review application over what it claims are certain untenable requirements especially for drugs already being sold below the ceiling price. India's National Pharmaceutical Pricing Authority (NPPA), on March 29 notified the ceiling prices of 103 formulations – it caps prices of drugs covered under the national list of essential medicines (NLEM) 2015 and further reflects the impact of the negative wholesale price index (WPI). Caps have been set for products such as sofosbuvir and raltegravir.

Focus Turns To Label After Panel Backs Acadia's Nuplazid

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If the **FDA** takes its outside experts' advice, **Acadia Pharmaceuticals Inc.** could finally be on its way to having a billion dollar drug on the US market: *Nuplazid* (pimavanserin), a selective inverse agonist of the 5-hydroxytryptamine 2A (5-HT2A) receptor, which the biotech is seeking as a treatment for psychosis associated with Parkinson's disease (PDP).

There currently are no medicines approved in the US to treat PDP. The positive outcome of the March 29 meeting of the FDA's Psychopharmacologic Drugs Advisory Committee (PDAC) not only bodes well for the likelihood for a US approval of Nuplazid in PDP – a decision that's expected by May 1 – but it also sets the stage for the drug's potential later as a treatment for Alzheimer's disease psychosis (ADP).

Acadia is expected to disclose data from its ongoing Phase II ADP trials of Nuplazid by the end of the year, noted analysts from Sagient Research's BioMedTracker, an affiliate of *Scrip*.

In the PDP indication, the PDAC voted 12-2 Nuplazid's benefits of about a 23% improvement in PDP symptoms, which the FDA called minimal, outweighed its risks of serious adverse events (SAEs), like cardiorespiratory arrest, heart attacks, respiratory distress, sepsis and septic shock, or death.

In Acadia's Phase III trial, SAEs, including death, occurred in 7.9% of patients taking Nuplazid 34mg in Study 020, versus 3.5% in those who got placebo.

"I think from a movement disorder clinician perspective, I have plenty of patients who would tell me they would gladly take a medication if they had moderate to severe psychosis and a one in 10 chance of completely resolving their symptoms," said panelist John Duda, director of the Parkinson's Disease Research Education and Clinical Center at Philadelphia Veteran's Affairs Medical Center and an associate professor of neurology at the University of Pennsylvania in Philadelphia.

"Although the benefit is not as great as I would have liked, it has some benefit. It may help a number of our patients, and we need something. This is a real big problem," said panelist Stan Fahn, a professor of neurology at Columbia University and director emeritus of the Movement Disorder Division at the Neurological Institute in New York.

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"I was persuaded by the really terrible quality of life that these patients have," said PDAC chair David Brent, academic chief in the Division of Child Adolescent Psychiatry at the University of Pittsburgh School of Medicine in Pennsylvania. "I think as long as they can be given an informed choice about the risks, I think they ought to have the option."

Brent said he also was convinced "by the fact there really is nothing else."

"Even if the effects are modest, you have to compare it to what's available right now, which with what we've been presented is nothing," he said.

In two earlier questions, the committee voted 12-2 that Acadia provided substantial evidence of the effectiveness for Nuplazid as a treatment for PDP and 11-3 the company had adequately characterized the safety profile of the medicine.

Based on the latter vote, the BioMedTracker analysts increased their likelihood for approval by 4% – from 90% to 94% – and said they expected approval for Nuplazid in the indication Acadia is seeking.

POSTMARKETING REQUIREMENTS

Other than whether the approval will come by May 1, the big question is what types of postmarketing requirements the FDA will impose on Nuplazid: A post-approval Phase IV study, a patient registry, a black-box warning or advice in the labeling to reassess use of the medicine after a certain period.

"We need a robust postmarketing program for this drug," declared Tobias Gerhard, an associate professor of pharmacy at Rutgers University in New Brunswick, NJ.

Bob Temple, deputy director for clinical science at the FDA's Center for Drug Evaluation and Research and acting deputy director of the Office of Drug Evaluation-I, appeared to be heavily leaning toward a registry.

But many on the committee called for a postmarketing study.

Temple, however, said it wasn't "easy for me to imagine" patients with PDP entering a postmarketing trial testing Nuplazid against a placebo.

And, he said, a trial evaluating Acadia's medicine against another active drug "would be uninformative."

Urmimala Sarakar, an associate professor in residence at the University of California, San Francisco, urged the FDA to consider requiring a large observational study on Nuplazid, "so that we can ensure that once it goes into real-world use, that benefits will outweigh the risks."

Temple said the FDA also has not made any decisions about a black-box warning, but most analysts said they anticipated the presence of one a likely outcome.

"But just how restrictive this label will be remains to be seen," noted JP Morgan analyst Cory Kasimov.

Another question is whether the FDA will include Nuplazid in the class of antipsychotics or determine the drug's unique mechanism of action would put it in a class of its own – a decision Temple said the agency has not yet made.

Some on the PDAC raised objections about classifying Nuplazid as an antipsychotic, declaring it would raise the chances of it being used widely off-label – a concern consumer representative Kim Witczak, the co-founder and executive director of the nonprofit Woody Matters in Minneapolis, MN, who voted "no" on all three questions, said was her biggest fear about the drug.

Executive Profile: Klaus Dugi, Boehringer Ingelheim's Tangoing Country Head

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Klaus Dugi, MD and Medical Director UK & Ireland, Boehringer Ingelheim

Klaus Dugi became MD and Medical Director of Boehringer Ingelheim UK and Ireland in September 2015, having previously served as chief medical officer at the German group. He also continues regularly to teach internal medicine and endocrinology at Heidelberg University. He spoke to *Scrip* in the latest instalment of our Executive Profile series, which lifts the C-suite mask worn by key people in the industry.

SCRIP: *What led you into the industry?*

KLAUS DUGI: At the age of 38, I was offered a tenured consultant position at Heidelberg University Hospital, but I felt I was not ready to know what I would be doing professionally for the next 27 years or so. I then met colleagues working in R&D at Boehringer Ingelheim and I was immediately impressed by their passion and the very positive overall BI culture and decided to take a plunge into the somewhat, at least for me, unknown. In addition, an opportunity to help develop new medicines for patients got me excited.

S: *At what point did you realize you were going to make a career in the pharma industry?*

KD: I guess that was when I was offered the position as Corporate Head of Medical Affairs. I was the Therapeutic Area Head for Metabolic Diseases at the time and was faced with the difficult decision of whether I wanted to stay in my area of expertise or take up more managerial roles.

S: *How did your first pharma job shape the rest of your career?*

KD: Early on, as the global medical lead for one of our diabetes pipeline compounds, the Medical sub-team I was chairing proposed some quite novel ways of developing a diabetes compound, e.g. by investigating patients earlier and by basing Go/No Go decisions on biomarkers.

My expectation was that management would turn us down as "newcomers," but they listened, empowered us as a team and we were ultimately successful. This convinced me that an aligned cross-functional team can push innovation through and this conviction has helped me throughout my career.

S: *Tell us about one change you effected in your organization that you believe was invaluable.*

KD: I helped to focus our organization more on innovative approaches such as "offerings beyond the pill." For example, I made sure we invested in people who were fully dedicated to these topics and I made sure the respective budget was ring fenced. The result is we are starting to see some very tangible projects emerging in this context.

S: *What has your proudest moment been?*

KD: Professionally, this happened last year on Sep. 17 in Stockholm when the results of the Empa-Reg Outcome study were presented at the EASD meeting. I was recruited to BI in 2003 to transfer the preclinical diabetes pipeline into the clinical research setting. To see the positive results of a 7,000-patient outcome trial, made possible by a fantastic team of which I had the privilege of working with for a number of years, was wonderful.

S: *And what about your most difficult moment?*

KD: I created a new important position at BI and hired someone externally to fulfil it. The person was fully committed to be successful and both he and his family moved to be close to the business. Due to a change in circumstances, I had to tell him about two years later that he had to leave. This was a very emotional and difficult discussion.

S: *Who do you admire in the industry, and why?*

KD: The out-going CEO at Boehringer, Andreas Barner. He is not only unique in his ability to instantly grasp complex matters but he also pays great attention to people and has truly been a role model for doing the right thing. Good illustrations of this are the topics of transparency and ethical conduct.

S: *What was your first ever job?*

KD: I worked as paramedic in Emergency Medicine. This was a great preparation for medical school and for the medical profession.

S:*What are the key things that shaped you when growing up?*

KD: My upbringing. One reason why I really like our values at BI of Trust, Respect, Empathy and Passion is that, most of the time; this is exactly the atmosphere I found growing up at home. I was the only one in our family to ever go to university and I received very strong support from my parents and the feeling that I can accomplish almost anything, if I work hard enough. Very important for my development was the fact that, at the age of 15, I was exposed to the 'Big World' when I spent one year as a high school exchange student in the US.

S: *Who was your biggest influence, and why?*

KD: Even as a child, I was always trying to find my own way and to not really look for role models. Having said this, my wife (and we have been married for 20 years) has probably been my biggest influence. She has made sure that I stay humble and also understand that a good balance between work and private life is very important.

S: *How do you get step back and get perspective?*

KD: By spending time and talking to my wife and 16-year-old

daughter. They have a wonderful way of putting things into the right perspective.

S: *How do you relax?*

KD: I do regular exercise, mostly on a bicycle, play chess (unfortunately mostly with a computer, but at the beginning of the year we had a friend from Germany visit us in London and we played hours of very enjoyable speed chess), and importantly, a weekend is not a good weekend if my wife and I do not get to dance Tango Argentino at least once!

S: *If you weren't a pharma executive, what would you be?*

KD: I would probably be working in an academic setting, because I always enjoyed the combined challenge of patient care, teaching and doing research. However, I believe that in a pharmaceutical company setting I can make a difference for more patients than in a hospital setting.

S: *What was your favorite subject at school?*

KD: That was maths! I even considered studying it at university but ultimately decided against it, because I felt studying medicine would provide me with more options.

S: *What is the one gadget that you can't leave home or office without?*

KD: It's my watch. It was recently in a shop for repair for several days and I suffered! I like being punctual and have a habit of checking the time quite regularly.

S: *What are you reading at the moment?*

KD: "The Art of Thinking Clearly" by Rolf Dobelli.

S: *What is your favourite book, and why?*

KD: Lord of the Rings by Tolkien. On rare occasions, it can be nice to "escape" the responsibilities of day-to-day life, and the three books did take me far away…

S: *What is your favourite piece of music, and why?*

KD: Romeo and Juliet by Sergei Prokofiev. I have loved this piece of music ever since I first heard it and within a few days of meeting my wife, we found out that this, together with another piece (Gymnopédie by Erik Satie) were our favourite pieces of classical music. But don't get me wrong, I also love contemporary music - and dancing to it!

S: *Tell us one myth about the industry that you'd like to set straight.*

KD: That people working in industry are in it for the money. I have had the privilege of working with a large number of colleagues both in BI and other companies (I was on the Executive Board of Directors of TransCelerate) and I can confidently say that these individuals were driven by a desire to do the right thing, to further science and to bring innovative medicines to patients that need them.

Sun Enters Japan Through Novartis Portfolio

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Sun Pharmaceutical Industries Ltd. is entering the Japanese pharma market by acquiring a bundle of 14 established prescription brands from Novartis AG's local subsidiary, in an anticipated move that echoes a similar transaction between Takeda Pharmaceutical Co. Ltd. and Teva Pharmaceutical Industries Ltd. last year.

A subsidiary of the Indian generics-focused firm will buy the therapeutically diverse portfolio – which has combined annual revenues of around $160m – for $293m in cash. Novartis will continue to carry out distribution activities for the products in Japan for a defined period until all relevant marketing authorizations are transferred to Sun.

The brands "will be marketed by a reliable and established local marketing partner under the Sun Pharma label," and this (undisclosed) partner will also take over distribution of the brands, Sun said in a statement.

Novartis in Japan told *Scrip*'s sister publication PharmAsia News that it was not releasing details of the individual products being transferred, and Sun also did not disclose the list of drugs.

The transaction follows on from the similar divestment by Takeda of a portfolio of mature branded drugs, although these are being moved over to a new minority-owned joint venture being set up in Japan this April with Teva, rather than being fully divested.

Speculation has been swirling since late last year that Sun was looking to do a deal for selected products in Japan, probably involving Novartis. Some other Indian firms, notably Lupin Ltd., are gearing up for a stronger push into Japan and the wider APAC region, helped by past and planned acquisitions.

Noting that the $73bn Japanese pharma sector "is a market of strategic interest for us," Sun's managing director Dilip Shanghvi hinted that the Novartis deal could be used as the foundation for an expanded Japan portfolio in the future.

Mature, long-listed branded products in Japan are often caught in a trap of low growth and regular price reductions under the country's biennial drug price revision scheme, being unable to benefit from either higher premiums for new innovative products or from the growth for outright generics.

The generics sector has been growing strongly in Japan under the shepherding of policies that provide doctors and pharmacists with various fee incentives, and patients' lower co-payment costs. The government has set an official target for generics to account for 80% by volume of the substitutable sector by March 2021.

Generics currently account for close to 50% by volume and around 27% by value of the total Japanese prescription market, although starting prices for first generics are being lowered as part of pricing policy changes next month.

Surprise Knockback For Safinamide Gives Azilect A Boost

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Just days after US WorldMeds signed up to commercialize the Parkinson's disease add-on therapy *Xadago* (safinamide) in the US, with US approval anticipated on its Mar. 29 PDUFA date, the product has been turned back by the FDA. The agency wants evaluation of the oral, once a day drug for its abuse liability and dependence/withdrawal effects before it can be approved, it said in a complete response letter.

The news caused the share price of the product's Italian developer, Newron Pharmaceuticals, to drop by 30% to CHF16.30 on Mar. 29, even though Newron underscored that the FDA had not called for any new safety or efficacy data, studies or analyses. On the flipside, it provides a fillip to Teva Pharmaceutical Industries, which was facing market share erosion for its own product *Azilect* (rasagiline) by Xadago. Like Xadago, Azilect is used as an adjunctive therapy to levodopa in later-stage Parkinson's patients.

Rx Securities analyst Samir Devani estimated that the new FDA requirement would cause a delay of around 18 months in Xadago reaching the US market.

> Azilect is expected to reach peak annual sales in 2016 prior to loss of exclusivity in the US starting in early 2017.

The news appears to come as a bolt from the blue for Newron and its licensees, since the product had received EU and Swiss approval without concerns over abuse potential and Newron CMO Ravi Anand had worked closely with the FDA on the current submission given the product's prior history of bureaucratic hitches at the US agency, a spokesperson for Newron told *Scrip*. However, the Controlled Substance Staff (CSS) at the FDA's Center for Drug Evaluation and Research (CDER) has a mandate to look at all drugs acting on the central nervous system to assess abuse potential, and from that perspective this could be seen as a routine request for information. "We would have assumed that a lack of data would have been addressed at a pre-NDA meeting or on filing and not at such a late stage of the review process," commented Dr Devani.

Dr Devani wrote that Newron had submitted abuse potential data from treated patients in its NDA, but that the company was now being asked for data also from healthy volunteers, although he understood that such data had not been requested previously. "We estimate a specific study would take approximately six months to complete and involve approximately 40-60 subjects," he stated in a note accompanying Rx Securities' downgrade from a buy to a hold recommendation on Newron's stock.

NEWRON MAY NEED TO RAISE CAPITAL

Newron's spokesperson said the firm was still hopeful of getting US approval for Xadago in 2016. The company had been banking on milestones and income from further licensing of the drug to help boost its revenues in 2016, when it is also expecting to increase R&D spending as it launches a pivotal efficacy study of its experimental treatment for the rare neurodevelopmental disorder Rett syndrome sarizotan and completes the Phase II study of NW-3509 as an add-on therapy in schizophrenia.

The setback with Xadago may necessitate a further fundraising round. Newron last raised $5.4m in a private placement in November 2015, following a $25.5m private placement in April 2015. Those shares were sold at CHF25.60 and CHF29.90 apiece, respectively. A total of 1.05m new shares were issued in the two placements, under a March 2015 authorization by shareholders to allocate up to 1.3m shares to raise capital.

Xadago was approved in Europe in February 2015 for mid-to-late stage Parkinson's, and is commercialized there by Newron's partner Zambon, also of Italy. Zambon, which holds worldwide marketing rights outside Japan/Asia, announced on Mar. 17 that it had signed a sub-licensing agreement for safinamide in the US with US WorldMeds, which sells a niche portfolio of specialty medicines. It revealed that US WorldMeds would "focus more than 60 sales representatives launching Xadago in the US." The Kentucky-based firm already sells the dopamine agonist *Apokyn* (apomorphine hydrochloride injection) for acute, intermittent treatment of reduced motor function episodes associated with advancing Parkinson's disease.

Zambon CCO Luca Primavera told *Scrip* that he was still confident of the drug's eventual US approval although the complete response letter had come as a surprise. He said that the agreement was still in place with US WorldMeds, but would not disclose if any upfront payment had already been made.

AZILECT BOON BEFORE GENERICS ARRIVE

The US is by far the most lucrative market for Parkinson's disease therapies, and Datamonitor Healthcare had forecast that by 2023 US sales of Xadago would account for about 65% of total product sales of $242m across the US, Japan and the five major EU markets of France, Germany, Italy, Spain and the UK.

Global Azilect sales by Teva and partner Lundbeck amounted to $514m in 2015. Azilect is expected to reach peak annual sales in 2016 prior to loss of exclusivity in the US starting in early 2017. Azilect and Xadago both inhibit the MAO-B enzyme in the brain that breaks down dopamine, and Datamonitor Healthcare has predicted that Xadago would take market share from Azilect in the US.

Parkinson's disease patients usually receive levodopa therapy, but long term treatment can cause motor function fluctuations (with on/off periods of motor function) as well as involuntary movements known as levodopa-induced dyskinesia (LID). Patients are therefore given add-on therapies to manage LID and "off-periods" of motor function as their disease progresses. Most of these treatments target the dopaminergic system implicated in the Parkinson's disease, while safinamide has a dual mechanism acting on both the dopaminergic and the glutamergic pathways, and the company's studies suggest that it can improve motor fluctuations without increasing the development of dyskinesia.

Pfizer inSPIREd By Late-Stage PCSK9 Data

Pfizer announced the latest data on its PCSK9 inhibitor, bococizumab, as it continues to chase the already marketed cholesterol drugs made by competitors. While data was positive, the market opportunity is not as large as once expected. Topline results from Pfizer's Phase III SPIRE-AI study were announced April 1. The trial included 299 patients with hyperlipidemia or mixed dyslipidemia who are currently taking statins, but still have LDL-cholesterol levels greater than 70 mg/dL. Dubbed AI because the drug was administered via an autoinjector pre-filled pen device, the trial also measured the usability of the autoinjector, as well as the drug's cholesterol-lowering ability.

CHMP Okays Samsung's Biosimilar

Samsung Bioepis' infliximab biosimilar, Flixabi, has won a green light from the European Medicines Agency's Committee for Medicinal Products for Human Use. The CHMP is recommending it be approved for a range of indications: rheumatoid arthritis, adult and pediatric Crohn's disease, ulcerative colitis, pediatric ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis. The European Commission will rubber stamp the recommendation, after which Flixabi will join not only the reference product, Janssen's blockbusting Remicade, but other infliximab biosimilars Mundipharma/Celltrion's Remsima and Hospira's Inflectra.

Opko Blames Rayaldee Snub On Manufacturer

Opko Health Inc. on March 30 disclosed it had received a complete response letter (CRL) from the FDA on the firm's secondary hyperparathyroidism (SHPT) drug *Rayaldee* (calcifediol) – blaming the snub on deficiencies with the company's third-party manufacturer, Catalent Pharma. Opko insisted there were no safety or efficacy issues and the FDA was not requiring any new clinical studies. Laidlaw & Co. analyst Yale Jen called the FDA's rejection a "small speed bump" for Rayaldee. Investors, however, drove shares of Opko down 11.3% on March 30, before closing at $9.90, down $1.17, or 10.6%. Opko is seeking approval to market Rayaldee as a treatment for SHPT in patients with stage 3 or 4 chronic kidney disease and vitamin D insufficiency, or a serum total 25-hydroxyvitamin D levels less than 30mg/mL.

Forum's Lead Drug Program Fails

Forum Pharmaceuticals' lead compound encenicline has failed to meet the endpoints in two Phase III trials for the treatment of cognitive impairment in schizophrenia patients. While Forum – which is developing the product in partnership with Mitsubishi Tanabe Pharma –plans to analyze the data from the COGNITIV SZ further before making any decision on the drug's future, development for encenicline seems unlikely to continue for this indication. Sagient Research's BioMedTracker database has given encenicline a likelihood of approval rating of just 12%, 39% below the average for a similar product at the same stage of development. Furthermore, a Phase III trial for encenicline, an orally administered alpha 7 agonist, as a treatment for improved cognition and clinical function in patients with Alzheimer's disease is already on a clinical hold; this was imposed by the US FDA in September 2015 due to safety issues.

Accelerated EU Committee Nod For J&J/Genmab's Darzalex

Janssen-Cilag (Johnson & Johnson) and Genmab's CD38 monoclonal antibody product *Darzalex* (daratumumab) has been granted the green light for approval in adults with relapsed and refractory multiple myeloma, under an accelerated procedure. The decision comes two months after Bristol-Myers Squibb's rival multiple myeloma product *Empliciti* (elotuzumab) received its own accelerated decision from the EMA's scientific committee, but ahead of another potential competitor, Takeda Pharmaceutical's oral proteasome inhibitor *Ninlaro* (ixazomib). In the US, Darzalex's approval came earlier than expected last November, pipping Empliciti to the post there by two weeks. The CHMP has recommended granting a conditional marketing authorisation for Darzalex specifically for the treatment of adults in patients whose previous treatment included a proteasome inhibitor and an immunomodulatory agent and whose disease worsened after treatment. By contrast, the SLAMF7 (signalling lymphocyte activation molecule family member 7) protein inhibitor Empliciti was given the nod for use earlier in the treatment paradigm in adult patients who have received at least one prior therapy, giving it a marketing edge, especially as Revlimid and dexamethasone are both widely used in multiple myeloma. However, Darzalex could eventually provide stronger competition as it is in development for use in treatment-naïve multiple myeloma patients, although Empliciti too is in a late-phase trial in treatment-naïve patients not eligible for stem cell transplant (ELOQUENT-1).Other threats on the horizon include the immuno-oncology agents like Merck & Co's *Keytruda* (pembrolizumab).

Summit's Antibiotic Spares The Microbiome And Spoils The C Diff Rods

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Summit Therapeutics' novel narrow-spectrum antibiotic ridinilazole (SMT19969) is highly effective in reducing recurrence in *Clostridium difficile* infections (CDI), and could address a major unmet need in the treatment of the disease, suggest Phase II data due to be presented at the ECCMID meeting in Amsterdam in April.

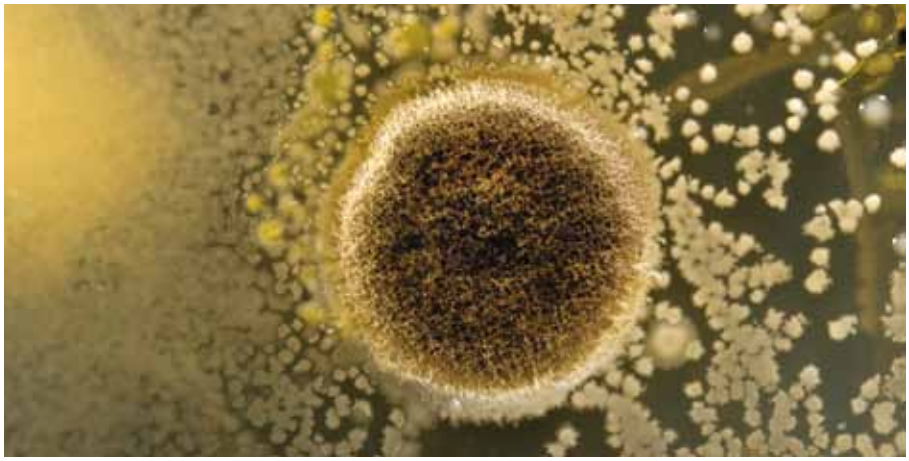
The data from the 100-patient CoDIFy study exceeded the expectations of the company and have excited experts in the field, said Summit CEO Glyn Edwards. The significant improvement in sustained clinical response seen in the trial suggests that ridinilazole has microbiome-sparing characteristics, meaning that it could help overcome a key problem in treating CDI.

Phase III trial planning is underway with studies due to start at the end of the year or early in 2017, Edwards said. As the company's main focus is on Duchenne muscular dystrophy, these will probably take place with a partner, to which end discussions are ongoing but nothing is expected to be announced before the third quarter.

The life-threatening infection occurs in patients whose microbiome has been disturbed, often by the use of broad-spectrum antibiotics, which allows the bacterial spores to colonize and produce toxins that cause inflammation and severe diarrhea. The problem is that the broad-spectrum antibiotics needed to treat the infection further deplete the microbiome, making recurrence common, and these repeat episodes are typically more severe, and have higher mortality rates and healthcare costs. Experts have long wanted a highly specific agent to treat the *C difficile* pathogen but leave the protective microbiome largely intact.

Edwards said that ridinilazole is the first truly narrow-spectrum antibiotic for this disease (other candidates were semi-selective) and said its microbiome-sparing properties do not seem to have come at the expense of antibiotic activity: the study shows ridinilazole provides a statistically just as good (and numerically better) antibiotic effect against the pathogen as vancomycin.

But exactly how ridinilazole works is still a bit of a mystery. It does not seem to act via a mechanism of any existing antibiotic, Edwards said. "We've ruled out all the current targets and we've still not nailed it down." But what is known is that the drug acts on cell division somehow. Normally when the rod-like bacteria divide, the cell wall pinches off to create a new bacterium, but ridinilazole causes this process to fail, creating long rods with separate nuclei that die rather than separate.



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While not knowing the primary target might raise some concerns over off-target effects in some, Edwards said he was confident of the toxicology and patient safety data to date. In the CoDIFy trial, the researchers found no clinically important differences in overall adverse event rates or serious adverse events between the two groups.

RESULTS

The latest data from CoDIFy being presented in Amsterdam show that patients who received ridinilazole (200 mg twice daily for 10 days) had a recurrence rate of 14.3% compared with 34.8% for the current standard of care vancomycin (125 mg four times per day for 10 days). This result, Summit said, drove the previously reported statistical superiority in sustained clinical response rates of ridinilazole over vancomycin (66.7% vs 42.4%) in the treatment of CDI. Sustained clinical response was defined as clinical cure at the end of treatment and no recurrence in the 30 days after therapy.

Rates of clinical cure at the end of treatment were 77.8% for ridinilazole and 69.7% for vancomycin, using a modified intent-to-treat population of patients with CDI diagnosed by the presence of free toxin in feces.

Furthermore, Summit said, ridinilazole treated patients showed no further damage to their microbiome during therapy with a proportion of patients showing initial evidence of recovery of key bacterial groups with roles in protecting from CDI. In contrast, vancomycin-treated patients experienced substantial damage to their gut microbiome which in many patients persisted during the 30-day post-treatment period.

Ridinilazole has received Qualified Infectious Disease Product (QIDP) designation and has been granted fast track status by the US FDA.

COMPETITORS

Other products in late-stage development for use in *C difficile* infection include Merck &Co's Phase III monoclonal antibody therapies, bezlotoxumab and actoxumab, which target the toxins produced by the bacterium and are given on top of standard-of-care antibiotic therapy. Merck's portfolio already includes *Dificid* (fidaxomicin), which is one of the two antibiotics specifically approved to treat *C difficile* infections, and it has another candidate, surotomycin, in Phase III studies. Also at the Phase III stage are Actelion's cadazolid and Seres Therapeutics' probiotic SER-109 (Phase II/III).

Biocon/Fujifilm Enter Lantus Biosimilar Fray

ANJU GHANGURDE anju.ghangurde@informa.com

Biocon and Fujifilm Pharma Co Ltd have received approval for their biosimilar insulin glargine from Japan's ministry of health, labour and welfare, scaling what the Indian firm termed as a "huge credibility milestone" and adding to pressure on innovator Sanofi's Lantus there.

The approval is significant, some experts say, given that the first biosimilar insulin glargine version from Eli Lilly & Co and Boehringer Ingelheim appears to have made early gains in the Japanese market, indicative of a general acceptance for biosimilars there. The Lilly/BI product was approved at the end of 2014 and launched in 2015.

Biocon's ready-to-use, prefilled disposable pen with 3ml of 100IU insulin glargine is expected to be launched in the first quarter of FY17. The partners aim to capture a significant share of the $144m Japanese glargine market - the second largest outside of North America and Europe and largely dominated by disposable pens, a company statement said.

"There would be a pricing discussion that happens and the launch of the product is subsequent to that and that should happen in the next couple of months," Biocon's CEO, Dr Arun Chandavarkar, told *Scrip* in a media call on March 28 when asked about reimbursement pricing for the product.

On the potential impact of Sanofi's Lantus follow-on product *Toujeo* (insulin glargine), a next-generation insulin, already on the Japanese market, Chandavarkar maintained that the he does not believe that the product would "influence" the launch of the firm's biosimilar of Lantus.

"To penetrate a market with a novel product or new formulation of a product there needs to be a significant clinical benefit. And if the significant clinical benefit is commensurate with the price point - basically it's an outcomes issue. My understanding is that insulin glargine would continue to be a dominant product in the Japanese market and likewise elsewhere in the world as well," he said.

Toujeo was approved in Japan last year to be sold under the trade name Lantus XR. Biocon said that approval for insulin glargine followed its successful completion of initial development and local Phase III clinical studies in over 250 Type 1 diabetes patients by its partner in Japan.

The Indian firm's manufacturing facilities for insulin glargine, and the disposable pen assembly facility have been approved by the Japanese regulatory authorities – latter was inaugurated in September 2015 for the launch of Biocon's insulin glargine pen branded as "Basalog One" in India.

While the approval for the biosimilar is seen as a significant achievement for Biocon and Fujifilm, experts underscore that the Indo-Japanese alliance will find itself up against well-entrenched competitors.

Puma Plummets On Another Neratinib NDA Delay

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Puma Biotechnology Inc. fell 21.1% to close at $27.92 per share on March 29 after it revealed a second major delay for the company's new drug application (NDA) submission to the US FDA for neratinib as an extended adjuvant treatment for early-stage HER2-positive breast cancer.

Los Angeles-based Puma has given back all of its gains and then some since the company's value spiked based on the first set of Phase III data for neratinib in July 2014. Puma has fallen 90% below its high of $275.07 in September 2014 based on minimal efficacy gains, high levels of grade 3 and 4 diarrhea, and now another regulatory delay for its lead drug candidate. The company said late on March 28 that it will submit an NDA in mid-2016 instead of during the first quarter of this year.

As was the case in December 2014 when Puma said its first quarter 2015 NDA submission would be delayed by one year, the company revealed that additional feedback from the FDA will again push back the timing of its application. The agency asked Puma to amend its statistical analysis plan, which will shift the time at which recurrent disease events and deaths were assessed and included in the Phase III ExteNET study's primary endpoint.

Puma first reported that neratinib provided a statistically significant improvement in disease-free survival versus placebo in the 2,821-patient ExteNET clinical trial in July 2014. The trial treated women in the extended adjuvant setting, which comes after adjuvant treatment with Roche's *Herceptin* (trastuzumab) – the population that the company will target with its NDA submission.

Neratinib is a tyrosine kinase inhibitor that blocks signal transduction through the epidermal growth factor receptors (EGFRs), HER1, HER2 and HER 4. The drug provided a 33% improvement in disease-free survival (DFS) versus placebo at one year (p=0.005). That changes to a 34% DFS improvement (p=0.004) under the FDA's recommended statistical analysis.

However, neratinib's efficacy has slipped in longer-term analyses with the Puma drug providing only a 26% improvement in DFS versus placebo after three years of treatment. The dwindling efficacy, including disappointing mid-stage neoadjuvant results, paired with unfortunate toxicity – more than a third of neratinib-treated patients experienced grade 3 or 4 diarrhea in ExteNET – has thrown the drug's commercial viability into doubt.

Sagient Research's BioMedTracker service gives neratinib a 34% likelihood of FDA approval, which is 1% below average for cancer drugs in similar stages of development.

Dr Reddy's COO On US Derma Build-up

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Dr Reddy's Laboratories (DRL) appears to be building on plans for its differentiated dermatology and neurology formulations in the US after gains on the approvals front.

It recently received FDA approval for a clutch of such products powered by low-risk innovation, including *Sernivo* (betamethasone dipropionate) spray for psoriasis and *Zembrace* SymTouch (sumatriptan succinate) injection, a drug-device combination for migraine.

In an interview with *Scrip*, Dr Reddy's Chief Operating Officer Abhijit Mukherjee outlined scale up efforts around the novel portfolio and plans for new filings. Mid-term opportunities in the proprietary products segment were earlier touted by the firm to have the potential to be "transformative" for business, if target labels are achieved.

SCRIP: *Would DRL be putting more feet on the ground, using alliances to build its targeted dermatology and neurology franchises in the US or would the 54-odd sales reps targeting around 8,000 dermatologists suffice for Sernivo, Zenavod (doxycycline) capsules?*

ABHIJIT MUKHERJEE: The US dermatology commercial organization will continue to be scaled to promote the product portfolio to US dermatologists. We are currently finalizing the sales force size and structure that will be leveraged to launch these products and position Promius Pharma, our US subsidiary, for additional growth in FY17 and beyond.

S: *Were the target labels achieved for the first wave of differentiated product approvals – Sernivo, Zenavod?*

AM: We are happy with how the FDA approved our product labels. We believe that the approved labels demonstrate the clinical and therapeutic benefits of the products for both psoriasis and rosacea patients.

S: *Are more NDA filings in the derma space –the zero contact time retinoid face wash – or the migraine assets anticipated in FY17?*

AM: We have continued to progress our dermatology pipeline and expect to file at least one or two late stage dermatology assets to the FDA in FY17. In addition, we look forward to continuing to work with the agency to progress our head lice program through an FDA approval filed in September 2015.

S: *DRL has commercialized four biosimilars in emerging markets. How has physician acceptance, penetration levels been in general and is uptake strongly linked to the discount offered in these markets?*

AM: Currently, we have commercialized rituximab, filgrastim, pegfilgrastim and darbepoetin in some of the emerging markets. The physician response to high quality, affordable biosimilars has been very promising and we continue to observe significant increase in volumes after launch of our biosimilars in all markets. We believe all the stakeholders in the ecosystem (patients, physicians, regulators and payers) will continue to demand high quality biosimilars and markets will not be solely driven by discounts.

S: *A US judge has likened the Biologics Price Competition and Innovation Act (BPCIA) to Winston Churchill's description of Russia: A riddle wrapped in a mystery inside an enigma. What are your views on the "patent dance"; does it give innovators unnecessary "extra-statutory" exclusivity?*

AM: The overall perspective of the biosimilar industry is that the patent provisions of the BPCIA are tough to traverse.

Given the nature of the "patent dance" provisions, as well as the 180 day notification requirement for commercial launch, the actual launch may be delayed anywhere between six months to more than a year (depending on when the FDA grants approval). This is a de facto additional "exclusivity," over and above the de jure 12 year exclusivity granted to a biologics product.

In addition, notwithstanding the confidentiality provisions, there is discomfort about the requirement of sharing of the biosimilar manufacturing information with the innovator, who are, after all, direct competitors.

Moreover, this sharing of dossier and manufacturing information is one-sided in nature. While the innovators have full access to the biosimiliar dossier and manufacturing info, the reverse is not true – biosimilars do not have access to anybody else's dossier and information, though they may well have their own IP to assert. The law appears to be more supportive of one of the parties, enabling the assertion of their IPR, vis-a-vis the other party.

S: *Australia earlier permitted pharmacists to substitute biosimilar infliximab for the reference product. Do you expect more markets to go that way and would DRL consider Australia as a potential early target market?*

AM: Allowing the substitution of a biosimilar for the reference product is indeed a welcome step. We see this increasingly happening in the EU as well. However, Australia follows similar guidelines as the EMA for product registration. Dr Reddy's continues to work with health authorities globally to support the development and implementation of a science-based evaluation process for biosimilars.

S: *What is DRL's broad position on the buy-versus-build approach in complex markets like Japan, China? Are alliances the way ahead?*

AM: In Japan, our approach has been partnership-building (virtual JV/strategic alliance) in oncology and the complex generics injectable space. Buy is not an immediate consideration. These markets require substantial cultural integration and awareness and local alliance for commercialization is critical for initial success and buy-in.

In China, we operate through a joint venture with Kunshan Rotam Reddy Pharmaceutical Co Ltd, a local player. Going forward, we intend to strengthen our presence through a combination of leverage filings and China-specific filings on a case-by-case basis to create value for the organization

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Diurnal Approaches Market

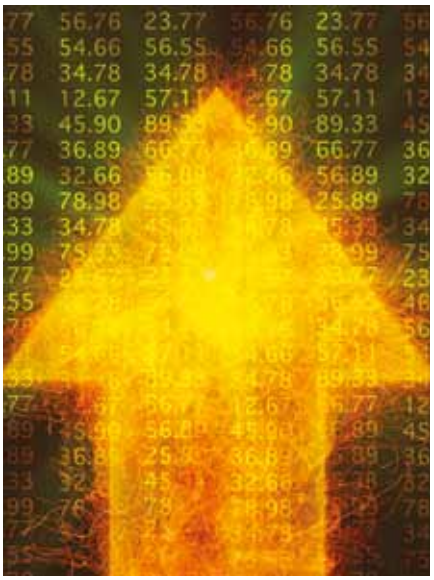
Two potential orphan drugs developed by the UK's newly public endocrinology speciality company, Diurnal Group, are in Phase III clinical trials, and the first of these, *Infacort* (immediate-release hydrocortisone) for pediatric patients with insufficient levels of the chemically-related essential hormone cortisol, could be approved in its first markets within 18 months, by the end of 2017. But the 20-member firm of employees and consultants is not overwhelmed by the prospect. Diurnal intends to market its products in Europe and the US itself, although it might consider licensees for countries outside of those regions.

Dr Reddy's Infuses Life Into XenoPort's Psoriasis Drug

Dr Reddy's Laboratories will take XenoPort's clinical-stage oral psoriasis NCE, XP23829, further in the US, infusing new hope in the prodrug of monomethyl fumarate (MMF) that has seen some safety issues in earlier studies and faces significant competition in the space. The Indian firm has entered into a $490m plus royalties deal with XenoPort, which has itself been speculated to be a potential sell-off candidate. XenoPort had previously discontinued development of XP23829 on its own and decided to seek a partner for the drug. The Santa Clara, California-based company says it's now fully focused on commercialization efforts for its restless leg syndrome therapy *Horizant* (gabapentin enacarbil) extended-release tablets. Dr Reddy's has exclusive US rights to develop and commercialize XP23829 for all indications. It expects to develop the drug as a potential treatment for moderate to severe chronic plaque psoriasis and possibly for relapsing forms of multiple sclerosis (MS).

Phase III Data Back Keryx's Plan

Keryx Biopharmaceuticals Inc. had a rough first year of sales for its oral, iron-based phosphate binder *Auryxia* (ferric citrate), but the company and it investors have high hopes that new Phase III data will support approval for a second indication that could double the drug's market. Boston-based Keryx rose 8.6% to close at $4.94 per share on March 29 after the company reported that 52% of pre-dialysis, stage 3 through 5 chronic kidney disease (CKD) patients with iron deficiency anemia (IDA) achieved a 1g/dL or greater increase in hemoglobin during a 16-week treatment period compared with 19% who received placebo ($p<0.001$). The data disclosure keeps Keryx on schedule to submit a supplemental new drug application (sNDA) to the US FDA during the third quarter of 2016.



SHUTTERSTOCK: wongwean

Genocea Boosted After Herpes Data Update

Genocea Biosciences Inc. is holding out hope that Phase II data from genital herpes patients treated with GEN-003 for 12 months will give the therapeutic vaccine a market advantage, and while the commercial potential is unclear given the mixed data the company reported on March 31, its stock price soared on the clinical trial update for its sole clinical drug candidate. GEN-003 showed somewhat sustained viral shedding rates and one of the vaccine doses generated a lesion-free rate for herpes patients that was comparable to the efficacy of currently available oral antiviral medicines after one year of treatment. However, the data picture is incomplete, since the placebo-controlled analysis ended after the first month of the study. Also, patients treated with the lower of two GEN-003 doses were better off 12 months after administration of the vaccine than people who were given the higher dose.

Amryt: New Rare Disease Player

A new orphan drug player - Amryt Pharma Plc- is coming to the London stock market heralding a promising pipeline and experienced leadership, arriving via a reverse takeover with Alternative Investment Market (AIM)-listed investment firm Fastnet Equity PLC. The result will be a drug company with big plans and a product that is already on the market. That was Fastnet's message on Mar. 31 when announcing plans to buy privately-owned Amryt Pharmaceuticals in a reverse takeover deal valued at £29.6m. A share placing will also bring in £10m to be used to develop the new company's lead therapy for a rare skin disorder - Episalvan – which is already approved in Europe to treat adults for accelerated healing of partial thickness wounds. The plan is to develop that asset for treating epidermolysis bullosa, or EB, a genetic skin disease that causes painful blisters from the slightest of friction.

VC Funding: Increasing Prior Rounds; New Strategy In Lieu Of An IPO?

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Many biotechnology companies raised new venture capital in 2015 within months of registering with the US Securities and Exchange Commission (SEC) to launch an initial public offering, but the trend seems to have reversed course in 2016.

Biotech firms seemed determined last year to send a signal to potential IPO investors that they were well-financed even without raising money in the stock market, because they had pockets full of new venture capital. By extending prior VC rounds this year, instead of raising new round, drug developers and their venture backers may be buying time until investors become interested in IPOs again.

Companies could just raise a series B or C round to make it to their next big milestones, but a handful of biotechs – like Envisia Therapeutics and several others this year – have added investors rather than launch a new fundraising campaign. The private biotech companies are wise to explore various VC options while the IPO market continues to show mixed returns for drug development firms.

Research Triangle Park, North Carolina-based Envisia's existing investors added cash to the company's previous $25m series A round, which was revealed in 2013 when the firm was spun out of Liquidia Technologies. Envisia will use its new funding to advance an ongoing clinical program, to take two other extended-release eye drugs into the clinic, and to obtain Phase II data from its programs.

The company will have data in May from the second of three cohorts in a Phase IIa clinical trial for ENV515 in glaucoma. The drug candidate, a proprietary formulation of *Travatan* (travoprost), could lower intraocular pressure for up to six months with a single dose in hopes of boosting patient compliance compared with the daily eye drops marketed by Novartis AG's Alcon unit.

Envisia plans to begin clinical testing in the first half of 2017 for ENV1105, a novel formulation of the steroid dexamethasone that is designed to treat diabetic macular edema (DME) every six months. The company's new funding also will support preclinical testing for ENV1305, a sustained-release anti-VEGF monoclonal antibody for age-related macular degeneration (AMD). All three of Envisia's products are formulated with Liquidia's Particle Replication in Non-Wetting Templates (PRINT) platform.

> Private biotech companies wise to explore VC options while IPO market shows mixed returns for drug development firms.

Other companies that recently added significant venture capital to previous VC funding rounds include Amplyx Pharmaceuticals, whose series B round surged to $49.2m to fund antifungal programs through Phase II; Galera Therapeutics Inc., which now has $42m for a Phase IIb drug to treat oral mucositis in cancer patients; and eFFECTOR Therapeutics Inc., a cancer drug developer in Phase I/II.

NO IPO, NO PROBLEM: NEW VC, PHILANTHROPIC FUNDS

Two new sources of venture and research capital are on their way to help the biotech ecosystem advance basic science and early-stage drug development programs.

First, ARCH Venture Partners is raising another $400m venture capital fund, according to a March 17 SEC filing, to back startups founded by experts in life sciences, physical sciences and information technology. ARCH's ninth fund will be the same size as its previous fund, unless the VC firm repeats its 2014 fundraising performance when ARCH set out to raise $250m and garnered $150m more than planned.

The Juno Therapeutics Inc. founding investor's recent investments include Unity Biotechnology, Lodo Therapeutics Corp., Scholar Rock, Petra Pharma and Codiak BioSciences.

Second, philanthropist and entrepreneur Paul Allen launched the Seattle, Washington-based Paul G. Allen Frontiers Group with an initial commitment of $100m to fund basic bioscience research. Allen, a Microsoft co-founder, previously funded the Allen Institute for Brian Science in 2003 and the Allen Institute for Cell Science in 2014.

The Allen Frontiers Group will invest broadly across bioscience via two programs known as Allen Discovery Centers and Allen Distinguished Investigators. The first two Discovery Centers will be located at Stanford University in California and Tufts University in Massachusetts, each of which will receive up to $30m from Allen and the universities' partners over eight years to research cells and understand how diseases work. Four scientists in California, Massachusetts and France received the first Distinguished Investigators grants to research synthetic biology, gene editing and neural circuits.

OTHER RECENT VC FINANCINGS (AND ONE DEAL)

Harvard University skipped over the venture capital portion of the typical biotech company life cycle when it licensed small molecules that target transcription-regulating enzymes to Merck & Co. Inc. for $20m up front plus development and commercialization milestone fees and tiered royalties. The compounds were developed in the lab of Matthew Shair to treat acute myeloid leukemia (AML) and other cancers.

Shair's lab never received venture capital. Instead, he and his colleagues worked with and received funding from Harvard's Blavatnik Biomedical Accelerator to identify molecules that "reached a stage of development that is unusual in most universities, but of great interest to the health care industry," Harvard's senior associate provost and chief technology development officer Isaac Kohlberg said in a statement from the university. Merck will take over clinical development, but it will collaborate with Shair's lab to further study transcriptional regulator enzymes.

VCs Compare Notes On Biotech Investment Landscape In 2016

LUCIE ELLIS lucie.ellis@informa.com

So far in 2016 the number and value of deals by pharma and biotech companies in the private sector has dropped significantly compared to recent years – but money is still there for start-ups with innovative technology and robust science, say venture capitalists.

During the recent European Life Science CEO Forum, a partnering meeting hosted by Sachs Associates in Zurich, Switzerland, *Scrip*'s Lucie Ellis sat down with three investors to discuss their current strategies, changes in the biotech market and the biggest concerns keeping them up at night.

Dr. Myoung-Ok Kwon is a venture partner for Arcus Ventures, a New York-based firm investing in oncology focused companies with innovative biopharmaceuticals or drug delivery platforms. Naveed Siddiqi is a partner for life sciences at Edmond de Rothschild Investment Partners (EDRIP), a private equity firm based in Paris, France. Dr. Markus Goebel is managing director at the Novartis Venture Fund, based in Basel, Switzerland.

LUCIE ELLIS: *What is your investment strategy and why do you operate this way?*

DR. MYOUNG-OK KWON: Arcus is focused on therapeutics but we also invest in some medical device companies. We target oncology companies mainly because the science in this area is of a high quality at the moment. If you compare the area to say neuroscience, oncology R&D is not so limited. Mostly we target companies with assets in the clinic, at a Phase I or Phase II stages of development, and the fund is focused on innovation more than specific indications or markets. Of course we have a strong interest in targeted cancer therapies but when seeking investments we are looking for assets that have a robust scientific rationale as there is a lot going on in this space. We usually invest between $5m and $7m in each new company.

NAVEED SIDDIQI: EDRIP has a balance approach to investing where we try to weigh risk, return and liquidity aspects for each investment. The firm has had a lot of success with this approach and out of approximately 50 investments we have made since the early 2000s, 14 companies have executed trade sales, 16 have launches initial public offerings and we still have about 20 active companies in the portfolio. Our interests range from very early to late-stage product candidates; for us it depends on each individual opportunity. The decision is contingent on how innovative a product is, what unmet need it is fulfilling and building a balanced investment portfolio .

Because a lot of our focus is in Europe, the firm prioritizes trade sales for our exits. It is very important to us that the product or business is attractive to a potential pharma partner, so we are careful to evaluate the novelty of a new therapeutic, how validated it is from a scientific perspective, and whether the company itself has the right insight to develop the new platform or drug with a new modality. For example, in orphan diseases we want to see that a company has researched an appropriate regulatory pathway for a new drug candidate. Furthermore, we want to know what the intellectual property landscape for a novel drug will look like. Often in some of the hot therapeutics platforms there is a lot of IP conflict – EDRIP wants to be able to navigate and understand that situation at the start.

Right now we are investing out of a €192m fund and awarding between €5m and €10m to companies as initial investments.

DR. MARKUS GOEBEL: A lot of opportunities come to us through established networks. Strong invitations come from former board members and VCs we have worked with well in the past. There are also unsolicited requests but these don't normally go far because these requests often come in with no clear direction. As early-stage investors we run a high risk, high return model. It is just natural to have to face attrition – but the ones that end successful are big successes.

In a series A Novartis Venture Fund invests between $8m and $12m. We do between four and eight investments a year.

LE: *What are your key areas of focus?*

MG: Currently the Novartis Venture Fund is taking a deep dive on immune-oncology but we are finding that this area is so well covered by big pharma – including Novartis Pharmaceuticals – that it is difficult, if not impossible, to discover something truly novel. This doesn't mean we will stay away from immuno-oncology; we are actively screening for novel technologies in that space. In other therapy areas this challenge might not be as pronounced but in principle it is the same. Gene therapy is another area of high interest, though it is a little less exciting now than it was just a year ago. These are only two examples of areas that are "hot" right now but this doesn't necessarily mean we will invest. In any area we seek solid science, technology and IP, as well as experienced management teams with strong investors and syndicate formation. If all these elements come together the risk of the investment is significantly risk reduced.

NS: EDRIP's interest is broad and in our current portfolio there is activity in a number of spaces, including the metabolic, inflammation, oncology, anti-infective and neurology fields. The unmet needs are what we focus on and medicine is a very extensive sector. Two thirds of disease still doesn't have either satisfactory treatment or any medical treatment available. We don't want to limit ourselves.

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Natural History Confounds Surrogate Endpoints

ANDY SMITH

Like the NASDAQ Biotech Index, the stock price of **BioMarin Pharmaceuticals Inc.** finished the shortened trading week about where it started, although this masked a drop of about 3% for BioMarin on the day it announced the results of its PRISM-2 Phase III study of pegvaliase in patients with phenylketonuria (PKU).

BioMarin's announcement stated in its title that pegvaliase "meets primary endpoint of blood phenylalanine reduction ($p<0.001$)." However, the adjective most commentators used to describe the study results was "mixed." This was because the key clinical cognitive secondary endpoints were not significantly different from placebo, and more than one was worse than placebo. Add to that the 39% rate of hypersensitivity adverse events with pegvaliase against placebo's 14%, and you have the recipe not just for mixed clinical trial results, but also for pureed prospects.

High levels of the essential amino acid phenylalanine are certainly diagnostic for most PKU patients. PKU is caused by either a double mutation in the enzyme which breaks down phenylalanine to tyrosine (another essential amino acid), or a deficiency in the cofactor of the enzyme. The recovery in BioMarin's stock price was probably a result of investors being persuaded by the company and its paid clinical advisers that phenylalanine is eventually correlated with cognitive function in PKU patients as well as being a surrogate endpoint of the disease. Whilst that is probably true, it does not explain why some of the patients worsened on pegvaliase as measured by some clinical endpoints, and it does not address the likely requirement from the FDA and payers for a demonstration of safety as well as clinical efficacy rather than a surrogate of clinical efficacy. All this controversy may still pass with the "totality of the data" – the old chestnut that no one has yet dared used to described the results from the open-label PRISM-1, PRISM-302 and placebo-controlled PRISM-2 studies, which is itself a euphemism for mixed or pureed data.

Until the FDA panel documents are published for the pegvaliase BLA, I am very comfortable having sold both our fund's BioMarin and Incyte Inc. holdings after returning from January's JP Morgan conference. Since that time, BioMarin's investment proposition has worsened significantly, as exemplified by last week's announcement of the pegvaliase clinical results. BioMarin has conducted much larger and much longer studies in PKU patients than PRISM-2. Some of these were so-called natural history studies that define the patient population and their disease progression under the current standard of care, which in the case of PKU is a severely restricted diet. Who better to design the placebo-controlled PRISM-2 than a company that is au fait with the current natural history of PKU? Why on earth then did BioMarin's clinical development team design, and its senior management team approve, an eight-week PRISM-2 study when even the analysts at Jefferies and Piper Jaffray noted (admittedly after the PRISM-2 event) that there was "not enough time for neurocog."

The reason why this one mistake has damaged both the pegvaliase approval potential and BioMarin's investment proposition is that it is not just one mistake. About a year ago BioMarin's management and its clinical development team signed off on the $680m acquisition of Prosensa Holding NV, only to see that due diligence and investment result in a savaging by an FDA review panel over the inconsistency and contradictory nature of the company's data, and a complete response letter requesting further clinical studies.

BioMarin's acquisition of Prosensa for its drug *Kyndrisa* (drisapersen) for Duchenne muscular dystrophy (DMD) was not the only connection between it and Sarepta Therapeutics Inc., which was also recently on the receiving end of a savage FDA review for its DMD drug candidate, eteplirsen. In Sarepta's case, the review panel had to be delayed until mid-April after Snowmageddon in late January and the review of four-year follow-up data. Last week a group of 36 DMD experts published an open letter urging the FDA to approve eteplirsen. In their flash note the analysts from Jefferies questioned whether the new data submitted would be sufficient to support approval of eteplirsen. In reviewing the totality of the evidence against eteplirsen, the Jefferies analysts noted the FDA's previous suggestion of a natural history study to more accurately assess the treatment effect of eteplirsen, and the agency's critique of Sarepta's dystrophin surrogate biomarker data due to its low and very variable levels.

The glossing over of the totality of the data against eteplirsen's approval next month was not the most surprising aspect of the physicians' letter. Rather, it was that there were 36 DMD specialist signatories even though Sarepta only treated 12 patients in its last open-label study, including a mere six at the proposed approved dose. Too many of them do protest, methinks.

"The glossing over of the totality of the data against eteplirsen's approval next month was not the most surprising aspect of the physicians' letter.

Andy Smith is chief investment officer of Mann Bioinvest. Mann Bioinvest is the investment adviser for the Magna BioPharma Income fund which has no position in the stocks mentioned, unless stated above. Dr Smith gives an investment fund manager's view on public life science companies. He has been lead fund manager for four life science–specific funds, including International Biotechnology Trust and the AXA Framlington Biotech Fund, and was awarded the Technology Fund Manager of the year for 2007.

Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

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Late-stage clinical developments for the week 25-31 March 2016

LEAD COMPANY	PARTNER COMPANY	DRUG	INDICATION	MARKET
REGULATORY APPROVAL				
Jazz Pharmaceuticals PLC	–	Defitelio (defibrotide sodium)	hepatic veno-occlusive disease (also known as sinusoidal obstruction syndrome)	US
AstraZeneca PLC	–	Tagrisso (osimertinib)	non-small-cell lung cancer (NSCLC)	Japan
Bayer AG	–	Kovaltry (octocog alfa)	hemophilia A	Japan
GlaxoSmithKline PLC	–	Nucala (mepolizumab)	asthma	Japan
Alexion Pharmaceuticals Inc.	–	Kanuma (sebelipase alfa)	lysosomal acid lipase deficiency	Japan
Eisai Co. Ltd.	–	Fycompa (perampanel hydrate)	epilepsy	Japan
Biocon Ltd.	FujiFilm Pharma Co. Ltd.	insulin glargine	type 1 diabetes	Japan
BioProducts Laboratory Ltd.	-	Coagadex (Factor X)	Factor X deficiency	EU
REGULATORY FILING ACCEPTED				
Gedeon Richter	Allergan Inc.	cariprazine	schizophrenia	EU
SUPPLEMENTAL REGULATORY FILING ACCEPTED				
Bristol-Myers Squibb Co.	–	Opdivo (nivolumab)	Hodgkin lymphoma	EU
ORPHAN DRUG DESIGNATION				
Actinium Pharmaceuticals Inc	–	Iomab-B (iodine-131 labeled CD45-targeting Ab)	bone marrow and stem cell transplant	US
Adaptimmune Ltd.	GlaxoSmithKline PLC	NY-ESO-1 (C259)	soft-tissue sarcoma	US
OxiGene Inc.	Azanta	CA4P (fosbretabulin)	neuroendocrine tumors	EU
FAST-TRACK STATUS				
OxiGene Inc.	Azanta	CA4P (fosbretabulin)	ovarian cancer	US
Vical Inc.	Astellas	VL-2397	invasive aspergillosis	US
COMPLETE RESPONSE LETTER				
Opko Health	–	Rayaldee (calcifediol)	secondary hyperparathyroidism	US
Newron Pharmaceuticals SpA	US WorldMeds	Xadago (safinamide)	Parkinson's disease	US
H Lundbeck	Takeda Pharmaceutical	Brintellix (vortioxetine)	cognitive dysfunction in depression (additional indication)	US
REGULATORY FILING				
Radius Health Inc.	–	abaloparatide-SC	osteoporosis	US
Shionogi & Co. Ltd.	–	naldemedine	opioid-induced constipation	US, Japan
Kamada Ltd.	Chiesi Farmaceutici SpA	alpha-1 antitrypsin	alpha-1 antitrypsin deficiency	EU
Lexicon Pharmaceuticals Inc.	–	telotristat etiprate	carcinoid syndrome	US
RESPONSE SUBMITTED TO COMPLETE RESPONSE LETTER				
Pain Therapeutics Inc.	Durect Corp.	Remoxy (oxycodone) extended-release tablets	chronic pain	US
SPECIAL PROTOCOL ASSESSMENT AGREEMENT				
Ohr Pharmaceutical Inc.	–	squalamine lactate (OHR-102)	wet age-related macular degeneration	US

Source: Sagient Research's BioMedTracker

UK biotech company **Tiziana Life Sciences plc.** has named ***Tiziano Lazzaretti*** as its chief financial officer. Lazaretti joins Tiziana, which specialises in novel molecule development, from Pharmentis Srl, where he served as chief finance director for five years. He has previously held senior positions at Alliance Boots Healthcare, Accenture and other listed companies including SNIA Spa and Fiat Group.

Actinium Pharmaceuticals Inc. has appointed ***Jennifer Liberi*** director, clinical operation. Liberi joins Actinium, a New York-based biopharma company, from Noven, where she also held the position of director, clinical operations. Prior to this, Liberi has had 10 years' of experience working at various global pharma companies including Novartis, Merck Research Laboratories and Bristol Myers-Squibb.

Adherium, an Australian company specialising in digital health technologies, has appointed ***John Tarplee***, formerly of ALK-Abello, senior vice president of business development, Europe. Tarplee's appointment comes in conjunction with the establishment of Adherium Europe Ltd., which will operate from Guildford, UK. Tarplee has over 30 years' of experience in the industry, having previously held positions at Sanof-Aventis, Abbott Laboratories and Fison Pharmaceuticals.

CEO and president of **ImmunoGen Inc.**, ***Daniel Junius*** will be retiring from the company. Junius has been the biotech's CEO since 2009 and following his retirement, he will continue to serve on ImmunoGen's board of directors.

Aimmune Therapeutics Inc. has appointed ***Douglas Sheehy*** general counsel and secretary. He joins the company with over 20 years' experience from Codexis Inc. where he was hired as general counsel and secretary in 2007. Most recently he was the company's chief administrative officer and previously he spent five years' in legal roles at CV Therapeutics Inc.

VistaGen Therapeutics Inc. has appointed ***Jerry Gin*** to its board of directors and Audit Committee. Gin has over 45 years' experience and is currently the co-founder and CEO of Nuvora Inc. and co-founder and chair of Livionex. Previously Gin co-founded Oculex Pharmaceuticals and served as president and CEO until it was acquired by Allergan. Prior to forming Oculex, Gin co-founded and took public ChemTrak. Before this Gin was director of new business development and strategic planning for Syva the diagnostic arm of Syntex Pharmaceuticals.

Anika Therapeutics, Inc., a US-based integrated orthopaedics medicines business, has appointed ***Stephen Mascioli*** chief medical officer (CMO) and ***Dana Alexander*** to the role of chief operations officer. Jean Bjerke has also joined the company as vice president of marketing. Mascioli has over 25 years' of leadership experience, having previously held the inaugural CMO position at Terumos Americas Holdings, before which he served as CMO of the Vascular Therapies division of Covidien, a global medical device company. Alexander has spent the last 14 years' in various leadership roles at Genzyme Corp., where he most recently served as senior director of biologics manufacturing operations. Bjerke brings 15 years' of marketing expertise to the role, having specialised with the orthopaedic device segments for Smith & Nephew and Depuy Orthopedics prior to joining Anika. He has previously been director for pharmaceutical and diagnostic businesses for Dow Chemical, and director of BioScience Labs.

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