

# BioCentury

WEEK OF APRIL 20, 2015

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## FDA'S ROCKET DOCKET

BY STEVE USDIN, WASHINGTON EDITOR

FDA is approving more cancer drugs, more rapidly than ever, and the trend is likely to continue, according to Richard Pazdur, director of the Office of Hematology and Oncology Drug Products at FDA's Center for Drug Evaluation and Research.

In an interview with BioCentury TV, Pazdur said unprecedented efficacy in early stage trials is prompting the agency to review cancer drug applications as quickly as possible, to approve cancer drugs based on single-arm and early stage trials, and to streamline review procedures for supplemental indications.

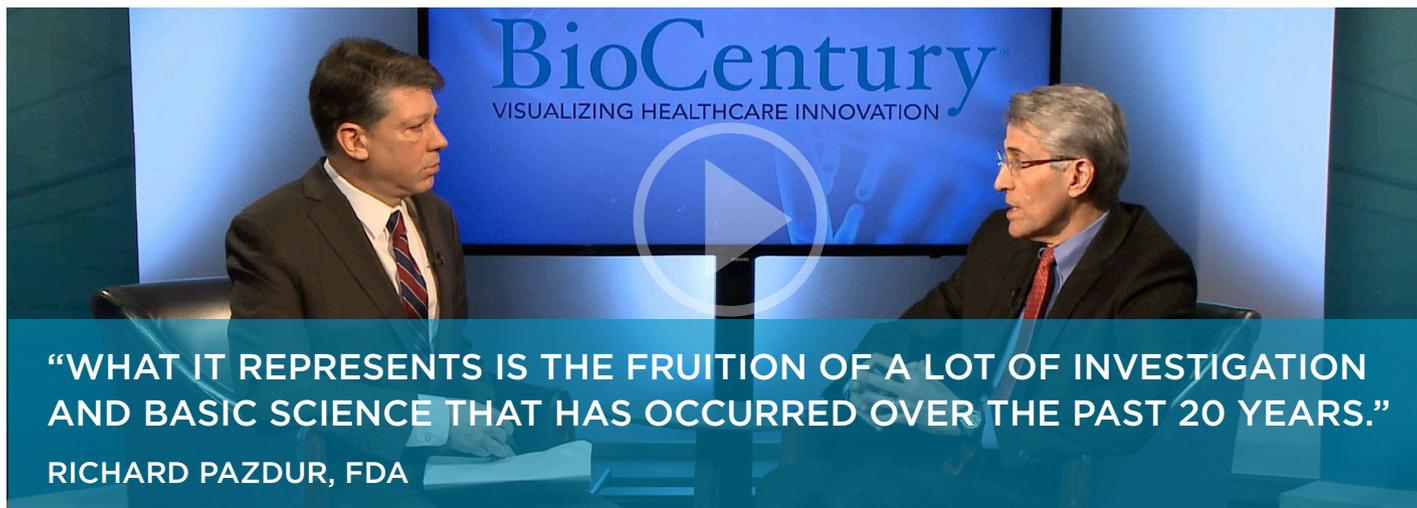
Pazdur's comments, and the reality on the ground, represent a complete reversal of the messages he and FDA were sending drug sponsors five and 10 years ago. Pazdur attributes the turnaround to advances in the scientific understanding of cancer that have made the development of drugs targeting molecular and immunological pathways possible.

In addition to scientific advances, Pazdur highlighted the role of patients in helping to shape cancer drug development.

He also pointed to areas where he feels FDA should improve its policies, such as creating regulations to compel sponsors to start Phase I trials in pediatric indications of targeted cancer therapies when companies start a Phase II trial in an adult indication.

Pazdur also noted that broad dissemination of early data "touted as major breakthroughs" is fueling demand for access to experimental drugs. As a result, he said FDA and drug sponsors should make it easier for patients to understand whether and how they can get access to unapproved cancer drugs outside of clinical trials.

Biosimilars are another area where FDA needs to focus attention, Pazdur said.



**“WHAT IT REPRESENTS IS THE FRUITION OF A LOT OF INVESTIGATION AND BASIC SCIENCE THAT HAS OCCURRED OVER THE PAST 20 YEARS.”**

**RICHARD PAZDUR, FDA**

## GETTING BETTER ALL THE TIME

Pazdur told BioCentury there is a simple explanation for his shift from skepticism to enthusiasm about new cancer drugs: “Drugs got better.”

Unambiguous efficacy signals make it easier, and quicker, for FDA to approve new cancer drugs, he said. FDA is consistently beating PDUFA goals by 50 days or more (see “Beating the Clock,” page 6).

“We’re not seeing drugs and arguing with sponsors about whether the drug should be approved or not,” Pazdur said. “What we’re asking our reviewers and the sponsor is how rapidly we can approve these drugs. We’re not dealing with drugs that have a response rate of 7%. We’re dealing with drugs that have response rates of 50, 60, 70%, so it’s a much easier regulatory decision whether the drug should be approved or not approved.”

Improvements in efficacy, which Pazdur noted are often accompanied by improved safety, are likely to continue because they are based on broad scientific advances, he said.

“I really see this as a major foundation change, and it really has to do with a better understanding of both the drug and the disease,” Pazdur said. “Really what it represents is the fruition of a lot of investigation and basic science that has occurred over the past 20 years.”

Efficacy and safety readouts from early studies are leading FDA to approve cancer drugs based on Phase II, and even in some cases Phase I trials, Pazdur said.

“When drugs have very profound activity in a particular disease, what we’re doing is basically expanding Phase I studies into cohorts of patients that could be entered into a registration schema,” Pazdur noted.

**Merck & Co. Inc.’s** Keytruda pembrolizumab is an example. FDA approved the drug in September 2014 based on a 24% response rate among 173 patients with advanced melanoma in a Phase Ib trial that was ongoing. The agency approved the drug for patients previously treated with **Bristol-Myers Squibb Co.’s** Yervoy ipilimumab.

“The traditional response rate for a Phase I study in oncology, for conventional cytotoxic drugs in the ’80s, ’90s, and the early part of this century was basically about 5%, or less than 5%,” Pazdur said. “What we’re

seeing is -- with targeted drugs and the new molecules that are targeting the immunological pathways -- response rates of sometimes 50%.”

## MEDIAN NOT THE MESSAGE

A strong efficacy signal led FDA to push for a very rapid review of BMS’s Opdivo nivolumab to treat patients with metastatic squamous non-small cell lung cancer (NSCLC) who have progressed on or after platinum-based chemotherapy, Pazdur told BioCentury TV in a program on the future of lung cancer therapies.

“I remember very well sitting down at my desk at home and opening up my computer and putting in the password, because the survival curves were protected in an encrypted email, and seeing those survival curves, and I was very impressed by them,” Pazdur said.

The data showed a 3.2-month survival advantage for patients who received Opdivo compared with those who received docetaxel.

Pazdur immediately began calling reviewers and the division director, Patricia Keegan, to talk about how to approach the review, because he thought it was important to get the drug to patients. “It really represented a paradigm shift in how we treat squamous cell lung cancer, especially in a second-line setting,” he said.

But Gideon Blumenthal added, “When we’re looking at these immunotherapy agents, the median is not the message.” Blumenthal is a clinical team leader in the Office of Hematology and Oncology Products, told BioCentury TV

“We learned this also in melanoma with ipilimumab and other PD-1 inhibitors,” Blumenthal said. “There are certain patients, and we don’t know exactly who those patients are as of yet, who derive a great deal of benefit, and even may have five-year survival. If you look at the melanoma literature, maybe 20% of patients can live five years out.”

FDA approved Opdivo on March 4, more than three months ahead of the PDUFA goal (see “Opdivo Urgency,” page 3).

Pazdur decided Opdivo needed to be approved quickly both because patients who had run out of options were waiting, and because the approval could affect ongoing lung cancer trials, such as the Lung-MAP trial, a master protocol trial designed to evaluate several compounds simultaneously to treat squamous cell lung cancer.



## OPDIVO URGENCY

FDA pulled out all the stops to approve [Bristol-Myers Squibb Co.](#)'s Opdivo nivolumab to treat patients with metastatic squamous non-small cell lung cancer who have progressed on or after platinum-based chemotherapy. The agency began reviewing trial data before it was available to the company, and completed the review in March, more than three months ahead of the PDUFA goal.

Opdivo is the first PD-1 modulator to be approved for NSCLC. Three other PD-1 or PD-L1 modulators are in Phase III NSCLC trials: MEDI4736 from [AstraZeneca plc](#), Keytruda pembrolizumab from [Merck & Co. Inc.](#) and RG7446 from [Genentech Inc.](#)

Full approval of Opdivo based on a survival advantage over docetaxel does not raise the bar for approval of other PD-1 modulators for NSCLC, FDA's Gideon Blumenthal told BioCentury TV. Blumenthal is a clinical team leader in the Office of Hematology and Oncology Products at the Center for Drug Evaluation and Research.

"It doesn't change our sense of urgency," Blumenthal said. He noted other modulators may have different toxicity profiles, and he added that they are being tested using different clinical design strategies.

"They're looking at various stages, different histologies, adenocarcinoma versus squamous. Some are looking at earlier stages, even adjuvant curative setting. So there's still a strong all-hands-on-deck mentality for some of these other agents," he said.

Blumenthal added the approval of Opdivo doesn't bar other agents from getting on the market quickly if, for example, the sponsors produce data demonstrating benefit is likely in a biomarker-enriched subpopulation.

BMS has worldwide rights to Opdivo from [Ono Pharmaceutical Co. Ltd.](#), excluding Asian countries where the partners have a joint development and marketing deal.

— STEVE USDIN



## MOVING UP IN BLOOD CANCERS

Hematologic cancer drug development has been so successful that FDA views it as a paradigm for the development of therapies for other kinds of cancer, Richard Pazdur, director of FDA's Office of Hematology and Oncology Products, told BioCentury TV.

He cited early successes in developing drugs for Hodgkin's disease, acute lymphoblastic leukemia (ALL) and childhood leukemia, as well as large cell and B cell lymphomas.

For some hematologic cancers, numerous drugs with different mechanisms of action have been approved, so there is a pressing need to study how they should be combined and sequenced, Pazdur said. Chronic lymphocytic leukemia (CLL) — for which nine treatments are approved — is an example.

Nicole Gormley, a medical officer in the Division of Hematology Products, noted two anti-CD20 mAbs have been approved for the indication: Arzerra ofatumumab from [Genmab A/S](#) and [Novartis AG](#), and Gazyva obinutuzumab from [Biogen Inc.](#) and [Genentech Inc.](#) Genentech and Biogen also market Rituxan rituximab, an anti-CD20 mAb that is used in combination with several of the newer CLL therapies.

FDA has also recently approved Imbruvica ibrutinib from [Johnson & Johnson](#) and [Pharmacyclics Inc.](#) (which is being acquired by [AbbVie Inc.](#)); and [Gilead Sciences Inc.](#)'s Zydelig idelalisib. Imbruvica is a Bruton's tyrosine kinase (Btk) inhibitor, while Zydelig is an inhibitor of PI3K delta.

The recent CLL approvals have been in "relatively refractory disease populations or relatively hard-to-treat CLL genetic subtypes," Pazdur noted. "But their true advantage is really going to be moving up to more of a front-line situation in combination with other drugs, and we're seeing this really very rapidly."

— STEVE USDIN

On March 10, the Lung-MAP trial leadership team announced that in response to the approval, the team was modifying the design of the immunotherapy sub-study of Lung-MAP. These modifications could lead to the addition of Opdivo to the control arm.

## RETURN TO SINGLE ARMS

Seeing large efficacy signals also has made FDA more comfortable with single-arm trials that it was just a short time ago.

In 2009, FDA and members of its Oncologic Drugs Advisory Committee criticized drug sponsors for trying to get drugs approved based on insufficient data packages that relied on single-arm trials. It seemed that FDA was going to stop accepting single-arm trials for cancer drugs.

Now FDA even promotes the use of single-arm studies for cancer drug approvals.

Such trials were the basis for 10 of FDA's 39 cancer drug approvals from January 2013 to the end of March 2015.

Pazdur noted single-arm trials have limitations, including a lack of safety data. "But one has to weigh that against the potential benefit of the drug," he said. "Obviously, if somebody's seeing an 80% response rate in a targeted population, and the general population has a 10% response rate, the risk/benefit and the uncertainty might be something that we would accept."

Pazdur said it also helps that companies are now conducting these studies in the context of bigger development programs, not as stand-alone efforts. "They're coming in with a single-arm trial, but they have ongoing randomized trials very early on in their development program because they have confidence in these drugs," he said. "That gives us a lot of confidence in approving these drugs on single-arm trials in small populations because we know that answers are going to be coming relatively quickly on these drugs."

## GETTING THE SEQUENCE RIGHT

The next step for cancers where there are multiple approved targeted and immunologic drugs is going to be determining how to deploy drugs in combination and in the correct sequence, according to Pazdur. "The real benefit of any of these drugs is how they are going to be used in combinations or sequentially. There's not going to be one drug that cures a cancer."

To move from transient responses to sustained remissions or even cures, "what we're really going to have to see is clinical trials that are using these drugs in some novel sequence, in a novel combination," Pazdur said.

The Office of Hematology and Oncology Drug Products is launching a project soon to help facilitate such trials, Pazdur said.

FDA plans to convene meetings of investigators to create blueprints for protocols to sequence and combine drugs for specific types of cancer.

"We're not so much interested in who's going to do the trials, or who should fund these trials, but more of a bigger picture issue of what do people really want to see? How should these drugs be moved into an adjuvant setting?" Pazdur said.

"Their true promise, both as single agents and in combination, are probably going to be in patients that are at high risk of developing recurrence, the so-called adjuvant setting, and those are the situations where we probably will be seeing an increased cure rate," he said.

The first blueprints are likely to be created for indications with numerous approved drugs, such as melanoma, chronic lymphocytic leukemia (CLL), renal cancer and NSCLC, Pazdur said.

## STREAMLINING SUPPLEMENTS

FDA also is implementing a new policy that is intended to streamline supplemental applications in cancer. Instead of conducting detailed analyses of the raw data, the agency will rely more on summary data submitted by sponsors.

## RAPID BIOSIMILARS UPTAKE

Richard Pazdur, director of the Office of Hematology and Oncology Drug Products in FDA's Center for Drug Evaluation and Research, predicts biosimilars will be adopted quickly.

"I think that they will be rapidly taken up. This is an area that is going to be somewhat a practice-changing issue of how people use biosimilars versus the innovator molecule, but I really do view this as a positive area of drug development," he said in a BioCentury TV interview.

The Office of Hematology and Oncology Drug Products reviewed and approved FDA's first biosimilar application, for Zarxio filgrastim-sndz from Novartis AG's Sandoz unit, a biosimilar version of Neupogen filgrastim from Amgen Inc. Several of the biosimilars in the pipeline are also cancer therapies.

The rate of uptake will depend in part on how well oncologists understand the biosimilars development and review process, Pazdur said. The key point, he said, is explaining that approval is "not about the clinical trial demonstrating safety and efficacy. We don't have to re-prove safety and efficacy."

Rather, Pazdur said, "the major foundation of the application is basically the analytics of how similar this molecule is to the innovator molecule. That is the foundation, the pyramid on which the decision is made. The clinical trial is really the apex of it, and really is less important than the analytics of the biosimilar."

— STEVE USDIN

## TARGETING OVARIAN CANCER

FDA's December 2014 approval of Lynparza olaparib, the first targeted therapy for ovarian cancer, could stimulate more drug development for ovarian cancer, according to Amy McKee, a clinical team leader in the agency's Office of Hematology and Oncology Products.

"We've heard from investigators in the community that they're getting approached more and more by companies that are wanting to jump into this space," McKee told BioCentury TV in an interview about the future of ovarian cancer therapies.

FDA approved the PARP inhibitor as monotherapy in patients with deleterious or suspected deleterious germline BRCA mutation detected by an FDA-approved test, who have been treated with three or more prior lines of chemotherapy.

In June 2014, the Oncologic Drugs Advisory Committee voted 11-2 against approval for a different indication: maintenance therapy for platinum-sensitive ovarian cancer. [AstraZeneca plc](#) originally applied for approval of Lynparza as maintenance treatment of platinum-sensitive relapsed ovarian, fallopian tube or peritoneal cancer in patients with germline BRCA mutations.

"We felt that the drug did have activity in the disease, and it was really trying to find out what the appropriate indication was, given the need for



this drug," Richard Pazdur, director of FDA's Office of Hematology and Oncology Products, told BioCentury.

McKee noted the approval was based on a single-arm trial using response rates only. "This is not typically what we think of for ovarian cancer," she said. "In the past, in upfront therapy, we've asked for overall survival."

McKee said the approval has been "a signal to the community" that the agency is willing to look at non-traditional populations and to consider response rate or progression-free survival endpoints.

— STEVE USDIN

## GETTING pCR RIGHT

Three years after publishing draft guidance on the use of pathologic complete response (pCR) as a surrogate endpoint for accelerated approval of neoadjuvant therapy for high-risk early stage breast cancer, FDA is uncertain about how to interpret the endpoint, according to Richard Pazdur, director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research.

Pazdur told BioCentury TV the agency did its own meta-analysis of trials, which led to "some questions" about the association between pCR and overall survival or disease-free survival. He emphasized FDA's view that pCR should be reserved for "drugs that really have demonstrated significant activity in other breast cancer disease settings."

Patients receiving neoadjuvant treatment "may not even need this drug, so we really have to be certain about the safety profile and what is going to be the effect," Pazdur said. "This is not a pathway for approval for all breast cancer drugs or marginal breast cancer drugs."

One area where a high correlation between pCR and risk of recurrence exists is triple-negative breast cancer.



FDA is working to facilitate an international master protocol to try to develop biomarker-driven targeted drugs for triple-negative breast cancer, Julia Beaver, a medical officer in FDA's Breast Oncology Group, told BioCentury TV.

— STEVE USDIN

“What we’re talking about is looking at basically the same type of application that would be submitted to the EMA or other regulatory authorities,” Pazdur said. EMA, unlike FDA, does not typically conduct independent analyses of raw data.

Amy McKee, a clinical team leader in the Office of Hematology and Oncology Products, said the process shaved months off the review time for an application from Roche’s Genentech Inc. to add cervical cancer to the label of Avastin bevacizumab. The August 2014 approval came after a review of less than four months.

“This was a streamlined review. We reviewed the study report and were able to approve the product in several months instead of the nine to 12 months it typically would take, and it provided an important new option for patients with cervical cancer who had very few options prior to this approval,” she said.

“There are two issues with the Avastin cervical application,” Pazdur told BioCentury. “Number one, there’s an extensive safety database that we have, not only from a clinical trials perspective, but also from a postmarketing perspective that goes over a decade now, so I think most people feel that we are very comfortable.”

“The second issue is that we’re dealing with an overall survival endpoint, which is a very hard objective endpoint, and it’s not subject to subjectivity or bias in its interpretation,” he said. The combination of those two factors led the agency to use the application as a pilot for a streamlined review process, looking at summary data rather than each line listing, he added.

Similarly, Pazdur highlighted FDA’s September 2013 approval of a label expansion for Perjeta pertuzumab from Genentech to include neoadjuvant breast cancer.

“Perjeta demonstrated eye-popping results in metastatic disease that I have not seen in my career, so it was not a big leap of faith to introduce that drug with that effect on metastatic disease into an earlier disease setting,” he said.

Pazdur said the new policy is intended for “supplemental indications where a sponsor might be submitting the third or fourth application of a molecule in a different disease, or in a similar disease to the one that was approved.”

## EXPANDING ACCESS

One area Pazdur thinks the agency and industry need to improve is procedures for obtaining unapproved drugs under FDA’s expanded access procedures.

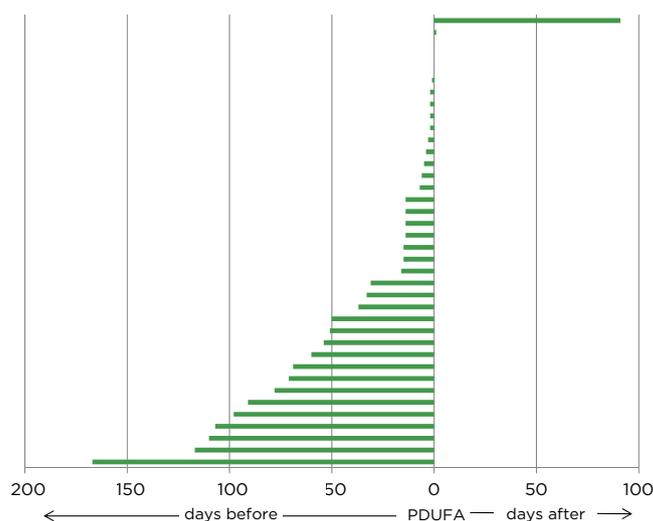
Pazdur said he is not suggesting that companies must offer expanded access. There are many reasons for a company to decide not to make experimental drugs available, including limited drug supply or concerns that early access will slow drug development or approval, he said. But he added patients should be able to find out easily whether expanded access is available and, if it is, how to avail themselves of the opportunity.

“All I’m asking for is transparency in the process,” Pazdur said.

FDA has taken some steps to make it easier to obtain expanded access. But Pazdur said, “It is quite a cumbersome process to obtain expanded access for an individual patient. One has to know who in a drug company to call. One has to know who in the FDA to call.”

## BEATING THE CLOCK

Since the start of 2013, FDA has approved 38 new or supplemental applications for cancer drugs. Twenty-three were approved at least two weeks before their PDUFA dates, 16 at least a month early and 10 at least two months early. Thirteen applications were approved within the week before, or on, their PDUFA dates. In one case, FDA extended the original PDUFA date by three months. Each line below represents one application. Conversions of accelerated approvals to full approvals are not included. *Source: FDA review documents*



## TRIAL DESIGNS

FDA is speeding cancer drugs to market by allowing sponsors to use single-arm and open-label trials, and by approving products based on response rate and progression-free survival. Since January 2013, only 10 of 38 approvals for new indications were based on double-blind, placebo-controlled trials, and overall survival was the primary endpoint for only seven of the approvals. Conversions of accelerated approvals to full approvals are not included. *Source: FDA review documents and drug labels.*

Study design	#	Approval endpoint	#
Open-label, randomized	18	Response rate	15
Double-blind, placebo-controlled	10	Progression-free survival	13
Single-arm	10	Overall survival	7
		PFS and OS as co-primary	1
		Other endpoints	2

In addition to improving FDA's procedures, Pazdur said the oncology research community and drug sponsors should make changes to help patients obtain expanded access.

"The process itself could be facilitated to really encourage patients that need these drugs," he said.

Pazdur said he has asked the American Society of Clinical Oncology (ASCO) and the [American Association for Cancer Research \(AACR\)](#) to make a "concerted effort" to get sponsors and presenters at their annual meetings to articulate what their plans are for expanded access or single-patient INDs.

## "WHEN WE'RE LOOKING AT THESE IMMUNOTHERAPY AGENTS, THE MEDIAN IS NOT THE MESSAGE."

GIDEON BLUMENTHAL, FDA

When presenters tout results as major breakthroughs, "patients are in the audience," he said. "They're facing a life-threatening disease with very few options. They want that drug."

ASCO has asked all authors submitting abstracts that report on clinical trials of new agents at this year's annual meeting to indicate whether or not the drug sponsor intends to offer an expanded access program.

"Whatever the answer, we are now contacting all presenters of relevant abstracts to ask that they include this information in their oral or poster presentations," ASCO CMO Richard Schilsky told BioCentury.

### PATIENT VOICES

Facilitating expanded access is part of a broader effort by FDA to engage patients more actively in drug development and regulation. In the context of cancer, Pazdur said patient-centered drug development "means hearing patients' voice in the design of trials and the execution of trials, and where the trials should be conducted."

Patient perspectives are also important for improving product labeling, Pazdur said. For example, he noted, "When one takes a look at oncology patients, I think one of the things patients fear the most is adverse events, the toxicities of the drugs."

Even cancer drugs with relatively favorable toxicity profiles can cause serious and life-threatening adverse events, and patients can play an important role in helping define and communicate about adverse events. "To get the patients to really have an understanding of what these adverse events are, to incorporate their voice in adverse event reporting, I think, is particularly important," Pazdur said.

In addition, more and better patient engagement is needed to help companies and regulators focus on symptom relief, according to Pazdur.

"The other avenue that needs to be looked at," Pazdur said, "is how these drugs affect not only survival and time-to-progression response rates, but how they also may ameliorate symptoms."

To address these issues, he said sponsors should consider conducting a separate trial with patient-reported outcomes (PROs) as the primary endpoints. "One of the problems that we've seen with many of these patient-reported outcomes is they're not really well integrated into the major clinical trial. They're added on at the end. There's a lot of missing data. There's not a statistical analysis plan," Pazdur noted.

### COMPELLING PEDIATRIC TRIALS

While targeted drugs and therapies targeting the immune system are driving progress in cancer, Pazdur said he is concerned that children are being left behind.

"We are moving away from cytotoxic drugs, and the advances that have occurred in pediatric oncology have dealt primarily in this space," he noted.

Pazdur said he "would strongly recommend" compelling sponsors that are developing targeted and immunologic therapies in adults to study those therapies "in clinical trials in children with tumors that have similar pathways or the same pathway."

"One of the things that we really have to look at is the earlier initiation of Phase I studies in pediatrics. It really doesn't make sense to me to have a drug completely developed in an adult indication and then the pediatric development program starts." <sup>bc</sup>

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### COMPANIES AND INSTITUTIONS MENTIONED

**AbbVie Inc.** (NYSE:ABBV), Chicago, Ill.  
**American Association for Cancer Research** (AACR), Philadelphia, Pa.  
**American Society of Clinical Oncology** (ASCO), Washington, D.C.  
**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.  
**Biogen Inc.** (NASDAQ:BIB), Cambridge, Mass.  
**Bristol-Myers Squibb Co.** (NYSE:BMJ), New York, N.Y.  
**European Medicines Agency** (EMA), London, U.K.  
**Genentech Inc.**, South San Francisco, Calif.  
**Genmab A/S** (CSE:GEN; OTCBB:GMXAY), Copenhagen, Denmark  
**Gilead Sciences Inc.** (NASDAQ:GILD), Foster City, Calif.  
**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.  
**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.  
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland  
**Ono Pharmaceutical Co. Ltd.** (Tokyo:4528), Osaka, Japan  
**Pharmacyclics Inc.** (NASDAQ:PCYC), Sunnyvale, Calif.  
**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland  
**U.S. Food and Drug Administration** (FDA), Silver Spring, Md.

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## STRATEGY

## METAMORPHOSES OF OVID

BY SUSAN SCHAEFFER, EDITOR

Neurology company [Ovid Therapeutics Inc.](#) is already tapping into the expertise of its new CEO, veteran dealmaker Jeremy Levin. The biotech is in-licensing molecules that have reached Phase III testing but are not approved in the U.S., and where there is a mechanism-based rationale for development in rare and Orphan diseases of the brain.

Hardly the first company to attempt to repurpose failed drugs, Ovid may have an ace up its sleeve in the form of extremely close ties to patients and their families, who will have a role in shaping development of the company's drug candidates.

Ovid's first deal, announced Thursday, brings in a candidate from [H. Lundbeck A/S](#) that is slated to enter Phase II in 2016 to treat Angelman syndrome and Fragile X. The deal includes exclusive, worldwide rights to gaboxadol, a selective extrasynaptic GABA A receptor agonist that Lundbeck and former partner [Merck & Co. Inc.](#) had taken through Phase III testing for insomnia.

In that setting, a combination of the U.S. regulatory requirements for demonstrating the lack of abuse potential and the pharmacokinetics of gaboxadol scuttled both the development program and the partnership. But according to Ovid, the PK problem that dogged the compound in the sleep setting will not be an issue in Angelman and Fragile X, where lower doses and lower peak concentrations are desired.

Angelman is a rare genetic disorder that is characterized by developmental delay, severe speech impairment, seizures, and movement and balance disorders (ataxia).

No drugs have been approved for Angelman and only two clinical trials have been run in the population, one testing levodopa and one minocycline; therefore, no endpoints have stood the test of regulatory review. In addition, the instruments used to assess key symptoms, including motor dysfunction and cognitive impairment, are not optimized for use in Angelman patients.

This is one area where Ovid will benefit from collaborations with two parent-led advocacy groups, the Angelman Syndrome Foundation (ASF) and the Foundation for Angelman Syndrome Therapeutics (FAST). The organizations maintain databases of patients and providers who treat Angelman, will provide input to the company's clinical trial advisory group and will help recruit patients for trials.

Levin plans to extend the model to other rare neurological diseases to build Ovid and keep it independent: in-licensing unapproved compounds with a large body of data, well understood pharmacology and a mechanistic link to disease, and collaborating closely with patients to ensure successful development.

Levin, who has been chairman of Ovid since 2014, was most recently president and CEO of [Teva Pharmaceutical Industries Ltd.](#); he previously led business development for [Bristol-Myers Squibb Co.](#) and [Novartis AG](#).

## GLIMPING THE PATHWAY

Ovid was founded last year by President and CSO Matthew During, a neuroscientist and physician whose lab pioneered the use of AAV in the brain.

"In the last five years, we've come to better know the genetic basis of Orphan neurological disorders, and also have animal models — predictive genetic models — that recapitulate the human phenotype," During told BioCentury. "And knowledge of small molecules, and cloning out receptors and subreceptors in the brain, have flourished in parallel over this time."

**"WHAT IS IMPORTANT TO ONE INDIVIDUAL WHOSE CHILD IS NOT YET WALKING MAY BE DIFFERENT FROM WHAT IS IMPORTANT TO AN INDIVIDUAL WHOSE CHILD IS WALKING."**

EILEEN BRAUN, ASF

Instead of screening libraries of compounds, During sought out drug candidates that had made it through Phase III testing but were not approved in the U.S.

"They had to have known pharmacology, a unique mechanism, and had to match the neurological disorder," he said.

Gaboxadol, now dubbed OV101, is one of six small molecules During has identified. The chemical names of the other five are not disclosed, but Levin disclosed the planned indications for three of them: OV201 is for Lewy body dementia, OV301 is for Dravet syndrome and OV401 is for Prader-Willi.

According to During, the molecules have extensive human data and have shown no rate-limiting toxicities. And because they have not been approved in the U.S., there will not be generic competition before Ovid's IP expires. For example, he said gaboxadol has patent protection at least through 2025.

## NEW PURPOSE

While gaboxadol didn't pan out in sleep disorders, During and Levin said the molecule's pharmacology is particularly suited for Angelman and Fragile X.

Lundbeck originally hoped gaboxadol would be differentiated in insomnia in part by not being regulated as a drug of abuse. In 2004, Lundbeck partnered the compound with Merck and told BioCentury it believed gaboxadol was the only molecule in development for insomnia that targeted the GABA binding site on GABA A receptors, and not the benzodiazepine binding site.

Gaboxadol binds to GABA A receptors with alpha4/delta subunits. At the time, Bjarke Ebert, then head of electrophysiology at Lundbeck, said the alpha4/delta subtype does not have a benzodiazepine binding site unlike most GABA A receptors. And unlike most GABA A receptors, he said, the alpha4/delta subtype is expressed outside of synapses.

But Lundbeck and Merck dropped gaboxadol in 2007, saying the “overall clinical profile” did not support continued development.

According to During, the problems were twofold. First, patients experienced hallucinations in a study in drug abusers that FDA requested to support approval as a nonscheduled hypnotic. However, During said the abuse study used three times the normal dose for insomnia, and he noted hallucinations are not uncommon in drug abusers.

Second, During said, Phase III efficacy results in the U.S. were not as good as those in Europe because of a PK problem. “In Phase III in normal individuals, they saw good results in women, but not in men,” he said.

“For the hypnotic use, Lundbeck and Merck needed to get a very high C<sub>max</sub>. It required super rapid absorption and high C<sub>max</sub>. When dosing in Americans, high meat consumption impacted not the area under the curve, but the C<sub>max</sub>. But we don’t want high C<sub>max</sub>,” he said.

The doses of gaboxadol used in animal models of Angelman are lower than those required for sedation.

“The key in Angelman and Fragile X and Rett syndromes is that synaptic dysfunction leads to reduction of GABA, and that leads to a reduction of tonic inhibition,” During said. “There is an exquisite need for low doses of GABA in the extrasynaptic spaces.”

Tonic inhibition is a basal level of inhibition on neurons that prevents over-excitability in order to maintain normal function.

Two other companies have development programs for neuroactive steroids that act on delta-containing GABA A receptors. Ganaxolone from [Marinus Pharmaceuticals Inc.](#) is expected to complete a Phase II study in Fragile X this year. [Sage Therapeutics Inc.](#) is developing SAGE-217 for Rett and Dravet syndromes and expects to begin Phase I testing this year.

Marinus spokesperson Lisa Caperelli said neurosteroids including ganaxolone exert anticonvulsant and anxiolytic effects via a dual mechanism of action at GABA A receptors. At nanomolar concentrations, they enhance tonic inhibition at extrasynaptic receptors by potentiating endogenous GABA, which is plentiful throughout the CNS.

At higher concentrations, they directly activate both synaptic and extrasynaptic GABA A receptors.

Sage has not disclosed the structure or precise mechanism of SAGE-217, except to say the molecule is a novel neuroactive steroid that acts as a positive allosteric modulator of synaptic and extrasynaptic GABA A receptor subtypes.

**“IF MY DAUGHTER IS ABLE TO FEED HERSELF, IF SHE CAN GET A SPOON OR A FORK TO HER MOUTH, THAT’S A HUGE BENEFIT, NOT ONLY TO AINSLEY BUT TO THE WHOLE FAMILY.”**

**PAULA EVANS, FAST**

#### MOTOR MECHANISM

Preclinical studies suggest gaboxadol could correct synaptic dysfunction and restore tonic inhibition in Angelman patients, leading to an improvement in symptoms such as motor dysfunction.

The condition is usually caused by loss of function of the maternal gene encoding ubiquitin protein ligase E3A (UBE3A; E6AP). Recent *in vitro* and *in vivo* studies showed that the mechanistic cause of ataxia in mice with a deficiency in maternal UBE3A is a decrease in tonic inhibition in cerebellar granule cells.

Normally, tonic inhibition is maintained when GABA — an inhibitory neurotransmitter — binds extrasynaptic GABA A receptors that contain the delta subunit. In the mouse models, a decrease in UBE3A induces a surplus of the GABA transporter GAT1, which in turn increases the uptake of GABA into neurons, and thus reduces concentrations of GABA in the extrasynaptic space.

In the mice, treatment with gaboxadol rescued motor function, improving gait and balance, and decreasing abnormal clasp reflexes. Results were published in *Science Translational Medicine* in 2012.

#### AMELIORATING SYMPTOMS

According to three parents of Angelman patients who spoke to BioCentury, even a small improvement in motor function could make a huge difference in quality of life, not just for the child with the condition, but for the entire family.

Eileen Braun, executive director of ASF and mother of a 24-year-old daughter with Angelman, noted there is a wide range of ability in Angelman syndrome. “What is important to one individual whose child is not yet walking may be different from what is important to an individual whose child is walking,” she said. “Anything we can do to improve quality of life for people with Angelman syndrome is hugely important for my daughter and patients with Angelman syndrome.”

Without a treatment that can reduce disability, lifelong care is a huge concern.

“Right now, because there is not a currently available comprehensive treatment, families are looking at lifelong care for individuals,” Braun said. “Long after parents pass away, these individuals will live on and will continue to have Angelman syndrome.”

Paula Evans, chairperson of FAST and mother of a 10-year-old daughter with Angelman, said motor function affects patient families every day.

“My daughter walks, but would I bring her to a playground and sit on a bench and check my messages? No. Everything she does she needs help with, from the time she gets up to the time she goes to bed,” Evans told BioCentury.

“If my daughter is able to feed herself, if she can get a spoon or a fork to her mouth, that’s a huge benefit, not only to Ainsley but to the whole family,” she said.

Rebecca Burdine, CSO of FAST and mother of a six-year-old daughter with Angelman, said an improvement in motor function that would enable her daughter to communicate using a device would be a huge benefit.

“My daughter does not walk. If she had an improvement in motor function so she could push a button on an iPad to tell me what she wants for dinner, that would be enormous,” she said.

Burdine is an associate professor in the Department of Molecular Biology at Princeton University. Her lab is researching how organs form and function in vertebrate embryos, with a focus on the heart and kidney.

## NAILING THE METRICS

Figuring out how to measure motor function and other symptoms that could be improved by gaboxadol, such as cognitive function, is one of Ovid’s biggest challenges.

“The biggest problem we are faced with is designing the best clinical trial, and the hardest aspect is to select the best endpoint,” During said.

He said Ovid plans to include endpoints assessing not only motor function, but also cognition and frequency of seizures.

The minocycline trial provided some clues. But the study, which was funded by FAST and conducted by academics, also highlighted the need for a randomized, controlled study with carefully selected endpoints. The open-label study in 25 patients ages 4-12 showed significant improvement in mean raw scores on the communication and fine motor subdomains of the Bayley Scales of Infant and Toddler Development 3rd Edition (BSID-III). BSID-III is a measure of development used to assess the cognitive, language and motor abilities of children ages 1 to 42 months.

“One of the issues with previous trials is that the scales are pretty noisy and are not optimized for children with Angelman,” During said.

For example, Burdine noted one of the tasks used to assess cognitive ability involves stacking four blocks on top of each other.

“My daughter cannot. The question is, does she understand the task? I would argue she understands but cannot make her arms do that,” Burdine said.

Burdine, Evans and During all said it is possible that an improvement in motor function in Angelman children could actually change the

understanding of their cognitive ability, because poor motor function impairs their ability to communicate.

To help select endpoints for the Phase II study, Ovid is assembling a clinical trials advisory group that will include clinicians, geneticists and clinical trials experts and will seek input from ASF and FAST.

Braun noted ASF is funding research into biomarkers and metrics to help evaluate the efficacy of drug candidates for Angelman.

During said the organizations also can help identify investigators and centers that may participate in the studies. He said FAST has a list of investigators with a specific interest in Angelman. And ASF told BioCentury it has established Angelman-specific clinics in Boston and North Carolina.

Importantly, both organizations can help Ovid recruit study participants.

“It’s a frightening prospect to take your non-verbal child who cannot communicate side effects — to enroll them in a trial is really daunting. You run the risk in a disorder like Angelman syndrome of not getting patients,” said Evans.

“It is really critical for us as a patient organization to be available to our community to answer questions. They need to know literally from step A, how will I be considered for a trial, all the way to what we think gaboxadol may be able to do,” she said.

During said details of the trial design will be firmed up over the coming months, but he estimated the double-blind, placebo-controlled study will enroll 30-50 patients in each arm, with 1:1 randomization. 

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## COMPANIES AND INSTITUTIONS MENTIONED

**Angelman Syndrome Foundation (ASF)**, Aurora, Ill.  
**Bristol-Myers Squibb Co.** (NYSE:BMJ), New York, N.Y.  
**Foundation for Angelman Syndrome Therapeutics (FAST)**, Downer’s Grove, Ill.  
**H. Lundbeck A/S** (CSE:LUN), Copenhagen, Denmark  
**Marinus Pharmaceuticals Inc.** (NASDAQ:MRNS), Radnor, Pa.  
**Merck & Co. Inc.** (NYSE:MRK), Whitehouse Station, N.J.  
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland  
**Ovid Therapeutics Inc.**, New York, N.Y.  
**Princeton University**, Princeton, N.J.  
**Sage Therapeutics Inc.** (NASDAQ:SAGE), Cambridge, Mass.  
**Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA), Petah Tikva, Israel

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## EMERGING COMPANY PROFILE

# EAST BY SOUTH

BY EMILY CUKIER-MEISNER, SENIOR WRITER

**Nuance Biotech Inc.** plans to in-license rights to develop and commercialize assets in China, with a twist on the standard model: it will include clinical trial sites in South Africa to improve the speed and efficiency of Phase II and III trials and make their results applicable to a broader patient population to support its partners' regulatory submissions in other markets.

Nuance was formed by former executives of Chinese specialty pharma **NovaMed Pharmaceuticals Inc.**, which was acquired by **SciClone Pharmaceuticals Inc.** in 2011 for about \$62 million. Nuance CEO Mark Lotter told BioCentury that NovaMed originally planned to in-license both clinical- and commercial-stage products, but early attention drawn to its commercial programs led the company to deprioritize clinical stage deals.

"That's the part of the model we never had a chance to execute on in the last venture, which I believe is more relevant today than seven or eight years ago," he said.

Compared to that time, said Lotter, the Chinese government is more actively discouraging premium pricing for off-patent branded products — through mandated price cuts or provincial bidding among competitors — putting pressure on companies to hasten patent-protected products onto the Chinese market.

Nuance will mirror NovaMed's strategy of in-licensing assets that are already marketed in China but could be manufactured cheaper and commercialized more efficiently by a local entity, as well as assets marketed in other countries that Nuance can develop and commercialize in China.

But in the least-explored prong of NovaMed's strategy — in-licensing clinical-stage assets — Nuance hopes to add a unique feature by running clinical trials in both China and South Africa.

According to Lotter, companies running global trials in crowded fields like oncology and immunology may try to supplement recruiting

### NUANCE BIOTECH INC.

Shanghai, China

**Technology:** N/A

**Disease focus:** Cancer, hepatic

**Clinical status:** N/A

**Founded:** 2014 by Mark Lotter, Bo Shao and Bill Guo

**University collaborators:** Undisclosed

**Corporate partners:** Undisclosed

**Number of employees:** 10

**Funds raised:** Undisclosed

**Investors:** Mark Lotter, Bo Shao and Bill Guo

**CEO:** Mark Lotter

**Patents:** None issued

shortfalls in the U.S. or EU with additional Chinese patients. But adding South Africa to the mix would give broader ethnic diversity — Caucasian, African and Asian, in particular Indian, patients — that could better supplement regulatory applications in the U.S., EU or elsewhere in the world.

"That would provide a broader data set that could be used for filing outside of China," he said.

Furthermore, Lotter said trials in South Africa cost less to run than trials in Europe or the U.S., and that CROs with an African presence, like **Quintiles Transnational Holdings Inc.**, have encouraged growth of clinical trial infrastructure.

"They have a well-established set of institutions, and clinics there that are very familiar in dealing with international studies," he said.

Moreover, Lotter brings his own experience in clinical trials from South Africa, where he was CEO at **Aspen Pharmacare Holdings Ltd.** This is amplified by board member Opper Greeff, who co-founded South African CRO **Clindepharm International Pty. Ltd.** in 1990 and remained with Quintiles after it bought the

CRO in 1997. Greeff is head of the department of pharmacology at the University of Pretoria.

Nuance will seek commercial rights to in-licensed assets in China and South Africa in exchange for funding and managing Phase II and III development in those countries, and ask for royalties in other markets where the partner files for approval.

Lotter said Nuance hopes to in-license one or two marketed assets a year, and have two or three clinical stage projects running at any given time.

He said the company plans to focus on one or two therapy areas in its commercial-stage deals, but is open to more in diversity in clinical-stage products, so long as they are "high-value assets" that stand out within their competitive space.

Lotter said the company's clinical-stage portfolio would span both innovative products and partially de-risked assets, such as established molecules being developed with new liposomal formulations, new delivery technologies or for new indications.

Rather than invest in manufacturing capability, Nuance plans to partner with accredited companies for manufacturing products within China.

He said Nuance is in discussions to license clinical-stage liver products and oncology products that include small molecules and gene therapies.

Nuance plans to begin raising a \$30 million series A round this quarter. **bc**

### COMPANIES AND INSTITUTIONS MENTIONED

**Aspen Pharmacare Holdings Ltd.** (JSE:APN), Durban, South Africa

**Nuance Biotech Inc.**, Shanghai, China

**Quintiles Transnational Holdings Inc.** (NYSE:Q), Research Triangle Park, N.C.

**SciClone Pharmaceuticals Inc.** (NASDAQ:SCLN), Foster City, Calif.

**University of Pretoria**, Hatfield, South Africa

**“I WOULD BE HAPPY TO TOLERATE ANY SIDE EFFECTS AND INCONVENIENCES CAUSED BY THE TREATMENTS, IF THEY WORKED FOREVER.”**

**COLLEEN DUFFEY, BREAST CANCER PATIENT**

## REGULATION

# GETTING PERSONAL IN BREAST CANCER

BY EMILY CUKIER-MEISNER, SENIOR WRITER

At its patient-focused drug development workshop on breast cancer, FDA departed from its normal script of asking patients what they were seeking in a new treatment and instead probed how patients weigh benefits and risks when choosing among existing therapies.

Some of the suggestions from patients who attended the April 2 workshop reflect ideas that industry has already adopted, such as developing prognostic tests that can predict responses to treatment and side effects. But the discussion also highlighted that in some cases, what is logical and desirable to patients cannot easily be delivered within the current regulatory and drug development framework.

The discussion also highlighted that patient decision-making criteria are highly variable, both across and within different subgroups.

“For young women out there, particularly those raising families — they are willing to put up with so much more toxicity for the sake of being there as long as they possibly can for their children,” said Ginny Knackmuhs, VP of the Metastatic Breast Cancer Network (MBCN), who was initially diagnosed in 1992 and was diagnosed with metastatic disease in 2009.

Quality of life played a bigger role for Susan Faris, who was diagnosed with metastatic breast cancer in 2012.

“My goal is to avoid systemic chemotherapy due to extreme side effects and disabling qualities. When I’ve exhausted targeted treatment, if my quality of life is greatly minimized, I will turn the systemic chemotherapies down and I will choose the right to die,” she said.

“The challenges really lie in the metastatic setting, where treatment right now goes on until you die, and the toxicities can be very consuming and impact quality of life,” said MBCN President Shirley Mertz. She

was diagnosed with early stage breast cancer in 1991 and metastatic disease in 2003.

However, for Colleen Duffey, who was diagnosed with stage IV HER2+ breast cancer in 2012, the biggest downside of any treatment was becoming resistant to it.

“I would be happy to tolerate any side effects and inconveniences caused by the treatments, if they worked forever,” she said.

She added: “I’m much more likely to die from the breast cancer than any side effects of treatment.”

## BEYOND AVERAGES

The most consistent feedback was that patients are not well served by data describing medians or lists of side effects. They want a precision approach.

FDA asked participants to consider taking a drug that prolonged survival an average of two months in a clinical trial, and was associated with diarrhea, rash and rare instances of serious toxicities such as liver injury and lung inflammation.

Some attendees thought the two-month survival benefit would not be worthwhile given the risk of life-threatening toxicities, or if side effects that affected quality of life were severe. But others thought the treatment could be worth trying because they might be exceptional responders — and they want pharmaceutical companies to use genomics to predict whether they will be, or whether they will be nonresponders or will experience severe side effects.

Patients at the workshop also wanted detailed data on how different subpopulations fared.

# “WHEN I’VE EXHAUSTED TARGETED TREATMENT, IF MY QUALITY OF LIFE IS GREATLY MINIMIZED, I WILL TURN THE SYSTEMIC CHEMOTHERAPIES DOWN AND I WILL CHOOSE THE RIGHT TO DIE.”

SUSAN FARIS, BREAST CANCER PATIENT

“My first question would be who is in that clinical trial, and how do they compare to me? Folks of different ethnicities and races are underrepresented in clinical trials,” said one patient who did not identify herself. “How do I know if I’m on the high or low end of the average, or not affected at all?”

Gilles Gallant, VP of oncology and clinical sciences at [BioMarin Pharmaceutical Inc.](#), who did not attend the workshop, was sympathetic to the desire for more data. But he cautioned data for small groups may not be strong enough to inform individual decision-making.

“Those subgroups are based on very small numbers of patients. When you have one or two patients, if you subtract one or two side effects it may completely change the results,” he told BioCentury. “It’s important people realize there is a limit to those subpopulations.”

Patients at the workshop also wanted standardized patient-reported outcomes to be required for late-stage clinical trials. Their concern was that doctors underreport side effects, and said lists of side effects, and their doctors’ descriptions of them, were unhelpful in conveying severity.

“I don’t think any of us who have been treated or are being treated for breast cancer know the magnitude: that we’re going to have the majority of those side effects, and how much we’re going to have them,” said Karen Durham, who was diagnosed with breast cancer 25 years ago and with metastatic disease in 2009.

“Physicians and clinicians use language we as patients don’t understand, and you’re asked to make decisions without the information you need,” added Sandy Finestone, who was diagnosed with breast cancer 30 years ago that did not recur.

Gallant said patient groups have encouraged BioMarin to include a validated patient-reported outcomes (PRO) tool in its Phase III study of the PARP inhibitor talazoparib. He said the company chose the EORTC quality of life questionnaire because it includes a supplementary module specific to breast cancer.

[Novartis AG](#)’s Alessandro Riva, global head of oncology development and medical affairs, told BioCentury the company has started to use a pain rating scale in its studies of LEE011 to treat breast cancer,

and plans to do so in future breast cancer trials. LEE011 is a cyclin dependent kinase 4 (CDK4) and CDK6 inhibitor that is in Phase III testing.

## PROGRESSION CONCESSIONS

One thing patients asked for at the meeting may be harder to accommodate in premarket trials: endpoints based solely on preventing new lesions, rather than requiring that products also stabilize or shrink existing lesions.

MBCN’s Mertz encouraged FDA to accept endpoints such as those described in a publication by Patricia Steeg, deputy chief of the women’s malignancies branch at the [National Cancer Institute](#).

Steeg proposed that for breast cancer patients at high risk of recurrence, such as those whose lesions don’t respond well to initial therapy or who have lymph node involvement at the time of surgery, antimetastatic compounds should be tested in Phase II with an endpoint of time to first metastasis.

For breast cancer patients with limited metastatic disease, she said antimetastatic compounds should be tested in Phase II with an endpoint of time to next metastasis.

She proposed that both trial constructions allow patients to continue receiving backbone therapies for existing lesions.

Mertz told BioCentury that when she asks pharmaceutical companies about developing drugs to prevent new metastases, “The response I would get is FDA does not entertain or consider clinical endpoints to be prevention of metastatic spread. They want to see that it reduces a tumor or is effective on a cancerous lesion.”

In a statement to BioCentury, FDA said it does not recommend time to metastasis as an endpoint because the timing of radiologic assessments can make it difficult to interpret, its assessment is not standardized, and it does not include survival. Plus, development of new metastases is already one component of a progression-free survival (PFS) analysis.

“PFS, as a composite of important factors that account for progression, includes deaths and thus can be a better correlate or direct demonstration of clinical benefit,” wrote FDA spokesperson Tim Irvin.



## COVER STORY

### ANTAGONIZING PSORIASIS

AnaptysBio believes its IL-36R mAb can compete in psoriasis with a new mechanism and will test drive it on a rare genetic form of the disease.

## STRATEGY

### IMI'S INNOVATION ECOSYSTEM

The EU's IMI 2 is armed with a bigger war chest than the prior iteration of the public-private partnership and has a much broader remit.

## PRODUCT R&D

### ASTELLAS OPTS FOR PR1

Astellas is continuing to tap academia for its oncology pipeline with an option from MD Anderson for a first-in-class mAb against the PR1 leukemia-associated antigen.

## FINANCE

### PUBLIC-PRIVATE PARTNERSHIP ROUNDUP

Janssen's gut collaboration with Irish microbiome institute; MRC improves PPP practices; Calico deals but doesn't talk; Biogen teams up with Columbia again.

## DISTILLERY

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What many patients appear to want, rather than strict use of a metastasis endpoint, is more appreciation for the value of treatments that stabilize disease even if they don't regress existing lesions.

Mertz said patients hope metastatic breast cancer can be managed by treatments over the long term, much like HIV/AIDS.

"Most of these trials aim at tumor shrinkage, and our endpoints would be to have the prevention of further spread to another area of the body while controlling the disease that's there," she said.

At least one company is conducting a Phase III trial with an endpoint that is explicitly sensitive to new lesions. [Galena Biopharma Inc.](#) is running a Phase III trial of NeuVax nelipepimut-S (E75) under an SPA with FDA, with the primary endpoint of three-year disease-free survival (DFS), defined as no local, regional or metastatic recurrences. OS is a secondary endpoint.

President and CEO Mark Schwartz said DFS is a better endpoint than OS in an adjuvant setting where patients respond successfully to their initial therapy, because even if the cancer recurs, it may take years to do so.

"Disease recurrence is a material medical event very relevant to the outcome of the patient. And just due to the time sequence, the practicalities of running a trial would prevent anybody from developing a drug in this indication if OS were the primary endpoint," he said.

Patients confirmed to be "disease-free" after receiving SOC — which may include surgery, radiation therapy and chemotherapy — are radiographically screened for recurrence every year through year three, and at years five and 10. Schwartz said breast cancer recurrence typically occurs within three years, with peak recurrence at 1-1.5 years.

He said the radiographic screening interval was chosen to balance the need for detection with risk of secondary malignancies associated with increased radiation exposure. Investigators may conduct ad hoc scans at their discretion if routine physical exams, blood counts or other study findings suggest recurrence.

The trial completed enrollment April 14, and Galena expects to reach the primary endpoint in 2018.

NeuVax is a vaccine consisting of an immunogenic peptide derived from EGFR2 and sargramostim.

FDA said next steps from its meeting include compiling a summary of patient testimony and written comments from the docket into a "Voice of the Patient" report to be published on the agency website. [FDA](#)

## COMPANIES AND INSTITUTIONS MENTIONED

**BioMarin Pharmaceutical Inc.** (NASDAQ:BMRN), Novato, Calif.  
**Galena Biopharma Inc.** (NASDAQ:GALE), Portland, Ore.  
**Metastatic Breast Cancer Network (MBCN)**, New York, N.Y.  
**National Cancer Institute (NCI)**, Bethesda, Md.  
**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland  
**U.S. Food and Drug Administration (FDA)**, Silver Spring, Md.

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## REGULATION

# JAPAN EMBARKS ON SAKIGAKE

BY TAMRA SAMI, SENIOR EDITOR

Japan has launched the next phase of its ambitious agenda for regulatory transformation, as the Pharmaceuticals and Medical Devices Agency next month will begin reviewing requests for designation under the new sakigake early access pathway that could cut approval times for innovative therapies in half.

Sakigake, formally called Forerunner Review Assignment, is an effort to rapidly turn Japanese innovation into new drugs, devices and regenerative medicines that could cure serious diseases, according to Alberto Grignolo, VP of global strategy and services at [Parexel International Corp.](#) The move is part of PMDA's five-year plan, which includes shortening approval times, enhancing safety and further globalizing Japan's pharmaceutical industry.

Many details still must be worked out, according to industry executives who spoke to BioCentury, but it is clear PMDA plans to use sakigake to get innovative therapies to market faster by working closely with sponsors.

Under the pathway, PMDA would shorten review times, encourage pre-application consultations — described as “*de facto* review before application” in a briefing document — and in some cases allow Phase III data to be submitted following the initial application.

Sponsors would see waiting times for clinical trial consultations cut from two months to one month. They would also receive a prioritized review target of six months, half the regular NDA or BLA review period.

In exchange for faster approvals, sakigake would require stronger postmarketing safety measures, including a potential extension of the drug re-examination period, which PMDA uses to reconfirm the clinical usefulness of approved drugs.

Sponsors may either apply for sakigake designation or, in some cases, PMDA will approach potential applicants directly.

## ONLY RADICAL IMPROVEMENTS WANTED

To qualify for designation, an experimental therapy must demonstrate “prominent effectiveness,” or “radical improvement” over existing therapies based on data on the mechanism of action or from preclinical or early stage clinical studies.

Sponsors must meet with PMDA to discuss their development plans before moving into Phase II trials in Japan. The agency said it prefers to meet sponsors as early as possible to help plan protocols for confirmatory studies and to create a predictable product development road map.

PMDA will assign a “concierge” manager to each sakigake sponsor to ensure a smoother path through the agency's review process.

In recent years, Grignolo noted, PMDA has requested more frequent consultations with industry, which has increased clarity on both sides and led to faster reviews.

**“FOR THE REGENERATIVE MEDICINES, WE WERE ALLOWED TO APPLY FOR THE PMDA CONSULTATION WITHOUT ANY WAITING TIME, SO WE ARE HAVING VERY GOOD COMMUNICATION WITH PMDA.”**

**TOSHIKAZU YOSHINAGA, HEALIOS**

“The consultation meetings are very well run, in Japanese and English, and they provide a venue for communication, dialogue and negotiation that is in many respects similar to what we experience from FDA or EMA,” he said.

## MAKING INNOVATION PRACTICAL

The sakigake designation system is part of a larger government strategy to “lead the world through the practical application of innovative medical products,” according to Ministry of Health, Labour and Welfare (MHLW) documents released in June 2014. The developing framework will include strategies to translate Japanese science into innovative medicines and medical devices for global markets.

“Japan is well recognized for its strength in basic research, which has allowed Japanese academia to produce many promising seeds,” MHLW stated. “However, it has also been pointed out that the weakness lies in finding practical application for these seeds.”

A key goal will be to develop innovative medicines that can launch first in Japan.

“Government support for the series of development steps from basic research through global expansion, for instance facilitation of streamlined research and development, is also important to nurture seeds into ‘first in class’ innovative medical products,” according to MHLW.

The sakigake pathway will allow Japan to “get products to the world as soon as possible,” said Kazuhiko Mori, director of MHLW's Evaluation and Licensing Division, in a speech this month at the Asia Partnership Conference of Pharmaceutical Associations in Tokyo.

In particular, Japan's discoveries in regenerative medicine have encouraged the government to take a hard look at its regulatory framework.

Shinya Yamanaka of [Kyoto University](#) won a Nobel Prize in 2012 for his research into induced pluripotent stem cells and adult stem cells, which was a “watershed moment for Japan,” Grignolo noted.

In fact, PMDA opened the sakigake pathway first to regenerative medicines, in November 2013. For regenerative medicines, only Phase I/II data is required for filing NDA/BLA submissions, said Toshikazu Yoshinaga, director of regulatory affairs at gene therapy company [Healios K.K.](#)

Yoshinaga told BioCentury that the company’s iPS cell-derived retinal pigment epithelial cells for the wet and dry forms of age-related macular degeneration (AMD) are under consideration for the sakigake pathway. Both compounds are in preclinical development in Japan.

**“THE CONSULTATION MEETINGS ARE VERY WELL RUN, IN JAPANESE AND ENGLISH, AND THEY PROVIDE A VENUE FOR COMMUNICATION, DIALOGUE AND NEGOTIATION THAT IS IN MANY RESPECTS SIMILAR TO WHAT WE EXPERIENCE FROM FDA OR EMA.”**

**ALBERTO GRIGNOLO, PAREXEL**

“For the regenerative medicines, we were allowed to apply for the PMDA consultation without any waiting time, so we are having very good communication with PMDA,” he said.

#### GLOBAL COMPANIES CAN APPLY

Multinational companies can also apply for sakigake designation, but compounds must be developed in Japan. And while applications can be filed simultaneously for multiregional clinical trials, Mori said MHLW’s expectation is that the product would be approved first in Japan.

The preference is for drugs to be originated in Japan, Grignolo said, but “a drug can be discovered outside Japan by either a Japanese or a non-Japanese company.” It would then “need to be developed in Japan either as the first development country or in parallel with another country, but never second to another country.”

Phase I trials could be conducted outside Japan, but Phase II trials must be started in Japan before other countries or in parallel as part of a multiregional trial, according to Grignolo.

“PMDA will always need evidence that a drug is safe and effective in Japanese patients living in Japan,” he added.

In its briefing materials, PMDA said it would also cooperate with overseas regulatory agencies to increase multiregional clinical studies in Japan.

#### FUMBLE NOT TO BE REPEATED

One example that could shed light on the evolving sakigake pathway is the case of [Pfizer Inc.](#)’s non-small cell lung cancer drug Xalkori crizotinib.

Japanese regulators were criticized when Xalkori was approved in the U.S. and South Korea before Japan even though applications based on Phase II data were filed simultaneously in the three countries.

Xalkori, a dual inhibitor of c-Met receptor tyrosine kinase and anaplastic lymphoma kinase (ALK) and other oncogenic variants, was discovered by Japanese researchers. The drug received accelerated approval in the U.S. in August 2011, but was not approved in Japan until May 2012.

“This drug was invented in Japan, and the NDA was simultaneously submitted, but the approval in Japan was far delayed from the U.S.,” Healios’ Yoshinaga told BioCentury. “MHLW intends not to repeat this.”

Whether Japan would approve a Xalkori-like therapy with Phase II data under the sakigake pathway is unclear, but regulators appear to be leaving the door open on a case-by-case basis.

Japan already reviews oncology drugs and Orphan drugs under a priority review program similar to U.S. FDA’s accelerated approval program and the EU’s conditional marketing authorization.

Most Japanese multinational pharmas contacted by BioCentury said it is too early to comment on the potential impact of the sakigake pathway, although [Takeda Pharmaceutical Co. Ltd.](#) has started to consider which of its compounds might qualify.

“We do not believe this is analogous to a U.S. accelerated approval where a confirmatory trial is required to confirm benefit of a surrogate endpoint,” said spokesperson Julia Ellwanger. “It does, however, seem clear that the postmarketing safety requirements will be more intensive than a standard approval.”

She added: “Details are still evolving. Takeda is evaluating its compounds to see which ones might qualify for the pathway.”<sup>bc</sup>

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#### COMPANIES AND INSTITUTIONS MENTIONED

- [Pfizer Inc.](#) (NYSE:PFE), New York, N.Y.
- [Healios K.K.](#), Tokyo, Japan
- [Japan Ministry of Health, Labour and Welfare \(MHLW\)](#), Tokyo, Japan
- [Kyoto University](#), Kyoto, Japan
- [Parexel International Corp.](#) (NASDAQ:PRXL)
- [Takeda Pharmaceutical Co. Ltd.](#) (Tokyo:4502), Osaka, Japan

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#### REFERENCES

- [Japan Ministry of Health, Labour and Welfare.](#) “Strategy of SAKIGAKE.” (2014)

## EBB &amp; FLOW

## LIKING JAPAN'S RETAIL EXODUS

At least one Japanese specialist investor hopes the ongoing rotation out of biotech by the country's retail investors is setting the stage for a new norm marked by a more mature, longer-term investor base and more rational growth.

Japanese biotech started a bull run in late 2012, when [Kyoto University](#) professor Shinya Yamanaka received a Nobel Prize for reprogramming mature cells to become pluripotent stem cells. BioCentury's equal price-weighted index of 31 Japanese biotechs was up nearly 400% at its peak in May 2013.

After several corrections, the index is well below its peak, but is still up 80% since the group began to heat up at the start of 2013. The BioCentury 100 index of U.S.-listed biotechs is up 151% over the same period.

FinTech Global Capital's Goro Takeda noted retail investors have been moving out of biotech and into high tech and other sectors as they become aware of the slower timelines and higher risk in the drug space.

Takeda said a regulatory setback for [3-D Matrix Ltd.](#) (JASDAQ:7777) and a clinical setback for [R-Tech Ueno Ltd.](#) (JASDAQ:4573), both in March, have added to the negative sentiment among retail investors. The Japanese biotech benchmark fell 6% in March and is now down 7% since the start of 2015. The BioCentury 100 is up 23% on the year.

Even though cell therapy company [SanBio Co. Ltd.](#) (Tokyo:4592) raised ¥8 billion (\$67.2 million) in its IPO in late March, Takeda said the deal came in below investor expectations. The book-building process for the IPO came after the 3-D Matrix and R-Tech news.

SanBio, which sold 4 million shares at ¥2,000 on Tokyo Stock Exchange's Mothers, closed Friday at ¥1,511.

"The price hasn't appreciated as much as they expected, so some of these short-term retail investors might be hesitant to invest in other biotechs," said Takeda.

Nonetheless, Takeda said SanBio's performance and the 3-D Matrix and R-Tech setbacks are actually positive events for Japanese biotech. "We'd love to see more long-term investors who really understand the inherent risk of biotech," he said, adding that larger, more sophisticated Japanese funds that have typically invested in other sectors have been moving into or ramping up investments in biotech.

Takeda said optimism about Japanese biotech, driven by Prime Minister Shinzo Abe's push to revitalize biotech and streamline regulatory processes, also will drive rational growth by more mature investors. And he expects positive catalysts, especially increasing M&A among Japanese biotechs, to spark investor optimism.

He cited the acquisition of [Heptares Therapeutics Ltd.](#) in the U.K. by [Sosei Group Corp.](#) (Tokyo:4565) (see [BioCentury](#), March 2, 2015).

—Jennifer Rhodes

## BIOCARTIS LOOKS TO GO BIG ON EURONEXT

[Biocartis Group N.V.](#)'s proposed flotation on Euronext would be the largest European IPO so far this year and the largest biotech IPO on Euronext since [Ipsen Group](#) (Euronext:IPN; Pink:IPSEY) raised €170.9 million (\$200.2 million) in 2005. Yet the deal falls well short of what other European companies are raising on the U.S. market and thus isn't likely to end the debate about where European companies should list.

**"WE'D LOVE TO SEE  
MORE LONG-TERM  
INVESTORS WHO  
REALLY UNDERSTAND  
THE INHERENT RISK  
OF BIOTECH."**

**GORO TAKEDA, FINTECH**

Biocartis is commercializing its Idylla molecular diagnostics platform for cancer and infectious diseases. Last week, the company said it plans to sell 8.7 million shares at €10–€11.50 per share in an IPO on Euronext and a private placement outside Belgium. If the deal prices at the top end of its range and the overallocation is sold, Biocartis would raise €115 million (\$121.5 million) and have a postmoney valuation of €465.2 million (\$491.4 million). The shares are expected to begin trading on May 4.

The IPO would be the largest on a European exchange since March 2014, when allergy company [Circassia Pharmaceuticals plc](#) (LSE:CIR) raised £202 million (\$337.5 million) on the LSE.

CFO Hilde Windels said Biocartis chose its home market because of strong name recognition among local investors, and noted U.S. investors can participate via the private placement.

But the deal still doesn't match what other life science companies have been able to raise in the U.S. For example, two Danish companies have raised more cash via NASDAQ IPOs in the past six months: autoimmune play [Forward Pharma A/S](#) (NASDAQ:FWP) raised \$220.5 million in October, while drug delivery company [Ascendis Pharma A/S](#) (NASDAQ:ASND) raised \$124.2 million in January.

Indeed, BioCentury's BCIQ database shows European biotechs raise significantly more cash when they go to the U.S. than when they list in their home markets. Since 2011, 22 European companies have raised \$1.5 billion through IPOs on NASDAQ, whereas 39 raised nearly the same amount of cash on European exchanges over the same period. On average, companies listing in the U.S. raised 81% more than their EU-listed counterparts: \$66.2 million vs. \$36.5 million.

European companies that add a dual U.S. listing also have been able to raise significant follow-on capital. For instance, [Galapagos N.V.](#) (Euronext:GLPG; Pink:GLPYY) has raised about \$192 million in five equity offerings since its 2005 IPO on Euronext. Last week, the company proposed to raise up to \$150 million in a listing on NASDAQ.

— Stephen Hansen

## X MARKS THE SPOT FOR ATLAS

With last week's close of its oversubscribed \$280 million tenth fund, [Atlas Venture](#) completed its transition into a solely life sciences-focused venture firm looking at early stage investments in therapeutics.

Atlas was a hybrid focused on tech and life sciences. But in October, the firm said its teams would be stronger if they raised independent funds, citing diverging ecosystems and business models (see [BioCentury, Oct. 6, 2014](#)).

The healthcare team retained the Atlas name and raised Atlas Fund X, which was originally targeting \$250 million. "The demonstrated returns coupled with the distinctiveness of our venture-creation model worked to play very well with the LP community," said Atlas' Bruce Booth.

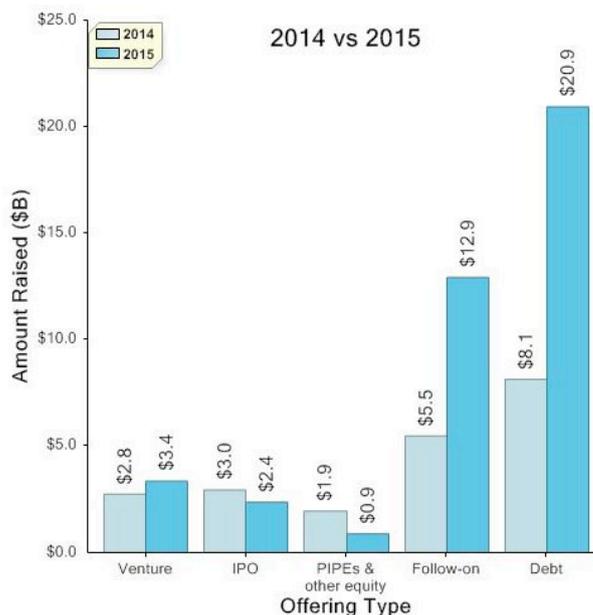
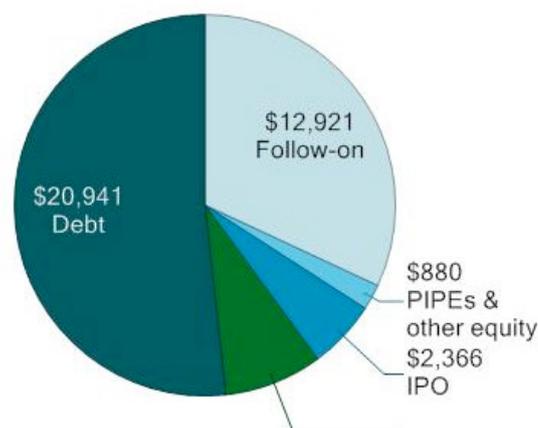
The firm doesn't disclose returns, but the past three years have seen four IPOs and six M&A events, most recently the acquisition of asset-centric anesthesia play [Annovation Biopharma Inc.](#) by [The Medicines Co.](#) (NASDAQ:MDCO).

About 75% of LPs in Fund X were existing investors in the hybrid funds, including [Amgen Inc.](#) (NASDAQ:AMGN) and [Novartis AG](#) (NYSE:NVS; SIX:NOVN), both of which are also corporate partners. New LPs include university endowments and foundations.

## MONEY RAISED IN 2015

Last week, the biotech industry raised \$2,243 million, bringing to \$40.5 billion the total raised year-to-date. In 2014, a total of \$54.6 billion was raised, including \$21.5 billion in debt, \$11.1 billion in follow-ons, \$3.9 billion in PIPEs and other equity, \$9.1 billion in IPOs, and \$9 billion in venture capital. Totals include overallocations and warrants, and are rounded to the nearest millions.

Total YTD: \$40,467 (\$M)



Atlas plans to stick to its strategy of giving small amounts of highly tranching seed funding to start-ups — often formed around ideas plucked from academia — and telling them to “prove” they are viable. Booth said the firm expects to start and finance four to six newcos a year over the next three to four years.

“We do expect during the seed phase to weed out the false positives early in their life cycle,” he added. “If we seed 20-25 companies, the life cycle investments that we’ll scale over time will probably be in 15 or so companies.”

Atlas employs a range of investment models, from building platform companies around big ideas to an asset-centric or build-to-buy approach. “Our interest is really driven by the quality and the tractability of the opportunity,” said Atlas’ Jean-François Formela. “The business model is going to fit the opportunity.”

He added: “You should expect a mix of deals and companies that are quite similar to Fund IX.”

“We’re exploring a couple dozen seed-stage concepts right now, a lot of interesting emerging biology and modality concepts,” said Booth.

Including Fund X, Atlas has over \$850 million in life science investments under management.

— *Jennifer Rhodes*

## PRENATAL AND BEYOND

Natera Inc. is keeping mum on its financing plans, but the commercial-stage molecular diagnostics company is the latest in a string of life sciences companies raising venture rounds beyond series D from a syndicate including crossover investors. Many have now gone public or are in the IPO queue.

Earlier this month, Natera raised \$55.5 million in a series F round led by new investor Sofinnova Ventures. Capital Research and Management; Franklin Templeton Investments; Jennison Associates; RA Capital; Healthcor Partners; and OrbiMed Advisors participated.

Sofinnova’s James Healy said the firm’s interest was both in Natera’s marketed Panorama Prenatal Aneuploidy Test and the potential of its non-invasive multiplex assay technology in cancer. “They have a core differentiated technology that allows them to do these highly multiplexed analyses off a single blood draw,” he said. “We believe the performance aspects of Natera’s technology should allow them to develop an interesting product in the cancer field.”

Natera plans to use the money to expand worldwide sales and marketing and for R&D. The company is not disclosing the development status of its cancer tests, which include non-invasive cell-free DNA-based tests for early detection and monitoring of ovarian, breast and lung cancers.

Natera’s assays use SNPs and statistical algorithms to analyze cfDNA for abnormalities. According to the company, analyzing cfDNA from a fetus during pregnancy is “technically similar” to analyzing cfDNA from a tumor, as both “are mixed in low concentrations with the DNA of the host.” Panorama differentiates between and analyzes maternal and fetal cfDNA.

Natera is the most recently disclosed investment from Sofinnova’s second dedicated life sciences fund. The firm is aiming to invest the \$500 million fund primarily in therapeutics, with 60-70% slated for companies with mid- to late-stage products ([see BioCentury, July 28, 2014](#)).

Healy declined to comment on whether Natera will be a one-off diagnostics investment, saying, “Each investment thesis has to stand on its own.” But he noted Sofinnova does have interest and experience in evaluating diagnostics companies, citing the firm’s support for the \$110 million debut fund from new VC HealthQuest Capital, which will invest in medical devices and molecular diagnostics ([see BioCentury, Sept. 1, 2014](#)).

“Natera is a leading genetics company that will help people diagnose and manage genetic diseases, which we believe will help give us more insight into the diagnostic trends that will be paired with treatment paradigms over time,” he added, noting that Sofinnova’s most active investment areas are Orphan genetic diseases and oncology.

Natera does not break out revenues from Panorama. bc

— *Jennifer Rhodes*

**“WE BELIEVE THE PERFORMANCE ASPECTS OF NATERA’S TECHNOLOGY SHOULD ALLOW THEM TO DEVELOP AN INTERESTING PRODUCT IN THE CANCER FIELD.”**

**JAMES HEALY, SOFINNOVA VENTURES**

## EARNINGS ON DECK

At least 14 biotechs are expected to report earnings this week.

Company	Date	Pre/post mkt	1Q15 EPS est	1Q14 EPS	Expected chg
<b>Actelion Ltd.</b> (SIX:ATLN)	4/21	Pre	CHF1.35	CHF1.46	-8%
<b>Amgen Inc.</b> (NASDAQ:AMGN)	4/21	Post	\$2.10	\$1.87	12%
<b>Illumina Inc.</b> (NASDAQ:ILMN)	4/21	Post	\$0.72	\$0.53	36%
<b>Abbott Laboratories</b> (NYSE:ABT)	4/22	Pre	\$0.42	\$0.41	2%
<b>Roche</b> (SIX:ROG; OTCQX:RHHBY)	4/22	Pre	NA	NA	NA
<b>Thermo Fisher Scientific Inc.</b> (NYSE:TMO)	4/22	Pre	\$1.61	\$1.53	5%
<b>AbbVie Inc.</b> (NYSE:ABBV)	4/23	Pre	\$0.85	\$0.71	20%
<b>Alexion Pharmaceuticals Inc.</b> (NASDAQ:ALXN)	4/23	Pre	\$1.32	\$1.53	-14%
<b>Baxter International Inc.</b> (NYSE:BAX)	4/23	Pre	\$0.88	\$1.09	-19%
<b>Eli Lilly and Co.</b> (NYSE:LLY)	4/23	Pre	\$0.76	\$0.70	9%
<b>Novartis AG</b> (NYSE:NVS; SIX:NOVN)	4/23	Pre	\$1.07	\$1.28	-16%
<b>RTI Surgical Inc.</b> (NASDAQ:RTIX)	4/23	Pre	\$0.03	\$0.01	200%
<b>AstraZeneca plc</b> (LSE:AZN; NYSE:AZN)	4/24	Pre	\$1.04	\$1.17	-11%
<b>Biogen Inc.</b> (NASDAQ:BIIB)	4/24	Pre	\$3.91	\$2.47	58%

## Analyst picks & changes

Company	Bank	Analyst	Coverage	Opinion	Wk chg	4/17 cls
<b>Aeterna Zentaris Inc.</b> (TSX:AEZ; NASDAQ:AEZS)	H.C. Wainwright	Swayampakula Ramakanth	Upgrade	Buy (from neutral)	23%	\$0.64
Ramakanth upgraded and introduced a \$1.25 target after Aeterna Zentaris announced a clear development path for Macrilen macimorelin for use in evaluating adult growth hormone deficiency (AGHD). Following a meeting with FDA, the company said it plans to conduct a new Phase III trial and a separate QT study, which will satisfy both FDA and EMA requirements. Ramakanth expects both trials to finish by YE17, and estimates revenues of about \$66M by 2025 for the oral ghrelin-mimetic growth hormone secretagogue.						
<b>Arrowhead Research Corp.</b> (NASDAQ:ARWR)	Jefferies	Eun Yang	Downgrade	Hold (from buy)	-10%	\$7.08
Yang also lowered her target to \$9 from \$30 on "lower-than-expected early efficacy data" for ARC-520 to treat HBV. Yang said early Phase IIa data shows single-dose ARC-520 has "modest" efficacy, but she awaits multi-dose data for potential deeper responses. The company expects to begin Phase IIb combination trials next half. ARC-520 comprises short interfering RNAs targeting two regions of the HBV genome conjugated to N-acetylgalactosamine-polymer and cholesterol ligands using Arrowhead's Dynamic Polyconjugate delivery system.						
<b>Galmed Pharmaceuticals Ltd.</b> (NASDAQ:GLMD)	Roth Capital Partners	Elemer Piros	New	Buy	13%	\$10.99
Piros initiated coverage with a \$20 target, calling Galmed a "serious contender" in the multi-billion dollar indication of non-alcoholic steatohepatitis (NASH). Galmed's Aramchol arachidyl amino cholanoic acid is in Phase IIb testing to treat NASH. He estimates the synthetic conjugate of cholic acid and arachidic acid could launch in 2020, with peak sales of about \$3B in 2024.						
<b>PTC Therapeutics Inc.</b> (NASDAQ:PTCT)	Cowen	Ritu Baral	Upgrade	Outperform (from market perform)	-1%	\$70.74
Baral also raised her target to \$120 from \$70 ahead of anticipated positive data from the Phase III ACT DMD trial of Translarna ataluren to treat nonsense mutation Duchenne muscular dystrophy (DMD). The data are expected in 4Q15. Baral believes the totality of Phase II data establishes proof of concept and de-risks the Phase III trial. In December, PTC began submitting a rolling NDA to FDA for Translarna to treat DMD, and the company believes the ACT DMD trial should form the basis for finalizing the submission. The small molecule that facilitates complete translation of proteins containing nonsense mutations has conditional approval in the EU for DMD.						

## BIOCENTURY 100 PRICE & VOLUME TREND

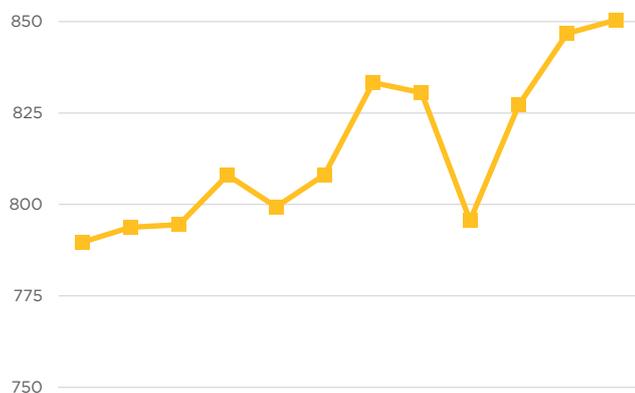
Cumulative weekly performance of 100 bioscience stocks. 12-week period. Line shows Price Level change (Left scale. Index base=1000 on May 10, 1996). Bars show cumulative volume in millions (right scale).



BioCentury tracks 771 issues that report prices and volume daily. The BioCentury 100 is a subset used to monitor price and volume trends

## BIOCENTURY LONDON INDEX

Weekly change in the combined market capitalization for 14 bioscience stocks listed on the LSE or AIM, 12-week period. Index base =1000 on May 10, 1996.



### BIOCENTURY 100 INDICATORS

Week ended 4/17/15

#### PRICES

7368.70  
up 1%

#### VOLUME

670.9M shrs  
up 12%

## PRICE GAINS

Stocks with greatest % price increase in the week ended 4/17. (Priced above \$2; 5,000 minimum share volume)

Company	Ticker	\$Close	\$Chg	% Chg	Vol(00)
Aduro Biotech <sup>1</sup>	ADRO	40.000	23.000	135%	99534
3-D Matrix	7777	¥1639.00	¥626.000	62%	89794
Great Basin	GBSN	4.080	1.140	39%	161319
Xbiotech <sup>1</sup>	XBIT	26.180	7.180	38%	14701
Novogen <sup>2</sup>	NVGN	7.630	2.000	36%	3456457
Galapagos	GLPG	€31.100	€8.105	35%	40378
Genfit	GNFT	€42.925	€10.835	34%	54737
Oramed	ORMP	8.170	1.940	31%	52794
Gene Techno Science	4584	¥3240.000	¥724.000	29%	4989
MediciNova <sup>3</sup>	MNOV	4.450	0.980	28%	84737

## PRICE DECLINES

Stocks with greatest % price decline (criteria as above).

Company	Ticker	\$Close	\$Chg	% Chg	Vol(00)
MabVax Therapeutics	MBVX	3.550	-1.070	-23%	11216
Pfenex	PFNX	15.120	-3.860	-20%	8593
Akebia	AKBA	8.310	-2.100	-20%	64010
Capricor Therapeutics	CAPR	6.570	-1.430	-18%	2146
Pernix Therapeutics	PTX	8.350	-1.740	-17%	131778
Flexion Therapeutics	FLXN	19.230	-3.800	-17%	4812
SanBio	4592	¥1511.000	¥273.000	-15%	17104
Immunicum	IMMU	SEK34.400	-SEK5.800	-14%	5394
Bavarian Nordic	BAVA	DKK329.00	-DKK54.50	-14%	17177
PledPharma	PLED	SEK28.400	-SEK4.600	-14%	3887

## VOLUME GAINS

Greatest changes in volume above 5,000 shares.

Company	Ticker	Vol(00)	%Chg	\$Close	\$Chg
MediciNova <sup>3</sup>	MNOV	84737	4107%	4.450	0.980
Celsion	CLSN	96418	2720%	2.950	0.350
Oramed	ORMP	52794	1650%	8.170	1.940
Akebia	AKBA	64010	1317%	8.310	-2.100
XTL <sup>4</sup>	XTLB	58146	941%	2.300	-0.047
Foamix	FOMX	56100	852%	10.890	1.020
PlasmaTech	PTBI	30851	828%	3.340	-0.164
Immune Design	IMDZ	23570	817%	26.510	1.860
Transition Therapeutics <sup>5</sup>	TTHI	4348	788%	7.900	0.910
Marinus	MRNS	6002	730%	9.240	0.175

1 IPO during the week. Price change from IPO price.

2 Includes volume from ASX and converted ADSs (IADS = 25 shares)

3 Includes volume from JASDAQ

4 Includes volume from Tel Aviv Stock Exchange and converted ADSs (IADS = 20 shares)

5 Includes volume from Toronto Stock Exchange (TSX)

## BIOCENTURY 100 ADVANCE-DECLINE TRENDS

Week ended	BC100 Price Level	BC100 Stocks gaining	Gaining vol. (00)	BC100 Stocks declining	Declining vol. (00)
Mar 20	7523.31	74	6414749.00	25	2130706.00
Mar 27	7101.60	7	530994.00	93	7377462.00
Apr 03	7039.49	42	2517957.00	58	3741051.00
Apr 10	7317.07	88	5411747.00	12	572726.00
Apr 17	7368.70	44	3469192.00	54	2979763.00

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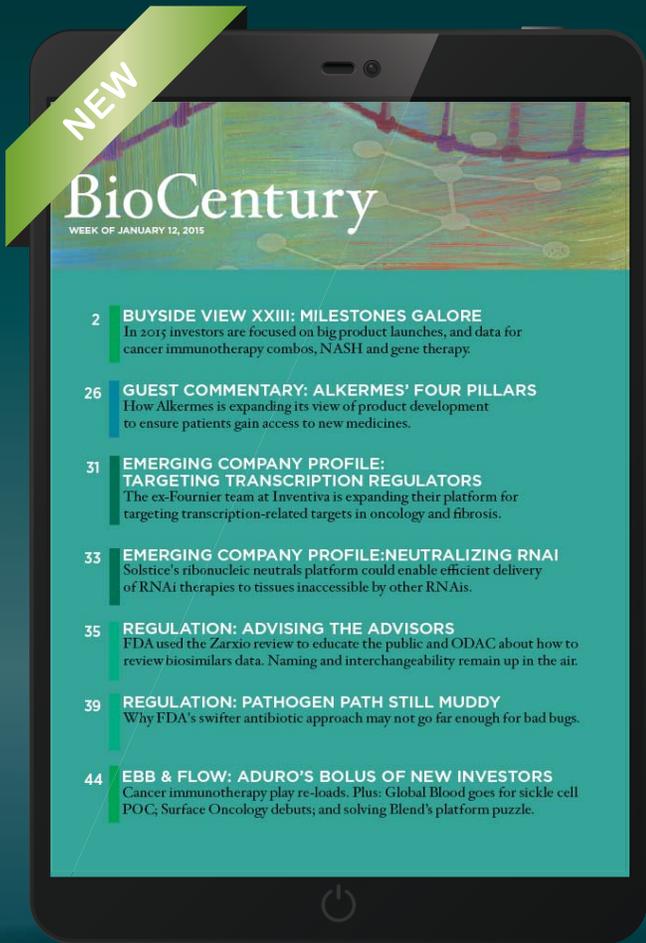
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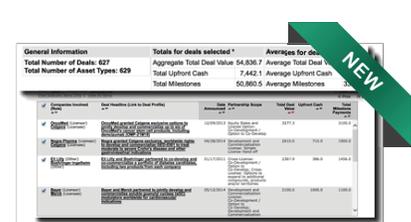
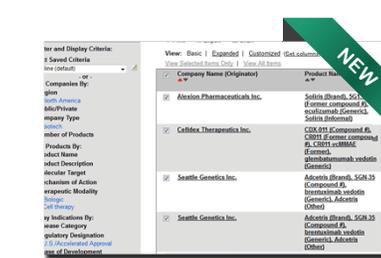
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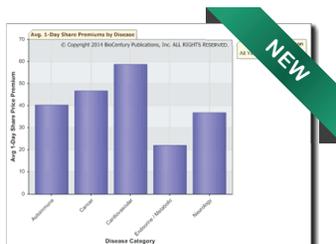
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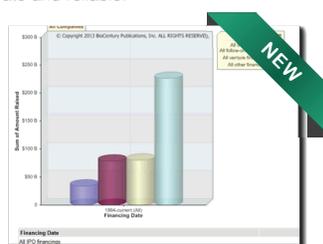


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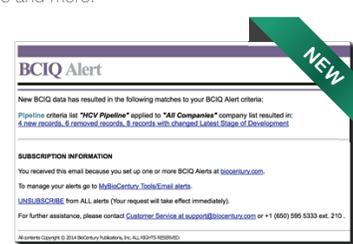


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This parallel opening session will focus on the state of European innovation in the earliest parts of drug discovery and development. Key stakeholders will debate where Europe stands on innovative basic science and on the ability to source that science for translation into the corporate setting.

**Panelists include:**

- **Dr. Simone Fishburn**, *Editor*, BioCentury Innovations (Moderator)
- **Dr. Jeanne Bolger**, *Vice President of Venture Investments*, Johnson & Johnson
- **Dr. Kevin Johnson**, *Partner*, Index Ventures
- **Dr. Werner Lanthaler**, *CEO*, Evotec
- **Dr. David Tapolczay**, *CEO*, MRC

### The China Bridge

How Europe is Amplifying its Innovation through China Deal-Making

**Panelists include:**

- **Dr. Debra Yu**, *Managing Director*, Labrador Advisors (Moderator)
- **Robert Braithwaite**, *Chairman and CEO*, Luqa Pharmaceuticals
- **Dr. Benjamin Li**, *CEO*, Lee's Pharma
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# BioCentury

WEEK IN REVIEW | POWERED BY BCIQ

WEEK OF APRIL 20, 2015

**1** **COMPANY NEWS**  
Deals, Sales & Marketing, Other  
News

**7** **CLINICAL NEWS**  
Regulatory, Clinical Results,  
Preclinical Results, Clinical Status

**20** **FINANCIAL NEWS**  
Completed Offerings, Proposed  
Offerings, Withdrawn Offerings,  
Amended Offerings, Other  
Financial News

## COMPANY NEWS

### DEALS

**Aeterna Zentaris Inc.** (TSX:AEZ;NASDAQ:AEZS), Quebec City, Quebec  
**Medical University of South Carolina**, Charleston, S.C.

Business: Pharmaceuticals

Aeterna Zentaris will transfer its discovery library of 100,000 compounds to the university, which will conduct screening and preclinical activities and submit to the biotech at least one candidate per year in the areas of oncology, neurology, endocrinology or women's health for 10 years starting in 2018. The university's South Carolina Center for Therapeutic Discovery and Development will own compounds discovered outside the areas of Aeterna Zentaris' therapeutic interest.

Aeterna Zentaris will have the first right of refusal to develop and commercialize product candidates submitted by the center. If Aeterna Zentaris does not exercise its option, the center may develop and commercialize submitted candidates. If Aeterna exercises its right, the center will be eligible for undisclosed royalties; Aeterna will be eligible for undisclosed royalties on net sales of products developed from rejected candidates. The partners declined to disclose financial terms.

**Argos Therapeutics Inc.** (NASDAQ:ARGS), Durham, N.C.

**Chongqing Lummy Pharmaceutical Co. Ltd.** (SGX:300006),  
Chongqing, China

Business: Infectious, Cancer

Argos granted Chongqing Lummy's Lummy Co. Ltd. subsidiary exclusive rights in China, including Hong Kong and Macau, and

Taiwan to develop and commercialize AGS-003 for oncology indications. Argos is conducting the Phase III ADAPT study of the second-generation RNA-loaded autologous dendritic cell immunotherapy to treat metastatic renal cell carcinoma (RCC). Lummy said it may develop AGS-003 to treat pancreatic, lung, liver, stomach, rectal, gastric and/or esophageal cancers. Lummy will be responsible for development costs required for approval.

Lummy also gained an option to develop and commercialize Argos' AGS-004, an autologous dendritic cell immunotherapy transfected with the patient's viral RNA antigens. It is in Phase II testing to treat chronic HIV-1 infection.

Lummy affiliate Tianyi Lummy International Holdings Group Ltd. and the China BioPharma Capital I Fund paid Argos \$10.1 million up front through the purchase of 1 million Argos shares at \$10.11. Positive results from an interim analysis of ADAPT, expected by year end, would trigger another \$10 million investment from Tianyi Lummy and the China BioPharma fund. Argos is eligible for up to \$20 million in additional regulatory and commercial milestones, plus double-digit royalties.

**Bayer AG** (Xetra:BAYN), Leverkusen, Germany

**Broad Institute of MIT and Harvard**, Cambridge, Mass.

Business: Cancer, Cardiovascular, Genomics

Bayer's Bayer Healthcare LLC subsidiary and the institute added cardiovascular genomics and drug discovery to a 2013 deal to jointly discover and develop therapeutics that selectively target cancer genome alterations. Bayer said financial terms are not disclosed (see BioCentury, Sept. 16, 2013).

**Bristol-Myers Squibb Co.** (NYSE:BMJ), New York, N.Y.

**Eli Lilly and Co.** (NYSE:LLY), Indianapolis, Ind.

Business: Cancer

Bristol-Myers will transfer full commercial rights to Eli Lilly for Erbitux cetuximab in the U.S., Canada and Puerto Rico. The deal is expected to close in 4Q15. BMS and Lilly have shared co-promotion rights in North America since Lilly acquired [ImClone Systems Inc.](#) in 2008 (see [BioCentury](#), Oct. 13, 2008).

Erbitux is marketed alone and in combination with other drugs to treat metastatic colorectal cancer and head and neck cancers. BMS is eligible for tiered royalties on net sales through September 2018. The companies declined to provide further financial terms.

**Can-Fite BioPharma Ltd.** (Tel Aviv:CFBI;NYSE-M:CANF), Petah Tikva, Israel

**Cipher Pharmaceuticals Inc.** (TSX:DND;NASDAQ:CPHR), Mississauga, Ontario

Business: Autoimmune

Can-Fite granted Cipher rights to commercialize Can-Fite's CF101 in Canada to treat moderate to severe psoriasis and rheumatoid arthritis. The adenosine A3 receptor (ADORA3) agonist has completed a Phase II/III trial to treat psoriasis and a Phase IIb trial to treat active RA. The partners said that the timing of regulatory submissions in Canada will be determined by the completion of the remaining clinical trial program.

Can-Fite will receive C\$1.7 million (\$1.3 million) up front and is eligible for up to C\$2 million (\$1.6 million) in milestones, plus a 16.5% royalty on net sales. Can-Fite is responsible for delivering finished product to Cipher. Cipher said it sees CF101 as being complementary to the company's Beteflam Patch, a self-adhesive medicated plaster containing 0.1% betamethasone valerat, in development to treat psoriasis. An NDS for the product is under review in Canada to treat inflammatory skin conditions, including chronic plaque psoriasis (see [BioCentury](#), March 16).

**Cancer Research Technology Ltd.**, London, U.K.

**The Institute of Cancer Research**, London, U.K.

**University of Manchester**, Manchester, U.K.

**Wellcome Trust**, London, U.K.

**Basilea Pharmaceutica AG** (SIX:BSLN), Basel, Switzerland

Business: Cancer

A consortium comprised of the institute, the university, CRT and the [Wellcome Trust](#) granted Basilea exclusive, worldwide rights to develop and commercialize pan-RAF inhibitors that block multiple RAF proteins, including BRAF. The preclinical small molecules originated from research at [the Institute of Cancer Research](#), which was funded by CRT's [Cancer Research UK](#) and [Wellcome Trust](#). Basilea said the kinases play a role in tumor cell proliferation.

The consortium will conduct Phase I testing for the lead compound this year, after which the biotech will assume operational responsibility. The consortium will receive an undisclosed upfront payment and is eligible for undisclosed milestones and tiered royalties. [Cancer Research Technology](#), [the Institute of Cancer Research](#) and [Basilea](#) declined to provide further details. [University of Manchester](#) could not be reached, and [Wellcome Trust](#) did not respond to inquiries in time for publication.

**CAPP Medical**, Palo Alto, Calif.

**Roche** (SIX:ROG;OTCQX:RHHBY), Basel, Switzerland

Business: Cancer

[Roche](#) acquired CAPP, a genomics research company developing technology to detect and monitor circulating tumor DNA. [Roche](#) said the technology may aid in selecting cancer therapies and monitoring tumor progression. [Roche](#) plans to bring CAPP's circulating tumor DNA technology to market as a research use only kit and plans to launch CE Mark- and FDA-approved kits. [Roche](#) declined to disclose financial terms, and CAPP could not be reached.

**CareFusion Corp.**, San Diego, Calif.

**Becton Dickinson and Co.** (NYSE:BDX), Franklin Lakes, N.J.

Business: Supply/Service

Becton acquired CareFusion, which provides hospitals with products and services, for \$58 per share or \$12.2 billion in cash and stock. The price is 26% premium to CareFusion's close of \$46.17 on Oct. 3, before the deal was announced. CareFusion shareholders will own about 8% of Becton.

**City of Hope**, Duarte, Calif.

**Mustang Therapeutics Inc.**, Duarte, Calif.

Business: Cancer, Gene/Cell therapy

[City of Hope](#) granted Mustang exclusive, worldwide rights to develop and commercialize a portfolio of clinical-stage chimeric antigen receptor (CAR) T cells. Mustang is a newco formed by [Coronado Biosciences Inc.](#) (NASDAQ:CNDO, Burlington, Mass.) and the center. The partners expect to start clinical trials this year at [City of Hope](#) to treat cancer. The center will receive up to \$40 million comprising an upfront payment and milestones. [City of Hope](#) is also eligible for royalties.

**Cold Spring Harbor Laboratory**, Cold Spring Harbor, N.Y.

**GlaxoSmithKline plc** (LSE:GSK;NYSE:GSK), London, U.K.

Business: Endocrine/Metabolic

The partners are discovering and developing small molecules to regulate the activity of protein tyrosine phosphatase 1B (PTP-1B; PTPN1) to treat obesity and Type II diabetes. GSK and Cold Spring will both contribute to product development. The partners declined to disclose financial terms and ownership rights.

**Genomics England Ltd.**, London, U.K.

**Helomics Corp.**, Pittsburgh, Pa.

Business: Diagnostic

Helomics partnered with Genomics England, a company owned and funded by the U.K. Department of Health, to use Helomics' tumor profiling technology to identify cancer biomarkers and develop cancer diagnostics. The agreement is part of the Genomics Expert Network for Enterprises (GENE) Consortium, a collaboration between 10 pharma and biotech and Genomics England to conduct a year-long industry trial to discover treatments and diagnostics for rare disease and cancer patients. Members of the GENE Consortium will be granted access to whole genome sequences and corresponding health information from up to 5,000 participants in the 100,000 Genomes Project. The 100,000 Genomes Project is Genomics England's initiative to sequence whole genomes from 100,000 NHS patients and link that data to patients' medical records by 2017 (see BioCentury, Aug. 4, 2014).

**H. Lundbeck A/S** (CSE:LUN), Copenhagen, Denmark

**Ovid Therapeutics Inc.**, New York, N.Y.

Business: Neurology

Lundbeck granted Ovid exclusive, worldwide rights to develop and commercialize gaboxadol (OV101). Ovid plans to begin Phase II testing next year to treat Angelman syndrome and Fragile X syndrome. Gaboxadol is a selective agonist of extrasynaptic GABA A receptors that contain the delta subunit. Lundbeck is eligible for undisclosed milestones and royalties and became a minority shareholder in Ovid.

Lundbeck and partner **Merck & Co. Inc.** (NYSE:MRK, Whitehouse Station, N.J.) terminated development of the compound to treat insomnia in 2007 after Phase III trials did not support further development (see BioCentury, April 2, 2007).

**iDD Biotech S.A.S.**, Lyon, France

**Genmab A/S** (CSE:GEN;OTCBB:GMXAY), Copenhagen, Denmark

Business: Cancer

Genmab purchased from iDD preclinical antibodies targeting tumor necrosis factor (TNF) receptor superfamily member 10b (TNFRSF10B; DR5; TRAILR2; CD262) and related patents. Genmab said TRAILR2 is a potential cancer target. Genmab declined to provide a timeline for next steps. iDD will receive €2.5 million (\$2.6 million) up front and is eligible for up to €101.5 million (\$107.2 million) in development and sales milestones, plus single-digit royalties. iDD did not respond to inquiries.

**Intarcia Therapeutics Inc.**, Boston, Mass.

**Numab AG**, Waedensil, Switzerland

Business: Autoimmune, Endocrine/Metabolic

Numab and Intarcia partnered to use Numab's antibody fragment technology and Intarcia's antibody delivery technology to discover and develop once- or twice-yearly monospecific and multispecific antibodies to treat diabetes, obesity and autoimmune diseases. Intarcia has exclusive, worldwide rights to develop and commercialize the generated antibodies and the option to extend the deal beyond the initial assets and targets.

Numab will receive an undisclosed upfront payment and is eligible for milestone payments and tiered single- to low-double-digit royalties. Numab declined to disclose further financial details, and Intarcia could not be reached.

**Japan Health Sciences Foundation**, Tokyo, Japan

**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan

**Kaketsuken**, Kumamoto, Japan

Business: Cancer

Takeda transferred its worldwide patent rights covering a preclinical HPV vaccine candidate to **Kaketsuken**. In October 2010, Japan Health and Takeda partnered to develop the vaccine to prevent cervical cancer. Takeda did not respond to inquiries in time for publication, and **Kaketsuken** could not be reached.

**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

**University College Cork**, Cork, Ireland

Business: Autoimmune

The university's Alimentary Pharmabiotic Center's Microbiome Institute partnered with the pharma's Janssen Biotech Inc. unit to explore the use of viruses as treatments and/or biomarkers for inflammatory bowel disease (IBD). Janssen declined to disclose details, and Microbiome Institute did not respond to inquiries.

**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

**Depomed Inc.** (NASDAQ:DEPO), Newark, Calif.

Business: Neurology

Depomed completed its purchase of U.S. rights to the Nucynta tapentadol analgesic franchise from **Johnson & Johnson's** Janssen Pharmaceuticals Inc. unit for \$1.1 billion in cash (see BioCentury, Jan. 19).

**Lexicon Pharmaceuticals Inc.** (NASDAQ:LXRX), The Woodlands, Texas

**Ipsen Group** (Euronext:IPN;Pink:IPSEY), Boulogne-Billancourt, France

Business: Cancer, Endocrine/Metabolic

The companies added Canada to a 2014 deal granting Ipsen exclusive rights to commercialize telotristat etiprate outside of North America and Japan. Ipsen will focus on commercializing the tryptophan hydroxylase 1 (TPH1; TPH) inhibitor to treat carcinoid syndrome, for which the compound is in Phase III testing (see BioCentury, Nov. 24, 2014).

Through the expansion, Lexicon is eligible to receive up to \$5 million comprising an undisclosed upfront payment and pre-commercialization milestones, plus additional undisclosed sales milestones and royalties.

**Mesoblast Ltd.** (ASX:MSB;Pink:MBLTY), Melbourne, Australia

**Celgene Corp.** (NASDAQ:CELG), Summit, N.J.

Business: Cancer, Transplant

Celgene purchased 15.3 million shares of Mesoblast stock for A\$58.4 million (\$44.2 million), or A\$3.82 per share. The price is a 19% premium to Mesoblast's close of A\$3.21 on April 10, the last trading day before the deal was announced. The 15.3 million shares represent a 4.5% stake in the company. With the purchase, Celgene obtained a six-month right of first refusal for Mesoblast's mesenchymal stem cell candidates in undisclosed cancers, inflammatory bowel diseases, acute graft-versus-host disease (GvHD) and organ transplant rejection.

The deal excludes Japanese rights in GvHD, which **JCR Pharmaceuticals Co. Ltd.** (Tokyo:4552, Ashiya, Japan) already holds. Mesoblast said licensing negotiations with Celgene may also include disease areas outside Celgene's right of first refusal, including rheumatoid arthritis (RA) and diabetic nephropathy.

**Myriad Genetics Inc.** (NASDAQ:MYGN), Salt Lake City, Utah

**AstraZeneca plc** (LSE:AZN;NYSE:AZN), London, U.K.

Business: Pharmacogenetics

AstraZeneca and Myriad expanded a 2013 deal and will use Myriad's BRACAnalysis CDx test to identify metastatic pancreatic cancer patients likely to respond to the pharma's Lynparza olaparib. Under the 2013 deal, the partners were using BRACAnalysis to identify ovarian breast cancer patients likely to respond to olaparib for enrollment in Phase III trials. Myriad declined to provide financial terms, and AZ did not respond to inquiries (see BioCentury, June 17, 2013).

**Ono Pharmaceutical Co. Ltd.** (Tokyo:4528), Osaka, Japan

**China Chemical & Pharmaceutical Co. Ltd. (CCPC)** (Taiwan:1701), Taipei, Taiwan

Business: Neurology

Ono granted CCPC exclusive, Taiwanese rights to develop and commercialize limaprost alfadex to treat lumbar spinal canal stenosis. CCPC is responsible for marketing approval in Taiwan, and Ono is eligible for undisclosed royalties. Ono declined to disclose financial terms, and CCPC could not be reached.

Ono and **Sumitomo Dainippon Pharma Co. Ltd.** (Tokyo:4506, Osaka, Japan) discovered the prostaglandin E1 analog through collaborative research. Ono markets it as Opalmon and Sumitomo markets it as Prorenal in Japan (see BioCentury, May 13, 2013).

**PatientsLikeMe Inc.**, Cambridge, Mass.

**AstraZeneca plc** (LSE:AZN;NYSE:AZN), London, U.K.

Business: Pharmaceuticals

PatientsLikeMe granted AstraZeneca access to its global network of patient-reported outcomes data under a five-year deal. AZ will initially use the data to develop therapies for respiratory disease, lupus, diabetes and cancer. The companies declined to disclose financial terms.

**Population Genetics Technologies Ltd.**, Babraham, U.K.

**Case Western Reserve University**, Cleveland, Ohio

Business: Diagnostic

Population Genetics and Case Western partnered to use Population Genetics' VeriTag next-generation sequencing technology to develop the VeX-HIV genotyping kit to determine HIV drug resistance in HIV-positive patients. Population Genetics said it plans to have the kit available for clinical use in a commercial setting in mid-2016. Population Genetics is funding research at Case Western that will assist in the development of the technology.

**Scilex Pharmaceuticals Inc.**, West Chester, Pa.

**Itochu Corp.** (Tokyo:8001;Pink:ITOCY), Tokyo, Japan

Business: Neurology

Itochu's Itochu Chemical Frontier Corp. company made an undisclosed investment in neurology company Scilex. The investment makes Itochu Scilex's largest investor. Scilex declined to provide further details, and Itochu could not be reached.

**T-Cell Factory B.V.**, Amsterdam, the Netherlands

**Kite Pharma Inc.** (NASDAQ:KITE), Los Angeles, Calif.

Business: Cancer

Cancer company Kite acquired T-Cell Factory for €20 million (\$21.1 million) in cash and stock and up to €242.5 million (\$256.2 million) in clinical, regulatory and sales milestones. The deal includes European clinical manufacturing facilities and T-Cell's TCR-GENERATOR technology for the discovery of tumor-specific T cell receptors. T-Cell Factory will now be a subsidiary of Kite and will be renamed Kite Pharma EU.

**Teva Pharmaceutical Industries Ltd.** (NYSE:TEVA), Petah Tikva, Israel

**Ignyta Inc.** (NASDAQ:RXDX), San Diego, Calif.

Business: Cancer

Ignyta purchased four oncology programs from Teva for 1.5 million shares of Ignyta's stock, which are valued at \$11.3 million based on Ignyta's close of \$7.50 on March 16, the day before the deal was announced.

The most advanced program is CEP-32496 (RXDX-105), which is in a Phase I/II trial for solid tumors, advanced unresectable melanoma and metastatic colorectal cancer. CEP-32496 is a small molecule BRAF kinase inhibitor. The deal includes three preclinical programs: CEP-40783 (RXDX-106), a selective, pseudo-irreversible inhibitor of AXL receptor tyrosine kinase (AXL; UFO) and c-Met receptor tyrosine kinase; CEP-40125 (RXDX-107), a nanoformulation of modified bendamustine; and TEV-44229 (RXDX-108), a selective inhibitor protein kinase C (PKC) iota (PRKCI) and next-generation PRKCI inhibitors. Ignyta plans on submitting an IND for RXDX-106 in 2H15 and for RXDX-107 in 1H16.

Concurrent with the deal, purchased Teva purchased an additional 1.5 million shares of Ignyta at \$10 per share as part of a larger registered direct offering. Following the deal and offering, Teva holds about 12% of Ignyta.

**University of Cincinnati**, Cincinnati, Ohio

**Arch Biopartners Inc.** (TSX-V:ACH;OTCBB:FOIFF), Toronto, Ontario

Business: Infectious

The university granted Arch a one-year option to license exclusive commercial rights to a pending U.S. patent covering a candidate to treat *Pseudomonas aeruginosa* respiratory infections. Arch plans to start a clinical trial this year to test the product in cystic fibrosis (CF) patients. The partners did not respond to inquiries.

Arch also said it extended for another year its one-year option to exclusively license rights from the university to U.S. Patent No. 8,557,300, which covers an approach to treat *P. aeruginosa* respiratory infections using acidified nitrite (see BioCentury, April 7, 2014).

**Vaccinex Inc.**, Rochester, N.Y.

**Five Prime Therapeutics Inc.** (NASDAQ:FPRX), South San Francisco, Calif.

Business: Antibodies

Five Prime and Vaccinex partnered to use Vaccinex's ActivMAB platform to discover mAbs against undisclosed targets identified by Five Prime's discovery platform. Five Prime will have exclusive, worldwide rights to develop and commercialize mAbs discovered by Vaccinex. Vaccinex will receive upfront fees, research support and performance payments and is eligible for milestone payments and low single-digit royalties. The companies could not provide details in time for publication.

## COMPANY NEWS

### SALES & MARKETING

**CombiMatrix Corp.** (NASDAQ:CBMX), Irvine, Calif.

**InterWest Health LLC**, Missoula, Mont.

Business: Diagnostic

InterWest will cover CombiMatrix's diagnostic laboratory services. InterWest has over 25,000 hospitals, physicians and other providers in their network and over 110,000 enrollees. CombiMatrix specializes in prenatal testing, miscarriage analysis and pediatric genetic testing.

**Critical Diagnostics**, San Diego, Calif.

Business: Diagnostic

**Critical Diagnostics** launched its Aspect-PLUS ST2 lateral flow immunoassay in the EU and the Asia-Pacific region. The assay measures the level of IL-1 receptor-like 1 (IL1RL1; ST2) to stratify chronic and acute heart failure patients by risk.

**Recombine Inc.**, New York, N.Y.

**Sequenom Inc.** (NASDAQ:SQNM), San Diego, Calif.

Business: Diagnostic

Sequenom and Recombine launched Sequenom's HerediT Universal genetic screening test in the U.S. The test screens for more than 250 genetic diseases and analyzes over 2,000 genetic mutations at preconception or during pregnancy. Recombine runs the test on its CarrierMap genetic carrier screening platform.

## COMPANY NEWS

### OTHER NEWS

**Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.

**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland

Business: Biosimilars

The U.S. District Court for the Northern District of California denied a motion from Amgen for a preliminary injunction seeking to delay the launch of biosimilar Zarxio filgrastim-sndz from Novartis' Sandoz Inc. generics unit over price erosion concerns that would cause the market to "irreversibly be changed." The judge said the likelihood of Amgen wrongfully suffering irreparable harm appears speculative and "does not merit injunctive relief." The biosimilar of Amgen's Neupogen filgrastim is the first approved biosimilar product in the U.S. Amgen filed the brief in the U.S. District Court for the Northern District of California. Earlier this year, Amgen filed an appeal to the U.S. Court of Appeals for the Federal Circuit (CAFC) after the district court denied Amgen's motion for a preliminary

injunction seeking to prevent a Zarxio launch (see BioCentury, March 23; March 30 & April 6).

Amgen previously said it will file a motion for an injunction pending appeal with the CAFC, but declined to provide a timeline. Sandoz has agreed not to launch its biosimilar in the U.S. until the earlier of May 11 or a ruling by the CAFC on Amgen's contemplated motion for an injunction pending appeal. Sandoz and Amgen requested the CAFC to hear the matter in its June calendar.

**Biogen Inc.** (NASDAQ:BIIB), Cambridge, Mass.

**Forward Pharma A/S** (NASDAQ:FWP), Copenhagen, Denmark  
Business: Autoimmune

Forward said the Patent Trials and Appeals Board of the U.S. Patent and Trademark Office (PTO) declared a patent interference and made Forward the senior party in a ruling concerning dimethyl fumarate (DMF), sold by Biogen as Tecfidera to treat multiple sclerosis. According to Forward, the appeals board declared the interference between patent application 11/576,871 from Forward and U.S. Patent No. 8,399,514 from Biogen. Both patents cover use of 480 mg DMF daily to treat MS. With Forward as the senior party, Biogen has the burden of proof to show that it invented the technology before Forward.

Forward said either party can file a motion challenging the other's IP; Forward expects the first motion in mid-2015. Biogen declined to comment on its legal strategy. Forward filed its patent application on Oct. 7, 2005, while Biogen filed its patent application on Feb. 8, 2007. Biogen's '514 patent expires on Feb. 2, 2028.

Forward Pharma has two additional pending patent applications in the U.S., three pending patent applications in the EU, and a German utility model, all of which cover the use of 480 mg DMF daily to treat MS. Last month, the European Patent Office declared an intention to grant a patent for EP14172398.1, one of the applications. Forward expects to begin a Phase III trial of FP187, an oral small molecule DMF, by 1Q16 to treat relapsing-remitting MS.

Biogen reported \$2.9 billion in 2014 Tecfidera sales worldwide, including \$2.4 billion in U.S. sales. In an August 2014 SEC filing, Forward said the PTO recommended declaring interference against Biogen's '514 patent.

**Broad Institute of MIT and Harvard**, Cambridge, Mass.

**University of California**, Berkeley, Calif.

Business: Functional genomics

The [University of California Berkeley](#) filed a patent interference request with the U.S. Patent and Trademark Office (PTO) related to 10 patents held by the [Broad Institute of MIT and Harvard](#) covering CRISPR-Cas9 (CRISPR-associated protein 9) gene editing technology. Broad said the PTO is reviewing the request and has not yet granted an interference.

Although Broad holds the first patents covering CRISPR-Cas9, UC Berkeley was first to file a patent application for the technique. UC Berkeley's application, filed in March 2013, has priority dating back to a provisional patent application filed in May 2012. Broad's first provisional filing was in December 2012. Broad's patent application was filed in October 2013 under an accelerated review protocol, allowing the application to jump the queue. UC Berkeley and Umea University also first demonstrated the technique in prokaryotic cells in *Science* in 2012. Broad later published the first evidence that it could work in mouse and human cells.

Under the Leahy-Smith America Invents Act (AIA) of 2011, UC Berkeley would have to show that it was first to invent the technique. The law states that U.S. patents filed before March 16, 2013, are regulated on a first-to-invent basis rather than a first inventor-to-file basis. Thus, if the PTO grants interference, the case may come down to the dates of entries in lab notebooks.

## CLINICAL NEWS

### REGULATORY

**Actavis plc** (NYSE:ACT), Dublin, Ireland

**Kyorin Pharmaceutical Co. Ltd.** (Tokyo:4569), Tokyo, Japan

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.

Product: Eklira Genuair acclidinium bromide (Bretaris Genuair, Tudorza Genuair) (Tudorza)

Business: Pulmonary

Kyorin said Japan approved Eklira Genuair acclidinium bromide for relief from symptoms arising from respiratory tract obstruction in patients with chronic obstructive pulmonary disorder (COPD). The product is an inhalable long-acting, selective M2 and M3 muscarinic receptor antagonist delivered using the Genuair inhaler. The product is approved as Tudorza Pressair in the U.S. and as Bretaris/Eklira Genuair in the EU.

In November, AstraZeneca acquired the respiratory disease business of **Almirall S.A.** (Madrid:ALM, Barcelona, Spain), including acclidinium bromide (see BioCentury, Nov. 24, 2014). Kyorin has exclusive, Japanese rights from Almirall to acclidinium bromide, and Actavis has U.S. rights to the product.

**Aethlon Medical Inc.** (OTCQB:AEMD), San Diego, Calif.

Product: Aethlon Hemopurifier

Business: Infectious

Aethlon said it submitted a Humanitarian Use Device (HUD) application to FDA for Aethlon Hemopurifier to treat Ebola virus infection. The product is an extracorporeal device that selectively absorbs viruses and immunosuppressive toxins from blood. Last year, Aethlon began an open-label, U.S. clinical trial of the product in about 10 HCV-infected patients with end-stage renal disease (ESRD) receiving chronic dialysis (see BioCentury, Jan. 19).

**AIMM Therapeutics B.V.**, Amsterdam, the Netherlands

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.

Product: RSV mAb (D25, MEDI8897)

Business: Infectious

AstraZeneca's **MedImmune LLC** unit said FDA granted Fast Track designation to MEDI8897 to prevent lower respiratory tract infection caused by respiratory syncytial virus (RSV) in infants and young children. The human IgG1 kappa mAb against RSV is in Phase Ib/IIa testing in healthy preterm infants. MedImmune has rights to develop the product from AIMM.

**Alere Inc.** (NYSE:ALR), Waltham, Mass.

Product: Alere q HIV-1/2 Detect

Business: Diagnostic

Alere received CE Mark approval for Alere q HIV-1/2 Detect assay to detect and identify and distinguish between HIV-1 subgroup M/N and O and HIV-2 infection in under 60 minutes using a blood sample from a finger or heel stick. The point-of-care (POC) diagnostic uses multiplexed RT-PCR for amplification and detection of nucleic acids.

**Alexion Pharmaceuticals Inc.** (NASDAQ:ALXN), Cheshire, Conn.

Product: Soliris eculizumab

Business: Hematology

The European Commission approved an expanded label for Soliris eculizumab from Alexion to include transfusion-naïve paroxysmal nocturnal hemoglobinuria (PNH) patients with high disease activity. Previously, the label said that the evidence of Soliris' clinical benefit is limited to transfusion-experienced PNH patients. Alexion said the European Commission also approved the addition of data to the label on the benefits of long-term treatment and the risks associated with treatment discontinuation in patients with atypical hemolytic uremic syndrome (aHUS) — its other approved indication. The humanized mAb targeting complement 5 (C5) is approved in the U.S. to treat aHUS and PNH.

**Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.

**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan

Product: Vectibix panitumumab

Business: Cancer

The European Commission approved an expanded label for Vectibix panitumumab from Amgen to include first-line treatment of wild-type Ras metastatic colorectal cancer (mCRC) in combination with FOLFIRI chemotherapy. The drug is approved in the EU in patients with wild-type Ras mCRC as a first-line treatment in combination with FOLFOX; as a second-line treatment in combination with FOLFIRI in those who have received first-line fluoropyrimidine-based chemotherapy; and as monotherapy after the failure of fluoropyrimidine-, oxaliplatin- and irinotecan-containing chemotherapy regimens. Amgen markets the human mAb against EGFR in the EU, U.S. and Canada, while Takeda has exclusive Japanese rights.

**Avedro Inc.**, Waltham, Mass.

Product: Riboflavin ophthalmic solution (VibeX)

Business: Ophthalmic

FDA issued a complete response letter to Avedro for an NDA for VibeX to treat progressive keratoconus or corneal ectasia following refractive surgery. The company said FDA requested more information, but that none of those areas are related to clinical safety or efficacy data in the NDA. The company did not provide further details.

In February, FDA's Dermatologic and Ophthalmic Drugs Advisory Committee voted 10-4, with 1 abstention, in support of approval for

the product (see BioCentury, March 2). Avedro markets riboflavin ophthalmic solution as VibeX outside the U.S. for use with the KXL System, a UVA irradiation device, for corneal cross-linking. Riboflavin serves as a photosensitizer, and UVA increases the formation of covalent bonds in collagen fibers by photosensitized oxidation.

**Blanchette Rockefeller Neurosciences Institute**, Morgantown, W.Va.

**Neurotrope Inc.** (OTCQB:NTRP), Newark, N.J.

Product: Bryostatin-1

Business: Neurology

Neurotrope said FDA granted Orphan Drug designation to bryostatin-1 to treat Fragile X syndrome. The protein kinase C (PKC) epsilon (PKCE) activator has completed a Phase IIa trial to treat Alzheimer's disease (AD) (see BioCentury, March 23). Neurotrope has a license to bryostatin-1 from the institute.

**Boehringer Ingelheim GmbH**, Ingelheim, Germany

Product: Pradaxa dabigatran etexilate (Pradax, Prazaxa)

Business: Cardiovascular

FDA accepted for review an sNDA from Boehringer for Pradaxa dabigatran etexilate to prevent deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have had primary elective total hip replacement surgery. Boehringer markets the direct oral thrombin inhibitor in the U.S. and EU to reduce the risk of stroke and blood clots in patients with non-valvular atrial fibrillation (AF); in the U.S. to treat DVT and PE and reduce the risk of recurrent DVT and PE in previously treated patients; and in the EU to treat and prevent recurrence of DVT and PE and to prevent venous thromboembolic (VTE) events in adults who have undergone elective total hip or knee replacement surgery.

**Curis Inc.** (NASDAQ:CRIS), Lexington, Mass.

Product: CUDC-907

Business: Cancer

FDA granted Orphan Drug designation to CUDC-907 from Curis to treat diffuse large B cell lymphoma (DLBCL). Next half, Curis plans to begin a Phase II trial of the dual phosphoinositide 3-kinase (PI3K) and histone deacetylase (HDAC) inhibitor in DLBCL. CUDC-907 is in Phase I testing to treat relapsed or refractory lymphoma or multiple myeloma (MM) and advanced or relapsed solid tumors.

**Cytori Therapeutics Inc.** (NASDAQ:CYTX; Xetra:XMPA), San Diego, Calif.

Product: Celution System

Business: Transplant

The China Food and Drug Administration (CFDA) approved Cytori's Celution System for autologous re-implantation or re-infusion of a patient's adipose-derived regenerative cells. The point-of-care system can be used to treat a variety of conditions, including soft tissue injury and limited blood flow. The product processes and purifies adult stem and regenerative cells from adipose tissue and is approved in over 40 countries. [Lorem Vascular Pty. Ltd.](#) (Beijing, China) has exclusive rights to commercialize Cytori's Celution System in China, Malaysia, Singapore and Australia under a 2013 deal (see BioCentury, Nov. 11, 2013). Lorem said it launched the device.

**DBV Technologies S.A.** (Euronext:DBV; NASDAQ:DBVT), Bagneux, France

Product: Viaskin Peanut (DBV-712)

Business: Inflammation

FDA granted breakthrough therapy designation to Viaskin Peanut from DBV to treat peanut allergy in children ages 6-11. DBV said it plans to start Phase III testing of the product by year end. The peanut proteins epicutaneously delivered by Viaskin patch technology has Fast Track designation in the U.S. to treat peanut allergy.

**Eagle Pharmaceuticals Inc.** (NASDAQ:EGRX), Woodcliff Lake, N.J.

Product: Bendamustine RTD (EP-3102)

Business: Cancer

FDA accepted for review an NDA for EP-3102 to treat chronic lymphocytic leukemia (CLL) and indolent B cell non-Hodgkin's lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. The PDUFA date is in December. The ready-to-dilute formulation of bendamustine, an alkylating agent, requiring 50 mL saline or a mixture of sodium chloride and dextrose has Orphan Drug designation for both indications. [Teva Pharmaceutical Industries Ltd.](#) (NYSE:TEVA, Petah Tikva, Israel) has exclusive U.S. commercialization rights to the compound from Eagle (see BioCentury, Feb. 23)

**Horizon Pharma plc** (NASDAQ:HZNP), Dublin, Ireland

Product: Actimmune interferon gamma-1b

Business: Neurology

FDA granted Fast Track designation to Horizon's Actimmune interferon gamma-1b to treat Friedreich's ataxia. This quarter, Horizon plans to start a Phase III trial of Actimmune in the indication, for which the product has Orphan Drug designation in the U.S. The interferon (IFN) gamma-1b is approved in the U.S. for children and adults with chronic granulomatous disease and severe, malignant osteopetrosis.

**The Medicines Co.** (NASDAQ:MDCO), Parsippany, N.J.

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.

Product: Kengreal Cangrelor (Kengrexal) (formerly AR-C69931MX)

Business: Cardiovascular

FDA's Cardiovascular and Renal Drugs Advisory Committee voted 9-2, with 1 abstention, to recommend approval of Kengreal cangrelor from [The Medicines Co.](#) as an adjunct to percutaneous coronary intervention (PCI) to reduce risk of periprocedural ischemic complications, including myocardial infarction (MI), stent thrombosis and ischemia-driven revascularization. The PDUFA date is June 23. The product is a reversible purinergic receptor P2Y<sub>12</sub> G protein-coupled 12 (P2RY12; P2Y12) antagonist.

In briefing documents released ahead of the meeting, FDA reviewers supported the approval of Kengreal for the indication specifically in patients for whom treatment with an oral P2Y<sub>12</sub> inhibitor prior to PCI is not feasible and when glycoprotein IIb/IIIa receptor antagonists are unlikely to be used.

Panelists generally agreed the sensitivity analyses of the Phase III CHAMPION PHOENIX trial supported the clinical benefit of Kengreal. However, some panelists who voted in favor of approval expressed concerns over the molecule's narrow benefit-risk profile. The committee also was mixed on whether the PHOENIX results could be interpreted independently from the discontinued Phase III CHAMPION PLATFORM and CHAMPION PCI trials.

Panelists agreed that Kengreal is a reasonable alternative to clopidogrel, the PHOENIX comparator, given at the start of PCI without pretreatment with an oral P2Y<sub>12</sub> inhibitor. The committee also agreed that the restricted use of glycoprotein IIb/IIIa inhibitors to treat thrombotic complications of PCI in the PHOENIX trial is consistent with current medical practice.

Last month, the European Commission approved cangrelor as Kengrexal to reduce thrombotic cardiovascular events in patients with coronary artery disease (CAD) undergoing PCI. In April 2014, FDA issued a complete response letter to [The Medicines Co.](#) for Kengreal for the indication and as bridging therapy for patients with stents who are at increased risk for thrombotic events when oral P2Y<sub>12</sub> therapy is interrupted due to surgery. [The Medicines Co.](#) has exclusive, worldwide rights to cangrelor from AstraZeneca (see [BioCentury](#), April 13, 2015; May 5, 2014 & Dec. 22, 2003).

**Momenta Pharmaceuticals Inc.** (NASDAQ:MNTA), Cambridge, Mass.

**Novartis AG** (NYSE:NVS; SIX:NOVN), Basel, Switzerland

Product: Glatopa glatiramer acetate (M356)

Business: Autoimmune

FDA approved an ANDA from Novartis' Sandoz unit and Momenta for once-daily Glatopa glatiramer acetate to treat relapsing forms of multiple sclerosis (MS). The selective major histocompatibility complex class II (MHCII) modulator is the first FDA-approved generic version of Copaxone from Teva Pharmaceuticals Industries Ltd. (NYSE:TEVA, Petah Tikva, Israel). Glatopa was approved as

a 20 mg/mL injection. Teva is converting patients from once-daily Copaxone to a thrice-weekly formulation of the drug, which has patent protection until 2030.

The approval triggered a \$10 million milestone payment to Momenta from Sandoz under a 2006 deal to develop and commercialize the generic product (see [BioCentury](#), July 31, 2006). Sandoz declined to provide pricing and launch timing information. In conjunction with the approval, FDA rejected a Citizen's Petition from Teva asking the agency not to approve Copaxone generics unless specific conditions demonstrating equivalence to the reference product were met.

**Ono Pharmaceutical Co. Ltd.** (Tokyo:4528), Osaka, Japan

**Servier**, Neuilly-sur-Seine, France

Product: Procoralan ivabradine (Corlanor) (ONO-1162) (formerly (S-16257))

Business: Cardiovascular

FDA approved an NDA from [Amgen Inc.](#) (NASDAQ:AMGN, Thousand Oaks, Calif.) for Corlanor ivabradine to treat chronic heart failure (CHF). Amgen, which made the announcement on April 15, plans to launch the selective I<sub>f</sub> channel inhibitor within 1 week at a wholesale acquisition price of \$375 per month. Specifically, Corlanor is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic CHF with left ventricular ejection fraction  $\leq 35\%$  who are in sinus rhythm with resting heart rate  $\geq 70$  beats per minute and either are on maximally tolerated doses of beta blockers or have a contraindication to beta blocker use.

The drug is marketed as Procoralan in more than 100 countries to treat stable angina and CHF. Amgen has exclusive U.S. commercialization rights to Corlanor from [Servier](#). Ono has Japanese rights from [Servier](#).

**Otsuka Pharmaceutical Co. Ltd.**, Tokyo, Japan

**AstraZeneca plc** (LSE:AZN; NYSE:AZN), London, U.K.

Product: Onglyza saxagliptin (BMS-477118, OPC-262)

Business: Endocrine/Metabolic

FDA's Endocrinologic and Metabolic Drugs Advisory Committee recommended that the agency add language about potential risks of heart failure to the labels of 2 dipeptidyl peptidase-4 (DPP-4; CD26) inhibitors to treat diabetes — Onglyza saxagliptin from AstraZeneca and Nesina alogliptin from [Takeda Pharmaceutical Co. Ltd.](#) (Tokyo:4502, Osaka, Japan). The recommendations came after the panel analyzed the data from 2 CV outcomes trials, SAVOR for Onglyza and EXAMINE for Nesina.

In both trials, the drugs met the primary endpoint of showing no increased risk of major adverse cardiovascular events (MACE). However, patients treated with Onglyza had a statistically significant 27% increase in hospitalization for heart failure in SAVOR. Patients taking Nesina had an increase of 19% in EXAMINE; the change was

not statistically significant. Heart failure was not a component of the MACE endpoint.

During the session to discuss SAVOR, 14 panel members voted to update the label for Onglyza to warn of a possible increase in heart failure, while 1 member, the consumer representative, voted that the drug should be withdrawn. Some members also suggested the label include language on the increased risk of all-cause mortality that was seen in SAVOR but not statistically significant.

In the session to discuss EXAMINE, 13 members of an expanded 16-member panel voted for an updated label, while 3 members recommended no change. The majority of panel members were concerned that the heart failure findings could point to a class-wide effect.

In both sessions, panel members agreed that AZ and Takeda had ruled out the possibility of increased risk of MACE based on FDA's 2008 guidance. The groups voted 13-1, with 1 abstention, that Onglyza had an acceptable CV risk profile and 16-0 that Nesina did.

The panel members did not recommend additional large randomized clinical trials to assess the risk of heart failure. Instead, most agreed that AZ's planned 180-patient study to assess potential mechanisms behind the increased risk, along with observational studies, would be sufficient.

Some panel members also suggested that FDA wait to make any final decisions on label changes until data are available from TECOS, a CV outcomes trial for another marketed DPP-4 inhibitor, Januvia sitagliptin from [Merck & Co. Inc.](#) (NYSE:MRK, Whitehouse Station, N.J.). TECOS data will be presented at the American Diabetes Association meeting in June. FDA didn't say when it would make a decision on the recommended label changes for Onglyza and Nesina or when it would review the TECOS data.

Januvia sales were \$3.9 billion in 2014, while Onglyza's sales were \$820 million over the same period. Takeda expects to report about ¥50 billion (\$420 million) in sales of Nesina for its FY14, which ended March 31. Otsuka has rights to Onglyza in Japan.

**Takeda Pharmaceutical Co. Ltd.** (Tokyo:4502), Osaka, Japan

Product: Nesina alogliptin (SYR-322)

Business: Endocrine/Metabolic

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## CLINICAL NEWS

### CLINICAL RESULTS

**Active Biotech AB** (SSE:ACTI), Lund, Sweden

**IpSEN Group** (Euronext:IPN; Pink:IPSEY), Boulogne-Billancourt, France

Product: Tasquinimod (TASQ) (ABR-215050)

Business: Cancer

Molecular target: S100 calcium binding protein A9 (S100A9) (calgranulin B) (MRP14)

Description: Oral quinoline-3-carboxamide derivative that binds S100 calcium binding protein A9 (S100A9; calgranulin B; MRP14)

**Indication:** Treat metastatic castration-resistant prostate cancer (CRPC)

**Endpoint:** Progression-free survival (PFS); overall survival (OS)

**Status:** Development discontinued

**Milestone:** NA

Active Biotech and Ipsen decided to discontinue all studies of tasquinimod in patients with prostate cancer after top-line data from the double-blind, international Phase III TASQ10 in ≥1,200 patients with CRPC who have not received chemotherapy showed that once-daily 0.25, 0.5 and 1 mg oral tasquinimod did not improve OS vs. placebo (HR=1.09, 95% CI: 0.94, 1.28). Tasquinimod did reduce the risk of radiographic cancer progression or death vs. placebo (rPFS HR=0.69, 95% CI: 0.60, 0.80).

Tasquinimod is also in the Phase II Umbrella trial in patients with advanced cancers that progressed after standard therapies. Ipsen and Active Biotech partnered in 2011 to co-develop and commercialize tasquinimod (see BioCentury, April 25, 2011).

**Alexion Pharmaceuticals Inc.** (NASDAQ:ALXN), Cheshire, Conn.

**Product:** Soliris eculizumab

**Business:** Transplant

**Molecular target:** Complement 5 (C5)

**Description:** Humanized mAb targeting complement 5 (C5)

**Indication:** Prevent acute antibody-mediated rejection in sensitized recipients of a kidney transplant from a deceased donor

**Endpoint:** Post-transplantation treatment failure rate at week 9 defined by a composite of biopsy-proven antibody-mediated rejection, graft loss, patient death and/or loss to follow-up

**Status:** Additional Phase II data

**Milestone:** NA

Data from 80 sensitized recipients of a kidney transplant from a deceased donor who received IV Soliris in an open-label, international Phase II trial showed that the post-transplantation treatment failure rate at week 9, the primary endpoint, was 11.3%. Of the 9 patients with post-transplantation treatment failure, 5 had biopsy-proven antibody-mediated rejection. Graft survival rates at 6 and 12 months were 93.7% and 87.1%, respectively. The patient survival rate at 6 and 12 months was 97.4%. Data will be presented at the American Transplant Congress in Philadelphia in May. Alexion previously reported preliminary data from 47 patients (see BioCentury, Sept. 23, 2013). Soliris is approved in nearly 50 countries to treat paroxysmal nocturnal hemoglobinuria (PNH) and in nearly 40 countries for atypical hemolytic uremic syndrome (aHUS).

**Amgen Inc.** (NASDAQ:AMGN), Thousand Oaks, Calif.

**Pfizer Inc.** (NYSE:PFE), New York, N.Y.

**Product:** Ibrance palbociclib (PD-0332991)

**Business:** Cancer

**Molecular target:** Cyclin dependent kinase 4 (CDK4); Cyclin dependent kinase 6 (CDK6)

**Description:** Oral small molecule cyclin dependent kinase 4 (CDK4) and CDK6 inhibitor

**Indication:** Treat estrogen receptor-positive, HER2-negative metastatic breast cancer

**Endpoint:** Progression-free survival (PFS); overall survival (OS), objective response rate (ORR), duration of response, clinical benefit rate (CBR), probability of patient survival, quality of life (QOL), time to deterioration and pharmacokinetics

**Status:** Phase III data

**Milestone:** NA

Top-line data from the double-blind, international Phase III PAOLOMA-3 (Study A5481023) trial in 521 patients with hormone receptor-positive, HER2-negative metastatic breast cancer whose disease has progressed after prior endocrine therapy was stopped early after a planned interim analysis by an independent DMC showed that once-daily 125 mg oral Ibrance plus Faslodex fulvestrant met the primary endpoint of improving PFS vs. placebo plus Faslodex. Pfizer plans to submit the data for presentation at the American Society of Clinical Oncology meeting in Chicago in May/June. Ibrance has accelerated approval in the U.S. in combination with letrozole as first-line treatment of postmenopausal women with estrogen receptor-positive, HER2-negative advanced breast cancer. Pfizer has rights to Ibrance from Amgen.

**Andrus Reo Ltd.**, Moscow, Russia

**Oncolytics Biotech Inc.** (TSX:ONC; NASDAQ:ONCY), Calgary, Alberta

**Product:** Reolysin

**Business:** Cancer

**Molecular target:** Not applicable

**Description:** Formulation of human reovirus type 3

**Indication:** Treat pancreatic cancer

**Endpoint:** Clinical benefit rate (CBR) defined by complete or partial response, or stable disease; progression-free survival (PFS) and safety

**Status:** Additional Phase II data

**Milestone:** NA

Additional data from the open-label, U.S. Phase II REO 017 trial in 33 chemotherapy-naïve patients with advanced or metastatic pancreatic cancer showed that first-line treatment with IV Reolysin plus gemcitabine led to a median overall survival (OS) of 10.2 months. Additionally, 1- and 2-year survival rates were 45% and 24%, respectively. Data were presented at the Royal Society of Medicine meeting in London. Oncolytics previously reported that Reolysin plus gemcitabine met the primary endpoint of ≥8 of 33 patients experiencing clinical benefit (see BioCentury, Feb. 21, 2011 & Dec. 5, 2011). Andrus Reo has rights to Reolysin from Oncolytics in the Commonwealth of Independent States (CIS) (see BioCentury, Feb. 25, 2013).

**Archimedes Pharma Ltd.**, Reading, U.K.

**Pharmalink AB**, Stockholm, Sweden

Product: Nefecon (PL-56)

Business: Renal

Molecular target: NA

Description: Enteric formulation of budesonide that downregulates the kidney's inflammatory process

Indication: Treat IgA nephropathy

Endpoint: Change from baseline in urine protein-to-creatinine ratio (UPCR) at 9 months; change from baseline in urine albumin-to-creatinine ratio (UACR) at 9 months, 24-hour albuminuria and estimated glomerular filtration rate (eGFR)

Status: Phase IIb data

Milestone: Phase IIb final data (3Q15)

The double-blind, European Phase IIb NEFIGAN trial in more than 150 patients with primary IgA nephropathy at risk of developing end-stage renal disease (ESRD) was stopped early after a planned interim analysis by a DSMB showed that once-daily oral Nefecon met the primary endpoint of reducing mean UPCR from baseline to 9 months vs. placebo ( $p=0.0066$ ). Patients received placebo or once-daily 8 or 16 mg Nefecon. Pharmalink declined to say when it plans to start a Phase III trial of Nefecon, but said it will meet with FDA and EMA after reporting final Phase IIb data in 3Q15. Pharmalink has exclusive, worldwide rights to use Archimedes' Targit drug delivery technology for use with Nefecon in the indication (see BioCentury, Dec. 19, 2011).

**Benitec Biopharma Ltd.** (ASX:BLT), Sydney, Australia

Product: TT-034

Business: Infectious

Molecular target: NA

Description: DNA-directed RNAi (ddRNAi) adenovirus vector (AAV) containing 3 RNAi elements

Indication: Treat chronic HCV genotype 1 infection

Endpoint: Safety; HCV viral load, liver biopsy and blood vector DNA levels in serum

Status: Interim Phase I/IIa data

Milestone: NA

Interim data from the 4 patients with chronic HCV genotype 1 infection in cohorts 1 and 2 of an open-label, U.S. Phase I/IIa trial showed that IV TT-034 led no to treatment-related serious adverse events. Additionally, liver biopsies from 3 evaluable patients confirmed that TT-034 produced the 3 expected silencing short hairpin RNAs (shRNAs) that are responsible for targeting different parts of the HCV genome. Benitec said the dose of TT-034 in cohorts 1 and 2 is sub-therapeutic and therefore the company did not expect that the amount of shRNA produced would lead to a reduction in HCV viral load. The trial is evaluating single ascending doses of TT-034 in up to 5 cohorts in 14 patients.

**Biogen Inc.** (NASDAQ:BIIB), Cambridge, Mass.

Product: Anti-LINGO-1 (BIIB033)

Business: Neurology

Molecular target: Leucine-rich repeat neuronal protein 1 (LINGO-1)

Description: Antibody against leucine-rich repeat neuronal protein 1 (LINGO-1)

Indication: Treat acute optic neuritis (AON)

Endpoint: Change in optic nerve conduction velocity (NCV) at week 24 for the affected eye from the baseline of unaffected fellow eye as determined by full-field visual evoked potential (FF-VEP); retinal nerve fiber layer (RNFL) and retinal ganglion cell layer/inner plexiform retinal layer thickness, low-contrast letter acuity (LCLA) and pharmacokinetics

Status: Additional Phase II data

Milestone: NA

Additional data from the per protocol (PP) population ( $n=69$ , defined as patients who received  $\geq 5$  of 6 doses) of the double-blind, international Phase II RENEW trial in 82 patients who suffered a first episode of AON showed that 100 mg/kg IV anti-LINGO-1 every 4 weeks for 6 doses led to a 41% improvement in recovery of optic NCV at week 32 for the affected eye from the baseline of the unaffected fellow eye vs. placebo (9.13 msec improvement compared to placebo,  $p=0.01$ ). Additionally, 53% of patients who received anti-LINGO-1 achieved normal or nearly normal FF-VEP latency vs. 26% for placebo. Data will be presented at the American Academy of Neurology meeting in Washington, D.C. on April 22.

Biogen previously reported top-line data from RENEW showing that anti-LINGO-1 missed the primary endpoint of recovery of optic NCV at week 24 for the affected eye from the baseline of the unaffected fellow eye vs. placebo (3.48 msec improvement compared to placebo,  $p=0.33$ ). At week 32, anti-LINGO-1 led to a 6.06 msec improvement on the endpoint compared to placebo ( $p=0.07$ ). In the PP population, anti-LINGO-1 led to a 34% improvement on the endpoint at week 24 vs. placebo (7.55 msec improvement compared to placebo,  $p=0.0504$ ) (see BioCentury, Jan. 12).

**Cellular Biomedicine Group Inc.** (NASDAQ:CBMG), Palo Alto, Calif.

Product: HaMPCs, ReJoin

Business: Autoimmune

Molecular target: NA

Description: Autologous human adipose tissue-derived mesenchymal precursor cells

Indication: Treat osteoarthritis (OA) of the knee

Endpoint: Change from baseline in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score at 12 months; safety, cartilage repair as measured by MRI, Short Form 36 (SF-36), visual analog scale (VAS) score and Lequesne Index of Severity of OA (ISOA) scores

Status: Interim Phase IIb data

Milestone: Phase IIb final data (year end 2015)

Interim data from 24 evaluable patients with OA of the knee in a single-blind, Chinese Phase IIb trial showed that 2 intra-articular injections of ReJoin given 3 weeks apart significantly reduced WOMAC scores from baseline to week 24 vs. sodium hyaluronate (16.42 vs. 6.83 points correlating to 47.12% and 16.32% improvements, respectively,  $p=0.017$ ). ReJoin non-significantly reduced VAS scores from baseline to week 24 in both the left (2.75 vs. 1.76 points correlating to 45.16% and 19.22% improvements, respectively,  $p=0.119$ ) and right (3.38 vs. 1.5 points correlating to 49.52% and 26.92% improvements, respectively,  $p=0.229$ ) knees vs. sodium hyaluronate. The trial enrolled 53 patients with OA of the knee.

**Cytori Therapeutics Inc.** (NASDAQ:CYTX; Xetra:XMPA), San Diego, Calif.

Product: ECCS-50

Business: Autoimmune

Molecular target: NA

Description: Autologous adipose tissue-derived stromal vascular fraction cells separated and concentrated using Cytori's Celution 800 System

Indication: Treat systemic sclerosis with hand disability

Endpoint: Change from baseline in Cochin Hand Function Scale (CHFS) at 2 years; hand pain as measured by a visual analog scale (VAS), Raynaud's Condition Score (RCS) and Scleroderma Health Assessment Questionnaire (SHAQ) score

Status: Phase I data

Milestone: Start Phase III (mid-2015)

The open-label, French Phase I Sclerdec-I trial in 12 female patients with systemic sclerosis with hand disability showed that subcutaneous ECCS-50 injected into the subcutaneous tissue of each finger reduced mean CHFS total score by 27.3 points, mean hand VAS score by 41.7 points, mean RCS by 4.3 points and mean SHAQ score by 0.6 points at 6 months compared to baseline ( $p \leq 0.001$  for all). At 12 months, Cytori said improvements in CHFS, RCS and SHAQ scores were consistent with 6-month data. No adverse events or safety concerns were reported. The trial was sponsored by Assistance Publique des Hopitaux de Marseille.

**Galapagos N.V.** (Euronext:GLPG; Pink:GLPYY), Mechelen, Belgium

**AbbVie Inc.** (NYSE:ABBV), Chicago, Ill.

Product: Filgotinib (GLPG0634)

Business: Autoimmune

Molecular target: Janus kinase-1 (JAK-1)

Description: Janus kinase-1 (JAK-1) inhibitor

Indication: Treat rheumatoid arthritis (RA)

Endpoint: Proportion of patients achieving a 20% improvement in American College of Rheumatology criteria (ACR20) at week 12; ACR50, ACR70, disease activity score using 28 joint counts (DAS28) and quality of life (QOL)

Status: Phase IIb data

Milestone: Phase IIb additional data (mid-2015)

The double-blind, international Phase IIb DARWIN 1 trial in 594 patients with moderate to severe RA who had an inadequate response to methotrexate showed that once-daily 200 mg and twice-daily 100 mg filgotinib as an add-on to methotrexate each met the primary endpoint of improving ACR20 response rate at week 12 vs. placebo as an add-on to methotrexate (69% and 80%, respectively, vs. 45%,  $p < 0.05$  and  $p < 0.001$ ). The once-daily 50 and 100 mg doses of filgotinib and twice-daily 25 and 50 mg doses of filgotinib missed the primary endpoint vs. placebo (56%, 62%, 57% and 59%, respectively). All doses of filgotinib met the secondary endpoints of improving ACR50 response rate and of reducing mean DAS28 score from baseline to week 12 vs. placebo. Specifically, once-daily filgotinib led to ACR50 response rates of 32% at the 50 mg dose ( $p < 0.05$ ), 39% at the 100 mg dose ( $p < 0.01$ ) and 43% at the 200 mg dose ( $p < 0.001$ ) and twice-daily filgotinib led to ACR50 response rates of 28% at the 25 mg dose ( $p < 0.05$ ), 34% at the 50 mg dose ( $p < 0.05$ ) and 55% at the 100 mg dose ( $p < 0.001$ ) vs. 15% for placebo.

Once-daily filgotinib led to mean reductions in DAS28 score from baseline to week 12 of 1.8 points at the 50 mg dose ( $p < 0.05$ ), 2.2 points at the 100 mg dose ( $p < 0.001$ ) and 2.5 points at the 200 mg dose ( $p < 0.001$ ) and twice-daily filgotinib led to mean reductions in DAS28 score of 1.9 points at the 25 mg dose ( $p < 0.01$ ), 2.1 points at the 50 mg dose ( $p < 0.001$ ) and 2.8 points at the 100 mg dose ( $p < 0.001$ ) vs. 1.2 points for placebo. Additionally, once-daily 200 mg and twice-daily 100 mg filgotinib each met the secondary endpoint of improving ACR70 response rate at week 12 vs. placebo (24% and 31%, respectively, vs. 8%,  $p < 0.05$  and  $p < 0.01$ ). Filgotinib was well tolerated. Galapagos expects to report 24-week data from the trial in mid-2015. Data from the Phase IIb DARWIN 2 trial of filgotinib as monotherapy are expected in a few weeks. AbbVie and Galapagos are partnered to develop and commercialize GLPG0634 (see BioCentury, March 5, 2012 & May 27, 2013).

**GW Pharmaceuticals plc** (LSE:GWP; NASDAQ:GWPH), Salisbury, U.K.

Product: Epidiolex cannabidiol

Business: Neurology

Molecular target: Cannabinoid receptors

Description: Oral liquid formulation of cannabidiol, a phytocannabinoid found in Cannabis sativa

Indication: Treat treatment-resistant epilepsy

Endpoint: NA

Status: Expanded access program additional data

Milestone: NA

Additional data from an open-label expanded access program in 137 evaluable children and young adults with treatment-resistant epilepsy who had  $\geq 12$  weeks of Epidiolex exposure showed that once-daily oral Epidiolex led to a 54% mean reduction in the number of seizures from baseline to week 12. In patients with Dravet syndrome ( $n=23$ ), Epidiolex led to a 53% reduction in the number of convulsive seizures. In patients with Lennox-Gastaut syndrome

(n=11), Epidiolex led to a 55% reduction in the number of atonic seizures. The expanded access program is treating epileptic patients in which anti-epileptic drugs have been unsuccessful in adequately controlling seizures, including severe forms of epilepsy as Dravet syndrome and Lennox-Gastaut syndrome. Data will be presented at the American Academy of Neurology meeting in Washington, D.C. on April 22. GW previously reported preliminary data from 27 patients in the program (see BioCentury, June 23, 2014). GW has started 1 of 2 planned Phase III trials of Epidiolex to treat Dravet syndrome and expects to start Phase III trials to treat Lennox-Gastaut syndrome this quarter.

**Inovio Pharmaceuticals Inc.** (NASDAQ:INO), Blue Bell, Pa.

Product: INO-3112

Business: Cancer

Molecular target: Human papillomavirus (HPV) antigens; Interleukin-12 (IL-12)

Description: Combination of VGX-3100, a DNA-based therapeutic vaccine targeting the E6 and E7 proteins of HPV 16 and 18, and INO-9012, an immune activator of IL-12

Indication: Treat HPV-associated head and neck cancer

Endpoint: Safety, immunogenicity, clinical response and progression-free survival (PFS)

Status: Preliminary Phase I/IIa data

Milestone: NA

Preliminary data from 4 patients with HPV-positive head and neck squamous cell carcinoma (SCC) in the open-label, U.S. Phase I/IIa HPV-005 trial showed that intramuscular INO-3112 followed by electroporation with Inovio's Cellectra device generated "strong" CD8+ T cell responses in 3 patients. In the first part of the trial, up to 10 patients will be treated with INO-3112 before and after resection of their tumor. In the second part, up to 10 patients will be treated with INO-3112 after completion of chemotherapy and radiation therapy. Data were presented at the World Vaccine Congress in Washington, D.C.

**Intellipharmaceuticals International Inc.** (TSX:I; NASDAQ:IPCI), Toronto, Ontario

Product: Rexista Oxycodone XR

Business: Neurology

Molecular target: Opioid receptor (OPR)

Description: Controlled-release, abuse-deterrent formulation of oral oxycodone

Indication: Treat pain

Endpoint: Bioequivalence to OxyContin oxycodone

Status: Phase I data

Milestone: NA

Top-line data from an open-label, crossover, blinded Phase I trial in fasted subjects showed that single doses of Rexista Oxycodone XR were bioequivalent to OxyContin as measured by peak plasma concentration (C<sub>max</sub>) and steady state area under the curve (AUC)

concentration. To meet the bioequivalence criteria, the 90% CI for the measures had to fall within 80-125%. The ratio of Rexista Oxycodone XR to OxyContin was 94.95% for C<sub>max</sub> (90% CI: 81.29%, 110.89%) and 100.54% for steady state AUC concentration (90% CI: 89.97%, 112.34%). Intellipharmaceuticals said it submitted an IND to FDA to start Phase III testing of Rexista Oxycodone XR. The company is developing the product under section 505(b)(2) of the Food, Drug and Cosmetic Act, which allows sponsors to reference data on safety and efficacy from the scientific literature or previously approved products.

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XR were bioequivalent to OxyContin as measured by peak plasma concentration (C<sub>max</sub>) and area under the curve (AUC) concentration. To meet the bioequivalence criteria, the 90% CI for the measures had to fall within 80-125%. The ratio of Rexista Oxycodone XR to OxyContin was 91.66% for C<sub>max</sub> (90% CI: 80.21%, 104.75%), 103.21% for AUC concentration (90% CI: 94.15%, 113.15%) and 107.39% for AUC concentration to infinity (90% CI: 98.62%, 107.39%). Intellipharmaceuticals said it submitted an IND to FDA to start Phase III testing of Rexista Oxycodone XR. The company is developing the product under section 505(b) (2) of the Food, Drug and Cosmetic Act, which allows sponsors to reference data on safety and efficacy from the scientific literature or previously approved products.

**MicroBiome Therapeutics LLC**, Broomfield, Colo.

Product: NM505

Business: Endocrine/Metabolic

Molecular target: NA

Description: Oral combination of metformin and a gastrointestinal microbiome modulator

Indication: Treat Type II diabetes in patients with metformin resistance

Endpoint: Metformin tolerance as measured by fecal frequency, consistency and score and incidence of diarrhea using the King's Stool Chart; fasting blood glucose, weight loss and safety

Status: Pilot trial data

Milestone: NA

A double-blind, crossover, U.S. pilot trial in 10 Type II diabetics intolerant to metformin showed that a preliminary formulation of NM505 met the primary endpoint of increasing metformin tolerance score at week 6 vs. a combination of metformin plus placebo (6.78 vs. 4.45 points, p=0.0006). The preliminary formulation of NM505 also met the secondary endpoint of reducing mean fasting glucose levels vs. a combination of metformin plus placebo (121.3 vs. 151.9 mg/dL, p<0.02). Data were published in *The Journal of Diabetes Science and Technology*. MicroBiome said it plans to develop NM505 under section 505(b)(2) of the Food, Drug and Cosmetic Act, which allows sponsors to reference data on safety and efficacy from the scientific literature or previously approved products.

**Pharmacyclics Inc.** (NASDAQ:PCYC), Sunnyvale, Calif.

**Johnson & Johnson** (NYSE:JNJ), New Brunswick, N.J.

Product: Imbruvica ibrutinib (PCI-32765)

Business: Cancer

Molecular target: Bruton's tyrosine kinase (Btk)

Description: Bruton's tyrosine kinase (Btk) inhibitor that covalently binds to cysteine residue 481

Indication: Treat Waldenstrom's macroglobulinemia

Endpoint: Overall response rate (ORR); safety, progression-free survival (PFS) and overall survival (OS)

Status: Additional Phase II data

Milestone: NA

Additional data from an open-label, U.S. Phase II trial in 63 symptomatic patients with previously treated Waldenstrom's macroglobulinemia showed that once-daily 420 mg oral Imbruvica led to an ORR of 90.5% after a median treatment duration of 19.1 months. The estimated 2-year PFS rate was 69.1% and the estimated 2-year OS rate was 95.2%. Additionally, Imbruvica reduced median serum IgM levels from 3,520 mg/dL at baseline to 880 mg/dL at the time of best response, increased median hemoglobin levels from 10.5 g/dL to 13.8 g/dL and reduced the percentage of bone marrow involvement from 60% to 25%. Furthermore, Imbruvica led to an ORR of 100% in patients carrying the L265P mutation in myeloid differentiation primary response gene 88 (MYD88) along with wild-type CXC chemokine receptor 4 (CXCR4; NPY3R). The trial was sponsored by the [Dana-Farber Cancer Institute](#). Data were published in *The New England Journal of Medicine*. Pharmacyclics previously reported data from 35 evaluable patients in the trial (see BioCentury, July 1, 2013).

Imbruvica has full approval in the U.S. as to treat CLL in patients with chromosome 17p deletion and to treat CLL in patients who have received ≥1 prior therapy and for Waldenstrom's macroglobulinemia. The drug also has accelerated approval in the U.S. to treat mantle cell lymphoma (MCL). Pharmacyclics is co-developing and co-commercializing Imbruvica with [Johnson & Johnson](#) under a 2011 deal (see BioCentury, Dec. 12, 2011). [AbbVie Inc.](#) (NYSE:ABBV, Chicago, Ill.) is acquiring Pharmacyclics (see BioCentury, March 9).

**Receptos Inc.** (NASDAQ:RCPT), San Diego, Calif.

Product: Ozanimod (formerly RPC1063)

Business: Autoimmune

Molecular target: Sphingosine 1-phosphate receptor 1 (S1PR1) (S1P1) (EDG1)

Description: Selective sphingosine-1-phosphate receptor 1 (S1PR1; S1P1; EDG1) modulator

Indication: Treat ulcerative colitis (UC)

Endpoint: Clinical remission at week 8; clinical response at week 8, change in Mayo score and mucosal improvement based on endoscopic assessment

Status: Additional Phase II data

Milestone: Start Phase III (2015)

Data from 103 patients with moderately to severely active UC in the 24-week maintenance period who achieved a clinical response at week 8 in the double-blind, international Phase II TOUCHSTONE trial showed that once-daily 0.5 and 1 mg oral ozanimod each significantly improved the proportion of patients in clinical remission at week 32 vs. placebo (p<0.05 for both). Additionally, high-dose ozanimod also met the secondary endpoint of improving clinical response at week 32 vs. placebo. Ozanimod was generally well tolerated. This year, Receptos plans to start a Phase III trial evaluating ozanimod to treat UC and a Phase II trial to treat Crohn's disease. The company has

previously reported 8- and 32-week data from the TOUCHSTONE trial (see BioCentury, Nov. 3, 2014 & Feb. 9, 2015).

**Replicor Inc.**, Montreal, Quebec

Product: REP 2139-Ca

Business: Infectious

Molecular target: NA

Description: Nucleic acid polymer (NAP)

Indication: Treat chronic HBV infection

Endpoint: Safety, NAP-induced clearance of serum hepatitis B surface antigen (HBsAg) and serum HBV DNA levels

Status: Phase II data

Milestone: NA

The open-label Phase II REP 102 trial in 12 treatment-naïve patients with chronic HBV infection showed that once-weekly 500 mg IV REP 2139-Ca for 20-62 weeks plus Pegasys peginterferon alfa-2a and/or Zadaxin thymalfasin was well tolerated. Additionally, 10 patients achieved a reduction or clearance of HBsAg. Furthermore, 4 patients achieved a long-term sustained virologic response (SVR) defined as serum HBV DNA levels of <500 copies/mL at >12 months after the end of treatment. Data were presented at the Lancet Viral Hepatitis meeting in Shanghai.

**Replicor Inc.**, Montreal, Quebec

Product: REP 2139-Ca

Business: Infectious

Molecular target: NA

Description: Nucleic acid polymer (NAP)

Indication: Treat chronic HBV infection

Endpoint: Safety, NAP-induced clearance of serum hepatitis B surface antigen (HBsAg) and serum HBV DNA levels

Status: Phase II data

Milestone: NA

The open-label Phase II REP 101 trial in 8 treatment-naïve patients with chronic HBV infection showed that once-weekly 400 mg IV REP 2139-Ca for 20-62 weeks was well tolerated. Additionally, 7 patients achieved a reduction or clearance of HBsAg. Furthermore, 2 patients achieved a long-term sustained virologic response (SVR) defined as serum HBV DNA levels of <500 copies/mL at >12 months after the end of treatment. Data were presented at the Lancet Viral Hepatitis meeting in Shanghai.

**Replicor Inc.**, Montreal, Quebec

Product: REP 2139-Ca

Business: Infectious

Molecular target: NA

Description: Nucleic acid polymer (NAP)

Indication: Treat chronic HBV infection

Endpoint: Safety, NAP-induced clearance of serum hepatitis B surface antigen (HBsAg) and serum HBV DNA levels

Status: Phase II data

Milestone: NA

The open-label Phase II REP 201 trial in 5 treatment-naïve patients with chronic HBV infection showed that once-weekly 500 mg IV REP 2139-Ca for 20-62 weeks plus Pegasys peginterferon alfa-2a with or without entecavir was well tolerated. Additionally, all 5 patients achieved a reduction or clearance of HBsAg. Furthermore, 4 patients achieved a long-term sustained virologic response (SVR) defined as serum HBV DNA levels of <500 copies/mL at >12 months after the end of treatment. Data were presented at the Lancet Viral Hepatitis meeting in Shanghai.

**The Rockefeller University**, New York, N.Y.

Product: 3BNC117

Business: Infectious

Molecular target: CD4

Description: Humanized anti-CD4 binding site mAb

Indication: Treat HIV-1 infection

Endpoint: Safety; pharmacokinetics

Status: Phase I data

Milestone: NA

An open-label, dose-escalation, U.S. and German Phase I trial in 17 patients with HIV-1 infection and 12 uninfected subjects showed that single doses of 1, 3, 10 and 30 mg/kg IV 3BNC117 were generally well tolerated with no serious adverse events reported. Additionally, a single 30 mg/kg dose of 3BNC117 reduced viral load in HIV patients by 0.8-2.5 log<sub>10</sub>. Data were published in *Nature*.

## CLINICAL NEWS

## PRECLINICAL RESULTS

**BioInvent International AB** (SSE:BINV), Lund, Sweden

Product: BI-1206

Business: Cancer

Indication: Treat lymphoma

In mice, BI-1206 prevented tumor cell internalization of Rituxan rituximab, a chimeric mAb against CD20 antigen, and subsequently increased cell surface accessibility and immune effector cell-mediated antitumor activity. Data were published in *Cancer Cell*. This year, BioInvent plans to start Phase I/II testing of the Fc gamma receptor IIb (CD32B; FCGR2B) antagonist.

## CLINICAL NEWS

## CLINICAL STATUS

**Advaxis Inc.** (NASDAQ:ADXS), Princeton, N.J.

Product: *Listeria monocytogenes*/PSA (Lm-LLO-PSA) vaccine (ADXS-PSA) (formerly ADXS31-142)

Business: Cancer

Molecular target: Prostate-specific antigen (KLK3) (PSA)

Description: Prostate-specific antigen (KLK3; PSA) incorporated in live attenuated vector

Indication: Treat metastatic castration-resistant prostate cancer (CRPC)

Endpoint: Safety; progression-free survival (PFS)

Status: Phase I/II started

Milestone: Phase I/II data (2016)

Advaxis began the open-label, dose-escalation, U.S. Phase I/II KEYNOTE-046 trial of IV ADXS-PSA alone and in combination with IV Keytruda pembrolizumab every 3 weeks in about 51 previously treated patients. The first part will evaluate ADXS-PSA alone. The second part will test the compound with Keytruda and includes a dose-expansion phase.

**Advaxis Inc.** (NASDAQ:ADXS), Princeton, N.J.

**Biocon Ltd.** (NSE:BIOCON; BSE:BIOCON), Bangalore, India

Product: ADXS-HPV (ADXS11-001) (formerly Lovaxin C)

Business: Cancer

Molecular target: NA

Description: Live Listeria monocytogenes-based immunotherapy expressing E7 transforming protein (Human papillomavirus-16) (HpV16gp2)

Indication: Treat recurrent cervical cancer

Endpoint: Dose-limiting toxicities (DLTs) and safety; immunogenicity and objective tumor response

Status: Phase I/II started

Milestone: NA

Advaxis began an open-label, dose-escalation, U.S. Phase I/II trial to evaluate up to 1\*10<sup>10</sup> colony forming units (CFUs) of ADXS-HPV in about 25 patients who have received 1 cytotoxic treatment regimen. Biocon has exclusive rights from Advaxis to co-develop and commercialize ADXS-HPV in India and 28 other emerging market territories (see BioCentury, Feb. 3, 2014).

**Arrowhead Research Corp.** (NASDAQ:ARWR), Pasadena, Calif.

Product: ARC-520

Business: Infectious

Molecular target: NA

Description: Short interfering RNAs targeting 2 regions of the HBV genome conjugated to N-acetylgalactosamine-polymer and cholesterol ligands using Arrowhead's Dynamic Polyconjugate delivery system

Indication: Treat chronic HBV infection

Endpoint: Depth and duration of hepatitis B surface antigen (HBsAg) reduction; safety and pharmacokinetics

Status: Phase IIb start

Milestone: Start Phase IIb (05/2015)

Next month, Arrowhead will start the double-blind, placebo-controlled Phase IIb Heparc-2004 trial to evaluate 1 mg/kg IV ARC-520 every 4 weeks for up to 3 doses in up to 12 HCV-infected patients maintained on entecavir or tenofovir therapy. Earlier this year, FDA placed a partial clinical hold on IV ARC-520. Arrowhead said the agency would allow the company to begin a multiple-dose study at 1 mg/kg ARC-520, instead of its proposed parallel study design of 2 and 4 mg/kg doses (see BioCentury, Jan. 19).

**BioPorto Diagnostics A/S** (CSE:BIOPOR), Gentofte, Denmark

Product: NGAL Test

Business: Diagnostic

Molecular target: Lipocalin (NGAL) (LCN2)

Description: In vitro test that detects the lipocalin (LCN2; NGAL) biomarker produced in the kidneys

Indication: Diagnose acute kidney injury (AKI)

Endpoint: Sensitivity as measured by proportion of patients with an NGAL value of  $\geq 250$  ng/mL and specificity as measured by proportion of patients with an NGAL value of  $< 250$  ng/mL; creatinine levels and urine output

Status: Clinical trial completed enrollment

Milestone: Submit Regulatory application (mid-2015); FDA action (year end 2015)

BioPorto completed enrollment of 250 ICU patients in a blinded, U.S. clinical trial comparing its NGAL Test vs. clinical diagnosis of AKI as determined by Kidney Disease Improving Global Outcomes (KDIGO) guidelines.

**Celtaxsys Inc.**, Atlanta, Ga.

Product: CTX-4430 (formerly EP-501)

Business: Dermatology

Molecular target: Leukotriene A4 hydrolase (LTA4H)

Description: Leukotriene A4 hydrolase (LTA4H) inhibitor

Indication: Treat moderate to severe acne vulgaris

Endpoint: Inflammatory lesion counts and safety; improvement in Investigator's Global Assessment (IGA) score and non-inflammatory lesion counts

Status: Phase II started

Milestone: NA

Celtaxsys began a double-blind, placebo-controlled, Australian and New Zealand Phase II trial to evaluate 100 mg oral CTX-4430 once daily for 12 weeks in about 156 patients.

**Clementia Pharmaceuticals Inc.**, Dorval, Quebec

**Roche** (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

Product: Palovarotene (R667) (formerly RG667, CLM-001)

Business: Musculoskeletal

Molecular target: Retinoic acid receptor gamma (RARG)

Description: Selective small molecule retinoic acid receptor gamma (RARG) agonist

**Indication:** Treat fibrodysplasia ossificans progressiva (FOP)  
**Endpoint:** Percentage of responders as assessed by plain radiographs; numeric heterotopic ossification scores and area of new heterotopic bone formed, plasma biomarker levels, volume of bone formation, soft tissue swelling and active range of motion  
**Status:** Phase II ongoing  
**Milestone:** NA

An independent DSMB recommended continuation of a double-blind, international Phase II trial evaluating oral palovarotene once daily for 42 days after a review of safety and efficacy data from the first cohort of 8 FOP patients ages  $\geq 15$ . The cohort received placebo or palovarotene at a starting dose of 10 mg for 14 days, followed by 5 mg for 28 days. The trial will now further test the dose and a lower dose of 5 mg for 14 days, followed by 2.5 mg for 28 days, in an additional 16 patients. Patients have the option of enrolling in a 12-month, open-label extension. Clementia has exclusive, worldwide rights to palovarotene from [Roche](#) (see BioCentury, Jan. 13, 2014).

**Concert Pharmaceuticals Inc.** (NASDAQ:CNCE), Lexington, Mass.

**Product:** D-Ivacaftor (C-10358)  
**Business:** Pulmonary  
**Molecular target:** NA  
**Description:** Oral deuterium-modified ivacaftor, a potentiator of cystic fibrosis transmembrane conductance regulator (CFTR)  
**Indication:** Treat cystic fibrosis (CF)  
**Endpoint:** Safety; pharmacokinetics  
**Status:** Phase I started  
**Milestone:** Start Phase I (2H15)

Concert began an open-label, Australian Phase I trial of oral C-10355 or C-10358 in about 16 healthy volunteers. A crossover portion will compare single doses of the compounds to determine which will be selected for further evaluation. The second portion will compare single ascending doses of the selected compound vs. a single dose of 150 mg oral Kalydeco ivacaftor. A Phase I trial evaluating multiple ascending doses of the selected compound is expected to start next half.

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**Dermira Inc.** (NASDAQ:DERM), Menlo Park, Calif.

**Product:** DRM01 (formerly VAL-001, QLT91382)  
**Business:** Dermatology  
**Molecular target:** Acetyl-Coenzyme A carboxylase (ACAC) (ACC)  
**Description:** Topical prodrug of an acetyl-Coenzyme A carboxylase (ACAC; ACC) inhibitor  
**Indication:** Treat moderate to severe facial acne vulgaris  
**Endpoint:** Change in the number of inflammatory and non-inflammatory lesion counts and  $\geq 2$ -grade improvement in Investigator's Global Assessment (IGA) score from baseline to week 12  
**Status:** Phase IIb started  
**Milestone:** Phase IIb data (1H16)

Dermira began a double-blind, vehicle-controlled, dose-ranging, North American Phase IIb trial to evaluate topical DRM01 for 12 weeks in about 400 patients.

**Ipsen Group** (Euronext:IPN; Pink:IPSEY), Boulogne-Billancourt, France

**Rhythm Pharmaceuticals Inc.**, Boston, Mass.

**Product:** Relamorelin (RM-131) (formerly BIM 28131)  
**Business:** Gastrointestinal  
**Molecular target:** Ghrelin  
**Description:** Ghrelin agonist  
**Indication:** Treat diabetic gastroparesis  
**Endpoint:** Change in vomiting episodes as assessed in the Diabetic Gastroparesis Symptom Severity Diary (DGSSD); change in nausea, early satiety, bloating, vomiting severity and abdominal pain as assessed by the DGSSD and change in gastric emptying breath test (GBET)  
**Status:** Phase IIb started  
**Milestone:** NA

Rhythm began a double-blind, placebo-controlled, international Phase IIb trial to evaluate 10, 30 and 100  $\mu\text{g}$  subcutaneous relamorelin twice daily for 12 weeks in about 400 Type I or Type II diabetics. [Actavis plc](#) (NYSE:ACT, Dublin, Ireland) has an exclusive option to acquire Rhythm's subsidiary Rhythm Health Inc., which is developing relamorelin (see BioCentury, Nov. 3, 2014). The partners said the option is exercisable following the completion of the Phase IIb trial. Rhythm has exclusive, worldwide rights to relamorelin from Ipsen (see BioCentury, March 15, 2010).

**Receptos Inc.** (NASDAQ:RCPT), San Diego, Calif.

**Product:** Ozanimod (RPC1063)  
**Business:** Autoimmune

**Molecular target:** Sphingosine 1-phosphate receptor 1 (S1PR1) (S1P1) (EDG1)

**Description:** Selective sphingosine-1-phosphate receptor 1 (S1PR1; S1P1; EDG1) modulator

**Indication:** Treat relapsing multiple sclerosis (MS)

**Endpoint:** Cumulative number of total new gadolinium-enhancing lesions as determined by MRI from week 12 to week 24 (Phase II) and annualized relapse rate (ARR) at 24 months (Phase III); number of gadolinium-enhancing lesions at week 24, cumulative number of new/enlarging T2 lesions from week 12 to week 24 and safety

**Status:** Completed Phase II/III enrollment

**Milestone:** Complete Phase III (1H17)

Receptos completed enrollment of about 1,200 patients in the double-blind, double-dummy, international Phase II/III RADIANCE trial comparing 0.5 and 1 mg oral ozanimod once daily vs. weekly Avonex interferon beta-1a. The company has an SPA from FDA for the trial. Last June, Receptos reported top-line data from the Phase II portion showing that both doses of ozanimod met the primary and secondary endpoints (see BioCentury, June 16, 2014; Sept. 15, 2014 & Sept. 22, 2014). Receptos plans to complete its Phase III program in 1H17.

**Recro Pharma Inc.** (NASDAQ:REPH), Malvern, Pa.

**Product:** Dexmedetomidine (Dex-IN)

**Business:** Neurology

**Molecular target:** Adrenergic receptor alpha 2 (ADRA2)

**Description:** Intranasal formulation of dexmedetomidine, an adrenergic receptor alpha 2 (ADRA2) agonist

**Indication:** Treat postoperative pain

**Endpoint:** Summed pain intensity difference over 48 hours (SPID48) starting on postoperative day 1; use of opioid rescue medication, opioid-related side effects and Patient Global Assessment (PGA) of pain control

**Status:** Phase II ongoing

**Milestone:** Phase II data (mid-2015)

Recro reduced target enrollment to 170 patients from 200-250 in the double-blind Phase II REC-14-013 trial of intranasal Dex-IN after a prespecified interim analysis. The analysis was to allow for sample size adjustment to maintain the ability to detect a difference in treatment effects between Dex-IN and placebo. The trial is evaluating 50 µg Dex-IN every 6 hours for 48 hours starting on postoperative day 1 in patients undergoing a bunionectomy.

**Xoma Corp.** (NASDAQ:XOMA), Berkeley, Calif.

**Servier**, Neuilly-sur-Seine, France

**Product:** Gevokizumab (S 78989, XOMA 052)

**Business:** Renal

**Molecular target:** Interleukin-1 (IL-1) beta

**Description:** Humanized IgG2 mAb against IL-1 beta

**Indication:** Treat diabetic nephropathy

**Endpoint:** Measured glomerular filtration rate (mGFR) at week 52

**Status:** Phase II started

**Milestone:** NA

**Servier** began a double-blind, placebo-controlled, international Phase II trial to evaluate subcutaneous gevokizumab for 52 weeks in 370 Type II diabetics. **Servier** has worldwide rights to develop and commercialize gevokizumab for Type II diabetes and cardiovascular indications and rights outside the U.S. and Japan to all other indications from Xoma (see BioCentury, Jan. 10, 2011).

*Week ended 4/17/15. Shares after offering refers to shares outstanding. Proceeds are gross, not net. Shares offered don't include overallocments. Currency rates used in the week: C\$=\$0.7917; €=\$1.0564; £=\$1.46; SEK=\$0.1129*

## FINANCIAL NEWS

### COMPLETED OFFERINGS

**Aduro Biotech Inc.** (NASDAQ:ADRO), Berkeley, Calif.

Business: Cancer  
Date completed: 2015-04-14  
Type: IPO  
Raised: \$119 million  
Shares: 7 million  
Price: \$17  
Shares after offering: 59 million  
Underwriters: BofA Merrill Lynch; Leerink Partners; William Blair; Canaccord  
Overallocation: 1.1 million

**Akebia Therapeutics Inc.** (NASDAQ:AKBA), Cambridge, Mass.

Business: Hematology, Cardiovascular  
Date completed: 2015-04-16  
Type: Follow-on  
Raised: \$60 million  
Shares: 7.3 million  
Price: \$8.25  
Shares after offering: 27.7 million  
Underwriters: UBS; Morgan Stanley; JMP Securities; Needham; Brean Capital  
Overallocation: 1.1 million

**BioAegis Therapeutics Corp.**, Morristown, N.J.

Business: Inflammation, Infectious  
Date completed: 2015-04-15  
Type: Venture financing  
Raised: \$8 million  
Investor: Not disclosed  
Note: The financing is a convertible note.

**Biodel Inc.** (NASDAQ:BIOD), Danbury, Conn.

Business: Endocrine/Metabolic, Drug delivery  
Date completed: 2015-04-15  
Type: Follow-on  
Raised: \$30 million  
Shares: 32.6 million  
Price: \$0.92  
Shares after offering: 57.2 million

Underwriters: William Blair; Ladenburg Thalmann; Roth Capital Partners  
Overallocation: 4.9 million

**BoneSupport AB**, Lund, Sweden

Business: Musculoskeletal  
Date completed: 2015-04-15  
Type: Venture financing  
Raised: \$14 million  
Investor: Existing investors

**Cidara Therapeutics Inc.** (NASDAQ:CDTX), San Diego, Calif.

Business: Infectious  
Date completed: 2015-04-15  
Type: IPO  
Raised: \$76.8 million  
Shares: 4.8 million  
Price: \$16  
Shares after offering: 13.5 million  
Underwriters: Jefferies; Leerink Partners; Wedbush; Needham; BTIG  
Overallocation: 720,000

**Cipher Pharmaceuticals Inc.** (TSX:DND; NASDAQ:CPHR), Mississauga, Ontario

Business: Endocrine/Metabolic, Neurology, Dermatology  
Date completed: 2015-04-13  
Type: Private placement of senior notes  
Raised: \$40 million  
Placement agent: Piper Jaffray  
Investor: Athyrium Capital Management  
Note: Cipher drew down \$40 million from a new \$100 million secured note financing. The five-year note bears 10.25% interest. The remaining \$60 million can be drawn down based on certain conditions to finance acquisitions. The lender also received seven-year warrants to purchase 600,000 shares at \$9.22.

**Clyde Biosciences Ltd.**, Glasgow, U.K.

Business: Supply/Service  
Date completed: 2015-04-13  
Type: Venture financing  
Raised: £2 million (\$2.9 million)  
Investors: Epidarex Capital; Scottish Investment Bank; Glasgow University Holdings

**Concordia Healthcare Corp.** (TSX:CXR; OTCQX:CHEHF), Oakville, Ontario

Business: Neurology, Inflammation, Cancer  
Date completed: 2015-04-13  
Type: Private placement of senior notes

Raised: \$735 million  
Investor: Institutional investors  
Note: The unsecured notes bear 7% interest and mature in 2023.

**Esperas Pharma Inc.**, Montreal, Quebec

Business: Cancer  
Date completed: 2015-04-13  
Type: Venture financing  
Raised: \$16.5 million  
Investors: TVM Life Science Ventures; Fonds de solidarite FTQ

**Foamix Pharmaceuticals Ltd.** (NASDAQ:FOMX), Rehovot, Israel

Business: Autoimmune, Dermatology, Drug delivery  
Date completed: 2015-04-15  
Type: Follow-on  
Raised: \$60 million  
Shares: 6.5 million  
Price: \$9.30  
Shares after offering: 29.1 million  
Underwriters: Barclays Capital; Cowen; Guggenheim Securities; Oppenheimer  
Overallotment: 967,741

**Guided Therapeutics Inc.** (OTCBB:GTHP), Norcross, Ga.

Business: Diagnostic  
Date completed: 2015-04-15  
Type: Private placement of common stock and warrants  
Raised: \$720,000  
Shares: 4 million  
Price: \$0.18  
Shares after offering: 101.2 million  
Investor: Accredited investors  
Note: Investors also received warrants to purchase up to 2 million shares.

**Horizon Pharma plc** (NASDAQ:HZNP), Dublin, Ireland

Business: Autoimmune, Inflammation, Neurology  
Date completed: 2015-04-15  
Type: Follow-on  
Raised: \$433.6 million  
Shares: 15.4 million  
Price: \$28.25  
Shares after offering: 145.3 million  
Underwriters: Citigroup; Jefferies; Cowen; Morgan Stanley  
Overallotment: 2.3 million

**Ignyta Inc.** (NASDAQ:RXDX), San Diego, Calif.

Business: Cancer, Diagnostic  
Date completed: 2015-03-17

Type: Direct public offering  
Raised: \$41.6 million  
Shares: 4.2 million  
Price: \$10  
Shares after offering: 23.7 million  
Investors: Teva Pharmaceuticals; and other investors

**Immune Design Corp.** (NASDAQ:IMDZ), Seattle, Wash.

Business: Infectious, Cancer  
Date completed: 2015-04-15  
Type: Follow-on  
Raised: \$79.5 million  
Shares: 3 million  
Price: \$26.50  
Shares after offering: 20 million  
Underwriters: Jefferies; Leerink Partners; Cowen; Wells Fargo  
Overallotment: 450,000

**Innocrin Pharmaceuticals Inc.**, Durham, N.C.

Business: Cancer  
Date completed: 2015-04-14  
Type: Venture financing  
Raised: \$28 million  
Investors: Eshelman Ventures; Novartis Venture Funds; Lilly Ventures; Hatteras Venture Partners; Intersouth Partners; A&B Equity Holdings

**KemPharm Inc.** (NASDAQ:KMPH), Coralville, Iowa

Business: Neurology  
Date completed: 2015-04-16  
Type: IPO  
Raised: \$56 million  
Shares: 5.1 million  
Price: \$11  
Shares after offering: 13.5 million  
Underwriters: Cowen; RBC Capital Markets; Canaccord; Oppenheimer  
Overallotment: 763,636

**Matinas BioPharma Holdings Inc.** (OTCQB:MTNB), Bedminster, N.J.

Business: Cardiovascular  
Date completed: 2015-04-10  
Type: Private placement of units  
Raised: \$5.1 million  
Units: 10.1 million  
Price: \$0.50 (unit)  
Shares after offering: 56.9 million  
Placement agent: SternAegis Ventures  
Investors: Company directors; company management

Note: Matinas raised \$5.1 million in the final close of a private placement offering, bringing the total raised to \$10 million. The company raised \$4.9 million in March. Each unit consists of a share and a five-year warrant to purchase a share at \$0.75.

**Merus Labs International Inc.** (TSX:MSL; NASDAQ:MSLI), Toronto, Ontario  
Business: Infectious, Dermatology  
Date completed: 2015-04-13  
Type: Follow-on  
Raised: C\$60 million (\$47.5 million)  
Shares: 19.7 million  
Price: C\$3.05  
Shares after offering: 101 million  
Underwriters: Clarus Securities; Cormark Securities; Canaccord; Laurentian Bank Securities Inc.; GMP Securities; TD Securities  
Overallotment: 3 million

**Miraculins Inc.** (TSX-V:MOM), Winnipeg, Manitoba  
Business: Diagnostic, Proteomics  
Date completed: 2015-04-10  
Type: Private placement of units  
Raised: C\$250,000 (\$197,925)  
Units: 2.5 million  
Price: C\$0.10 (unit)  
Shares after offering: 41.8 million

Note: Each unit comprises a share and a two-year warrant to purchase a share at C\$0.15.

**MolMed S.p.A.** (Milan:MLM), Milan, Italy  
Business: Cancer  
Date completed: 2015-04-09  
Type: Rights offering  
Raised: €49.8 million (\$52.6 million)  
Shares: 187.3 million  
Price: €0.27  
Shares after offering: 421.5 million

**Novacyt S.A.** (Euronext:ALNOV), Velizy-Villacoublay, France  
Business: Supply/Service  
Date completed: 2015-04-13  
Type: Private placement  
Raised: €2.2 million (\$2.3 million)  
Shares: 442,000  
Shares after offering: 6.7 million  
Investors: Alto Invest; Nyenburgh; existing investors

**Omeicos Therapeutics GmbH**, Berlin, Germany  
Business: Cardiovascular  
Date completed: 2015-04-15

Type: Venture financing  
Raised: €6.2 million (\$6.5 million)  
Investors: Vesalius Biocapital Partners; SMS Investments; VC Fonds Berlin; High-Tech Gruenderfonds; KfW

**Peptonic Medical AB** (AktieTarget:PMED), Vaxjo, Sweden  
Business: Endocrine/Metabolic, Genitourinary  
Date completed: 2015-03-31  
Type: Private placement  
Raised: SEK14.5 million (\$1.7 million)  
Shares: 1.5 million  
Price: SEK9.85  
Shares after offering: 9.4 million  
Investors: New investors; existing investors

**Pernix Therapeutics Holdings Inc.** (NASDAQ:PTX), Morristown, N.J.  
Business: Infectious  
Date completed: 2015-04-17  
Type: Private placement of senior convertible notes  
Raised: \$130 million  
Shares outstanding prior: 38.4 million  
Investor: Institutional investors  
Note: The unsecured notes bear 4.25% interest, mature on April 1, 2021, and initially convert at \$11.47.

**ProMetic Life Sciences Inc.** (TSX:PLI; OTCQX:PFSCF), Laval, Quebec  
Business: Cancer, Autoimmune, Dermatology  
Date completed: 2015-04-14  
Type: Follow-on  
Raised: C\$50.1 million (\$39.6 million)  
Shares: 19.3 million  
Price: C\$2.60  
Shares after offering: 573.4 million  
Underwriter: Canaccord  
Overallotment: 2.9 million

**Sage Therapeutics Inc.** (NASDAQ:SAGE), Cambridge, Mass.  
Business: Neurology  
Date completed: 2015-04-15  
Type: Follow-on  
Raised: \$120 million  
Shares: 2.3 million  
Price: \$52.50  
Shares after offering: 28.1 million  
Underwriters: JPMorgan; Goldman Sachs; Leerink Partners; Cowen  
Overallotment: 342,857

**StemBioSys Inc.**, San Antonio, Texas  
Business: Gene/Cell therapy  
Date completed: 2015-04-01

Type: Venture financing  
Raised: \$8 million  
Investors: Targeted Technology Fund; angel investors

**Voyager Therapeutics Inc.**, Cambridge, Mass.  
Business: Neurology, Gene/Cell therapy  
Date completed: 2015-04-13  
Type: Venture financing  
Raised: \$60 million  
Investors: Brookside Capital; Partner Fund Management; Wellington Management; Casdin Capital LLC; and other undisclosed investors

**XBiotech Inc.** (NASDAQ:XBIT), Austin, Texas  
Business: Antibodies  
Date completed: 2015-04-14  
Type: IPO  
Raised: \$76 million  
Shares: 4 million  
Price: \$19  
Shares after offering: 31.7 million  
Underwriter: WR Hambrecht

## FINANCIAL NEWS

### PROPOSED OFFERINGS

**Cleveland BioLabs Inc.** (NASDAQ:CBLI), Buffalo, N.Y.  
Business: Cancer, Other, Hematology  
Date announced: 2015-04-10  
Type: Follow-on  
To be raised: Up to \$10 million  
Units: TBD  
Price prior: \$3.67  
Underwriter: Ladenburg Thalmann  
Note: The company is selling units comprising shares and warrants or units comprising preferred stock and warrants.

**DelMar Pharmaceuticals Inc.** (OTCQX:DMPI), Vancouver, B.C.  
Business: Cancer  
Date announced: 2015-04-10  
Type: Follow-on  
To be raised: Up to \$10 million  
Shares: TBD  
Price prior: \$0.71  
Underwriters: Maxim Group; Roth Capital Partners  
Note: The company is seeking to transfer its listing to NASDAQ or NYSE MKT from OTCQX.

**Galapagos N.V.** (Euronext:GLPG; Pink:GLPYY), Mechelen, Belgium  
Business: Autoimmune, Musculoskeletal, Functional genomics  
Date announced: 2015-04-15  
Type: Follow-on  
To be raised: Up to \$150 million  
Shares: TBD  
Price prior: €29  
Underwriters: Morgan Stanley; Credit Suisse; Cowen; Nomura; Bryan, Garnier & Co.  
Note: Galapagos proposed to list its ADSs on NASDAQ. Each ADS represents one ordinary share.

**Innocoll AG** (NASDAQ:INNL), Athlone, Ireland  
Business: Drug delivery, Neurology, Infectious  
Date announced: 2015-04-10  
Type: Follow-on  
To be raised: Up to \$19.2 million  
Shares: TBD  
Price prior: \$7.30  
Underwriter: Piper Jaffray  
Note: Innocoll is selling ADSs. Each ordinary share represents 13.25 ADSs.

**Pfenex Inc.** (NYSE-M:PFNX), San Diego, Calif.  
Business: Biosimilars, Supply/Service  
Date announced: 2015-04-15  
Type: Follow-on  
To be raised: TBD  
Shares: 2.3 million  
Price prior: \$18.25  
Underwriters: Barclays Capital; Evercore; William Blair  
Overallotment: 750,000  
Note: Shareholders plan to sell 2.7 million shares in a secondary offering.

**RXi Pharmaceuticals Corp.** (NASDAQ:RXII), Westborough, Mass.  
Business: Dermatology, Gene/Cell therapy  
Date announced: 2015-04-13  
Type: Private placement of common stock and warrants  
To be raised: Up to \$20 million  
Shares: TBD  
Price prior: \$0.84  
Shares outstanding prior: 31.2 million  
Placement agent: H.C. Wainwright

**Sphere Medical Holding plc** (LSE:SPHR), Cambridge, U.K.  
Business: Diagnostic, Supply/Service  
Date announced: 2015-04-13  
Type: Placing and open offer

To be raised: Up to £13.2 million (\$19.3 million)  
Shares: 82.4 million  
Price: 16p

Note: The offering comprises up to £12 million (\$17.5 million) in a placing and up to £1.2 million (\$1.8 million) in an open offer, in which shareholders are eligible to purchase one share for every eight held. The offering is subject to shareholder approval at a general meeting on April 30.

## FINANCIAL NEWS

### WITHDRAWN OFFERINGS

**Clarus Therapeutics Inc.**, Northbrook, Ill.

Business: Endocrine/Metabolic  
Date announced: 2015-04-15  
Type: IPO  
Underwriters: Citigroup; Credit Suisse; Canaccord; Needham  
Note: Clarus withdrew its IPO on NASDAQ, citing market conditions.

## FINANCIAL NEWS

### AMENDED OFFERINGS

**Biocartis Group N.V.**, Mechelen, Belgium

Business: Diagnostic  
Date announced: 2015-04-15  
Type: IPO  
To be raised: Up to €100 million (\$105.6 million)  
Shares: 8.7 million  
Price: €10-€11.50  
Underwriters: KBC; Kempen & Co.; Petercam  
Note: Biocartis amended its IPO and now plans to sell up to 8.7 million shares at €10-€11.50. Earlier this month, the company filed to list its shares on Euronext Brussels.

**CoLucid Pharmaceuticals Inc.**, Durham, N.C.

Business: Neurology  
Date announced: 2015-04-10  
Type: IPO  
To be raised: TBD  
Shares: TBD  
Price: TBD  
Underwriters: Piper Jaffray; Stifel, Nicolaus; William Blair  
Note: CoLucid amended its IPO on NASDAQ and removed its proposed amount to be raised. The company filed to raise up to \$86.3 million in March.

**NeuroMetrix Inc.** (NASDAQ:NURO), Waltham, Mass.

Business: Neurology  
Date announced: 2015-04-13  
Type: Follow-on  
To be raised: Up to \$30 million  
Units: 9.9 million  
Price prior: \$2.05  
Underwriters: Maxim Group; Dawson James Securities  
Overallotment: 1.5 million

Note: NeuroMetrix amended its offering and now plans to sell up to 9.9 million shares. Investors will also receive five-year warrants to purchase up to 9.9 million shares. NeuroMetrix originally proposed to raise up to \$15 million in an offering of units in April 2013.

**OpGen Inc.**, Gaithersburg, Md.

Business: Diagnostic, Bioinformatics, Pharmacogenetics  
Date announced: 2015-04-14  
Type: IPO  
To be raised: Up to \$37.5 million  
Shares: 3.8 million  
Price: \$8-\$10  
Underwriters: Maxim Group; National Securities  
Overallotment: 562,500

Note: OpGen amended its IPO on NASDAQ and added National Securities as an underwriter. Earlier this month, the company amended its IPO to sell up to 3.8 million shares at \$8-\$10. Last month, the company filed to raise up to \$34.5 million.

**Viking Therapeutics Inc.**, San Diego, Calif.

Business: Endocrine/Metabolic, Musculoskeletal, Hematology  
Date announced: 2015-04-10  
Type: IPO  
To be raised: Up to \$22.5 million  
Shares: 2.5 million  
Price: \$7-\$9  
Underwriters: Laidlaw; Felt  
Overallotment: 375,000

Note: Viking amended its IPO on NASDAQ and now plans to sell up to 2.5 million shares at \$7-\$9. Last September, the company amended its IPO to sell 5 million shares at \$10-\$12. Last July, Viking filed to raise up to \$57.5 million.

## FINANCIAL NEWS

### OTHER FINANCIAL NEWS

**Castle Biosciences Inc.**, Friendswood, Texas

Business: Diagnostic  
Date announced: 2015-04-14

Note: Castle Biosciences secured a \$6 million credit facility from Silicon Valley Bank. The company declined to disclose whether it drew down funds from the facility.

**Dyax Corp.** (NASDAQ:DYAX), Burlington, Mass.

Business: Inflammation, Ophthalmic

Date announced: 2015-04-13

Note: Dyax raised \$30 million through the sale of 1.1 million shares at \$27 to cover the overallotment from its April 7 follow-on, bringing the total raised to \$229.8 million. The company, which closed Friday at \$27.97, has 145.3 million shares outstanding.

**Galena Biopharma Inc.** (NASDAQ:GALE), Portland, Ore.

Business: Cancer

Date announced: 2015-04-10

Note: Galena raised \$5.3 million through the sale of 3.7 million shares at \$1.46 to cover the overallotment from its March 13 follow-on, bringing the total raised to \$43.3 million. The company, which closed Friday at \$1.40, has 161.7 million shares outstanding.

**Joben Bio-Medical Co. Ltd.**, Changzhi Township, Taiwan

Business: Cancer, Neurology

Date announced: 2015-04-10

Note: Joben Bio-Medical began the formal process to list on the GreTai Securities Market in Taiwan by applying as an emerging stock on the exchange. The company expects to begin trading as an emerging stock on April 20. To obtain a formal listing on the GreTai exchange, companies must first trade as an emerging stock for at least six months or meet other requirements.

**New Enterprise Associates**, Baltimore, Md.

Business: Finance

Date announced: 2015-04-15

Note: [New Enterprise Associates](#) raised a total of \$3.2 billion for two funds, including \$2.8 billion for NEA 15 and \$350 million for an adjunct fund, NEA 15 Opportunity Fund. The firm had targeted \$2.5 billion for NEA 15.

The firm plans to allocate 35% of NEA 15 towards healthcare, focusing on biopharma, healthcare services and medical devices. The fund will invest in both early and late-stage companies worldwide. The firm will co-invest the opportunity fund alongside NEA's other funds in companies that require more capital. NEA 15 is the firm's fourth consecutive fund to exceed \$2.5 billion. NEA closed its fourteenth fund at \$2.6 billion in 2012.

The firm's healthcare investments include T cell therapy company [Adaptimmune Ltd.](#) (Abingdon, U.K.), cancer immunotherapy play [Surface Oncology Inc.](#) (Cambridge, Mass.) and diabetes company [Intarcia Therapeutics Inc.](#) (Boston, Mass.).

**TVM Capital**, Munich, Germany

Business: Finance

Date announced: 2015-04-13

Note: TVM Capital Life Science announced a first close of \$50 million for its China BioPharma Capital I fund. The fund includes an investment from [Chongqing Lummy Pharmaceutical Co. Ltd.](#) (SZSE:300006, Chongqing, China). The firm plans to invest in Western companies that intend to obtain licenses to develop and commercialize pharmaceuticals in China.

TVM closed its asset-focused TVM Life Science Ventures VII fund in October 2014 at \$201.6 million (see BioCentury, Oct. 13, 2014).

## BIOCENTURY WEEK IN REVIEW

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